APPENDIX G

Toxicity Profiles

TOXICOLOGICAL PROFILE FOR ALUMINUM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2008

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Aluminum, Draft for Public Comment, was released in September 2006. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel

and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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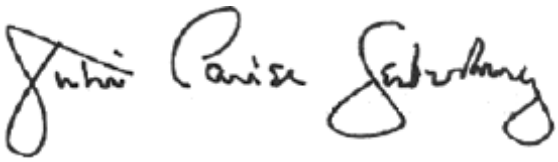

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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99 499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for aluminum. The panel consisted of the following members:

1. Dr. Jerrold Abraham, Professor of Family Medicine, Upstate Medical University, Syracuse, New York,

2. Dr. Michael Aschner, Director, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, and

3. Dr. Robert Yokel, Professor, Division of Pharmaceutical Sciences, University of Kentucky, College of Pharmacy, Lexington, Kentucky.

These experts collectively have knowledge of aluminum's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about aluminum and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Aluminum (in some form, e.g., in compounds with other elements such as oxygen, sulfur, or phosphorus) has been found at elevated levels in at least 596 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which aluminum is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance at high levels may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact. However, it should be noted that aluminum is a very abundant and widely distributed element and will be found in most rocks, soils, waters, air, and foods. You will always have some exposure to low levels of aluminum from eating food, drinking water, and breathing air.

If you are exposed to aluminum, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS ALUMINUM?

Description	Aluminum is the most abundant metal in the earth's crust and it is widely distributed. Aluminum is a very reactive element and is never found as the free metal in nature. It is found combined with other elements, most commonly with oxygen, silicon, and fluorine. These chemical compounds are commonly found in soil, minerals (e.g., sapphires, rubies, turquoise), rocks (especially igneous rocks), and clays. Aluminum as the metal is obtained from aluminum-containing minerals, primarily bauxite. Aluminum metal is light in weight and silvery-white in appearance.
Uses • **Aluminum metal**	Aluminum is used to make beverage cans, pots and pans, airplanes, siding and roofing, and foil. Powdered aluminum metal is often used in explosives and fireworks.
• **Aluminum compounds**	Aluminum compounds are used in many diverse and important industrial applications such as alums (aluminum sulfate) in water-treatment and alumina in abrasives and furnace linings.
• **Consumer products**	Aluminum is found in consumer products including: • antacids • astringents • buffered aspirin • food additives • antiperspirants • cosmetics

For more information on the physical and chemical properties of aluminum and its production, disposal, and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO ALUMINUM WHEN IT ENTERS THE ENVIRONMENT?

Sources	Aluminum occurs naturally in soil, water, and air. High levels in the environment can be caused by the mining and processing of aluminum ores or the production of aluminum metal, alloys, and compounds. Small amounts of aluminum are released into the environment from coal-fired power plants and incinerators.
Break down • **Air** • **Water and soil**	Aluminum cannot be destroyed in the environment. It can only change its form or become attached or separated from particles. Aluminum particles in air settle to the ground or are washed out of the air by rain. However, very small aluminum particles can stay in the air for many days. Most aluminum-containing compounds do not dissolve to a large extent in water unless the water is acidic or very alkaline.

For more information on aluminum in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO ALUMINUM?

Food—primary source of exposure	Unprocessed foods like fresh fruits, vegetables, and meat contain very little aluminum. Aluminum compounds may be added during processing of foods, such as: • flour • baking powder • coloring agents • anticaking agents An average adult in the United States eats about 7–9 mg of aluminum per day in their food.
Air	Most people take in very little aluminum from breathing. Levels of aluminum in the air generally range from 0.005 to 0.18 micrograms per cubic meter ($\mu g/m^3$), depending on location, weather conditions, and type and level of industrial activity in the area. Most of the aluminum in the air is in the form of small suspended particles of soil (dust). Aluminum levels in urban and industrial areas may be higher and can range from 0.4 to 8.0 $\mu g/m^3$.

Water and soil	The concentration of aluminum in natural waters (e.g., ponds, lakes, streams) is generally below 0.1 milligrams per liter (mg/L). People generally consume little aluminum from drinking water. Water is sometimes treated with aluminum salts while it is processed to become drinking water. But even then, aluminum levels generally do not exceed 0.1 mg/L. Several cities have reported concentrations as high as 0.4–1 mg/L of aluminum in their drinking water.
Consumer Products	People are exposed to aluminum in some cosmetics, antiperspirants, and pharmaceuticals such as antacids and buffered aspirin. • Antacids have 300–600 mg aluminum hydroxide (approximately 104–208 mg of aluminum) per tablet, capsule, or 5 milliliter (mL) liquid dose. Little of this form of aluminum is taken up into the bloodstream. • Buffered aspirin may contain 10–20 mg of aluminum per tablet • Vaccines may contain small amounts of aluminum compounds, no greater than 0.85 mg/dose.

For more information on how you might be exposed to aluminum, see Chapter 6.

1.4 HOW CAN ALUMINUM ENTER AND LEAVE MY BODY?

Enter your body	
• **Inhalation**	A small amount of the aluminum you breathe will enter your body through your lungs.
• **Ingestion**	A very small amount of the aluminum in food or water will enter your body through the digestive tract. An extremely small amount of the aluminum found in antacids will be absorbed.
• **Dermal contact**	A very small amount may enter through your skin when you come into contact with aluminum.
Leave your body	Most aluminum in food, water, and medicines leaves your body quickly in the feces. Much of the small amount of aluminum that does enter the bloodstream will quickly leave your body in the urine.

For more information on how aluminum enters and leaves the body, see Chapter 3.

1.5 HOW CAN ALUMINUM AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Workers **• Inhalation**	Workers who breathe large amounts of aluminum dusts can have lung problems, such as coughing or changes that show up in chest X-rays. The use of breathing masks and controls on the levels of dust in factories have largely eliminated this problem. Some workers who breathe aluminum-containing dusts or aluminum fumes have decreased performance in some tests that measure functions of the nervous system.
Humans **• Oral**	Oral exposure to aluminum is usually not harmful. Some studies show that people exposed to high levels of aluminum may develop Alzheimer's disease, but other studies have not found this to be true. We do not know for certain that aluminum causes Alzheimer's disease. Some people who have kidney disease store a lot of aluminum in their bodies. The kidney disease causes less aluminum to be removed from the body in the urine. Sometimes, these people developed bone or brain diseases that doctors think were caused by the excess aluminum. Although aluminum-containing over the counter oral products are considered safe in healthy individuals at recommended doses, some adverse effects have been observed following long-term use in some individuals.
Laboratory animals **• Inhalation** **• Oral**	Lung effects have been observed in animals exposed to aluminum dust. Scientists do not know if these effects are dur to the aluminum or to the animals breathing in a lot of dust. Studies in animals show that the nervous system is a sensitive target of aluminum toxicity. Obvious signs of damage were not seen in animals after high oral doses of aluminum. However, the animals did not perform as well in tests that measured the strength of their grip or how much they moved around.

Further information on the health effects of aluminum in humans and animals can be found in Chapters 2 and 3.

1.6 HOW CAN ALUMINUM AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in children	Brain and bone disease caused by high levels of aluminum in the body have been seen in children with kidney disease. Bone disease has also been seen in children taking some medicines containing aluminum. In these children, the bone damage is caused by aluminum in the stomach preventing the absorption of phosphate, a chemical compound required for healthy bones. Aluminum is found in breast milk, but only a small amount of this aluminum will enter the infant's body through breastfeeding. Typical aluminum concentrations in human breast milk range from 0.0092 to 0.049 mg/L. Aluminum is also found in soy-based infant formula (0.46–0.93 mg/L) and milk-based infant formula (0.058–0.15 mg/L).
Birth defects	We do not know if aluminum will cause birth defects in people. Birth defects have not been seen in animals. Very young animals appeared weaker and less active in their cages and some movements appeared less coordinated when their mothers were exposed to large amounts of aluminum during pregnancy and while nursing. In addition, aluminum also affected the animal's memory. These effects are similar to those that have been seen in adults. It does not appear that children are more sensitive than adult animals.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ALUMINUM?

Food	You cannot avoid exposure to aluminum because it is so common and widespread in the environment. Exposure to the levels of aluminum that are naturally present in food and water and the forms of aluminum that are present in dirt and aluminum pots and pans are not considered to be harmful. Eating large amounts of processed food containing aluminum additives or frequently cooking acidic foods in aluminum pots may expose a person to higher levels of aluminum than a person who generally consumes unprocessed foods and uses pots made of other materials (e.g., stainless steel or glass). However, aluminum levels found in processed foods and foods cooked in aluminum pots are generally considered to be safe.

Consumer products	Limiting your intake of large quantities of aluminum-containing antacids and buffered aspirin and using these medications only as directed is the best way to limit exposure to aluminum from these sources. As a precaution, such products should have child-proof caps or should be kept out of reach of children so that children will not accidentally injest them.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ALUMINUM?

Detecting exposure	All people have small amounts of aluminum in their bodies. It can be measured in the blood, bones, feces, or urine.
Measuring exposure	Urine and blood aluminum measurements can tell you whether you have been exposed to larger-than-normal amounts of aluminum, especially for recent amounts. Measuring bone aluminum can also indicate exposure to high levels of aluminum, but this requires a bone biopsy.

Information about tests for detecting aluminum in the body is given in Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as “not-to-exceed” levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for aluminum include the following:

Drinking water	The EPA has recommended a Secondary Maximum Contaminant Level (SMCL) of 0.05–0.2 mg/L for aluminum in drinking water. The SMCL is not based on levels that will affect humans or animals. It is based on taste, smell, or color.
Consumer products	The FDA has determined that aluminum used as food additives and medicinals such as antacids are generally safe. FDA set a limit for bottled water of 0.2 mg/L.
Workplace air	OSHA set a legal limit of 15 mg/m^3 (total dust) and 5 mg/m^3 (respirable fraction) aluminum in dusts averaged over an 8-hour work day.

For more information on regulations and advisories, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDC-INFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

1. PUBLIC HEALTH STATEMENT

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ALUMINUM IN THE UNITED STATES

Aluminum is ubiquitous; the third most common element of the earth's crust. It is naturally released to the environment from the weathering of rocks and volcanic activity. Human activities such as mining also result in the release of aluminum to the environment. Aluminum levels in environmental media vary widely depending upon the location and sampling site. In general, background levels of aluminum in the atmosphere are low, typically ranging from about 0.005 to 0.18 μg/m^3. Much higher levels are routinely observed in urban and industrial locations. Aluminum levels in surface water is usually very low (<0.1 mg/L); however, in acidic waters or water high in humic or fulvic acid content, the concentration of soluble aluminum increases due to the increased solubility of aluminum oxide and aluminum salts. Its concentration in soils varies widely, ranging from about 7 to over 100 g/kg.

In the environment, aluminum exists in only one oxidation state (+3), and does not undergo oxidation-reduction reactions. It can react with other matter in the environment to form various complexes. The fate and transport of aluminum is largely controlled by environmental factors such as pH, salinity, and the presence of various species with which it may form complexes. In general, the solubility and mobility of aluminum in soil is greatest when the soil is rich in organic matter capable of forming aluminum-organic complexes and when the pH is low, such as in areas prone to acid rain or in acidic mine tailings.

The general population is primarily exposed to aluminum through the consumption of food items, although minor exposures may occur through ingestion of aluminum in drinking water and inhalation of ambient air. Aluminum found in over-the-counter medicinals, such as antacids and buffered aspirin, is used as a food additive, and is found in a number of topically applied consumer products such as antiperspirants, and first aid antibiotic and antiseptics, diaper rash and prickly heat, insect sting and bite, sunscreen and suntan, and dry skin products. The concentration of aluminum in foods and beverages varies widely, depending upon the food product, the type of processing used, and the geographical areas in which food crops are grown (see Section 6.4). Based on the FDA's 1993 Total Diet Study dietary exposure model and the 1987–1988 U.S. Department of Agriculture (USDA) Nationwide Food Consumption Survey, the authors estimated daily aluminum intakes of 0.10 mg Al/kg/day for 6–11-month-old infants; 0.30–0.35 mg Al/kg/day for 2–6-year-old children; 0.11 mg Al/kg/day for 10-year-old children; 0.15–0.18 mg Al/kg/day for 14–16-year-old males and females; and 0.10–0.12 mg Al/kg/day for adult (25–30- and 70+-year-old) males and females. Users of aluminum-

containing medications who are healthy (i.e., have normal renal function) can ingest much larger amounts of aluminum than in the diet, possibly as high as 12–71 mg Al/kg/day from antacid/anti-ulcer products and 2–10 mg Al/kg/day from buffered analgesics when taken at recommended dosages.

Gastrointestinal absorption of aluminum is low, generally in the range of 0.1–0.4% in humans, although absorption of particularly bioavailable forms such as aluminum citrate may be on the order of 0.5–5%. Although large bolus doses of as much as half a gram of aluminum as aluminum hydroxide throughout the day can be ingested during antacid therapy, absorption of aluminum hydroxide is usually $\leq$0.01% of the intake amount. Bioavailability of aluminum varies depending mainly on the chemical form of the ingested compound (i.e., type of anion) and the concurrent exposure to dietary chelators such as citric acid, ascorbic acid, or lactic acid. The total body burden of aluminum in healthy human subjects is approximately 30–50 mg. Normal levels of aluminum in serum are approximately 1–3 μg/L. Of the total body burden of aluminum, about one-half is in the skeleton, and about one-fourth is in the lungs.

2.2 SUMMARY OF HEALTH EFFECTS

There are numerous studies that have examined aluminum's potential to induce toxic effects in humans exposed via inhalation, oral, or dermal exposure. Most of these findings are supported by a large number of studies in laboratory animals. Occupational exposure studies and animal studies suggest that the lungs and nervous system may be the most sensitive targets of toxicity following inhalation exposure. Respiratory effects, in particular impaired lung function and fibrosis, have been observed in workers exposed to aluminum dust or fumes; however, this has not been consistently observed across studies and it is possible that co-exposure to other compounds contributed to observed effects. Respiratory effects (granulomatous lesions) have also been observed in rats, hamsters, and guinea pigs. There is concern that these effects are due to dust overload rather than a direct effect of aluminum in lung tissue. Occupational studies in workers exposed to aluminum dust in the form of McIntyre powder, aluminum dust and fumes in potrooms, and aluminum fumes during welding provide suggestive evidence that there may be a relationship between chronic aluminum exposure and subclinical neurological effects such as impairment on neurobehavioral tests for psychomotor and cognitive performance and an increased incidence of subjective neurological symptoms. With the exception of some isolated cases, inhalation exposure has not been associated with overt symptoms of neurotoxicity. A common limitation of these occupational exposure studies is that aluminum exposure has not been well characterized. The available animal inhalation studies are inadequate for assessing the potential for aluminum-induced neurotoxicity because

the only neurological end points examined were brain weight and histology of the brain; no function tests were performed.

There is limited information on aluminum toxicity following dermal exposure. Application of aluminum compounds to the skin, such as aluminum chloride in ethanol or alum, may cause rashes in some people. Skin damage has been observed in mice, rabbits, and pigs exposed to aluminum chloride or aluminum nitrate, but not following exposure to aluminum sulfate, aluminum hydroxide, aluminum acetate, or aluminum chlorhydrate.

There is a fair amount of human data on the toxicity of aluminum following oral exposure. However, the preponderance of human studies are in patients with reduced renal function who accumulated aluminum as a result of long-term intravenous hemodialysis therapy with aluminum-contaminated dialysis fluid and, in many cases, concurrent administration of high oral doses of aluminum to regulate phosphate levels (i.e., reduce uptake of phosphate by binding it in the gut) and have limited usefulness in predicting toxicity in the general population because the very large aluminum exposure levels and impaired renal function results in aluminum accumulation. Dialysis encephalopathy syndrome (also referred to as dialysis dementia) can result from this accumulation of aluminum in the brain. Dialysis encephalopathy is a degenerative neurological syndrome, characterized by the gradual loss of motor, speech, and cognitive functions. Another neurological effect that has been proposed to be associated with aluminum exposure is Alzheimer's disease. Although a possible association was proposed over 40 years ago, this association is still highly controversial and there is little consensus regarding current evidence. A number of studies have found weak associations between living in areas with elevated aluminum levels in drinking water and an increased risk (or prevalence) of Alzheimer's disease; other studies have not found significant associations. In contrast, no significant associations have been found between tea consumption or antacid use and the risk of Alzheimer's disease; although the levels of aluminum in tea and antacids are very high compared to drinking water, aluminum from these sources is poorly absorbed. The available data do not suggest that aluminum is a causative agent of Alzheimer's disease; however, it is possible that it may play a role in the disease development.

Aluminum is found in several ingested over-the-counter products such as antacids and buffered aspirin; clinical studies on health effects of aluminum medicinals in people with normal renal function have been identified. These aluminum-containing products are assumed to be safe in healthy individuals at recommended doses based on historical use. The assumed safety of aluminum is also partly due to the generally regarded as safe (GRAS) status of aluminum-containing food additives. However, there is

some indication that adverse effects can result from long-term use of aluminum-containing medications in some healthy individuals. There are a number of case reports of skeletal changes (e.g., osteomalacia) in adults and children with normal kidney function due to long-term antacid use for the treatment of gastrointestinal disorders. These skeletal effects are secondary to hypophosphatemia and phosphate depletion caused by aluminum impairing phosphorus absorption by binding with dietary phosphorus.

There is a rather extensive database on the oral toxicity of aluminum in animals. These studies clearly identify the nervous system as the most sensitive target of aluminum toxicity and most of the animal studies have focused on neurotoxicity and neurodevelopmental toxicity. Other adverse effects that have been observed in animals orally exposed to aluminum include impaired erythropoiesis in rats exposed to 230 mg Al/kg/day and higher, erythrocyte damage (as evidenced by decreases in hemoglobin, hematocrit, and erythrocyte osmotic fragility, and altered erythrocyte morphology) in rats exposed to 230 mg Al/kg/day and higher, increased susceptibility to infection in mouse dams exposed to 155 mg Al/kg/day, delays in pup maturation following exposure of rats to 53 mg Al/kg/day, and decreases in pup body weight gain in rats and mice exposed to 103 mg Al/kg/day and higher.

Neurodegenerative changes in the brain, manifested as intraneuronal hyperphosphorylated neuro-filamentous aggregates, is a characteristic response to aluminum in certain species and nonnatural exposure situations generally involving direct application to brain tissue, particularly intracerebral and intracisternal administration and *in vitro* incubation in rabbits, cats, ferrets, and nonhuman primates. Oral studies in rats and mice have not found significant histopathological changes in the brain under typical exposure conditions; however, altered myelination was found in the spinal cord of mouse pups exposed to 330 mg Al/kg/day on gestation day 1 through postnatal day 35. Overt signs of neurotoxicity are rarely reported at the doses tested in the available animal studies ($\leq$330 mg Al/kg/day for bioavailable aluminum compounds); rather, exposure to these doses is associated with subtle neurological effects detected with neurobehavioral performance tests. Significant alterations in motor function, sensory function, and cognitive function have been detected following exposure to adult or weanling rats and mice or following gestation and/or lactation exposure of rats and mice to aluminum lactate, aluminum nitrate, and aluminum chloride. The most consistently affected performance tests were forelimb and/or hindlimb grip strength, spontaneous motor activity, thermal sensitivity, and startle responsiveness. Significant impairments in cognitive function have been observed in some studies, although this has not been found in other studies even at higher doses. Adverse neurological effects have been observed in rats and mice at doses of 100–200 mg Al/kg/day and neurodevelopmental effects have been observed in rats and mice at doses of 103–330 mg Al/kg/day.

A number of human studies have examined the occurrence of cancer among aluminum industry workers and found a higher-than-expected cancer mortality rate, but this is probably due to the other potent carcinogens to which they are exposed, such as polycyclic aromatic hydrocarbons (PAHs) and tobacco smoke. Available cancer studies in animals have not found biologically relevant increases in malignant tumors. The International Agency for Research on Cancer (IARC) concluded that aluminum production was carcinogenic to humans and that pitch volatiles have fairly consistently been suggested in epidemiological studies as being possible causative agents. The Department of Health and Human Services and EPA have not evaluated the human carcinogenic potential of aluminum.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for aluminum. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for aluminum. Results from human and animal studies suggest that the respiratory tract, particularly the lung, is a sensitive target of airborne aluminum toxicity; human studies also suggest that the nervous system may also be a target of

inhaled aluminum. Interpretation of the human data is complicated by the lack of exposure assessment and the potential for concomitant exposure to other toxic compounds. Numerous studies have found impaired lung function in a variety of aluminum workers (Abbate et al. 2003; Al-Masalkhi and Walton 1994; Bast-Pettersen et al. 1994; Bost and Newman 1993; Burge et al. 2000; Chan-Yeung et al. 1983; Herbert et al. 1982; Hull and Abraham 2002; Jederlinic et al. 1990; Korogiannos et al. 1998; Miller et al. 1984b; Radon et al. 1999; Simonsson et al. 1985; Vandenplas et al. 1998). Other effects that have been observed include occupational asthma (Abramson et al. 1989; Burge et al. 2000; Kilburn 1998; Vandenplas et al. 1998) and pulmonary fibrosis (Al-Masalkhi and Walton 1994; De Vuyst et al. 1986; Edling 1961; Gaffuri et al. 1985; Gilks and Churg 1987; Jederlinic et al. 1990; Jephcott 1948; McLaughlin et al. 1962; Mitchell et al. 1961; Musk et al. 1980; Riddell 1948; Shaver 1948; Shaver and Riddell 1947; Ueda et al. 1958; Vallyathan et al. 1982).

Acute-, intermediate-, and chronic-duration animal studies have also reported respiratory effects. These respiratory effects include increases in alveolar macrophages, granulomatous lesions in the lungs and peribronchial lymph nodes, and increases in lung weight (Drew et al. 1974; Klosterkotter 1960; Pigott et al. 1981; Steinhagen et al. 1978; Stone et al. 1979). The lung effects observed in humans and animals are suggestive of dust overload. Dust overload occurs when the volume of dust in the lungs markedly impairs pulmonary clearance mechanisms. Lung overload is not dependent on the inherent toxicity of the compound, and dust overloading has been shown to modify both the dosimetry and toxicological effects of the compound (Morrow 1988). When excessive amounts of widely considered benign dusts are persistently retained in the lungs, the resultant lung effects are similar to those observed following exposure to dusts that are highly toxic to the lungs. Because it is unclear whether the observed respiratory effects are related to aluminum toxicity or to dust overload, inhalation MRLs based on respiratory effects were not derived.

Subtle neurological effects have also been observed in workers chronically exposed to aluminum dust or fumes. These effects include impaired performance on neurobehavioral tests (Akila et al. 1999; Bast-Pettersen et al. 2000; Buchta et al. 2003, 2005; Hänninen et al. 1994; Hosovski et al. 1990; Polizzi et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Sjögren et al. 1990) and increased reporting of subjective neurological symptoms (Bast-Pettersen et al. 1994, 2000; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Sim et al. 1997; Sjögren et al. 1990, 1996; White et al. 1992). Neurological exams in the available animal studies (Steinhagen et al. 1978; Stone et al. 1979) have been limited to measurement of brain weight and/or histopathology of the brain; no function tests were performed. The identification of neurotoxicity as a sensitive end point in workers

exposed to aluminum dust and fumes is well supported by a large number of animal studies reporting a variety of neurobehavioral alterations following oral exposure. However, the poor characterization of aluminum exposure in the occupational exposure studies precludes using these studies to develop an inhalation MRL for aluminum.

Oral MRLs

Data on health effects of ingested aluminum in humans are unsuitable for MRL consideration because studies have centered on specific patient populations (i.e., dialysis, neurodegenerative disease) and are not the types typically used in risk evaluation. Studies in patients with reduced renal function who accumulated aluminum as a result of long-term intravenous hemodialysis therapy with aluminum-contaminated dialysate and the use of aluminum-containing phosphate binding agents provide evidence that aluminum is an important etiologic factor in dialysis-related health disorders, particularly the neurological syndrome dialysis encephalopathy. The effects are manifested under unnatural exposure conditions in which the gastrointestinal barrier is bypassed (exposure to aluminum in dialysate fluid) and aluminum excretion is impaired by the poor renal function. There are case reports of skeletal changes (e.g., osteomalacia) consequent to long-term ingestion of antacids in healthy adults and children with normal kidney function (Carmichael et al. 1984; Chines and Pacifici 1990; Pivnick et al. 1995; Woodson 1998), but these effects are attributable to an interaction between aluminum and phosphate in the gut (aluminum binds with phosphate in the gut resulting in decreased phosphate absorption and hypophosphatemia). Although the use of aluminum medicinals in people is widespread, there are a limited number of experimental studies that examined the potential toxicity of the aluminum in these medicinals in individuals with normal renal function.

Derivation of an MRL(s) for aluminum based on animal studies is complicated by limitations in the database, particularly the lack of information on aluminum content in the base diet. As discussed in the introduction to Section 3.2.2, commercial laboratory animal feeds contain high levels of aluminum that can significantly contribute to total experimental exposure. Due to the likelihood of significant base dietary exposure to aluminum, studies with insufficient information on aluminum content in the base diet must be assumed to underestimate the actual aluminum intake. The magnitude of the underestimate can be considerable; for example, approximate feed concentrations of 250 and 350 ppm aluminum reported in some rat and mouse studies, respectively (Colomina et al. 1998; Domingo et al. 1993; Oteiza et al. 1993), are roughly equivalent to daily doses of 25 mg Al/kg/day (rats) and 68 mg Al/kg/day (mice), which represents a significant portion of the lethal dose for these species. Consequently, although studies with

inadequate data on base dietary levels of aluminum provide useful information on health effects of aluminum, no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) from these studies cannot be assumed to be accurate, are not suitable for comparing with effect levels from studies that used diets with known amounts of aluminum, and are inappropriate for MRL consideration.

The available data were considered inadequate for derivation of an acute-duration oral MRL for aluminum. Two studies were identified that provided sufficient information on the levels of aluminum in the basal diet. McCormack et al. (1979) and Domingo et al. (1989) did not find any significant alterations in pup viability/lethality, pup body weight, or the incidence of malformation in rats exposed to 110 mg Al/kg/day as aluminum chloride in the diet on gestation days 6–19 (McCormack et al. 1979) or 141 mg Al/kg/day as aluminum nitrate administered via gavage on gestation days 6–15 (Domingo et al. 1989). Neither study evaluated the potential neurotoxicity of aluminum following acute-duration exposure; intermediate-duration studies provide strong evidence that the nervous system (in adults and developing organisms) is the most sensitive target of aluminum toxicity.

- An MRL of 1 mg Al/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to aluminum.

A fair number of animal studies have examined the oral toxicity of aluminum following intermediate-duration exposure. A subset of these studies that provide information on the aluminum content of the basal diet and involved exposure to aluminum via the diet or drinking water will be the focus of this discussion. With the possible exception of reproductive function, these studies have examined most potential end points of aluminum toxicity. Systemic toxicity studies have not consistently reported adverse effects in rats exposed to up to 284 mg Al/kg/day (Domingo et al. 1987b; Gomez et al. 1986; Konishi et al. 1996), mice exposed to doses as high as 195 mg Al/kg/day (Oteiza et al. 1989), or dogs exposed to doses as high as 88 mg Al/kg/day (Katz et al. 1984; Pettersen et al. 1990). An increased susceptibility to bacterial infections was observed in mouse dams exposed to 155 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Yoshida et al. 1989). However, a similar aluminum dose did not result in a change in susceptibility in virgin female mice exposed to 107 mg Al/kg/day as aluminum lactate in the diet for 6 weeks (Yoshida et al. 1989). Immunological alterations (decreased spleen concentrations of interleukin-2, interferon g, and tumor necrosis factor and a decrease in CD^{4+} cells) were observed in mice exposed to 200 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through postnatal day 180 (Golub et al. 1993). There is limited information on the potential for aluminum to induce reproductive effects. Although a number of studies have reported no

alterations in the occurrence of resorption, litter size, sex ratio, or pup body weight, no studies have examined fertility or potential effects on sperm morphology or motility. A significant alteration in gestation length was observed in mice exposed to 155 or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation 21 (Donald et al. 1989); in the aluminum exposed mice, 4 of the 17 litters were born earlier or later (days 17, 19, or 20 versus day 18 in controls) than control litters. However, this has not been reported in other studies in mice or rats (Colomina et al. 2005; Golub and Germann 2001; Golub et al. 1992a, 1995).

The preponderance of available intermediate-duration studies has focused on the potential for aluminum to induce neurological and neurodevelopmental effects. Although neurotoxicity of aluminum has not been established in people with normal renal function, the data for dialysis encephalopathy (as well as some occupational studies) establish that the human nervous system is susceptible to aluminum and neurotoxicity is a well-documented effect of aluminum in orally-exposed in mice and rats. A wide variety of behavioral tests were conducted in rats and mice, in which the most consistently affected behaviors involve motor function. Alterations in forelimb and hindlimb grip strength have been observed in adult mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 90 days (Golub et al. 1992b), mice (6 weeks of age at study beginning) exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993), the offspring of mice exposed on gestation day 1 through lactation day 21 to 155 mg Al/kg/day (Donald et al. 1989; Golub et al. 1995) or 250 mg Al/kg/day (Golub et al. 1995) as aluminum lactate, and the offspring of rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 15 days prior to mating and on gestation day 1 through lactation day 21 (Colomina et al. 2005). Decreases in spontaneous motor activity were observed in mice exposed to 130 mg Al/kg/day for 6 weeks (Golub et al. 1989) or 195 mg Al/kg/day for 90 days (Golub et al. 1992b). Motor impairments have also been detected in mice in the wire suspension test in which offspring exposed to 130 mg Al/kg/day had a shorter latency to fall from the wire and in the rotorod test in which offspring exposed to 260 mg Al/kg/day had a higher number of rotations (which occur when the animals lost its footing, clung to the rod, and rotated with it for a full turn) (Golub and Germann 2001). Neurobehavioral alterations that have occurred at similar dose levels include decreased responsiveness to auditory or air-puff startle (Golub et al. 1992b, 1995), decreased thermal sensitivity (Golub et al. 1992a), increased negative geotaxis latency (Golub et al. 1992a), and increased foot splay (Donald et al. 1989). Additionally, one study found significant impairment in performance of the water maze test in offspring of mice exposed to 130 mg Al/kg/day on gestation day 1 through lactation day 21 (Golub and Germann 2001). Colomina et al. (2005) did not find alterations in this test in rats exposed to 53 mg Al/kg/day; however, this study did not run probe tests, which showed significant

alterations in the Golub and Germann (2001) study. Other studies have utilized passive avoidance tests or operant training tests to evaluate potential impairment of cognitive function. However, the interpretation of the results of these tests is complicated by an increase in food motivation in aluminum exposed mice (Golub and Germann 1998).

There is also strong evidence that gestational and/or lactational exposure can cause other developmental effects. Gestation and/or lactation exposure can result in significant decreases in pup body weight gain in rats and mice (Colomina et al. 2005; Golub and Germann 2001; Golub et al. 1992a). The decreases in pup body weight are often associated with decreases in maternal body weight during the lactation phase of the study; however, decreases in body weight have also been observed in a cross-fostering study when gestation-exposed pups were nursed by control mice (Golub et al. 1992a). Other studies involving gestation and lactation exposure to aluminum did not find changes in pup growth in mice (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1995). In rats, a delay in physical maturation, particularly delays in vagina opening, testes descent, and incisor eruption, has been reported at 53 mg Al/kg/day (Colomina et al. 2005). In the Colomina et al. (2005) study, a delay in vagina opening was observed in rat offspring exposed to 53 mg Al/kg/day. The number of days to vagina opening was 31.1, 40.9, and 45.9 days in the control, 53, and 103 mg Al/kg/day groups, respectively. Delays in maturations were also observed for testes descent (23.9, 22.8, and 27.1 days in the control, 53, and 103 mg Al/kg/day groups, significant at 103 mg Al/kg/day) and incisor eruption in males (5.5, 6.1, and 5.3 days, significant at 53 mg Al/kg/day, but not at 103 mg Al/kg/day). Significant delays in vagina opening and testes descent were also observed at 103 mg Al/kg/day in the offspring of rats similarly exposed but with the addition of restraint stress on gestation days 6–20. The mean number of days to maturation in the control, 53, and 103 mg Al/kg/day groups were 32.5, 40.4, and 44.9 days for vagina opening and 24.9, 23.2, and 27.7 days for testes descent. However, another study by Colomina et al. (1999) did not find significant delays in vagina opening or testes descent, but did find significant delays in pinna attachment and eye opening following administration of 75 mg/kg/day (15 mg Al/kg/day) aluminum chloride via intraperitoneal injection to mice on gestation days 6–15. Another study did not find delays in pinna attachment, eye opening, or incisor eruption in the offspring of rats administered via gavage 73 mg Al/kg/day as aluminum chloride (aluminum content of the diet was not reported) on gestation days 8–20 (Misawa and Shigeta 1992). Collectively, these studies provide equivocal evidence that aluminum induces delays in maturation.

The Golub et al. (1989), Golub and Germann (2001), and Colomina et al. (2005) studies identified the lowest LOAELs for the critical effects (neurotoxicity, neurodevelopmental toxicity, and delays in

maturation) and were considered as possible principal studies. Golub et al. (1989) identified the lowest LOAEL for neurotoxicity. In this study in which mice were exposed to aluminum lactate in the diet for 6 weeks, significant decreases in total activity and vertical activity (rearing) were observed at 130 mg Al/kg/day; no significant alterations were observed at 62 mg Al/kg/day. One limitation of this study is that motor activity was the only neurobehavioral test evaluated; other studies have shown that grip strength is one of the more sensitive end points. Golub and Germann (2001) examined a number of sensitive end points of neurodevelopmental toxicity in the offspring of mice exposed to aluminum lactate in the diet on gestation day 1 through lactation day 21, after which the pups were fed a diet containing the same levels of aluminum as the dams on postnatal days 21–35. The study identified a NOAEL of 26 mg Al/kg/day and a LOAEL of 130 mg Al/kg/day for alterations in tests of motor function (a shorter latency to fall off a wire) and cognitive function (impaired performance in the water maze test). This study used a suboptimal diet, which complicates the interpretation of the study results. The dietary levels of phosphorus, calcium, magnesium, iron, and zinc were lower than the National Research Council's recommendation in an attempt to mimic the intakes of these nutrients by young women. The investigators noted that even though the intakes of several nutrients were below the recommendations, the diet was not deficient. The impact of the suboptimal diet on the developmental toxicity of aluminum is not known. The observed effects are similar to those reported in other studies, as are the adverse effect levels. In the Colomina et al. (2005) study, a significant decrease in forelimb grip strength was observed in the offspring of rats exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water (with citric acid added to increase aluminum absorption) for 15 days prior to mating and during gestation and lactation; grip strength was not adversely affected at 53 mg Al/kg/day. This study also found significant delays in vagina opening at 53 mg Al/kg/day. As previously noted, there are limited data to confirm or refute the identification of delays in maturation as a critical effect of aluminum. The delays in maturation may be secondary to decreases in maternal weight or food intake or decreases in pup body weight and/or food intake; however, these data are only reported for some time periods. The Golub et al. (1989) study was not selected as the principal study because the NOAEL of 62 mg Al/kg/day identified in this study is higher than the dose associated with delayed maturation in the Colomina et al. (2005) study. The Golub and Germann (2001) and Colomina et al. (2005) studies were selected as co-principal studies. A short description of these studies follows.

In the Golub and Germann (2001) study, groups of pregnant Swiss Webster mice were exposed to 0, 100, 500, or 1,000 mg Al/kg diet on gestational days 0–21 and during lactation until day 21. On postnatal day (PND) 21, one male and one female pup from each litter were placed on the same diet as the dam. The offspring were exposed until PND 35. The composition of the diet was modified from the National

Research Council's recommendations; the investigators noted that the nutrients were reduced to correspond to the usual intake of these nutrients by young women. The average daily intakes of phosphorus, calcium, magnesium, iron, and zinc in women aged 18–24 years are 83, 56, 71, 69, and 67% of the recommended dietary allowance (RDA); these percents were used to modify the recommended dietary intake for the mice used in this study. Doses of 26, 130, and 260 mg Al/kg/day are calculated by averaging reported estimated doses of 10, 50, and 100 mg Al/kg/day for adults (i.e., at beginning of pregnancy) and 42, 210, and 420 mg Al/kg/day maximal intake during lactation. The doses at lactation were calculated using doses estimated in previous studies with similar exposure protocols performed by the same group of investigators (Golub et al. 1995). At 3 months of age, the females were tested for neurotoxicity using the Morris water maze. At 5 months of age, males were tested for motor activity and function using rotarod, grip strength, wire suspension, mesh pole descent, and beam traversal tests. No alterations in pregnancy weight gain or pup birth weights were observed. At PND 21, significant decreases in pup body weights were observed at 130 and 260 mg Al/kg/day. No information on maternal weight gain during lactation was reported; however, the investigators noted that the decrease in pup weight was not associated with reduced maternal food intake. At PND 35, the decrease in body weight was statistically significant at 260 mg Al/kg/day. On PND 90, female mice in the 260 mg Al/kg/day group weighed 15% less than controls. Decreases in heart and kidney weights were observed at 260 mg Al/kg/day in the females. Also, increases in absolute brain weight were observed in females at 26 mg Al/kg/day and relative brain weights were observed at 26 or 260 mg Al/kg/day, but not at 130 mg Al/kg/day. In the males, significant decreases in body weight were observed at 130 (10%) and 260 (18%) mg Al/kg/day at 5 months; an increase in food intake was also observed at these doses. In the Morris maze (tested at 3 months in females), fewer animals in the 260 mg Al/kg/day group had escape latencies of <60 seconds during sessions 1–3 (learning phase) and a relocation of the visible cues resulted in increased latencies at 130 and 260 mg Al/kg/day. Body weight did not correlate with latency to find the platform or with the distribution of quadrant times. The investigators concluded that controls used salient and/or nonsalient cues, 26 and 130 mg Al/kg/day animals used both cues, but had difficulty using only one cue, and 260 mg Al/kg/day animals only used the salient cues. In the males tested at 5 months, a significant decrease in hindlimb grip strength was observed at 260 mg Al/kg/day, an increase in the number of rotations on the rotorod as observed at 260 mg Al/kg/day, and a shorter latency to fall in the wire suspension test was observed at 130 and 260 mg Al/kg/day. The investigators noted that there were significant correlations between body weight and grip strength and number of rotations. When hindlimb grip strength was statistically adjusted for body weight, the aluminum-exposed mice were no longer significantly different from controls; the number of rotations was still significantly different from control after adjustment for body weight.

In the Colomina et al. (2005) study, groups of female Sprague Dawley rats were exposed to 0, 50, or 100 mg Al/kg/day aluminum nitrate nonahydrate in drinking water; citric acid (710, 355, and 710 mg/kg/day in the control, 50, and 100 ppm groups, respectively) was added to the drinking water to increase aluminum absorption. The adult rats were exposed to aluminum for 15 days prior to mating and during gestation and lactation periods; after weaning, the pups were exposed to the same aluminum concentration as the mothers from PND 21 through 68. The basal diet (Panlab rodent chow) contained 41.85 µg Al/g diet. Aluminum doses were calculated by adding the basal dietary aluminum doses (calculated using reference values for mature Sprague-Dawley rats) to reported aluminum doses from water; the total aluminum doses were 3, 53, and 103 mg Al/kg/day. In addition to aluminum exposure, some animals in each group underwent restraint stress for 2 hours/day on gestation days 6–20; the restraint consisted of placing the rats in cylindrical holders. The following neurobehavioral tests were performed on the offspring: righting reflex (PNDs 4, 5, 6), negative geotaxis (PNDs 7, 8, 9), forelimb grip strength (PNDs 10–13), open field activity (PND 30), passive avoidance (PND 35), and water maze (only tested at 53 mg/kg/day on PND 60). The rats were killed on PND 68. No significant alterations in body weight, food consumption, or water consumption were observed during gestation in the dams exposed to aluminum. The investigators noted that decreases in water and food consumption were observed during the lactation period in the rats exposed to 103 mg Al/kg/day, but the data were not shown and maternal body weight during lactation was not mentioned. No significant alterations in the number of litters, number of fetuses per litter, viability index, or lactation index were observed. Additionally, no differences in days at pinna detachment or eye opening were observed. Age at incisor eruption was significantly higher in males exposed to 53 mg/kg/day, but not in males exposed to 103 mg/kg/day or in females. A significant delay in age at testes descent was observed at 103 mg/kg/day and vagina opening was delayed at 53 and 103 mg/kg/day. A decrease in forelimb grip strength was observed at 103 mg/kg/day; no alterations in other neuromotor tests were observed. Additionally, no alterations in open field behavior or passive avoidance test were observed. In the water maze test, latency to find the hidden platform was decreased in the 53 mg/kg/day group on test day 2, but not on days 1 or 3; no significant alteration in time in the target quadrant was found.

The Golub and Germann (2001) and Colomina et al. (2005) studies identify four end points that could be used as the point of departure for derivation of the intermediate-duration oral MRL:

(1) latency to fall off wire in wire suspension test; adverse effect level of 130 mg Al/kg/day, no effect level of 26 mg Al/kg/day (Golub and Germann 2001);

(2) latency to locate the platform following cue relocation in the water maze test; adverse effect level of 130 mg Al/kg/day, no effect level of 26 mg Al/kg/day (Golub and Germann 2001);

(3) decreased forelimb grip strength; adverse effect level of 103 mg Al/kg/day, no effect level of 53 mg Al/kg/day (Colomina et al. 2005); and

(4) delay in vagina opening; adverse effect level of 53 mg Al/kg/day, no effect level not identified (Colomina et al. 2005).

Benchmark dose (BMD) modeling was considered for each of these end points. As discussed in Appendix A, BMD modeling was not used to identify the point of departure due to incomplete reporting of the data or because the models did not provide adequate fit.

Using a NOAEL/LOAEL approach, the NOAEL of 26 mg Al/kg/day identified in the Golub and Germann (2001) study was selected as the point of departure for the MRL. An MRL based on this NOAEL should be protective for neurological effects, neurodevelopmental effects, and for delays in maturation. Dividing the NOAEL by an uncertainty factor of 100 (10 to account for the extrapolation from mice to humans and 10 for human variability) and a modifying factor of 0.3 to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet results in an MRL of 1 mg Al/kg/day. No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggest that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

- An MRL of 1 mg Al/kg/day has been derived for chronic-duration oral exposure (365 days or longer) to aluminum.

A small number of animal studies examined the chronic toxicity of aluminum. Schroeder and Mitchener (1975a, 1975b) examined the systemic toxicity of aluminum following lifetime exposure of rats and mice to very low doses of aluminum sulfate in the drinking water. Although the levels of aluminum in the diet were not reported, they are assumed to be low because the animals were fed a low-metal diet in metal-free environmental conditions. Studies conducted by Roig et al. (2006) and Golub et al. (2000) primarily

focused on the neurotoxicity of aluminum following lifetime exposure (gestation day 1 through 24 months of age). In the Golub et al. (2000) study, significant decreases in forelimb and hindlimb grip strength, and a decrease in thermal sensitivity were observed in mice exposed to 100 mg Al/kg/day; negative geotaxis was significantly altered at 18 months, but not at 24 months. No effect on horizontal activity was observed. A 10% increase in body weight and a 20% decrease in body weight were observed in the males and females, respectively. In a companion study by this group, no significant cognitive impairments were found in the Morris water maze test; in fact, aluminum-exposed mice performed better than controls in the learning tasks. Roig et al. (2006) also found no significant alterations in performance on the Morris water maze in rats exposed to 100 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid). Although significant differences were found between the two aluminum groups (50 and 100 mg Al/kg/day); this was primarily due to the improved performance (as compared to controls, no significant differences) in the 50 mg Al/kg/day group. Roig et al. (2006) also found no significant alterations in open field activity.

Based on the results of these chronic-duration studies, the decreases in forelimb and hindlimb grip strength and the decrease in thermal sensitivity identified in the Golub et al. (2000) study were selected as the critical effect for derivation of a chronic-duration oral MRL for aluminum. The selection of these end points, and neurotoxicity in general, is well supported by the findings of a number of intermediate-duration studies that indicate that this is one of the most sensitive targets of aluminum toxicity (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 2001; Golub et al. 1992a, 1995).

In the Golub et al. (2000) study, groups of 8 male and 10 female Swiss Webster mice were exposed to 7 or 1,000 μg Al/g diet as aluminum lactate in a purified diet. The investigators estimated adult doses of <1 and 100 mg/kg/day. The mice were exposed to aluminum from conception (via feeding the dams) through 24 months of age. Body weight, food intake, and clinical signs were determined during the last 6 months of the study. A neurobehavioral test battery (foot splay, temperature sensitivity, negative geotaxis, and grip strength), 1 hour spontaneous activity measurement, and auditory startle tests were conducted at 18 and 24 months. In a companion study, groups of 6–9 male and female Swiss Webster mice or 7 male and female C57BL/6J mice (number per sex were not reported) were exposed to 7 or 1,000 μg Al/g diet as aluminum lactate in a purified diet (<1 and 100 mg/kg/day) from conception (via feeding the dams) through 24 months of age. Body weight, food intake, and clinical signs were determined during the last 6 months of the study. A neurobehavioral test battery (foot splay, temperature sensitivity, negative geotaxis, and grip strength) and Morris maze testing were performed at 22–23 months of age. In the principal study, no significant alterations in mortality were observed. A

significant decrease in body weight was observed in the female mice (approximately 20%). In the males, there was a significant increase in body weight (approximately 10%). No significant alterations in food intake were observed in either sex. However, food intake/g body weight was significantly higher in the aluminum-exposed mice. No significant alterations in the occurrence of clinical signs or indications of neurodegenerative syndromes were found. Significant increases in relative spinal cord, heart, and kidney weights were found. Significant alterations in negative geotaxis and tail withdrawal time in the temperature sensitivity test (males only) were observed at 18 months. At 24 months, significant alterations in forelimb and hindlimb grip strength and temperature sensitivity were found in male and female mice. Forelimb and hindlimb grip strengths were decreased and thermal sensitivity was decreased, as evidenced by an increase in tail withdrawal times. Auditory startle response tests could not be completed in the older mice. Similarly, vertical spontaneous movement could not be measured; no effect on horizontal movement was found. In the companion study, no alterations in neurobehavioral battery test performance were observed; the investigators note that this may be due to the small number of animals per group. In general, aluminum-exposed mice performed better on the water maze test than controls.

A chronic-duration oral MRL was derived using the LOAEL of 100 mg Al/kg/day for decreased forelimb and hindlimb grip strength and decreased thermal sensitivity identified in the Golub et al. (2000) study. A BMD approach for deriving an MRL was not utilized because the Golub et al. (2000) study only tested one aluminum group. The MRL of 1 mg Al/kg/day was calculated by dividing the LOAEL of 100 mg Al/kg/day by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and a modifying factor of 0.3 to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet. No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggest that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of aluminum. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

Once mineral-bound aluminum is recovered from ores, it forms metal compounds, complexes, or chelates. Examples of the different forms of aluminum include aluminum oxide, aluminum chlorhydrate, aluminum hydroxide, aluminum chloride, aluminum lactate, aluminum phosphate, and aluminum nitrate. The metal itself is also used. With the exception of aluminum phosphide, the anionic component does not appear to influence toxicity, although it does appear to influence bioavailability. Aluminum phosphide, which is used as a pesticide, is more dangerous than the other forms; however, this is because of the evolution of phosphine gas (a potent respiratory tract and systemic toxin) rather than to the exposure to aluminum.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a

considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

No studies were located regarding death following acute- or intermediate-duration inhalation exposure to various forms of aluminum in humans.

Several deaths have been reported after occupational exposure to a finely powdered metallic aluminum used in paints, explosives, and fireworks (Mitchell et al. 1961); it should be noted that changes in production technology have resulted in decreased occupational exposures to finely powdered aluminum. In one case, a 19-year-old male who worked in an atmosphere heavily contaminated with this powder developed dyspnea after 2.5 years. This symptom grew worse, and the man had to stop working 3 months later and died after a further 8 months. Before death, respiratory excursion was poor and chest X-rays showed signs of pulmonary nodular interstitial fibrosis. Of a total of 27 workers examined in this factory,

2 died and 4 others had radiological changes on chest X-rays. Total dust in the workplace air was 615–685 mg Al/m^3, and respirable dust was 51 mg Al/m^3. Chemical analysis showed the dust to be 81% metallic aluminum and 17% various oxides and hydroxides of aluminum. There have also been a number of case reports of deaths of workers exposed to aluminum flake powder (McLaughlin et al. 1962), welding fumes (Hull and Abraham 2002), or smelter fumes (Gilks and Churg 1987); it is likely that the cause of death in these men was respiratory tract damage.

No studies were located that evaluated death from an intermediate-duration inhalation exposure in animals to aluminum or its compounds. Of the experiments performed in animals, none has shown death from inhalation exposure to aluminum or its compounds. For example, no deaths were reported following an acute 4-hour exposure to up to 1,000 mg Al/m^3 as aluminum oxide in groups of 12–18 male Fischer 344 rats (Thomson et al. 1986) or following chronic exposure to 2.18–2.45 mg Al/m^3 as refractory alumina fiber for 86 weeks in groups of 50 male and female Wistar rats (Pigott et al. 1981).

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, dermal, or body weight effects in humans or metabolic effects in animals after acute-duration inhalation exposure to various forms of aluminum.

The highest NOAEL values and all LOAEL values for inhalation exposure from each reliable study for systemic effects in each species and duration category for aluminum are shown in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. No studies were located regarding respiratory effects following acute-duration inhalation exposure to various forms of aluminum in humans.

A number of studies have examined the potential for airborne aluminum to induce respiratory effects in chronically exposed workers. Exposure to aluminum fumes and dust occurs in potrooms where hot aluminum metal is recovered from ore, in foundries where aluminum alloys are melted and poured into molds, in welding operations, and the production and use of finely powdered aluminum. Because these workers were also exposed to a number of other toxic chemicals including sulfur dioxide, polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, hydrogen fluoride, and chlorine, it is difficult to ascribe the respiratory effects to aluminum. Wheezing, dyspnea, and/or impaired lung function have been

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Rat (Fischer- 344)	5 x 4 hr	Resp	10 M	200 M (multifocal microgranulomas in lungs)		Thomson et al. 1986 Aluminum flakes	
					50 M (increased lactate dehydrogenase, glucose-6-phosphate dehydrogenase, and alkaline phosphatase activity in lavage fluid)			
2	Hamster (Golden Syrian)	3 d 4 or 6 hr/d (NS)	Resp		33 M (alveolar wall thickening and increased number of macrophages; bronchopneumonia)		Drew et al. 1974 Aluminum chlorhydrate	
			Bd Wt		33 M (unspecified decreased body weight)			
3	Hamster (Golden Syrian)	3 d 4 or 6 hr/d (NS)	Resp	3 M	7 M (13% increased lung weight)		Drew et al. 1974 Aluminum chlorhydrate	
4	Hamster (Golden Syrian)	3 d 4 hr/d (NS)	Resp		10 M (approximately 24% increased lung weight)		Drew et al. 1974 Aluminum chlorhydrate	

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
5	Hamster (Golden Syrian)	3 d 4 hr/d	Resp		31 (alveolar wall thickening and increased number of macrophages and heterophils)		Drew et al. 1974 Aluminum chlorhydrate	
6	Rabbit (New Zealand)	5 d 4 hr/d (NS)	Resp		43 (alveolar wall thickening, increased number of macrophage; 65% increase in lung weight)		Drew et al. 1974 Aluminum chlorhydrate	
INTERMEDIATE EXPOSURE								
Systemic								
7	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d (NS)	Resp	0.061	0.61 (increase in alveolar macrophages; granulomatous lesions in lungs)		Steinhagen et al. 1978 Aluminum chlorhydrate	
			Cardio	6.1				
			Gastro	6.1				
			Hemato	6.1				
			Musc/skel	6.1				
			Hepatic	6.1				
			Renal	6.1				
			Endocr	6.1				
			Dermal	6.1				
			Ocular	6.1				
			Bd Wt	6.1				

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
8	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d	Resp	0.065 M	0.65 M (12% increased relative lung weight)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				
			Bd Wt	5.4				
9	Gn Pig (Hartley)	6 mo 5 d/wk 6 hr/d (NS)	Resp	0.061	0.61 (increase in alveolar macrophages; granulomatous lesions in lungs)		Steinhagen et al. 1978 Aluminum chlorhydrate	
			Cardio	6.1				
			Gastro	6.1				
			Hemato	6.1				
			Musc/skel	6.1				
			Hepatic	6.1				
			Renal	6.1				
			Endocr	6.1				
			Dermal	6.1				
			Ocular	6.1				
			Bd Wt	6.1				

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
10	Gn Pig (Hartley)	6 mo 5 d/wk 6 hr/d	Resp	0.65	5.4 (19-23% increased relative lung weight)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				
			Bd Wt	5.4				
11	Hamster (Golden Syrian)	5 or 6 wk 5 d/wk 6 hr/d	Resp		10 M (alveolar thickening and increased number of foci of macrophages and heterophils)		Drew et al. 1974 Aluminum chlorhydrate	
CHRONIC EXPOSURE								
Systemic								
12	Rat (Wistar)	86 wk 5 d/wk 6 hr/d (NS)	Resp	2.45			Pigott et al. 1981 Aluminum oxide	
13	Rat (Fischer- 344)	12-24 mo 5 d/wk 6 hr/d	Resp	0.65	5.4 (108-274% increased relative lung weight at 2 years)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				
			Bd Wt	0.65	5.4 (16-26% decrease in body weight at 2 years)			
14	Gn Pig (Hartley)	12-21 mo 5 d/wk 6 hr/d	Resp		0.065 M (21% increased relative lung weight at 2 years)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
			Bd Wt	5.4				

a The number corresponds to entries in Figure 3-1.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; Gn pig = guinea pig; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation

Acute (≤14 days)

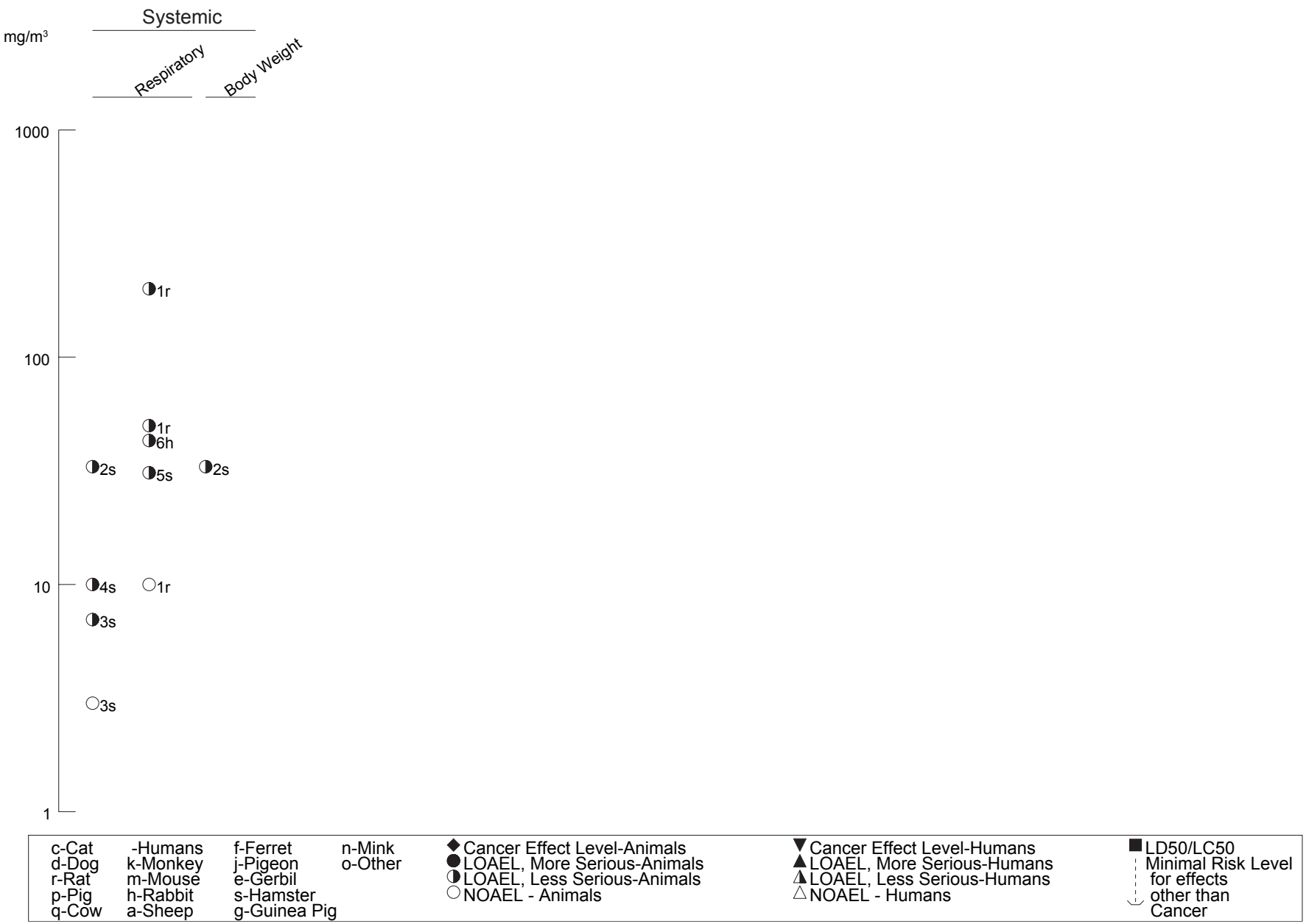


Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation *(Continued)*

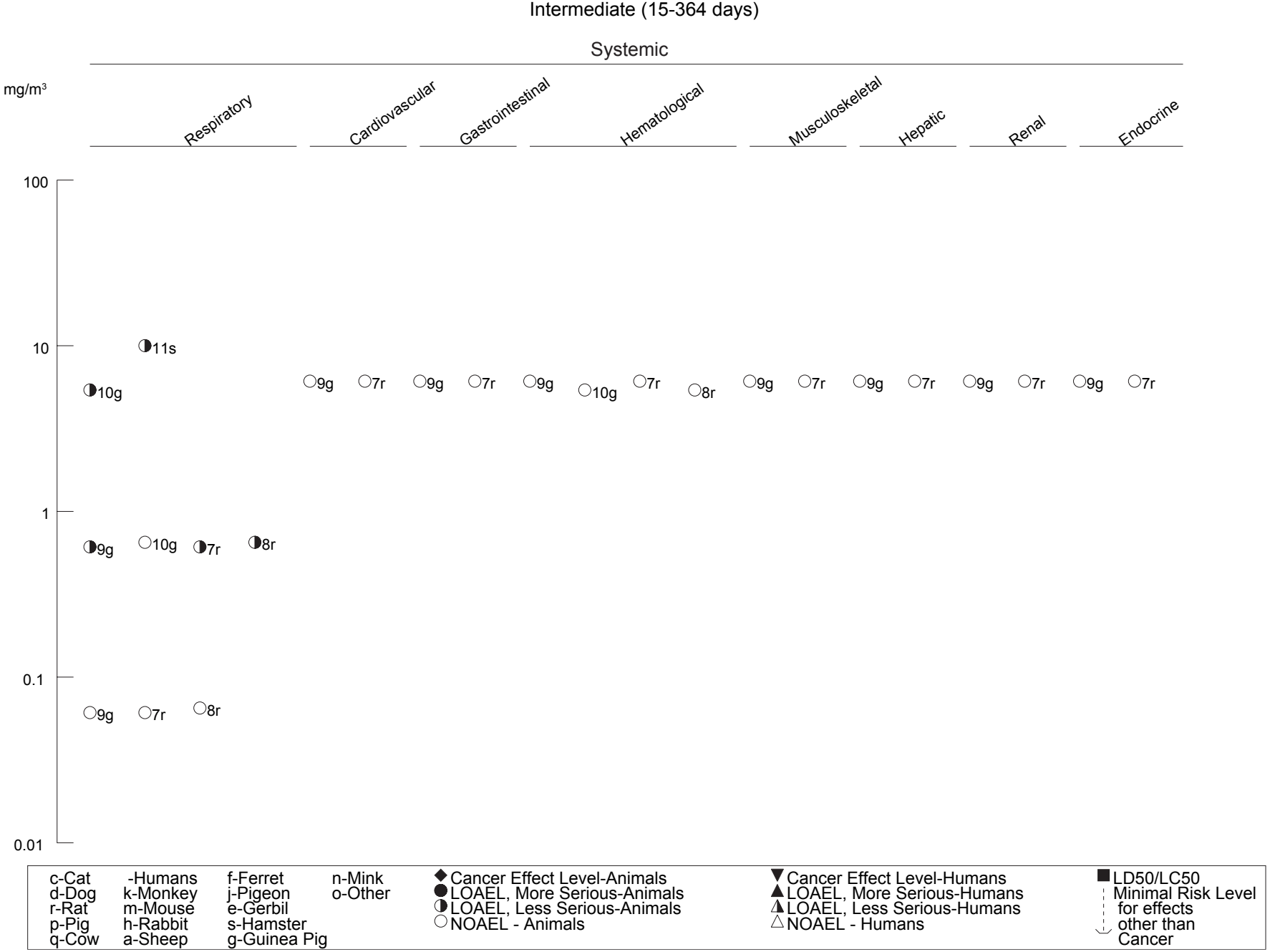


Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation *(Continued)*

Intermediate (15-364 days)

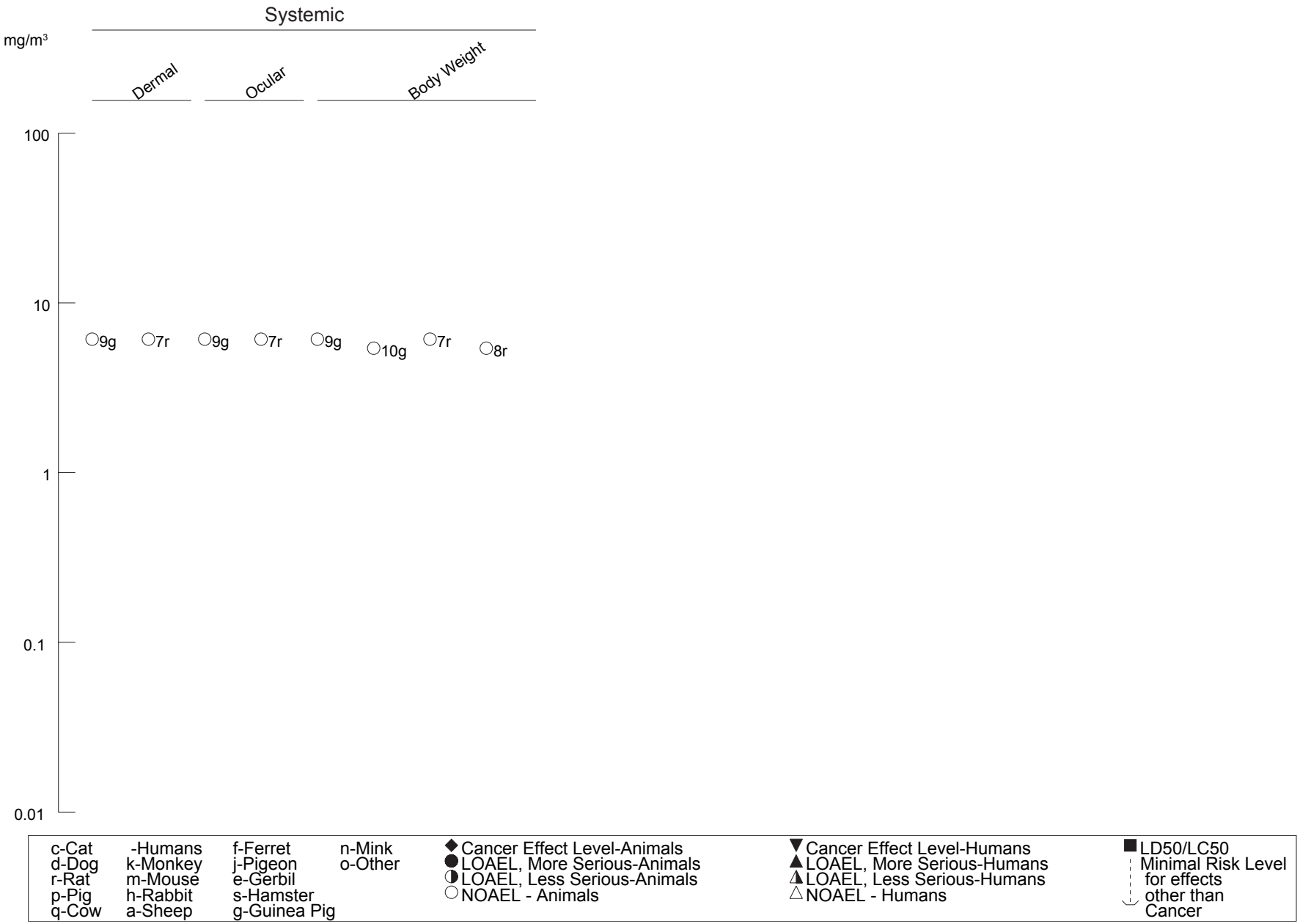
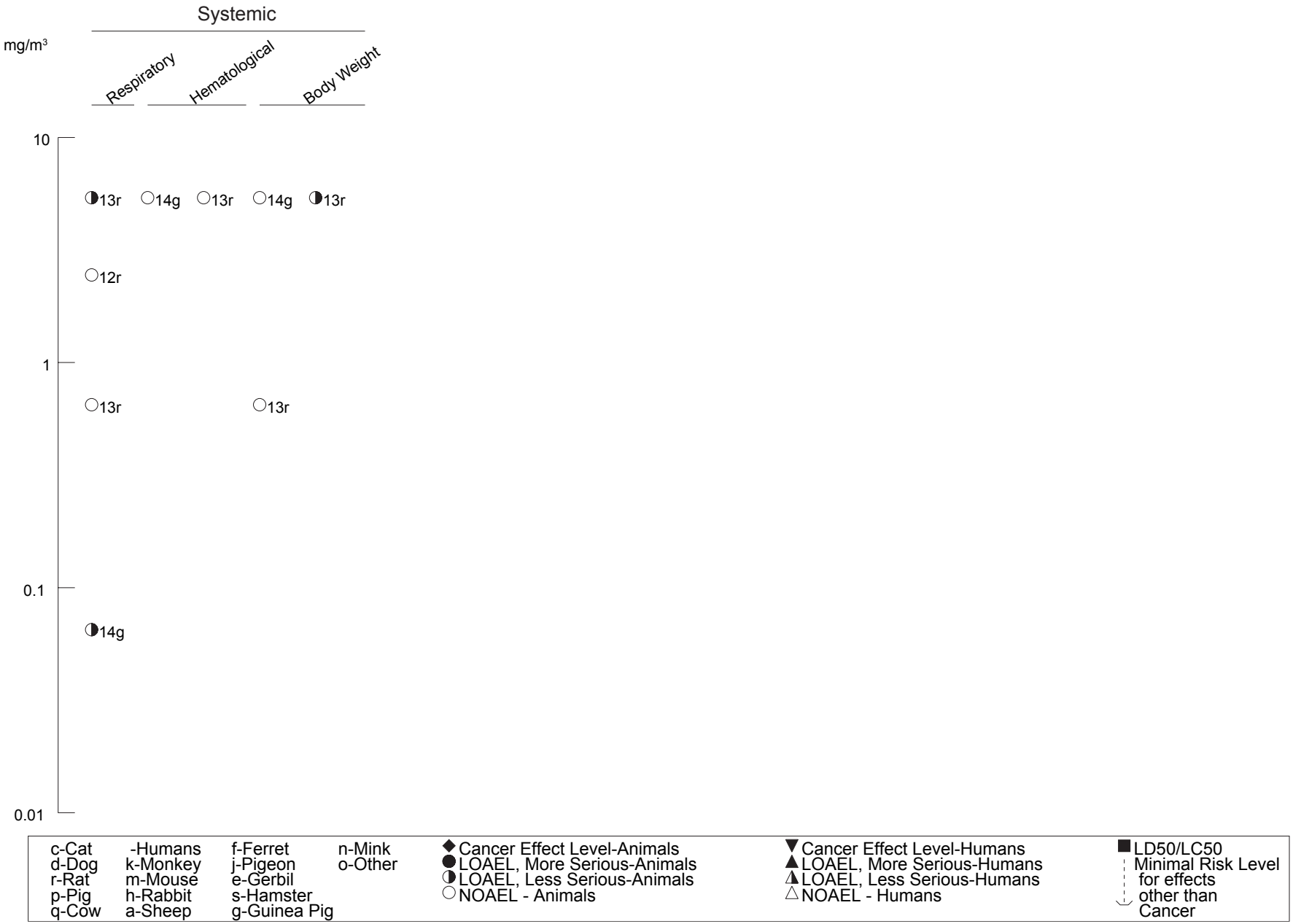


Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation *(Continued)*

Chronic (≤365 days)



observed in potroom workers (Bast-Pettersen et al. 1994; Chan-Yeung et al. 1983; Radon et al. 1999; Simonsson et al. 1985), foundry workers (Al-Masalkhi and Walton 1994; Burge et al. 2000; Halatek et al. 2006), workers exposed to fine aluminum dust (including grinders) (Jederlinic et al. 1990; Korogiannos et al. 1998; Miller et al. 1984b), a worker spray painting with an aluminum paint (Bost and Newman 1993), and welders (Abbate et al. 2003; Herbert et al. 1982; Hull and Abraham 2002; Vandenplas et al. 1998), although other studies have not found a significant effect (Musk et al. 2000). Occupational asthma has been reported in aluminum potroom workers (as reviewed by Abramson et al. 1989 and Kilburn 1998); there is some debate whether the asthma is related to exposure to respiratory irritants, such as hydrogen fluoride and chlorine, or due to aluminum exposure. Case reports provide suggestive evidence that chronic exposure to aluminum may cause occupational asthma. An asthmatic reaction was observed following a bronchial provocation test an aluminum foundry worker (Burge et al. 2000) and an aluminum welder (Vandenplas et al. 1998).

Pulmonary fibrosis is the most commonly reported respiratory effect observed in workers exposed to fine aluminum dust (pyropowder), alumina (aluminum oxide), or bauxite. However, conflicting reports are available on the fibrogenic potential of aluminum. In some of the cases, the fibrosis was attributed to concomitant exposure to other chemicals. For example, pulmonary fibrosis has been observed in a number of bauxite workers or potroom workers (De Vuyst et al. 1986; Gaffuri et al. 1985; Gilks and Churg 1987; Jederlinic et al. 1990; Jephcott 1948; Musk et al. 1980; Riddell 1948; Shaver 1948; Shaver and Riddell 1947); in these workers, it is very likely that there was simultaneous exposure to silica and that the latter was the causative agent rather than the aluminum. Some of the earliest cases of pulmonary fibrosis were reported in German munition workers exposed to pyropowder (Goralewski 1947). Case reports of fibrosis in workers exposed to finely ground aluminum have been also been reported by Edling (1961), McLaughlin et al. (1962), Mitchell et al. (1961), and Ueda et al. (1958). However, other studies have not found any radiological evidence of pulmonary fibrosis in workers exposed to alumina (Meiklejohn and Posner 1957; Posner and Kennedy 1967) or fine aluminum powder (Crombie et al. 1944). It is believed that the conflicting study results are due to differences in the lubricant used to retard surface oxidation during milling (Dinman 1987). Stearic acid is the most commonly used lubricant in the aluminum industry; the stearic acid combines with the aluminum to form aluminum stearate. Exposure to the aluminum stearate does not appear to be fibrogenic to workers (Crombie et al. 1944; Meiklejohn and Posner 1957; Posner and Kennedy 1967). In contrast, the previous and now discontinued use of a nonpolar aliphatic oil lubricant, such as mineral oil, has been associated with fibrosis (Edling 1961; McLaughlin et al. 1962; Mitchell et al. 1961; Ueda et al. 1958). Pulmonary fibrosis has also been observed in an aluminum arc welder (Vallyathan et al. 1982), an aluminum production worker exposed to

aluminum oxide fumes (Al-Masalkhi and Walton 1994), and in workers in an unspecified aluminum industry (Akira 1995). There is also some evidence suggesting aluminum-induced pneumoconiosis (Hull and Abraham 2002; Korogiannos et al. 1998; Kraus et al. 2000), pulmonary alveolar proteinosis (Miller et al. 1984b), interstitial pneumonia (Herbert et al. 1982), and granulomas (Cai et al. 2007; Chen et al. 1978; De Vuyst et al. 1987); however, these reports are based on a small number of cases, which limits their interpretation.

Respiratory effects typically associated with inhalation of particulates and lung overload have been observed in animals. The pulmonary toxicity of alchlor (a propylene glycol complex of aluminum chlorhydrate), a common component of antiperspirants, was examined in hamsters in a series of studies conducted by Drew et al. (1974). A 3-day exposure to 31 or 33 mg Al/m^3 resulted in moderate-to-marked thickening of the alveolar walls due to neutrophil and macrophage infiltration and small granulomatous foci at the bronchioloalveolar junction (a likely site of particulate deposition). A decrease in the severity of the pulmonary effects was observed in animals killed 3, 6, 10, or 27 days after exposure termination. Similar pulmonary effects were observed in rabbits exposed to 42 mg Al/m^3 for 5 days (Drew et al. 1974). Significant increases in absolute lung weights have been observed in hamsters exposed for 3 days to ≥7 mg Al/m^3 (no effects were observed at 3 mg Al/m^3) and in rabbits exposed to 43 mg Al/m^3 for 5 days (no effects were observed in rabbits exposed to 48 or 39 mg Al/m^3 for 1 or 4 days, respectively). In rats exposed to aluminum flakes for 5 days, there were alterations in the cytological (increase in the number of polymorphonuclear neutrophils [PMNs]) and enzymatic (increased activity of alkaline phosphatase and lactate dehydrogenase) content of the lavage fluid at ≥50 mg Al/m^3 and multifocal microgranulomas in the lungs and hilar lymph nodes at ≥100 mg Al/m^3 (Thomson et al. 1986). The enzymatic changes in the lavage fluid probably resulted from the presence of PMNs, increased phagocytosis of alveolar macrophages, and Type II cell hyperplasia.

Similar pulmonary effects were observed in animals following intermediate-duration exposure. An increase in the number of alveolar macrophages and heterophils were observed in hamsters exposed to 10 mg Al/m^3 as alchlor for 6 hours/day, 5 days/week for 2, 4, or 6 weeks (Drew et al. 1974). The severity was directly related to exposure duration. Granulomatous nodules and thickening of the alveolar walls due to infiltration of heterophils and macrophages were observed 2 weeks after termination of a 6-week exposure. An increase in the number of alveolar macrophages and granulomatous lesions in the lungs and peribronchial lymph nodes were also observed in rats and guinea pigs exposed to 0.61 or 6.1 mg Al/m^3 aluminum chlorhydrate for 6 hours/day, 5 days/week for 6 months (Steinhagen et al. 1978); the severity of the alterations was concentration-related. In addition, statistically significant increases in

absolute and relative lung weight were observed in the rats exposed to 6.1 mg Al/m^3; the authors noted that pulmonary edema was not observed in these rats. No statistically significant histological alterations or changes in lung weight were observed at 0.061 mg Al/m^3. Suggestive evidence of alveolar macrophage damage was observed in rats following a 5-month exposure (6 hours/day, 5 days/week) to either aluminum chloride (0.37 mg Al/m^3) or aluminum fluoride (0.41 mg Al/m^3); increases in lysozyme levels, protein levels (aluminum chloride only), and alkaline phosphatase (aluminum chloride only) were observed in the lavage fluid (Finelli et al. 1981). Alveolar proteinosis was observed in rats, guinea pigs, and hamsters exposed to ≥15, 20, or 30 mg/m^3 of several types of aluminum flake powders; the particle sizes ranged from 2.5 to 4.8 μm (Gross et al. 1973). The investigators noted that aluminum powders did not induce pulmonary fibrosis in the guinea pigs or hamsters; in rats, foci of lipid pneumonitis were observed. A similar exposure to aluminum oxide did not result in alveolar proteinosis, pulmonary fibrosis, or pneumonitis; effects were limited to foci consisting of alveoli filled with macrophages; the particle size of the aluminum oxide dust was much smaller (0.8 μm) than the aluminum flake powders. Interpretation of this study is limited by the lack of incidence data and the high mortality observed in treated and control animals.

There are limited data on the pulmonary toxicity of aluminum in animals following chronic exposure. Increases in relative lung weights (21–274%) have been observed in rats and guinea pigs exposed to 5.1 mg Al/m^3 aluminum chlorhydrate for 6 hours/day, 5 days/week for approximately 2 years (Stone et al. 1979). Lung weights were not affected at 0.61 mg Al/m^3. It should be noted that this study did not conduct histological examinations of the lungs. Pigott et al. (1981) did not find evidence of lung fibrosis in rats exposed to 2.18 or 2.45 mg/m^3 manufactured or aged Saffil alumina fibers; Saffil alumina fiber is a refractory material containing aluminum oxide and about 4% silica. The animals were exposed for 86 weeks followed by a 42-week observation period.

Cardiovascular Effects. No studies were located regarding cardiovascular effects of various forms of aluminum following acute- or intermediate-duration inhalation exposure in humans. Dilation and hypertrophy of the right side of the heart were reported in male factory workers chronically exposed by inhalation to aluminum flake powder and who eventually died (McLaughlin et al. 1962; Mitchell et al. 1961). The cardiac effects may have been secondary to pulmonary fibrosis and poor pulmonary function. Epidemiological studies of aluminum industry workers failed to identify an increase in deaths related to cardiovascular disease (Milham 1979; Mur et al. 1987; Rockette and Arena 1983; Theriault et al. 1984a). Cohort sizes ranged from 340 to 21,829 men. Results of cardiovascular tests (electrocardiogram, blood

pressure measurement) were similar between 22 aluminum workers exposed for 10 years or more and an unexposed control group of 16 men (Bast-Pettersen et al. 1994).

No histological alterations were observed in the hearts of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects of various forms of aluminum following acute-, intermediate-, or chronic-duration inhalation exposure in humans or acute- or chronic-duration inhalation exposure in animals. No histological changes were observed in the gastrointestinal tissues of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Hematological Effects. No studies were located regarding hematological effects of various forms of aluminum following acute-duration inhalation exposure in humans. No adverse hematological effects were noted in a group of seven workers following 6 months of exposure to aluminum fumes or dust (Mussi et al. 1984). Exposure levels from personal sampling ranged from 1 to 6.2 mg Al/m^3, predominantly as aluminum oxide. Decreased red blood cell hemoglobin and increased erythrocyte sedimentation rates were reported in the case of a male aluminum industry worker chronically exposed by inhalation to aluminum flake powder (McLaughlin et al. 1962). A prolongation of prothrombin time was seen in 30 of 36 aluminum workers chronically exposed by inhalation to alumina dust (Waldron-Edward et al. 1971). The authors suggested that increasing serum aluminum levels may be used to provide beneficial antithrombogenic effects (Waldron-Edward et al. 1971).

No studies were located regarding hematological effects in animals after acute-duration inhalation exposure to aluminum or its compounds. No hematological effects were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6–24 months (Steinhagen et al. 1978; Stone et al. 1979).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects following acute- or intermediate-duration inhalation exposure to various forms of aluminum in humans. Two case reports have been identified in which finger clubbing was observed in male factory workers chronically exposed to aluminum powder (De Vuyst et al. 1986; McLaughlin et al. 1962). Joint pain was reported by a female worker exposed by inhalation to dried alunite residue (a hydrated sulphate of aluminum and

potassium) for 18 months (Musk et al. 1980). Schmid et al. (1995) did not find any significant alterations in bone mineral content (assessed via osteodensitometry) in workers exposed to aluminum powder (average concentration 12.1 mg/m^3) for an average duration of 12.6 years.

No studies were located regarding musculoskeletal effects following acute- or chronic-duration inhalation exposure to aluminum or its compounds in animals. No histological changes were observed in the muscle or bone of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Hepatic Effects. No studies were located regarding hepatic effects in humans following acute- or chronic-duration inhalation exposure to various forms of aluminum. Intermediate occupational inhalation exposure to aluminum fumes, dusts, or powders did not affect liver function or hepatic microanatomy in a group of seven workers as determined from biopsy samples (Mussi et al. 1984).

In animals, no histological or organ weight changes were observed in livers of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). No acute- or chronic-duration inhalation studies examining the liver were identified.

Renal Effects. No studies were located regarding renal effects in humans following acute-duration inhalation exposure to various forms of aluminum.

No adverse effects on renal function or standard urine tests have been noted in humans following intermediate-duration inhalation exposure to aluminum fumes or dust (Mussi et al. 1984) or chronic-duration inhalation exposure to metallic aluminum powder (De Vuyst et al. 1987; McLaughlin et al. 1962).

No histological or organ weight changes were observed in kidneys of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Endocrine Effects. No studies were located regarding endocrine effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. Post-mortem enlargement of

the thyroid was reported in the case of a male factory worker chronically exposed by inhalation to aluminum flake powder (McLaughlin et al. 1962).

No studies were located regarding endocrine effects in animals following acute- or chronic-duration inhalation exposure to aluminum or its compounds. No adverse histological changes were observed in the adrenal, thyroid, or pituitary glands of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Dermal Effects. No studies were located regarding dermal effects in animals following acute- or chronic-duration inhalation exposure to various forms of aluminum. No histologic changes of the skin were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Ocular Effects. No studies were located regarding ocular effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. No adverse effects were observed during an eye examination in a man chronically exposed by inhalation to metallic aluminum and aluminum oxide powders (De Vuyst et al. 1987).

No studies were located regarding ocular effects in animals following acute- or chronic-duration inhalation exposure to aluminum or its compounds. No histological changes were observed in the eyes of Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation exposure to aluminum or its compounds. Unspecified body weight decreases were reported for male Golden Syrian hamsters acutely exposed via whole-body inhalation to 3, 10, or 33 mg Al/m^3 as alchlor, a common component of antiperspirants (Drew et al. 1974). In contrast, no body weight effects were observed in Sprague-Dawley rats exposed by inhalation to 0.37 mg Al/m^3 as aluminum chloride or 0.41 mg Al/m^3 as aluminum fluoride dust for 5 months (Finelli et al. 1981), or in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978) or to 0.61 mg Al/m^3 as aluminum chlorhydrate for up to 24 months (Stone et al. 1979). Significant reduction in body weight (>10%) was observed in Fischer 344 rats after 24 months of exposure to 6.1 mg/m^3 as aluminum chlorhydrate. No effect on body weight was seen in Hartley guinea

pigs similarly exposed (Stone et al. 1979). These NOAEL and LOAEL values are recorded in Table 3-1 and plotted in Figure 3-1.

Metabolic Effects. No studies were located regarding metabolic effects in humans following acute- or chronic-duration inhalation exposure to various forms of aluminum. No adverse effect on phosphate metabolism was identified in humans following intermediate-duration inhalation exposure to aluminum fumes or dust (Mussi et al. 1984).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological/lymphoreticular effects in humans after acute- or intermediate-duration inhalation exposure to various forms of aluminum. Helper T-lymphocyte alveolitis and blastic transformation of peripheral blood lymphocytes in the presence of soluble aluminum compounds *in vitro* were found in an individual with sarcoid-like epitheliod granulomas and exposed to metallic aluminum and aluminum dust (De Vuyst et al. 1987). Additional testing 1 year after termination of exposure indicated the man no longer had alveolitis. A significantly higher percentage of $CD4^{-}CD8^{+}$ T lymphocytes were observed in aluminum electrolytic workers (He et al. 2003).

Several animal studies have found histological alterations in the lymphoreticular system, in particular granulomas in the hilar lymph nodes; these effects are secondary to the pulmonary effects (Steinhagen et al. 1978; Thomson et al. 1986) and resulted from the removal of aluminum from the lungs by alveolar macrophages.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. A number of studies have investigated the neurotoxic potential in workers chronically exposed to aluminum. With the exception of isolated cases (for example, McLaughlin et al. 1962), none of these studies reported overt signs of neurotoxicity in workers exposed to aluminum dust (potroom and foundry workers) (Bast-Pettersen et al. 1994; Dick et al. 1997; Hosovski et al. 1990; Sim et al. 1997; White et al. 1992), in aluminum welders (Hänninen et al. 1994; Sjögren et al. 1996), or in miners exposed to McIntyre powder (finely ground aluminum and aluminum oxide) (Rifat et al. 1990). Higher incidences of subjective neurological symptoms (e.g., incoordination, difficulty buttoning, problems concentrating, headaches, depression, fatigue) were reported in aluminum potroom or foundry workers at aluminum smelters (Halatek et al. 2005; Iregren et

al. 2001; Sim et al. 1997; Sińczuk-Walczak et al. 2003; White et al. 1992), workers exposed to aluminum flake powder (Iregren et al. 2001), and aluminum welders (Bast-Pettersen et al. 2000; Riihimäki et al. 2000; Sjögren et al. 1990). Among the studies examining the potential association between neurological symptoms and aluminum exposure estimates (urinary and/or blood aluminum levels), some found a significant association (Riihimäki et al. 2000; Sińczuk-Walczak et al. 2003) and others did not (Bast-Pettersen et al. 2000; Iregren et al. 2001; Kiesswetter et al. 2007).

Subclinical effects have been reported in various types of aluminum workers. Significant alterations in performance tests assessing reaction time, eye-hand coordination, memory, and/or motor skills were found in aluminum foundry workers (Hosovski et al. 1990; Polizzi et al. 2001), aluminum welders (Akila et al. 1999; Bast-Pettersen et al. 2000; Buchta et al. 2005; Riihimäki et al. 2000; Sjögren et al. 1990), electrolyte workers (He et al. 2003), and miners exposed to McIntyre powder (Rifat et al. 1990). Three studies of aluminum welders did not find significant decrements in neurobehavioral performance as compared to controls; however, significant correlations between aluminum exposure estimates (urinary or plasma aluminum levels or air aluminum levels) and memory and/or reaction-time tests were found (Bast-Pettersen et al. 2000; Buchta et al. 2003; Hänninen et al. 1994). Other studies did not find alterations in neuroperformance tests in aluminum potroom workers (Sim et al. 1997) or aluminum welders (Kiesswetter et al. 2007); two studies in aluminum welders did not find effects on motor performance (Buchta et al. 2003, 2005). A higher incidence of subclinical tremors was found in a study of potroom workers (Bast-Pettersen et al. 1994); another study did not find a significant alteration (Dick et al. 1997). Several studies have examined aluminum's potential to induce quantitative EEG changes; some studies found alterations (Hänninen et al. 1994; Riihimäki et al. 2000; Sińczuk-Walczak et al. 2003) and others did not (Iregren et al. 2001). In general, the available occupational exposure studies poorly characterize aluminum exposure. Some of the studies reported aluminum air concentrations for a single time period (Dick et al. 1997; Sim et al. 1997; Sjögren et al. 1996; White et al. 1992) or a couple of time periods (Buchta et al. 2003; Kiesswetter et al. 2007), but did not have earlier monitoring data when aluminum exposures may have been higher. A meta-analysis using data from most of these studies found a statistically significant decline in performance on the digit symbol neurobehavioral test (Meyer-Baron et al. 2007). Although decreases in performance were observed for other neurobehavioral tests, the differences were not statistically significant. The lack of adequate exposure monitoring data, potential exposure to other neurotoxicants, and the different types of aluminum exposure make it difficult to draw conclusions regarding the neurotoxic potential of inhaled aluminum in workers.

Three studies have examined the possible association between occupational exposure to aluminum and the risk of Alzheimer's disease. Two case-control studies did not find a significant association between occupational exposure to aluminum dust or fumes and the risk of Alzheimer's disease (Graves et al. 1998; Salib and Hillier 1996). Another study of former aluminum dust-exposed workers (retired for at least 10 years) found some impairment in some tests of cognitive function; the investigators raised the possibility that cognitive impairment may be a pre-clinical indicator of Alzheimer's disease (Polizzi et al. 2002).

No studies were located regarding neurological effects in animals following acute-duration inhalation exposure to various forms of aluminum. No brain weight or histological changes were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to up to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). No brain weight effects were observed in Sprague-Dawley rats exposed by inhalation to 0.37 mg Al/m^3 as aluminum chloride or 0.41 mg Al/m^3 as aluminum fluoride for 5 months, although tissues were not examined histologically (Finelli et al. 1981). No brain weights were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m^3 as aluminum chlorhydrate for up to 24 months (Stone et al. 1979).

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following acute-, intermediate-, or chronic-duration inhalation exposure to various forms of aluminum.

No reliable studies were located regarding reproductive effects in animals following acute- or chronic-duration inhalation exposure to various forms of aluminum. No histological changes were observed in reproductive tissues of Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). These NOAEL values are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to various forms of aluminum.

3.2.1.7 Cancer

No studies were located regarding cancer effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum.

A reported high incidence of bladder cancer in a region of Quebec, Canada where aluminum production takes place (Wigle 1977) resulted in the initiation of a case-control study (Theriault et al. 1984a). Workers in five aluminum reduction plants were assessed with respect to incidence of bladder cancer. The number of men working in the plants was 300–1,200 except for one plant with 7,800 workers. The number of bladder cancer cases was collected from regional hospitals over a 10-year period, and the number of current or former employees from the aluminum plants identified. For each case, three controls who had never had bladder cancer were selected. Detailed occupational histories of each man (case and controls) were collected from the companies and included each division, department, and job to which the men had been assigned; smoking history; and estimated assessment of tar and PAH exposure (based on benzene soluble material and benz(a)pyrene concentrations in workplace air) for each occupation. An index of lifetime exposure of each worker to tar and PAHs was created. Over the 10-year study period, 488 cases of bladder cancer were found in men from the designated regions. Of these, 96 were identified as being current or former aluminum company employees, and 11 were eliminated from the study because they had worked <12 months at the companies. The distribution of tumors was as follows: transitional epitheliomas grade I (n=3), grade II (n=43), grade III (n=18), and grade IV (n=21). The mean age at diagnosis was 61.7 years, and the mean age at first employment in aluminum work was 28.2 years. The interval between beginning of employment in the aluminum industry and diagnosis was 23.9 years. A higher proportion of cases than controls were smokers. The risk for bladder cancer was highest in workers in Soderberg reactor rooms (where the reduction process takes place), and risk increased steadily with time worked in this department. The risk also increased steadily with estimated exposure to tar and PAHs. The interaction between cigarette smoking and PAH exposure in the generation of bladder cancer was more than additive.

Several studies on cancer mortality patterns have been conducted in aluminum reduction factory workers (Gibbs and Horowitz 1979; Milham 1979; Mur et al. 1987; Rockette and Arena 1983). The workplace inhalation exposure was to aluminum dust or fumes for chronic durations, but the exposure levels were not determined. In addition to aluminum, most workers were concurrently exposed by inhalation to known carcinogens, such as tobacco smoke or PAHs from coal tars. In a historical prospective study of 2,103 aluminum production workers, standardized mortality ratios (SMRs) of 117 for lung cancer

(35 cases), 180 for pancreatic cancer (9 cases), and 184 for all lymphatic and hematopoietic cancers (17 cases) were observed (Milham 1979). Smoking histories were not available, and only the SMR for lymphatic and hematopoietic cancers were statistically significant. In a study that focused on mortality from lung cancer in a group of 5,406 aluminum production workers (Gibbs and Horowitz 1979), a dose-response relationship was observed between lung cancer mortality and both years of exposure to tar and "tar-years" in specific occupations. A study of mortality patterns in 21,829 aluminum production workers in the United States (Rockette and Arena 1983) indicated that the risk of lung cancer mortality increased among workers with ≥25 years of experience in the carbon bake department, who presumably had higher exposure to potential hydrocarbon carcinogens than other workers. Increased deaths from bladder and hematolymphopoietic cancers were also reported.

Based on current evidence, the International Agency for Research on Cancer (IARC) has stated (IARC 1984) that "the available epidemiological studies provide limited evidence that certain exposures in the aluminum production industry are carcinogenic to humans, giving rise to cancer of the lung and bladder. A possible causative agent is pitch fume." It is important to emphasize that the potential risk of cancer in the aluminum production industry is probably due to the presence of known carcinogens (e.g., PAHs) in the workplace and is not due to aluminum or its compounds.

No reliable studies were located regarding cancer effects in animals following acute- or intermediate-duration inhalation exposure to aluminum or its compounds. An increase in cancer was not observed in male and female Wistar rats exposed via whole-body inhalation to atmospheres containing 2.18–2.45 mg Al/m^3 as alumina fibers (≈96% aluminum oxide) for 86 weeks (Pigott et al. 1981).

3.2.2 Oral Exposure

Major sources of human oral exposure to aluminum include food (due to its use in food additives, food and beverage packaging, and cooking utensils), drinking water (due to its use in municipal water treatment), and aluminum-containing medications (particularly antacid/antiulcer and buffered aspirin formulations) (Lione 1985b). Dietary intake of aluminum, estimated to be in the 0.10–0.12 mg Al/kg/day range in adults (Pennington and Schoen 1995), has not been of historical concern with regard to toxicity due to its presence in food and the generally recognized as safe (GRAS) status of aluminum-containing food additives by the FDA. Users of aluminum-containing medications that are healthy (i.e., have normal kidney function) can ingest much larger amounts of aluminum than in the diet, possibly as high as 12–

71 mg Al/kg/day from antacid/antiulcer products and 2–10 mg Al/kg/day from buffered analgesics when taken at recommended dosages (Lione 1985b).

The oral toxicity of aluminum in animals is well-studied, although many of the studies are limited by a lack of reported information on aluminum content in the base diet. Commercial grain-based feeds for laboratory animals contain high levels of aluminum that typically far exceed the aluminum content of the human diet. Commercial laboratory animal chow can significantly contribute to total experimental exposure, as well as provide excess and variable amounts of essential and nonessential trace minerals and metal binding ligands that can alter aluminum uptake in comparison to diets that are semipurified or purified in which trace metal levels are precisely determined (Golub et al. 1992b). Base diets containing 250–350 ppm Al were used in some rat and mouse studies, but this cannot be assumed to be a normal or representative concentration range because analyses for aluminum were not routinely performed, substantial brand-to-brand and lot-to-lot variations are apparent, and formal surveys of aluminum content of laboratory animal feed are not available. For example, concentrations ranging from 60 to 280 ppm Al for Panlab rodent standard diet (Colomina et al. 1998; Domingo et al. 1987a, 1993) and 120–8,300 ppm for Purina Rodent Laboratory Chow (Fleming and Joshi 1987; Provan and Yokel 1990; Varner et al. 1994, 1998) have been reported. Due to the likelihood of significant base dietary exposure to aluminum, studies with insufficient information on aluminum content in the base diet must be assumed to underestimate the actual aluminum intake. The magnitude of the underestimate can be considerable. For example, based on approximate values of 250 ppm (Colomina et al. 1998; Domingo et al. 1993) and 350 ppm (Oteiza et al. 1993) for Al in feed used in some studies in rats and mice, respectively, and using reference values for food consumption and body weight in rats and mice (EPA 1988) for ingestion during the period from weaning to 90 days, estimated doses of 25 mg Al/kg/day (rats) and 68 mg Al/kg/day (mice) may be provided by diet alone. These figures can represent a significant portion of the intake for which Table 3-2 reports health effects in animal studies. Consequently, although studies with inadequate data on base dietary levels of aluminum provide useful information on health effects of aluminum, NOAELs and LOAELs from these studies cannot be assumed to be accurate, they may not be suitable for comparison with effect levels from studies that used diets with known amounts of aluminum, and are not included in Table 3-2 and Figure 3-2. Studies for which data on base dietary aluminum content are available are mainly limited to those conducted by Golub and coworkers (Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1989, 1992a, 1992b, 1994, 1995, 2000; Oteiza et al. 1993) and Domingo and coworkers (Colomina et al. 1992, 1994, 1998, 2005; Domingo et al. 1987a, 1987b, 1989, 1993; Gomez et al. 1986, 1991; Paternain et al. 1988; Roig et al. 2006).

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (G)				261 (LD50)	Llobet et al. 1987 Aluminum nitrate	
2	Rat (Sprague-Dawley)	once (G)				370 (LD50)	Llobet et al. 1987 Aluminum chloride	
3	Rat (Sprague-Dawley)	once (G)				162 (LD50)	Llobet et al. 1987 Aluminum bromide	
4	Mouse (Swiss-Webster)	once (G)				286 (LD50)	Llobet et al. 1987 Aluminum nitrate	
5	Mouse (Swiss-Webster)	once (G)				222 (LD50)	Llobet et al. 1987 Aluminum chloride	
6	Mouse (Swiss-Webster)	once (G)				164 (LD50)	Llobet et al. 1987 Aluminum bromide	
7	Mouse (Dobra Voda)	once (G)				770 M (LD50)	Ondreicka et al. 1966 Aluminum chloride	
8	Mouse (Dobra Voda)	once (G)				980 M (LD50)	Ondreicka et al. 1966 Aluminum sulfate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
9	Rabbit (New Zealand)	once (GW)				540 F (5/5 died)	Yokel and McNamara 1985 Aluminum lactate	
Developmental								
10	Rat (Sprague-Dawley)	Gd 6-19 (F)		110			McCormack et al. 1979 Aluminum chloride	
11	Mouse (Swiss)	Gd 6-15 (GW)		141 F			Domingo et al. 1989 Aluminum hydroxide	
INTERMEDIATE EXPOSURE								
Systemic								
12	Rat (NS)	100 d (W)	Bd Wt		97 M (decreased body weight gain in aged rats)		Colomina et al. 2002 Aluminum nitrate	Citric acid was added to water to increase absorption.
13	Rat (Sprague-Dawley)	100 d (W)	Cardio	284 F			Domingo et al. 1987b Aluminum nitrate	
			Hemato	284 F				
			Hepatic	284 F				
			Renal	284 F				
			Bd Wt	284 F				

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Rat (Sprague-Dawley)	1 mo (W)	Resp	133 F			Gomez et al. 1986 Aluminum nitrate	
			Cardio	133 F				
			Gastro	133 F				
			Hemato	52 F	79 F (hyperemia in the red pulp of the spleen)			
			Hepatic	79 F	133 F (hyperemia in the liver, periportal monocytic infiltrate in liver)			
			Renal	133 F				
			Bd Wt	133 F				
15	Rat (Wistar)	10 wk (F)	Musc/skel	90 M			Konishi et al. 1996 Aluminum lactate	
			Bd Wt	90 M				
16	Rat (Sprague-Dawley)	8 mo (W)	Hemato		230 F (decreased hemoglobin, hematocrit and haptoglobin levels, increased reticulocyte levels; inhibition of CFU-E proliferation)		Vittori et al. 1999 Aluminum citrate	
17	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)	Bd Wt	330 F			Donald et al. 1989 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Mouse (Swiss-Webster)	6 wk (F)	Bd Wt	130 F			Golub et al. 1989 Aluminum lactate	
19	Mouse (Swiss-Webster)	Gd 1-21 Ld 1-21 Gd 1- Ld 21 (F)	Bd Wt		250 F (decreased body weight gain in lactating mice)		Golub et al. 1992a Aluminum lactate	
20	Mouse (Swiss-Webster)	90 d (F)	Bd Wt	195 F			Golub et al. 1992b Aluminum lactate	
21	Mouse (Swiss-Webster)	7-10 wk (F)	Bd Wt	170 F			Oteiza et al. 1989 Aluminum lactate	
22	Mouse (Swiss-Webster)	5 or 7 wk (F)	Hemato	195 F			Oteiza et al. 1993 Aluminum chloride	
			Hepatic	195 F				
			Bd Wt	195 F				
23	Dog (Beagle)	6 mo (F)	Cardio	88			Katz et al. 1984 Aluminum phosphate	
			Hemato	88				
			Hepatic	88				
			Renal	88				
			Endocr	88				
			Ocular	88				

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
24	Dog (Beagle)	26 wk (F)	Cardio	75			Pettersen et al. 1990 Aluminum phosphate	
			Hemato	75				
			Renal	75				
			Endocr	75				
Immuno/ Lymphoret								
25	Human	3 x/d 6 wk (F)		25			Gräske et al. 2000 Aluminum hydroxide	
26	Rat (Sprague-Dawley)	100 d (W)		259 F			Domingo et al. 1987b Aluminum nitrate	
27	Rat (Sprague-Dawley)	1 mo (W)		52 F	79 F (hyperemia in the red pulp of the spleen)		Gomez et al. 1986 Aluminum nitrate	
28	Mouse (Swiss-Webster)	Gd 0- pnd 180 (F)			200 (in offspring: 19% increased absolute spleen weights; depressed spleen cell concentrations of interleukin-2, interferon-g and tumor necrosis factor-a; deficiency of CD4+ cells in T-cell populations)		Golub et al. 1993 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Mouse (Swiss-Webster)	6 wk (F)		107 F			Yoshida et al. 1989 Aluminum lactate	
30	Mouse (Swiss-Webster)	Gd 1- pnd 31 (F)			155 F (increased susceptibility to bacterial infection in dams)		Yoshida et al. 1989 Aluminum lactate	
Neurological								
31	Rat (NS)	100 d (W)		97 M			Colomina et al. 2002 Aluminum nitrate	Citric acid was added to water to increase absorption.
32	Rat (Sprague-Dawley)	6.5 mo (W)		125 M			Domingo et al. 1996 Aluminum nitrate	Citric acid was added to water to improve aluminum absorption.
33	Rat (Wistar)	daily 3 mo (W)		21.5 M	43.1 M (impairment of post-rotatory nystagmus)		Mameli et al. 2006 Aluminum chloride	
34	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)		330 F			Donald et al. 1989 Aluminum lactate	
35	Mouse (Swiss-Webster)	NR (F)		100 M			Golub and Germann 1998 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Mouse (Swiss-Webster)	6 wk (F)		62 F	130 F (decreased total activity and vertical activity)		Golub et al. 1989 Aluminum lactate	
37	Mouse (Swiss-Webster)	Gd 1-21 Ld 1-21 Gd 1- Ld 21 (F)		250 F			Golub et al. 1992a Aluminum lactate	
38	Mouse (Swiss-Webster)	90 d (F)			195 F (decreased forelimb and hindlimb grip strengths and startle response, decreased total activity, horizontal activity, and percent interval with high activity counts)		Golub et al. 1992b Aluminum lactate	
39	Mouse (Swiss-Webster)	Gd 1- pnd 170 (F)		100 M	200 M (increased cage mate aggression)		Golub et al. 1995 Aluminum lactate	
40	Mouse (Swiss-Webster)	5 or 7 wk (F)			195 F (reduced forelimb and hindlimb grip strength)		Oteiza et al. 1993 Aluminum chloride	
41	Dog (Beagle)	26 wk (F)		75			Pettersen et al. 1990 Aluminum phosphate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
42	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)			155 F (altered gestational length)		Donald et al. 1989 Aluminum lactate	
43	Mouse (Swiss-Webster)	Gd 1-21 Ld 1-21 Gd 1- Ld 21 (F)		250 F			Golub et al. 1992a Aluminum lactate	
Developmental								
44	Rat (Sprague-Dawley)	15 d premating Gd 1- Ld 21 (W)			103 (decreased forelimb grip strength, decreased pup body weight)		Colomina et al. 2005 Aluminum nitrate	Citric acid was added to water to increase absorption.
					53 (delay in vaginal opening)			
45	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)			155 (decreased forelimb and increased hindlimb grip strength and increased foot splay in weanlings)		Donald et al. 1989 Aluminum lactate	
46	Mouse (Swiss-Webster)	Gd 1- pnd 35 (F)		330 M			Golub and Germann 1998 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
47	Mouse (Swiss-Webster)	Gd 0- Ld 21, pnd 21-35 (F)		26[b]	130 (impaired performance on the water maze test in females, shorter latency to fall in wire suspension test in males)		Golub and Germann 2001 Aluminum lactate	Diet levels of phosphorus, calcium, magnesium, iron, and zinc were marginally adequate.
48	Mouse (Swiss-Webster)	Gd 1- pnd 35 (F)			330 (altered myelination in spinal cord)		Golub and Tarara 1999 Aluminum lactate	
49	Mouse (Swiss-Webster)	Gd 1-19 Gd 1- Ld 21 Ld 1-21 (F)			250 (decrease in pup weight, crown-rump length, forelimb grip strength in gestation exposed group, increase in hindlimb grip and tail withdrawal times in gestation and lactation exposed groups, increase in negative geotaxis latency in lactation exposed groups)		Golub et al. 1992a Aluminum lactate	
50	Mouse (Swiss-Webster)	Gd 1- pnd 21 (F)			155 (decreased fore- and hindlimb grip strengths and startle response)		Golub et al. 1995 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
51	Mouse (Swiss-Webster)	Gd 1- pnd 31 (F)		330			Yoshida et al. 1989 Aluminum lactate	Assessed immunotoxicity.
CHRONIC EXPOSURE								
Systemic								
52	Rat (Sprague-Dawley)	Gd 1- Ld 21 weaning-1 yr of age or 2 yr of age (W)	Bd Wt	103 M			Roig et al. 2006 Aluminum nitrate	Citric acid was added to water to increase absorption.
53	Rat (Long- Evans)	2.5 yr (W)	Resp	0.6			Schroeder and Mitchener 1975a Aluminum sulfate	
			Cardio	0.6				
			Hepatic	0.6				
			Renal	0.6				
			Bd Wt	0.6				
54	Mouse (Swiss-Webster)	2 yr conception to 24 mo (F)	Bd Wt		100 F (20% decrease in body weight gain)		Golub et al. 2000 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
55	Mouse (Swiss)	lifetime (W)	Resp	1.2			Schroeder and Mitchener 1975b Aluminum sulfate	
			Cardio	1.2				
			Hepatic	1.2				
			Renal	1.2				
			Bd Wt	1.2				
Neurological								
56	Rat (Sprague-Dawley)	Gd 1- Ld 21 weaning-1 yr of age or 2 yr of age (W)		103 M			Roig et al. 2006 Aluminum nitrate	Citric acid was added to water to increase absorption.
57	Mouse (Swiss-Webster)	2 yr conception to 24 mo (F)			100[c]	(decreased forelimb and hindlimb grip strength, decreased thermal sensitivity)	Golub et al. 2000 Aluminum lactate	

a The number corresponds to entries in Figure 3-2.

b Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.9 mg Al/kg/day; dose divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

c Used to derive a chronic-duration oral MRL of 0.3 mg Al/kg/day; dose divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CFU-E = colony-forming unit-erythroid; d = day(s); (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; Immuno/Lymphoret = immunological/lymphoreticular; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; NR = not reported; pnd = post-natal day; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

Acute (≤14 days)

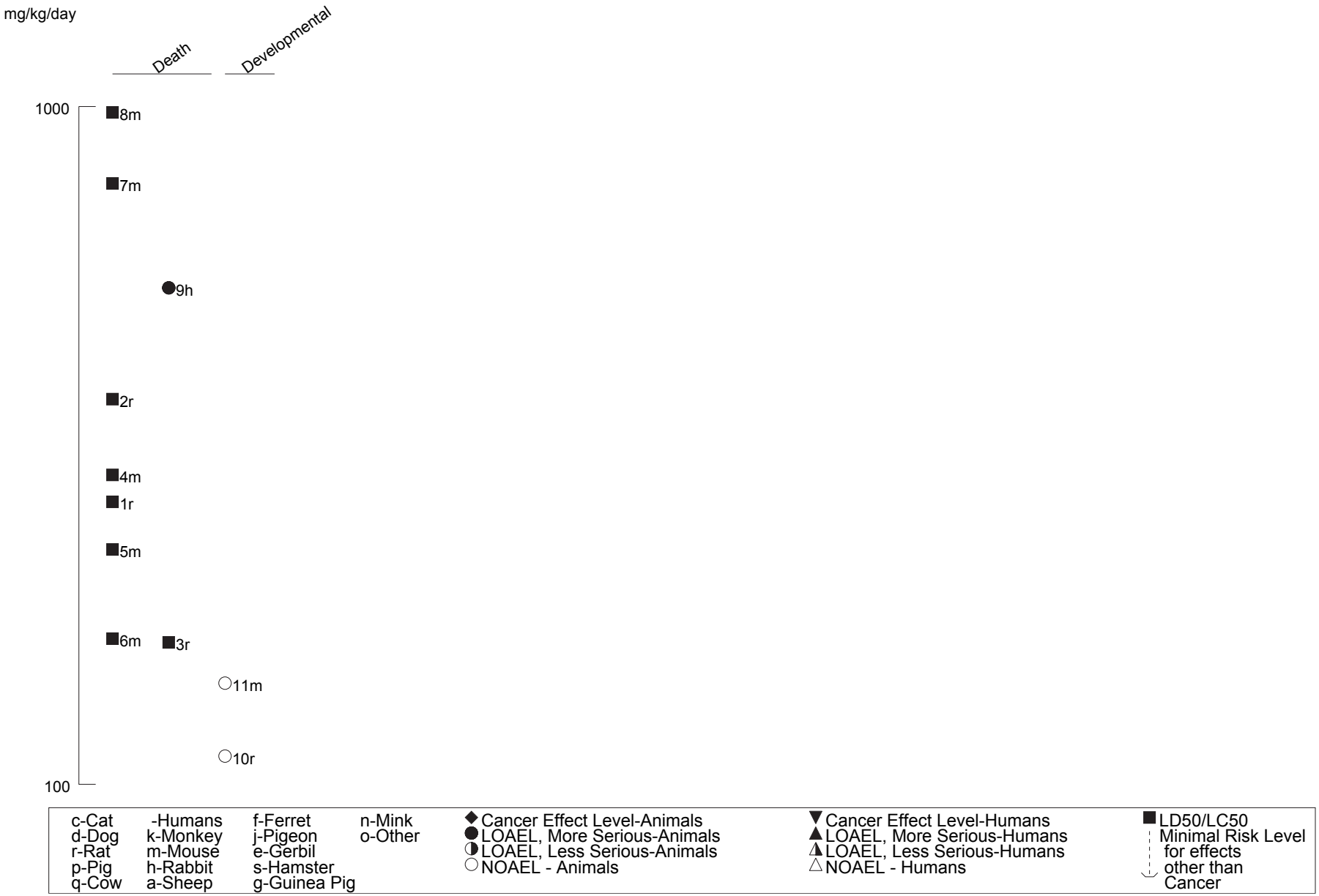


Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral *(Continued)*

Intermediate (15-364 days)

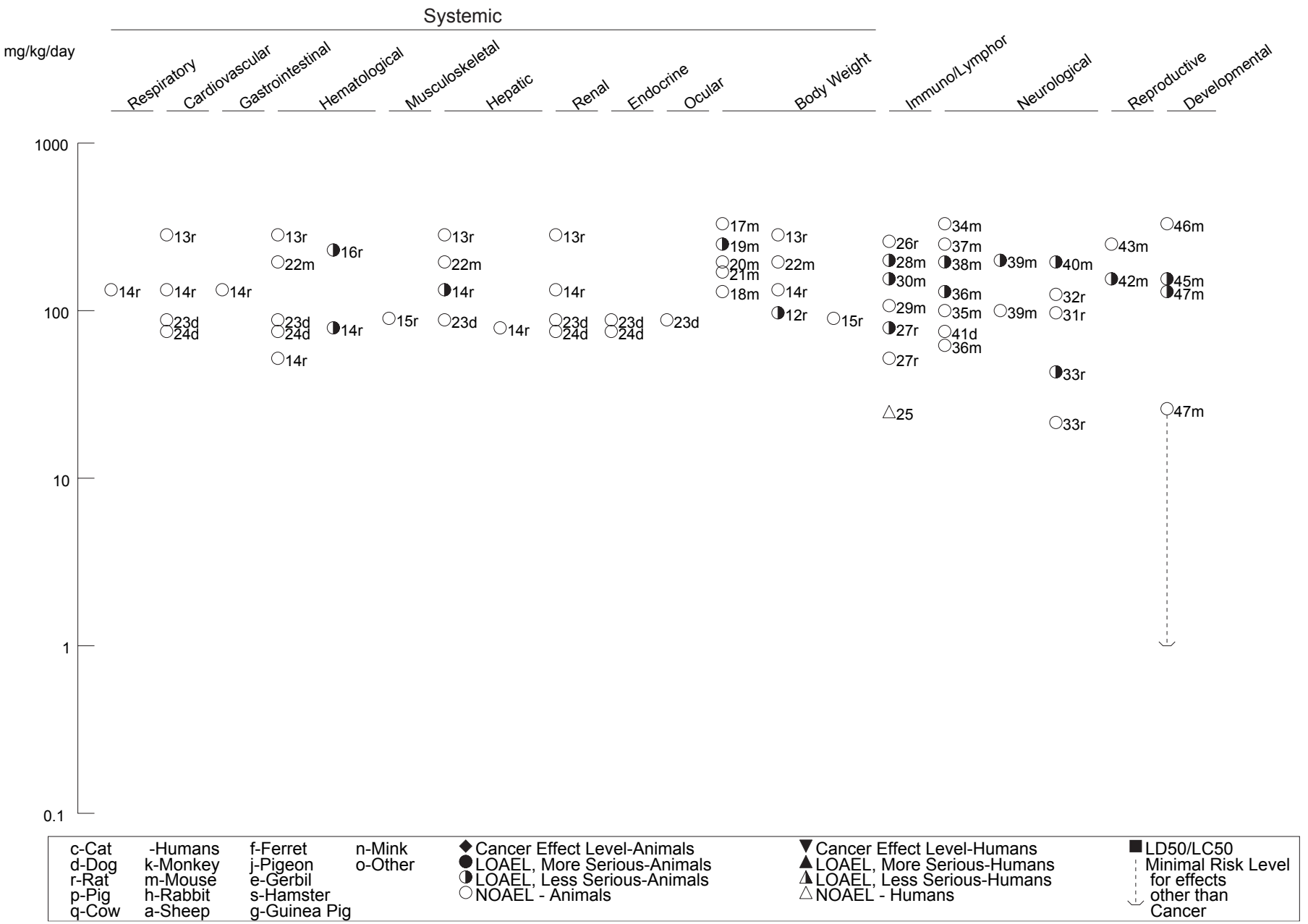


Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral *(Continued)*

Intermediate (15-364 days)

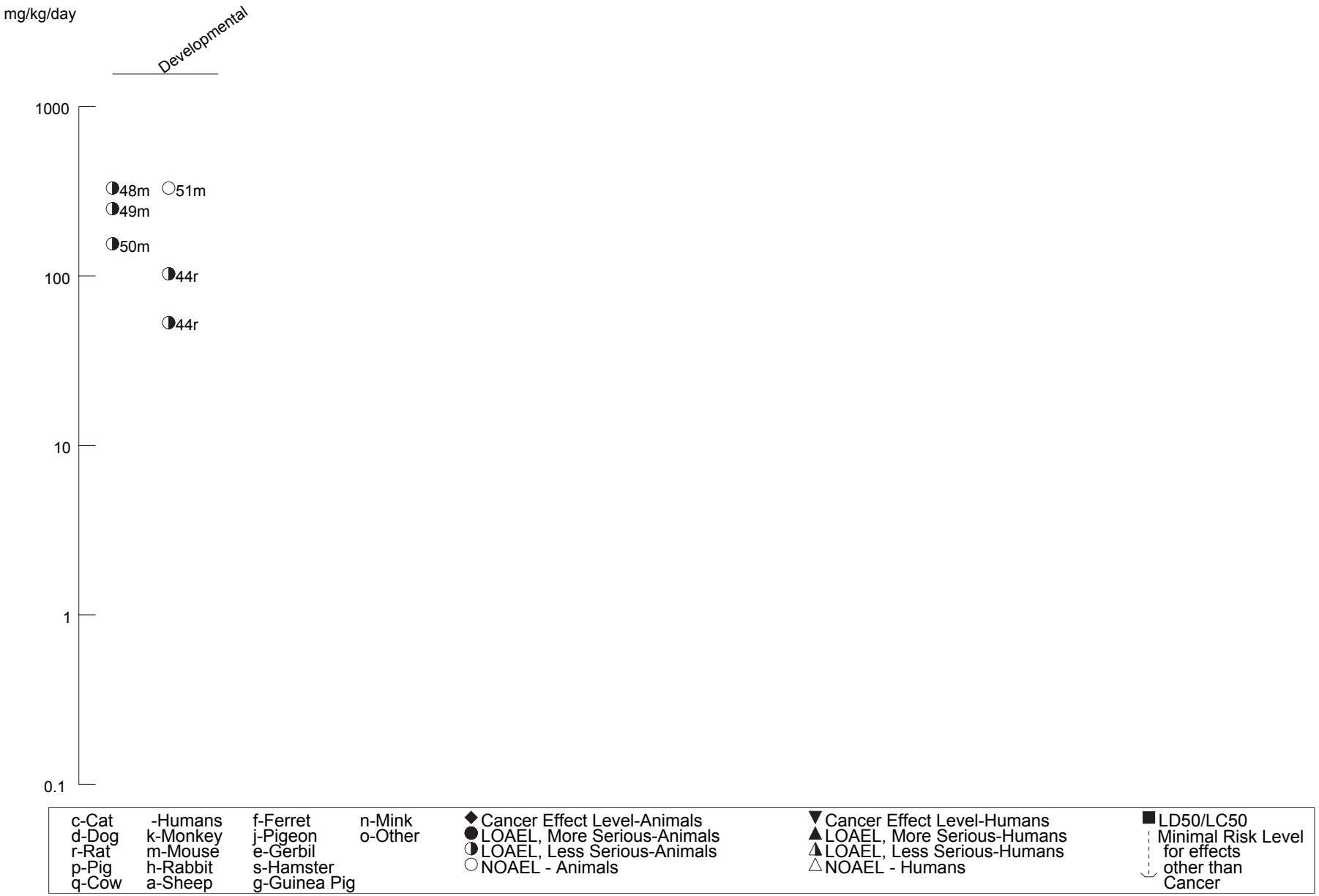
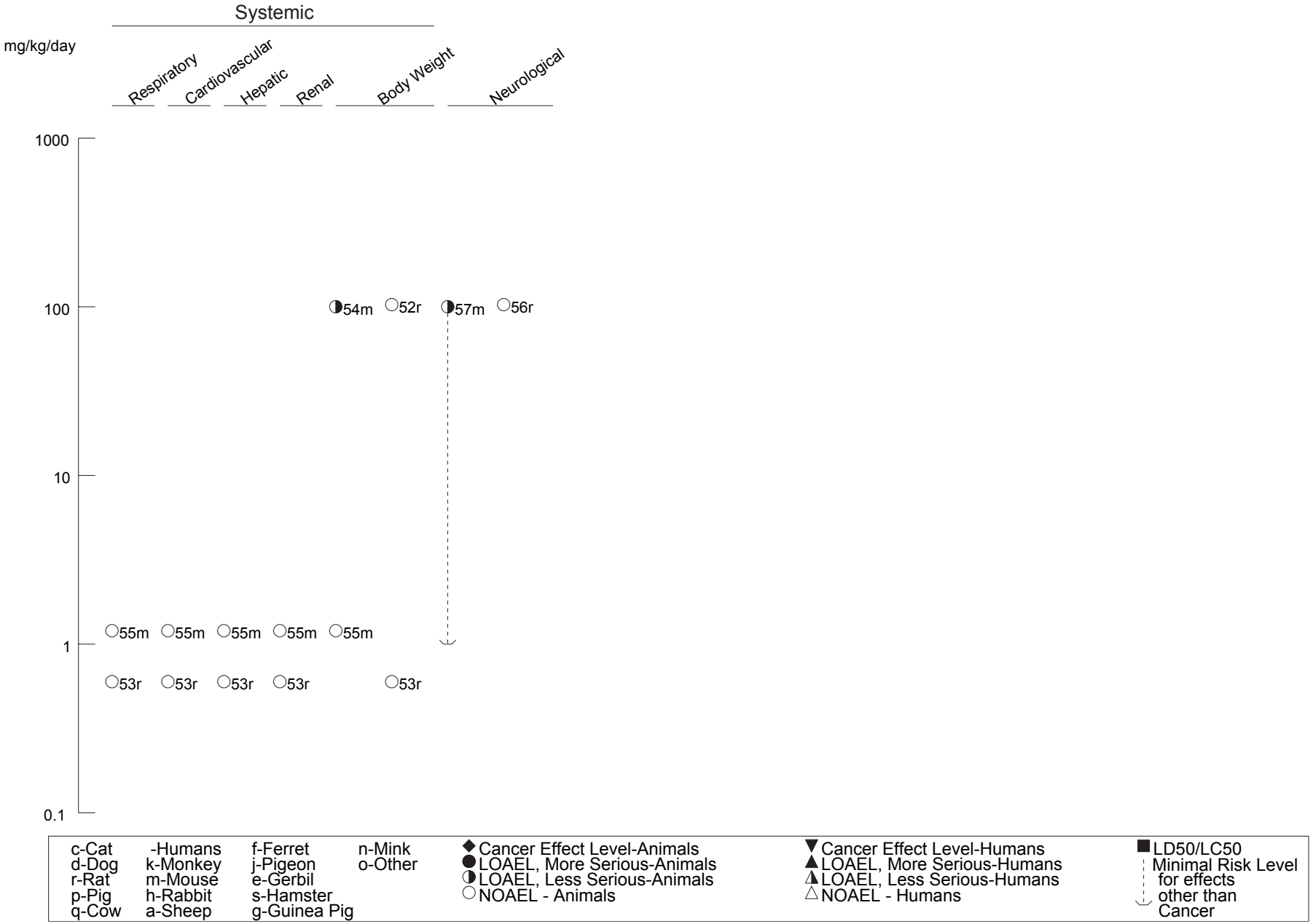


Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral *(Continued)*

Chronic (≥365 days)



Although levels of human oral intake of aluminum may be characterized, it is important to recognize that the amount of aluminum ingested does not provide an actual estimate of exposure without information on bioavailability of the form of aluminum ingested. Similarly, effective doses in the animal studies, including the exact underestimate of aluminum intake in animal studies with insufficient information on aluminum in the base diet, cannot be known without information on bioavailability of the aluminum. As discussed in Section 3.3.1.2, the bioavailability of aluminum is influenced by the form in which it is ingested and the presence of other substances in the gastrointestinal tract, particularly complexing moieties in foods, which may significantly enhance or hinder absorption.

3.2.2.1 Death

No aluminum-related deaths in healthy humans have been reported after oral exposure. One aluminum compound that can be life threatening to humans is aluminum phosphide, a grain fumigant. Accidental or volitional ingestion (to commit suicide) of large amounts has caused death (Chopra et al. 1986; Khosla et al. 1988). The toxicity from this compound is due to the exposure to phosphine gas, which is produced in the gastrointestinal tract after the aluminum phosphide is ingested.

Aluminum caused death in laboratory animals only at doses that are high compared to normal human exposure. Data on acute lethality of ingested aluminum are summarized below. For aluminum bromide, LD_{50} (lethal dose, 50% kill) values of 162 and 164 mg Al/kg have been reported in Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al. 1987). For the nitrate form, LD_{50} values of 261 and 286 mg Al/kg have been reported for Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al. 1987). For the chloride form, LD_{50} values of 370, 222, and 770 mg Al/kg have been reported for Sprague-Dawley rats, Swiss Webster mice, and male Dobra Voda mice, respectively (Llobet et al. 1987; Ondreicka et al. 1966). The LD_{50} for aluminum sulfate in male Dobra Voda mice was reported as 980 mg Al/kg (Ondreicka et al. 1966). Time to death and clinical signs were not reported in these studies. A single gavage exposure to 540 mg Al/kg as aluminum lactate was fatal to all 5 lactating female New Zealand rabbits tested (Yokel and McNamara 1985). Time to death was reported as 8–48 hours.

Intermediate-duration oral exposure to aluminum has also been shown to cause death. Mortality occurred in female Swiss Webster mice exposed to aluminum lactate in the diet for 42 days throughout gestation and lactation at doses of 184 or 280 mg Al/kg/day (Golub et al. 1987), but not at 330 mg Al/kg/day in a different study (Donald et al. 1989) by the same group of investigators. Severe signs of neurotoxicity (ataxia, paralysis) were noted prior to the deaths. The effects in the Golub et al. (1987) study appear to be

related to semipurified diet composition. In particular, the formulation of the diet was revised by Donald et al. (1989) (and in subsequent studies by Golub and coworkers) by adding a "more generous provision" of several essential nutrients, particularly trace minerals (including calcium, magnesium, phosphate), to avoid the toxicity associated with the aluminum in the original diet. One of nine pregnant Swiss Webster mice that consumed 250 mg Al/kg/day as aluminum lactate in the revised purified diet died (Golub et al. 1992a). No mortality was observed in male Sprague-Dawley rats (7–10 per group) orally exposed to 70 mg Al/kg/day as aluminum chloride in water for 30, 60, or 90 days (Dixon et al. 1979), or up to 158 mg Al/kg/day as aluminum hydroxide in the feed for 16 days (Greger and Donnaubauer 1986); these doses do not include aluminum in the base diet. No male or female Beagle dogs (4/sex/group) died following dietary exposure to 75–80 mg Al/kg/day as sodium aluminum phosphate and base levels of aluminum in the feed for 26 weeks (Pettersen et al. 1990). In chronic-duration studies, exposure to aluminum at 100 mg Al/kg/day as aluminum lactate in the diet or 103 mg Al/kg/day as aluminum nitrate with added citric acid in drinking water did not result in significant alterations in mortality (Golub et al. 2000; Roig et al. 2006).

All reliable LOAEL values for death in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values for oral exposure from each reliable study for systemic effects in each species and duration category for aluminum are shown in Table 3-2 and plotted in Figure 3-2; only studies providing information on the levels of aluminum in the base diet are included in Table 3-2 and Figure 3-2.

Respiratory Effects. No studies were located regarding respiratory effects of various forms of aluminum following intermediate- or chronic-duration oral exposure in humans. Acute-duration oral exposure to aluminum phosphide has been shown to cause pulmonary edema in persons following accidental or volitional ingestion (Chopra et al. 1986; Khosla et al. 1988). The toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

No studies were located regarding respiratory effects of various forms of aluminum following acute-duration oral exposure in animals. Intermediate- and chronic-duration studies found no organ weight or histological changes in the lungs in rats exposed to 70 mg Al/kg/day as aluminum chloride in drinking

water (base dietary aluminum not reported) for 30, 60, or 90 days (Dixon et al. 1979), rats exposed to 133 mg Al/kg/day as aluminum nitrate in drinking water and base diet for 1 month (Gomez et al. 1986), rats or mice exposed to 0.6 and 1.2 mg Al/kg/day as aluminum potassium sulfate in drinking water (base dietary aluminum not reported), respectively, for 2–2.5 years (Schroeder and Mitchener 1975a, 1975b), or mice exposed to 979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994).

Cardiovascular Effects. No studies were located regarding cardiovascular effects of various forms of aluminum following intermediate- or chronic-duration oral exposure in humans. Acute-duration oral exposure to aluminum phosphide has been shown to cause tachycardia, hypotension, cardiovascular electrocardiographic abnormalities, subendocardial infarction, and transient atrial fibrillation in persons who either ingested it accidentally or in suicide attempts (Chopra et al. 1986; Khosla et al. 1988). However, toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

No studies were located regarding cardiovascular effects of aluminum or its compounds following acute-duration oral exposure in animals. No histological changes were observed in the hearts of male Sprague-Dawley rats given up to 70 mg Al/kg/day as aluminum chloride in drinking water (base dietary aluminum not reported) for 30, 60, or 90 days (Dixon et al. 1979). Similarly, no organ weight or histological changes were found in the hearts of female Sprague-Dawley rats that ingested 133 or 284 mg Al/kg/day as aluminum nitrate in drinking water and base diet for up to 1 month (Gomez et al. 1986) or 100 days, respectively (Domingo et al. 1987b). No organ weight or histological changes were observed in the hearts of dogs that consumed up to 75 mg Al/kg/day (Katz et al. 1984) or 88 mg Al/kg/day (aluminum levels of base diet not provide) (Pettersen et al. 1990) as sodium aluminum phosphate in the diet for 6 months.

Cardiovascular effects were not observed in animals following chronic-duration exposure to aluminum compounds. No histological changes were observed in the hearts of male and female Long Evans rats or Swiss mice given 0.6 or 1.2 mg Al/kg/day as aluminum potassium sulfate in drinking water, respectively, for 2–2.5 years (Schroeder and Mitchener 1975a, 1975b) or B6C3F1 mice that ingested 979 mg Al/kg/day as aluminum potassium sulfate in the diet for 20 months (Oneda et al. 1994). Aluminum levels in the base diet were not reported in these rat and mouse studies, although the animals were fed a low-metal diet in metal-free environmental conditions in the Schroeder and Mitchener (1975a, 1975b) studies.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects of various forms of aluminum following intermediate- or chronic-duration exposure in humans. Unspecified gastrointestinal and bowel problems were reported by people who, for 5 days or more, may have consumed water that contained unknown levels of aluminum sulfate accidentally placed in a water treatment facility in England (Ward 1989). Forty-eight of the exposed persons were examined, but the number of people with gastrointestinal complaints was not reported. It should be noted that the water supply also contained elevated levels of copper and lead which leached from the plumbing systems due to the greater acidity of the water (pH <4). Aluminum and copper levels in body tissues were reported as elevated in scalp hair and fingernails. Acute-duration oral exposure to aluminum phosphide has been shown to cause vomiting and abdominal pain in persons who ingested it either accidentally or in suicide attempts (Chopra et al. 1986; Khosla et al. 1988). However, as noted above, toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

No studies were located regarding gastrointestinal effects of aluminum or its compounds following acute-duration oral exposure in animals. No organ weight or histological changes were observed in the gastrointestinal tissues of female Sprague-Dawley rats given 133 mg Al/kg/day as aluminum nitrate in drinking water and base diet for up to 1 month (Gomez et al. 1986), or in male or female B6C3F1 mice that ingested 979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994).

Hematological Effects. No studies were located regarding hematological effects of various forms of aluminum following acute-, intermediate-, or chronic-duration exposure in humans after oral exposure to aluminum or its compounds.

Repeated exposure to aluminum appears to adversely affect the hematological system of rats and mice. Significant decreases in hemoglobin, hematocrit, and/or erythrocyte osmotic fragility were observed in rats exposed to 420 mg Al/kg/day as aluminum citrate in drinking water for 15 weeks (Garbossa et al. 1998), mice exposed to 13 mg Al/kg as aluminum citrate administered via gavage 5 days/week for 22 weeks (Garbossa et al. 1996), rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months (Vittori et al. 1999), and rats exposed via drinking water to 54.7 mg Al/kg/day as aluminum sulfate in a sodium citrate solution for 18 months (Farina et al. 2005). Exposure to lower concentrations or for shorter durations resulted in no significant damage to the erythrocytes. No alterations in hemoglobin, hematocrit, and/or erythrocyte osmotic fragility were observed in mice exposed to 13 mg Al/kg as aluminum citrate or aluminum chloride administered via gavage 5 days/week for 2 weeks

(Garbossa et al. 1996), rats exposed to 133 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986), mice exposed to 195 mg Al/kg/day as aluminum citrate in the diet for 5 or 7 weeks (Oteiza et al. 1993), rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), rats exposed to 27 mg Al/kg as aluminum citrate administered via gavage 5 days/week for 15 weeks (Garbossa et al. 1996), or dogs exposed to 75 or 88 mg Al/kg/day as aluminum phosphate in the diet for 6 months (Katz et al. 1984; Pettersen et al. 1990). The studies conducted by Domingo et al. (1987b), Gomez et al. (1986), Oteiza et al. (1993), Pettersen et al. (1990), and Vittori et al. (1999) provided information on the levels of aluminum in the base diet; the remaining studies did not provide this information. As highlighted by the Garbossa et al. (1996) study, which used multiple durations, the erythrocytic effects appear to be duration sensitive. No alterations in hemoglobin or hematocrit levels were observed in mice exposed to 13 mg Al/kg as aluminum citrate administered via gavage for 2 weeks; however, significant decreases in these parameters were observed when the exposure was continued for 22 weeks. Additionally, aluminum can alter mature erythrocyte morphology; anisocytosis (abnormal variations in cell size), anisochromia (unequal degree of cell staining), and poikilocytosis (abnormal variation in cell shape) have been observed in rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months (Vittori et al. 1999). Hyperemia in the red pulp of the spleen was reported in rats exposed to 79 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986); this may be indicative of erythrocyte damage.

There is some evidence that aluminum may affect iron levels in blood; however, this has not been well studied and the results are not consistent across studies. Vittori et al. (1999) did not find significant alterations in plasma iron levels or total iron binding capacity in rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months; however, impaired iron uptake and decreased iron incorporation into heme were measured in bone marrow cells. Farina et al. (2005) found significant decreases in blood iron concentrations and no change in total iron binding capacity in rats exposed to 54.7 mg Al/kg/day as aluminum sulfate in a sodium citrate solution in drinking water for 18 months. Florence et al. (1994) reported decreases in serum iron levels, total iron binding capacity, and transferring saturation in rats exposed to 75 mg Al/kg/day as aluminum citrate in the diet for 6 months; however, the statistical significance of these findings was not reported.

Several studies have shown that aluminum can adversely affect erythropoeisis. Intermediate-duration exposure has been associated with significant inhibition of colony forming units-erythroid (CFU-E) development in bone marrow of mice exposed to 13 mg Al/kg as aluminum citrate or aluminum chloride administered via gavage 5 days/week for 2 or 22 weeks (Garbossa et al. 1996), rats exposed to 27 mg

Al/kg as aluminum citrate administered via gavage 5 days/week for 15 weeks (Garbossa et al. 1998), rats exposed to 420 mg Al/kg/day as aluminum citrate in drinking water for 15 weeks (Garbossa et al. 1998), and rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months (Vittori et al. 1999); the aluminum content of the base diet was not reported in the Garbossa et al. (1996, 1998) studies. Chronic-duration studies did not examine this end point.

Musculoskeletal Effects. Joint pains were common symptoms reported in people in England who, for 5 days or more, consumed unknown levels of aluminum sulfate in drinking water which also contained elevated levels of copper and lead (Ward 1989). Osteomalacia has been observed in healthy individuals following long-term use of aluminum-containing antacids and in individuals with kidney disease. There are numerous case reports of osteomalacia and rickets in otherwise healthy infants and adults using aluminum-containing antacids for the treatment of gastrointestinal illnesses (i.e., ulcers, gastritis, colic) (Carmichael et al. 1984; Chines and Pacifici 1990; Pivnick et al. 1995; Woodson 1998). The aluminum in the antacids binds with dietary phosphorus and prevents its absorption resulting in hypophosphatemia and phosphate depletion. Osteomalacia, characterized by a softening of the bone and resulting in increased spontaneous fractures and pain, has been well documented in dialyzed uremic adults and children exposed to aluminum-contaminated dialysate or orally administered aluminum-containing phosphate-binding agents (Andreoli et al. 1984; Griswold et al. 1983; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989). Decreased aluminum urinary excretion caused by impaired renal function and possibly an increase in gastrointestinal absorption of aluminum (Alfrey 1993) results in increased aluminum body burden leading to markedly increased bone aluminum levels and the presence of aluminum between the junction of calcified and noncalcified bone. For more information on renal patients and aluminum, see Section 3.10.

Although long-term oral exposure to aluminum results in an increase in aluminum levels in the bone (Ahn et al. 1995; Konishi et al. 1996), there is no histological evidence that under normal physiological conditions that the accumulation of aluminum alters the bone structure. No histological alterations were observed in the tibias of male Wistar rats fed 100 mg Al/kg/day as aluminum lactate (aluminum levels in the base diet not reported) for 10 weeks (Konishi et al. 1996).

Hepatic Effects. No studies were located regarding hepatic effects of various forms of aluminum following intermediate- or chronic-duration exposure in humans. Hepatic dysfunction was reported in 1 of 15 people acutely exposed to unspecified amounts of aluminum phosphide (Khosla et al. 1988).

However, the toxicity, as noted above was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

Most animal studies did not find significant alterations in liver weights or liver histology following intermediate- or chronic-duration oral exposure. Hyperemia and periportal monocytic infiltrate were observed in the livers of female Sprague-Dawley rats given 133 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986). Mild hepatocyte vacuolation was found in male dogs exposed to 75 mg Al/kg/day in the diet for 26 weeks (Pettersen et al. 1990), but the study authors concluded that the hepatic effects probably resulted from a drastic reduction in food consumption and a decrease in body weight.

The remaining studies conducting liver histopathological examinations did not find significant alterations in rats exposed to 70 mg Al/kg/day as aluminum chloride in drinking water for 30, 60, or 90 days (Dixon et al. 1979), rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), mice exposed to 49 mg Al/kg/day as aluminum chloride in drinking water for 180 days (Ondreicka et al. 1966), dogs exposed to 88 mg Al/kg/day as aluminum phosphate in the diet for 6 months (Katz et al. 1984), mice exposed to 979 mg Al/kg/day as aluminum sulfate in the diet for 20 months (Oneda et al. 1994), or rats or mice exposed to 0.6 or 1.2 mg Al/kg/day as aluminum sulfate, respectively, in drinking water for a lifetime (Schroeder and Mitchener 1975a, 1975b). Only the Domingo et al. (1987b) and Ondreicka et al. (1966) studies included the levels of aluminum in the base diet.

Renal Effects. No studies were located regarding renal effects of various forms of aluminum following intermediate- or chronic-duration exposure in humans. Acute-duration oral exposure to aluminum phosphide has been shown to cause renal failure, significant proteinuria, and anuria in persons who ingested it either accidentally or in suicide attempts (Chopra et al. 1986; Khosla et al. 1988). However, toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

Several intermediate- or chronic-duration studies examined for possible effects on the kidneys; most studies did not find any adverse effects. Mild tubular “glomerularnephritis” was observed in dogs exposed to 75 mg Al/kg/day as sodium aluminum phosphate in the diet for 26 weeks (Pettersen et al. 1990); however, the study investigators did not consider this effect to be adverse because it was not accompanied by clinical evidence of kidney dysfunction. The effect may have been secondary to the

drastic reduction in feed intake and decreased body weight also observed in these dogs. No alterations in kidney histopathology were observed in rats exposed to 70 mg Al/kg/day as aluminum chloride in drinking water for 30–90 days (Dixon et al. 1979), rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), mice exposed to 49 mg Al/kg/day as aluminum chloride in drinking water for 180 days (Ondreicka et al. 1966), dogs exposed to 88 mg Al/kg/day as aluminum phosphate in the diet for 6 months (Katz et al. 1984), mice exposed to 979 mg Al/kg/day as aluminum sulfate in the diet for 20 months (Oneda et al. 1994), or rats or mice exposed to 0.6 or 1.2 mg Al/kg/day as aluminum sulfate, respectively, in drinking water for a lifetime (Schroeder and Mitchener 1975a, 1975b). With the exception of the Domingo et al. (1987b), Pettersen et al. (1990), and Ondreicka et al. (1966) studies, information on the levels of aluminum in the base diet was not reported.

Endocrine Effects. No studies were located regarding endocrine effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

No studies were located regarding endocrine effects of aluminum or its compounds following acute-duration exposure in animals. No organ weight or histological changes were observed in the thyroid, adrenal, or pituitary glands of male and female Beagle dogs that consumed up to 75 (Pettersen et al. 1990) or 88 (Katz et al. 1984) mg Al/kg/day as sodium aluminum phosphate in the diet for 6 months; the doses in the Katz et al. (1984) study do not include aluminum in the base diet.

Dermal Effects. No studies were located regarding dermal effects of various forms of aluminum following intermediate- or chronic-duration oral exposure in humans. Skin rashes were common symptoms reported by 48 people in England who consumed drinking water containing unknown levels of aluminum sulfate for approximately 5 days (Ward 1989). The water also contained elevated levels of copper and lead.

No studies were located regarding dermal effects of aluminum or its compounds following acute-duration exposure in animals. A localized loss of fur on the tip of the snout was observed in mice that ingested 130 mg Al/kg/day as aluminum lactate and base dietary aluminum for 6 weeks, but the effect was considered to be a sign of poor condition in the colony and not clearly attributable to aluminum exposure (Golub et al. 1989).

Ocular Effects. No studies were located regarding ocular effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

No studies were located regarding ocular effects of various forms of aluminum following acute-duration exposure in animals. No adverse ocular changes were found in male and female Beagle dogs that consumed up to 88 mg Al/kg/day as sodium aluminum phosphate in the diet for 6 months (Katz et al. 1984); these doses do not include aluminum in the base diet.

Body Weight Effects. No studies were located regarding body weight effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

Most studies have not found significant alterations in body weight gain in rats or mice following acute exposure to 73–192 mg Al/kg/day as aluminum lactate or aluminum hydroxide with citric acid (Bernuzzi et al. 1986; Domingo et al. 1989; Gomez et al. 1991; Misawa and Shigeta 1992), intermediate-duration exposure to 20–399 mg Al/kg/day as aluminum lactate, aluminum chloride, aluminum hydroxide, or aluminum nitrate (Bernuzzi et al. 1989b; Bilkei-Gorzo 1993; Domingo et al. 1987b; Donald et al. 1989; Golub et al. 1989, 1992b, 1995; Gomez et al. 1986; Greger and Donnaubauer 1986; Konishi et al. 1996; Ondreicka et al. 1966; Oteiza et al. 1989), or chronic-duration exposure to 0.6–979 mg Al/kg/day as aluminum nitrate with citric acid, aluminum lactate, or aluminum sulfate (Golub et al. 2000; Oneda et al. 1994; Roig et al. 2006; Schroeder and Mitchener 1975a, 1975b). Of the studies reporting reductions of body weight gain, many involved gestational and/or lactational exposure; significant decreases in body weight gain were observed in rats administered via gavage 409 mg Al/kg/day as aluminum hydroxide with citric acid on gestation days 6–15 (Gomez et al. 1991), rats administered via gavage 38 mg Al/kg/day as aluminum nitrate on gestation days 6–14 (Paternain et al. 1988), rats administered via gavage 70 mg Al/kg/day as aluminum chloride on gestation days 0–16 (Sharma and Mishra 2006), and mice exposed to 200 or 250 mg Al/kg/day aluminum lactate in the diet on gestation day 0 through lactation day 21 (Golub et al. 1987, 1992a). A decrease in body weight was also observed in aged rats exposed to 97 mg Al/kg/day as aluminum nitrate with citric acid for 100 days (Colomina et al. 2002) and rats administered via gavage 53 mg Al/kg/day as aluminum chloride for 30 days (Rajasekaran 2000). In a lifetime exposure study, Golub et al. (2000) reported a 20% decrease in body weight gain in female mice exposed to 100 mg Al/kg/day as aluminum lactate in the diet; however, in a separate group of mice similarly exposed to 100 mg Al/kd/day as aluminum lactate, no significant alterations in body weight gain were observed (Golub et al. 2000).

3.2.2.3 Immunological and Lymphoreticular Effects

There are limited data on the potential for aluminum to induce immunological effects in humans. Intermediate-duration exposure to 25 mg Al/kg/day as aluminum hydroxide in the form of an antacid suspension for 6 weeks did not affect immunoglobulin and interleukin concentrations or production, natural killer (NK) cells, or B- and T-lymphocyte populations or proliferation; a significant reduction in, primed cytotoxic T- cells (CD8+CD45R0+ population) was observed (Gräske et al. 2000). The toxicological significance of this finding in the absence of other alterations is not known.

Very few animal studies examined the potential immunotoxicity of aluminum. Intermediate-duration exposure of mice to 13 mg Al/kg/day as aluminum citrate administered via gavage 5 days/week for 22 weeks resulted in a significantly higher proliferation of lymph node cells and had no effect on spleen cell proliferation (Lauricella et al. 2001). This suggests that while aluminum might induce alterations in cell immune response, the stimulating or suppressing effects could depend on the dose, route of administration, exposure duration, or cell population. There is some evidence that developmental exposure to aluminum may adversely affect the immune system in young animals. A 19% increase in spleen weights, depressed spleen cell concentrations of interleukin-2, interferon-γ and tumor necrosis factor-α, and a deficiency of CD4+ cells in T-cell populations were observed in Swiss Webster mice exposed to aluminum from conception through 6 months of age (Golub et al. 1993). The maternal animals consumed 200 mg Al/kg/day as aluminum lactate in the diet from conception through lactation and the offspring were subsequently fed the same diet as the dams. Susceptibility to bacterial infection was increased in offspring of Swiss-Webster mice exposed to dietary aluminum lactate in a dose of 155 mg Al/kg from conception through 10 days of age, but not in 6-week-old mice exposed to 107 mg Al/kg/day for 6 weeks (Yoshida et al. 1989). Susceptibility to infection was evaluated by assessing survival following intravenous inoculation with *Listeria monocytogenes* at the end of the exposure periods.

No organ weight or histological changes in spleen and/or thymus were observed in female Sprague-Dawley rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), male Sprague-Dawley rats given 70 mg Al/kg/day as aluminum chloride in drinking water for 30, 60, or 90 days (Dixon et al. 1979), or male and female mice exposed to 979 mg Al/kg/day as aluminum potassium sulfate in the diet for 20 months (Oneda et al. 1994). The doses in all of the above studies except Lauricella et al. (2001), Dixon et al. (1979), and Oneda et al. (1994) include aluminum in the base diet.

The highest reliable NOAEL value and all reliable LOAEL values in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

The neurotoxicity of aluminum following oral exposure has been well established in humans with renal insufficiency and animals; however, it has not been adequately investigated in healthy humans. The human database consists of case reports of acute accidental or intentional exposure to aluminum, an acute exposure study in healthy individuals, studies of patients undergoing dialysis treatment, and studies examining the possible association between aluminum ingestion and Alzheimer's disease.

Memory loss, fatigue, depression, behavioral changes, and learning impairment were reported in five children who, over a 5-day period, consumed drinking water containing unknown levels of aluminum sulfate, which was accidentally placed in a water-treatment facility in England (Ward 1989). The water also contained elevated levels of copper and lead, a highly neurotoxic element, which leached from the plumbing systems due to the greater acidity of the water. Thus, the role of aluminum in the onset of the neurological symptoms is unclear. Acute-duration oral exposure to aluminum phosphide (19–157 mg Al/kg) caused altered sensorium in 4 of 16 persons who ingested it either accidentally or in suicide attempts (Khosla et al. 1988). Restlessness and loss of consciousness were observed in 10 of 15 people who ingested unknown amounts of aluminum phosphide (Chopra et al. 1986). The toxicity associated with aluminum phosphide ingestion was probably due to the formation of highly toxic phosphine gas rather than the aluminum exposure.

Uremic persons represent a population at risk for aluminum-related dementia (Alfrey 1993). Prolonged dialysis with aluminum-containing dialysates, possibly combined with oral treatment with aluminum hydroxide to control hyperphosphatemia, has produced a characteristic neurotoxicity syndrome which has been referred to as "dialysis dementia" (Alfrey 1987; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989). Alfrey (1993) describes two types of aluminum neurotoxicity in uremic patients: acute and classical. The acute form is caused by high levels of aluminum in the dialysate, the co-ingestion of aluminum-containing phosphate binders and citrate, or the rapid rise in serum aluminum following desferoxamine treatment. The onset of neurotoxicity is rapid and marked by confusion, muscle twitching, grand mal seizures, coma, and death. Plasma levels of aluminum are typically >500 μg/L; normal levels are approximately 1–3 μg/L (House 1992; Liao et al. 2004). The classical type results from chronic

parenteral or oral aluminum exposures and is characterized by a gradual onset of neurobehavioral disorders and, eventually, death. These neurological effects have been observed in adults and children (Alfrey 1993; Griswold et al. 1983). Plasma levels are estimated to be 100–200 μg/L. Limiting aluminum exposure in uremic persons (for example, the use of aluminum-free dialysates and aluminum-free phosphate binding agents) essentially eliminates these neurotoxic effects.

Alzheimer's disease is a neurodegenerative disorder, which is manifested clinically as a progressive deterioration of memory and cognition. The primary neuropathological characteristics of Alzheimer's disease are neuronal loss and the formation of neurofibrillary tangles, senile plaques with amyloid deposits and neuropil threads, and cerebrovascular amyloid deposition. The etiology of Alzheimer's disease is complex, with genetics playing a critical role; there is also evidence that the environment may modify the risk. The possible association between aluminum and Alzheimer's disease was proposed over 40 years ago; however, the evidence that aluminum may or may not be a risk factor is inconsistent and inconclusive. A number of lines of evidence have been used to support the relationship between aluminum and Alzheimer's disease (Flaten 2001; Munoz 1998); these include elevated levels of aluminum in the brains of individuals with Alzheimer's disease, the well-established neurotoxicity of aluminum, and epidemiology studies finding a geographical association between aluminum levels in drinking water and Alzheimer's disease. In the last 25 years, a number of epidemiology and animal studies have investigated this possible association; an animal model that fully mimics human Alzheimer's disease has not been identified. Many of the epidemiology studies have been criticized for flawed patient selection, poor comparability of exposed and control groups, poor exposure assessment, inaccurate diagnosis of Alzheimer's disease, and weak statistical correlations (Nieboer et al. 1995; Schupf et al. 1989). A number of these studies have found significant associations between individuals living in areas with elevated aluminum levels in drinking water and the prevalence of Alzheimer's disease (or a surrogate such as dementia or cognitive impairment) (Flaten 1990; Forbes et al. 1992, 1994; Gauthier et al. 2000; Jacqmin et al. 1994; Jacqmin-Gadda et al. 1996; Martyn et al. 1989; McLachlan et al. 1996; Michel et al. 1990; Neri and Hewitt 1991; Rondeau et al. 2000, 2001); the aluminum content of the water typically exceeded 0.10 mg Al/L. The odds ratios (or relative risks) were typically <2.0 (Flaten 1990; Jacqmin et al. 1994; Martyn et al. 1989; McLachlan et al. 1996; Neri and Hewitt 1991), although some studies, particularly studies that controlled for other risk factors such as age, education level, and family history of dementia, estimated higher odds ratios (Gauthier et al. 2000; Rondeau et al. 2000). In contrast, several studies did not find significant associations between aluminum exposure and the risk of Alzheimer's disease (or cognitive impairment (Forster et al. 1995; Martyn et al. 1997; Sohn et al. 1996;

Wettstein et al. 1991; Wood et al. 1988); the levels of aluminum in the drinking water were similar to the levels in studies finding positive associations.

Additionally, there are studies that examined the possible association between Alzheimer's disease and ingestion of aluminum from sources other than drinking water, particularly tea and antacids. The aluminum levels in tea are typically 10–50 times higher than levels found in drinking water; similarly, the levels of aluminum in antacids (typically containing aluminum hydroxide) are very high compared to drinking water levels. No significant associations between tea consumption (Forster et al. 1995; McDowell et al. 1994) or antacid use (Amaducci et al. 1986; Broe et al. 1990; Colin-Jones et al. 1989; Forster et al. 1995; Graves et al. 1990; Heyman et al. 1984; McDowell et al. 1994) and Alzheimer's disease have been found. A small scale study did find a significant relationship between consumption of food containing aluminum additives and the risk of Alzheimer's disease (Rogers and Simon 1999); however, this was based on a very small number of cases. The contrast between the results of the drinking water studies, many of which found a weak association between living in areas with high aluminum levels in drinking water and Alzheimer's disease, and the tea and antacid studies may be due to the difference in aluminum bioavailability. The presence of tannins and other organic constitutes found in tea may significantly reduce aluminum absorption; the aluminum hydroxide found in antacids is poorly absorbed. Although the aluminum speciation was not provided in most drinking water studies, in a study by Gauthier et al. (2000), organic monomeric aluminum was the only aluminum species significantly associated with Alzheimer's disease. The bioavailability of organic aluminum compounds such as aluminum citrate, aluminum lactate, and aluminum maltolate is much greater than for inorganic aluminum compounds (Froment et al. 1989a; Yokel and McNamara 1988).

In conclusion, the available data suggest that aluminum is not likely the causative agent in the development of Alzheimer's disease. However, aluminum may play a role in the disease development by acting as a cofactor in the chain of pathological events resulting in Alzheimer's disease (Flaten 2001).

Amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia (PD) are neurodegenerative diseases that have also been associated with aluminum exposure. ALS is a progressive disease of the central nervous system that is characterized by an accumulation of neurofibrillary tangles. In Guam, Southwest New Guinea, and the Kii Peninsula of Honshu Island in Japan, there is an unusually high prevalence of ALS and PD. This may be related to the natural abundance of highly bioavailable aluminum compounds coupled with the virtual lack of magnesium and calcium in the areas' drinking water supplies and soil. The consumption of the neurotoxic seed of the false sago palm tree may also play a key role in the

prevalence of ALS and PD in these areas. It has been proposed that long-term dietary deficiencies of calcium, rendering a secondary hyperparathyroid state, in the presence of highly bioavailable aluminum compounds and enhanced gastrointestinal absorption of aluminum can result in neuronal degeneration. In a study designed to evaluate effects of high aluminum and low calcium levels in the diet, much like the conditions associated with Guam and other similar areas, Cynomolgus monkeys were placed on a low calcium diet either with or without supplemental aluminum and manganese (Garruto et al. 1989). Chronic calcium deficiency alone produced neurodegenerative effects, although neurofibrillary changes were most frequently seen in the monkey on a low calcium diet supplemented with aluminum and manganese.

There are limited data on the neurotoxicity of ingested aluminum in healthy individuals. An acute exposure study conducted by Molloy et al. (2007) did not find any significant alterations in performance in neurobehavioral tests with a mean aluminum blood level of 280–300 μg/L at the time of testing. Although neurotoxicity of aluminum has not been established or adequately studied in people who are healthy (i.e., have normal renal function), there is conclusive evidence that aluminum compounds are neurotoxic in orally-exposed animals. As discussed below and in Section 3.2.2.6, numerous intermediate-duration studies in mice and rats found various neurotoxic effects in exposed adults and developing offspring.

Many of the animal neurotoxicity studies are complicated by a lack of reported information on aluminum content in the base diet. This is an important issue because, as discussed in the introduction to Section 3.2.2, commercial rodent laboratory feed has a high aluminum content which can significantly contribute to total exposure. Dosages in studies with insufficient information on aluminum content in the base diet therefore must be assumed to underestimate the actual experimental dosages. The magnitude of the underestimate may be considerable, particularly for maternal dietary intake during lactation (an exposure period used in many neurobehavioral studies of aluminum in mice), which can be markedly (often 2-fold) higher than in nonlactating adults. Consequently, although aluminum studies with inadequate data on base dietary levels of aluminum provide useful information on neurotoxicity, NOAELs and LOAELs from these studies cannot be assumed to be accurate and are not suitable for comparing with effect levels from studies that used diets with known amounts of aluminum. There is particular concern for the adequacy of neurotoxicity NOAEL and LOAEL values for aluminum because sensitive neurotoxic effects may occur in rodents at aluminum intake levels close to those provided by commercial diet alone. Based on these concerns, only neurotoxicity studies providing information on base dietary aluminum content are included in Table 3-2.

In general, oral exposure to aluminum is not associated with marked signs of neurotoxicity in animals. In a study by Golub et al. (1987), ataxia, splaying and dragging of hindlimbs, and paralysis were observed in mouse dams exposed to 200 mg Al/kg/day as aluminum lactate during gestation and lactation. Other studies involving exposure to higher aluminum doses have not noted significant increases in the incidence of overt signs of neurotoxicity (Donald et al. 1989; Golub et al. 1992a). It is possible that the levels of essential trace minerals in the diet used by Golub et al. (1987) were too low and may have contributed to the severity of the observed effects. The diet formulation used by this group was revised by adding a "more generous provision" of several essential nutrients, particularly trace minerals (including calcium, magnesium, phosphate), to avoid the marked maternal neurotoxicity associated with their absence in the original diet (Donald et al. 1989). Due to the apparent nutritional insufficiency of the diet used by Golub et al. (1987), the results of this study are not included in Table 3-2. Another overt sign of toxicity is an increase in cage mate aggression in male mice exposed to 200 mg Al/kg/day from gestation day 1 through postnatal day 170 (Golub et al. 1995).

The overall weight of evidence strongly indicates that oral exposure to aluminum results in functional and cognitive alterations. Motor function and sensory function are affected by aluminum exposure. Decreases in forelimb and/or hindlimb grip strength have been observed in mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993) or 13 weeks (Golub et al. 1992b; Oteiza et al. 1993) and in mice exposed to 100 mg Al/kg/day for over 2 years (Golub et al. 2000). In contrast, no alterations in grip strength were observed in mouse dams exposed to 250 mg Al/kg/day (Golub et al. 1992a) or 330 mg Al/kg/day (Donald et al. 1989) as aluminum lactate in the diet on gestation day 1 through lactation day 21 or in mice exposed to 200 mg Al/kg/day on gestation day 1 through postnatal day 170 (Golub et al. 1995). No significant alterations have been observed for footsplay or negative geotaxis following intermediate duration exposure to 195 mg Al/kg/day or 200 mg Al/kg/day as aluminum lactate in the diet (Golub et al. 1992b, 1995; Oteiza et al. 1993) or mouse dams exposed to 250 mg Al/kg/day (Golub et al. 1992a) or 330 mg Al/kg/day as aluminum lactate in diet on gestation day 1 through lactation day 21 (Donald et al. 1989). A chronic-duration study found impaired performance on the negative geotaxis test after 18 months of exposure to 100 mg Al/kg/day as aluminum lactate in the diet, but not after 24 months of exposure (Golub et al. 2000).

Significant decreases in spontaneous motor activity have also been reported in rats and mice exposed to aluminum chloride or aluminum lactate in the diet for at least 6 weeks. Effects are typically observed at doses of 130 mg Al/kg/day and higher. A decrease in total spontaneous activity, vertical activity

(rearing), and horizontal activity were observed in mice exposed to 130 mg Al/kg/day for 6 weeks (Golub et al. 1989). In mice exposed to 195 mg Al/kg/day, decreases in total activity, horizontal activity, and percentage of intervals with high activity counts were found after 90 days of exposure, but not after 45 days of exposure (Golub et al. 1992b). Decreases in spontaneous motor activity have also been observed in rats exposed to aluminum chloride in the diet for 7 weeks or 11 months (Commissaris et al. 1982); the amounts of aluminum added to the diet were 184 and 66 mg Al/kg/day, respectively; however, the aluminum content of the basal diet was not reported. Gavage exposure to a relatively low dose (53 mg Al/kg/day as aluminum chloride; aluminum content of the diet not reported) was also associated with a decrease in spontaneous motor activity. Exposure to lower doses of aluminum lactate or aluminum nitrate (with added citric acid) has not been associated with decreases in motor activity. No alterations in motor activity (as assessed in open field tests) were found in rats exposed to 97 mg Al/kg/day for 100 days (Colomina et al. 2002), 125 mg Al/kg/day for 6.5 months (Domingo et al. 1996), or 103 mg Al/kg/day for 1 or 2 years (Roig et al. 2006). Similarly, no alterations in total activity or horizontal activity were observed in mice exposed to 100 mg Al/kg/day as aluminum lactate in the diet during gestation, lactation, and postnatally until 2 years of age (Golub et al. 2000). However, the investigators noted that the automated activity monitor used in this study did not detect vertical movement of the older rats and that their previous study (Golub et al. 1989) found that vertical movement was more sensitive than horizontal movement. Another chronic-duration study (Roig et al. 2006) found no significant alterations in the total distance traveled or the total number of rearings in rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (citric acid added) from gestation day 1 through 2 years of age. Exposure to doses as high as 1,252 mg Al/kg/day as aluminum hydroxide (aluminum content of the basal diet was not reported) for 30 or 60 days (Thorne et al. 1986, 1987); the poor absorption of aluminum hydroxide probably contributed to this very high NOAEL.

Several tests of sensory function have resulted in significant alterations. Decreases in thermal sensitivity were observed following chronic exposure of mice to 100 mg Al/kg/day as aluminum lactate in the diet (Golub et al. 2000). Changes in thermal sensitivity was not observed in mice exposed to 195 mg Al/kg/day as aluminum lactate for 5–7 weeks (Oteiza et al. 1993) or 13 weeks (Golub et al. 1992b) or mouse dams exposed to 250 mg Al/kg/day (Golub et al. 1992a) or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Donald et al. 1989). As with thermal sensitivity, conflicting results have been observed for startle responsiveness. Decreased responses to auditory and/or air puff stimuli were observed in mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993) or 90 days (Golub et al. 1992b). However, no changes in startle responsiveness were observed in mice exposed to 250 or 330 mg Al/kg/day as

aluminum lactate in the diet on gestation day 1 through lactation day 21 (Donald et al. 1989; Golub et al. 1992a). Impairment of post-rotatory nystagmus was observed in rats exposed to 43.1 mg Al/kg/day as aluminum chloride in drinking water (dietary aluminum levels not reported) for 3 months; no alterations were observed at 21.5 mg Al/kg/day (Mameli et al. 2006).

The potential effect of aluminum on cognitive function has been assessed in a number of studies using passive avoidance, operant training, or water maze tests. Aluminum does not appear to adversely affect performance on passive avoidance or operant training tests at lower oral doses. No significant alterations have been observed in rats exposed to 97 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 100 days (Colomina et al. 2002), rats exposed to 125 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 6.5 months (Domingo et al. 1996), or rats exposed to 830 mg Al/kg/day or as high as 1,252 mg Al/kg/day as aluminum hydroxide in the diet (aluminum levels of basal diet were not reported) for 60 or 30 days, respectively (Thorne et al. 1987). Another study found improved performance on operant training tasks in mice exposed to 100 mg Al/kg/day in the diet for an intermediate duration (Golub and Germann 1998); the authors attributed this to an increase in food motivation in the aluminum-exposed mice. It is not known if an increased food motivation also influenced the results of the other studies. At higher aluminum doses, performance on operant training tasks is adversely affected. Impaired retention of learned responses were observed in rats exposed to 346 mg Al/kg/day as aluminum sulfate in the drinking water (aluminum content of the diet was not reported) (Connor et al. 1989) or 70 mg Al/kg/day as aluminum chloride in drinking water (aluminum content of the basal diet was not reported) for 90 days (Zhang et al. 2003). Another study found impaired learning (more trials were needed to reach the acquisition criterion), but no effect on retention or recall in rats exposed to 66 mg Al/kg/day as aluminum chloride in the diet (aluminum content of the basal diet was not reported) (Commissaris et al. 1982).

Because maze tests did not typically involve a food reward, these studies controlled for the potential confounder of food motivation. Impaired learning in a labyrinth maze test was observed in rats receiving gavage doses of 6 mg Al/kg/day as aluminum chloride or 35 mg Al/kg/day as aluminum hydroxide with citric acid (aluminum content of the diet was not reported) for 90 days (Bilkei-Gorzo 1993). In Morris water maze tests, impaired learning and memory was observed following gavage doses of 500 mg Al/kg/day of an unreported aluminum compound for 90 days (Jing et al. 2004). In contrast, no significant alterations in performance on the water maze test were found in rats exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water for a chronic duration (Roig et al. 2006).

A number of studies have conducted histopathological examinations of the brain of rats, mice, and dogs following oral exposure to aluminum and have not found significant alterations (Dixon et al. 1979; Domingo et al. 1987b; Gomez et al. 1986; Katz et al. 1984; Oneda et al. 1994; Pettersen et al. 1990); the aluminum doses ranged from 70 to 979 mg Al/kg/day. In contrast to these results, Abd El-Rahman (2003) reported spongioform changes in the neurons of the hippocampus, nuclear deformity, neurofibrillary degeneration, and foci of demyelination in rats receiving gavage doses of 85.9 mg Al/kg/day as aluminum sulfate (aluminum content of the diet was not reported).

Neurotoxicity has been extensively studied in developing mice and rats that were exposed to aluminum during gestation, lactation, and/or directly via diet following weaning. As summarized in Section 3.2.2.6, effects on reflexes and simple motor behaviors were commonly found in aluminum-exposed developing animals, whereas effects on learning and memory have not been consistently shown.

All reliable NOAEL and LOAEL values for neurological effects in adults in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

Several studies evaluated reproductive effects of acute-duration oral exposure to aluminum in animals. An increased incidence of resorptions occurred in female BALB/c mice treated with 41 mg Al/kg/day as aluminum chloride by gavage (aluminum in base diet not reported) on gestation days 7–16 (Cranmer et al. 1986). No reproductive effects were observed in female Sprague-Dawley rats exposed to 158 mg Al/kg/day as aluminum hydroxide or aluminum citrate by gavage and base diet from gestation day 6 to 15 (Gomez et al. 1991), or in THA rats treated with 73.1 mg Al/kg/day as aluminum chloride by gavage (aluminum in base diet not reported) from gestation day 7 to 16 (Misawa and Shigeta 1992). In a study of female reproductive system development (Agarwal et al. 1996), offspring of rats that were gavaged with aluminum lactate on gestation days 5–15 showed a transient irregularity of the estrus cycle (increased number of abnormal cycle lengths) at 250 mg Al/kg/day; doses as high as 1,000 mg Al/kg/day did not affect other end points (gonad weights, anogenital distance, time to puberty, duration of induced pseudopregnancy, or numbers of superovulated oocytes). The inconsistent findings summarized above may reflect differences in susceptibility among different strains/species of animals or compound

differences in toxicity or bioavailability. Additionally, because levels of aluminum in the base diet were not reported by Agarwal et al. (1996), Misawa and Shigeta (1992), or Cranmer et al. (1986), the doses in these studies are likely to underestimate actual aluminum intake.

In a combination acute- and intermediate-duration study, no adverse effects on fertility or other general reproductive indices were found in female rats that were exposed to 38–77 mg Al/kg/day as aluminum nitrate by gavage and base diet for 14 days prior to mating with males that were similarly treated for 60 days pre-mating (Domingo et al. 1987c). These exposures were continued throughout mating, gestation, parturition, and weaning and caused a reduction in the growth of the offspring in all treated groups, but the effects were negligible and transient (slight decreases in body weight, body length, and tail length observed on postpartum days 1 and 4 were no longer evident at time of weaning). An intermediate-duration oral study in male rats found that sperm count was decreased following exposure to 2.5 mg Al/kg/day as aluminum chloride for 6–12 months (Krasovskii et al. 1979). The method of oral exposure was not specified but is presumed to be gavage, no information on aluminum in the base diet was reported, and reproductive function was not evaluated. No adverse reproductive effects were seen in male Sprague-Dawley rats, as assessed by plasma gonadotropin levels, histopathological evaluation, and serial matings, following exposure to 70 mg Al/kg/day as aluminum chloride in drinking water for up to 90 days (Dixon et al. 1979); this dose does not include base dietary aluminum.

Mating success (numbers of litters and offspring) was not affected in a three-generation study with Dobra Voda mice that were exposed to 49 mg Al/kg/day as aluminum chloride in drinking water and base diet over a period of 180–390 days (Ondreicka et al. 1966). No reproductive effects were observed in pregnant Swiss Webster mice that consumed 250 mg Al/kg/day as aluminum lactate throughout gestation and lactation (Golub et al. 1992a). However, an alteration in gestation length was observed in pregnant Swiss Webster mice that consumed 155 mg Al/kg/day as aluminum lactate in the diet during gestation and lactation (Donald et al. 1989). The effect on gestation length was small but statistically significant; all litters in the control group (7.5 mg Al/kg/day) were born on gestation day 18, whereas 4 of 17 litters exposed to ≥155 mg Al/kg/day were born earlier or later (gestation days 17, 19, or 20).

No organ weight or histological changes were observed in the gonads of male and female Beagle dogs that consumed 93 mg Al/kg/day as acidic sodium aluminum phosphate (a common human food additive) in the diet for 6 months (Katz et al. 1984); this dose does not include base dietary aluminum. In another study with dogs, two of four male Beagles that were fed 75 mg Al/kg/day as basic sodium aluminum phosphate and base dietary aluminum for 26 weeks had decreased testicular weight and moderate

seminiferous tubule germinal epithelial cell degeneration and atrophy (Pettersen et al. 1990). No changes in reproductive tissue weight or histology occurred in the males at lower doses (≤27 mg Al/kg/day) or in female Beagles similarly exposed to ≤80 mg Al/kg/day. The investigators concluded that the testicular changes appeared to be secondary to palatability-related reductions in food consumption and body weight, and therefore, are not clearly direct effects of aluminum.

Chronic studies showed no histological changes in the testes or ovaries of male and female Wistar rats fed a diet containing unspecified levels of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972), or in B6C3F1 mice that ingested 979 mg Al/kg/day as dietary aluminum potassium sulfate for 20 months (Oneda et al. 1994). The doses in the latter study do not include aluminum in the base diet. Neither mouse study assessed reproductive function.

The highest reliable NOAEL and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects of various forms of aluminum following acute- or chronic-duration oral exposure in healthy humans. The only human data on developmental effects come from infants with renal failure and premature infants. Their responses are probably not indicative of responses expected in normal infants. Osteomalacia and increased bone and serum levels of aluminum were reported in three infants with kidney failure who had been treated orally with >100 mg of Al/kg/day as aluminum hydroxide from the first or sixth month of life (Andreoli et al. 1984; Griswold et al. 1983), and in healthy infants ingesting aluminum-containing antacids (Pivnick et al. 1995). Progressive encephalopathy was also observed among children with severe renal disease ingesting aluminum-containing phosphate binders (Finberg et al. 1986; Griswold et al. 1983).

A large number of studies have examined the developmental toxicity of aluminum in rats and mice. A variety of effects have been found including decreased pup survival/increased pup mortality, decreased growth, delayed maturation, and impaired neurodevelopment. Increases in pup mortality, typically occurring within the first 4 postnatal days, have been observed in rats exposed to 155 mg Al/kg/day as aluminum chloride in the diet on gestational days 8–20 (Bernuzzi et al. 1986), 200 mg Al/kg/day as aluminum lactate administered via gavage on postnatal days (PND) 5–14 (Bernuzzi et al. 1989a), and 272 mg Al/kg/day as aluminum chloride or 378 mg Al/kg/day as aluminum lactate in the diet on gestation

days 1–20. Interpretation of the results of these studies is limited by the lack of information on the aluminum content of the basal diet. Another study found a decrease in the number of live pups per litter and an increase in the number of dead young per litter on PND 21 in the offspring of rats administered via gavage 51 mg Al/kg/day as aluminum nitrate for 14 days prior to mating, on gestation days 1–20, and lactation days 1–21 (Domingo et al. 1987c). The gavage administration route may have influenced the results of this study; other studies involving exposure to aluminum nitrate, aluminum citrate, or aluminum lactate via drinking water or diet have not reported increases in mortality at doses as high as 330 mg Al/kg/day as aluminum lactate in the diet on gestation days 1 through PND 35 (Colomina et al. 1992, 2005; Golub and Germann 1998, 2001; Golub et al. 1992a, 1995; McCormack et al. 1979).

Numerous studies have reported decreases in pup body weight gain (Bernuzzi et al. 1986, 1989a, 1989b; Colomina et al. 2005; Domingo et al. 1987a, 1987c, 1989; Golub and Germann 2001; Golub et al. 1992a; Gomez et al. 1991; Misawa and Shigeta 1992; Paternain et al. 1988; Sharma and Mishra 2006). Since some of these studies did not report the aluminum content of the basal diet, their usefulness in establishing dose-response relationships is limited. With few exceptions, most studies have shown that aluminum does not adversely affect birth weight in the absence of effects on maternal body weight (Colomina et al. 2005; Domingo et al. 1989; Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1992a, 1995; Gomez et al. 1991; McCormack et al. 1979). The possible exception to this finding was decreases in birth weight observed in the offspring of rats administered aluminum nitrate via gavage at doses of ≥38 mg Al/kg/day on gestation day 1 through lactation day 21 (Domingo et al. 1987c) or 77 mg Al/kg/day on gestation day 14 through lactation day 21 (Domingo et al. 1987a); neither study reported whether there were significant effects on maternal body weight gain. Paternain et al. (1988) also reported a decrease in pup body weight in rats receiving gavage doses of 38 mg Al/kg/day as aluminum nitrate on gestation days 6–14; a decrease in maternal weight gain was also reported at this dose level. Although most studies did not find effects on birth weights, several studies did find decreases in post-birth pup body weights; however, this finding was not consistent across studies. Lower pup body weights starting on PND 10 were observed in mouse pups exposed to aluminum during gestation only, during lactation only, or during gestation and lactation (Golub et al. 1992a); a decrease in maternal body weight gain was observed in the dams exposed during lactation. This study suggests that aluminum may influence growth directly and may not be only related to changes in maternal body weight during lactation. Similarly, decreases in body weights were observed on PND 12, 16, and 21 in the pups exposed to 100 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid) on gestation day 1 through lactation day 21; a decrease in maternal food and water intake was also observed at this dose level (Colomina et al. 2005). A third study found decreases in pup body weight at PND 21 in

mice exposed to 130 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 2001). The lower body weights were still present at 5 months of age even though aluminum exposure was stopped on PND 35; an increase in food intake was also observed in these animals. In contrast to these studies, no adverse effects on body weight were observed in mouse pups exposed to 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 21 or 35 (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1995).

Gestational exposure to aluminum does not appear to result in an increase in the occurrence of malformation and anomalies, although reductions in ossification have been observed (Gomez et al. 1991; Sharma and Mishra 2006). Delays in ossification were observed at doses that also resulted in decreases in pup body weight. Some alterations in physical maturation have been observed in rats exposed to aluminum nitrate in drinking water (with added citric acid) on gestation day 1 through lactation day 21 (Colomina et al. 2005). The observed effects included significant delay in vagina opening at 53 or 103 mg Al/kg/day, testes descent at 103 mg Al/kg/day, and incisor eruption in males at 53 mg Al/kg/day. No effects on days to pinna detachment or eye opening were observed. No delays on pinna detachment, eye opening, or incisor eruption were observed in rats administered via gavage 73 mg Al/kg/day as aluminum chloride (aluminum content of the diet not reported) on gestation days 8–20 (Misawa and Shigeta 1992).

Animal studies provide strong evidence that gestational and/or lactational exposure to aluminum impairs the development of the nervous system. Potential neurodevelopmental effects have been evaluated using a variety of functional tests and cognitive tests. Because comparisons between studies are difficult due to differences in the exposure period, subroute of exposure, lack of information on the aluminum levels in the basal diet, and age of assessment, the results for each test will be presented separately. Significant impairment in the righting reflex and grasping reflex were observed in rat pups exposed to 272 mg Al/kg/day as aluminum chloride or 194 mg Al/kg/day as aluminum lactate in the diet (aluminum content of the basal diet was not reported) on gestation days 1–20 (Bernuzzi et al. 1989b); no reflex alterations were observed at 96 mg Al/kg/day for aluminum chloride or aluminum lactate. Impairment of the righting reflex was also observed in the offspring of rats exposed to 155 mg Al/kg/day as aluminum chloride on gestation days 8–20 (Bernuzzi et al. 1986); grasping reflex was not significantly affected at this dose level or at 192 mg Al/kg/day. Exposure of pups to gavage doses of 300 mg Al/kg/day as aluminum lactate on PND 5–14 did not adversely affect the grasping reflex (Bernuzzi et al. 1989a). Righting reflex was also not affected in pups exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005).

Four studies examined temperature sensitivity; increases in sensitivity were observed in the offspring of mice exposed to 250 mg Al/kg/day as aluminum lactate in the diet on lactation days 1–21 (Golub et al. 1992a) or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 42 (Golub et al. 1995). No effects were observed in mice exposed to 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lacation day 21 or to 250 mg Al/kg/day as aluminum lactate in the diet on gestation days 1–21 (Golub et al. 1992a).

A variety of motor function tests have been used to assess neurodevelopmental toxicity. Dosing pups with 300 mg Al/kg/day as aluminum lactate on PND 5–14 resulted in impairment of the suspension test and locomotor coordination (Bernuzzi et al. 1989a). Locomotor coordination was also altered in rat offspring exposed to 399 mg Al/kg/day as aluminum chloride in the diet on gestation days 1–20 (Bernuzzi et al. 1989b). No effects on the suspension test or locomotor coordination were observed in the offspring of rats exposed to 192 mg Al/kg/day as aluminum chloride in the diet on gestation days 8–20 (Bernuzzi et al. 1986). No information on the aluminum content of the basal diet was reported in the Bernuzzi studies. Alterations in the performance on the negative geotaxis test were found in mouse pups exposed to 250 mg Al/kg/day as aluminum lactate in the diet on lactation days 1–21 (Golub et al. 1992a) and in rat pups exposed to 399 mg Al/kg/day as aluminum chloride in the diet on gestation days 1–20 (Bernuzzi et al. 1989b), 200 mg Al/kg/day as aluminum lactate administered to pups on PND 5–14 (Bernuzzi et al. 1989a), or 155 mg Al/kg/day as aluminum chloride in the diet on gestation days 8–20 (Bernuzzi et al. 1986). No alterations in negative geotaxis results were found in mice exposed to 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 21 (Donald et al. 1989; Golub et al. 1995) or in rat pups exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water (citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005).

Exposure to aluminum during gestation and/or lactation has consistently resulted in decreases in forelimb and/or hindlimb grip strength. Decreases in grip strength have been observed in mice exposed to 155 mg Al/kg/day as aluminum lactate in diet on gestation day 1 through lactation day 21 (Donald et al. 1989; Golub et al. 1995), 250 mg Al/kg/day as aluminum lactate on gestation days 1–21 or lactation days 1–21 (Golub et al. 1992a), or 130 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 2001) and in rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (with citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005). In other motor tests, increases in the number of rotations on a rotorod and a shorter latency to fall in a wire suspension test were observed in mice exposed to 260 or 130 mg Al/kg/day, respectively, as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 2001). Foot splay

has been observed in the mice exposed to 155 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Donald et al. 1989), but not in mice exposed to 250 mg Al/kg/day as aluminum lactate in the diet on gestation days 1–21 or lactation days 1–21 (Golub et al. 1992a). In open field tests of motor activity, significant delays in pivoting, longer latencies, and more rearings were observed in the offspring of rats administered via gavage 73 mg Al/kg/day as aluminum chloride (aluminum content of the diet was not reported) (Misawa and Shigeta 1992). No effect on open field tests were observed in rat pups exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005).

Cognitive function effects were evaluated in passive avoidance tests, operant conditioning tests and water maze tests. No adverse effects were observed in operant conditioning tests in mice exposed to 155 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Golub et al. 1995) or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 1998) and in passive avoidance tests in rats exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid) on gestation day 1 through lactation day 21 (Colomina et al. 2005). The studies in mice noted that the aluminum-exposed pups often performed better than the controls; this may be due to an increase in food motivation in the aluminum-exposed rats rather than a direct effect on cognitive function. Impaired learning, as measured using the Morris water maze, was observed in mice exposed to 260 mg Al/kg/day as aluminum lactate in the diet from gestation day 0 to PND 21 and on PND 21–35 (tested at 90 days of age) (Golub and Germann 2001). When the salient and nonsalient cues were rotated, an increase in the escape latency was found at 130 and 260 mg Al/kg/day. The investigators found exposure to >130 mg Al/kg/day resulted in differences in how the mice used the salient and nonsalient cues; no effects were observed at 26 mg Al/kg/day. A study in rats exposed to 103 mg Al/kg/day (Colomina et al. 2005) did not find any significant effects in the water maze test. However, this study did not use probe trials; the alteration observed in the Golub and Germann studies were detected in the probe trials.

The highest reliable NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding cancer in humans after oral exposure to various forms of aluminum.

Animal bioassays have found no conclusive evidence for carcinogenicity of aluminum. Significantly increased incidences of gross tumors were reported for Long Evans rats (only in males) and Swiss mice (only in females) given 0.6 or 1.2 mg Al/kg/day as aluminum potassium sulfate in drinking water, respectively, for 2–2.5 years (Schroeder and Mitchener 1975a, 1975b). Aluminum levels in the base diet were not reported in these studies, although the animals were fed a low-metal diet in metal-free environmental conditions. At gross necropsy, 13/25 (52%) aluminum-treated male rats were found to have tumors compared to 4/26 (15.4%) controls. Six of the tumors in the aluminum-treated males were malignant compared to two malignancies in the control rats. The incidences of gross tumors in the female mice were 19/41 (46.3%) and 14/47 (29.8%) in exposed and control groups, respectively. The incidence of "lymphoma leukemia" was significantly increased (10/41 versus 3/47 in controls) in the female mice. A dose-response relationship could not be determined for either species because only one aluminum dose was used and the types of tumors and organs in which they were found were not specified. Very few study details were reported in this paper and it is unclear if the investigators grouped several types of tumors into the "lymphoma leukemia" category. Another study in rats (Wistar) found no increase in the incidence of neoplasms in male and female rats fed diets containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972).

There were no exposure-related increased incidences of tumors, other proliferative lesions or nonneoplastic lesions in 60 male or 60 female B6C3F1 mice that ingested ≤979 mg Al/kg/day as aluminum potassium sulfate in the diet for 20 months (Oneda et al. 1994). The level of aluminum in the base diet was not reported. The incidence of spontaneous hepatocellular carcinoma was significantly decreased in the high-dose males (5.5% compared to 20.5% in controls).

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to various forms of aluminum.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, ocular, body weight, or metabolic effects in humans or animals after dermal exposure to various forms of aluminum.

The highest NOAEL values and all LOAEL values for dermal exposure from each reliable study for systemic effects in each species and duration category for aluminum are shown in Table 3-3.

Musculoskeletal Effects. Information on potential musculoskeletal effects associated with dermal exposure of aluminum is limited to a case report of a woman reporting bone pain after a 4-year exposure to aluminum chlorhydrate in antiperspirant (Guillard et al. 2004). No osseous abnormalities were detected via radiography, and C-reactive protein levels and bone-specific serum parameters (alkaline phosphatase, γ-glutamyl transferase, calcium, phosphate) were within reference ranges; however, plasma aluminum levels were approximately 10 times higher than reference levels. Termination of aluminum exposure resulted in decreases in plasma aluminum levels and a disappearance of bone pain.

No studies were located regarding musculoskeletal effects in animals following dermal exposure to aluminum.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to various forms of aluminum. Aluminum compounds are widely used in antiperspirants without harmful effects to the skin or other organs (Sorenson et al. 1974). Some people, however, are unusually sensitive to topically applied aluminum compounds. Skin irritation was reported in subjects following the application of aluminum chloride hexahydrate in ethanol used for the treatment of axillary or palmar hyperhidriosis (excessive sweating) (Ellis and Scurr 1979; Goh 1990) or the use of a crystal deodorant containing alum (Gallego et al. 1999).

No studies were located regarding dermal effects in animals following intermediate- or chronic- duration dermal exposure to various forms of aluminum.

Skin damage has been observed in female TF_1 Carworth mice, New Zealand rabbits, and Large White pigs following the application of 10% aluminum chloride (0.005–0.1 g Al) or aluminum nitrate (0.006–0.013 g Al) for 5 days; but not from aluminum sulfate, hydroxide, acetate, or chlorhydrate (Lansdown 1973). The damage consisted of hyperplasia, microabscess formation, dermal inflammatory cell infiltration, and occasional ulceration. These results suggest that the development of adverse dermal effects from exposure to aluminum depends upon its chemical form.

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
ACUTE EXPOSURE									
Systemic									
Mouse (TFI)	5 d 1 x/d	Dermal	2.5 F Percent (%)	5 F Percent (%)	(slight to moderate hyperplasia)	25 F Percent (%)	(severe hyperplasia with focal ulceration)	Lansdown 1973 Aluminum chloride	
Mouse (TFI)	5 d 1 x/d	Dermal	25 F Percent (%)					Lansdown 1973 Aluminum chlorhydrate	
Mouse (TFI)	5 d 1 x/d	Dermal	10 F Percent (%)					Lansdown 1973 Aluminum sulfate	
Mouse (TFI)	5 d 1 x/d	Dermal		10 F Percent (%)	(epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)			Lansdown 1973 Aluminum chloride	
Mouse (TFI)	5 d 1 x/d	Dermal	10 F Percent (%)					Lansdown 1973 Aluminum hydroxide	
Mouse (TFI)	5 d 1 x/d	Dermal	10 F Percent (%)					Lansdown 1973 Aluminum acetate	

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Mouse (TFI)	5 d 1 x/d	Dermal		10 F Percent (%)	(epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Aluminum nitrate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Aluminum chloride	
Rabbit (New Zealand)	5 d 1 x/d	Dermal	25 Percent (%)				Lansdown 1973 Aluminum acetate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal	10 Percent (%)				Lansdown 1973 Aluminum sulfate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal	10 Percent (%)				Lansdown 1973 Aluminum hydroxide	

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Rabbit (New Zealand)	5 d 1 x/d	Dermal	10 Percent (%)				Lansdown 1973 Aluminum acetate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Aluminum nitrate	
Pig (Large White)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Aluminum chloride	
Pig (Large White)	5 d 1 x/d	Dermal	25 Percent (%)				Lansdown 1973 Aluminum chlorhydrate	
Pig (Large White)	5 d 1 x/d	Dermal	10 Percent (%)				Lansdown 1973 Aluminum sulfate	
Pig (Large White)	5 d 1 x/d	Dermal	10 Percent (%)				Lansdown 1973 Aluminum hydroxide	

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Pig (Large White)	5 d 1 x/d	Dermal	10 F Percent (%)				Lansdown 1973 Aluminum acetate	
Pig (Large White)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Aluminum nitrate	

d = day(s); F = female; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; x = time(s)

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological/lymphoreticular effects in humans after intermediate- or chronic-duration dermal exposure to various forms of aluminum.

Several children and one adult who had previous injections of vaccines or allergens in an aluminum-based vehicle showed hypersensitivity to aluminum chloride in a patch test (Böhler-Sommeregger and Lindemayr 1986; Veien et al. 1986). Dermal hypersensitivity to aluminum appears to be rare in humans.

No studies were located regarding immunological/lymphoreticular effects in animals after dermal exposure to various forms of aluminum.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after acute- or intermediate-duration dermal exposure to various forms of aluminum. Graves et al. (1990) examined the association between Alzheimer's disease and the use of aluminum-containing antiperspirants in a case-control study using 130 matched pairs. The Alzheimer's disease was clinically diagnosed at two geriatric psychiatric centers; the controls were friends or nonblood relatives of the Alzheimer patients. Information on lifetime use of antiperspirants/deodorant was collected via a telephone interview with the subject's spouse. No association was found between Alzheimer's disease and antiperspirant/deodorant use, regardless of aluminum content (odds ratio of 1.2; 95% confidence interval of 0.6–2.4). When only users of aluminum-containing antiperspirants/deodorants were examined, the adjusted odds ratio was 1.6 (95% confidence interval of 1.04–2.4). A trend (p=0.03) toward a higher risk of Alzheimer's with increasing use of aluminum-containing antiperspirants/ deodorants was also found.

No studies were located regarding the following health effects in humans or animals after dermal exposure to various forms of aluminum:

3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.3 GENOTOXICITY

Although aluminum complexes with deoxyribonucleic acid (DNA), particularly at lower pHs (Dyrssen et al. 1987; Karlik et al. 1980), negative results have been observed in *in vitro* assays (summarized in Table 3-4) for reverse mutations in *Salmonella typhimurium* (Marzin and Phi 1985), DNA damage in *Escherichia coli* (Olivier and Marzin 1987), rec assay using *Bacillus subtilis* (Kada et al. 1980; Kanematsu et al. 1980; Nishioka 1975), forward mutations in the thymidine kinase locus of L5178Y mouse lymphoma cells (Oberly et al. 1982), and morphological transformation in Syrian hamster cells (DiPaola and Casto 1979). However, other studies have shown that aluminum can induce DNA cross-linking in rat ascites hepatoma cells (Wedrychowski et al. 1986), micronuclei formation in human peripheral blood lymphocytes (Banasik et al. 2005; Migliore et al. 1999; Roy et al. 1990), and chromosome aberrations in human peripheral blood lymphocytes (Roy et al. 1990). Using FISH analysis, Migliore et al. (1999) was unable to conclude whether the micronuclei resulted from clastogenic and aneuploidogenic mechanism, although a higher (not statistically significant) percentage of micronuclei contained whole chromosomes. An *in vivo* study also found significant increases in chromosome aberrations in the mone marrow cells of mice receiving an intraperitoneal dose of aluminum chloride (Manna and Das 1972). There was a significant increase in chromatid-type aberrations over the controls, and these occurred in a nonrandom distribution over the chromosome complement; no dose-response relationship could be demonstrated, although the highest dose of aluminum chloride did produce the greatest number of aberrations.

3.4 TOXICOKINETICS

Aluminum is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally. Approximately 0.1–0.6% of ingested aluminum is usually absorbed, although absorption of less bioavailable forms, such as aluminum hydroxide, can be on the order of 0.1%. The unabsorbed aluminum is excreted in the feces. The bioavailability of aluminum is strongly influenced by the aluminum compound and the presence of dietary constituents which can complex with aluminum and

Table 3-4. Genotoxicity of Aluminum *In Vitro*

Species (test system)	End point	Results	Reference
Salmonella typhimurium	Gene mutation	–	Marzin and Phi 1985
Escherichia coli	DNA damage	–	Olivier and Marzin 1987
Bacillus subtilis	Rec assay	–	Kada et al. 1980; Kanematsu et al. 1980; Nishioka 1975
L5178Y mouse lymphoma cells	Forward mutation	–	Oberly et al. 1982
Syrian hamster embryo cells	Transformation assay	–	DiPaola and Casto 1979
Rat ascites hepatoma cells	DNA cross-linking	+	Wedrychowski et al. 1986
Human peripheral blood lymphocytes	Micronuclei formation	+	Banasik et al. 2005; Migliore et al. 1999; Roy et al. 1990
Human peripheral blood lymphocytes	Chromosome abberrations	+	Roy et al. 1990

– = negative result; + = positive result

thereby enhance or inhibit its absorption. The main mechanism of absorption is probably passive diffusion through paracellular pathways. Aluminum binds to various ligands in the blood and distributes to every organ, with highest concentrations found in bone and lung tissues. Absorbed aluminum is excreted principally in the urine and, to a lesser extent, in the bile. Studies on aluminum uptake and elimination rates indicate that a near steady-state is maintained in most healthy adults, with aluminum body burdens varying slightly up and down over time with an overall small rate of increase over the lifespan. Nevertheless, blood and tissue aluminum levels are increased in persons exposed to high levels of aluminum, such as those associated with long-term use of antacids. The levels return to normal upon cessation of exposure. Under certain atypical conditions (e.g., poor renal function with increased aluminum load), levels of aluminum in the body may raise high enough to cause toxicity in humans. The main target organs under these conditions appear to be the central nervous system and bone. The molecular mechanism of aluminum bone and neurotoxicity has not been established.

Aluminum can form complexes with many molecules in the body (organic acids, amino acids, nucleotides, phosphates, carbohydrates, macromolecules). Many aluminum compounds have low solubility products, so their "free" aluminum ions (e.g., hydrated $Al(H_2O)_6^{3+}$) occur in very low concentrations. The toxicokinetics of aluminum can vary, depending on the nature of these complexes. For example, aluminum bound in a low-molecular-weight complex could be filtered at the renal glomeruli and excreted, while aluminum in a high-molecular-weight complex (aluminum transferrin) would not.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Evidence for absorption of aluminum after inhalation exposure in humans is available from several occupational studies. Occupational exposure to aluminum fumes, dusts, and flakes has resulted in increases in serum, tissue, and urinary levels of aluminum. Significantly higher serum aluminum levels were observed in 279 workers exposed to aluminum powder as compared to unexposed workers; the preshift plasma levels were 4.92 and 3.60 µg/L, respectively (Gitelman et al. 1995); no significant differences in postshift plasma levels were found between the aluminum workers (5.12 µg/L) and unexposed controls (4.16 µg/L). Results of an autopsy on a stone mason presumably exposed to aluminum showed that tissue levels of aluminum were substantially higher than those of a group of 24 individuals presumably not exposed to aluminum in the workplace (Teraoka 1981). Following an 8-hour exposure to a time-weighted average (TWA) concentration of 2.4 mg/m^3 aluminum, urinary levels in 3 previously unexposed volunteers rose from 3 to 4–414 µg/L (Sjögren et al. 1985). Increased urinary

aluminum levels have also been observed in workers exposed to 0.025 (median respirable concentration) or 5 mg/m^3 (TWA concentrations) aluminum dust (Gitelman et al. 1995; Mussi et al. 1984) or 2.4 or 5 mg/m^3 (TWA concentrations) aluminum fumes (Mussi et al. 1984; Sjögren et al. 1985). Indirect evidence for inhalation absorption of aluminum was reflected in a fall in urinary aluminum levels from 82 to 29 μg/L in workers following a 16–37-day exposure-free interval (Sjögren et al. 1988).

The percentage of aluminum absorbed following inhalation exposure was not reported in occupational toxicokinetic studies (Gitelman et al. 1995; Mussi et al. 1984; Pierre et al. 1995; Sjögren et al. 1985, 1988). However, a fractional absorption of 1.5–2% was estimated based on the relationship between urinary aluminum excretion and the airborne soluble aluminum to which workers were exposed (Yokel and McNamara 2001). Data from Mussi et al. (1984) suggest that the fractional absorption of aluminum from lung to blood is higher in individuals exposed to aluminum fumes as compared to aluminum dust. This is consistent with knowledge that particle size influences the deposition pattern in the lungs and absorption.

It is considered that systemic absorption of airborne aluminum occurs via the lungs, gastrointestinal tract after mucociliary clearance from the respiratory tract (ICRP 1994), or intranasal absorption via olfactory neurons. Gitelman et al. (1995) found a better correlation between respirable aluminum air concentrations and urinary aluminum output than between total aluminum air concentrations and urinary aluminum output, suggesting that some of the aluminum was absorbed through the lungs. Studies by Perl and Good (1987) and Zatta et al. (1993) have demonstrated that aluminum may directly enter the brain via the olfactory tract; the aluminum crosses the nasal epithelium and reaches the brain via axonal transport.

Several animal studies indicate that aluminum is retained in the lung after inhalation exposure to aluminum oxide (Christie et al. 1963; Thomson et al. 1986) and aluminum chlorhydrate (Steinhagen et al. 1978; Stone et al. 1979). However, no significant increases in aluminum in tissues other than the lungs or serum were seen, indicating that lung retention rather than absorption was taking place (Steinhagen et al. 1978; Stone et al. 1979).

3.4.1.2 Oral Exposure

Aluminum present in food and drinking water is poorly absorbed through the gastrointestinal tract. Several small scale human studies estimated aluminum absorption efficiencies of 0.07–0.39% following administration of a single dose of the radionuclide aluminum-26 (^{26}Al) in drinking water (Hohl et al.

1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). Fractional absorption was estimated by measuring aluminum levels in urine; it is likely that most of these studies (with the exception of Stauber et al. 1999) underestimated gastrointestinal absorption because the amount of aluminum retained in tissues or excreted by non-renal routes was not factored into the absorption calculations. Several animal studies also utilized ^{26}Al to estimate aluminum bioavailability from drinking water. When aluminum levels in urine and bone were considered, absorption rates of 0.04–0.06% were estimated in rats (Drueke et al. 1997; Jouhanneau et al. 1993); when liver and brain aluminum levels were also considered, an absorption rate of 0.1% was estimated (Jouhanneau et al. 1997). Another study that utilized a comparison of the area under the plasma aluminum concentration-time curve after oral and intravenous administration of ^{26}Al estimated an oral aluminum bioavailability of 0.28% (Yokel et al. 2001a).

Two human studies examined the bioavailability of aluminum in the diet. An absorption efficiency of 0.28–0.76% was estimated in subjects ingesting 3 mg Al/day (0.04 mg Al/kg/day) or 4.6 mg Al/day (0.07 mg Al/kg/day) (Greger and Baier 1983; Stauber et al. 1999). When 125 mg Al/day (1.8 mg Al/kg/day) as aluminum lactate in fruit juice was added to the diet, aluminum absorption decreased to 0.094% (Greger and Baier 1983). Yokel and McNamara (2001) suggested that the bioavailability of aluminum from the diet is 0.1% based on daily urinary excretion levels of 4–12 µg and average aluminum intakes by adults in the United States of 5,000–10,000 µg/day.

The bioavailability of aluminum is dependent on the form in which it is ingested and the presence of dietary constituents with which the metal cation can complex (see Section 3.5.1). Ligands in food can have a marked effect on absorption of aluminum, as they can either enhance uptake by forming absorbable (usually water soluble) complexes (e.g., with carboxylic acids such as citric and lactic), or reduce it by forming insoluble compounds (e.g., with phosphate or dissolved silicate). Evidence strongly suggests that the complexing agent of most importance to aluminum uptake in humans is citric acid (or its conjugate base citrate), which is a constituent of many foods and beverages and can be present in the gut in high concentrations (Reiber et al. 1995). It is well-documented in both human and animal studies that blood and tissue levels of aluminum can be increased by simply increasing the consumption of citric acid (i.e., with no concurrent increase in aluminum ingestion), or other dietary chelators such as ascorbic acid and lactic acid (DeVoto and Yokel 1994; Domingo et al. 1991; Florence et al. 1994; Molitoris et al. 1989; Partridge et al. 1989; Slanina et al. 1984, 1985, 1986; Testolin et al. 1996; Weberg and Berstad 1986). The amount of a 976 mg (approximately 14 mg/kg) dose of aluminum as aluminum hydroxide in antacid tablets absorbed by 7–10 volunteers were estimated as 0.004, 0.03, or 0.2% when the antacids were

suspended in tap water (pH 9.2), orange juice (pH 4.2), or citric acid (pH 2.4), respectively (Weberg and Berstad 1986). Absorption was estimated as the amount excreted in urine in 72 hours divided by the amount ingested. A more recent study using ^{26}Al estimated aluminum absorption rates of 0.523, 0.0104, and 0.136% in two subjects receiving a single dose of aluminum citrate, aluminum hydroxide, or aluminum hydroxide dissolved in a citrate solution, respectively (Priest et al. 1996). This is consistent with another study reporting absorption levels of 0.37–0.57% in humans ingesting 280 mg Al as aluminum hydroxide in sodium citrate and citric acid (Taylor et al. 1998). A fourth study reported a higher absorption level (1%) in one subject administered ^{26}Al in a sodium citrate solution (Day et al. 1991).

A comparison of the bioavailability of different aluminum compounds was conducted by Yokel and McNamara (1988). Bioavailability in rabbits following a single maximum safe dose was estimated by comparing areas under the plasma concentration-time curves after oral and intravenous dosing. The estimated bioavailability of the water-soluble compounds aluminum chloride (333 mg Al/kg), aluminum nitrate (934 mg Al/kg), aluminum citrate (1,081 mg Al/kg), and aluminum lactate (2,942 mg Al/kg) in rabbits was 0.57, 1.16, 2.18, and 0.63%, respectively. Aluminum absorption in rabbits similarly treated with the water-insoluble compounds aluminum hydroxide (780 mg Al/kg), aluminum borate (2,736 mg Al/kg), aluminum glycinate (1,351 mg Al/kg), and aluminum sucrose sulfate (20,867 mg Al/kg) was 0.45, 0.27, 0.39, and 0.60%, respectively (Yokel and McNamara 1988). Similarly, Schönholzer et al. (1997) examined aluminum absorption following oral exposure to ^{26}Al in rats. The bioavailability of aluminum hydroxide, aluminum citrate, aluminum citrate with added sodium citrate, or aluminum maltolate following a single gavage dose was 0.1, 0.7, 5.1, and 0.1%, respectively.

The presence of food in the stomach appeared to delay the absorption of ^{26}Al, but did not significantly alter the amount of aluminum absorbed in rats (Yokel et al. 2001a). Aluminum bioavailability was 0.23% with no food in the stomach and 0.21% when food was present. Similarly, there were no differences in absorption when the ^{26}Al was added to hard water (300 mg calcium carbonate/L added) or soft water.

Considering the available human and animal data as discussed above, it is likely that the oral absorption of aluminum can vary 10-fold based on chemical form alone. Although bioavailability appears to generally parallel water solubility, insufficient data are available to directly extrapolate from solubility in water to bioavailability. Additionally, due to available dietary ligands such as citrate, lactate, and other organic carboxylic acid complexing agents, the bioavailability of any particular aluminum compound can be markedly different in the presence of food than under empty stomach conditions.

3.4.1.3 Dermal Exposure

There are limited human data on the dermal absorption of aluminum. Aluminum compounds are common additives in underarm antiperspirants. The active ingredient is usually an aluminum chlorhydrate salt, which is thought to form an obstructive plug of aluminum hydroxide within the sweat duct (Hostynek et al. 1993; Reiber et al. 1995). Using ^{26}Al labeled aluminum chlorohydrate applied to the underarm of two subjects, Flarend et al. (2001) estimated that 0.012% of the applied aluminum was absorbed through the skin. The study investigators cautioned against using these results to extrapolate dermal absorption following repeated exposure to aluminum.

Dermal absorption studies were not located for animals; however a study by Anane et al. (1995) found increased levels of aluminum in the urine of mice exposed to 0.1 or 0.4 μg/day aluminum chloride (0.01–0.04 μg Al/day) applied daily to a 4 cm^2 shaved area for 130 days. Interpretation of this study is limited due to the lack of control measures to prevent the animals from licking their fur and thus ingesting aluminum.

3.4.1.4 Other Routes of Exposure

Flarend et al. (1997) estimated aluminum absorption in rabbits following intramuscular injection of ^{26}Al labelled aluminum hydroxide or aluminum phosphate adjuvants used for vaccines. Aluminum from both solutions was absorbed, appearing in the blood as early as 1 hour after injection. Three times as much aluminum from the aluminum phosphate adjuvant was absorbed during the first 28 days after exposure; since the terminal phase of the blood concentration curve was not reached by that time, this difference may be due to differences in the rate of absorption.

3.4.2 Distribution

Aluminum occurs normally in all body tissues of humans (Ganrot 1986). The total body burden of aluminum in healthy human subjects is approximately 30–50 mg (Alfrey 1981, 1984; Alfrey et al. 1980; Cournot-Witmer et al. 1981; Ganrot 1986; Hamilton et al. 1973; Tipton and Cook 1963). Normal levels of aluminum in serum are approximately 1–3 μg/L (House 1992; Liao et al. 2004). Of the total body burden of aluminum, about one-half is in the skeleton, and about one-fourth is in the lungs (Ganrot 1986). The normal level of aluminum in adult human lungs is about 20 mg/kg wet weight (w/w) and increases with age due to an accumulation of insoluble aluminum compounds that have entered the body via the

airways (Ganrot 1986). Most of the aluminum in other parts of the body probably originates from food intake. Reported normal levels in human bone tissue range from 5 to 10 mg/kg (Alfrey 1980; Alfrey et al. 1980; Cournot-Witmer et al. 1981; Flendrig et al. 1976; Hamilton et al. 1973; Tipton and Cook 1963). Aluminum is also found in human skin (Alfrey 1980; Tipton and Cook 1963), lower gastrointestinal tract (Tipton and Cook 1963), lymph nodes (Hamilton et al. 1973), adrenals (Stitch 1957; Tipton and Cook 1963), and parathyroid glands (Cann et al. 1979). Low aluminum levels (0.3–0.8 mg/kg w/w) are found in most soft tissue organs, other than the lungs (Hamilton et al. 1973; Tipton and Cook 1963).

The normal level of aluminum in the human brain ranges from 0.25 to 0.75 mg/kg w/w, with gray matter containing about twice the concentration found in the white matter (Alfrey et al. 1976; Arieff et al. 1979; McDermott et al. 1978; Roider and Drasch 1999). There is evidence that with increasing age of humans, aluminum concentrations may increase in the brain tissue (Alfrey 1980; Crapper and DeBoni 1978; Markesbery et al. 1981; McDermott et al. 1979; Stitch 1957; Tipton and Shafer 1964); aluminum levels in serum may also increase with aging (Zapatero et al. 1995).

3.4.2.1 Inhalation Exposure

Limited information is available regarding the distribution of aluminum following inhalation exposure in humans or animals. Results of an autopsy of a stone mason presumed to have been exposed to aluminum by inhalation indicated elevated concentrations of aluminum in the lungs (2,000 ppm), hilar lymph nodes (3,200 ppm), liver (130 ppm), and spleen (520 ppm) (Teraoka 1981). The aluminum levels in the tissues of control subjects were 230, 2,000, 19, and 22 ppm, respectively. Rats and guinea pigs given intermediate or chronic inhalation exposures to aluminum chlorhydrate accumulated aluminum primarily in the lungs (Steinhagen et al. 1978; Stone et al. 1979). The only other organs with significant accumulation of aluminum were the adrenal glands (Stone et al. 1979) and the peribronchial lymph nodes (Steinhagen et al. 1978; Stone et al. 1979). No appreciable aluminum accumulation was observed in the brain, heart, spleen, kidneys, or liver of either species.

During inhalation exposure to aluminum and its compounds, the lungs distribute and deposit the material based on particle size (ICRP 1994). A portion of the particles are exhaled, some are trapped in the nasopharyngeal and upper respiratory areas and deposited in the gastrointestinal tract by mucosal movement and mucocilliary action, and a portion of the small particles reach the alveoli where they can be transferred to blood (especially for soluble compounds), or taken up by alveolar macrophages through

phagocytosis and transported to pulmonary lymph nodes for insoluble compounds. Pulmonary concentration of aluminum increases with age.

3.4.2.2 Oral Exposure

There are limited data on the distribution of aluminum in humans. Clearance of ^{26}Al from the blood was assessed in two male volunteers orally exposed to 100 mg aluminum as aluminum chloride (Hohl et al. 1994). Plots of the serum and urine concentrations showed several slope changes, indicating that the clearance from blood involves one central and three peripheral compartments with turnover rates ranging from 0.003 to 9 h^{-1}.

The distribution of aluminum in animals after oral exposure has been evaluated in a number of studies (Cranmer et al. 1986; Deng et al. 2000; Dlugaszek et al. 2000; Domingo et al. 1993; Gomez et al. 1997a, 1997b; Greger and Donnaubauer 1986; Julka et al. 1996; Ogasawara et al. 2002; Santos et al. 1987; Sutherland and Greger 1998; Walton et al. 1995; Yokel and McNamara 1985; Yokel et al. 1999; Zafar et al. 1997). These studies are particularly informative because they demonstrate that, although bioavailability of aluminum is low, aluminum tissue concentrations can increase substantially following oral exposure, and provide information on distribution of aluminum in various tissues. Aluminum is not equally distributed throughout the body following oral exposure. Aluminum accumulation was typically higher in the spleen, liver, bone, and kidneys than in the brain, muscle, heart, or lung (Greger and Sutherland 1997). Eight days after a single gavage dose of 2.6 mg of ^{26}Al as aluminum chloride, the descending order of aluminum levels was bone>spleen>liver>kidney (Zafar et al. 1997). To evaluate the retention of aluminum in tissues following oral exposure, rats were fed a diet supplemented with aluminum hydroxide for an intermediate-duration exposure period (Greger and Donnaubauer 1986). Relative to controls, treated rats had increased aluminum concentrations in bone, muscle, and kidneys. Aluminum concentrations in these tissues decreased significantly 3 days after withdrawal of aluminum hydroxide from the diet. Tissue concentrations of aluminum were similar for treated and control rats 7 days after withdrawal.

Once into the blood, aluminum is believed to be present almost exclusively in the plasma where it is bound mainly to transferrin (Ganrot 1986; Harris and Messori 2002; Martin 1986); recent data suggest that over 90% of the aluminum in serum is bound to transferrin (Harris and Messori 2002). There is *in vitro* evidence indicating that aluminum can bind to the iron-binding sites of transferrin (Moshtaghie and Skillen 1986), and that Al^{+3} may compete with similar ions in binding to transferrin (Ganrot 1986). As

reviewed by Priest (2004), approximately 10% of the aluminum in blood is found in the erythrocytes; peak levels occur 1 day after peak serum aluminum levels were reached. The half-life of aluminum in the erythrocytes appears to longer than the half-life in plasma. In addition to binding with transferrin, Al^{+3} is also known to bind to a considerable extent to bone tissue, primarily in the metabolically active areas of the bone (Ganrot 1986).

Cellular uptake of aluminum by organs and tissues is believed to be relatively slow and most likely occurs from the aluminum bound to transferrin (Ganrot 1986). It is likely that the density of transferrin receptors in different organs influences the distribution of aluminum to organs (Morris et al. 1989). Within cells, Al^{+3} accumulates in the lysosomes, cell nucleus, and chromatin. In organs composed of postmitotic cells, this accumulation would be expected to lead to an increase of the Al^{+3} concentration; however, in other organs, a steady state is expected to be reached between the Al^{+3} accumulation and the elimination of dead cells that are replaced by cells with a lower Al^{+3} content. The cells that accumulate the most aluminum are large, long-lived postmitotic cells, such as in neurons (Ganrot 1986).

In addition to distribution of aluminum to the brain (hippocampus), bone, muscle, and kidneys of orally exposed animals, there is evidence in animals that aluminum crosses the placenta and accumulates in the fetus and distributes to some extent to the milk of lactating mothers (Cranmer et al. 1986; Golub et al. 1996; Yokel 1985; Yokel and McNamara 1985). Aluminum levels were increased in both fetuses and placentas of mice treated throughout gestation with aluminum chloride (Cranmer et al. 1986). The concentration of aluminum in milk of rats that ingested 420 mg Al/kg/day as aluminum lactate in the diet during gestation and lactation increased at least 4-fold beginning on postnatal day 12 (Golub et al. 1996). Peak concentrations of aluminum were detected in the milk of lactating rabbits 12–24 hours after a single large gavage dose of aluminum lactate; however, the amount of aluminum in milk as a percentage of the total oral dose was not reported (Yokel and McNamara 1985). Aluminum levels of rabbit pups exposed during lactation were not significantly different from levels in control pups, suggesting that only a small amount of the aluminum in breast milk is absorbed by the offspring (Yokel 1985).

Age-related differences in the distribution of aluminum has been observed in rats exposed to 0, 50, or 100 mg Al/kg/day as aluminum nitrate in the drinking water with added citrate (Gomez et al. 1997a). The levels of aluminum in the brain and bone were significantly higher in the older rats (16 months of age at study beginning) compared to young (21 days of age) or adult (8 months of age) rats; this was observed in the control and aluminum-treated rats. Liver aluminum levels were significantly higher in adult and older rats as compared to the young rats.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to aluminum or its compounds. Elevated levels of aluminum have been observed in the liver, brain, lung, and kidneys of Swiss mice dermally exposed to 0.4 μg/day aluminum chloride (0.04 μg Al/day) for 20 days during gestation (Anane et al. 1997). Elevated levels of aluminum were also observed in the fetus, providing evidence of transplacental transfer of aluminum. As noted previously, this study did not prevent the mice from licking their fur.

3.4.2.4 Other Routes of Exposure

When there is inadequate elimination of aluminum from the body, as in nondialyzed uremic patients, increased aluminum concentrations are detected in serum, bone tissue, liver, spleen, brain, and skeletal muscle (Alfrey et al. 1980; Arieff et al. 1979). In hemodialysis patients exposed by infusion to large amounts of aluminum over long periods of time (with inadequate removal of aluminum by the kidneys and dialysis machines), increased aluminum concentrations are observed mostly in the spleen, followed by the liver and skeletal system (Alfrey 1980; Alfrey et al. 1980). A study in rabbits found a significantly lower serum half-life in renally-impaired animals, as compared to renally-intact animals (27 hours versus 14 hours); this is likely due to the diminished volume of distribution in the renally-impaired rabbits (Yokel and McNamara 1988).

The distribution of aluminum following intravenous, subcutaneous, intraperitoneal, and intramuscular exposure has been evaluated in studies with experimental animals (Cranmer et al. 1986; Du Val et al. 1986; Flarend et al. 1997; Leblondel and Allain 1980; Yokel and McNamara 1985, 1989; Yokel et al. 2001b). Results of these animal studies indicate that aluminum distributes to a number of tissues, organs, and biological fluids (Du Val et al. 1986; Leblondel and Allain 1980; Yokel and McNamara 1989).

In rabbits given a single intravenous dose of aluminum lactate, aluminum concentrations did not increase above controls in the cerebellum, white brain tissue, hippocampus, spinal cord, adrenal glands, bone, heart, testes, or thyroid (Yokel and McNamara 1989). Treated animals did have significant increases of aluminum in the liver, serum, bile, kidneys, lungs, and spleen. Throughout the 128 day study, the liver of exposed rabbits had over 80% of the total body burden of aluminum. Persistence of aluminum in the various tissues, organs, and fluids varied. Estimated half-times of aluminum were 113, 74, 44, and 42 days in the spleen, liver, lungs, and serum, respectively. The kidneys of treated rabbits demonstrated

two half-times with an initial time of 4.2 and 2.3 days for the renal cortex and renal medulla, respectively, and a second half-time of >100 days for kidney in general; the relative amounts subject to each half-time were not addressed. The half-life of aluminum in the brain of rats receiving an intravenous dose of aluminum citrate was approximately 150 days (Yokel et al. 2001b).

Subcutaneous injection of rabbits with aluminum chloride daily for 28 days was associated with significant accumulation of aluminum (measured at the end of the exposure period) in bone, followed in order by significantly increased aluminum concentrations in renal cortex, renal medulla, liver, testes, skeletal muscle, heart, brain white matter, hippocampus, and plasma (Du Val et al. 1986). Because the brain tissue of treated rabbits had the lowest aluminum concentrations of the tissues evaluated, the authors suggested that there was a partial blood-brain barrier to entry of aluminum.

Distribution of aluminum to tissues following intraperitoneal exposure depends in part on the type of aluminum compound administered and on the aluminum concentration in blood (Leblondel and Allain 1980). Mice were administered 54 mg Al/kg as aluminum chloride, nitrate, lactate, or gluconate by a single intraperitoneal injection. The blood concentrations of aluminum, which reached a peak within 20 minutes, increased significantly with gluconate (99.5 mg/L), increased to high levels with lactate (4.5 mg/L), and increased marginally with nitrate and chloride (0.3 mg/L). Aluminum concentrations in the brain tissue of treated mice significantly increased only with aluminum gluconate and only at extremely high blood aluminum concentrations of 20–100 mg/L; the half-life of aluminum in the brain was approximately 90 minutes. At blood aluminum concentrations of 2–4 mg/L, there was no increase in brain aluminum with any of the compounds evaluated. Interpretation of this study is limited by the short monitoring period (apparently 80 minutes); thus, the study does not take into consideration possible differences in absorption rate between aluminum compounds. Differences in brain aluminum levels following administration of different aluminum compounds may also be due to the presence of carrier systems that can transport aluminum into or out of the brain; this has been demonstrated for aluminum citrate (Allen et al. 1995).

Following intramuscular administration of aluminum hydroxide or aluminum phosphate vaccine adjuvants in rabbits, increased levels of ^{26}Al were found in the kidney, spleen, liver, heart, lymph nodes, and brain (in decreasing order of aluminum concentration) (Flarend et al. 1997).

There is also evidence from animal studies indicating that aluminum administered parenterally accumulates to a small extent in the milk of lactating mothers, and that aluminum crosses the placenta and

accumulates in fetal tissue (Cranmer et al. 1986; Yokel and McNamara 1985; Yumoto et al. 2000). Intraperitoneal exposure of pregnant mice to aluminum chloride on gestation days 7–16 has been associated with significantly increased concentrations of aluminum in both placental and fetal tissues (Cranmer et al. 1986). Following a single subcutaneous injection of ^{26}Al on gestation day 15, 0.2 and 0.21% of the dose was detected in the placenta and fetus, respectively, 5 days after the injection (Yumoto et al. 2000). Within the fetus, the level of ^{26}Al in the brain was as high as 30% of that in the fetal liver; in contrast, the level of ^{26}Al in the brain of the dam was only 1% of the level in the liver. Intravenous, intraperitoneal, or subcutaneous exposure of lactating rats, rabbits, or mice to aluminum lactate or aluminum chloride has been associated with increased concentrations of aluminum in milk (Muller et al. 1992; Yokel and McNamara 1985). The amount of aluminum detected in milk 24 hours after exposure was estimated to be 2.4% of the intravenous dose and 3.3% of the subcutaneous dose (Yokel and McNamara 1985). Subcutaneous injection of ^{26}Al in rats on lactation day 1 through 20, resulted in significant elevation in aluminum levels in the suckling rats (Yumoto et al. 2000, 2003). On lactation day 2, elevated levels of ^{26}Al were detected in the liver, but not in the kidney, brain, or blood; ^{26}Al was detected in these tissues on lactation day 9 (Yumoto et al. 2000).

3.4.3 Metabolism

As an element, aluminum is always found attached to other chemicals, and these affinities can change within the body. In living organisms, aluminum is believed to exist in four different forms: as free ions, as low-molecular-weight complexes, as physically bound macromolecular complexes, and as covalently bound macromolecular complexes (Ganrot 1986). The free ion, Al^{+3}, is easily bound to many substances and structures; therefore, its fate is determined by its affinity to each of the ligands and their relative amounts and metabolism. Aluminum may also form low-molecular-weight complexes with organic acids, amino acids, nucleotides, phosphates, and carbohydrates. These low-molecular-weight complexes are often chelates and may be very stable. The complexes are metabolically active, particularly the nonpolar ones. Because aluminum has a very high affinity for proteins, polynucleotides, and glycosaminoglycans, much of the aluminum in the body may exist as physically bound macromolecular complexes with these substances. Metabolically, these macromolecular complexes would be expected to be much less active than the smaller, low-molecular-weight complexes. Aluminum may also form complexes with macromolecules that are so stable that they are essentially irreversible. For example, evidence suggests that the nucleus and chromatin are often sites of aluminum binding in cells (Crapper McLachlan 1989; Dyrssen et al. 1987; Ganrot 1986; Karlik et al. 1980).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Urinary excretion is the primary route of elimination of absorbed aluminum after inhalation exposure in humans. Elevated levels of aluminum in urine have been detected in aluminum welders and aluminum flake workers (Letzel et al. 1996; Ljunggren et al. 1991; Mussi et al. 1984; Pierre et al. 1995; Rossbach et al. 2006; Schaller et al. 2007; Sjögren et al. 1985, 1988). Six volunteers had urinary levels of 14–414 μg/L aluminum compared to concentrations of <3 μg/L prior to a 1-day exposure to 0.3–10.2 mg Al/m^3 in welding fumes (Sjögren et al. 1985). The urinary aluminum levels of 7 welders exposed occupationally to aluminum fumes or dust for 6 months were increased 3-fold after an 8-hour workshift compared to concentrations at the beginning of the day (Mussi et al. 1984). Several investigators (Letzel et al. 1996; Rossbach et al. 2006; Sjögren et al. 1988) have found a linear relationship between post-shift urinary aluminum levels and levels of aluminum in air among welders.

Occupational exposure studies suggest that the urinary excretion of aluminum is biphasic. The excretion half-time for the first phase ranged from 7.5 to 9 days among workers exposed to welding fumes or aluminum dust (Pierre et al. 1995; Sjögren et al. 1985, 1988). The half-times for the second phase ranged from 6.8 to 24 weeks (Schaller et al. 2007; Sjögren et al. 1988, 1991); the wide range of half-times may reflect the character of the inhaled aluminum (welding fume particles or aluminum flake particles) and the duration of exposure.

No studies were located regarding excretion in animals after inhalation exposure to aluminum or its compounds.

3.4.4.2 Oral Exposure

Following ingestion in humans, absorbed aluminum from the blood is eliminated in the kidney and excreted in the urine (Gorsky et al. 1979; Greger and Baier 1983; Kaehny et al. 1977; Recker et al. 1977; Sutherland and Greger 1998). The unabsorbed aluminum is excreted primarily in the feces. An acute exposure of 4 days to 54.3 mg Al/kg as aluminum carbonate produced peak concentrations ranging from 4- to 10-fold elevation in base-line urinary levels; the average urinary excretion rate being 495 μg/day during exposure (Recker et al. 1977). In humans, 0.09 and 96% of the aluminum intake per day was cleared through the urine and feces, respectively, during exposure to 1.71 mg Al/kg/day as aluminum lactate in addition to 0.07 mg Al/kg/day in basal diet for 20 days (Greger and Baier 1983). Urinary

aluminum concentrations were significantly elevated in volunteers who received aluminum hydroxide and aluminum carbonate (Kaehny et al. 1977). Patients taking aluminum antacids in the diet had only a 3-fold increase in urinary aluminum levels (Gorsky et al. 1979), suggesting that most of the aluminum hydroxide was not absorbed and was excreted directly into the feces.

Excretion of aluminum may be lower in premature compared to full-term infants (Bougle et al. 1991). Plasma levels of aluminum in premature infants were 14.6 μg/L compared to 7.8 μg/L in full-term infants, and absolute urinary excretion was reduced. The aluminum-creatinine ratio in the urine was similar in both groups, indicating that the lower excretion in the premature infants may be due to lower metabolic and glomerular filtration rates, thus increasing the risk of aluminum accumulation in this group.

Excretion data collected in animal studies are consistent with the results from human studies. A single oral dose of 11 mg aluminum resulted in a 14-fold increase in urine aluminum levels, as compared to baseline levels, in healthy Sprague-Dawley rats (Ittel et al. 1987). The aluminum was primarily excreted during the first 24-hour period, and was comparable to baseline levels 5 days postexposure. Similarly exposed uremic rats excreted more aluminum than the healthy rats; the study authors postulated that this increase in excretion was probably due to increased gastrointestinal absorption. Rats administered a single dose of one of eight aluminum compounds (all contained 35 mg aluminum) excreted in the urine 0.015–2.27% of the initial dose (Froment et al. 1989b). The range most likely reflects differences in gastrointestinal absorption. Following administration of a single dose of 6.7–27 mg Al/kg, 1.3–2.8% of the dose was excreted within the first 3 hours; the percent of the dose excreted in the urine did not differ among the three dose groups (Sutherland and Greger 1998).

Fecal aluminum represents unabsorbed aluminum as well as aluminum excreted via bile. Within 15 minutes of rats receiving a gavage dose of 6.7–27 mg Al/kg, the levels of aluminum in bile were significantly higher than in controls (Sutherland and Greger 1998). The percentage of the total dose excreted in bile during the first 3 hours after dosing ranged from 0.06 to 0.14%. In the control group, 25.0 mmol aluminum were excreted in the bile compared to 7.9 mmol in the urine.

3.4.4.3 Dermal Exposure

No studies were located regarding the excretion in humans and animals after dermal exposure to aluminum or its compounds.

3.4.4.4 Other Routes of Exposure

Human and animal studies have investigated the aluminum retention in the body. Within the first day of receiving a single injection of ^{26}Al citrate, approximately 59% of the dose was excreted in the urine of six subjects; 72 and 1.2% was excreted in the urine and feces, respectively, during the first 5 days (Talbot et al. 1995). At the end of 5 days, it was estimated that 27% of the dose was retained in the body (Priest et al. 1995; Talbot et al. 1995). When ^{26}Al levels were monitored more than 3 years after a single subject received the injection, a half-life of approximately 7 years was calculated (Priest et al. 1995). However, when the subject was re-examined approximately 10 years after the injection, a half-life of about 50 years was estimated (Priest 2004).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen

1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

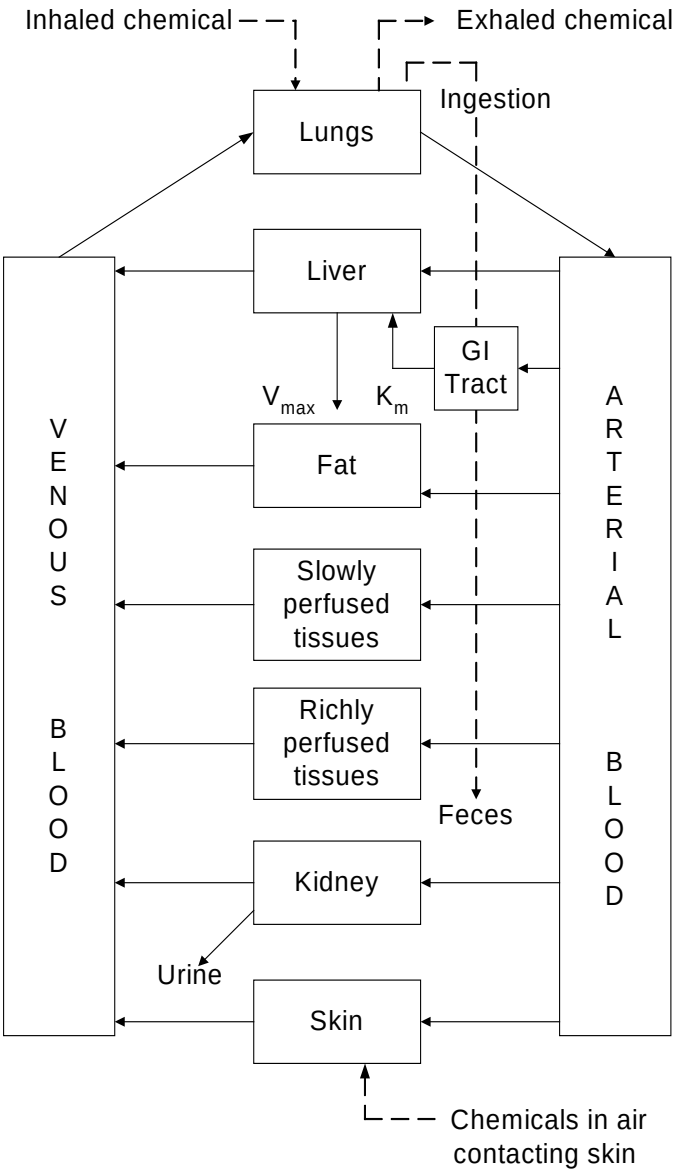
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for aluminum exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

A PBPK/PD model that can be used in risk assessment to predict the concentrations of aluminum delivered to target tissues (particularly the brain) or to examine the relationship between target tissue dose and the observed responses was not located. However, a biokinetic model has been developed to describe the absorption, distribution, and excretion of aluminum (Kislinger et al. 1997; Nolte et al. 2001; Steinhausen et al. 2004). This model allows for the prediction of aluminum levels under different physiological conditions such as renal failure or iron deficiency/overload. The model is an open compartment model comprised of a central compartment, three peripheral compartments, additional compartments for the gastrointestinal tract (stomach, duodenum, and residual intestinal tract), and excretion primarily via kidney output into urine. The central compartment comprises the blood plasma and interstitial fluid; in both compartments, the aluminum is bound to large proteins such as transferrin

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan et al. 1994

and to small soluble molecules such as citrate. The peripheral compartments are: (1) the liver and spleen, which are supplied by aluminum from plasma transferrin (this compartment is characterized by a rapid exchange with the central compartment and no significant long-term storage of aluminum); (2) the muscles, heart, and kidney tissues, which are supplied aluminum from interstitial transferrin; and (3) the bones, which are supplied by aluminum from interstitial tissue citrate (this compartment is characterized by rapid accumulation of aluminum and long-term storage). Aluminum is primarily excreted via ultrafilterable citrate-bound aluminum of plasma via the kidneys into the urine; a minor excretion path is transport of transferrin-bound aluminum of plasma via the liver into the residual intestinal tract.

3.5 MECHANISMS OF ACTION

The mechanism of action for aluminum toxicity is not known, but the element is known to compete in biological systems with cations, especially magnesium (Macdonald and Martin 1988) despite an oxidation state difference, and to bind to transferrin and citrate in the blood stream (Ganrot 1986). It may also affect second messenger systems and calcium availability (Birchall and Chappell 1988), and irreversibly bind to cell nucleus components (Crapper McLachlan 1989; Dyrssen et al. 1987). Aluminum has also been shown to inhibit neuronal microtubule formation. However, much more work is needed before a mechanism can be proposed.

3.5.1 Pharmacokinetic Mechanisms

Gastrointestinal absorption of aluminum is low, generally in the range of 0.01–0.6% in humans as discussed in Section 3.3.1.2. Absorption of aluminum compounds is largely determined by its ionic availability in the aqueous conditions of the gut, which is mainly related to pH, the presence of complexing ligands with which the metal can form absorbable aluminum species, and the chemical form (type of anion) of the ingested compound (DeVoto and Yokel 1994; Reiber et al. 1995). In acidic aqueous conditions such as in the stomach (pH≈2) aluminum primarily occurs as a monomolecular hexahydrate, $Al(H_2O)_6^{+3}$, which is generally abbreviated Al^{+3} and referred to as “free” aluminum (Reiber et al. 1995). The acidic conditions and mixing/residence time in the stomach appear to ensure that the majority of consumed aluminum will be solubilized to monomolecular species (most likely free Al^{+3}), regardless of the compound and form (e.g., food, drinking water or antacid tablets) in which it was ingested. The solubilized aluminum that is in the stomach can recomplex with the anion from the original aluminum compound that was ingested or form new complexes with dietary ligands. The dietary constituents that appear to play a particularly important role in the complexation process include simple mono-, di-, and tricarboxylic acids (particularly citric acid). The vast majority of the solubilized

aluminum is not complexed. As pH increases in the duodenum, a series of aluminum hydroxy complexes are formed by successive deprotonation so that in near-neutral conditions such as in the intestines, the predominant form is aluminum hydroxide ($[Al(OH)_3]$), which is rapidly precipitated as insoluble by the near-neutral pH conditions, and is ultimately excreted in the feces.

The mechanism by which aluminum is absorbed and the chemical forms of aluminum able to pass through the intestinal wall are not completely understood (DeVoto and Yokel 1994; Exley et al. 1996; Lione 1985a; Priest 1993; Reiber et al. 1995; van der Voet 1992; Wilhelm et al. 1990). Available data, mainly results of *in vitro* (everted gut) and *in situ* (intestinal perfusion) studies in rats (e.g., Feinroth et al. 1982; Froment et al. 1989b; Provan and Yokel 1990), suggest that aluminum is mainly absorbed as neutral complexes by passive diffusion through intercellular tight junction (paracellular channel) pathways (i.e., via spaces between cells rather than through the cells themselves). However, adequate information is not available to rule out transcellular transport (cellular internalization), and both paracellular and transcellular pathways may be involved. Transcellular transport is also likely to be a passive process; possible mechanisms include cell-mediated endocytosis, simple diffusion of neutral and possibly lipophilic aluminum complexes, and facilitative diffusion via cation-specific channels (Exley et al. 1996). Active transport of Al^{+3} via iron absorption pathways may also contribute to the absorption of aluminum, but the role of iron pathways in aluminum absorption is incompletely elucidated (DeVoto and Yokel 1994) and complicated by the primary differences in oxidation states (2+ and 3+), which would argue against the two following an identical pathway. The predominant uptake mechanism remains unresolved due to insufficient data in the existing studies, particularly failure to characterize or control for intraluminal conditions affecting aluminum absorption, especially pH differences which can influence aluminum speciation, presence of dietary and other gut substances that can influence solubility of aluminum via formation of complexes, and quantity of available aluminum. These data insufficiencies complicate reconciling different results and postulated mechanisms between studies, and extrapolating to human *in vivo* physiochemical conditions (i.e., identifying the chemical form and mechanism of aluminum absorption in humans).

As previously discussed, absorption of aluminum is markedly increased by the presence of citrate. The mechanism is not fully characterized, but it is thought that citrate enhances gut bioavailability by increasing the permeability of the paracellular channels, possibly via disruption in calcium homeostasis (DeVoto and Yokel 1994; Exley et al. 1996; Froment et al. 1989b; Molitoris et al. 1989; Provan and Yokel 1988). It currently appears that aluminum is not absorbed across the gastrointestinal epithelium as a citrate complex, but that citrate expedites the absorption of aluminum by maintaining the aluminum in a

form that can be readily incorporated into one or more mechanisms of absorption (Exley et al. 1996). This mechanism may be unique to the aluminum-citrate complex, which would be consistent with the apparent greater bioavailability of aluminum citrate compared to other carboxylic acid chelates. Other factors such as parathyroid hormone (through stimulation of $1,25(OH)_2D_3$ production) and vitamin D have also been suggested to enhance the absorption of aluminum, but the data are largely inconclusive.

Mechanisms of inhalation absorption of aluminum are not well characterized, although it seems likely that relatively large aluminum-containing particles retained in the respiratory tract are cleared to the gastrointestinal tract by ciliary action. As has been observed with typical particulates (ICRP 1994), it is hypothesized that aluminum particles that are small enough (<5 μm diameter) to penetrate the lung's protective removal mechanisms may contribute to overall body levels by dissolution and direct uptake from alveoli into the blood stream, or by macrophage phagocytosis (Priest 1993; Reiber et al. 1995).

3.5.2 Mechanisms of Toxicity

In the cases in which human aluminum toxicity has occurred, the target organs appear to be the lung, bone, and the central nervous system. No specific molecular mechanisms have been elucidated for human toxicity to aluminum. In animal models, aluminum can also produce lung, bone, and neurotoxicity, as well as developmental effects in offspring.

Bone Toxicity. Two types of osteomalacia have been associated with aluminum exposure. The first type has been observed in healthy individuals using aluminum-containing antacids to relieve the symptoms of gastrointestinal disorders such as ulcers, colic, or gastritis. The aluminum in the antacids binds with dietary phosphorus and impairs gastrointestinal absorption of phosphorus. The observed osteomalacia and rickets is directly related to the decreased phosphate body burden. Osteomalacia is well documented in dialyzed uremic patients exposed to aluminum via dialysis fluid or orally administered aluminum used to control hyperphosphatemia. In the case of the uremic patient, bone aluminum levels are markedly increased and the aluminum is present between the junction of calcified and noncalcified bone (Alfrey 1993). The osteomalacia is characterized by increased mineralization lag time, osteoid surface, and osteoid area, relatively low parathyroid hormone levels, and mildly elevated serum calcium levels.

Neurotoxicity. Various neurotoxic effects of aluminum have been induced in animals, ranging from neurobehavioral and neurodevelopmental alterations following repeated oral exposures in mice and rats to neurodegenerative pathological changes in the brain caused by acute parenteral administration in

nonrodent species. Numerous mechanistic studies of aluminum neurotoxicity have been performed, but no single unifying mechanism has been identified (Erasmus et al. 1993; Jope and Johnson 1992; Strong et al. 1996); it is likely that more than one mechanism is involved. The main sites of action of aluminum are difficult to discern because the studies have been performed using a variety of exposure methods (including a number of different *in vivo* injections and *in vitro* systems) and animal species, and a number of typical effects are not common to all species and exposure circumstances (i.e., are only expressed using certain models of neurotoxicity). Although insufficient data are available to fully understand the mechanism(s) of aluminum toxicity, some general processes that are involved have been identified. Changes in cytoskeletal proteins, manifested as hyperphosphorylated neurofilamentous aggregates within the brain neurons, is a characteristic response to aluminum in certain species (e.g., rabbits, cats, ferrets, and nonhuman primates) and exposure situations (e.g., intracerebral and intracisternal administration). Similar neurofibrillary pathological changes have been associated with several neurodegenerative disorders, suggesting that the cause of aluminum-related abnormal neuronal function may involve changes in cytoskeletal protein functions in affected cells. The neurofilamentous aggregates appear to mainly result from altered phosphorylation, apparently by posttranslational modifications in protein synthesis, but may also involve proteolysis, transport and synthesis (Jope and Johnson 1992; Strong et al. 1996). Interactions between these processes probably contribute to the induction of the phosphorylated neurofilaments. Each of the processes can be influenced by kinases, some of which are activated by second messenger systems. For example, aluminum appears to influence calcium homeostasis and calcium-dependent processes in the brain via impairment of the phosphoinositide second messenger-producing system (which modulates intracellular calcium concentrations); calcium-activated proteinases may be affected, which could alter the distribution and concentration of cytoskeletal proteins and other substates (Gandolfi et al. 1998; Jope and Johnson 1992; Julka and Gill 1995; Kaur and Gill 2005; Kaur et al. 2006; Mundy et al. 1995; Nostrandt et al. 1996; Sarin et al. 1997; Shafer and Mundy 1995). Another process that may contribute to neurodegeneration is apoptosis (Fu et al. 2003; Ghribi et al. 2001; Johnson et al. 2005; Suarez-Fernandez et al. 1999).

The species (rodents) in which aluminum-induced neurobehavioral effects (e.g., changes in locomotor activity, learning and memory) have been observed fail to develop significant cytoskeletal pathology, but exhibit a number of neurochemical alterations following *in vivo* or *in vitro* exposure (Erasmus et al. 1993; Strong et al. 1996). Studies in these animals indicate that exposure to aluminum can affect permeability of the blood-brain barrier (Yokel et al. 2002; Zheng 2001), cholinergic activity (Kaizer et al. 2005; Kohila et al. 2004; Zatta et al. 2002), signal transduction pathways (Montoliu and Felipo 2001), lipid peroxidation (Deloncle et al. 1999; El-Demerdash 2004; Fraga et al. 1990; Khanna and Nehru 2007;

Nehru and Anand 2005), and impair neuronal glutamate nitric oxide-cyclic GMP pathway (Cucarella et al. 1998; Hermenegildo et al. 1999; Llansola et al. 1999; Rodella et al. 2004), as well as interfere with metabolism of essential trace elements (e.g., iron) because of similar coordination chemistries and consequent competitive interactions.

3.5.3 Animal-to-Human Extrapolations

The appropriateness of extrapolating health effects of aluminum in animals to humans cannot be conclusively determined due to limitations of the human database. Information on toxicity of aluminum in humans is not extensive because the preponderance of studies are in patients with reduced renal function who accumulated aluminum as a result of long-term intravenous hemodialysis therapy with aluminum-containing dialysis fluid and, in many cases, concurrent administration of high oral doses of aluminum to regulate phosphate levels. No clinical studies on health effects of aluminum medicinals in people with normal renal function have been performed, largely due to the fact that exposures typically consist of over-the-counter products such as antacids and buffered aspirins that have been assumed to be safe in healthy individuals at recommended doses based on historical use. The assumed safety of aluminum is also partly due to the FDA-approved GRAS status of aluminum-containing food additives. Other human data largely consist of studies of aluminum-exposed workers that are limited by the lack of quantitative exposure data and/or co-exposure to other chemicals. Subtle neurological effects have been observed in workers chronically exposed to aluminum dust or aluminum fumes, but these studies only provide suggestive evidence that there may be a relationship between chronic aluminum exposure and neurotoxic effects in humans. Aluminum is generally considered to be neurotoxic in animals, and there is an adequate basis to conclude that neurotoxicity/neurodevelopmental toxicity is the critical effect of oral exposure in animals. Whether the subtle neurotoxic effects seen in adult and developing animals exposed to relatively low doses of aluminum would definitely manifest in humans under similar exposure conditions remains to be determined.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a

naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to aluminum. No *in vitro* studies were located regarding endocrine disruption of aluminum.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There is a limited amount of information available on the toxicity of aluminum in children. As with adults, neurological and skeletal (osteomalacia) effects have been observed in children with impaired renal function (Andreoli et al. 1984; Griswold et al. 1983). These effects are related to an abnormal accumulation of aluminum due to exposure to aluminum-contaminated dialysate, use of aluminum containing phosphate binding gels, and impaired renal excretion of aluminum. These effects are not likely to occur in children with normal renal function. Skeletal effects have also been observed in children on long-term total parenteral nutrition containing elevated levels of aluminum. Another subpopulation of children that may be particularly sensitive to the toxicity of aluminum is preterm infants. The observed elevated plasma aluminum levels may be due to the higher aluminum content of premature infant formula and/or limited renal capacity of preterm infants to excrete aluminum (Tsou et al. 1991). Bougle et al. (1991) reported plasma aluminum levels of 14.6 μg/L in preterm infants compared to 7.8 μg/L in full-term infants; decreased urinary aluminum levels at comparable creatinine normalized rates were also found. Bishop et al. (1997) found significant decreases in the Bayley Mental Development Index in pre term infants receiving a standard intravenous feeding solution compared to pre term infants receiving an aluminum-depleted feeding solution. Growth reduction, hypotonia, muscle weakness, and craniosynostosis (premature ossification of the skull and obliteration of the sutures) have been observed in healthy infants following prolonged used of oral antacids for the treatment of colic (Pivnick et al. 1995). These effects were related to secondary hypophosphatemia caused by aluminum binding to phosphate in the gut and markedly reduced phosphate absorption.

Most of the available data come from animal studies that examined the distribution, neurotoxicity, and skeletal toxicity of aluminum at several ages (e.g., gestationally exposed, neonatal, young, adult, and older animals). Yokel and McNamara (1985) did not find any age-related differences in the systemic clearance or half-time of aluminum lactate in rabbits following intravenous, oral, or subcutaneous exposure. Oral exposure to aluminum nitrate resulted in higher brain aluminum levels in young rats as compared to older rats, but there was no difference in toxicity between young and adult rats (Gomez et al. 1997a). In other tissues examined, the aluminum levels in the young rats tended to be lower than in the adult or older animals (Gomez et al. 1997b). Fetal exposure may result in a higher distribution of aluminum to the brain, as compared to adults. In the fetuses of rats receiving a single subcutaneous injection of aluminum on gestation day 5, the amount of the radiolabelled aluminum in the brain was 30%

higher than in the liver; in the dams, brain aluminum levels were only 1% of the levels found in the liver (Yumoto et al. 2000).

Aluminum is distributed transplacentally, and elevated levels of aluminum have been measured in the fetus and placenta following oral, dermal, or parenteral exposure to aluminum (Anane et al. 1997; Cranmer et al. 1986; Yumoto et al. 2000). There is also evidence that oral or parenteral exposure to aluminum can result in elevated levels in breast milk (Golub et al. 1996; Muller et al. 1992; Yokel 1985; Yokel and McNamara 1985; Yumoto et al. 2000, 2003); the form of aluminum in breast milk was not reported. Although levels of aluminum in breast milk were elevated in aluminum-exposed rabbit does, the concentrations in the pups were not significantly different from control levels, suggesting that the aluminum was poorly absorbed (Yokel 1985). In contrast, subcutaneous injection of ^{26}Al in rats on lactation day 1 through 20 resulted in significant elevation in aluminum levels in the suckling rats (Yumoto et al. 2000).

The most sensitive known effect following oral exposure to aluminum is neurotoxicity. Neurotoxic effects have been observed in adult animals, weanling animals, and in animals exposed during gestation, gestation and lactation, and lactation-only (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1987, 1992a, 1992b, 1994, 1995; Oteiza et al. 1993). When neurological tests were performed in adult mice exposed to aluminum during development (gestation and lactation exposure) (Golub et al. 1995), the pattern of neurological effects (alterations in grip strength and startle response) was similar to those observed in mice exposed to aluminum as adults (Golub et al. 1992b; Oteiza et al. 1993) and in mice exposed to aluminum during development and adulthood (Golub et al. 1995). Additionally, the LOAELs for these effects were similar in the three groups, thus suggesting that the developing fetus and children may have a similar sensitivity as adults to the neurotoxic effects of aluminum.

A series of studies in which rabbits received subcutaneous doses of aluminum lactate suggest that the neurotoxicity of aluminum may be age-dependent. Subcutaneous administration of aluminum lactate resulted in alterations in learning and memory in gestationally-exposed rabbits and adult rabbits. A biphasic effect (enhancement after low doses and attenuation after high doses) on learning and memory was observed in the *in utero*-exposed rabbits (treatment on gestational days 2 through 27) (Yokel 1985) and an attenuated effect was observed in the adults (Yokel 1987), but no effects were observed in neonatal or immature rabbits (Yokel 1987). The apparent age-dependence of the toxicity of aluminum in

this study may be a reflection of the different ages at evaluation rather than age of exposure (Golub et al. 1995).

Another aluminum effect which appears to be age-related is skeletal toxicity. Increased carpal joint width, suggestive of poor bone calcification, was observed in immature rabbits receiving 20 subcutaneous doses of aluminum lactate, but was not seen in neonatal or adult rabbits (Yokel 1987).

A study by Sanchez et al. (1997) found significant age-related effects on aluminum interactions with essential elements (e.g., calcium, magnesium, zinc). Decreases in concentration of some essential elements in a number of tissues were observed in young rats orally exposed to aluminum lactate (as compared to adults); the decreases included liver and spleen calcium levels, bone magnesium levels, and brain manganese levels.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to aluminum are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by aluminum are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Aluminum

Aluminum can be measured in the blood, bone, urine, and feces (see Chapter 7 for description of available methods). Since aluminum is found naturally in a great number of foods, it is found in everyone. Unfortunately, exposure levels cannot be related to serum or urine levels very accurately, primarily because aluminum is very poorly absorbed by any route and its oral absorption in particular can be quite affected by other concurrent intakes. There is an indication that high exposure levels are reflected in urine levels, but this cannot be well quantified as much of the aluminum may be rapidly excreted. Aluminum can also be measured in the feces, but this cannot be used to estimate absorption.

3.8.2 Biomarkers Used to Characterize Effects Caused by Aluminum

There are no known simple, noninvasive tests which can be used as biomarkers of effects caused by aluminum. D’Haese et al. (1995) proposed the use of the DFO (deferoxamine) test to identify individuals with aluminum-related bone disease/aluminum overload. This test involves administering a challenge dose of the chelator deferoxamine to individuals with suspected aluminum-induced bone disease. However, iron supplementation may interfere with the test results (Huang et al. 2001).

For more information on biomarkers for renal and hepatic effects of chemicals see *ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (Agency for Toxic Substances and Disease Registry 1990) and for information on biomarkers for neurological effects see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

It is well documented that citrate, a common component of food, markedly enhances the gastrointestinal absorption of concurrently ingested aluminum (Alfrey 1993; Day et al. 1991; DeVoto and Yokel 1994; Froment et al. 1989b; Molitoris et al. 1989; Priest et al. 1996; Provan and Yokel 1988; Slanina et al. 1986; Weberg and Berstad 1986; Yokel and McNamara 1988). The effect has been shown with a variety of aluminum compounds and several forms of citrate in both experimental and clinical studies. The combination of citrate and aluminum has been responsible for a number of deaths in uremic patients, and the clinical implications of the interaction has led some investigators to advise against concomitant exposure to aluminum and citrate in any form (e.g., antacids and orange juice), especially to patients with impaired renal function. As discussed in Sections 3.3.1.2 and 3.5.1, citrate complexes with aluminum to form a species that is particularly bioavailable in the near-neutral pH conditions of the intestines.

Unlike citrate, it is likely that the presence of silicic acid in food and drink will decrease the bioavailability of aluminum by providing a strong competitive binding site for it within the gut contents, thus making the metal less available for absorption (Priest 1993). This is supported by two studies that show a decrease in retention of aluminum in response to higher doses of silicon when human volunteers ingested both chemicals together (Bellia et al. 1996; Edwardson et al. 1993; Jugdaohsingh et al. 2000); Jugdaohsingh et al. (2000) only found this effect when oligometric silica was administered (monomeric silica did not affect aluminum absorption). As discussed in Section 3.5.1, there are some data that suggest that aluminum absorption can be enhanced by parathyroid hormone and vitamin D, but the data are inconclusive.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to aluminum than will most persons exposed to the same level of aluminum in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of aluminum, or compromised function of organs affected by aluminum. Populations who are at greater risk due to their unusually high exposure to aluminum are discussed in Section 6.7, Populations with Potentially High Exposures.

The major population at risk for aluminum loading and toxicity consists of individuals with renal failure. In a study by Alfrey (1980), 82% of nondialyzed uremic patients and 100% of dialyzed uremic patients had an increased body burden of aluminum. The decreased renal function and loss of the ability to excrete aluminum, ingestion of aluminum compounds to lessen gastrointestinal absorption of phosphate, the aluminum present in the water used for dialysate, and the possible increase in gastrointestinal absorption of aluminum in uremic patients can result in elevated aluminum body burdens. The increased body burdens in uremic patients has been associated with dialysis encephalopathy (also referred to as dialysis dementia), skeletal toxicity (osteomalacia, bone pain, pathological fractures, and proximal myopathy), and hematopoietic toxicity (microcytic, hypochromic anemia). Preterm infants may also be particularly sensitive to the toxicity of aluminum due to reduced renal capacity (Tsou et al. 1991).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to aluminum. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to aluminum. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to aluminum:

Schonwald S. 2004. Aluminum. In: Dart RC, ed. Medical toxicology. 3rd ed. New York, NY: Lippincott, Williams, and Wilkins, 1387-1390.

Haddad, CM, Shannon MW, Winchester, JF. 1998. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: WB Saunders, 186.

Leikin JB, Paloucek FP. 2002. Leikin and Paloucek's poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 214-217.

3.11.1 Reducing Peak Absorption Following Exposure

There are limited data on reducing aluminum absorption following exposure. There is good evidence that aluminum is absorbed by a pericellular energy-independent and sodium-dependent process (Provan and Yokel 1988). If this is correct, then treatments that block pericellular processes can be used to minimize or prevent intestinal uptake of aluminum. Ranitidine may also decrease aluminum absorption (Leikin and Paloucek 2002).

3.11.2 Reducing Body Burden

In persons with normal renal function, the body burden can be reduced simply by limiting exposure (Schonwald 2004). Avoidance of aluminum-containing products, such as aluminum-containing phosphate binding gels, dialysate, and parenteral solutions, is recommended for patients with renal failure. Avoidance of co-administration of aluminum compounds and citrate compounds is also advised. Administration of a chelator such as desferrioxamine (DFO) may also help reduce aluminum body burden. DFO is a chelating agent that competes with complexing ligands such as transferrin and citrate that might deliver aluminum to tissues or otherwise redistribute it within the body. For example, DFO treatment has been used to facilitate the removal of aluminum from bone and its entry into the blood where it can be removed by hemodialysis (Haddad et al. 1998). DFO is also used in dialyzed uremic patients for the treatment of neurological, hematopoietic, and skeletal toxicity. In rats, administration of DFO resulted in a large reduction in the half life of aluminum in the brain; 55 days in the DFO-treated rats versus 150 days in controls (Yokel et al. 2001b). It should be noted that the clinical usefulness of DFO is limited by a variety of toxic effects including hypotension, skin rashes, stimulation of fungal growth, and possibly cataract formation. There is some evidence that other chelators may also be effective in reducing aluminum body burden. 1,2-Dimethyl-3-hydroxypyrid-4-one was shown to enhance urinary aluminum excretion in aluminum-loaded rats (Gomez et al. 1999; Yokel et al. 1997). Another study showed that (4-methyl-6-trifluoromethyl-6-pyrimidin-2-il)-hydrazine was effective in decreasing the levels of aluminum in the brains of mice (Missel et al. 2005), although DFO was more effective in lowering the brain aluminum levels. Tiron (4,5-dihydroxy-1,3-benzene disulfonic acid di-sodium salt) administered during aluminum exposure to pregnant rats resulted in significant decreases in aluminum levels in the blood, brain, placenta, and fetus (Sharma and Mishra 2006). Another chelator tested in this study, 4-tricloromethyl-1-H-pyrimidin-2-one, was not effective. Administration of folic acid, melatonin, silicic acid, and beer (due to its silicon content) has been shown to decrease accumulated aluminum in tissues including bone, kidney, and brain in rats or mice (Abd-Elghaffar et al. 2005; Baydar et al. 2005; Gonzalez-Muñoz et al. 2007).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action for aluminum toxicity is not fully understood; thus, there are no known ways of interfering with its mechanism of action. Some pathways of aluminum chloride toxicity include induced lipid peroxidation, altered enzyme activity, overexpression of hippocampal Aβ immunoreactivity, and biochemical parameters. These toxic effects were shown to be improved in rats or mice when

administered vitamin E, vitamin C, selenium, beer (due to its silicon content), centrophenoxine (an anti-aging drug), and the herbal medicines *Dipsacus asper Wall* extract and *Bacopa moniera* (Chinoy et al. 2004; El-Demerdash 2004; Gonzalez-Muñoz et al. 2007; Jyoti and Sharma 2006; Nedzvetsky et al. 2006; Nehru and Bhalla 2006; Nehru et al. 2007; Saba-El Rigal 2004; Zhang et al. 2003).

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of aluminum is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of aluminum.

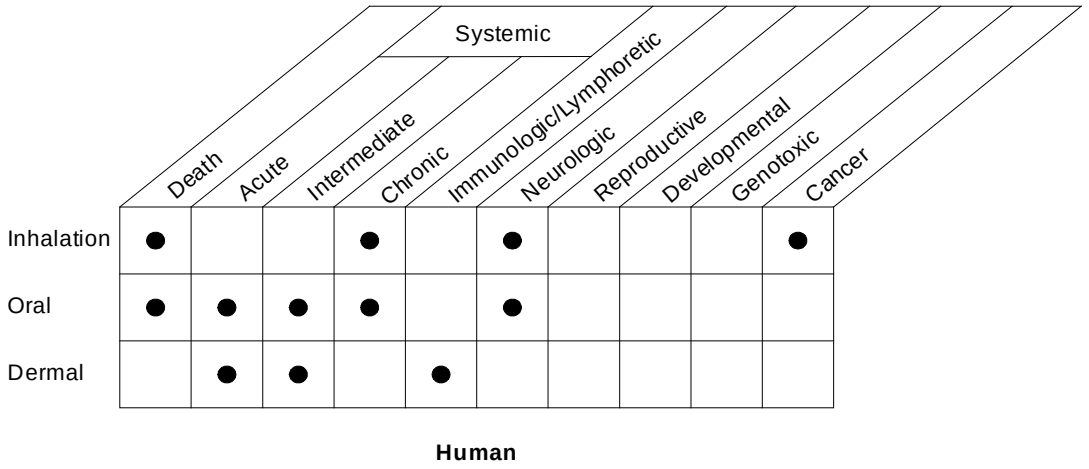
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Aluminum

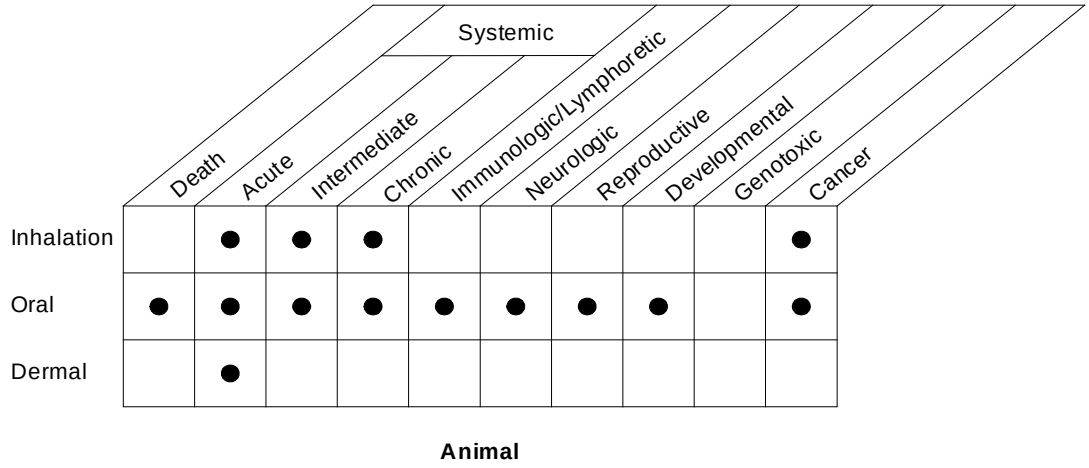
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to aluminum are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of aluminum. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Information on human health effects from inhaled aluminum is available from epidemiological studies and case studies of aluminum workers. This includes data on death, chronic effects, and cancer.

Figure 3-4. Existing Information on Health Effects of Aluminum



Human



Animal

● Existing Studies

Information on oral exposure is available only from specialized cases, such as people who consumed a grain fumigant to try to commit suicide, individuals consuming large doses of aluminum-containing antacids, and dialyzed and nondialyzed uremic patients consuming aluminum compounds prescribed as phosphate binding agents. Information on dermal effects in humans is available from patch tests.

In animals, information on effects from inhalation exposure is available for pure aluminum flakes, aluminum chlorhydrate antiperspirants, and a propylene glycol complex of aluminum chlorhydrate. Effects following oral exposure to several aluminum salts are available for adults and newborn animals. One acute dermal study is available.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are no studies that examined the acute toxicity of aluminum following inhalation, oral, or dermal exposure. A small number of animal studies have examined the acute toxicity of inhaled aluminum. The results of these inhalation studies suggest that the lung may be a sensitive target for toxicity (Drew et al. 1974; Thomson et al. 1986); the observed effects are similar to those that would occur with dust overload. The data are insufficient to determine if these effects are solely due to dust overload or to an interaction between aluminum and lung tissue; thus, an inhalation MRL was not derived. Additional inhalation studies are needed to evaluate whether the respiratory tract is a target of aluminum toxicity; these studies should also examine potential neurological effects, another sensitive target of aluminum toxicity. The acute systemic toxicity of orally administered aluminum has not been well investigated; most of the available data examined the developmental toxicity of aluminum (Bernuzzi et al. 1986, 1989a; Cranmer et al. 1986; Domingo et al. 1989; Gomez et al. 1991; McCormack et al. 1979; Misawa and Shigeta 1992; Paternain et al. 1988) or aluminum lethality (Llobet et al. 1987; Ondreicka et al. 1966). Two studies examining potential effects other than developmental toxicity only examined a small number of end points (Garbossa et al. 1996; Ondreicka et al. 1966). The Ondreicka et al. (1966) study examined potential body weight effects and Garbossa et al. (1996) examined hematological indices; neither study examined for potential neurological effects, which has been shown to be the most sensitive end point following intermediate- or chronic-duration exposure. Oral exposure studies that examined a wide range of potential effects, including neurotoxicity, are needed to identify the critical target of toxicity and establish dose-response relationships. There are limited data on the dermal toxicity of aluminum. A mouse study conducted by Lansdown (1973) found skin damage following application of a number of aluminum compounds. Because aluminum is found in a number of topical

products, additional dermal exposure studies would be useful to fully assess the potential toxicity of aluminum following dermal exposure.

Intermediate-Duration Exposure. There is a limited amount of intermediate-duration human data on the toxicity of aluminum. Neurological and skeletal effects have been observed in uremic patients (Alfrey 1987; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989); however, it is not likely that individuals with normal renal function would experience these effects. Intermediate-duration inhalation studies in animals identified the lung as a sensitive target of toxicity (Drew et al. 1974; Steinhagen et al. 1978; Stone et al. 1979). It is not known if these effects, particularly the granulomatous lesions, are a response to dust overload or an interaction of aluminum with lung tissue; thus, an intermediate-duration inhalation MRL was not derived for aluminum. Additional inhalation studies are needed to evaluate the mechanisms of lung toxicity to determine whether the effects are due to dust overload or aluminum; inhalation studies examining a wide-range of potential end points, including the nervous system, would be useful for identifying the most sensitive effect of inhaled aluminum. A fair number of studies have examined the toxicity of aluminum following intermediate-duration oral exposure. Although most of the studies focused on the neurotoxicity and neurodevelopmental toxicity of aluminum, the available studies have examined potential systemic (Dixon et al. 1979; Domingo et al. 1987b; Farina et al. 2005; Garbossa et al. 1996, 1998; Gomez et al. 1986; Katz et al. 1984; Ondreicka et al. 1966; Oteiza et al. 1993; Pettersen et al. 1990; Vittori et al. 1999), immunological (Golub et al. 1993; Lauricella et al. 2001; Yoshida et al. 1989), and reproductive (Dixon et al. 1979; Donald et al. 1989; Katz et al. 1984; Krasovskii et al. 1979; Ondreicka et al. 1966; Pettersen et al. 1990) end points. A series of studies conducted by Mahieu and associates (Mahieu et al. 1998, 2003, 2005, 2006) found small changes in sodium and phosphate excretion and urine concentrating ability (under conditions of water deprivation), but no changes in overall renal function (glomerular filtration rate or clearance), in rats administered aluminum hydroxide or aluminum lactate via intraperitoneal injection. Although several oral exposure studies did not find histological alterations in the kidneys, none of these studies examined renal function; the results of the Mahieu studies suggest the need for a study examining renal function following oral exposure to aluminum. The available intermediate-duration studies clearly identify the nervous system as the most sensitive target of aluminum toxicity (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 2001; Golub et al. 1989, 1992a, 1992b, 1995; Oteiza et al. 1993). An intermediate-duration oral MRL was derived based on Golub and Germann (2001) and Colomina et al. (2005) co-principal studies; the critical effect was neurodevelopmental effects and delays in physical maturation. No studies have examined the dermal toxicity of aluminum; animal studies would provide useful information on

aluminum's potential to induce dermal effects following repeated exposure and whether it can cause systemic or neurological effects.

Chronic-Duration Exposure and Cancer. Aluminum has been implicated in causing neurological (Banks et al. 1988; Liss and Thornton 1986), musculoskeletal, (Alfrey 1987; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989), and hematopoietic (Jeffery et al. 1996) effects in individuals with impaired renal function. Respiratory and neurological effects have been observed in workers exposed to finely ground aluminum and aluminum welding fumes. Impaired lung function has been observed in workers employed in various aluminum industries including potrooms, foundry, and welders (Abbate et al. 2003; Al-Masalkhi and Walton 1994; Bast-Pettersen et al. 1994; Bost and Newman 1993; Burge et al. 2000; Chan-Yeung et al. 1983; Hull and Abraham 2002; Jederlinic et al. 1990; Korogiannos et al. 1998; Miller et al. 1984b; Radon et al. 1999; Simonsson et al. 1985; Vandenplas et al. 1998). Other studies have provided some suggestive evidence that aluminum exposure can result in occupational asthma (Abramson et al. 1989; Akira 1995; Al-Masalkhi and Walton 1994; Burge et al. 2000; Vandenplas et al. 1998) or pulmonary fibrosis (De Vuyst et al. 1986; Edling 1961; Gaffuri et al. 1985; Jederlinic et al. 1990; Jephcott 1948; McLaughlin et al. 1962; Mitchell et al. 1961; Musk et al. 1980; Riddell 1948; Shaver 1948; Shaver and Riddell 1947; Ueda et al. 1958; Vallyathan et al. 1982). A common limitation of most of these occupational exposure studies is co-exposure to other compounds, such as silica, which can also damage the respiratory tract. Subtle neurological effects have been observed in workers exposed to aluminum dust in the form of McIntyre powder, aluminum dust and fumes in potrooms, and aluminum fumes during welding (Bast-Pettersen et al. 1994; Buchta et al. 2003, 2005; Dick et al. 1997; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Polizzi et al. 2001; Sim et al. 1997; Sjögren et al. 1990, 1996; White et al. 1992). Inhalation animal studies have focused on the pulmonary toxicity of aluminum (Pigott et al. 1981; Stone et al. 1979). Data were considered inadequate for derivation of a chronic-duration inhalation MRL. Additional inhalation studies are needed to identify the critical target of aluminum toxicity following inhalation exposure. Several studies have examined the systemic toxicity of aluminum following chronic oral exposure (Farina et al. 2005; Golub et al. 2000; Oneda et al. 1994; Roig et al. 2006; Schroeder and Mitchener 1975a, 1975b). These studies identified two potential targets of toxicity: the nervous system (Golub et al. 2000) and the hematopoeitic system (Farina et al. 2005). A chronic-duration oral MRL was derived based on the neurotoxicity observed in the Golub et al. (2000) study. A comparison between the dose-response relationship of neurotoxicity and the alterations in hematological parameters cannot be conducted because the Farina et al. (2005) study did not provide information on the level of aluminum in the base diet and both studies only utilized one aluminum-exposure group. Additional studies on the toxicity of aluminum

following chronic-duration exposure utilizing multiple dose levels would be useful in comparing the sensitivity of these two effects.

The available data do not indicate that aluminum is a potential carcinogen. It has not been shown to be carcinogenic in epidemiological studies in humans, nor in animal studies using inhalation, oral, and other exposure routes (Oneda et al. 1994; Ondreicka et al. 1966; Pigott et al. 1981; Schroeder and Mitchener 1975a, 1975b). Although these studies have limitations ranging from use of only one species to a single exposure level and limited histological examinations, the evidence strongly suggests that aluminum is not carcinogenic, indicating that additional carcinogenicity testing is not warranted at this time.

Genotoxicity. Several *in vitro* studies have found significant increases in the occurrence of micronuclei formation (Banasik et al. 2005; Migliore et al. 1999; Roy et al. 1990) and chromosome aberrations (Roy et al. 1990) in human lymphocytes; no human *in vivo* studies were identified. One study examined the *in vivo* genotoxicity of aluminum and found clastogenic changes in mice receiving an intraperitoneal injection of aluminum chloride (Manna and Das 1972). *In vitro* studies in mammalian and bacterial systems have not found mutagenic alterations (DiPaola and Casto 1979; Kada et al. 1980; Kanematsu et al. 1980; Marzin and Phi 1985; Nishioka 1975; Oberly et al. 1982; Olivier and Marzin 1987). Further genotoxicity studies, particularly *in vivo* exposures, would be useful for verifying the results of the Manna and Das (1972) study and for evaluating other potential end points of genotoxicity.

Reproductive Toxicity. No studies were located regarding reproductive effects of various forms of aluminum following inhalation, oral, or dermal exposure in humans. No histological alterations were observed in the reproductive tissues of rats or guinea pigs exposed to airborne aluminum chlorhydrate (Steinhagen et al. 1978); this study did not examine reproductive function. A number of oral-exposure studies examining reproductive end points in several animal species were identified. In general, the results of these studies suggest that aluminum is not associated with alterations in fertility (Dixon et al. 1979; Domingo et al. 1987c), mating success (Dixon et al. 1979; Ondreicka et al. 1966), or number of implantations, implantation losses, or litter size (Bernuzzi et al. 1989b; Domingo et al. 1987c, 1989; Golub et al. 1992a; Gomez et al. 1991; Misawa and Shigeta 1992). Further studies in this area do not appear to be necessary at this time.

Developmental Toxicity. No studies human studies examining the potential of aluminum to induce developmental effects in humans exposed to aluminum via inhalation, ingestion, or dermal contact were located. Developmental toxicity studies in animals have shown that oral gestational exposure to

aluminum induced skeletal variations such as delayed ossification in rats and mice under conditions that enhanced its uptake, particularly maternal intake of compounds that are highly bioavailable (e.g., aluminum citrate and nitrate), concurrent exposure to dietary constituents that contribute to increased absorption of aluminum (e.g., citrate), and/or bolus administration by gavage (Colomina et al. 1992; Gomez et al. 1991; Paternain et al. 1988). There is some evidence that oral developmental exposure to aluminum affected the immune system in young mice (Golub et al. 1993; Yoshida et al. 1989) and may delay physical maturation (Colomina et al. 2005). Neurobehavioral deficits have been observed in oral studies of weanling and young developing mice and rats exposed to aluminum by gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone (Bernuzzi et al. 1986, 1989a, 1989b; Colomina et al. 2005; Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1987, 1992a, 1992b, 1994, 1995; Misawa and Shigeta 1992; Muller et al. 1990). The most frequently affected neurobehavioral effects in the exposed weanlings and young mice included increases in grip strength and landing foot splay and decreased thermal sensitivity. The effects most commonly found in mice exposed during development and tested as adults, or tested only as adults, included decreases in spontaneous motor activity, grip strength, and startle responsiveness, indicating that the pattern of neurobehavioral impairment in developing animals was different from adults.

Although the neurodevelopmental toxicity of aluminum is well-documented in animals, there are a number of data needs that preclude fully assessing the significance of the findings to human health (Golub and Domingo 1996). An important issue not adequately addressed in the existing studies is the potential for effects on more complex central nervous system functions, including learning and memory and sensory abilities. This type of animal testing would help determine the generality or specificity of aluminum neurodevelopmental toxicity and provide a better basis for its assessment in children. Additional information that is needed to more fully characterize the neurodevelopmental toxicity of aluminum includes data on whether effects are transient and reversible or whether they persist and cause permanent changes after exposures are terminated. Additionally, it would be informative to verify that the central nervous system is the critical developmental end point for aluminum by obtaining data on effects in noncentral nervous system organs known to be targets of aluminum toxicity in adults. Additional investigations of the skeletal component of the aluminum developmental toxicity syndrome are particularly needed because permanent effects on bone growth and strength could occur during periods of rapid mineralization not investigated in existing studies, such as early infancy and adolescence. New developmental toxicity studies should include a range of low oral doses that encompasses the

neurotoxicity NOAEL on which the intermediate-duration MRL is based, as well adequately characterized levels of aluminum in the base diet.

Additional information on compound bioavailability is also needed to better evaluate the developmental toxicity of aluminum. Because the developmental effects of orally administered aluminum appear to be dependent on the bioavailability of the form in which it is administered and the presence of dietary components that promote aluminum uptake, additional information on compound-related differences in aluminum uptake and effectiveness during pregnancy and postnatal development would help in assessing the relevance of the animal data to oral exposures in humans. For example, gavage administration of low doses of aluminum (38–77 mg Al/kg/day) as aluminum nitrate during gestation induced skeletal variations in rats (Paternain et al. 1988), indicating that the LOAEL for this effect is below the neurotoxicity NOAEL of 62 mg Al/kg/day for aluminum lactate in adult mice used to derive the MRL. The Paternain et al. (1988) LOAEL was not considered to be appropriate for MRL consideration due to concern that gavage does not realistically represent environmental aluminum intake (i.e., the LOAEL could be unnaturally low compared to dietary exposure because the skeletal effects could be related to phosphate binding caused by the bolus administration), and that nitrate represents an unusually bioavailable form of aluminum. Additional information on the bioavailability of different forms and amounts of aluminum exposure would help establish how well oral aluminum exposure regimens in animals (e.g., gavage as tested by Paternain et al. [1988]) approximate the oral bioavailability of aluminum from water or food in humans. This kind of information is needed to verify that the MRL is based on the most appropriate end point (i.e., neurotoxicity in adults rather than skeletal developmental toxicity), especially considering that no NOAEL has been identified for either skeletal developmental effects (Paternain et al. 1988) or neurodevelopmental effects (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1992a, 1992b, 1994, 1995). Information on fetal uptake of aluminum administered in forms that have been already evaluated for prenatal developmental toxicity could indicate if the aluminum nitrate in the Paternain et al. (1988) study was effective because it is the most available to the fetus.

Immunotoxicity. A few reports indicate hypersensitivity in children and adults who have received aluminum-containing vaccines (Bergfors et al. 2005; Böhler-Sommeregger and Lindemayr 1986; Castelain et al. 1988; Veien et al. 1986). A human oral exposure study (Gräske et al. 2000) did not find alterations in the concentrations of immunoglobulin, interleukin, natural killer cells, or B- or T-lymphocyte populations in humans ingesting an antacid suspension for 6 weeks. No other human exposure studies examining immunological end points were located. Histological alterations have been observed in the lymphoreticular system, particularly granulomas in the hilar lymph nodes, of animals

exposed to airborne aluminum (Steinhagen et al. 1978; Thomson et al. 1986); these effects were probably secondary to the pulmonary effects rather than the result of direct damage to lymphoreticular tissue. The available inhalation studies did not conduct function tests. Histopathological examination of lymphoreticular tissues has shown no effect after oral administration of aluminum in rats (Dixon et al. 1979; Domingo et al. 1987b; Gomez et al. 1986; Katz et al. 1984; Ondreicka et al. 1966). Alteration in lymph node proliferation was observed in rats (Lauricella et al. 2001), and there is some evidence that developmental exposure to aluminum can affect the immune system in young mice (Golub et al. 1993; Yoshida et al. 1989). A battery of immune function tests following developmental and intermediate- or chronic-duration oral exposure may provide important information on characterizing the immunotoxic potential of aluminum, especially the age-sensitivity of effects. Aluminum-related dermal sensitivity appears to be very rare in humans; further studies do not appear to be necessary.

Neurotoxicity. There are suggestive data that the nervous system may be a sensitive target in humans. Subtle neurological effects, such as impaired performance on neurobehavioral tests and increases in objective symptoms, have been observed in workers exposed to aluminum dust and fumes, McIntyre powder, or welding fumes (Bast-Pettersen et al. 1994; Buchta et al. 2003, 2005; Dick et al. 1997; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Polizzi et al. 2001; Sim et al. 1997; Sjögren et al. 1990, 1996; White et al. 1992). Although a number of studies have examined the possible association between aluminum exposure and Alzheimer's disease (Flaten 1990; Forbes et al. 1992, 1994; Forster et al. 1995; Gauthier et al. 2000; Graves et al. 1998; Jacqmin et al. 1994; Jacqmin-Gadda et al. 1996; Martyn et al. 1989, 1997; McLachlan et al. 1996; Michel et al. 1990; Neri and Hewitt 1991; Polizzi et al. 2002; Rondeau et al. 2000, 2001; Salib and Hillier 1996; Sohn et al. 1996; Wettstein et al. 1991; Wood et al. 1988), a causal link between aluminum exposure and Alzheimer's disease has not been shown, and a number of factors may influence the risk of developing Alzheimer's disease. Nevertheless, continued monitoring of aluminum intake and incidence of neurological disease in humans is important to clarify aluminum's role in the Alzheimer's disease process.

The neurotoxicity of aluminum is well-documented in animals and has been manifested following oral or parenteral routes of exposure; however, there are very limited data on neurotoxicity following inhalation or dermal exposure. Inhalation studies have conducted histological examinations of the brain (Steinhagen et al. 1978; Stone et al. 1979), but have not conducted neurobehavioral function tests; no dermal exposure neurotoxicity studies were located. Studies are needed by these routes of exposure to establish whether it is a sensitive target following inhalation or dermal exposure. In rats and mice orally exposed to aluminum for intermediate or chronic durations, the neurotoxicity is manifested in neuromotor,

behavioral, and cognitive changes (Bilkei-Gorzo 1993; Commissaris et al. 1982; Connor et al. 1989; Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1989, 1992a, 1992b, 1995, 2000; Jing et al. 2004; Oteiza et al. 1993; Zhang et al. 2003). Additional low-dose studies in which levels of aluminum in the base diet are adequately characterized would be useful in establishing the NOAEL/LOAEL boundary. Oral exposure studies are also needed to evaluate the potential neurotoxicity of aluminum following acute-duration exposure and to confirm or refute the potential for aluminum to induce cognitive effects. Additionally, neurotoxicology studies measuring blood aluminum levels would be useful in determining the relevance of the animal data to humans. Research issues related to neurodevelopmental effects of aluminum are discussed in the Data Needs section on Developmental Toxicity.

Epidemiological and Human Dosimetry Studies. There are numerous reports of adverse health effects, primarily respiratory and neurological effects, in workers exposed to airborne aluminum (Abbate et al. 2003; Abramson et al. 1989; Akira 1995; Al-Masalkhi and Walton 1994; Bast-Pettersen et al. 1994; Bost and Newman 1993; Buchta et al. 2003, 2005; Burge et al. 2000; Chan-Yeung et al. 1983; De Vuyst et al. 1986; Dick et al. 1997; Edling 1961; Gaffuri et al. 1985; Hänninen et al. 1994; Hosovski et al. 1990; Hull and Abraham 2002; Iregren et al. 2001; Jederlinic et al. 1990; Jephcott 1948; Korogiannos et al. 1998; McLaughlin et al. 1962; Miller et al. 1984b; Mitchell et al. 1961; Musk et al. 1980; Polizzi et al. 2001; Radon et al. 1999; Riddell 1948; Rifat et al. 1990; Riihimäki et al. 2000; Shaver 1948; Shaver and Riddell 1947; Sim et al. 1997; Simonsson et al. 1985; Sjögren et al. 1990, 1996; Ueda et al. 1958; Vallyathan et al. 1982; Vandenplas et al. 1998; White et al. 1992). However, a common limitation of the occupational exposure data is that the exposure levels have not been well quantified and workers were often exposed to a number of other chemicals. A number of studies have examined the possible association between Alzheimer's disease and aluminum exposure in air (Polizzi et al. 2002; Salib and Hillier 1996) and drinking water (Flaten 1990; Forbes et al. 1992, 1994; Forster et al. 1995; Gauthier et al. 2000; Graves et al. 1998; Jacqmin et al. 1994; Jacqmin-Gadda et al. 1996; Martyn et al. 1989, 1997; McLachlan et al. 1996; Michel et al. 1990; Neri and Hewitt 1991; Rondeau et al. 2000, 2001; Sohn et al. 1996; Wettstein et al. 1991; Wood et al. 1988). These studies have reported conflicting results and have been criticized for poor subject selection, exposure assessment, and diagnosis of Alzheimer's disease. Further studies are important in helping to determine whether there is a cause-and-effect relationship between chronic aluminum exposure and the development of Alzheimer's disease. There are also a number of studies reporting bone damage and neurological effects in individuals with chronic renal failure (Alfrey 1993); however, kidney failure increases the risk for developing aluminum-related effects; thus, these data have limited usefulness in predicting health effects in the general population. Aluminum is found in a number of over-the-counter products, such as antacids; however, controlled studies

examining potential adverse effects in healthy individuals ingesting these products long-term have not been located and are needed.

Biomarkers of Exposure and Effect. Reliable methods for determining tissue and plasma levels of aluminum exist. The mechanism of action for aluminum toxicity is not known, hence it is not known whether biomarkers of effect exist or not.

Exposure. Although aluminum can be measured in blood (Alfrey et al. 1980; Arieff et al. 1979; Ganrot 1986), urine (Gorsky et al. 1979; Greger and Baier 1983; Kaehny et al. 1977; Mussi et al. 1984; Recker et al. 1977; Sjögren et al. 1985, 1988), and feces (Greger and Baier 1983), the aluminum body burden rapidly declines upon termination of exposure (except in the lungs, where retention takes place). Also, tissue levels do not correlate with exposure except that higher-than-average tissues levels of aluminum correlate with increased exposure. There is some suggestive evidence that erythrocyte aluminum levels may be reflective of long-term aluminum exposure (Priest 2004), but a possible relationship between ingestion and erythrocyte aluminum levels has not been established. Additional studies examining the possible relationship between urine, blood, or other tissue levels and aluminum exposure would be useful in establishing biomarkers of exposure.

Effect. No biomarkers of effect have been identified for aluminum. The mechanisms of action for aluminum toxicity is not known and there is considerable research in identifying the mechanism(s) of neurotoxicity (Cucarella et al. 1998; Deloncle et al. 1999; El-Demerdash 2004; Fraga et al. 1990; Hermenegildo et al. 1999; Kaizer et al. 2005; Kohila et al. 2004; Llansola et al. 1999; Montoliu and Felipo 2001; Nehru and Anand 2005; Rodella et al. 2004; Yokel et al. 2002; Zatta et al. 2002; Zheng 2001). Studies on the mechanism of action of aluminum may lead to biochemical tests that can be used in the early identification of aluminum toxicity.

Absorption, Distribution, Metabolism, and Excretion. Available data indicate that the gastrointestinal absorption of aluminum is often in the range of 0.1–0.6% in humans, although absorption of poorly available aluminum compounds such as aluminum hydroxide can be <0.01% (Day et al. 1991; DeVoto and Yokel 1994; Ganrot 1986; Greger and Baier 1983; Hohl et al. 1994; Jones and Bennett 1986; Nieboer et al. 1995; Priest 1993; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). Bioavailability of aluminum varies mainly due to differences in the form of the ingested compound and dietary constituents (i.e., the kinds and amounts of ligands in the stomach with which absorbable aluminum species can be formed). The apparent 10-fold range in aluminum absorption has not been

systematically documented using a variety of aluminum compounds and the most suitable analytical techniques. Radiochemical studies are desired because they facilitate accurate quantitation of the small percentages of ingested aluminum that are absorbed and provide a means to distinguish endogenous aluminum from administered aluminum and from aluminum contamination of samples (Priest 1993). Additional toxicokinetic studies using ^{26}Al would help to better characterize the likely range of aluminum bioavailability. This kind of information is needed because an amount of aluminum ingested does not provide an estimate of exposure without information on bioavailability of the form in which it is ingested. In particular, if bioavailability in a particular human scenario differs from bioavailability in the MRL study, or is not known, extrapolation may not be appropriate because exposure depends on bioavailability as well as intake. Information on the bioavailability of aluminum in rodent laboratory feed would also be useful for extrapolating from animal to human exposure. Studies investigating the extent of absorption of aluminum into the placenta and fetal blood circulation would be useful in assessing the relevance of developmental effects in animals to human exposures.

There are limited data on the distribution of aluminum following inhalation or dermal exposure, although it is likely that the distribution would be similar to distribution following oral exposure. Ingested aluminum is not equally distributed throughout the body; higher levels are found in the bone, spleen, liver, and kidney (Greger and Donnaubauer 1986; Greger and Sutherland 1997; Zafar et al. 1997). In the blood, aluminum is primarily found in the plasma bound to transferrin (Ganrot 1986; Harris and Messori 2002; Martin 1986). Metabolism of the element does not occur (Ganrot 1986). Absorbed aluminum is primarily excreted in the urine with a small amount of absorbed aluminum excreted in the feces (Gorsky et al. 1979; Greger and Baier 1983; Kaehny et al. 1977; Recker et al. 1977; Sjögren et al. 1985, 1988). A main deficiency is whether aluminum can cross into the brains of healthy humans in sufficient amounts to cause neurological diseases. Further animal experiments, possibly using ^{26}Al as a tracer, would be useful in determining which, if any, levels and routes of exposure may lead to increased aluminum uptake in the brain.

Comparative Toxicokinetics. The animal data indicate that the nervous system is a sensitive target of toxicity for aluminum following oral exposure, as summarized in the Data Needs sections on Neurotoxicity and Developmental Toxicity. Human data also suggest that the nervous system is a sensitive target; a number of neurological effects have been observed in aluminum workers (Bast-Pettersen et al. 1994; Buchta et al. 2003, 2005; Dick et al. 1997; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Polizzi et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Sim et al. 1997; Sjögren et al. 1990, 1996; White et al. 1992). The toxicokinetic properties of aluminum have been

studied in human and animals. The results of these studies suggest that the absorption, distribution, and excretion properties of aluminum are similar across species. There are very few comparative studies examining the toxicokinetic properties of different aluminum compounds; these studies would be useful in extrapolating toxicity data across species.

Methods for Reducing Toxic Effects. The mechanisms of absorption of aluminum have not been established. Studies that elucidated these mechanisms would be useful for establishing methods or treatments for reducing absorption and distribution of aluminum to sensitive targets. The chelating agent DFO has been used to reduce the aluminum body burden (Haddad et al. 1998; Yokel et al. 2001b); however, the clinical usefulness of DFO is limited by a variety of toxic effects. Other chelators such as 1,2-dimethyl-3-hydroxypyrid-4-one and (4-methyl-6-trifluoromethyl-6-pyrimidin-2-il)-hydrazine have also been shown to reduce the aluminum body burden (Gomez et al. 1999; Missel et al. 2005;Yokel et al. 1997). Studies that identify other methods for reducing aluminum body burden would be useful. The mechanism of toxicity has not been established for most of the toxic end points. Additional information on the mechanisms of toxicity would be useful for developing methods for reducing the toxicity of aluminum.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

The available data suggest that the targets of aluminum toxicity in children would be similar to those in adults. However, there is conflicting evidence on whether the threshold of toxicity, particularly neurotoxicity, would be lower in children. Multiple species studies using a relevant route of exposure, such as ingestion, and examining a wide range of effects in immature, mature, and older animals would be useful in assessing the children's susceptibility to the toxicity of aluminum. Additionally, there are no studies on the influence of immature renal function on aluminum retention in the body and no studies on the long-term effects of aluminum exposure on skeletal maturation or neurotoxicity. There are some data suggesting age-related differences in the toxicokinetic properties of aluminum. A study in rats found higher levels of aluminum in the brain and bone of aged rats (aged 18 months) compared to young rats (aged 21 days) (Gomez et al. 1997a); similar findings were observed in the controls and aluminum-treated rats.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

There are a large number of ongoing studies covering many aspects of aluminum toxicity. Studies supported by the federal government are listed in Table 3-5.

Table 3-5. Ongoing Studies on Aluminum

Investigator	Study Topic	Institution	Sponsor
Longnecker M	Use of aluminum in toenails as a biomarker of exposure		National Institute of Environmental Health Sciences
Yokel R	Aluminum bioavailability from foods	University of Kentucky	National Institute of Environmental Health Sciences
Bondy S	Aluminum/iron interactions in neurodegenerative disease	University of California Irvine	National Institute of Environmental Health Sciences
DeWitt DA	Mechanism of aluminum-induced neurodegeneration in Alzheimer's disease	Liberty University	National Institutes of Health
Swyt-Thomas CR	Role of aluminum in Alzheimer's disease		National Institutes of Health

Source: FEDRIP 2006

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Aluminum is a naturally occurring element that appears in the second row of Group 13 (IIIA) of the periodic table (O'Neil et al. 2001). Table 4-1 lists common synonyms and other pertinent identification information for aluminum and selected aluminum compounds.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Aluminum is a silvery-white, malleable, and ductile metal. In moist air, a protective oxide coating of aluminum oxide is formed on its surface. In compounds, aluminum typically occurs in its +3 oxidation state (Lide 2005; O'Neil et al. 2001). Table 4-2 lists important physical and chemical properties of aluminum and selected aluminum compounds.

Table 4-1. Chemical Identity of Aluminum and Compounds[a]

Characteristic	Information		
Chemical name	Aluminum	Aluminum chloride	Aluminum chlorohydrate (anhydrous)
Synonym(s)	Aluminium[b]; alumina fibre; metana; aluminium bronze; aluminum dehydrated; aluminium flake; aluminum powder; aluminum-27; Noral aluminum; PAP-1	Aluminum trichloride; aluminum chloride (1:3); Pearsall	Aluminol ACH; aluminum chloride hydroxide oxide, basic; aluminum chloride oxide; aluminum oxychloride; PAC 250A; Astringen; Chlorhydrol; Locron
Chemical formula	Al	$AlCl_3$	Unspecified[d]
Chemical structure	Al	$Al^{3+}(Cl^-)_3$	Unspecified
Identification numbers:			
CAS registry	7429-90-5	7446-70-0	1327-41-9
EINECS	231-072-3	231-208-1	215-477-2
NIOSH RTECS	BD330000	BD0525000	No data
EPA hazardous waste code	No data	D003	No data
EPA Pesticide Chemical Code	000111	013901	No data
DOT/UN/NA/IMCO shipping	UN 1309; UN 1396; IMO 4.1; IMO 4.3; NA 9260	UN 1726; UN 2581; IMO 8.0	No data
HSDB	507	607	No data

Table 4-1. Chemical Identity of Aluminum and Compounds[a]

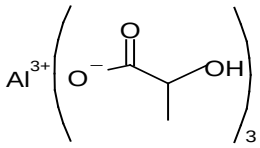
Characteristic	Information		
Chemical name	Aluminum hydroxide	Aluminum lactate	Aluminum nitrate
Synonym(s)	alpha-Alumina trihydrate; alumina hydrate; alumina hydrated; aluminum oxide trihydrate; aluminum oxide hydrate; aluminum (III) hydroxide; hydrated alumina; hydrated aluminum oxide; aluminum hydrate; aluminum trihydrate; hydrated alumina; Alcoa 331/C 30BF/C 330/C 333; Alugel; Alumigel; BACO AF260; British Aluminum AF260; Calmogastrin; Higilite H 31S/ H 32/ H 42; Hychol 705; Hydrafil; Hydral 705/710; Martinal A/A-S/F-A; Reheis F 1000	Aluminum, tris (2-hydroxypropanoato-O^1,O^2); propanoic acid, 2-hydroxy-, aluminum complex; aluminum tris (α-hydroxypropionate)	Aluminum trinitrate; aluminum (III) nitrate (1:3); nitric acid, aluminum salt; nitric acid, aluminum (3+) salt
Chemical formula	$Al(OH)_3$	$C_9H_{15}AlO_9$	$Al(NO_3)_3$
Chemical structure	$Al^{3+}\ (OH^-)_3$		$Al^{3+}\ (NO_3^-)_3$
Identification numbers:			
CAS registry	21645-51-2	18917-91-4	13473-90-0[f]
EINECS	244-492-7	242-670-9	236-751-8
NIOSH RTECS	BD0940000	No data	No data
EPA hazardous waste code	No data	No data	No data
EPA Pesticide Chemical Code	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	UN 1438; IMO 5.1
HSDB	575	No data	574

Table 4-1. Chemical Identity of Aluminum and Compounds[a]

Characteristic	Information		
Chemical name	Aluminum oxide	Aluminum phosphate	Aluminum phosphide
Synonym(s)	Activated aluminum oxide; α-alumina; aluminum sesquioxide; aluminum trioxide; β-aluminum oxide; γ-alumina; Almite; Alon; Aloxite; Alumite; Alundum; Campalox; Dispal Alumina; Exolon XW 60; Faserton; Hypalox II; Ludox CL; Martoxin; Microgrit WCA; Poraminar	Aluminum ortho-phosphate; phosphoric acid; aluminum salt (1:1); Aluphos; Phosphaljel; Phosphalugel; aluminum monophosphate	Aluminum monophosphide; AL-Phos; AlP; Celphos; Delicia; Delicia Gastoxin; Detia; Phostoxin; Quickphos
Chemical formula	Al_2O_3	$AlPO_4$	AlP
Chemical structure	$(Al^{3+})_2\ (O^{2-})_3$	$Al^{3+}\ PO_4^{3-}$	$Al\equiv P$
Identification numbers:			
CAS registry	1344-28-1	7784-30-7	20859-73-8
EINECS	215-691-6	232-056-9	244-088-0
NIOSH RTECS	BD1200000	TB6450000	BD1400000[c]
EPA hazardous waste code	No data	No data	P006
EPA Pesticide Chemical Code	No data	No data	066501
DOT/UN/NA/IMCO shipping	No data	No data	UN 1397; UN 3048; IMO 4.3; IMO 6.1
HSDB	506	No data	6035

Table 4-1. Chemical Identity of Aluminum and Compounds[a]

Characteristic	Information		
Chemical name	Aluminum fluoride	Aluminum sulfate anhydrous	Aluminum carbonate
Synonym(s)	Aluminum trifluoride	Alum; aluminum sulfate (2:3); cake alum; filter alum; papermaker's alum; pearl alum; pickle alum; aluminum trisulfate; sulfuric acid, aluminum salt (3:2)	Carbonic acid, aluminium salt
Chemical formula	AlF_3	$Al_2(SO_4)_3$	$Al_2O_3 \bullet CO_2$; normal aluminum carbonate $Al_2(CO_3)_3$ is not known as an individual compound[e]
Chemical structure	$Al^{3+}\ (F^-)_3$	$(Al^{3+})_2\ (SO_4{}^{2-})_3$	No data
Identification numbers:			
CAS registry	7784-18-1	10043-01-3	53547-27-6
EINECS	232-051-1	233-135-0	238-440-2
NIOSH RTECS	BD0725000	BD1700000	No data
EPA hazardous waste code	No data	No data	No data
EPA Pesticide Chemical Code	No data	013906	No data
DOT/UN/NA/IMCO shipping	No data	NA 9078; NA 1760	No data
HSDB	600	5067	No data

Table 4-1. Chemical Identity of Aluminum and Compounds[a]

Characteristic	Information	
Chemical name	Aluminum potassium sulfate	Alchlor
Synonym(s)	Alum potassium; burnt alum; sulfuric acid, aluminum potassium salt (2:1:1); Tai-Ace K 150; Tai-Ace K 20	Aluminum chloride hydroxide propylene glycol complex
Chemical formula	$AlKO_8S_2$	Unspecified
Chemical structure	$K^+ Al^{3+} (SO_4^{2-})_2$	Unspecified
Identification numbers:		
CAS registry	10043-67-1	52231-93-3
EINECS	233-141-3	No data
NIOSH RTECS	No data	No data
EPA hazardous waste code	No data	No data
EPA pesticide chemical code	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	No data	No data

[a]All information obtained from ChemIDplus 2006, ChemFinder 2008, and HSDB 2008, except where noted.
[b]British spelling (Lewis 2001)
[c]NIOSH 1997
[d]Aluminum chlorohydrate: CAS No. 12042-91-0; Chemical formula: $Al_2ClH_5O_5.xH_2O$ (ChemIDplus 2006)
[e]Lewis 2001
[f]Aluminum nitrate nonahydrate (CAS No. 7784-27-2)

CAS = Chemical Abstracts Service; DOT/UN/NA/IMO = Department of Transportation/United Nations/North America/ Intergovernmental Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Commercial Chemical Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Aluminum and Compounds[a]

Property	Information		
Chemical name	Aluminum	Aluminum chloride	Aluminum chlorohydrate
Molecular weight	26.98	133.34	No data
Color	Silver white	White when pure, ordinarily gray or yellow to greenish	Glassy[b]
Physical state	Malleable, ductile metal; cubic crystal	White hexagonal deliquescent or moisture sensitive plates	Solid[b]
Melting point	660 °C	192.6 °C	No data
Boiling point	2,327 °C	182.7 °C at 752 mm Hg (sublimation temperature)	No data
Density (g/cm^3)	2.70	2.48	No data
Odor	Odorless	Strong odor of hydrogen chloride	No data
Odor threshold:			
Water	No data	0.5 mg/L (calculating on the aluminum ion)	No data
Air	No data	No data	No data
Solubility:			
Water	Insoluble in water	Reacts violently with water producing hydrochloric acid and heat	Dissolves in H_2O, forming slightly turbid colloidal solutions (up to 55% w/w)[b]
Other solvents	Soluble in HCl, H_2SO_4, hot water, and alkalies	Soluble in benzene, carbon tetrachloride, chloroform	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
pH	No data	No data	~4.3 (15% aqueous solution)[b]
Vapor pressure	1 mm Hg at 1,284 °C	1 mm Hg at 100 °C	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	Finely divided aluminum dust is easily ignited	Not combustible, but heating may produce irritants and toxic gases	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Aluminum and Compounds[a]

Property	Information		
Chemical name	Aluminum hydroxide	Aluminum lactate	Aluminum nitrate
Molecular weight	78.01	294.19[b]	213.00
Color	White	Colorless[c]	Colorless[d]
Physical state	Bulky, amorphous powder	Powder[c]	Rhombic crystals[d]
Melting point	300 °C	No data	73 °C[d]
Boiling point	No data	No data	Decomposes at 135 °C[d]
Density (g/cm^3)	2.42	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Insoluble in water	Freely soluble in water[b]	Very soluble in water[d]
Other solvents	Soluble in alkaline or acid solutions	No data	Very soluble in alcohol; very slightly soluble in acetone; almost insoluble in ethyl acetate, pyridine[d]
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
pH	No data	No data	Aqueous solution is acidic[d]
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Aluminum and Compounds[a]

Property	Information		
Chemical name	Aluminum oxide	Aluminum phosphate	Aluminum phosphide
Molecular weight	101.94	121.95[b]	57.95
Color	White	White[b]	Dark gray or dark yellow
Physical state	Crystalline powder	Infusible powder[b]	Cubic crystals
Melting point	approximately 2,000 °C	>1,460 °C[b]	2,550 °C
Boiling point	2,980 °C	No data	No data
Density (g/cm^3)	4.0 at 20 °C	2.56[b]	2.85 at 15 °C
Odor	Odorless	No data	Garlic odor
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Soluble in cold water, 0.000098 g/100 cc; insoluble in hot water	Practically insoluble in water[b]	Decomposes[b]
Other solvents	Very slightly soluble in acid, alkali	Practically insoluble in acetic acid; very slightly soluble in concentrated HCl and HNO_3 acids[b]	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
pH	No data	No data	No data
Vapor pressure	1 mm Hg at 2,158 °C	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Aluminum and Compounds[a]

Property	Information		
Chemical name	Aluminum fluoride	Aluminum sulfate	Aluminum carbonate
Molecular weight	83.98	342.14	No data
Color	White	White, lustrous	White[c]
Physical state	Hexagonal crystals	Crystals, pieces, granules or powder	Lumps or powder[c]
Melting point	1,291 °C	Decomposes at 770 °C	No data
Boiling point	Sublimes at 1,272 °C and 760 mm Hg	No data	No data
Density (g/cm^3)	3.10	1.61	No data
Odor	No data	Odorless	No data
Odor threshold:			No data
Water	No data	No data	
Air	No data	No data	
Solubility:			
Water	0.559 g/100 mL at 25 °C	Soluble in 1 part H_2O	Insoluble[c]
Other solvents	Sparingly soluble in acids and alkalies; insoluble in alcohol and acetone	Insoluble in ethanol	Dissolves in hot HCl or H_2SO_4 acid[c]
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
pH	No data	Aqueous solution (1 g/mL) not less than 2.9	No data
Vapor pressure	1 mm Hg at 1,238 °C	Essentially zero	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Aluminum and Compounds[a]

Property	Information	
Chemical name	Aluminum potassium sulfate	Alchlor
Molecular weight	258.20	No data
Color	White	No data
Physical state	Powder	No data
Melting point	92 ºC[e]	No data
Boiling point	Loses 18 H_2O at 64.5 °C; anhydrous at 200 °C[e]	No data
Density (g/cm^3)	1.75[e]	No data
Odor	Odorless[e]	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water	1 gram dissolves in about 20 mL of cold water, about 1 mL of boiling water	No data
Other solvents	Practically insoluble in alcohol	No data
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
pH	Aqueous solutions are acidic	No data
Vapor pressure	No data	No data
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	Noncombustible[e]	No data
Explosive limits	No data	No data

[a]All information obtained from HSDB 2008, except where noted.
[b]O'Neil et al. 2001
[c]Lewis 2001
[d]Aluminum nitrate nonahydrate (CAS No. 7784-27-2)
[e]$Al_2(SO_4)_3 \cdot K_2SO_4 \cdot 24H_2O$ (Lewis 2001)

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Aluminum is the most abundant metal and the third most abundant element in the earth's crust, comprising about 8.8% by weight (88 g/kg). It is rarely found free in nature and is found in most rocks, particularly igneous rocks, which contain aluminum as aluminosilicate minerals (Staley and Haupin 1992). Bauxite is a naturally occurring, heterogeneous material consisting of primarily one or more aluminum hydroxide minerals in addition to a variety of aluminosilicates, iron oxide, silica, titania, and other impurities in trace amounts. It is the most important raw material for the production of aluminum. More than 90% of the bauxite consumed in the United States in 2006 was converted to alumina (Al_2O_3) for the production of aluminum (USGS 2007d). Other raw materials sometimes used in the production of aluminum include cryolite, aluminum fluoride, fluorspar, corundum, and kaolin minerals (Browning 1969; Dinman 1983; IARC 1984; Lide 2005; O'Neil et al. 2001; USGS 2007a).

In 2006, primary aluminum was produced in 42 countries, with China, Russia, Canada, and the United States, in decreasing order of metal produced, accounting for 53% of the total world production of 31.9 million metric tons. In 2006, 5 U.S. companies, operating 13 primary aluminum smelters, produced an estimated 2.3 million metric tons of aluminum metal. Six smelters were temporarily idled. In the United States, about 3 million metric tons of aluminum were recovered from purchased scrap in 2006, with 64% of this coming from new (manufacturing) scrap and 36% from old scrap (discarded aluminum products) (USGS 2007b, 2007c).

In 2006, Australia, Brazil, and China accounted for approximately 58% of the total world bauxite product of 178 million metric tons. World production of alumina was estimated to be 69.2 million metric tons in 2006, with Australia and China as leading producers, accounting for 46% of the world's alumina production. U.S. production of alumina, which is nearly all derived from imported metallurgical-grade bauxite, was 4.61 million metric tons in 2006 (USGS 2007a, 2007d).

The principal method used in producing aluminum metal involves three major steps: refining of bauxite by the Bayer process to produce alumina, electrolytic reduction of alumina by the Hall-Héroult process to produce aluminum, and casting of aluminum into ingots (Browning 1969; Dinman 1983; IARC 1984).

In the first step (Bayer process), bauxite ($Al_2O_3 \cdot H_2O$) is digested at high temperature and pressure in a strong solution of caustic soda. The resulting hydrate is then crystallized and calcined in a kiln to produce

alumina (aluminum oxide). In the second step (Hall-Héroult process), alumina is reduced to aluminum metal by an electrolytic process involving carbon electrodes and cryolite flux ($3NaF \cdot AlF_3$). The electrolytic reduction process of transforming alumina into aluminum is carried out in electrolytic cells or pots. The areas where this occurs are called potrooms. Two types of electrolytic cells may be used, a prebake or a Söderberg cell. Their design differs, but the principle is the same. Alumina is dissolved in the cell in an electrolyte at a high temperature (950–970 °C) and a low voltage (4–6 volts). A high current is applied to the melted fraction. The alumina is reduced to aluminum at the cathode and the metal sinks to the bottom of the electrolytic cell. The aluminum is then removed by siphoning. The oxygen from the alumina migrates to the carbon anode of the cell, where it reacts to form carbon dioxide and carbon monoxide. The aluminum produced using the Hall-Héroult electrolytic reduction process may be refined to a maximum purity of 99.9%. In the third step (casting), aluminum is taken from the cell to holding furnaces from which it is poured into molds and cast into aluminum ingots (IARC 1984; Lewis 2001; Staley and Haupin 1992). Current U.S. manufacturers of aluminum are given in Table 5-1.

Aluminum is also an integral part of a variety of aluminum compounds used in industrial, domestic, consumer, and medicinal products. The methods of production for these compounds are described in the following section. Current U.S. manufacturers of selected aluminum compounds are given in Table 5-2.

Aluminum chloride can be produced by the reaction of purified gaseous chlorine with molten aluminum, as well as by the reaction of bauxite with coke and chlorine at about 875 °C (Lewis 2001).

Aluminum fluoride can be produced by heating ammonium hexafluoroaluminate to red heat in a stream of nitrogen. Other methods include the action of hydrogen fluoride gas on aluminum trihydrate; the reaction of hydrogen fluoride on a suspension of aluminum trihydrate followed by calcining the hydrate formed; fusion of cryolite or sodium fluoride with aluminum sulfate; or the reaction of fluosilicic acid on aluminum hydrate (HSDB 2007; Lewis 2001; O'Neil et al. 2001).

Aluminum hydroxide is produced from bauxite. The bauxite ore is first dissolved in a solution of sodium hydroxide, and then the aluminum hydroxide is precipitated from the sodium aluminate solution by neutralization (as with carbon dioxide) or by autoprecipitation (Bayer process) (Lewis 2001).

Aluminum nitrate as the nonahydrate is formed by dissolving aluminum or aluminum hydroxide in dilute nitric acid and allowing the resulting solution to crystallize (Grams 1992; Lewis 2001).

Table 5-1. U.S. Manufacturers of Aluminum[a]

Company	Location
Alcan Aluminum Corporation, Alcan Specialty Aluminas	Sebree, Kentucky
Alcoa, Inc., Alcoa Primary Metals	Alcoa, Tennessee
	Badin, North Carolina
	Goose Creek, South Carolina
	Massena, New York
	Wenatchee, Washington
Alcoa Intalco Works	Ferndale, Washington
Century Aluminum	Hawesville, Kentucky
	Ravenswood, West Virginia
Columbia Falls Aluminum Company	Columbia Falls, Montana
Eastalco Aluminum Company	Frederick, Maryland
Noranda Aluminum Inc.	New Madrid, Missouri
Northwest Aluminum Company	The Dalles, Oregon
Ormet Primary Aluminum Corporation	Hannibal, Ohio

[a]Derived from SRI 2007

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
Alumina, calcined (Aluminum oxide)		
Alcoa, Inc., Alcoa World Alumnia	Point Comfort, Texas	
Almatis, Inc.	Bauxite, Arkansas	
Gramercy Alumina LLC	Gramercy, Louisiana	
Ormet Primary Aluminum Corporation	Burnside, Louisiana	
Sherwin Alumina Company	Corpus Christi, Texas	
Aluminas (specialty grades)		
Albemarle Corporation	Pasadena, Texas	
Almatis, Inc.	Bauxite, Arkansas	
AluChem, Inc.	Cincinnati, Ohio	
Axens North America	Savannah, Georgia	
BASF Catalysts LLC, Adsorbents and Catalysts	Port Allen, Louisiana	
	Vidalia, Louisiana	
Huber Engineered Materials	Fairmount, Georgia	
Porocel Corporation	Little Rock, Arkansas	
Saint-Gobain Ceramics & Plastics, Inc., Grains & Powders Division	Worcester, Massachusetts	
Sasol North America Inc., Ceralox Division	Westlake, Louisiana	
	Tucson, Arizona	
SPI Pharma Group	Lewes, Delaware	
Treibacher Schleifmittel North America, Inc.	Niagara Falls, New York	
UOP, LLC	Baton Rouge, Louisiana	
Washington Mills Electro Minerals Company	Niagara Falls, New York	
Aluminum ammonium sulfate		
Holland Company, Inc.	Adams, Massachusetts	
Aluminum chlorhydrate (aluminum chloride, basic)		
GEO Specialty Chemicals, Inc., Aluminum Products Group	Baltimore, Maryland	
	Bastrop, Louisiana	
	Counce, Tennessee	
The Gillette Company, North Chicago Manufacturing Center	North Chicago, Illinois	
Gulbrandsen Companies, Gulbrandsen Chemicals, Inc.	Orangeburg, South Carolina	
Gulbrandsen Companies, Gulbrandsen Technologies, Inc.	La Porte, Texas Phillipsburg, New Jersey	
Puerto Rico Alum Corporation	Penuelas, Puerto Rico	
Reheis, Inc.	Berkeley Heights, New Jersey	

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
Summit Research Labs	Huguenot, New York	
	Phoenix, Arizona	
	Somerset, New Jersey	
Thatcher Company	Salt Lake City, Utah	
Aluminum chloride (anhydrous)[c]		
Gulbrandsen Companies, Gulbrandsen Chemicals, Inc.	Orangeburg, South Carolina	25
Toth Aluminum Corporation	Vacherie, Louisiana	10[d]
Vanchlor Company, Inc.	Lockport, New York	15
Aluminum chloride (hydrous)[e]		
Arkema, Inc., Specialty Chemicals Division	Axis, Alabama	2
Chattem, Chemicals, Inc.	Chattanooga, Tennessee	1
Delta Chemical Corporation	Ashtabula, Ohio	10
	Baltimore, Maryland	50
GEO Specialty Chemicals, Inc., Aluminum Products Group	Baltimore, Maryland	9
	Bastrop, Louisiana	6
The Gillette Company, North Chicago Manufacturing Center	North Chicago, Illinois	Not applicable
Gulbrandsen Companies, Gulbrandsen Technologies, Inc.	Phillipsburg, New Jersey	9
Holland Company, Inc.	Adams, Massachusetts	Not applicable
Puerto Rico Alum Corporation	Penuelas, Puerto Rico	1
Reheis, Inc.	Berkeley Heights, New Jersey	3
Southern Ionics, Inc.	Westlake, Louisiana	60
Summit Research Labs	Huguenot, New York	Not applicable
	Phoenix, Arizona	Not applicable
	Somerset, New Jersey	Not applicable
Aluminum chloride (aluminum trichloride)		
Mallinckrodt, Inc., Pharmaceuticals Group	St. Louis, Missouri	
Aluminum chlorohydrate (polyaluminum chloride)		
Delta Chemical Corporation	Ashtabula, Ohio	
	Baltimore, Maryland	
GEO Specialty Chemicals, Inc., Aluminum Products Group	Baltimore, Maryland Bastrop, Louisiana	
Gulbrandsen Companies, Gulbrandsen Chemicals, Inc.	Orangeburg, South Carolina	
Gulbrandsen Companies, Gulbrandsen Technologies, Inc.	La Porte, Texas Phillipsburg, New Jersey	
Holland Company, Inc.	Adams, Massachusetts	

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
Kemiron Companies, Inc.	Kalama, Washington	
	Savannah, Georgia	
	Spokane, Washington	
Puerto Rico Alum Corporation	Penuelas, Puerto Rico	
Summit Research Labs	Huguenot, New York	
	Phoenix, Arizona	
	Somerset, New Jersey	
Aluminum fluoride		
Alcoa, Inc., Alcoa World Alumina	Point Comfort, Texas	60
CERAC, Inc.	Milwaukee, Wisconsin	Not applicable
ConocoPhillips	Billings, Montana	<1[f]
	Ponca City, Oklahoma	<1[f]
Ozark Fluorine Specialties, Inc.	Tulsa, Oklahoma	<2
Aluminum hydroxide		
Almatis, Inc.	Bauxite, Arkansas	
Franklin Industries, Inc., Franklin Industrial Minerals	Dalton, Georgia	
Gramercy Alumina LLC	Gramercy, Louisiana	
Huber Engineered Materials	Fairmount, Georgia	
	Kennesaw, Georgia	
	Quincy, Illinois	
IMERYS Pigments & Additives	Talking Rock, Georgia	
Sherwin Alumina Company	Corpus Christi, Texas	
Aluminum nitrate		
Blue Grass Chemical Specialties, LLC	New Albany, Indiana	
Mallinckrodt Baker, Inc.	Phillipsburg, New Jersey	
Mineral Research and Development	Harrisburg, North Carolina	
Thatcher Company	Salt Lake City, Utah	
Aluminum phosphate (aluminum orthophosphate)		
Innophos, Inc.	Chicago Heights, Illinois	
Johnson Matthey, Inc., Alfa Aesar	Ward Hill, Massachusetts	
PCS Phosphate Co., Inc.	Cincinnati, Ohio	
United-Erie, Inc.	Erie, Pennsylvania	
Aluminum phosphide[g]		
Bernardo Chemical, Ltd, Inc.		
Degesch America, Inc.		
Inventa Corporation		
Midland Fumigant, Inc.		
Pestcon Systems, Inc.		

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
Aluminum potassium sulfate (Potash alum)		
Holland Company, Inc.	Adams, Massachusetts	
Aluminum sodium sulfate (Soda alum)		
General Chemical Corporation	East St. Louis, Illinois	
Aluminum sulfate (Alum, commercial)		
Alchem, Inc.	Rockwell, North Carolina	
Bay Chemical and Supply Company	Odem, Texas	
C & S Chemicals, Inc.	Austell, Georgia	
	Bartow, Florida	
	Joliet, Illinois	
	Randolph, Minnesota	
	Waycross, Georgia	
Delta Chemical Corporation	Ashtabula, Ohio	
	Baltimore, Maryland	
GAC Chemical Corporation	Searsport, Maine	
Gemini Industries, Inc.	Santa Ana, California	
General Chemical Corporation	Ashdown, Arkansas	
	Augusta, Georgia	
	Catawba, South Carolina	
	Cedar Springs, Georgia	
	Cleveland, Ohio	
	Covington, Virginia	
	Denver, Colorado	
	Detroit, Michigan	
	East Point, Georgia	
	East St. Louis, Illinois	
	Hopewell, Virginia	
	Indianapolis, Indiana	
	Jacksonville, Florida	
	Johnsonburg, Pennsylvania	
	Kalamazoo, Michigan	
	Macon, Georgia	
	Marrero, Louisiana	
	Menasha, Wisconsin	
	Middletown, Ohio	
	Pine Bluff, Arkansas	
	Pittsburg, California	
	Port St. Joe, Florida	
	Saukville, Wisconsin	
	Savannah, Georgia	

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
	Springfield, Tennessee	
	Tacoma, Washington	
	Tampa, Florida	
	Toledo, Ohio	
	Vancouver, Washington	
	Wisconsin Rapids, Wisconsin	
GEO Specialty Chemicals, Inc., Aluminum Products Group	Bastrop, Louisiana	
	Chattanooga, Tennessee	
	Childersburg, Alabama	
	Counce, Tennessee	
	Demopolis, Alabama	
	De Ridder, Louisiana	
	Georgetown, South Carolina	
	Monticello, Mississippi	
	Pennington, Alabama	
	Plymouth, North Carolina	
	Savannah, Georgia	
W. R. Grace & Co., Grace Davison	Curtis Bay, Maryland	
	Lake Charles, Louisiana	
Holland Company, Inc.	Adams, Massachusetts	
Kemira Companies, Inc.	Antioch, California	
	Savannah, Georgia	
	Spokane, Washington	
Mallinckrodt Baker, Inc.	Paris, Kentucky	
Mallinckrodt, Inc., Pharmaceuticals Group	St. Louis, Missouri	
National Alum Corporation	Woodbine, Georgia	
Puerto Rico Alum Corporation	Penuelas, Puerto Rico	
Rhodia, Inc., Services & Specialties Division	Dominguez, California	
	Portland, Oregon	
Russ Chemical Company, Inc.	Odessa, Texas	
Southern Ionics, Inc.	Baton Rouge, Louisiana	
	Calhoun, Tennessee	
	Chickasaw, Alabama	
	Pasadena, Texas	
	Westlake, Louisiana	
	West Point, Mississippi	
Thatcher Company	Henderson, Nevada	
	Missoula, Montana	
	Salt Lake City, Utah	

Table 5-2. U.S. Producers of Selected Aluminum Compounds[a]

Company	Location	Annual capacity (10^3 metric tons)[b]
U.S. Aluminate Company, Inc.	Fairfield, Ohio	
	Michigan City, Indiana	
Sodium aluminosilicate		
Albemarle Corporation	Pasadena, Texas	
W.R. Grace & Co., Grace Division	Curtis Bay, Maryland	
	Lake Charles, Louisiana	
Huber Engineered Materials	Etowah, Tennessee	
	Havre de Grace, Maryland	
	Longview, Washington	
The PQ Corporation, Zeolyst and Catalyst Division	Kansas City, Kansas	
UOP, LLC	Chickasaw, Alabama	
Zeolyst International	Kansas City, Kansas	
Sodium aluminum phosphate		
ICL Performance Products L.P.	Carondelet, Missouri	
Innophos, Inc.	Chicago Heights, Illinois	
	Nashville, Tennessee	

[a]Derived from SRI 2007
[b]SRI Consulting estimates as of February 1, 2007; annual capacities were only reported for aluminum chloride (anhydrous), aluminum chloride (hydrous), and aluminum fluoride.
[d]Unit is currently idle.
[c]Capacities are on 100% $AlCl_3$ basis.
[e]Capacities, which are expressed as 100% $AlCl_3$, are nominal and easily expandable.
[f]Aluminum fluoride is reclaimed from refinery operations in small quantities.
[g]Manufacturers for aluminum phosphide were obtained from EPA 1998.

Aluminum oxide is produced during the recovery of bauxite, which is crushed, ground, and kiln dried, followed by leaching with sodium hydroxide, forming sodium aluminate, from which alumina trihydrate is precipitated and calcined (Bayer process). Aluminum sulfate obtained from coal mine waste waters can be reduced to aluminum oxide (HSDB 2007; Lewis 2001).

Aluminum phosphide can be manufactured in a high degree of purity, by heating aluminum and phosphorus. It can also be prepared from red phosphorus and aluminum powder, or from aluminum and zinc phosphide (HSDB 2007; O'Neil et al. 2001).

Aluminum sulfate is manufactured by reacting freshly precipitated pure aluminum hydroxide, bauxite, or kaolin, with an appropriate quantity of sulfuric acid. The resulting solution is evaporated and allowed to crystallize. Aluminum sulfate can also be produced by the treatment of pure kaolin or aluminum hydroxide or bauxite with sulfuric acid. The insoluble silic acid is removed by filtration and the sulfate is obtained by crystallization. It can be prepared similarly from waste coal mining shale and sulfuric acid (HSDB 2007; Lewis 2001).

Table 5-3 lists the facilities in each state that manufacture or process aluminum (fume or dust), the intended use, and the range of maximum amounts of aluminum that are stored on site. Table 5-4 lists the facilities in each state that manufacture or process aluminum oxide (fibrous form), the intended use, and the range of maximum amounts of aluminum oxide that are stored on site. The data listed in Tables 5-3 and 5-4 are derived from the Toxics Release Inventory (TRI05 2007). Only certain types of facilities were required to report (EPA 1995). Therefore, this is not an exhaustive list.

5.2 IMPORT/EXPORT

In 2006, nearly all of the 12.3 million metric tons of bauxite used in the United States was imported. Domestic mines have supplied <1% of the U.S. requirements for bauxite for many years. Import sources for bauxite (2002–2005) are Jamaica (31%), Guinea (30%), Brazil (17%), Guyana (12%), and other (10%). Import sources for alumina (2002–2005) are Australia (19%), Suriname (29%), Jamaica (9%), and other (12%). More than 90% of the bauxite consumed in the United States in 2006 was converted to alumina (USGS 2007a, 2007d).

Table 5-3. Facilities that Produce, Process, or Use Aluminum (Fume or Dust)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	10,000	99,999	12
AL	37	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
AR	39	0	499,999,999	1, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14
AZ	17	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 11, 12, 13
CA	71	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	11	1,000	999,999	1, 2, 4, 5, 8, 11, 12
CT	20	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
DE	4	1,000	9,999	2, 3, 4, 6, 7, 8, 11
FL	15	0	999,999	1, 5, 7, 8, 9, 11, 12
GA	21	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
IA	41	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
ID	7	10,000	999,999	1, 3, 4, 5, 7, 12, 13
IL	93	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	113	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	25	0	9,999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12
KY	63	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
LA	16	0	9,999,999	1, 5, 6, 7, 8, 10, 11, 12, 13
MA	10	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
MD	13	1,000	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9
ME	5	100	99,999	1, 3, 4, 5, 8, 9, 12
MI	80	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	28	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
MO	49	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MS	16	0	9,999,999	1, 3, 5, 7, 8, 10, 11, 12
NC	39	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	2	1,000	9,999	1, 5, 8
NE	5	1,000	99,999	1, 5, 6, 7, 8, 11, 12
NH	3	100	499,999,999	8
NJ	52	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13
NV	11	100	499,999,999	1, 2, 3, 5, 7, 8, 9, 10, 12, 13
NY	36	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12
OH	120	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	26	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
OR	29	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
PA	105	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	6	100	99,999	4, 8, 12
RI	3	1,000	999,999	7, 8, 9
SC	29	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
TN	60	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13

Table 5-3. Facilities that Produce, Process, or Use Aluminum (Fume or Dust)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TX	64	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	18	0	9,999,999	1, 4, 5, 7, 8, 11, 12, 13
VA	27	0	999,999	1, 2, 3, 5, 7, 8, 11, 12
VT	3	0	999,999	8, 11, 12
WA	20	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
WI	49	0	499,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13, 14
WV	17	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12
WY	1	1,000	9,999	7

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI05 2007 (Data are from 2005)

Table 5-4. Facilities that Produce, Process, or Use Aluminum Oxide (Fibrous Forms)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	2	10,000	999,999	10
AL	56	1,000	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
AR	41	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
AZ	16	1,000	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
CA	96	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
CO	13	100	9,999,999	2, 5, 7, 8, 10, 11, 12, 13
CT	35	0	99,999,999	2, 3, 4, 7, 8, 10, 11, 12
DE	5	10,000	9,999,999	6, 7, 8, 10
FL	24	1,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
GA	59	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
HI	3	10,000	999,999	10, 12
IA	21	100	49,999,999	1, 2, 3, 4, 5, 7, 8, 11, 12
IL	89	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	89	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
KS	25	100	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12
KY	55	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
LA	47	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MA	38	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MD	22	1,000	499,999,999	1, 2, 3, 4, 5, 6, 7, 10, 11, 12, 13
ME	7	1,000	999,999	6, 7, 8, 11, 12
MI	67	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MN	27	100	99,999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12
MO	56	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MS	22	1,000	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
MT	11	0	499,999,999	2, 3, 6, 10, 11, 12
NC	50	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
ND	4	1,000	9,999,999	7, 10
NE	10	1,000	999,999	2, 4, 8, 10, 11, 12, 13
NH	12	1,000	499,999,999	1, 2, 3, 4, 7, 8, 9, 11, 12
NJ	45	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NM	6	1,000	999,999	7, 8, 10, 11, 12
NV	3	100	999,999	1, 5, 6, 8, 9, 10
NY	78	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OH	145	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OK	41	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
OR	14	100	99,999,999	2, 3, 4, 6, 8, 10, 11, 12
PA	115	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PR	9	100	9,999,999	2, 3, 7, 8, 10, 11, 12

Table 5-4. Facilities that Produce, Process, or Use Aluminum Oxide (Fibrous Forms)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
RI	2	10,000	99,999	2, 3, 7
SC	42	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12
SD	4	1,000	99,999	5, 8, 11
TN	70	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
TX	103	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
UT	19	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
VA	30	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
VI	1	1,000,000	9,999,999	10
VT	6	1,000	99,999	8, 11, 12
WA	38	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
WI	43	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WV	34	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
WY	5	10,000	999,999	6, 10, 11

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI05 2007 (Data are from 2005)

5.3 USE

In 2006, transportation accounted for an estimated 40% of domestic consumption of aluminum, predominantly as automotive applications, with the remainder used in packaging, 28%; building, 13%; consumer durables, 7%; electrical, 5%; and other, 7% (USGS 2007c).

Aluminum chloride, anhydrous form, is used as an acid catalyst (especially in Friedel-Crafts-type reactions), as a chemical intermediate for other aluminum compounds, in the cracking of petroleum, in the manufacture of rubbers and lubricants, and as an antiperspirant. The hexahydrate form is used in preserving wood, disinfecting stables and slaughterhouses, in deodorants and antiperspirants, in cosmetics as a topical astringent, in refining crude oil, dyeing fabrics, and manufacturing parchment paper (O'Neil et al. 2001).

Aluminum chlorohydrate is an ingredient in commercial antiperspirant and deodorant preparations and is also used for water purification and treatment of sewage and plant effluent (Lewis 2001)

Aluminum hydroxide (alumina trihydrate) is used as an adsorbent, emulsifier, ion-exchanger, mordant in dyeing, and filtering medium. It is also used in the manufacturing of glass, paper, ceramics and pottery, printing inks, lubricating compositions, detergents, in the waterproofing of fabrics, in antiperspirants, dentifrices, and as a vaccine adjuvant (Baylor et al. 2002; Lewis 2001; O'Neil et al. 2001). Aluminum hydroxide is used as a flame retardant in the interiors of automobiles, commercial upholstered furniture, draperies, wall coverings, and carpets (Subcommittee on Flame-Retardant Chemicals 2000). Aluminum hydroxide is used as an antacid (O'Neil et al. 2001). Finely divided (0.1–0.6 microns) aluminum hydroxide is used for rubber reinforcing agent, paper coating, filler, and cosmetics (Lewis 2001). Aluminum hydroxide is also used pharmaceutically, as an antihyperphosphatemic, to lower the plasma phosphorus levels of patients with renal failure (O'Neil et al. 2001).

Aluminum nitrate is used in textiles (mordant), leather tanning, the manufacturing of incandescent filaments, catalysts in petroleum refining, nucleonics, anticorrosion agent, nitrating agent, and antiperspirants (Lewis 2001; O'Neil et al. 2001).

In 2006, 96% of the bauxite consumed in the United States was refined to alumina (aluminum oxide), with the remaining 4% consumed in nonmetallurgical uses, such as abrasives, chemicals, and refactories. Of the total alumina used in the United States in 2006, approximately 87% was used for primary

aluminum smelters and the remainder was used for nonmetallurgical uses, including abrasives, chemicals, refactories, and in specialty industries (USGS 2007a, 2007d). Other uses of aluminum oxide are in the manufacture of ceramics, electrical insulators, catalyst and catalyst supports, paper, spark plugs, crucibles and laboratory works, adsorbent for gases and water vapors, chromatographic analysis, fluxes, light bulbs, artificial gems, heat resistant fibers, food additive (dispersing agent), and in hollow-fiber membrane units used in water desalination, industrial ultrafiltration, and hemodialysis (HSDB 2007; Lewis 2001). Another application of aluminum oxide, which may have wide occupational use in the future, is as a dosimeter for measuring personnel radiation exposure (McKeever et al. 1995; Radiation Safety Guide 1999; Radiation Safety Newsletter 1998).

Aluminum phosphate is used in ceramics, dental cements, cosmetics, paints and varnishes, pharmaceuticals (antacid), and in paper and pulp industries (Lewis 2001; O'Neil et al. 2001). It is also used as a vaccine adjuvant (Baylor et al. 2002; Malakoff 2000). Aluminum phosphate, as basic sodium aluminum phosphate (SALP), is used as an emulsifying agent in pasteurized processed cheese, cheese food, and cheese spread. Acidic SALP is used as a leavening agent in cereal foods and related products, such as self-rising flour, prepared cake mixes, pancakes, waffles, and refrigerated or frozen dough or batter products (Chung 1992; Saiyed and Yokel 2005).

Aluminum phosphide is a fumigant used primarily for indoor fumigation of raw agricultural commodities, animal feeds, processed food commodities, and non-food commodities in sealed containers or structures to control insects, and for outdoor fumigation of burrows to control rodents and moles in nondomestic areas, noncropland, and agricultural areas. Aluminum phosphide reacts with the moisture in the atmosphere to produce phosphine gas, which is the substance that is active as a pesticide. Based on available pesticide survey usage information for 1987–1996, the estimated annual usage of aluminum phosphide is about 1.6 million pounds active ingredient. Major uses of aluminum phosphide include fumigation of wheat, peanuts, and stored corn. It was noted that usage estimates for aluminum phosphide are not precise due to scarcity of usage data sources for postharvest agriculture and non-agriculture uses/sites. All aluminum phosphide containing products have been classified as restricted use (EPA 1998). According to the National Pesticide Information Retrieval System, there are five active registrants for aluminum phosphide (NPIRS 2008).

Aluminum sulfate (alum) is used in leather tanning, sizing paper, as a mordent in dyeing, water purification, fireproofing and waterproofing of cloth, clarifying oils and fats, treating sewage, waterproofing concrete, deodorizing and decolorizing of petroleum, antiperspirants, and agricultural

pesticide. It is also used as a food additive, a foaming agent in fire foams, and in the manufacturing of aluminum salts (Lewis 2001; O'Neil et al. 2001). Aluminum sulfate, as sodium aluminum sulfate, is a component of household baking powder (Chung 1992). Alum is also used as a vaccine adjuvant (Baylor et al. 2002; Malakoff 2000). Aluminum potassium sulfate (potash alum) is used in dyeing (mordant), paper, matches, paints, tanning agents, waterproofing agents, aluminum salts, food additives, baking powder, water purification, astringent, and cement hardener (Lewis 2001). Aluminum ammonium sulfate (ammonium alum) is used in dyeing (mordant), water and sewage purification, sizing paper, retanning leather, clarifying agent, food additive, the manufacture of lakes and pigments, and fur treatment (Lewis 2001).

Other aluminum compounds that are used as food additives include aluminum silicates (anticaking agents) and aluminum color additives (lakes) (Saiyed and Yokel 2005; Soni et al. 2001).

5.4 DISPOSAL

Production of finished aluminum products by industrial facilities typically results in the generation of very large amounts of solid aluminum hydroxide anodizing residues (Saunders 1988). These aluminum-anodizing residues are currently classified as nonhazardous under the Federal Resource Conservation and Recovery Act (RCRA) regulations. These residues are typically dewatered to reduce the volume of waste prior to being landfilled. However, the heavy metal content of these solid waste residues can be of concern, especially in production processes using two-step anodizing systems that employ solutions containing elevated heavy metal concentrations. For these types of plants, Saunders (1988) has proposed implementation of a caustic-etch recovery system that will limit both the volume of aluminum-anodizing residue and the heavy metal content of the residue. Additional information on regulations and standards for aluminum and aluminum compounds is summarized in Chapter 8.

Approximately 24.7×10^6 and 1.15×10^5 pounds of aluminum (fume or dust) and aluminum oxide (fibrous forms) were reported for on-site disposal and other releases in 2004. On-site disposal or other releases include emissions to the air, discharges to bodies of water, disposal at the facility to land, and disposal in underground injection wells. Approximately 23.7×10^6 and 1.20×10^6 pounds of aluminum (fume or dust) and aluminum oxide (fibrous forms), respectively, were reported for off-site disposal and other releases in 2004. An off-site disposal or other release is a discharge of a toxic chemical to the environment that occurs as a result of a facility's transferring a waste containing a TRI chemical off-site for disposal or

other release (TRI04 2006). The TRI data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list.

In the United States, about 3 million metric tons of aluminum was recovered from purchased scrap in 2006, with 64% of this coming from new (manufacturing) scrap and 36% from old scrap (discarded aluminum products). Aluminum used beverage cans accounted for about 54% of the reported old scrap consumption in 2006. According to the Aluminum Association, Inc., the recycling rate for used aluminum beverage cans in 2004 was 51.6% (USGS 2007b, 2007c).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

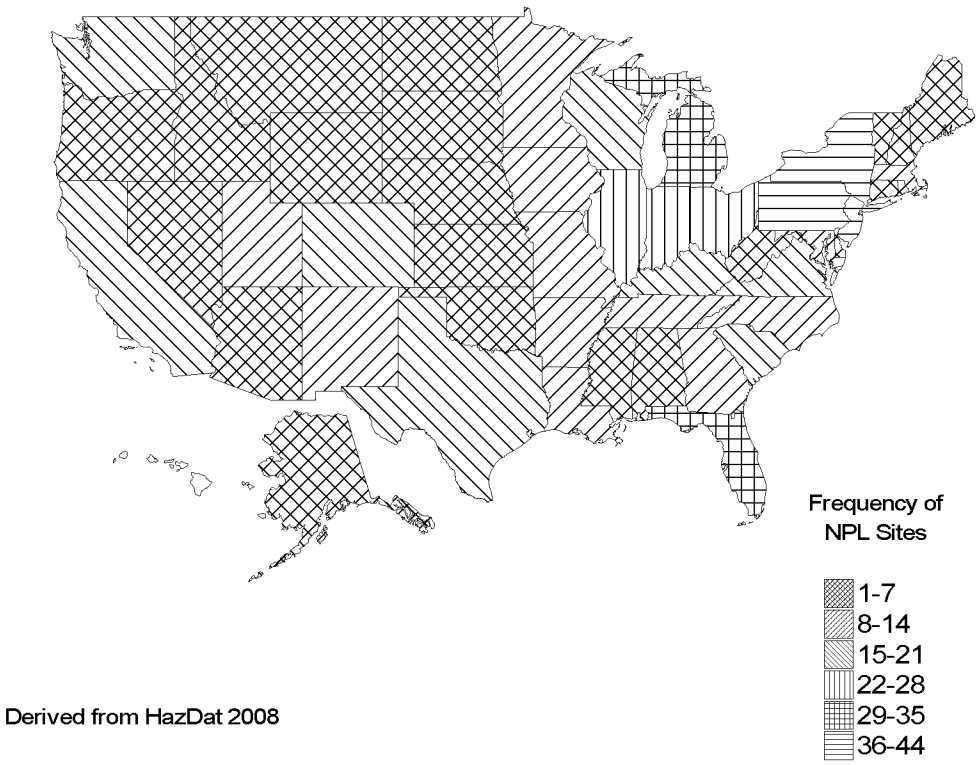
Aluminum has been identified in at least 596 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). However, the number of sites evaluated for aluminum is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 590 are located within the United States, 2 are located in Guam, 3 are located in the Commonwealth of Puerto Rico, and 1 is located in the Virgin Islands (not shown).

Aluminum is the most abundant metal and the third most abundant element in the earth's crust, comprising about 8.8% by weight (88 g/kg). It is never found free in nature and is found in most rocks, particularly igneous rocks as aluminosilicate minerals (Lide 2005; Staley and Haupin 1992). Aluminum is also present in air, water, and many foods. Aluminum enters environmental media naturally through the weathering of rocks and minerals. Anthropogenic releases are in the form of air emissions, waste water effluents, and solid waste primarily associated with industrial processes, such as aluminum production. Because of its prominence as a major constituent of the earth's crust, natural weathering processes far exceed the contribution of releases to air, water, and land associated with human activities (Lantzy and MacKenzie 1979).

The behavior of aluminum in the environment depends upon its coordination chemistry and the characteristics of the local environment, especially pH. The major features of the biogeochemical cycle of aluminum include leaching of aluminum from geochemical formations and soil particulates to aqueous environments, adsorption onto soil or sediment particulates, and wet and dry deposition from the air to land and surface water.

Generally, aluminum is not bioaccumulated to a significant extent. However, certain plants can accumulate high concentrations of aluminum. For example, tea leaves may contain very high concentrations of aluminum, >5,000 mg/kg in old leaves (Dong et al. 1999). Other plants that may contain high levels of aluminum include Lycopodium (Lycopodiaceae), a few ferns, Symplocos (Symplocaceae), and Orites (Proteaceae) (Jansen et al. 2002). Aluminum does not appear to accumulate to any significant degree in cow's milk or beef tissue and is, therefore, not expected to undergo biomagnification in terrestrial food chains (DOE 1984). Similarly, because of its toxicity to many aquatic organisms, including fish, aluminum does not bioconcentrate in aquatic organisms to any significant degree (Rosseland et al. 1990).

Figure 6-1. Frequency of NPL Sites with Aluminum Contamination



Background concentrations of aluminum in rural air typically range from 0.005 to 0.18 μg/m^3 (Hoffman et al. 1969; Pötzl 1970; Sorenson et al. 1974), whereas concentrations in urban and industrial areas can be considerably higher, ranging from 0.4 to 8.0 μg/m^3 (Cooper et al. 1979; Dzubay 1980; Kowalczyk et al. 1982; Lewis and Macias 1980; Moyers et al. 1977; Ondov et al. 1982; Pillay and Thomas 1971; Sorenson et al. 1974; Stevens et al. 1978). Concentrations of aluminum are highly variable in drinking water, ranging from <0.001 to 1.029 mg/L (Schenk et al. 1989). The use of alum (aluminum sulfate) as a flocculent in water treatment facilities typically leads to high aluminum concentrations in finished waters (DOI 1970; Letterman and Driscoll 1988; Miller et al. 1984a). In a survey of 186 community water systems, the median aluminum concentration in finished water receiving coagulation treatment using alum was 0.112 mg/L, compared to 0.043 mg/L in finished water that received no coagulation treatment (Miller et al. 1984a). Dissolved aluminum concentrations in surface and groundwater vary with pH and the humic acid content of the water. High aluminum concentrations in natural water occur only when the pH is <5; therefore, concentrations in most surface water are very low.

Since aluminum is ubiquitous in the environment, the general population will be exposed to aluminum by the inhalation of ambient air and the ingestion of food and water. The consumption of foods containing aluminum-containing food additives are a major sources of aluminum in the diet (Saiyed and Yokel 2005; Soni et al. 2001). The use of other consumer items such as antiperspirants, cosmetics, internal analgesics (buffered aspirins), anti-ulcerative medications, antidiarrheals, and antacids that also contain aluminum compounds will result in exposure to aluminum. The intake of aluminum from food and drinking water is low, especially compared with that consumed by people taking aluminum-containing medicinal preparations. Daily intakes of aluminum from food range from 3.4 to 9 mg/day (Biego et al. 1998; MAFF 1999; Pennington and Schoen 1995), whereas aluminum-containing medications contain much higher levels of aluminum, for example 104–208 mg of aluminum per tablet/capsule/5 mL dose for many antacids (Zhou and Yokel 2005). While aluminum is naturally present in food and water, the greatest contribution to aluminum in food and water by far is the aluminum-containing additives used in water treatment and processing certain types of food such as grain-based products and processed cheese. Aluminum has no known physiological role in the human body (Nayak 2002).

The aluminum content of human breast milk generally ranged from 9.2 to 49 μg/L (Fernandez-Lorenzo et al. 1999; Hawkins et al. 1994; Koo et al. 1988; Simmer et al. 1990; Weintraub et al. 1986). Soy-based infant formulas contain higher concentrations of aluminum, as compared to milk-based infant formulas or breast milk. Recent reports provide average aluminum concentrations of 460–930 μg/L for soy-based

infant formulas and 58–150 µg/L for milk-based formulas (Fernandez-Lorenzo et al. 1999; Ikem et al. 2002; Navarro-Blasco and Alvarez-Galindo 2003).

Occupational exposures to aluminum occur during the mining and processing of aluminum ore into metal, recovery of scrap metal, production and use of aluminum compounds and products containing these compounds, and in aluminum welding. Individuals living in the vicinity of industrial emission sources and hazardous waste sites; individuals with chronic kidney failure requiring long-term dialysis or treatment with phosphate binders; patients requiring intravenous fluids; infants, especially premature infants fed soy-based formula containing high levels of aluminum; and individuals consuming large quantities of antacids, anti-ulcerative medications, antidiarrheal medications may also be exposed to high levels of aluminum.

According to the Toxic Chemical Release Inventory, in 2005, total releases of aluminum (fume or dust) to the environment (including air, water, and soil) from 329 large processing facilities were 45.6 million pounds (~2.07×10^4 metric tons) (TRI05 2007). In addition, in 2005, total releases of aluminum oxide (fibrous forms) to the environment (including air, water, and soil) from 59 large processing facilities were 2.59 million pounds (~1180 metric tons) (TRI05 2007). Tables 6-1 and 6-2 list amounts released from these facilities grouped by state. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces,

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Aluminum (Fume or Dust)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	0	0	0	0	1	0	0	0
AL	4	2,453	0	0	45,887	48,344	2,453	45,887	48,340
AR	3	0	0	0	0	3	0	750	750
AZ	4	7,167	0	0	230,729	237,900	7,217	230,679	237,896
CA	16	182,017	0	0	1,662,654	1,844,688	1,802,363	42,364	1,844,727
CO	1	1,500	0	0	53,058	54,559	1,500	53,058	54,558
CT	2	0	0	0	0	2	0	0	0
FL	5	1,624	0	0	23	1,652	1,624	23	1,647
GA	10	37,680	0	0	108,219	145,909	37,680	108,871	146,551
IA	8	11,570	0	0	43,052	54,630	11,570	43,052	54,622
ID	2	2,864	0	0	653,345	656,211	518,203	138,006	656,209
IL	16	62,008	0	0	520,607	582,631	62,008	525,882	587,890
IN	29	149,220	0	0	10,023,429	10,172,678	149,225	10,024,174	10,173,399
KS	3	0	0	0	0	3	0	0	0
KY	13	254,892	0	0	2,799,380	3,054,285	2,419,281	634,991	3,054,272
LA	4	1,184	0	0	13	1,201	1,197	0	1,197
MA	2	No data	No data	No data	No data	No data	No data	0	0
MD	2	0	0	0	0	2	0	0	0
MI	16	17,862	0	0	1,215,365	1,233,243	17,862	1,224,508	1,242,370
MN	6	58,268	0	0	157,233	215,507	58,268	157,277	215,545
MO	8	29,495	0	0	1,941,390	1,970,893	1,828,685	7,037,274	8,865,959
MS	1	0	0	0	550	551	0	550	550
NC	8	62,432	0	0	55,340	117,780	63,182	54,590	117,772
NE	2	0	0	0	31,105	31,107	21,263	9,842	31,105
NJ	6	4,413	0	0	5,222	9,641	4,413	5,222	9,635
NM	1	No data	No data	No data	No data	No data	No data	0	0
NV	4	259	0	0	330,084	330,347	330,343	0	330,343
NY	7	58,438	312	0	198,222	256,979	60,436	213,027	273,463
OH	33	50,159	2	0	2,170,512	2,220,706	253,161	2,237,892	2,491,053
OK	9	9,654	0	0	447,920	457,583	10,416	447,158	457,574
OR	4	646	0	0	1,295	1,945	646	1,295	1,941
PA	23	8,594	0	0	294,833	303,450	8,866	317,627	326,493
RI	1	No data	No data	No data	No data	No data	No data	0	0
SC	4	7,841	0	0	750	8,595	7,841	1,500	9,341
TN	21	93,021	0	0	887,911	980,953	185,281	795,651	980,932
TX	19	89,879	0	0	7,670,584	7,760,481	2,590,719	5,171,544	7,762,262

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Aluminum (Fume or Dust)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
UT	6	187	0	0	372,634	372,827	147,182	225,639	372,821
VA	2	137	0	0	1,000	1,139	137	1,000	1,137
WA	4	846	0	0	128,819	129,669	846	129,421	130,267
WI	14	75,933	0	0	289,933	365,880	75,933	290,099	366,032
WV	5	3,112	0	0	4,732,012	4,735,129	3,112	4,732,012	4,735,124
Total	329	1,285,354	314	0	37,073,110	38,359,108	10,682,912	34,900,865	45,583,777

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Aluminum Oxide (Fibrous Forms)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	2	0	0	0	0	0	0	0	0
AR	1	0	0	0	0	0	0	0	0
CA	1	0	No data	0	0	0	0	0	0
CO	1	0	5	0	480	2,749	485	2,749	3,234
CT	1	0	0	0	0	0	0	0	0
GA	2	16	175	0	2,957	0	191	2,957	3,148
IA	2	0	0	0	40,320	0	0	40,320	40,320
IL	5	76	0	0	122,002	22,660	76	144,662	144,738
IN	3	901	250	0	5	10	1,156	10	1,166
KY	3	243	0	0	26,631	0	243	26,631	26,874
LA	2	0	0	0	0	0	0	0	0
MI	2	0	0	0	375,000	0	0	375,000	375,000
MO	1	250	0	0	750	0	1,000	0	1,000
NC	4	56	10	0	60,797	4,342	61	65,144	65,205
NE	1	2	0	0	20	0	22	0	22
NM	1	0	0	0	0	0	0	0	0
NY	2	250	0	0	0	29,808	250	29,808	30,058
OH	2	980	0	0	110,958	0	980	110,958	111,938
OK	1	0	No data	0	0	0	0	0	0
PA	6	247	0	0	178,893	6,781	247	185,674	185,920
SC	2	14	0	7	23,556	424	14	23,987	24,001
TN	4	3	0	0	0	0	3	0	3
TX	4	11	0	0	431,166	0	11	431,166	431,177
VA	2	500	0	0	37,159	0	37,409	250	37,659
WI	3	260	0	0	1,059,128	0	1,059,138	250	1,059,388

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Aluminum Oxide (Fibrous Forms)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WV	1	0	0	0	48,000	0	48,000	0	48,000
Total	59	3,810	440	7	2,517,822	66,774	1,149,287	1,439,565	2,588,852

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 1.29 million pounds (~586 metric tons) of aluminum (fume or dust) to the atmosphere from 329 domestic manufacturing and processing facilities in 2005, accounted for about 2.8% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). Estimated releases of 3,810 pounds (~1.73 metric tons) of aluminum oxide (fibrous forms) to the atmosphere from 59 domestic manufacturing and processing facilities in 2005, accounted for about 1.5% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). These releases are summarized in Tables 6-1 and 6-2.

Aluminum is released to the environment by both natural processes and anthropogenic sources. Because of its prominence as a major constituent of the earth's crust, natural processes far exceed the contribution of anthropogenic releases to the environmental distribution of aluminum (Lantzy and MacKenzie 1979). Anthropogenic releases are primarily to the atmosphere. The largest source of airborne aluminum-containing particulates is the flux of dust from soil and the weathering of rocks (Lee and Von Lehmden 1973; Sorenson et al. 1974). In addition, aluminum-containing dust is generated by volcanic activity (Varrica et al. 2000). Human activities, such as mining and agriculture, contribute to this wind-blown dust (Eisenreich 1980; Filipek et al. 1987). About 13% of atmospheric aluminum is attributed to anthropogenic emissions (Lantzy and MacKenzie 1979). The major anthropogenic sources of aluminum-containing particulate matter include coal combustion, aluminum production, and other industrial activities, such as smelting, that process crustal minerals (Lee and Von Lehmden 1973). Aluminum concentrations in air particulate emissions from iron and steel foundries and brass and bronze refineries range from about 100 to 1,000 ppm (Lee and Von Lehmden 1973). Que Hee et al. (1982) also found that aluminum was one of the most abundant elements quantified in coal stack emissions from power plants located in both the eastern and western United States. In addition, in U.S. cities, motor vehicle emissions contribute an estimated 0.9–9% of the observed elemental concentration of aluminum in these atmospheres (Ondov et al. 1982).

Aluminum has been identified in air samples collected at 14 of the 596 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 2008).

6.2.2 Water

Estimated releases of 314 pounds (~0.14 metric tons) of aluminum (fume or dust) to surface water from 329 domestic manufacturing and processing facilities in 2005, accounted for about 0.0007% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). Estimated releases of 440 pounds (~0.20 metric tons) of aluminum oxide (fibrous forms) to surface water from 59 domestic manufacturing and processing facilities in 2005, accounted for about 0.017% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). These releases are summarized in Tables 6-1 and 6-2.

Aluminum occurs ubiquitously in natural waters as a result of the weathering of aluminum-containing rocks and minerals. Of the known geochemical responses to environmental acidification, the best documented is the mobilization of aluminum from terrestrial to aquatic environments (Campbell et al. 1992). This mobilization of aluminum is often episodic in nature and is associated with pH depressions (acidification) occurring during the spring snowmelt or associated with erosion from specific storm events (Campbell et al. 1992; Nelson and Campbell 1991; Rosseland et al. 1990).

Aluminum concentrations in surface waters can be increased directly or indirectly by human activity through industrial and municipal discharges, surface run-off, tributary inflow, groundwater seepage, and wet and dry atmospheric deposition (Eisenreich 1980). For example, aluminum is released to surface waters in the effluent from bauxite processing and aluminum manufacturing facilities at concentrations that can be toxic to aquatic life (His et al. 1996; Trieff et al. 1995). However, the effluents of these facilities typically contain not only aluminum, but also a complex mixture of heavy metals such as iron, chromium, and mercury, as well as minerals, silica, and other compounds, and synergistic effects of these metals and compounds cannot be ruled out. The use of aluminum sulfate and other aluminum compounds as coagulating agents in the treatment of raw drinking water supplies can significantly increase the total aluminum content in finished water (Cech and Montera 2000; Henshaw et al. 1993; Miller et al. 1984a; Qureshi and Malmberg 1985; USGS 1984b). Weathering of sulfide ores exposed to the atmosphere in inactive mines and tailings dumps releases large quantities of sulfuric acid and metals such as aluminum (Filipek et al. 1987). Increasingly, acid environments caused by such acid mine drainage or by acid rain will subsequently cause an increase in the dissolved aluminum content of the surrounding waters (Brusewitz 1984; Filipek et al. 1987). In addition, atmospheric deposition is a source of aluminum input to surface water. The atmospheric loading of aluminum to Lake Michigan was estimated to be 5 million

kg/year, of which 74% was to the southern basin where the influence of agricultural and industrial activity (e.g., steel manufacturing and cement production) was greatest (Eisenreich 1980).

Aluminum has been identified in surface water and groundwater samples collected at 251 and 391 of the 596 NPL hazardous waste sites, respectively, where it has been detected in some environmental media (HazDat 2008).

6.2.3 Soil

Estimated releases of 37.1 million pounds (~$1.68x10^4$ metric tons) of aluminum (fume or dust) to soils from 329 domestic manufacturing and processing facilities in 2005, accounted for about 81% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). Estimated releases of 2.52 million pounds (~1,140 metric tons) of aluminum oxide (fibrous forms) to soils from 59 domestic manufacturing and processing facilities in 2005, accounted for about 97% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). An additional 7 pounds (3 kilograms) of aluminum oxide (fibrous forms) were released via underground injection (TRI05 2007). These releases are summarized in Tables 6-1 and 6-2.

Aluminum is the most abundant metal and the third most abundant element in the earth's crust, comprising about 8.8% by weight (88 g/kg) (Staley and Haupin 1992). Aluminum can be released naturally by the weathering of aluminum-containing rocks. Aluminum is also released to soil as a major constituent of many mining wastes and is also contained in solid wastes from coal combustion and aluminum reduction and other metal processing operations (DOI 1983, 1984). Wilson et al. (2002) estimated that several hundred thousand pounds of aluminum containing chaff have been release to the Chesapeake Bay during research and training operations by the Naval Research Laboratory-Chesapeake Bay Detachment over the past 25 years.

Aluminum has been identified in soil and sediment samples collected at 253 and 190 of the 596 NPL hazardous waste sites, respectively, where it has been detected in some environmental media (HazDat 2008).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Aluminum is the most abundant metal in the earth's crust, but is never found in its elemental state in nature. In compounds, aluminum occurs in its only oxidation state (+3) (Lide 2005). Aluminum occurs widely in nature with silicates, such as mica and feldspar, as the hydroxo oxide (bauxite), and as cryolite (Na_3AlF_6) (Cotton et al. 1999). Aluminum's behavior in the environment is strongly influenced by its coordination chemistry. Aluminum partitions between solid and liquid phases by reacting and complexing with water molecules and anions such as chloride, fluoride, sulfate, nitrate, phosphate, and negatively charged functional groups on humic materials and clay.

The transport and partitioning of aluminum in the environment is determined by its chemical properties, as well as the characteristics of the environmental matrix that affect its solubility. At a pH >5.5, naturally occurring aluminum compounds exist predominantly in an undissolved form such as gibbsite, $Al(OH)_3$, or as aluminosilicates except in the presence of high amounts of dissolved organic material or fulvic acid, which binds with aluminum and can cause increased dissolved aluminum concentrations in streams and lakes (Brusewitz 1984). Organic acids have been found to be important weathering agents for dissolving and transporting aluminum in an alpine soil environment (Litaor 1987). The ability of these organic acids to complex aluminum in sub-alpine soil solutions was found to increase as the pH rose from 3.8 to 5 (Dahlgren and Ugolini 1989). In this study, dissolved aluminum was found primarily as organic complexes when organic carbon/metal ratios were >50 (Dahlgren and Ugolini 1989).

In general, decreasing pH (acidification) results in an increase in mobility for monomeric forms of aluminum (Goenaga and Williams 1988), which is of concern with respect to the occurrence of acid rain and the release of acid mine drainage. Aluminum in soil solutions and surface waters in a mining region rich in metallic sulfides was in a labile form, as Al-SO_4 and Al^{3+} species. Acidic conditions are created by the microbial oxidation of sulfides in tailing piles, resulting in sulfuric acid. In contrast, in areas not affected by acidification, aluminum in solution was partitioned between labile and non-labile forms, the latter being predominantly bound to fluorine (Alvarez et al. 1993). In soils, the most soluble form of aluminum under acidic conditions is nonsilicaceous, organically-bound aluminum (Mulder et al. 1989).

In groundwater or surface water systems, an equilibrium with a solid phase form is established that largely controls the extent of aluminum dissolution which can occur. In acid sulfate waters resulting from mine drainage, gibbsite and kaolinite are not stable, and the solubility of the minerals jurbanite

($Al(SO_4)(OH)\cdot H_2O$) or alunite ($KAl_3(SO_4)_2(OH)_6$) may control aluminum levels (Filipek et al. 1987). In a Colorado alpine watershed soil, the chemical equilibria of aluminum in interstitial water at a pH range of 4.4–7.2 were controlled by amorphous aluminosilicate rather than gibbsite (Litaor 1987).

In addition to the effect of pH on mobility, the type of acid entering environmental systems may also be important. Nitric acid was found to leach more aluminum from soil columns representative of high-elevation forest floor soils than did sulfuric acid (James and Riha 1989). However, in mineral horizons below the forest floor, the study found that concentrations of aluminum leached by these acids did not differ from concentrations of aluminum leached by distilled, deionized water at a pH of 5.7. The authors concluded that soluble constituents from the forest floor affected the aluminum solubility in the underlying mineral horizons under the leaching conditions that they used. These constituents may have included natural buffering agents which resist changes in pH and, therefore, negate or mediate the effect of the acid.

The ability of mineralized soil to control the migration of aluminum was observed in another study. Acidic leachate from coal waste containing aluminum was percolated through soil containing varying amounts of calcium carbonate (Wangen and Jones 1984). Soluble aluminum was found to decrease dramatically as the pH of the percolating leachate increased and aluminum oxide precipitates formed; at pH 6, no dissolved aluminum was measured. The authors concluded that alkalinized carbonaceous soils provide the best control material for acidic leachates from coal mineral wastes.

The adsorption of aluminum onto clay surfaces can be a significant factor in controlling aluminum mobility in the environment, and these adsorption reactions, measured in one study at pH 3.0–4.1, have been observed to be very rapid (Walker et al. 1988). However, clays may act either as a sink or a source for soluble aluminum depending on the degree of aluminum saturation on the clay surface (Walker et al. 1988).

The presence of high levels of suspended solids in stream surface water during storm episodes resulted in higher concentrations of adsorbed aluminum than in the absence of suspended solids (Goenaga and Williams 1988). The increased adsorption was not strictly linear, with higher concentrations of suspended solids due to variations in the particle size distribution and the nature of the particles.

Within the pH range of 5–6, aluminum complexes with phosphate and is removed from solution. Because phosphate is a necessary nutrient in ecological systems, this immobilization of both aluminum

and phosphate may result in depleted nutrient states in surface water (Brusewitz 1984). Conversely, aluminum has been added to a nutrient-rich lake in Sweden with some success in an effort to arrest the "aging process" caused by an overabundance of phosphate (Jernelov 1971).

Aluminum salt coagulants are used in the treatment of potable drinking water, and unretained aluminum (approximately 11% of the added aluminum) was found to be transported through a water distribution system (Driscoll and Letterman 1988).

Aluminum, as a constituent of soil, weathered rock, and solid waste from industrial processes, is transported through the atmosphere as windblown particulate matter and is deposited onto land and water by wet and dry deposition. Atmospheric loading rates of aluminum to Lake Michigan were estimated at 5 million kg/year (Eisenreich 1980). In this study, most of the aluminum was generally associated with large particles that were deposited near their source. In a study, the wet and dry deposition of aluminum was measured biweekly for 1 year at two sites on Massachusetts Bay, Turro and Nahant. The average total deposition rate was 0.1 g/m^2-year, of which 29% was in rain (wet deposition) (Golomb et al. 1997).

Plant species and cultivars of the same species differ considerably in their ability to take up and translocate aluminum to above-ground parts (Kabata-Pendias and Pendias 1984). Tea leaves may contain very high concentrations of aluminum, >5,000 mg/kg in old leaves (Dong et al. 1999). Other plants that may contain high levels of aluminum include Lycopodium (Lycopodiaceae), a few ferns, Symplocos (Symplocaceae), and Orites (Proteaceae) (Jansen et al. 2002). Aluminum is often taken up and concentrated in root tissue (Kabata-Pendias and Pendias 1984). In sub-alpine ecosystems, the large root biomass of the Douglas fir, *Abies amabilis*, takes up aluminum and immobilizes it, preventing large accumulation in above-ground tissue (Vogt et al. 1987). It is unclear to what extent aluminum is taken up into root food crops and leafy vegetables. An uptake factor (concentration of aluminum in the plant/concentration of aluminum in soil) of 0.004 for leafy vegetables and 0.00065 for fruits and tubers has been reported (DOE 1984), but the pH and plant species from which these uptake factors were derived are unclear. Based upon these values, however, it is clear that aluminum is not taken up in plants from soil, but is instead biodiluted.

Transfer coefficients of 0.0002 $(kg/day)^{-1}$ for uptake into milk and 0.0015 $(kg/day)^{-1}$ for uptake into beef tissue have been reported (DOE 1984). The transfer coefficients represent the fraction of daily aluminum intake in feed that is transferred to a kilogram of milk or beef muscle. Based upon the above values,

aluminum is not transferred to beef muscle or milk from feed to any appreciable extent and therefore would not be expected to bioaccumulate in terrestrial food chains.

The potential for accumulation of aluminum has been studied in several aquatic species including fish (Buckler et al. 1995; Cleveland et al. 1991; Hamdy 1993; McDonald et al. 1991; Wilkinson and Campbell 1993), amphibians (Freda and McDonald 1990), crustaceans (Madigosky et al. 1991), snails (Brooks et al. 1992), aquatic insects (Frick and Herrmann 1990; Guerold et al. 1995; Krantzberg and Stokes 1990), and aquatic plants (Albers and Camardese 1993; Vuori et al. 1990). Bioconcentration of aluminum in fish is a function of the water quality (e.g., pH and total organic carbon) (Cleveland et al. 1989).

Brook trout have been shown to accumulate slightly more aluminum (measured as whole-body residues) at pH 5.6–5.7 than at pH 6.5–6.6 (Cleveland et al. 1989). Cleveland et al. (1991) reported that the estimated steady-state bioconcentration factors (BCF) for aluminum in brook trout were 215, 123, and 36 at pH 5.3, 6.1, and 7.2, respectively. When transferred to water of the same pH without added aluminum, brook trout eliminated aluminum from tissues more rapidly at pH 5.3 than at pH 6.1 and 7.2. In tissues of smallmouth bass, aluminum concentrations were higher and more variable in gill tissue than in other tissues (Brumbaugh and Kane 1985). Aluminum concentrations in rainbow trout from an alum-treated lake, an untreated lake, and a hatchery were highest in gill tissue and lowest in muscle (Buergel and Soltero 1983). Aluminum residue analyses in brook trout have shown that whole-body aluminum content decreases as the fish advance from larvae to juveniles (Cleveland et al. 1989). These results imply that the aging larvae begin to decrease their rate of aluminum uptake, to eliminate aluminum at a rate that exceeds uptake, or to maintain approximately the same amount of aluminum while the body mass increases. The decline in whole-body aluminum residues in juvenile brook trout may be related to growth and dilution by edible muscle tissue that accumulated less aluminum than did the other tissues (Cleveland et al. 1989). Wilkinson and Campbell (1993) studied aluminum uptake in Atlantic salmon at a pH of 4.5 under conditions simulating spring snowmelt. These authors reported that gill uptake was slow, approaching a steady state only after 3 days of exposure. The greatest fraction of the gill-associated aluminum was not sorbed to the gill tissue, but to the gill mucus. The authors believe that the mucus appears to retard aluminum transport from solution to the membrane surface, thus delaying the acute biological response of the fish. Buckler et al. (1995) reported concentrations of aluminum in whole-body tissue of the Atlantic salmon exposed to high concentrations of aluminum ranging from 3 μg/g (for fish exposed to 33 μg/L) to 96 μg/g (for fish exposed to 264 μg/L) at pH 5.5. After 60 days of exposure, BCFs ranged from 76 to 190 and were directly related to the aluminum exposure concentration. In acidic waters (pH 4.6–5.3) with low concentrations of calcium (0.5–1.5 mg Ca/L), labile aluminum between

25 and 75 µg/L is toxic (Rosseland et al. 1990). Because aluminum is toxic to many aquatic species, it is not bioaccumulated to a significant degree (BCF <300) in most fish and shellfish; therefore, consumption of contaminated fish does not appear to be a significant source of aluminum exposure in humans.

Aluminum uptake for the leopard frog (*Rana pipiens*) was positively correlated to exposure time and pH; however, no BCF values were reported because the authors felt that the body aluminum accumulation was too variable for useful prediction of the exposure history or physiological status of the frogs (Freda and McDonald 1990).

Bioconcentration of aluminum has also been reported for several aquatic invertebrate species. BCF values ranging from 0.13 to 0.5 in the whole-body were reported for the snail, *Helix aspersa*, fed a single 24-hour meal containing aluminum in a barley-flour pellet (Brooks et al. 1992). Madigosky et al. (1991) reported high tissue residues of aluminum in the red swamp crayfish (*Procambarus clarkii*) collected from roadside drainage ditches in Louisiana. Mean aluminum concentrations as µg/g dry weight in crayfish from roadside ditches ranged from 1.75 to 6.39 in abdominal muscle, 3.1–22.74 in the hepatopancreas, 309.4–981.50 in the alimentary tract, 10.85–77.45 in the exoskeleton, and 30–140 in the blood. These values were significantly elevated above those of control crayfish where the concentrations (µg Al/g dry weight) were 1.22 in abdominal muscle, 1.42 in the hepatopancreas, 26.97 in the alimentary tract, 4.28 in the exoskeleton, and 37.9 in the blood.

Bioconcentration of aluminum has also been reported for aquatic insects. Frick and Herrmann (1990) reported aluminum accumulation in mayfly nymphs (*Heptagenia sulphurea*) at low pH (4.5). The nymphs were exposed at two concentrations (0.2 and 2 mg Al/L) and for two exposure times (2 and 4 weeks), the longer time period including a molting phase. When nymphs were exposed to the higher concentration of aluminum for two instar periods, with a molt in between, the aluminum content (2.34 mg Al/g dry weight) nearly doubled compared with that of a one-instar treatment (1.24 mg Al/g dry weight). The major part of the aluminum was deposited in the exuviae of the nymphs, as the aluminum determination in the nymphs showed a 70% decrease in aluminum content after molting. These authors speculate that internally accumulated aluminum in the nymphs may be transferred to terrestrial predators (e.g., birds). They also hypothesized that externally deposited aluminum may be transferred to terrestrial food chains by aquatic invertebrates that leave the water in their last instar to molt on shore. An important contribution to the idea of biomagnification of aluminum was made by Nyholm (1981). Using semi-quantitative multi-element microanalysis, he related impaired breeding of pied flycatchers (*Ficedula hypoleuca*) in Sweden to the occurrence of aluminum in the bone marrow of the birds. A diet of

stoneflies was suspected of forming a link between the lake and the terrestrial predators. Although the matter is far from clear, Nyholm (1981) seems to imply that the insects (stoneflies) were adults and that these could contain significant amounts of aluminum even after having left the exuviae behind (Frick and Herrmann 1990).

Vuori et al. (1990) sampled tufts of the aquatic moss, *Fontinalis dalecarlica*, from the River Lestijoki in Western Finland. The concentrations of aluminum in the water were low (87–196 µg/L, pH 6.5–7.0) relative to the concentrations in the young terminal shoots of *F. dalecarlica* appeared to be quite high (303–1,852 µg/g dry weight). The authors concluded that there was an effective accumulation of aluminum in the moss tissue. Albers and Camardese (1993) compared concentrations of aluminum and other metals in aquatic species of three acidified (pH≈5) and three nonacidified (pH≈6.5) constructed wetlands. They found that the metal content of *Sparganium americanum* (bur-reed) was only slightly affected by acidification.

6.3.2 Transformation and Degradation

As an element, aluminum cannot be degraded in the environment, but may undergo various precipitation or ligand exchange reactions. Aluminum in compounds has only one oxidation state (+3), and would not undergo oxidation-reduction reactions under environmental conditions. Aluminum can be complexed by various ligands present in the environment (e.g., fulvic and humic acids). The solubility of aluminum in the environment will depend on the ligands present and the pH.

6.3.2.1 Air

Aluminum-containing particulate matter in the atmosphere is mainly derived from soil and industrial processes where crustal materials (e.g., minerals) are processed. Aluminum is found as silicates, oxides, and hydroxides in these particles (Eisenreich 1980). Aluminum compounds cannot be oxidized and atmospheric transformations would not be expected to occur during transport. If aluminum metal particulates were released to air during metal processing, they would be rapidly oxidized.

6.3.2.2 Water

The trivalent aluminum ion is surrounded by six water molecules in solution (Cotton et al. 1999). The hydrated aluminum ion, $[Al(H_2O)_6]^{3+}$, undergoes hydrolysis, in which a stepwise deprotonation of the coordinated water ligands forms bound hydroxide ligands (e.g., $[Al(H_2O)_5(OH)]^{2+}$, $[Al(H_2O)_4(OH)_2]^{+}$)

(Snoeyink and Jenkins 1980). The speciation of aluminum in water is pH dependent. The hydrated trivalent aluminum ion is the predominant form at pH levels below 4. Between pH 5 and 6, the predominant hydrolysis products are $Al(OH)^{2+}$ and $Al(OH)_2^{+}$, while the solid $Al(OH)_3$ is most prevalent between pH 5.2 and 8.8. The soluble species $Al(OH)_4^{-}$ is the predominant species above pH 9, and is the only species present above pH 10 (Martell and Motekaitis 1989). Polymeric aluminum hydroxides appear between pH 4.7 and 10.5, and increase in size until they are transformed into colloidal particles of amorphous $Al(OH)_3$, which crystalize to gibbsite in acid waters (Brusewitz 1984). Polymerization is affected by the presence of dissolved silica; when enough silica is present, aluminum is precipitated as poorly crystallized clay mineral species (Bodek et al. 1988).

Hydroxyaluminum compounds are considered amphoteric (e.g., they can act as both acids and bases in solution) (Cotton et al. 1999). Because of this property, aluminum hydroxides can act as buffers and resist pH changes within the narrow pH range of 4–5 (Brusewitz 1984).

Monomeric aluminum compounds, typified by aluminum fluoride, chloride, and sulfate, are considered reactive or labile compounds, whereas polymeric aluminum species react much more slowly in the environment (USGS 1984a). Aluminum has a stronger attraction for fluoride in an acidic environment compared to other inorganic ligands (Brusewitz 1984). Fulvic acid is also an important ligand for aluminum under acidic conditions, and it has been observed that as the temperature is lowered, the rate of complexation of aluminum with fluoride is considerably slowed, while the rate of complexation between aluminum and fulvic acid is only slightly decreased in rate (Plankey and Patterson 1987). This suggests that during snow-melt conditions, when aluminum and hydrogen ion concentrations increase, complexation with fulvic acid could preferentially occur over complexation with fluoride.

6.3.2.3 Sediment and Soil

Aluminum is present in many primary minerals. The weathering of these primary minerals over time results in the deposition of sedimentary clay minerals, such as the aluminosilicates kaolinite and montmorillonite. The weathering of soil results in the more rapid release of silicon, and aluminum precipitates as hydrated aluminum oxides such as gibbsite and boehmite, which are constituents of bauxites and laterites (Bodek et al. 1988). Aluminum is found in the soil complexed with other anions, such as fluoride, sulfate, and phosphate.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to aluminum depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of aluminum in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on aluminum levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring aluminum in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

There are varying levels of aluminum in the atmosphere, depending on the location of the sampling site, meteorologic conditions, and the level of industrial activity or traffic in the area. Aluminum levels are expected to be low in areas influenced by the ocean and high in areas with wind-blown soil. Background concentrations of aluminum in the atmosphere generally range from 0.005 to 0.18 μg/m^3 (Hoffman et al. 1969; Pötzl 1970; Sorenson et al. 1974). In rural areas of Hawaii, aluminum concentrations have been measured at a range of 0.005–0.032 μg/m^3 (Hoffman et al. 1969), whereas a concentration range of 0.27–0.39 μg/m^3 has been reported in Manitoba National Park in Canada (AEC 1971). Atmospheric aluminum concentrations in U.S. cities and industrial areas are considerably higher, ranging from about 0.4 to 8.0 μg/m^3 (Cooper et al. 1979; Dzubay 1980; Kowalczyk et al. 1982; Lewis and Macias 1980; Moyers et al. 1977; Ondov et al. 1982; Pillay and Thomas 1971; Sorenson et al. 1974; Stevens et al. 1978). The range of the concentration of aluminum in fine (<1–2.5 μm) and course (2.5–10 μm) particles from two industrial areas, Southeast Chicago, Illinois and East St. Louis, Illinois were 22–539 ng/m^3 (125 ng/m^3 mean) and 24–1,370 ng/m^3 (153 ng/m^3 mean), respectively, for fine particles and 8.2–1760 ng/m^3 (390 ng/m^3 mean) and 17–2,120 ng/m^3 (442 ng/m^3 mean), respectively, for coarse particles. At a rural site (Bondville, Illinois), the aluminum concentrations in fine and coarse particles ranged from 32 to 293 ng/m^3 (95 ng/m^3 mean) and from 32 to 3,120 ng/m^3 (338 ng/m^3 mean), respectively which was not much different than the aluminum concentration from the industrial sites (Sweet et al. 1993). A mean aluminum concentration of 474.6 ng/m^3 (range 38.4–2,619.6 ng/m^3) was reported in particulate matter collected in air from downtown Rio de Janeiro, Brazil; samples were collected during the period from September 2001 to August 2002 (Quiterio et al. 2004). Mean aluminum concentrations in winter and summer indoor air sampled in 1999 were 41 and 39 ng/m^3 in the homes of 46 high school students from West Central Harlem, New York City who participated in the Toxic Exposure Assessment a Columbia/Harvard (TEACH) study (Kinney et al. 2002). Aluminum concentrations can also vary with

seasonal meteorological conditions. For example, in Mackinac Island, Michigan, summer concentrations averaged about 0.25 μg/m^3, while winter concentrations were only about 0.18 μg/m^3 (AEC 1971).

6.4.2 Water

The concentrations of dissolved aluminum in water vary with pH and the humic-derived acid content of the water (Brusewitz 1984). Aluminum is only sparingly soluble in water between pH 6 and 8. Because the pH of about 95% of naturally-occurring water is between 6 and 9 and since high aluminum concentrations occur in surface water bodies only when the pH is <5, the aluminum concentration in most natural waters is extremely low (Filipek et al. 1987; Snoeyink and Jenkins 1980; Sorenson et al. 1974). In general, aluminum concentrations in surface waters at pH levels above 5.5 will be <0.1 mg/L (Brusewitz 1984; Miller et al. 1984a; Sorenson et al. 1974; Taylor and Symons 1984). However, even at neutral pH levels, higher aluminum concentrations have been found in lakes with a high humic acid content (Brusewitz 1984). Aluminum concentrations in marinewaters tend to be much lower (i.e., <0.001 mg/L) than those found in freshwater lakes and streams (Brusewitz 1984), probably because of increased alkalinity in marinewater compared to fresh water.

At lower pH levels, the aluminum content significantly increases because of increased solubility of aluminum oxide and salts in acidic solutions. For example, aluminum has been found at concentrations of up to 90 mg/L in tributaries that drain mines containing massive sulfide deposits (Filipek et al. 1987). In heavily contaminated surface waters in a mining region rich in sulfides, the water was highly acidic (pH <3.5) and the levels of soluble aluminum were >2 mmol/L (50 mg/L) (Alvarez et al. 1993). Similarly, surface water samples contaminated with acidic mine drainage collected at seven different locations in the vicinity of abandoned coal mines in west-central Indiana had aluminum concentrations of 6.0–269 mg/L (Allen et al. 1996). The pH ranged from 2.1 to 3.4 at these sites.

Aluminum was detected at dissolved aluminum concentrations ranging from 0.001 to 2.760 mg/L with a mean concentration of 0.074 mg/L in 456 of 1,577 raw surface water samples collected during a 5-year survey at various locations across the United States (DOI 1970). Dissolved aluminum concentrations were detected in about 48% of the 380 finished drinking waters sampled and ranged from 0.003 to 1.6 mg/L with a mean of 0.179 mg/L (DOI 1970). In another survey of 186 community water systems, median aluminum concentrations for all finished drinking water samples ranged from 0.026 to 0.161 mg/L (Miller et al. 1984a). These authors further reported that the median aluminum concentration in finished water that received no coagulation treatment was 0.043 mg/L (range, 0.016–1.167 mg/L)

compared to the median of 0.112 mg/L (range, 0.014–2.670 mg/L) in finished water receiving alum (aluminum sulfate) coagulation treatment. In the supplies in which no coagulant was used during treatment, 29% of supplies using surface water as their source had aluminum concentrations exceeding 0.05 mg/L, whereas only 4% of supplies using groundwater sources exceeded this level. When aluminum coagulants were used, 69% of all supplies had residual aluminum concentrations >0.05 mg/L (Miller et al. 1984a). In another study, the aluminum content in treated water at facilities using alum coagulation treatment of raw waters ranged from about 0.01 to 1.3 mg/L with a mean of about 0.157 mg/L (Letterman and Driscoll 1988). Tap water samples were collected in 1998 in the service area of East Houston, Texas water purification plant; 44% of these samples had aluminum concentrations >0.2 mg/L. Aluminum concentrations as high as 0.53 mg/L were observed in samples collected near the treatment plant that used an alum coagulant. An average decrease of 7 μg/L/km was observed along the distribution system (Cech and Montera 2000).

Schenk et al. (1989) measured aluminum concentrations in drinking water collected primarily in the western and central parts of the United States from outlets from which water was consumed rather than from the original water treatment plant. Aluminum concentrations in drinking water in various regions of the United States are listed in Table 6-3. Although aluminum concentrations in drinking water may range from undetectable to 1.029 mg/L, aluminum concentrations in most drinking water in the United States were generally <0.1 mg/L (Schenk et al. 1989). While several water sources in the west coast states (California, Oregon, and Washington) were found to contain undetectable concentrations of aluminum (<0.001 mg/L), several cities in other geographic areas of the United States had high aluminum concentrations (>0.4 mg/L). These included Peoria, Illinois (0.467 mg/L); Coos Bay, Oregon (0.483 mg/L); Watertown, South Dakota (0.502 mg/L); Waco, Texas (0.520 mg/L); Yellowstone National Park, Wyoming (0.608 mg/L); Philadelphia, Pennsylvania (0.688 mg/L); and Charleston, South Carolina (1.029 mg/L).

Henshaw et al. (1993) studied concentrations of various components, including aluminum, in drinking water derived from the Great Lakes in six communities in the United States and Ontario, Canada. Alum was used as a coagulant in all six communities. It was found that aluminum concentrations were generally higher in treated waters as compared to raw water. Between 1986 and 1990, mean aluminum concentrations in raw water were 0.020–0.053, 0.058–0.070, 0.012–0.023, 0.020–0.037, and 0.058–0.476 mg/L in Milwaukee, Wisconsin; Rochester, New York; Thunder Bay, Ontario; Toronto, Ontario; and Windsor, Ontario, respectively. Between 1986 and 1990, mean aluminum concentrations in treated water were 0.085–0.200, 0.070–0.115, 0.027–0.032, 0.080–0.139, and 0.113–0.727 mg/L in Gary,

Table 6-3. Aluminum Concentrations Detected in Drinking Water in Various Regions of the United States

U.S. States	Aluminum concentration (µg/L)[a]
California	0–274
Colorado	42–166
Hawaii	12–124
Idaho	28–63
Illinois	3–467
Indiana	1–137
Kansas	12–245
Kentucky	9–400
Louisiana	12–210
Michigan	6–123
Minnesota	24–93
Missouri	2–368
Montana	11–98
New York[b]	254–299
Nevada	5–126
Ohio	2–245
Oregon	0–483
Pennsylvania[c]	688
South Carolina	2–1,029
South Dakota	2–502
Tennessee[d]	45
Texas	1–520
Utah	19–51
Washington	0–118
Wisconsin	12–118
Wyoming	16–608

[a]Range in values reported for each state
[b]Water sampled in New York City only
[c]Water sampled in Philadelphia only (one sample)
[d]Water sampled in Memphis only (one sample)

Source: Schenk et al. 1989

Indiana; Rochester, New York; Thunder Bay, Ontario; Toronto, Ontario; and Windsor, Ontario, respectively. Data for raw water in Gary, Indiana and treated water in Milwaukee, Wisconsin were not provided (Henshaw et al. 1993). Aluminum concentrations in 172 samples of bottled water sold in Canada ranged from <0.010 to 0.568 μg/g (<0.010–0.567 mg/L), with a mean of 0.027 μg/g (0.027 mg/L) (Dabeka et al. 1992). Drinking water from 35 cities and villages in Galicia, northwest Spain were analyzed for dissolved aluminum during 1997 to 2003; an average aluminum concentration of 0.126 mg/L was reported, with concentrations ranging from 0.008 to 0.650 mg/L (Rubinos et al. 2007).

Aluminum has been measured in atmospheric precipitation (i.e., rain and snow) in the United States at concentrations up to 1.2 mg/L (Dantzman and Breland 1970; DOI 1971; Fisher et al. 1968; USGS 1964). Aluminum has been measured in rainwater samples collected during the Global Change Expedition in the North Atlantic Ocean (Lim and Jickells 1990). These authors reported that comparisons between acid-leachable and total (dissolved plus particulate) trace aluminum concentrations suggest that the acid-leachable fraction of aluminum can significantly underestimate total concentrations of aluminum in rainwater. Acid-leached mean concentrations of aluminum in rainwater collected during three rainfall events in the North Atlantic were 33.7, 12.2, and 1.99 μg/L. Overall, the acid-leached concentrations of aluminum in rainwater for seven rainfall events ranged from 1.14 to 35.2 μg/L. These values were compared with acid-leachable aluminum concentrations in precipitation from remote areas which ranged from 2.1 to 15.44 μg/L. Total (dissolved plus particulate) aluminum concentrations in North Atlantic precipitation samples collected in 1988 ranged from 6.1 to 827 μg/L (Lim and Jickells 1990).

Aluminum concentrations in groundwater wells at neutral pH generally fall below 0.1 mg/L (Brusewitz 1984). In areas receiving acid precipitation, aluminum concentrations in groundwater may be >10 times the concentrations found in areas with neutral pH levels in the water (Brusewitz 1984), possibly due to precipitation of aluminum compounds in the more alkaline medium, or the reaction of aluminum with available silicates. In another study, Miller et al. (1984a) reported that the median concentration of aluminum in finished water obtained from groundwater was 0.031 mg/L (range, 0.014–0.290 mg/L) as compared to the median concentration in surface water of 0.043 mg/L (range, 0.016–1.167 mg/L). These authors also reported that, while 55% of the raw surface waters sampled contained aluminum concentrations >0.05 mg/L, only 4% of the raw groundwater samples contained aluminum concentrations >0.05 mg/L.

6.4.3 Sediment and Soil

Aluminum is the most abundant metal and the third most abundant element in the earth's crust, comprising about 8.8% by weight (88 g/kg) (Staley and Haupin 1992). Its concentration in soils varies widely, ranging from about 0.07% by weight (0.7 g/kg) to over 10% by weight (100 g/kg) (Sorenson et al. 1974; USGS 1984c). Varying concentrations are found in different soil samples taken from the same area and in areas with different vegetation types (Brusewitz 1984; Sorenson et al. 1974). In Hawaii, aluminum contents were much higher with concentrations ranging from 79 to 317 g/kg (Moomaw et al. 1959). Soils in Florida and parts of Georgia, Texas, Oklahoma, and Michigan contain <20 g/kg of soil, whereas soils from portions of the Pacific Northwest, New England, Colorado, and Nevada have concentrations >80 g/kg (Sparling and Lowe 1996). Mean aluminum concentrations in cultivated and uncultivated soil samples collected during a number of field studies were 33 g/kg (range 7–>100 g/kg) for subsurface soils in the eastern United States, 54 g/kg (range 5–>100 g/kg) in subsurface soils in the western United States, and 57 g/kg (range 13–76 g/kg) in surface soils collected in Colorado (Connor and Shacklette 1975). Ma et al. (1997) reported a mean aluminum concentration of 0.730 g/kg (range 0.01–4.300 g/kg) in 40 surface soil samples from Florida. Aluminum concentrations in 1,903 soils samples collected from the United States, as well as the Virgin Islands, Guam, and Puerto Rico, were reported to range from 0.5 to 142 g/kg, with a median value of 46 g/kg (Burt et al. 2003). A median aluminum concentration of 1.8 mg/kg was reported in soils collected form 25 playgrounds located in urban Uppsala, Sweden's fourth largest city (Ljung et al. 2006).

Aluminum concentrations in soil also vary with different vegetation types. For example, aluminum concentrations in the soils of coniferous forests are often higher than in soils of beech forests since coniferous forests tend to have more acid soils (Brusewitz 1984). Alternate views of the data are that the acidic soil produced by conifers can preferentially mobilize aluminum from deeper layers toward surface soil, or that conifers over beech preferentially grow in soils rich in aluminum and it is their metabolic processes which produce more acidic soil.

Concentrations of various elements in 541 streambed-sediment samples collected from 20 study areas in the conterminous United States (1992–1996) were analyzed as part of the National Water-Quality Assessment Program of the U.S. Geological Survey. Aluminum was present in all samples; concentrations ranged from 1.4 to 14% by weight (14–140 g/kg), with a median of 6.4% by weight (64 g/kg) (Rice 1999). Mean aluminum concentrations in sediments collected in 1993 and 1994 from Lake Erie, Lake Ontario, and the Niagara River ranged from 1.339 to 13.823 g/kg dry weight (Lowe and

Day 2002). Mean aluminum concentrations in sediments collected from three lakes in central Texas near a coal-fired power plant were 5.32, 8.16, and 8.64% in the Gibbons Creek Reservoir, Hall Lake, and Yarboro Lake, respectively (Menounou and Presley 2003). A mean aluminum concentration of 56.1 g/kg was reported in sediments form Terra Nova Bay, Antarctica (Giordano et al. 1999).

6.4.4 Other Environmental Media

Aluminum occurs naturally in many edible plants and is added to many processed foods. The concentrations in foods and beverages vary widely, depending upon the food product, the type of processing used, and the geographical areas in which food crops are grown (Brusewitz 1984; Sorenson et al. 1974). In general, the foods highest in aluminum are those that contain aluminum additives (e.g., processed cheese, grain products, and grain-based desserts) (Greger 1992; Pennington 1987; Saiyed and Yokel 2005). Because of the variability of reported concentrations of aluminum in foods, the many new manufactured food products on the market, and the increasing use of aluminum as a packaging material, a wide range of beverages and foods have been analyzed. The aluminum concentrations in a number of beverages, foods, and food products are listed in Table 6-4. Most unprocessed foods, (with the exception of some herbs and tea leaves) typically contain <5 mg/kg aluminum (Greger 1992; MAFF 1999; Pennington 1987; Schenk et al. 1989). Concentrations of aluminum in foods generally ranged from <0.15 mg/kg in eggs, apples, raw cabbage, corn, and potatoes to 695 mg/kg in American cheese (Greger 1992; MAFF 1999; Pennington 1987; Schenk et al. 1989). López et al. (2000) measured aluminum concentrations in 17 different spices and aromatic herbs widely consumed in Spain and in the Mediterranean diet; concentrations ranged from 3.74 to 56.50 mg/kg dry weight in cinnamon and oregano, respectively.

The high aluminum concentrations seen in some processed foods (e.g., processed cheeses, baked goods, and nondairy cream substitutes) are likely to have been introduced into the foods as additives, such as the anti-caking agent, sodium aluminosilicate, which is present in salt, nondairy creamers, and many other powdered materials (Table 6-4) (Saiyed and Yokel 2005; Schenk et al. 1989). The most commonly used food additives containing aluminum are: acidic sodium aluminum phosphate (leavening agent in baked goods); basic sodium aluminum phosphate (emulsifying agent in processed cheese); aluminum sulfates (acidifying agents); bentonite (materials-handling aid); aluminum color additives (lakes) from various food dyes; and aluminum silicates (anti-caking agents) (Greger 1992; Saiyed and Yokel 2005).

Table 6-4. Estimated Aluminum Concentrations of Selected Foods

Foods	Aluminum concentration	Reference
Beverages (mg/L)		
Fruit juices (e.g., orange, reconstituted lemon, peach)	0.043–4.130	Schenk et al. 1989
Soft drinks (e.g., ginger ale, diet cola)	0.103–2.084	Schenk et al. 1989
Alcoholic beverages (e.g., beer, wine, wine coolers, champagne)	0.067–3.20	Schenk et al. 1989
Spirits (e.g., brandy, vodka, whiskey)	0.148–0.635	Schenk et al. 1989
Tea, steeped from tea bags	0.424–2.931	Schenk et al. 1989
Teas (1% extract)	0.378–3.55	Schenk et al. 1989
Herbal teas (1% extract)	0.14–1.065	Schenk et al. 1989
Instant coffee (1% solution)	0.02–0.581	Schenk et al. 1989
Whole coffee (3% extract)	0.235–1.163	Schenk et al. 1989
Beverages	1.3[a]	MAFF 1999
Animal products (mg/kg)		
Beef, cooked[a]	0.2	Greger et al. 1985
Cheese (e.g., Swiss, cheddar, bleu)	3.83–14.1	Schenk et al. 1989
Cheese, (e.g., cottage, cheddar, Swiss)	0.12–19	Pennington 1987
Cheese, American	411–695	Pennington 1987
Cheese, processed	297	Greger et al. 1985
Chicken, with skin, cooked[a]	0.7	Greger et al. 1985
Egg, chicken	0.107	Schenk et al. 1989
Eggs, scrambled	2.865	Schenk et al. 1989
Eggs, cooked[a]	0.1	Greger et al. 1985
Eggs	0.14	MAFF 1999
Fish (cod), cooked[a]	0.4	Greger et al. 1985
Fish, salmon	5.44	Schenk et al. 1989
Fish, herring	0.127	Schenk et al. 1989
Fish	6.1	MAFF 1999
Ham, cooked[a]	1.2	Greger et al. 1985
Meat products	1.9	MAFF 1999
Milk, whole	0.06–2	Pennington 1987
Milk (skim, whole, and powdered)	0.028–7.9	Schenk et al. 1989
Milk	0.07	MAFF 1999
Poultry	0.3	MAFF 1999
Salami	1.12	Pennington 1987
Yoghurt, plain low-fat	1.12	Pennington 1987
Yoghurt, strawberry, sweetened	0.63	Pennington 1987
Fruits (mg/kg)		
Apple, fresh	0.14	Pennington 1987

Table 6-4. Estimated Aluminum Concentrations of Selected Foods

Foods	Aluminum concentration	Reference
Banana, fresh	0.05	Pennington 1987
Grapes, fresh	1.81	Pennington 1987
Peaches, fresh	0.51	Pennington 1987
Raisins, dried	3.08	Pennington 1987
Strawberries, fresh	2.25	Pennington 1987
Fresh fruit	0.29	MAFF 1999
Fruit products	0.82	MAFF 1999
Grains (mg/kg)		
Biscuits, baking powder, refrigerated type	16.3	Pennington 1987
Bread, white	0.351	Schenk et al. 1989
Bread, white	2.33	Pennington 1987
Bread, whole wheat	2.91	Pennington 1987
Bread, pumpernickel	13.2	Schenk et al. 1989
Bread	6.6	MAFF 1999
Cereal (e.g., Post Raisin Bran®, Malt-o-Meal Wheat Cereal®)	0.040–29.33	Schenk et al. 1989
Miscellaneous cereals	5.2	MAFF 1999
Corn chips	1.23	Pennington 1987
Cornbread, homemade	400	Pennington 1987
Muffin, blueberry	128	Pennington 1987
Oatmeal, cooked	0.68	Pennington 1987
Oats	2.21–4.18	Schenk et al. 1989
Rice, cooked[a]	1.7	Greger et al. 1985
Rice, yellow, Rice-a-Roni®	1.97	Schenk et al. 1989
Spaghetti, cooked[a]	0.4	Greger et al. 1985
Vegetables and legumes (mg/kg)		
Asparagus	4.4	Greger et al. 1985
Beans, green, cooked[a]	3.4	Greger et al. 1985
Beans, navy, boiled	2.06	Pennington 1987
Cabbage, raw	0.1	Greger et al. 1985
Cauliflower, cooked[a]	0.2	Greger et al. 1985
Corn, boiled	0.1	Pennington 1987
Cucumber, fresh, pared	0.11	Pennington 1987
Green vegetables	3.1	MAFF 1999
Lettuce	0.6	Greger et al. 1985
Lettuce	0.08	Schenk et al. 1989
Peanut butter	2.0	Greger et al. 1985
Peanut butter, natural	6.29	Schenk et al. 1989
Peas, cooked[a]	1.9	Greger et al. 1985

Table 6-4. Estimated Aluminum Concentrations of Selected Foods

Foods	Aluminum concentration	Reference
Potatoes, unpeeled, boiled[a]	0.1	Greger et al. 1985
Potatoes, unpeeled, baked	2.4	Greger et al. 1985
Potato, red	3.63	Schenk et al. 1989
Potato, sweet	1.01	Schenk et al. 1989
Potatoes	0.9	MAFF 1999
Spinach, cooked[a]	25.2	Greger et al. 1985
Tomatoes, cooked[a]	0.1	Greger et al. 1985
Other vegetables	2.7	MAFF 1999
Canned vegetables	0.97	MAFF 1999
Herbs and spices (mg/kg dry weight)		
Basil	24.80–27.30	López et al. 2000
Cinnamon	18.54–56.50	López et al. 2000
Garlic	13.60–15.25	López et al. 2000
Mustard	30.40–38.56	López et al. 2000
Nutmeg	22.81–24.80	López et al. 2000
Oregano	3.74–40.41	López et al. 2000
Pepper, black	5.79–24.41	López et al. 2000
Thyme	6.35–7.90	López et al. 2000
Other food products (mg/kg)		
Baking powder, commercial (Na Al sulfate containing)	20,000–26,000	Sorenson et al. 1974
Candy, milk chocolate	6.84	Pennington 1987
Chocolate cookie, Oreo®	12.7	Schenk et al. 1989
Cocoa	45	Greger et al. 1985
Nondairy creamer	25.7–94.3	Schenk et al. 1989
Nuts	4.0	MAFF 1999
Oils and fats	1.1	MAFF 1999
Pickles with aluminum additives	39.2[b]	Greger et al. 1985
Pickles	0.126–9.97	Schenk et al. 1989
Salad dressing, Kraft Miracle Whip®	3.7	Schenk et al. 1989
Salt with aluminum additives	164	Greger et al. 1985
Salt	31.3–36.6	Schenk et al. 1989
Soup	0.032–3.6	Schenk et al. 1989
Sugars and preserves	2.7	MAFF 1999

[a]Food not cooked or stored in aluminum pans, trays, or foil.

Commercially available teas contain high concentrations of aluminum; 30–45% of this aluminum may be dissolved into an infusion of tea (Dong et al. 1999). Aluminum concentrations ranging from 0.2 to 9.5 mg/L have been reported in tea (Baxter et al. 1989; Flaten and Odegard 1988; Koch et al. 1989; Schenk et al. 1989; Müller et al. 1998; Pennington 1987; Pennington and Jones 1989; Kralj et al. 2005; Mehra et al. 2007). Fairweather-Tait et al. (1987) reported that approximately one-third of the aluminum in commercially available tea leaves was extracted into the tea (1.0 g tea/100 mL water); aluminum concentrations ranged from 2.7 to 4.9 mg/L in the tea after 5 minutes. Fimreite et al. (1997) reported aluminum concentrations of 4–5 mg/L in tea after 10 minutes. Schenk et al. (1989) reported that herbal teas contain lower concentrations of aluminum than ordinary tea (0.140–1.065 mg/L). Total aluminum concentrations in black, green, and red tea infusions ranging from 0.5 to 4.0 mg/L, with 10–35% of the total aluminum from an anion-exchange column as aluminum citrate. The remaining aluminum, which was strongly retained by the column, likely corresponds to aluminum species bound to penolic compounds. Addition of lemon or milk was found to change the distribution of the aluminum species in the tea infusions (Kralj et al. 2005).

Brewed coffee (3% extract) and instant coffee (1% solution) contain aluminum concentrations of 0.235–1.163 and 0.02–0.581 mg/L, respectively (Schenk et al. 1989). Aluminum concentrations ranging from 0.1 to 0.34 mg/L have been reported in coffee (Koch et al. 1989; Müller et al. 1998). Another report provided aluminum concentration in coffee beans ranging from 11 to 21 mg/kg (Koch et al. 1989). The aluminum content of ground coffee beans has been measured at 51.8 mg/kg (Lione et al. 1984). López et al. (2000) reported aluminum concentrations in coffee ranging from 25.60 to 29.08 mg/kg dry weight. Müller et al. (1998) reported an aluminum concentration of 19 mg/kg dry weight in ground coffee. Lione et al. (1984) estimated that brewing coffee in a new aluminum pot can add from 0.88 mg (immediately after brewing) to 1.18 mg aluminum (after 12-hour storage in the pot and subsequent reheating) to each cup.

Aluminum concentrations in wines and spirits were 0.388–3.2 and 0.148–0.635 mg/L, respectively (Schenk et al. 1989). Lopez et al. (1998) reported mean aluminum concentrations in alcoholic beverages consumed in Spain; concentrations were 94.8–1,682.6, 36.5–795.2, and 15.7–739.6 µg/L in wine, beer, and other alcoholic beverages (cider, brandy, rum, whisky, gin, anisette, and liquor), respectively.

In fiscal years 1985/1986, the FDA conducted a survey of elements in fresh clams and oysters collected from U.S. coastal areas in use for shellfish production (Capar and Yess 1996). The average concentration (wet weight basis) of aluminum found in the four shellfish categories surveyed were: clams (hardshell),

23±23 mg/kg (n=74); clams (softshell), 115±110 mg/kg (n=59); Eastern oyster, 33±26 mg/kg (n=104); and Pacific oyster, 30±28 mg/kg (n=46). Cod and bluefin tuna from the Northwest Atlantic Ocean contained an average of 1 and 0.4 mg/kg of aluminum, respectively, in muscle tissue (Hellou et al. 1992a, 1992b).

Cooking foods in aluminum pots and pans or storing foods in aluminum foil or cans may increase the aluminum content in some foods since aluminum may dissolve when in contact with a salty, acidic, or alkaline food (Abercrombie and Fowler 1997; Greger et al. 1985; King et al. 1981; Muller et al. 1993b; Nagy and Nikdel 1986). Aluminum concentrations in precooked foods (e.g., applesauce, green beans, beef, eggs, ham, pudding, rice, and tomato sauce) ranged from <0.1 to 21.6 mg/kg, while concentrations in the foods after cooking in conditioned aluminum pans and stainless steel pans ranged from 0.24 to 125 mg/kg and from <0.1 to 3.4 mg/kg, respectively (Greger et al. 1985). Acidic foods, such as tomatoes, tomato sauce, and applesauce, especially when cooked for >15 minutes, tended to accumulate more aluminum than other foods (Greger et al. 1985). Greger et al. (1985) also reported that foods cooked in new aluminum cookware had higher aluminum concentrations than foods cooked in old aluminum cookware or aluminum cookware that had been treated to simulate use. In addition, the aluminum concentrations in the foods prepared in any aluminum cookware (old, new, or treated to simulate use) had higher aluminum concentrations than the same foods cooked in stainless steel cookware. A study by Lin et al. (1997) noted that cooking with aluminum utensils may be an important aluminum exposure source for patients with chronic renal disease.

Abercrombie and Fowler (1997) reported in a small sampling of canned drinks stored at 15–20 °C, the aluminum content ranged from <0.1 to 74 mg/kg depending on the product and storage time. This study concluded that there appeared to be little basis for concern about the ingestion of aluminum when the internal protective coating of cans remains intact, the cans are stored properly, and the contents are consumed in a reasonable period of time. Fairweather-Tait et al. (1987) reported mean aluminum concentrations in Coca-Cola® and Pepsi-Cola® of 0.09 and 0.05 µg/g, respectively. Average aluminum concentrations in various beverages purchased in Australia, New Zealand, and Thailand were 0.90 and 0.15 in non-cola soft drinks in aluminum cans and glass bottles, respectively, and 0.66 and 0.24 in cola drinks in aluminum cans and glass bottles, respectively. Aluminum concentrations averaged 0.16 mg/L in beer in either aluminum cans or glass bottles (Duggan et al. 1992). Muller et al. (1993b) reported migration of aluminum from aluminum cans (unlacquered) into Coca-Cola® (pH 2.5) and diet Coca-Cola® (pH 3.0), and that the concentration of aluminum increased as the storage period increased. Concentrations of aluminum ranged from 46 to 170 µg/L in Coca-Cola® (storage for 40–101 days) and

from 14 to 250 µg/L in diet Coca-Cola® (storage for 44–173 days), respectively. Vela et al. (1998) examined the change in aluminum concentration in beer packaged in aluminum cans over time. Two brands of beer stored at 5 °C showed little change in aluminum concentration over 5 months. However, when stored at 23 °C, the concentrations increased from 50.0 to 546.5 µg/L and from 108.0 to 414.0 µg/L for the two brands of beer after 5 months. Joshi et al. (2003) studied the potential for the migration of aluminum into commercial sauces packaged in aluminum pouches. The results of this study indicated that after 45 days at 22 and 50 °C samples showed only minor changes in aluminum content as compared to fresh samples.

Aluminum concentrations of 0.6–3.7 and 0.1–0.4 mg/g were reported in four different types of tobacco and two samples of cannabis, respectively (Exley et al. 2006). Various elements were determined in tobacco used in the manufacture of 12 brands of cigarettes in the United States; aluminum concentrations ranged from 0.699 to 1.2 mg/g (Iskander et al. 1986).

Aluminum compounds are also used extensively in the manufacture of cosmetics (e.g., aluminum hexahydrate in deodorants) and in medical treatments (e.g., aluminum hydroxide in antacids to control gastric hyperacidity or aluminum oxide in dental ceramic implants) (Brusewitz 1984; FDA 2002; NIH 2004; NRC 1982). Many antacids contain 300–600 mg aluminum hydroxide (approximately 104–208 mg of aluminum) per tablet/capsule/5 mL dose (Zhou and Yokel 2005). Lione (1985a) reported aluminum content/dose (single tablet or 5 mL liquid) for antacids, internal analgesics (buffered aspirins), antidiarrheals, and anti-ulcerative drugs. The aluminum content per dose (single tablet or 5 mL liquid) ranged from 35 to 208 mg for antacids, 9–52 mg for buffered aspirins, 36–1,450 mg for antidiarrheal drugs, and 207 mg for an anti-ulcerative drug. Potential daily aluminum dosage ranged from 126 to 5,000 mg for these medications (Lione 1985a). Aluminum hydroxide (1–5%) is found in car polishes and paints and aluminum chlorohydrate (>1–20%) is found in antiperspirants and deodorants (NIH 2004).

Fernandez-Lorenzo et al. (1999) reported mean aluminum concentrations of 225.9 (8–1,149), 69.0 (20–204), and 152.5 (104–201) µg/L in infant formulas, whole cow's milk, and soy milk, respectively, in a study in Spain. Ikem et al. (2002) reported mean aluminum concentrations of 58, 92, and 150 µg/L in milk-based powdered formulas from Nigeria, the United Kingdom, and the United States, respectively. Mean aluminum concentrations of 101 and 460 µg/L were reported for milk-based liquid formulas from the United Kingdom and soy-based powder formulas from the United States, respectively. Daily intakes of aluminum for infants in the United States were estimated to be 97, 573, and 361 µg/day for milk-based powder formulas, soy-based powder formulas, and hypoallergenic powder formulas from the United

States (Ikem et al. 2002). Navarro-Blasco and Alvarez-Galindo (2003) reported aluminum concentrations in soy-based infant formulas from Spain that ranged from 313 to 3,479 µg/L, with a mean of 930 µg/L. Mean aluminum concentrations in other types of Spanish infant formula were 499, 237, 252, 292, 574, 687, and 453 µg/L for preterm formula, non-adapted starter formula, adapted starter formula, follow-up formula, lactose-free formula, hypoallergenic formula, and inform error diet formula, respectively. Aluminum concentrations were determined in infant formulas and food in Turkey (Sipahi et al. 2006). Aluminum concentrations in cereal-, milk-, cereal plus milk-based baby food were reported to be 6.43, 8.02, and 7.43, 3.33 and 13.15 µg/g, respectively. Aluminum concentrations in starches and rice flours, traditionally used in baby foods, were also reported as 3.33 and 13.15 µg/g, respectively (Sipahi et al. 2006).

Older reports on aluminum concentrations in infant formulas are also available; however, it is not known if these values would be necessarily representative of aluminum levels in infant formulas currently on the market and available to consumers. Aluminum concentrations in cow's milk-based infant formulas generally ranged from 4 to 700 µg/L and from 5 to 2,500 µg/L in soy-based infant formulas (Baxter et al. 1989, 1990, 1991; Bloodworth et al. 1991; Simmer et al. 1990). Average aluminum concentrations in infant formula from Canada were 0.129, 0.217, and 0.717 µg/g in ready-to-use, concentrated, and powder milk-based infant formulas, respectively. Aluminum concentrations in Canadian soy-based formulas were 1.98, 1.41, and 9.44 µg/g in ready-to-use, concentrated, and powder milk-based infant formulas, respectively (Dabeka and McKenzie 1990).

The median aluminum level in breast milk collected from 12 Canadian women was reported to be 14 µg/L (range <5–45 µg/L) (Koo et al. 1988). In an Australian study, Weintraub et al. (1986) reported human breast milk concentrations of 30 µg/L. Simmer et al. (1990) reported a mean aluminum concentration of 49 µg/L in breast milk collected from Australian women. Hawkins et al. (1994) reported a mean breast milk aluminum concentrations of 9.2 µg/L collected from 15 nursing mothers in the United Kingdom. In a study of Croatia women, an average aluminum concentration in breast milk was 380 µg/L, with a range of 4 to 2,670 µg/L (Mandić et al. 1995). Fernandez-Lorenzo et al. (1999) reported mean aluminum concentrations of 23.9 µg/L (range 7–42 µg/L) in human milk in a study in Spain. Baxter et al. (1991) reported a mean aluminum concentration of 27 µg/L (range 3–79 µg/L) in a study in the United Kingdom.

Concentrations of aluminum in whole blood and plasma have been reported to range from 0.14 to 6.24 mg/L and from 0.13 to 0.16 mg/L, respectively (Sorenson et al. 1974). Aluminum concentrations in

serum have been reported as 1.46 and 0.24 mg/L, using neutron activation and atomic absorption analysis, respectively (Berlyne et al. 1970). An aluminum concentration in serum of 0.037 mg/L was reported using flameless atomic absorption analysis (Fuchs et al. 1974). Versieck and Cornelis (1980) discussed the possibility of aluminum contamination in blood and plasma samples from some of these early studies. This may question the reliability of aluminum levels reported in some older reports. House (1992) reported a geometric mean aluminum concentration of 0.0267 mg/L in serum and plasma for 71 office employees who were not occupationally exposed to aluminum. Mean plasma or serum aluminum concentrations were reported from various studies ranging from 0.0016 to 0.035 mg/L (House 1992). Drablos et al. (1992) analyzed aluminum serum concentrations in 230 nonexposed workers (controls) and reported a mean aluminum serum concentration of 0.005 mg/L. Nieboer et al. (1995) reviewed 34 studies on aluminum concentrations in serum or plasma, and also reported that aluminum serum concentrations in the general population were typically <0.01 mg/L. In an investigation of workers at an open bauxite mine in Surinam, serum aluminum concentrations of 24 men working in the mine for an average of 24 years were low and not statistically different from controls (de Kom et al. 1997). Razniewska and Trzcinka-Ochocka (2003) reported mean aluminum concentrations of 0.99 and 9.75 μg/L in serum and urine, respectively, in 18 healthy subjects not using medications containing aluminum.

A mean aluminum concentration of 23.21 μg/L (range 5.98–206.93 μg/L) was reported in serum samples collected form 533 female children (6–8 years old) living in Riyadh City, Saudi Arabia (Al-Saleh and Shinwari 1996). Hawkins et al. (1994) reported plasma aluminum concentrations in infants fed various formulas and breast milk. A mean plasma aluminum concentration of 8.6 μg/L was reported in breast fed infants; mean aluminum concentrations in plasma of infants fed various formulas ranged from 9.2 to 15.2 μg/L. Mean aluminum plasma concentrations of 9.9, 8.4, and 13.4 μg/L in breastfed infants at birth, 1 month, and 3 months of age, respectively. Infants on soy-based infant formulas, containing 1,600–1,700 μg/L of aluminum, were reported to have mean aluminum plasma concentrations of 8.2–12.4, 7.6–8.5, and 10.8–12.4 μg/L at birth, 1 month, and 3 months of age, respectively (Litov et al. 1989).

Aluminum concentrations in the urine can serve as an indicator of increased exposure to aluminum because a large proportion of ingested aluminum passes quickly through the body. Drablos et al. (1992) analyzed aluminum urine concentrations in 230 nonexposed workers (controls) and reported a mean aluminum urine level of 0.005 mg/L (range, 0.001–0.037 mg/L). Nieboer et al. (1995) reviewed eight studies on aluminum concentrations in urine and reported that aluminum urine concentrations in healthy individuals typically ranged from 0.0027 to 0.0081 mg/L. In a Finnish study of aluminum in urine from 3,212 occupationally exposed workers, mostly aluminum welders, between 1993 and 1996, the average

annual urinary aluminum level was 1.4 µmol/L (0.038 mg/L) and the range was 1.08–2.04 µmol/L (0.029–0.055 mg/L) (Valkonen and Aitio 1997). The samples, collected as part of a routine occupational health program, were collected after the weekend as a morning specimen. The mean urinary aluminum concentration in 44 nonexposed persons, who did not use antacid preparations, was 0.33 µmol/L (0.0089 mg/L), and the range and standard deviation were 0.07–0.82 µmol/L (0.002–0.022 mg/L) and 0.18 µmol/L (0.0022 mg/L), respectively. The mean serum aluminum concentration of 21 of these nonexposed individuals was 0.06 µmol/L (0.0016 mg/L), and the range and standard deviation were 0.02–0.13 µmol/L (0.0005–0.0035 mg/L) and 0.03 µmol/L (0.0008 mg/L), respectively. Drablos et al. (1992) studied aluminum concentrations in workers at an aluminum fluoride plant. Mean aluminum concentrations in urine were 0.011 mg/L (range, 0.002–0.046 mg/L) for 15 plant workers, 0.032 mg/L (range, 0.006–0.136 mg/L) for 7 foundry workers, and 0.054 mg/L (range, 0.005–0.492 mg/L) for 12 potroom workers as compared to 0.005 mg/L (range, 0.001–0.037 mg/L) for 230 unexposed controls. Mean aluminum concentrations were 5.06 and 3.74 µg/L in blood, and 6.56 and 6.35 µg/L in urine of 103 workers in the optoelectronic industry and 67 controls, respectively (Liao et al. 2004). Pre- and postshift average aluminum concentrations in urine ranging from 0.13 to 0.153 mg/L were reported in welders from the construction industry (Buchta et al. 2005). Aluminum concentrations in human breast tissue and breast tissue fat of 4–437 nmol/g (0.1–12 µg/g) dry weight and 3–192 nmol/g oil (0.08–5.18 µg/g oil), respectively, have been reported (Exley et al. 2007).

Nieboer et al. (1995) reported background concentrations of aluminum in bone of 1–3 µg/g dry weight. Background aluminum concentrations in brain tissues (primarily grey matter) of healthy individuals typically ranges from 1 to 3 µg/g dry weight or <0.5 µg/g wet weight (Nieboer et al. 1995). Markesbery et al. (1984) determined trace element concentrations in various human brain regions in infants through adults. Aluminum concentrations were shown to increase with increasing age. Mean aluminum concentrations in adults were 0.467 µg/g wet weight, as compared to 0.298 µg/g wet weight in infants. Overall aluminum concentrations ranged from ≤0.050 to 3.05 µg/g, with the highest mean aluminum concentrations in the globus pallius (0.893 µg/g) and the lowest in the superior parietal lobule (0.282 µg/g).

Metal concentrations were determined in spermatozoa and seminal plasma from men working in two industrial companies, a refinery and a polyolefin factory, 40 km east of Helsinki, Finland, and from sperm bank donor candidates from Helsinki, Finland in 1994. Aluminum concentrations in the factory employees were 0.93 and 0.54 mg/kg in spermatozoa and seminal plasma, respectively, and were 2.52 and 0.87 mg/kg in spermatozoa and seminal plasma, respectively, in the donor candidates. The

authors attributed the lower concentrations in the factory workers to good quality of occupational protection in the factories. In addition, the factory employees lived in the countryside as compared to the donor candidates, who lived in a more urban area (Hovatta et al. 1998). Mean aluminum concentrations in seminal plasma of 2,200, 1,530, and 270 µg/L were reported in samples collected from men working in smelter, refinery, and chemical industries respectively. A mean concentration of 460 µg/L was reported in hospital workers (control group) (Dawson et al. 2000). Mean aluminum concentrations ranged from 18.0 to 101.0 µg/L in seminal plasma collected from 64 apparently healthy men (21–35 years of age) recruited from the University of Texas (Dawson et al. 1998). A mean aluminum concentration of 15.0 µg/L was reported in sweat collected from the arms of 15 normal, healthy subjects while exercising (Omokhodion and Howard 1994). Sighinolfi et al. (1989) reported aluminum concentration ranging from 25 to 102 µg/L in human saliva.

Aluminum concentrations in hair ranging from 0.1 to 36 µg/g have been reported (Alder et al. 1976; Caroli et al. 1994). Imahori et al. (1979) measured various elements in 202 human hair samples collected from a local population in the Tokyo metropolitan area. Aluminum was detected in 95 and 99 of the male and female hair samples, respectively. Mean aluminum concentrations were 13.7 mg/kg (range <0.24–65.0 mg/kg) and 13.6 mg/kg (<1.93–67.1 mg/kg) in male and female hair samples, respectively. Kobayashi et al. (1989) reported mean hair aluminum concentrations of 3.9 and 6.2 µg/g in patients with senile dementia of Alzheimer type and a control group, respectively. Shore and Wyatt (1983) reported aluminum concentrations of 7.5 and 6.2 ppm (µg/g) in hair from patients with Alzheimer's disease and age-matched (nondemented) controls, respectively. Elemental concentrations were determined in hair from children (6–15 years old) living in environmentally degraded districts of the East Aral Sea region (Kazakhstan and Uzbekistan). Mean aluminum concentrations were 89.5 and 113.6 mg/kg in samples collected from two regions, Kazalinsk and Zhanakorgan, respectively (Chiba et al. 2004). Wilhelm et al. (1989) reported that use of hair analysis as an indicator of systematically incorporated metals may not be reliable, since endogenous metal concentrations in hair may be masked by the uptake of metals, including aluminum, from exogenous sources.

Human albumin solutions and other biological products intended for human use may contain aluminum because aluminum compounds are used in their manufacture or as a result of contamination. In albumin products, aluminum is generally introduced as a contaminant from filters, filter aides, buffer solutions, and anticoagulants, as well as the container itself. The aluminum level in a 5% pooled human albumin solution was 0.507 µg/mL (Progar et al. 1996).

Metal concentrations were measured in two lichen species (*Parmelic conspersa* and *Xanthoria calcicola*) from the island of Vulcano and around Mt. Etna, Sicily. Aluminum concentrations were 14,619 and 17,964 mg/kg dry weight in lichens collected near Mt. Etna and Vulcano, respectively (Varrica et al. 2000).

Mean aluminum concentrations in the soft tissues of zebra mussels (*Dreissena polymorpha*) collected in 1993 and 1994 from Lake Erie, Lake Ontario, and the Niagara River ranged from 232 to 5,030 mg/kg dry weight (Lowe and Day 2002). Whole fish composites were analyzed for various metals as part of a survey of 167 lakes in the northeastern United States as part of the Environmental Monitoring and Assessment Program (1992–1994); a mean aluminum concentration of 8.26 mg/kg wet weight (range 0.26–114.5 mg/kg wet weight) was reported (Yeardley et al. 1998). Aluminum concentrations ranged from 2 to 4 mg/kg dry weight in the livers of various seabirds collected from the northern Pacific Ocean in 1992 (Elliott 2005). Mean aluminum concentrations in the feathers of nestling black-crowned night-herons in the Chesapeake and Delaware Bays ranged from 9.18 to 78.85 mg/kg dry weight (Golden et al. 2003).

An aluminum concentration of 25,948 mg/kg was reported in house dust from residences in Ottawa, Canada (Butte and Heinzow 2002).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Since aluminum is ubiquitous in the environment, the general population will be exposed to aluminum by inhalation of ambient air and the ingestion of food and water. Pennington and Schoen (1995) reported average daily intakes of 8–9 and 7 mg/day for adult men and woman, respectively, based on an FDA Total Diet Study. According to the 1997 total diet study conducted by the Food Standards Agency, the average U.K. population dietary exposure to aluminum was estimated to be 3.4 mg/day (MAFF 1999). Greger (1992) estimated that most adults consume 1–10 mg aluminum per day from natural sources. Biego et al. (1998) reported a daily average intake for aluminum of 4.2 mg in a study in France. Food additives containing aluminum, including preservatives, coloring agents, anticaking agents, and leavening agents are major dietary sources of aluminum in the United States (Saiyed and Yokel 2005; Soni et al. 2001).

In a report on FDA's Total Diet Study, the foods highest in aluminum were those suspected of containing aluminum additives (e.g., processed cheese, grain products, and grain-based desserts) (Pennington 1987).

Measured daily dietary intakes of aluminum were reported to range from 2 to 14 mg/day. The major contributors to aluminum in the diet are grain products (24–49%), dairy products (17–36%), desserts (9–26%), and beverages (5–10%) (Pennington 1987). FDA revised their Total Diet Study in 1991 to reflect current food consumption patterns and to include additional sex-age groups (Pennington and Schoen 1995). Dietary intakes ranged from 0.7 mg/day for infants to 11.5 mg/day for 14–16-year-old males. The aluminum intake of adult males ranged from 8 to 9 mg/day and that for adult females was about 7 mg/day. Dietary intakes for 2-, 6-, and 10-year-old children were 4.6, 6.5, and 6.8 mg/day, respectively. Aluminum intakes per kilogram of body weight were 0.10 mg/kg for infants, 0.35 mg/kg for 2-year-old children, and 0.30 mg/kg for 10-year-old children. The other sex age groups had aluminum intakes of 0.10–0.15 mg/kg, except for 14–16-year-old males who had an aluminum intake of 0.18 mg/kg. Principal sources for aluminum were milk and diary products (36%), fish and crustaceans (29%), cereals (16%), and vegetables (8%).

Saiyed and Yokel (2005) reported the aluminum content in various foods in the United States with aluminum food additives. Cheese from a frozen pizza was reported to contain up to 14 mg of aluminum from basic sodium aluminum phosphate. An equivalent amount of cheese from a ready-to-eat restaurant pizza contained 0.03–0.09 mg of aluminum. Up to 1.5 mg of aluminum were found in single serving packets of nondairy creamer containing sodium aluminosilicate. Products such as baking powder, pancake and waffle mixes, and ready-to-eat pancakes contained up to 180 mg of aluminum per serving (Saiyed and Yokel 2005).

Cooking in aluminum containers often results in statistically significant, but not biologically important, increases in the aluminum content of some foods. In one study, increases in the aluminum content of foods after contact with aluminum utensils were <1 mg/kg for 47% of the food examined and <10 mg/kg for 85% of the food examined (Pennington and Schoen 1995). The migration of aluminum from cookware into food will increase with the acidity of the food and the duration of exposure. For example, red current juice was prepared by boiling berries for 3 hours in either an aluminum or stainless steel pot. The aluminum concentrations of the juice prepared in the aluminum pot was 89.1 mg/L, whereas the juice prepared in the stainless steel pot was 1.83 mg/L (Valkonen and Aitio 1997). Aluminum was also shown to migrate into fish baked on aluminum foil. Increases in aluminum concentration ranged from a factor of 2 for saithe fillets baked on aluminum foil without added ingredients (0.10–0.21 mg/kg) to a factor of about 70 for mackerel fillets grilled on aluminum foil with onion rings and mixed spices (0.07–5.04 mg/kg). The migration of aluminum into foods appeared to be dependent on factors such as temperature, duration of cooking, the composition and pH of the food, and the presence of other

substances (e.g., organic acids and salt) (Ranau et al. 2001). A study by Lin et al. (1997) noted that cooking with aluminum utensils may be an important aluminum exposure source for patients with chronic renal disease.

The intake of aluminum in foods is low compared with the amount of aluminum consumed when taking aluminum-containing medication, such as antacids, buffered aspirins, antidiarrheal agents, and certain anti-ulcer drugs at their recommended dosages (Lione 1983, 1985a; Pennington and Schoen 1995; Soni et al. 2001; Zhou and Yokel 2005). Antacids and buffered aspirin, which are often taken in multiple daily doses for prolonged periods, contain 4–562 mg/kg of aluminum (Lione 1983; Schenk et al. 1989; Shore and Wyatt 1983). For example, according to Pennington and Schoen (1995), buffered aspirin may contain 10–20 mg of aluminum per tablet. Many antacids contain 300–600 mg aluminum hydroxide (approximately 104–208 mg of aluminum) per tablet/capsule/5 mL dose (Zhou and Yokel 2005). Other exposures to aluminum can occur through the use of cosmetics and other consumer products containing aluminum compounds (Lewis 2001; NIH 2004; O'Neil et al. 2001).

Pennington and Schoen (1995) reported average daily intakes of 8–9 and 7 mg/day for adult men and woman, respectively, based on an FDA Total Diet Study. According to the 1997 total diet study conducted by the Food Standards Agency, the average U.K. population dietary exposure to aluminum was estimated to be 3.4 mg/day (MAFF 1999). Biego et al. (1998) reported a daily average intake for aluminum of 4.2 mg in a study in France.

Lione (1985a) estimated that 126–728 and 840–5,000 mg were possible daily doses of aluminum consumed in buffered aspirins and antacids products, respectively. These doses are from 6 to almost 40 times and 42–250 times greater, respectively, than aluminum doses obtained from consumption of food. When large oral loads of aluminum (1,000–4,000 mg/day) in the form of antacids are ingested, some of this excess aluminum is absorbed, usually <1% of the intake amount in healthy individuals (Gorsky et al. 1979; Kaehny et al. 1977; Reiber et al. 1995).

Median concentrations of aluminum in drinking water not receiving coagulation treatment and that receiving coagulation treatment have been reported as 0.043 and 0.112 mg/L, respectively (Miller et al. 1984a). If the total dose of aluminum obtained from water is calculated based on an estimated consumption of 1.4 L/day, the amount of aluminum ingested would respectively be 0.06 and 0.16 mg/day or roughly 1% of the 7–9 mg/day for adults from dietary sources.

While the intake of aluminum is mainly through the ingestion of food and drinking water, inhalation of ambient air represents a small contribution to an individual's exposure to aluminum (Browning 1969). Background concentrations of aluminum in the atmosphere generally range from 0.005 to 0.18 μg/m^3 in the United States (Hoffman et al. 1969; Sorenson et al. 1974). If the inhalation rate is taken to be 20 m^3/day, then the total amount of aluminum obtained from inhalation of 0.18 μg/m^3 would be 3.6 μg/day, suggesting that ambient air is not normally a major exposure pathway for aluminum. This is negligible compared with the estimated dietary intake for adults of 7–9 mg/day. However, the aluminum content of air in urban and industrial areas has been reported to be considerable higher, ranging from 0.4 to 8.0 μg/m^3 (Cooper et al. 1979; Dzubay 1980; Kowalczyk et al. 1982; Lewis and Macias 1980; Moyers et al. 1977; Ondov et al. 1982; Pillay and Thomas 1971; Sorenson et al. 1974; Stevens et al. 1978). If the inhalation rate is taken to be 20 m^3/day, then the total amount of aluminum inhaled would range from 8 to 160 μg/day, which is still negligible compared with the aluminum intake from dietary sources. Dusts arising from soil, especially in industrial or agricultural areas (Eisenreich 1980), and from the metal surfaces of air conditioners can contain large amounts of aluminum (Crapper McLachlan 1989), resulting in high localized concentrations and, subsequently, in higher exposures. Typically, however, for the general population, inhalation is likely to be less important as an exposure pathway than is dietary exposure to aluminum, but may represent a source of greater exposure in some urban environments.

Occupational exposure to aluminum occurs not only in the refining of the primary metal, but also in secondary industries that use aluminum products (e.g., aircraft, automotive, and metal products), and aluminum welding (Nieboer et al. 1995). Three major steps are involved in primary aluminum production. Aluminum is first extracted with caustic soda from bauxite ore, precipitated as aluminum hydroxide, and subsequently converted to aluminum oxide in a calcination process. In the second step, the oxide is dissolved in molten cryolite (Na_3AlF_6) and electrolyzed to yield the pure molten metal. The electrolytic cells are called pots and the work area is called the potroom. Casting is the final step in the process where molten aluminum is poured into ingots in the foundry. Exposure is primarily to aluminum hydroxide and oxide in the initial extraction and purification process, to aluminum oxide and aluminum fluoride in the potroom (as well as to tar-pitch volatiles including PAHs), and to partially oxidized aluminum metal fumes in the foundry (Drablos et al. 1992; IARC 1984; Nieboer et al. 1995).

Most of the studies of occupational exposure (aluminum refining and metal industry workers) to aluminum have dealt with inhalation of aluminum-containing dust particles. Rarely is a worker exposed solely to aluminum-containing dust; exposure to mixtures of aluminum with fine respirable particles or other toxic chemicals is more prevalent. For example, it had been observed that the incidence of bladder

cancer was unusually high among aluminum reduction workers. An epidemiological study showed that volatile PAHs in coal tar pitch, however, were the actual causative agents (Theriault et al. 1984a). Synergism among metal dusts, fine particles, toxic chemicals including PAHs, and cigarette smoke is a highly plausible cause of skin irritation and cancers appearing in workers for many industrial processes involving aluminum.

According to the National Occupational Exposure Study (NOES) conducted by NIOSH from 1981 to 1983, the industries with the largest numbers of workers potentially exposed to aluminum and aluminum compounds include: plumbing, heating, and air conditioning; masonry and other stonework; electrical work; machinery except electrical; certified air transportation equipment; electrical components; fabricated wire products; general medical and surgical hospitals; industrial buildings and warehouses; and special dies, tools, jigs, and fixtures (NIOSH 1991).

A group of 44 aluminum welders in the train body and truck trailer construction industry were monitored for aluminum exposure (Buchta et al. 2005). Median aluminum concentrations of 5.6 mg/m^3 (range: 0–31.5 mg/m^3) and 4.5 mg/m^3 (range: 1.3–15.6 mg/m^3) in respirable dust in air were reported in welding fumes in 1999 and 2001, respectively. Median aluminum concentrations in aluminum welders were 152.7 µg/L (range: 2.9–656.3 µg/L) and 145.5 µg/L (range: 5.0–656.3 µg/L) in urine in pre- and post-shift samples in 2001, respectively. Median aluminum concentrations in aluminum welders were 10.6 µg/L (range: 3.3–40.3 µg/L) and 14.3 µg/L (range: 3.8–51.0 µg/L) in plasma in pre- and post-shift samples in 2001, respectively (Buchta et al. 2005).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths,

sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

As with adults, exposures of children to aluminum from breathing air, drinking water, and eating food is generally low. As aluminum is part of the natural environment and found widely in soils, rocks, and foods, exposure to low levels of aluminum is unavoidable. Children are likely to ingest dirt from their unwashed hands or when playing with soils and may be exposed to aluminum in this manner. Children living in proximity to hazardous waste sites or industries that release aluminum to the environment may be exposed to higher levels of aluminum than are found in the natural environment via ingestion of aluminum contained in soil, or via inhalation of aluminum from soil that is entrained in air. While aluminum contained in dirt may be in many forms, some of these forms may be embedded in minerals not bioavailable even in the acid environment of the stomach.

When FDA revised their Total Diet Study in 1991, several sex-age groups relating to children were included (Pennington and Schoen 1995). Average dietary intakes of aluminum in children are shown in Table 6-5. Dietary intakes of aluminum for children ranged from 0.7 mg/day for infants to 11.5 mg/day for 14–16-year-old males. Aluminum intakes per kilogram of body weight for children ranged from 0.10 mg/kg for infants to 0.35 mg/kg for 2-year-old children. The major sources of aluminum in food by age-sex group are shown in Table 6-6. Processed foods containing aluminum additives such as processed cheese and grain-based products constitute the foods with the largest quantities of aluminum and the largest components of the dietary intake of children. Soy-based formula may contain high quantities of aluminum and infants on such formula would have much higher dietary intakes of aluminum than other infants. Pennington and Schoen (1995) reported that soy-based infant formula was a major contributor to aluminum for infants, contributing 0.161 mg/day.

As with adults, aluminum intake from aluminum-containing medication, such as antacids, buffered aspirins, and antidiarrheal agents would overwhelm ordinary dietary intakes (Pennington and Schoen 1995). Children may be exposed to aluminum from aluminum-containing medications, vaccinations, parenteral feeding, dialysis fluids, and treatment for hyperphosphatemia (Advenier et al. 2003; Andreoli et al. 1984; Baylor et al. 2002; Bougle et al. 1991; Bozynski et al. 1989; Chedid et al. 1991; Goyens and Brasseur 1990; Griswold et al. 1983; Klein et al. 1989; Koo et al. 1986, 1992; Malakoff 2000; Milliner et al. 1987; Moreno et al. 1994; Naylor et al. 1999; Offit and Jew 2003; Randall 1983; Robinson et al. 1987; Salusky et al. 1990; von Stockhausen et al. 1990; Warady et al. 1986). Advenier et al. (2003) reported a mean aluminum concentration of 1.6 μmol/L (0.043 mg/L) in parenteral nutrition solutions, resulting

Table 6-5. Dietary Intakes of Aluminum in Children

	Aluminum intake	
Age-sex group	(mg/day)	(mg/kg)
6–11-Months	0.7	0.10
2-Years	4.6	0.35
6-Years	6.5	0.30
10-Years	6.8	0.11
14–16-Years (females)	7.7	0.15
14–16-Years (males)	11.5	0.18

Source: Pennington and Schoen 1995

Table 6-6. Major Sources of Aluminum in Food by Age-Sex Group

	Aluminum/day	
Foods by age-sex group (Al/day)	mg	Percent of total intake
6–11-month-old infants (0.7 mg)		
Soy-based formula	0.161	23.0
American processed cheese	0.122	17.4
Yellow cake with icing	0.088	12.6
Green beans, strained	0.038	5.4
Pancakes	0.029	4.1
Total	**0.438**	**62.6**
2-year-old children (4.6 mg)		
Cornbread	1.580	34.3
American processed cheese	1.037	22.5
Yellow cake with icing	0.384	8.3
Fish sticks	0.173	5.4
Pancakes	0.113	2.5
Tortillas	0.093	2.0
Muffins	0.093	2.0
Fruit drink from powder	0.079	1.7
Taco/tostada	0.071	1.5
Tea	0.061	1.3
Total	**3.684**	**80.1**
6-year-old children (6.5 mg)		
American processed cheese	1.382	21.3
Yellow cake with icing	1.091	16.8
Pancakes	0.752	11.6
Fish sticks	0.529	8.1
Cornbread	0.450	6.9
Tortillas	0.297	4.6
Taco/tostada	0.209	3.2
Muffins	0.202	3.1
Hamburger	0.104	1.6
Fruit drink from powder	0.105	1.6
Total	**5.121**	**78.8**
10-year-old children (6.8 mg)		
American processed cheese	1.498	22.0
Cornbread	1.105	16.3
Pancakes	0.858	12.6
Tortillas	0.344	5.1
Yellow cake with icing	0.350	5.1
Fish sticks	0.280	4.1
Taco/tostada	0.259	3.8

Table 6-6. Major Sources of Aluminum in Food by Age-Sex Group

	Aluminum/day	
Foods by age-sex group (Al/day)	mg	Percent of total intake
Muffins	0.207	3.0
Chocolate cake with icing	0.141	2.1
Chocolate snack cake	0.144	2.1
Total	**5.186**	**76.3**
14–16-year-old females (7.7 mg)		
American processed cheese	2.139	27.8
Yellow cake with icing	0.906	11.8
Cornbread	0.781	10.1
Taco/tostada	0.682	8.9
Pancakes	0.668	8.7
Tortillas	0.325	4.2
Muffins	0.219	2.8
Cheeseburger	0.183	2.4
Tea	0.159	2.1
Fish sticks	0.125	1.6
Total	**6.187**	**80.4**
14–16-year-old males (11.5 mg)		
Cornbread	4.209	36.6
American processed cheese	1.978	17.2
Pancakes	1.038	9.0
Yellow cake with icing	0.925	8.0
Taco/tostada	0.398	3.5
Tortillas	0.398	3.5
Cheeseburger	0.310	2.7
Tea	0.225	2.0
Hamburger	0.211	1.8
Fish sticks	0.170	1.5
Total	**9.862**	**85.8**

Source: Pennington and Schoen 1995

in a mean aluminum daily intake of 0.08 μmol/kg/day (0.002 mg/kg/day). An upper limit of 0.90 μg/L for aluminum in all large-volume parenteral solutions used in total parenteral nutrition therapy was set by the FDA (Advenier et al. 2003). Aluminum compounds such as aluminum hydroxide, aluminum phosphate, or aluminum sulfate (alum) are commonly used as an adjuvant in many vaccines licensed by the FDA; the amount of aluminum in vaccines is limited to no more than 0.85 mg/dose (Baylor et al. 2002).

Elevated levels of aluminum may be found in the tissues and fluids of children undergoing treatments, such as parenteral feeding or dialysis, or if they are receiving aluminum-containing medications (Advenier et al. 2003; Andreoli 1990; Andreoli et al. 1984; Bougle et al. 1991; Bozynski et al. 1989; Chedid et al. 1991; Goyens and Brasseur 1990; Griswold et al. 1983; Klein et al. 1989; Koo et al. 1986, 1992; Milliner et al. 1987; Moreno et al. 1994; Naylor et al. 1999; Robinson et al. 1987; Roodhooft et al. 1987; Salusky et al. 1986, 1990; von Stockhausen et al. 1990); however, these levels are atypical of the general population.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to aluminum (see Section 6.5), there are several groups within the general population that have potentially higher exposures (higher than background) than the general population. These populations include members of the general population living in the vicinity of industrial emission sources and hazardous waste sites, individuals with chronic kidney failure requiring long-term hemodialysis treatment, infants fed a formula diet containing high levels of aluminum, and individuals consuming large quantities of antacid formulations for gastric disorders, anti-ulcerative medications, buffered analgesics for arthritis, or antidiarrheal medications. Furthermore, the elderly are at risk because of multiple chronic diseases including ulcers and other gastrointestinal diseases, rheumatoid arthritis, and renal disorders. Aluminum has been detected in virtually all food products (especially plant-derived and processed foods), ambient air, drinking water, and soils. Substantially higher concentrations of aluminum have been detected in localized areas around some industrial and hazardous waste disposal sites.

Individuals living or working in proximity to aluminum production facilities may be exposed to higher concentrations of aluminum in the ambient air than members of the general population. In addition, individuals living in proximity to hazardous waste sites may be exposed to aluminum via ingestion of aluminum contained in soil from their unwashed hands when working or playing with contaminated soils

and sediments. Children in particular are likely to ingest dirt from their unwashed hands, or inhale resuspended dust during near-ground activities. If residential wells are the primary source of drinking water, this may also pose a risk to human health via consumption of contaminated drinking water.

Individuals with chronic renal failure requiring long-term hemodialysis treatment are another group within the general population that may be exposed to greater than background levels of aluminum (Alfrey 1987; Chappuis et al. 1988, 1989; Chedid et al. 1991; Fernández-Martin et al. 1998; Griswold et al. 1983; Lione 1985a; Marumo et al. 1984; Muller et al. 1993b; Salusky et al. 1990; Winterberg et al. 1987). Elevated levels of aluminum may be found in the tissues and fluids of individuals undergoing treatments, such as hemodialysis, or if they are receiving aluminum-containing medications (Chappuis et al. 1988, 1989; Chedid et al. 1991; Griswold et al. 1983; Marumo et al. 1984; Salusky et al. 1990; Tsukamoto et al. 1979; Winterberg et al. 1987); however, these levels are atypical of the general population. Aluminum levels in virtually every body tissue are significantly higher in this group of patients if aluminum is present in the dialysate (Alfrey et al. 1980; Cooke and Gould 1991). In addition, Main and Ward (1992) reported a 10-fold increased serum aluminum concentration in a hemodialysis patient after she was prescribed effervescent analgesic tablets containing citrate. This patient was already taking aluminum hydroxide capsules. Once the effervescent analgesic tablets were discontinued, the patient's serum aluminum levels fell to acceptable levels within 3 weeks. Since citrate appeared to enhanced aluminum absorption, these authors stated that patients with renal failure taking aluminum compounds should not be prescribed citrate-containing preparations. In a study by Fernández-Martin et al. (1998), a decrease in serum aluminum concentrations in patients on hemodialysis over the past 10 years was observed, from 61.8 μg/L in 1988 to 25.7 μg/L in 1996. These reductions have been achieved due to the restriction of the use of oral aluminum hydroxide, as well as to the use of adequate water treatment systems.

The oral intake of aluminum tends to be higher for children than for adults (Greger 1992). Calculations based on the FDA's Total Diet Study suggest that 2-year-old children (13 kg body weight) consumed almost 3 times as much aluminum per kg body weight as adult males (75 kg body weight) or adult females (60 kg body weight), respectively (0.48 versus 0.18 and 0.15 mg aluminum/kg body weight, respectively) (Greger 1992). Infants fed milk-based or soy-based infant formulas can be exposed to higher concentrations of aluminum than infants fed breast milk or cows' milk (see Section 6.4.4). Within this group, the infants believed to be most at risk would be preterm infants with impaired renal function because they would be less able to excrete the absorbed aluminum (Bishop 1992; Greger 1992; Koo et al. 1988, 1992; Weintraub et al. 1986).

As discussed in Section 6.4.4, individuals consuming large quantities of antacid formulations, anti-ulcerative medications, buffered analgesics, or antidiarrheal medications are exposed to higher than background doses of aluminum in their diet. Lione (1985a) estimated that 126–728 and 840–5,000 mg were possible daily doses of aluminum consumed in buffered aspirins for rheumatoid arthritis and antacid products, respectively. These doses are 6–40 and 42–250 times greater, respectively, than aluminum doses obtained from consumption of foods (3.4–9 mg/day) (Biego et al. 1998; MAFF 1999; Pennington and Schoen 1995).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of aluminum is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of aluminum.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of aluminum and various aluminum-containing compounds are sufficiently well defined to allow an assessment of the environmental fate of these compounds (HSDB 2008; Lewis 2001; Lide 2005; O'Neil et al. 2001). No additional data are needed at this time.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2005, became available in May of 2007. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Because aluminum compounds occur naturally (Browning 1969; Dinman 1983; IARC 1984; NRC 1982) and are widely used in industry, in the manufacture of household products, and in processing, packaging, and preserving food (Browning 1969; Lewis 2001; O'Neil et al. 2001; Stokinger 1981; Venugopal and Luckey 1978), the potential for human exposure to these compounds through ingestion of food and water and inhalation of airborne particulates is substantial. Recent data on production, import/export, and use are available (Lewis 2001; O'Neil et al. 2001; USGS 2007a, 2007c). Information on disposal of aluminum compounds is limited. In the United States, about 3 million metric tons of aluminum was recovered from purchased scrap in 2005 (USGS 2007b, 2007c). TRI data are available for releases of aluminum, as fume or dust and as aluminum oxide (fibrous forms) (TRI05 2007). Additional information on disposal would be useful in assessing the potential for the release of and exposure to aluminum compounds.

Environmental Fate. Aluminum partitions to air, water, soil, and plant material. As an element, aluminum cannot be degraded in the environment; it can undergo various precipitation or ligand exchange reactions in the environment. Its partitioning to various media is determined by the physical and chemical properties of the aluminum compound and the characteristics of the environmental matrix that affects its solubility (Brusewitz 1984; Dahlgren and Ugolini 1989; Filipek et al. 1987; Goenaga and Williams 1988; James and Riha 1989; Litaor 1987; Mulder et al. 1989; Wangen and Jones 1984). Aluminum is transported through the atmosphere primarily as a constituent of soil and other particulate matter (Eisenreich 1980). Transformations are not expected to occur during transport of aluminum through the atmosphere. Aluminum partitions between solid and liquid phases by reacting and complexing with water molecules, anions, and negatively charged functional groups on humic materials and clay (Bodek et al. 1988). Information on the environmental fate of aluminum is sufficient to permit a general understanding of transport and transformation in all environmental media. No additional information is needed at this time.

Bioavailability from Environmental Media. Aluminum compounds are deposited in the lungs following inhalation (Christie et al. 1963; Steinhagen et al. 1978; Stone et al. 1979; Thomson et al. 1986) and are poorly absorbed following ingestion (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). A fractional absorption of 1.5–2% was estimated based on the relationship between urinary aluminum excretion and the airborne soluble aluminum to which workers were exposed (Yokel and McNamara 2001). Very limited information is available regarding absorption following dermal contact; however, this pathway of exposure is not expected to be significant. Additional

information on absorption following ingestion of soils contaminated with aluminum compounds and dermal contact would be useful in assessing bioavailability following exposure via these routes, particularly at hazardous waste sites.

Food Chain Bioaccumulation. Little information is available on the uptake of aluminum into food crops. Uptake into root crops is of particular importance, since many plant species concentrate aluminum in their roots (DOE 1984; Kabata-Pendias and Pendias 1984; Vogt et al. 1987). The limited information available on bioconcentration in animals appears to indicate that aluminum is not significantly taken up by livestock (DOE 1984). The fact that in studies dealing with aluminum in food, aluminum is generally present in low concentrations in fruit, vegetables, and meat products that do not contain aluminum additives or have other contact with aluminum (e.g., cooked in aluminum pots) (Greger et al. 1985; MAFF 1999; Pennington 1987; Pennington and Schoen 1995; Schenk et al. 1989; Sorenson et al. 1974), would support a conclusion that aluminum does not bioaccumulate in the food chain. Because of its toxicity to many aquatic species, aluminum does not bioconcentrate appreciably in fish and shellfish and therefore, it would not be a significant component of the diet of animals that feed upon them (Rosseland et al. 1990). Further studies on the uptake of aluminum by plants, especially those grown on acid soils, would be useful in expanding a limited database and characterizing the importance of food chain bioaccumulation of aluminum as a source of exposure for particular population groups.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of aluminum in contaminated media at hazardous waste sites are needed so that the information obtained on levels of aluminum in the environment can be used in combination with the known body burden of aluminum to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Estimates of human exposure to aluminum from food (Biego et al. 1998; Greger 1992; MAFF 1999; Pennington 1987; Pennington and Schoen 1995; Saiyed and Yokel 2005; Schenk et al. 1989; Sorenson et al. 1974), drinking water (Cech and Montera 2000; DOI 1970; Letterman and Driscoll 1988; Miller et al. 1984a; Schenk et al. 1989), and air (Browning 1969; Crapper McLachlan 1989; Sorenson et al. 1974) are available, as are estimates from exposure from antacids, buffered analgesics, antidiarrheal and anti-ulcerative compounds (Lione 1983, 1985a; Schenk et al. 1989; Shore and Wyatt 1983; Zhou and Yokel 2005). Information on the intake of aluminum from vitamins and other dietary supplements is lacking and would be useful in estimating human exposure. Additional information on the occurrence of

aluminum in the atmosphere, surface water, groundwater, and soils surrounding hazardous waste sites would be helpful in updating estimates of human intake.

Exposure Levels in Humans. Measurements of the aluminum content in human tissues, especially in blood (Berlyne et al. 1970; de Kom et al. 1997; Drablos et al. 1992; Fuchs et al. 1974; House 1992; Liao et al. 2004; Nieboer et al. 1995; Razniewska and Trzcinka-Ochocka 2003; Sorenson et al. 1974), urine (Buchta et al. 2005; Drablos et al. 1992; Liao et al. 2004; Nieboer et al. 1995; Razniewska and Trzcinka-Ochocka 2003; Valkonen and Aitio 1997), and breast milk (Baxter et al. 1991; Fernandez-Lorenzo et al. 1999; Hawkins et al. 1994; Koo et al. 1988; Mandić et al. 1995; Simmer et al. 1990; Weintraub et al. 1986), are available. However, Versieck and Cornelis (1980) discussed the possibility of aluminum contamination in blood and plasma samples from some of early studies. This may question the reliability of aluminum levels reported in some older reports.

Measurements of aluminum in other human tissues and fluids, such as bone, brain, saliva, spermatozoa, and seminal fluid are also available (Dawson et al. 1998, 2000; Hovatta et al. 1998; Markesbery et al. 1984; Nieboer et al. 1995; Sighinolfi et al. 1989). However, recent biological monitoring data, particularly for aluminum in blood and urine, are limited. More recent information would be useful in assessing current exposure levels. Additional biological monitoring data for populations surrounding hazardous waste sites would be useful in helping to better characterize human exposure levels.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Measurements of the aluminum content in tissues, blood, and urine of children who have been exposed to aluminum, as well as unexposed children, are limited. Chiba et al. (2004) reported aluminum concentrations in hair of children. Al-Saleh and Shinwari (1996) reported aluminum concentrations in serum samples of girls aged 6–8 years. Hawkins et al. (1994) and Litov et al. (1989) reported plasma aluminum concentrations in infants fed various formulas and breast milk. Studies measuring aluminum concentrations in tissues, blood, and urine of specialized groups of children (e.g., infants with renal failure or on parenteral nutrition) have also been reported (Advenier et al. 2003; Andreoli 1990; Andreoli et al. 1984; Bougle et al. 1991; Bozynski et al. 1989; Chedid et al. 1991; Goyens and Brasseur 1990; Griswold et al. 1983; Klein et al. 1989; Koo et al. 1986, 1992; Milliner et al. 1987; Moreno et al. 1994; Naylor et al. 1999; Robinson et al. 1987; Roodhooft et al. 1987; Salusky et al. 1986, 1990; von Stockhausen et al. 1990).

Additional information monitoring aluminum concentrations in children would be useful in assessing both the normal aluminum content of children and the effect of exposure on aluminum concentrations in children. This information would also be useful in assessing differences in the effect of aluminum exposure on children to that of adults. While the largest source of aluminum exposure in adults is from aluminum-containing medications and cosmetics, we do not know the amount of such products that may be given to children. Additional information on the intake of available aluminum from soil during childhood activities, or the placental transfer to fetal blood, especially among pregnant women taking antacids as a result of abdominal upsets, would be useful in assessing exposure levels in children.

Data are available on the intake of aluminum in food eaten by children and from their diet (Dabeka and McKenzie 1990; Koo et al. 1988; Pennington and Schoen 1995; Pennington 1987; Simmer et al. 1990; Weintraub et al. 1986). Aluminum concentrations in human breast milk, infant formula, and cow's milk have been reported. The aluminum content of human breast milk generally ranged from 9.2 to 49 μg/L, lower than that reported in infant formulas (Fernandez-Lorenzo et al. 1999; Hawkins et al. 1994; Koo et al. 1988; Simmer et al. 1990; Weintraub et al. 1986). Soy-based infant formulas contain higher concentrations of aluminum, as compared to milk-based infant formulas or breast milk. Recent reports provide average aluminum concentrations ranging from 460 to 930 μg/L for soy-based infant formulas and from 58 to 150 μg/L for milk-based formulas (Fernandez-Lorenzo et al. 1999; Ikem et al. 2002; Navarro-Blasco and Alvarez-Galindo 2003). Infant formulas are much higher in aluminum than human breast milk. Daily intakes of aluminum for infants in the United States were estimated to be 97, 573, and 361 μg/day from milk-based powder formulas, soy-based powder formulas, and hypoallergenic powder formulas, respectively (Ikem et al. 2002).

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for aluminum were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2006) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-7.

Table 6-7. Ongoing Studies on Aluminum

Investigator	Affiliation	Research description	Sponsor
Longnecker, M	Not provided	This research proposes to study elemental concentrations in toenails, which may provide a good measure of exposure for various elements, including aluminum.	NIH
Yokel, RA	University of Kentucky, Lexington, Kentucky	The overall objective of the proposed research is to test the null hypothesis that the bioavailability of aluminum is comparable from foods and from drinking water.	NIH

NIH = National Institutes of Health

Source: FEDRIP 2006

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring aluminum, its metabolites, and other biomarkers of exposure and effect to aluminum. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Because of the ubiquitous nature of aluminum, contamination is a major problem encountered in the analysis of aluminum by all methods except accelerator mass spectroscopy (AMS) using radioactive ^{26}Al. When using the other methods, all items used during collection, preparation, and assay should be checked for aluminum contribution to the procedure. Only by taking these stringent precautions will one be able to produce accurate results. A variety of analytical methods have been used to measure aluminum levels in biological materials, including AMS, graphite furnace atomic absorption spectrometry (GFAAS), flame atomic absorption spectrometry (FAAS), eletrothermal atomic absorption spectrometry (ETAAS), neutron activation analysis (NAA), inductively coupled plasma-atomic emission spectrometry (ICP-AES), inductively coupled plasma-mass spectrometry (ICP-MS), and laser microprobe mass spectrometry (LAMMA) (Roggli et al. 1999; Maitani et al. 1994; Owen et al. 1994; Razniewska and Trzcinka-Ochocka 2003; Van Landeghem et al. 1994) (see Table 7-1). Front-end separation techniques such as chromatography are frequently coupled with analytical methods.

AMS is a technique that can now be used to accurately determine the atomic content in as little as a few milligrams of biological material. AMS has been used in the past for measuring long-lived radionuclides that occur naturally in our environment, but it is suitable for analyzing the ratio of the concentrations of radioactive ^{26}Al to stable ^{27}Al in biological samples. AMS combines a particle accelerator with ion sources, large magnets, and detectors, and is capable of a detection limit of one atom in 10^{15} (1 part per quadrillion [ppq]). This method has biomedical applications regarding the uptake and distribution of aluminum in the body, but is dependent upon the availability of the radioactive ^{26}Al tracer, which is

Table 7-1. Analytical Methods for Determining Aluminum in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Serum	Direct injection into atomizer	GFAAS	Low µg/L levels	No data	King et al. 1981
Serum	Dilution with water; addition of EDTA	GFAAS	2 µg/L	No data	Alderman and Gitelman 1980
Serum	Centrifugation and injection of supernatant	GFAAS	14.3 µg/L	97–102%	Bettinelli et al. 1985
Serum (Al-organic acid species)	Addition of sodium bicarbonate; direct injection into chromatography column	HPLC/ICP-AES	No data	No data	Maitani et al. 1994
Serum (Al-organic acid species)	Dilution with mobile phase; fractions collected for ETAAS analysis	HPLC/ETAAS	No data	98–100% in spiked and synthetic serum	Wrobel et al. 1995
Serum (Al-organic acid species)	Addition of citrate buffer; direct injection into chromatography column	HPLC/ETAAS	0.12 µg/L	99.2±12.4%	Van Landeghem et al. 1994
Plasma	Dilution	GFAAS	3–39 µg/L	97–105%	Wawschinek et al. 1982
Whole blood, plasma, or serum	Dilution with water	GFAAS	24 µg/L	No data	Gardiner et al. 1981
Whole blood	Addition of sodium citrate; centrifugation; injection of supernatant	GFAAS	Low µg/L levels	No data	Gorsky and Dietz 1978
Whole blood	Dilution with Triton X-100	GFAAS	1.9 µg/L (serum); 1.8 µg/L (plasma); 2.3 µg/L (whole blood)	No data	Van der Voet et al. 1985
Urine	Digestion; ion-exchange clean-up	NAA	50 µg/L	No data	Blotcky et al. 1976
Urine and blood	Dilution with water	GFAAS or ICP-AES	Low µg/L levels	No data	Sanz-Medel et al. 1987
Urine and serum	Dilution with 0.2% nitric acid and water	ETAAS	0.6 µg/L (serum and urine)	No data	Razniewska and Trzcinka-Ochocka (2003)
Urine	Direct injection	GFAAS	Low µg/L levels	No data	Gorsky and Dietz 1978
Urine	Direct injection	GFAAS	Low µg/L levels	No data	Gorsky and Dietz 1978

Table 7-1. Analytical Methods for Determining Aluminum in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine and blood	Dilution with water	ICP-AES	1 µg/L (urine); 4 µg/L (blood)	No data	Allain and Mauras 1979
Biological tissues	Homogenization with EDTA	GFAAS	0.002–10.057 µg/g	95–106%	LeGendre and Alfrey 1976
Biological tissues	Freeze-drying; grinding for homogenization	NAA	8 µg/g	No recovery; RSD <10%	Wood et al. 1990
Biological tissues	Drying; nitric acid digestion; dilution with water	GFAAS	0.5 µg/g	80–117%	Bouman et al. 1986
Biological tissues	Mounting of paraffin sections of formalin fixed tissue on carbon discs; deparaffin sample	SEM/EDXA	0.1% by weight in a detected particle	NA	Abraham and Burnett 1985
Kidney, liver, urine	Acid digestion; dilution with water	ICP-AES	No data	98.8±8.6% in liver	Maitani et al. 1994
Kidney, liver, femur	Microwave nitric acid digestion; addition of internal standard, dilution with eluent	SEC/ICP-MS	0.04 µg/g	100±14% of spiked Al in reference material	Owen et al. 1994
Brain	Freeze drying; acid digestion; dilution with potassium dichromate matrix modifier	GFAAS	0.03 µ/g	No data	Xu et al. 1992a
Brain	Fixing and embedding in polymer matrix; sectioning and staining to visualize Al deposits; laser vaporization of selected sample surface into mass spectrometer	LAMMA	Low µg/g range	No data	Lovell et al. 1993
Hair	Isopropanol wash; nitric acid digestion; dilution with water	GFAAS	0.65 µg/g	84–105%	Chappuis et al. 1988
Human blood, urine, serum, feces	Acid digestion, Parr bomb technique, microwave, or hot plate method	ICP-AES	1 µg/L	>75%	Que Hee and Boyle 1988
Human milk/infant formula	Homogenization; microwave digestion with boiling nitric acid/hydrogen peroxide	ICP-MS	4.8–11 ng/g	No data	de la Flor St. Remy et al. 2004

Table 7-1. Analytical Methods for Determining Aluminum in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human milk/cow milk/infant formula	Dilution with ultrapure water	ICP-MS	3 µg/L	No data	Martino et al. 2000
All	None	AMS	1 ppq	NA	Flarend and Elmore 1997

AMS = accelerated mass spectroscopy; EDTA = ethylene diamine tetra acetic acid; EDXA = dispersive x-ray analysis; ETAAS = electrothermal atomic absorption spectrometry; GFAAS = graphite furnace atomic absorption spectrometry; HLPC/ICP-AES = high-performance liquid chromatography/ICP-AES; ICP-AES = inductively coupled plasma - atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry; LAMMA = laser ablution microprobe mass spectrometry; NA = not applicable; NAA = neutron activation analysis; ppq = parts per quadrillion; SEC/ICP-MS = size-exclusion chromatography/ICP-AES/mass spectrometry; SEM = scanning electron microscopy

produced using a cyclotron. The first step in the analysis process is the chemical extraction of aluminum (both stable and radioactive) from the biological sample using a method which is free of aluminum contamination. The extractant is loaded into a holder and inserted through a vacuum lock into the ion source, which then employs ion bombardment to ionize the sample atoms. These are removed from the sample using magnets, and are separated by mass and charge by accelerators, bending magnets, and electron stripper screens. An electrostatic analyzer selects particles based on their energy, and a gas ionization detector counts the ions one at a time using a rate of energy loss assessment that distinguishes between any competing isobars. The amount of ^{26}Al can be calculated from the measured ratio of ^{26}Al to ^{27}Al and the amount of carrier added during the chemical preparation of the sample (Elmore and Phillips 1987; Flarend and Elmore 1997).

GFAAS is the most common technique used for the determination of low-ppb (μg/L) levels of aluminum in serum, plasma, whole blood, urine, and biological tissues (Alder et al. 1977; Alderman and Gitelman 1980; Bettinelli et al. 1985; Bouman et al. 1986; Chappuis et al. 1988; Couri et al. 1980; Gardiner and Stoeppler 1987; Gorsky and Dietz 1978; Guillard et al. 1984; Keirsse et al. 1987; Rahman et al. 1985; Savory and Wills 1986; CEC 1984; van der Voet et al. 1985; Wrobel et al. 1995; Xu et al. 1992a). This is because GFAAS offers the best combination of sensitivity, simplicity, and low cost. When used as a detector for high-performance liquid chromatography (HPLC), GFAAS can analyze for species of complexed or bound aluminum which have been separated into fractions on the chromatography column (Van Landeghem et al. 1994).

NAA has been used to determine low levels of aluminum in biological tissues and urine (Blotcky et al. 1976; Savory and Wills 1986; Wood et al. 1990; Yukawa et al. 1980). NAA involves the bombardment of a sample with neutrons, which transforms some of the stable ^{27}Al atoms into several radioactive aluminum isotopes beginning with ^{28}Al, and measurement of the induced radioactivity. Advantages of NAA include good sensitivity and relative independence from matrix (or media) effects and interferences. Moreover, this technique can be used to detect almost all elements of environmental concern in the same sample (Sheldon et al. 1986). One major problem with using NAA with aluminum is the need to correct for interfering reactions with phosphorus and silicon, which produce the same radioisotope (^{28}Al) of aluminum. Other disadvantages of this technique include its high cost, the limited availability of nuclear reactors for NAA analysis, the short 2.25-minute half-life of ^{28}Al that requires prompt analysis of the sample following bombardment with neutrons, and disposal problems of radioactive waste.

The ICP-AES technique, also referred to as ICP-optical emission spectroscopy (ICP-OES), has been reported for the measurement of aluminum in biological materials and is an excellent alternative to

GFAAS for those laboratories possessing the appropriate instrumentation (Allain and Mauras 1979; Lichte et al. 1980; Maitani et al. 1994; Que Hee and Boyle 1988; Que Hee et al. 1988; Sanz-Medel et al. 1987). ICP-AES is a multi-elemental technique that is relatively free of chemical interferences. The matrix problems that can exist in atomic absorption spectrometry (AAS) are minimized in ICP-AES due to the very high excitation temperature of the sample (Savory and Wills 1986). The limits of detection for the ICP-AES method have been reported to be about 1 and 4 μg aluminum/L of urine and blood, respectively (Allain and Mauras 1979). A major problem with using the ICP-AES technique is the intense and broad emission of calcium, which increases the aluminum background and can raise the detection limit for this element (Allain and Mauras 1979; Que Hee and Boyle 1988; Savory and Wills 1986). Titanium also interferes with aluminum analysis (Que Hee and Boyle 1988). Also, the relatively high cost and complexity of this technique can limit its routine use in many laboratories. However, ICP-AES, especially ICP-MS, technologies have advanced recently largely through the efforts of the Department of Energy, and the cost of analysis has declined considerably.

Inductively coupled plasma-mass spectrometry (ICP-MS) is a powerful technique that uses an inductively coupled plasma as an ion source and a mass spectrometer as an ion analyzer. It can measure the presence of >75 elements in a single scan, and can achieve detection limits down to parts per trillion (ppt) levels for many elements—levels that are two or three orders of magnitude lower than those obtained by ICP-AES (Keeler 1991). It is more expensive than ICP-AES and requires more highly skilled technical operation. Aluminum levels in urine and saliva were detected down to 0.02 μg/mL and in blood serum to 0.001 μg/mL using ICP-MS (Ward 1989). Speciation studies have employed ICP-MS as a detector for aluminum in tissue fractions separated by size-exclusion chromatography (SEC) with detection limits of 0.04 μg/g in femur, kidney, and brain (Owen et al. 1994). ICP-MS has been used to determine metal concentrations, including aluminum, in human milk, cow milk, and infant formulas (de la Flor St. Remy et al. 2004; Martino et al. 2000).

LAMMA has been utilized for the analysis of aluminum in brain tissue affected with Alzheimer's disease (Lovell et al. 1993). This analytical technique of nuclear microscopy can simultaneously image and analyze features in unstained and untreated tissue sections, and therefore avoids contamination problems associated with tissue prepared using conventional chemical techniques. Lovell et al. (1993) reported aluminum concentrations in neurofibrillary tangle (NFT)-bearing neurons and in NFT-free neurons in brain tissue from seven autopsy-confirmed Alzheimer's disease patients. LAMMA was also used in a study that did not detect aluminum in pyramidal neurons in brain tissue from Alzheimer's disease patients (Makjanic et al. 1998). However, in tissue that had been subject to conventional procedures such as

fixation and osmication, aluminum was observed in both neurons and surrounding tissue. The method, however, requires rigorous histological sectioning and preparation prior to analysis, specialized analytical equipment, and highly trained personnel.

Secondary ion mass spectrometry (SIMS) is an analytical method that can be used for the imaging of aluminum and other metals in a variety of materials or biological specimins (Goldsmith et al. 1999; Linton and Goldsmith 1992). This technique uses a primary ion beam to generate secondary ions from the specimen, which are analyzed by mass spectrometry. Spatial resolution is reported to be comparable to that attainable with electron microscopy.

Adequate digestion methods are important in the determination of all metals, including aluminum. Que Hee and Boyle (1988) showed that Parr bomb digestions were always superior to hot plate digestions for many elements, including aluminum, in feces, liver, and testes. Microwaving in closed vessels produced lower aluminum recoveries in liver than Parr bomb digestions. The Parr bomb values for citrus leaves were within 5% of the NBS certified values.

Abraham and Burnett (1983) described a method for quantitative analysis of inorganic particulate burden *in situ* in tissue sections using scanning election microscopy (SEM) with backscattered election (BSE) imaging and energy dispersive x-ray analysis (EDXA). This method can compliment bulk tissue analysis since the analyst can observe the association of certain elements within a particle and the particle size. This information can be correlated to cellular or tissue changes with the types, locations, and concentrations of particles within the tissue. In addition, small samples (<1 µg) can be analyzed. EDXA, which is used to identify the chemical composition of the mineral, allows for separation of particulates into two major classes, endogenous and exogenous. Endogenous particles contain calcium or iron in combination with phosphorus as major constituents along with smaller amounts of sodium, magnesium, and potassium. The remaining particles are considered exogenous, and are divided into three major classes: silica, silicates, and metals. This method has been used to identify aluminum particulates in various human tissues, including lung, kidney, brain, and bone (Baxter et al. 1985; Hull and Abraham 2002; Jederlinic et al. 1990; Perl and Brody 1980; Perl et al. 1982).

Razniewska and Trzcinka-Ochocka (2003) reported a method for the determination of aluminum concentrations in blood serum and urine using ETAAS. Serum and urine samples were analyzed directly following dilution with 0.2% nitric acid and water. The detection limit was reported to be 0.6 µg/L for

serum and urine, with a quantification limit of 1.2 µg/L. This method provided reliable aluminum levels at concentrations observed among non-exposed, healthy individuals.

7.2 ENVIRONMENTAL SAMPLES

A number of analytical techniques have been used for measuring aluminum concentrations in environmental samples. These include GFAAS, FAAS, NAA, ICP-AES, ICP-MS, spectrophotometry using absorbance and fluorescence detection, phosphorimetry, chromatography, and gas chromatography equipped with an electron capture detector (GC/ECD) (Andersen 1987, 1988; AOAC 1990; APHA 1998a, 1998b, 1998c, 1998d; Dean 1989; Fernandez de la Campa et al. 1988; EPA 1983a, 1983b, 1994a, 1994b, 1994c, 2000; Fleming and Lindstrom 1987; Gardiner et al. 1987; NIOSH 1994, 2003a, 2003b, 2003c; OSHA 2001, 2002; USGS 1996). They are summarized in Table 7-2.

There are three NIOSH methods (7300, 7301, and 7303) that analyze elements, including aluminum, in air by ICP-AES; these methods differ only in the digestion method. NIOSH method 7013 analyzes aluminum in air using FAAS. In all of these NIOSH methods, particulate from the air is collected over a filter, either a 0.8-µm cellulose ester membrane or a 5.0-µm polyvinyl chloride membrane. The applicable working ranges are 0.5–10 mg/m^3 for a 100-L air sample by Method 7013, 0.005–2.0 mg/m^3 for a 500-L air sample by Methods 7300 and 7301, and up to 100 mg/m^3 in a 500-L sample for Method 7303. The digestion procedures in Method 7013 (nitric acid) will not dissolve alumina (Al_2O_3); lithium borate fusion is needed. The digestion procedure in Method 7300 (nitric/perchloric acid) may not completely solubilize some species of aluminum; alternative producers are cited in the method (NIOSH 1994, 2003a, 2003b, 2003c).

Method ID-121 (OSHA 2002) can be used to determine the amount of aluminum particulates in the workplace atmosphere. Airborne particulates are collected on filters using calibrated sampling pumps and the samples are analyzed using flame atomic absorption or emission spectrometry. This method can also determine aluminum contained in wipe and bulk samples. Method ID-109-SG (OSHA 2001) determines aluminum oxide in workplace atmospheres. In this method sample filters are fused with a flux containing lithium borate, ammonium nitrate, and sodium bromide in platinum crucibles in order to solubilize the aluminum oxide.

Method 990.08 (AOAC 1990) determines metals, including aluminum, in solid wastes (coal fly ash, industrial and electroplating sludges, mine tailings, river sediment, and soils).

Table 7-2. Analytical Methods for Determining Aluminum in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect sample on MCE filter, followed by digestion by HNO_3	Method 7013 (FAAS)	2 µg/sample	No data	NIOSH 1994
Air	Collect sample on MCE or PVC filter, followed by nitric/perchloric acid ashing	Method 7300 (ICP-AES)	0.115 µg/filter	101.5–105.4% (MCE) 77.4–92.9% (PVC)	NIOSH 2003a
Air	Collect sample on MCE filter, followed by hot block/HCl/HNO_3 digestion	Method 7303 (ICP-AES)	0.111 µg/mL	No data	NIOSH 2003b
Air	Collect sample on MCE or PVC filter, followed by aqua regia ashing	Method 7301 (ICP-AES)	0.115 µg/filter	99.6–208.1% (MCE) -1.9–112.1% (PVC)	NIOSH 2003c
Air	Collect sample on MCE or PVC filter, followed by HNO_3 digestion or extraction with deionized water	Method ID-121 (FAAS or AES)	0.02 µg/mL	94.5% (average)	OSHA 2002
Air (Al_2O_3)	Collect sample on LAPVC filter, followed by fusion with $LiBO_2/NH_4NO_3$/NaBr	Method ID-109-SG (FAAS)	0.5 µg/mL	96% (average)	OSHA 2001
Water	Filter and acidify filtrate with HNO_3 and analyze	Method 3113 B (GFAAS)	3 µg/L	No data	APHA 1998a
Water	Digest sample with HNO_3/HCl and analyze	Method 3120 B (ICP-AES)	40 µg/L	No data	APHA 1998b
Water	Filter and acidify filtrate with HNO_3 and analyze	Method 3125 (ICP-MS)	0.03 µg/L	98.42% (mean)	APHA 1998c
Water	Acidify with H_2SO_4, add ascorbic acid, buffer and dye (Erichrome cyanine R); measure absorbance at 535 nm	Method 3500-Al B (Spectro-photo-meter)	6 µg/L	No data	APHA 1998d
Water, waste water, and solid wastes	For dissolved constituents: filter, acidify filtrate, and analyze; for samples containing solids: digestion with HNO_3/HCl prior to analysis	Method 200.7 (ICP-AES)	45 µg/L	88–113%	EPA 1994a

Table 7-2. Analytical Methods for Determining Aluminum in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water, waste water, sludges, and soils	For dissolved constituents: filter, acidify filtrate, and analyze; for samples containing solids: digestion with HNO_3/HCl prior to analysis	Method 200.8(ICP-MS)	1.0 µg/L (aqueous) 0.4 mg/kg (solids)	100.4% (average)	EPA 1994b
Water, waste water, sludges, and soils	For dissolved constituents: filter, acidify filtrate, and analyze; for samples containing solids: digestion with HNO_3/HCl prior to analysis	Method 200.9 (GFAAS)	7.8 µg/L	97.1–111.7%	EPA 1994c
Water	For dissolved constituents: filter, acidify filtrate, and analyze; for samples containing solids: digestion with HNO_3/HCl prior to analysis	Method 6010C (ICP-AES)	30 µg/L	No data	EPA 2000
Water	Filter, acidify filtrate, and analyze	Method I-1472-95 (ICP-AES)	5 µg/L	86.1–99.9%	USGS 1996
Water and waste water	For dissolved constituents, filter, acidify filtrate, and analyze; for suspended metals digest with HNO_3 and analyze	Method 202.1 (FAAS)	100 µg/L	No data	EPA 1983a
Water and waste water	For dissolved constituents, filter, acidify filtrate, and analyze; for suspended metals digest with HNO_3 and analyze	Method 202.2 (GFAAS)	3 µg/L	No data	EPA 1983b
Solid wastes	Digest sample in HNO_3/H_2O_2 /HCl, dilute with water; remove particulate matter	Method 990.08 (ICP-AES)	45 µg/L	No data	AOAC 1990
Soil	Filter sample and clean-up on chromatography column	GFAAS	No data	No data	Gardiner et al. 1987
Fly ash	Dry sample in vacuum and irradiate	NAA	No data	Not applicable	Fleming and Lindstrom 1987
Plants	Digest sample with nitric acid and analyze	Spectro-photo-meter	7 µg/L	Not applicable	Dean 1989

Table 7-2. Analytical Methods for Determining Aluminum in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Rock, magma, soil, paint, citrus leaves	Acid digest sample using Parr bomb or microwave	ICP-AES	0.001 µg/L	90%	Que Hee and Boyle 1988
Dialysis fluids	Dilute sample with acidic Triton X-100	Phosphor-imetry	3 µg/L	No data	Andersen 1987
Dialysis fluids	Add Ferron and cetyl-trimethylammonium bromide solution to sample and measure phosphorescence at 586 nm	Phosphor-imetry	5.4 µg/L	No data	Fernandez de la Campa et al. 1988
Rock, soil	Digest with acid	AMS	10^{-15} g/g sample	Not applicable	Flarend and Elmore 1997

AMS = accelerated mass spectroscopy; FAAS = flame atomic absorption spectrometry; GC/ED = gas chromatography/electron capture detector; GFAAS : graphite furnace atomic absorption spectrometry; ICP-AES = inductively couples plasma-atomic absorption spectrometry; ICP-MS = inductively couples plasma-mass spectrometry LAPVC = Low Ash Polyvinyl Chloride; MCE = mixed cellulose ester; NAA = neutron activation analysis; PVC = polyvinyl chloride

Method 200.7 (EPA 1994a) provides procedures for determination of metals, including aluminum, in solution in water, wastewater, and solid wastes. Method 200.8 (EPA 1994b) provides procedures for determination of dissolved elements, including aluminum in groundwater, surface water, and drinking water, as well as determination of total recoverable element concentrations in these waters as well as waste waters, sludges and soils samples. Method 200.9 (EPA 1994c) provides procedures for the determination of dissolved and total recoverable elements, including aluminum, by graphite furnace atomic absorption (GFAA) in groundwater, surface water, drinking water, storm runoff, industrial and domestic wastewater, as well as determination of total recoverable elements in sediment, sludges, and soil.

GFAAS and FAAS are the techniques (Methods 202.1 and 202.2) recommended by EPA for measuring low levels of aluminum in water and waste water. Detection limits of 100 and 3 µg of aluminum/L of sample were obtained using the FAAS and GFAAS techniques, respectively (EPA 1983a, 1983b). Spectrophotometry and GC/ECD have also been employed to measure low-ppb (µg/L) levels of aluminum in water (Dean 1989; Ermolenko and Dedkov 1988; Gosink 1975). Flow-injection systems using absorbance (Benson et al. 1990) and fluorescence detection (Carrillo et al. 1992) have been used to monitor aqueous aluminum levels in the field and in the laboratory setting, with detection limits as low as 0.3 µg/L. Ion chromatography using spectrophoto-metric detection and on-line preconcentration gives an effective detection limit <1 µg/L in aqueous samples. GFAAS is the method of choice for measuring low-ppb levels of aluminum in dialysis fluids (Andersen 1987, 1988; Woolfson and Gracey 1988).

The GFAAS and NAA techniques have been employed for measuring aluminum levels in soil and fly ash, respectively (Fleming and Lindstrom 1987; Gardiner et al. 1987). Que Hee and Boyle (1988) employed ICP/AES to measure aluminum in rocks, soils, volcano magma, and print. Aluminum silicate matrices require disruption by hydrofluoric acid/nitric acid digestion in Parr bombs to achieve >90% recoveries of aluminum and other elements in preparation for ICP-AES analysis using wet ashing (Que Hee and Boyle 1988). Aluminum in air particulates and filters has been determined by pressurized digestion and ICP-AES detection (Dreetz and Lund 1992). Microwave digestions in closed polypropylene bottles gave the same concentrations of aluminum for rocks and soils.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of aluminum is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of aluminum.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. GFAAS is the method of choice for measuring low-ppb levels of aluminum in whole blood, serum, plasma, urine, and various biological tissues (Alder et al. 1977; Alderman and Gitelman 1980; Bettinelli et al. 1985; Bouman et al. 1986; Chappuis et al. 1988; Couri et al. 1980; Gardiner and Stoeppler 1987; Gorsky and Dietz 1978; Guillard et al. 1984; Keirsse et al. 1987; Rahman et al. 1985; Savory and Wills 1986; CEC 1984; van der Voet et al. 1985). Chromatographic techniques coupled with GFAAS detection have been used to separate various metal species and determine aluminum content in serum (Maitani et al. 1994; Van Landeghem et al. 1994). The NAA and ICP-AES methods have also been used to measure ppb levels of aluminum in biological tissues and fluids (Blotcky et al. 1976; Savory and Wills 1986; Yukawa et al. 1980). ICP-MS has the requisite sensitivity to detect low-ppb levels of aluminum (Ward 1989) in biological and environmental media though it is more expensive than GFAAS. However, the cost of ICP-MS, as well as ICP-AES, analyses has decreased significantly over the last few years. LAMMA can detect aluminum deposits in specific structures of the brain and might be used to correlate the effects of aluminum accumulation (Lovell et al. 1993).

SEM/EDXA allows for quantitative analysis of inorganic particulate burden *in situ* in tissue sections. This method can compliment bulk tissue analysis since the analyst can observe the association of certain elements within a particle and the particle size. This information can be correlated to cellular or tissue

changes with the types, locations, and concentrations of particles within the tissue (Abraham and Burnett 1983).

Although sensitive analytical methods are available for measuring the presence of aluminum in biological tissues and fluids, it is not known whether data collected using these techniques have been used to correlate the levels of aluminum in biological materials to exposure and effect levels. The problem of contamination during tissue preparation (Makjanic et al. 1998) makes this task more challenging.

Razniewska and Trzcinka-Ochocka (2003) noted that there was a need for a simple and sensitive method for the routine measurement of aluminum concentrations in serum and urine. These authors reported a method measuring aluminum concentrations in serum and urine using ETAAS. This method provided reliable results at concentrations observed among non-exposed, healthy individuals. There is a need for additional methods that can measure aluminum concentrations in blood and urine at low concentrations, approximately 1–10 µg/L.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. FAAS and ICP-AES have been used to measure aluminum in air (Dreetz and Lund 1992; NIOSH 1994, 2003a, 2003b, 2003c; OSHA 2001, 2002). For measuring aluminum in water and waste water, spectrophotometry (Benson et al. 1990; Carrillo et al. 1992; Ermolenko and Dedkov 1988), GC/ECD (Gosink 1975), and FAAS and GFAAS (EPA 1983a, 1983b) have been employed. GFAAS has been used to analyze aluminum in the soil (Gardiner et al. 1987), and GFAAS (Andersen 1987) as well as phosphorimetry (Fernandez de la Campa et al. 1988) have been useful in determining aluminum levels in dialysis fluids. The method used to measure aluminum levels in flyash is NAA (Fleming and Lindstrom 1987). The media of most concern for potential exposure to aluminum are water and dialysis fluids. GFAAS technique is sensitive for measuring background levels of aluminum in water (EPA 1983b) and dialysis fluids (Andersen 1987; Woolfson and Gracey 1988) and levels of aluminum at which health effects might begin to occur. GFAAS and FAAS are the techniques (Methods 202.1 and 202.2) recommended by EPA for detecting aluminum levels in water and waste water (EPA 1983a, 1983b). GFAAS is the method of choice for measuring low-ppb levels of aluminum in dialysis fluids (Andersen 1987; Woolfson and Gracey 1988). ICP-AES has been utilized to detect aluminum in biological media (leaves, feces, serum, blood, liver, spleen, kidney, urine, and testes) and environmental matrices (rocks, soils, water, volcano magma, paint) in addition to other elements (Que Hee and Boyle 1988) and, more recently, ICP-MS has been shown to be useful for even more sensitive analyses of such media. No additional methods for detecting elemental aluminum in environmental media appear to be necessary at

this time. A need exists for developing a range of NIST analytical standards for calibrating instruments and assessing the accuracy and precision of the various analytical methods.

7.3.2 Ongoing Studies

The information in Table 7-3 was found as a result of a search of the Federal Research in Progress database (FEDRIP 2006).

Table 7-3. Ongoing Studies on Aluminum

Investigator	Affiliation	Research description	Sponsor
Mutti, A.	University of Parma, Parma, Italy	The present research project is aimed at applying the most sensitive, selective and specific reference analytical techniques to the study of the composition of exhaled breath condensate in chronic obstructive pulmonary disease patients using ETAAS and ICP-MS.	NIH
Progar, J	Not provided	The goal of the research program is directed toward the development of analytical methodology to determine the quantitative, qualitative, and/or structural identification of inorganic chemical constituents and impurities in drug and biological products through spectrometric means, including FAAS, GFAAS, FES, ICP-AES, and ICP-MS.	NIH
May, JC	Not provided	The research goal is to ensure the safety, purity and potency of vaccines and other biological products through research relating to the development of new or improved accurate, validated, qualitative and/or quantitative methods for the determination and/or characterization of the chemical preservatives, stabilizers, inactivators, adjuvants, residual moisture, protein and other chemical constituents of vaccines and biological products.	NIH

ETAAS = Electro-thermal atomic absorption spectroscopy; FAAS = flame atomic absorption spectrometry; FES = flame emission spectrometry; GFAAS = graphite furnace atomic absorption spectrometry; ; ICP-AES = inductively coupled argon plasma-emission spectrometry ICP-MS = Inductively coupled plasma - mass spectrometry; NIH = National Institutes of Health

Source: FEDRIP 2006

8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines regarding aluminum and aluminum compounds in air, water, and other media are summarized in Table 8-1.

ATSDR has derived an intermediate-duration oral minimal risk level (MRL) of 1 mg Al/kg/day for aluminum. This MRL is based on a NOAEL of 26 mg Al/kg/day and a LOAEL of 130 mg Al/kg/day for neurodevelopmental effects in the offspring of mice exposed to aluminum lactate in the diet on gestation day 1 through lactation day 21 followed by pup exposure until postnatal day 35 (Golub and Germann 2001). The MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) and a modifying factor of 0.3 to account for the higher bioavailability of the aluminum lactate used in the principal study, as compared to the bioavailability of aluminum in the human diet and drinking water.

ATSDR has derived a chronic-duration oral MRL of 1 mg Al/kg/day for aluminum. This MRL is based on a LOAEL of 100 mg Al/kg/day for neurological effects in mice exposed to aluminum lactate in the diet during gestation, lactation, and postnatally until 2 years of age (Golub et al. 2000). The MRL was derived by dividing the LOAEL by an uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability) and a modifying factor of 0.3 to account for the higher bioavailability of the aluminum lactate used in the principal study, as compared to the bioavailability of aluminum in the human diet and drinking water.

EPA has not derived a reference dose (RfD) or reference concentration (RfC) for aluminum, but has derived an RfD for aluminum phosphide of $4x10^{-4}$ mg/kg/day based on a NOAEL of 0.51 mg/kg of food or 0.025 mg/kg/day (phosphine) converted to 0.043 mg/kg/day of aluminum phosphide for body weight and clinical parameters observed in a rats during a chronic oral study (IRIS 2008).

Table 8-1. Regulations and Guidelines Applicable to Aluminum and Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification for aluminum production	Group 1[a]	IARC 1987
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines for aluminum[b]	≤0.1 mg/L in large water treatment facilities	WHO 2004
		≤0.2 mg/L in small water treatment facilities	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA) for aluminum and compounds (as Al)		ACGIH 2005
	Metal dust	10 mg/m^3	
	Pyro powders	5 mg/m^3	
	Soluble salts	2 mg/m^3	
	Alkyls (NOS)	2 mg/m^3	
	TLV (8-hour TWA) for aluminum oxide[c]	10 mg/m^3	
EPA	AEGL-1 for aluminum phosphide[d]	Not recommended due to insufficient data	EPA 2006a
	AEGL-2 for aluminum phosphide[d]		
	10 minutes	4.0 ppm	
	30 minutes	4.0 ppm	
	60 minutes	2.0 ppm	
	4 hours	0.50 ppm	
	8 hours	0.25 ppm	
	AEGL-3 for aluminum phosphide[d]		
	10 minutes	7.2 ppm	
	30 minutes	7.2 ppm	
	60 minutes	3.6 ppm	
	4 hours	0.90 ppm	
	8 hours	0.45 ppm	
	Hazardous air pollutant	No data	EPA 2006c 42 USC 7412

Table 8-1. Regulations and Guidelines Applicable to Aluminum and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NIOSH	REL (10-hour TWA)		NIOSH 2005
	Aluminum	10 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	
	Aluminum oxide	15 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	
OSHA	PEL (8-hour TWA) for general industry for aluminum metal (as Al) and aluminum oxide	15 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	OSHA 2007b 29 CFR 1910.1000
	PEL (8-hour TWA) for shipyard industry for aluminum metal (as Al) and aluminum oxide	15 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	OSHA 2007a 29 CFR 1915.1000
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act for aluminum sulfate	Yes	EPA 2006b 40 CFR 116.4
	Drinking water standards and health advisories	0.05–0.2 mg/L	EPA 2006f
	National primary drinking water standards	No data	EPA 2003
	National secondary drinking water standards for aluminum	0.05–0.2 mg/L	EPA 2008 40 CFR 143.3
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act for aluminum sulfate	5,000 pounds	EPA 2006h 40 CFR 117.3
	Water quality criteria for human health for aluminum		EPA 2006e
	Freshwater CMC	750 µg/L	
	Freshwater CCC	87 µg/L	
c. Food			
FDA	Bottled drinking water for aluminum	0.2 mg/L	FDA 2005 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification for aluminum oxide	A4[e]	ACGIH 2005
EPA	Carcinogenicity classification for aluminum phosphide	No data	IRIS 2008
	RfC for aluminum phosphide	No data	
	RfD for aluminum phosphide	$4x10^{-4}$ mg/kg/day	

Table 8-1. Regulations and Guidelines Applicable to Aluminum and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Identification and listing of hazardous substances; hazardous waste number for aluminum phosphide	P006	EPA 2006d 40 CFR 261, Appendix VIII
	Pesticide classified as restricted use for aluminum phophide	Yes[f]	EPA 2006g 40 CFR 152.175
	Pesticide exemptions from the requirement of a tolerance		EPA 2006l 40 CFR 180.910
	Aluminum hydroxide (for use as a diluent and carrier)	Yes[g]	
	Aluminum oxide (for use as a diluent)	Yes[g]	
	Aluminum sulfate (for use as a safener adjuvant)	Yes[g]	EPA 2006m 40 CFR 180.920
	Superfund, emergency planning, and community right-to-know		EPA 2006i 40 CFR 302.4
	Designated CERCLA hazardous substance	Yes	
	Reportable quantity		
	Aluminum phosphide	100 pounds	
	Aluminum sulfate	5,000 pounds	
	Effective date of toxic chemical release reporting		EPA 2006k 40 CFR 372.65
	Aluminum (fume or dust)	01/01/87	
	Aluminum oxide (fibrous forms)	01/01/87	
	Aluminum phosphide	01/01/95	
	Extremely hazardous substances and their threshold planning quantities for aluminum phosphide	500 pounds	EPA 2006j 40 CFR 355, Appendix A

Table 8-1. Regulations and Guidelines Applicable to Aluminum and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification	No data	NTP 2004

[a]Group 1: carcinogenic to humans
[b]Reason for not establishing a guideline value: owing to limitations in the animal data as a model for humans and the uncertainty surrounding the human data, a health-based guideline value cannot be derived; however, practicable levels based on optimization of the coagulation process in drinking-water plants using aluminium-based coagulants are derived: $\leq$0.1 mg/L in large water treatment facilities, and $\leq$0.2 mg/L in small facilities.
[c]TWA: the value is for particulate matter containing no asbestos and <1% crystalline silica.
[d]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.
[e]A4: not classifiable as a human carcinogen.
[f]Pesticide classified as restricted use: limited to use by or under the direct supervision of a certified applicator for agricultural crop uses. Criteria influencing restriction includes inhalation hazard to humans.
[g]Pesticide exemptions from the requirement of a tolerance: residues of the following materials are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Level; Al = aluminum; CERCLA = Comprehensive Environmetnal Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CCC = Criterion Continuous Concentration; CMC = Criteria Maximum Concentration; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NOS = not otherwise specified; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar

ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Aluminum
CAS Numbers: 7429-90-5
Date: June 2008
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 46
Species: Mouse

Minimal Risk Level: 1 [X] mg/kg/day [ ] ppm

Reference: Golub MS, Germann SL. 2001. Long-term consequences of developmental exposure to aluminum in a suboptimal diet for growth and behavior in Swiss Webster mice. Neurotoxicol Teratol 23:365-372.

Experimental design: Groups of pregnant Swiss Webster mice were exposed to 0, 100, 500, or 1,000 mg Al/kg diet on gestational days 0–21 and during lactation until day 21. On PND 21, one male and one female pup from each litter were placed on the same diet as the dam. The offspring were exposed until PND 35. The composition of the diet was modified from the National Research Council's recommendations; the investigators noted that the nutrients were reduced to correspond to the usual intake of these nutrients by young women. The average daily intakes of phosphorus, calcium, magnesium, iron, and zinc in women aged 18–24 years are 83, 56, 71, 69, and 67% of the RDA; these percents were used to modify the recommended dietary intake for the mice used in this study. Doses of 26, 130, and 260 mg Al/kg/day are calculated by averaging reported estimated doses of 10, 50, and 100 mg Al/kg/day for adults (i.e., at beginning of pregnancy) and 42, 210, and 420 mg Al/kg/day maximal intake during lactation. The doses at lactation were calculated using doses estimated in previous studies with similar exposure protocols performed by the same group of investigators (Golub et al. 1995). At 3 months of age, the females were tested for neurotoxicity using the Morris water maze. At 5 months of age, males were tested for motor activity and function using rotarod, grip strength, wire suspension, mesh pole descent, and beam traversal tests.

Effect noted in study and corresponding doses: No alterations in pregnancy weight gain or pup birth weights were observed. At PND 21, significant decreases in pup body weights were observed at 130 and 260 mg/kg/day. No information on maternal weight gain during lactation was reported; however, the investigators noted that the decrease in pup weight was not associated with reduced maternal food intake. At PND 35, the decrease in body weight was only significant at 260 mg/kg/day. On PND 90, female mice in the 260 mg/kg/day group weighed 15% less than controls. Decreases in heart and kidney weights were observed at 260 mg/kg/day in the females. Also, decreases in absolute brain weight were observed in females at 260 mg/kg/day and relative brain weights were observed at 26 or 260 mg/kg/day. In the males, significant decreases in body weight were observed at 130 (10%) and 260 (18%) mg/kg/day at 5 months; an increase in food intake was also observed these doses. In the Morris maze (tested at 3 months in females), fewer animals in the 260 mg/kg/day group had escape latencies of <60 seconds during sessions 1–3 (learning phase) and a relocation of the visible cues resulted in increased latencies at 130 and 260 mg/kg/day. Body weight did not correlate with latency to find the platform or with the distribution of quadrant times. The investigators concluded that controls used salient and/or nonsalient cues, 26 and 130 mg/kg/day animals used both cues, but had difficulty using only one cue, and 260 mg/kg/day animals only used the salient cues. In the males tested at 5 months, a significant decrease in hindlimb grip strength was observed at 260 mg/kg/day, an increase in the number of rotations on the rotorod as observed at 260 mg/kg/day, and a shorter latency to fall in the wire suspension test as was

observed at 130 and 260 mg/kg/day. The investigators noted that there were significant correlations between body weight and grip strength and number of rotations. When hindlimb grip strength was statistically adjusted for body weight, the aluminum-exposed mice were no longer significantly different from controls.

Reference: Colomina MT, Roig JL, Torrente M, et al. 2005. Concurrent exposure to aluminum and stress during pregnancy in rats: effects on postnatal development and behavior of the offspring. Neurotoxicol Teratol 27:565-574.

Experimental design: Groups of female Sprague-Dawley rats were exposed to 0, 50, or 100 mg Al/kg/day aluminum nitrate nonahydrate in drinking water; citric acid (710, 355, and 710 mg/kg/day in the control, 50, and 100 ppm groups, respectively) was added to the drinking water to increase aluminum absorption. The adult rats were exposed to aluminum for 15 days prior to mating and the during gestation and lactation periods; after weaning, the pups were exposed to the same aluminum concentration as the mothers from postnatal day 21 through 68. The basal diet (Panlab rodent chow) contained 41.85 µg Al/g diet. Aluminum doses were calculated by adding the basal dietary aluminum doses (calculated using reference values for mature Sprague-Dawley rats) to reported aluminum doses from water; the total aluminum doses were 3, 53, and 103 mg Al/kg/day. In addition to aluminum exposure, some animals in each group underwent restraint stress for 2 hours/day on gestation days 6–20; the restraint consisted of placing the rats in cylindrical holders. The following neurobehavioral tests were performed on the offspring: righting reflex (PNDs 4, 5, 6), negative geotaxis (PNDs 7, 8, 9), forelimb grip strength (PNDs 10–13), open field activity (PND 30), passive avoidance (PND 35), and water maze (only tested at 53 mg/kg/day on PND 60). On PND 68, rats were killed and aluminum levels were measured in the cortex, hippocampus, striatum, cerebellum, and brainstem.

Effect noted in study and corresponding doses: No significant alterations in body weight, food consumption, or water consumption were observed during gestation in the dams exposed to aluminum. The investigators noted that decreases in water and food consumption were observed during the lactation period in the rats exposed to 103 mg Al/kg/day, but the data were not shown, and maternal body weight during lactation was not mentioned. No significant alterations in the number of litters, number of fetuses per litter, viability index, or lactation index were observed. Additionally, no differences in days at pinna detachment or eye opening were observed. Age at incisor eruption was significantly higher in males exposed to 53 mg/kg/day, but not in males exposed to 103 mg/kg/day or in females. A significant delay in age at testes descent was observed at 103 mg/kg/day and vagina opening was delayed at 53 and 103 mg/kg/day. A decrease in forelimb grip strength was observed at 103 mg/kg/day; no alterations in other neuromotor tests were observed. Additionally, no alterations in open field behavior or passive avoidance test were observed. In the water maze test, latency to find the hidden platform was decreased in the 53 mg/kg/day group on test day 2, but not on days 1 or 3; no significant alteration in time in the target quadrant was found.

Dose and end point used for MRL derivation: The Golub and Germann (2001) and Colomina et al. (2005) studies identify four end points that could be used as the point of departure for derivation of the intermediate-duration oral MRL:

(1) latency to fall off wire in wire suspension test; adverse effect level of 130 mg Al/kg/day, no effect level of 26 mg Al/kg/day (Golub and Germann 2001);
(2) latency to locate the platform following cue relocation in the water maze test; adverse effect level of 130 mg Al/kg/day, no effect level of 26 mg Al/kg/day (Golub and Germann 2001);
(3) decreased forelimb grip strength; adverse effect level of 103 mg Al/kg/day, no effect level of 53 mg Al/kg/day (Colomina et al. 2005); and

(4) delay in vagina opening; adverse effect level of 53 mg Al/kg/day, no effect level not identified (Colomina et al. 2005).

Benchmark dose modeling was considered for each of these end points. Continuous variable models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the data. A change of 1 standard deviation from control was selected as the BMR. Benchmark dose modeling was not conducted for latency to fall from the wire and forelimb grip strength because it is unclear whether the data reported in Table 5 (Golub and Germann 2001) and Figure 2 (Colomina et al. 2005), respectively, was for the mean ±SEM or the mean ± standard deviation. For delay in maturation, none of the available models provided an adequate fit (as assessed by the p-values for variance); therefore, the data set is unsuitable for BMD modeling. For the change in the latency to find the platform, the constant variance linear model provided an adequate fit. However, the BMD (419 mg Al/kg/day) and BMDL (186 mg Al/kg/day) were higher than the dose at which the change in latency was statistically significant (130 mg Al/kg/day), suggesting that using the change of 1 standard deviation from controls may not be an appropriate BMR for these data.

Using a NOAEL/LOAEL approach, the NOAEL of 26 mg Al/kg/day identified in the Golub and Germann (2001) study was selected as the point of departure for the MRL.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifying Factors used in MRL derivation:

[X] 0.3 to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet.

No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggested that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Golub and Germann (2001): Doses of 26, 130, and 260 mg Al/kg/day are calculated by averaging reported estimated doses of 10, 50 and 100 mg Al/kg/day for adults (i.e., at beginning of pregnancy), and 42, 210, and 420 mg Al/kg/day maximal intake during lactation. The doses at lactation were calculated using doses were estimated in previous studies with similar exposure protocols performed by the same group of investigators (e.g., Golub et al. 1995).

Colomina et al. (2005): Doses of 3, 53, and 103 mg Al/kg/day were calculated by adding the basal dietary aluminum doses (calculated using reference values for mature Sprague-Dawley rats) to reported aluminum doses from water.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The neurotoxicity and neurodevelopmental toxicity of aluminum are well-documented effects of aluminum in orally-exposed in mice and rats. A wide variety of behavioral tests were conducted in rats and mice; alterations in motor function were the most consistently observed effects. Decreases in forelimb and/or hindlimb grip strength have been observed in adult mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 90 days (Golub et al. 1992b), mice (6 weeks of age at study beginning) exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993), the offspring of mice exposed on gestation day 1 through lactation day 21 to 155 mg Al/kg/day (Donald et al. 1989; Golub et al. 1995) or 250 mg Al/kg/day (Golub et al. 1995) as aluminum lactate, and the offspring of rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 15 days prior to mating and on gestation day 1 through lactation day 21 (Colomina et al. 2005). Decreases in spontaneous motor activity were observed in mice exposed to 130 mg Al/kg/day for 6 weeks (Golub et al. 1989) or 195 mg Al/kg/day for 90 days (Golub et al. 1992b). Motor impairments have also been detected in mice in the wire suspension test in which offspring exposed to 130 mg Al/kg/day had a shorter latency to fall from the wire and in the rotorod test in which offspring exposed to 260 mg Al/kg/day had a higher number of rotations (which occur when the animals lost its footing, clung to the rod, and rotated with it for a full turn) (Golub and Germann 2001). Neurobehavioral alterations that have occurred at similar dose levels include decreased responsiveness to auditory or air-puff startle (Golub et al. 1992b, 1995), decreased thermal sensitivity (Golub et al. 1992a), increased negative geotaxis latency (Golub et al. 1992a), and increased foot splay (Donald et al. 1989). Additionally, one study found significant impairment in performance of the water maze test in offspring of mice exposed to 130 mg Al/kg/day on gestation day 1 through lactation day 21 (Golub and Germann 2001). Colomina et al. (2005) did not find alterations in this test in rats exposed to 53 mg Al/kg/day; however, this study did not run probe tests, which showed significant alterations in the Golub and Germann (2001) study. Other studies have utilized passive avoidance tests or operant training tests to evaluate potential impairment of cognitive function. However, the interpretation of the results of these tests is complicated by an increase in food motivation in aluminum exposed mice (Golub and Germann 1998).

In addition to the neurodevelopmental effects, there is also strong evidence that gestational and/or lactational exposure can cause other developmental effects. Aluminum does not appear to result in an increase in the occurrence of malformations and anomalies and does not typically affect birth weight. Gestation and/or lactation exposure can result in significant decreases in pup body weight gain in rats and mice (Colomina et al. 2005; Golub and Germann 2001; Golub et al. 1992a). The decreases in pup body weight are often associated with decreases in maternal body weight during the lactation phase of the study; however, decreases in body weight have also been observed in a cross-fostering study when gestation-exposed pups were nursed by control mice (Golub et al. 1992a). Other studies involving gestation and lactation exposure to aluminum did not find changes in pup growth in mice (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1995). In rats, a delay in physical maturation, particularly delays in vagina opening, testes descent, and incisor eruption, has been reported at 53 mg Al/kg/day (Colomina et al. 2005).

Agency Contacts (Chemical Managers): Sam Keith, Dennis Jones, Zemoria Rosemond

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Aluminum
CAS Numbers: 7429-90-5
Date: June 2008
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 56
Species: Mouse

Minimal Risk Level: 1 [X] mg/kg/day [ ] ppm

Reference: Golub MS, Germann SL, Han B, et al. 2000. Lifelong feeding of a high aluminum diet to mice. Toxicology 150:107-117.

Experimental design: Groups of 8 male and 10 female Swiss Webster mice were exposed to 7 or 1,000 μg Al/g diet as aluminum lactate in a purified diet. The investigators estimated adult doses of <1 and 100 mg/kg/day. The mice were exposed to aluminum from conception (via feeding the dams) through 24 months of age. Body weight, food intake, and clinical signs were determined during the last 6 months of the study. Neurobehavioral test battery (foot splay, temperature sensitivity, negative geotaxis, and grip strength), 1 hour spontaneous activity, and auditory startle tests were conducted at 18 and 24 months.

In a companion study, groups of 6–9 male and female Swiss Webster mice or 7 male and female C57BL/6J mice (number per sex were not reported) were exposed to 7 or 1,000 μg Al/g diet as aluminum lactate in a purified diet (<1 and 100 mg/kg/day) from conception (via feeding the dams) through 24 months of age. Body weight, food intake, and clinical signs were determined during the last 6 months of the study. Neurobehavioral test battery (foot splay, temperature sensitivity, negative geotaxis, and grip strength) and Morris maze testing were at 22–23 months of age.

Effect noted in study and corresponding doses: In the principal study, no significant alterations in mortality were observed. A significant decrease in body weight was observed in the female mice (approximately 20%). In the males, there was a significant increase in body weight (approximately 10%). No significant alterations in food intake were observed in either sex. However, food intake/g body weight was significantly higher in the aluminum exposed mice. No significant alterations in the occurrence of clinical signs or indications of neurodegenerative syndromes were found. Significant increases in relative spinal cord, heart, and kidney weights were found. Significant alterations in negative geotaxis and tail withdrawal time in the temperature sensitivity test (males only) were observed at 18 months. At 24 months, significant alterations in forelimb and hindlimb grip strength and temperature sensitivity were found in male and female mice. Forelimb and hindlimb grip strength was decreased and thermal sensitivity was decreased, as evidenced by an increase in tail withdrawal times. Auditory startle response tests could not be completed in the older mice. Similarly, vertical spontaneous movement could not be measured; no effect on horizontal movement was found.

In the companion study, no alterations in neurobehavioral battery test performance were observed; the investigators note that this may be due to the small number of animals per group. In general, aluminum-exposed mice performed better on the water maze test than controls.

Dose and end point used for MRL derivation: A LOAEL of 100 mg Al/kg/day for decreased forelimb and hindlimb grip strength and decreased thermal sensitivity. A benchmark dose approach for deriving an MRL was not utilized because the Golub et al. (2000) study only tested one aluminum group.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifying Factors used in MRL derivation:

[X] 0.3 to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet.

No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggested that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No (doses corresponding to food ppm levels were reported by investigators).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: A small number of animal studies examined the chronic toxicity of aluminum. Schroeder and Mitchener (1975a, 1975b) examined the systemic toxicity of aluminum following lifetime exposure of rats and mice to very low doses of aluminum sulfate in the drinking water. Although the levels of aluminum in diet were not reported, they are assumed to be low because the animals were fed a low-metal diet in metal-free environmental conditions. Studies conducted by Roig et al. (2006) and Golub et al. (2000) primarily focused on the neurotoxicity of aluminum following lifetime exposure (gestation day 1 through 24 months of age). In the Golub et al. (2000) study, significant decreases in forelimb and hindlimb grip strength, and a decrease in thermal sensitivity were observed in mice exposed to 100 mg Al/kg/day; negative geotaxis was significantly altered at 18 months, but not at 24 months. No effect on horizontal activity was observed. A 10% increase in body weight and a 20% decrease in body weight were observed in the males and females, respectively. In a companion study by this group, no significant cognitive impairments were found in the Morris water maze test; in fact, aluminum-exposed mice performed better than controls in the learning tasks. Roig et al. (2006) also found no significant alterations in performance on the Morris water maze in rats exposed to 100 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid). Although significant differences were found between the two aluminum groups

(50 and 100 mg Al/kg/day), this was primarily due to the improved performance (as compared to controls, no significant differences) in the 50 mg Al/kg/day group. Roig et al. (2006) also found no significant alterations in open field activity.

Additional support for the selection of these end points, and neurotoxicity in general, comes from a number of intermediate-duration studies that indicate that this is one of most sensitive targets of aluminum toxicity (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 2001; Golub et al. 1992a, 1995).

Agency Contacts (Chemical Managers): Sam Keith, Dennis Jones, Zemoria Rosemond

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

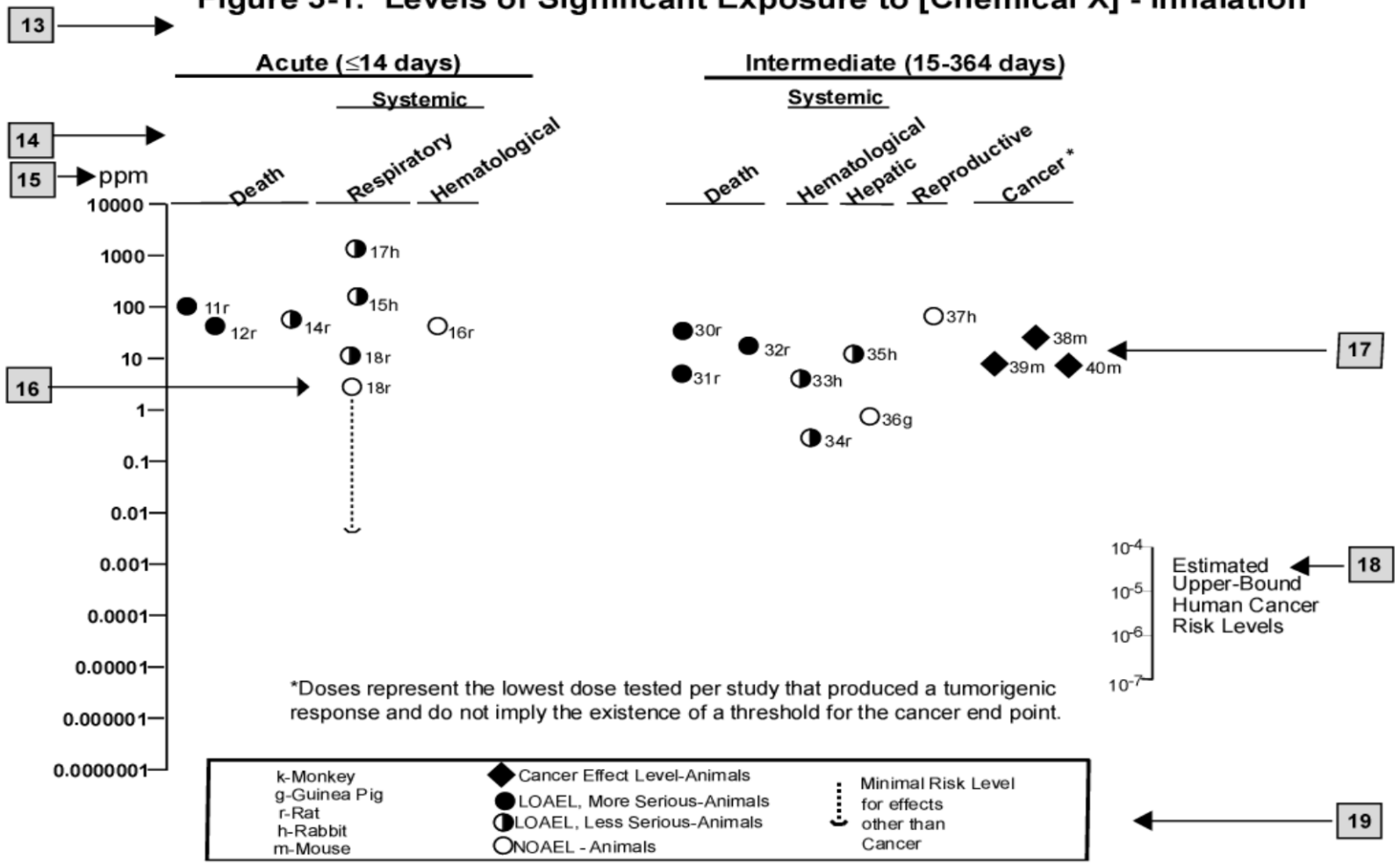
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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TOXICOLOGICAL PROFILE FOR
2,3-BENZOFURAN

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

September 1992

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 2,3-benzofuran and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). 2,3-Benzofuran has been found in at least 5 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for 2,3-benzofuran. As EPA evaluates more sites, the number of sites at which 2,3-benzofuran is found may change. This information is important for you to know because 2,3-benzofuran may cause harmful health effects and because these sites are potential or actual sources of human exposure to 2,3-benzofuran.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as 2,3-benzofuran, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS 2,3-BENZOFURAN?

2,3-Benzofuran is a colorless, sweet-smelling, oily liquid which does not mix with water. 2,3-Benzofuran is made by processing coal into coal oil. 2,3-Benzofuran may also be formed during other uses of coal or oil. The part of the coal oil that contains 2,3-benzofuran is made into a plastic called coumarone-indene resin. Coumarone-indene resin can then be used to make paint, varnish, glue, and floor tiles, and it is allowed on food products and packages. We know very little about how 2,3-benzofuran might get into the environment or what happens to it after it gets there.

More information on the properties and uses of 2,3-benzofuran and how it behaves in the environment may be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO 2,3-Benzofuran?

2,3-Benzofuran has been found in a few places in the air and water. In most instances, when it was found; the amount that was there was not measured. We do not know what the levels of 2,3-benzofuran are in soil, air, water, or food. The reason that 2,3-benzofuran has not often been found could be that 2,3-benzofuran usually attaches to particles, and is not free in the air or water. We do not know where 2,3-benzofuran comes from, except when it is

found near fuel-processing factories. Workers who make coal oil or coumarone-indene resin might be exposed to 2,3-benzofuran. Cigarette smoke has some 2,3-benzofuran in it. Coumarone-indene resin is allowed in food packages and as a coating on oranges and grapefruit. .We do not know how often the resin is used or whether any 2,3-benzofuran in it gets into the food.

More information on how you might be exposed to 2,3-benzofuran is given in Chapter 5.

1.3 HOW CAN 2,3-BENZOFURAN ENTER AND LEAVE MY BODY?

We know very little about how 2,3-benzofuran can enter or leave your body. Some 2,3-benzofuran can enter your body from the environment if it is in the water that you drink, the food that you eat, or the air that you breathe. We do not know how much you would take in or when and how it would leave your body.

More information on how 2,3-benzofuran enters and leaves the body is given in Chapter 2.

1.4 HOW CAN 2,3-BENZOFURAN AFFECT MY HEALTH?

The effect of 2,3-benzofuran on your health depends on how much you take into your body. In general, the more you take in, the greater the chances that an effect will occur. No studies have been done to test the effects of 2,3-benzofuran on the health of humans. Studies in animals show that 2,3-benzofuran can damage the liver and kidneys if large amounts are given within a short time, and that very large amounts can kill. We do not know whether exposure to 2,3-benzofuran can affect your ability to have children or can harm an unborn baby.

Studies in animals show that exposure to 2,3-benzofuran at moderate levels over a long time can damage the liver, kidneys, lungs, and stomach. The brain, muscles, and heart do not seem to be seriously damaged by long-term exposure. Some rats and mice that received 2,3-benzofuran for their whole lives developed cancer of the kidney, lung, liver, or stomach. However, no cases of cancer in humans have been linked to exposure to 2,3-benzofuran. More information on the health effects of 2,3-benzofuran in humans and animals can be found in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 2,3-BENZOFURAN?

2,3-Benzofuran can be measured in your blood or in your milk if you are a nursing mother. The test is specific for 2,3-benzofuran but it requires special equipment and is not easily available. The test may only be able to detect 2,3-benzofuran for a certain period of time because it is not known how long 2,3-benzofuran remains in the body after you have been exposed to it.

Also, the test only shows that you have been exposed; it cannot predict which health effects, if any, you will develop.

More information on how 2,3-benzofuran can be measured in exposed humans is given in Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

No standards have been set for exposure to 2,3-benzofuran. The Food and Drug Administration specifies the quantity of coumarone-indene resin that may be used on food and in food packages.

More information on government regulations for 2,3-benzofuran can be found in Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 2,3-benzofuran and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for 2,3-benzofuran based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELS) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of 2,3-benzofuran are indicated in Figure 2-l. Cancer effects could occur at lower exposure levels, but excess risks have not been estimated.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

No studies were located regarding the following health effects in humans or animals after inhalation exposure to 2,3-benzofuran:

2.2.1.1 Death
2.2.1.2 Systemic Effects
2.2.1.3 Immunological Effects
2.2.1.4 Neurological Effects
2.2.1.5 Developmental Effects
2.2.1.6 Reproductive Effects
2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to 2,3-benzofuran. Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after inhalation exposure to 2,3-benzofuran.

2.2.2 Oral Exposure

No studies were located regarding health effects in humans after oral exposure to 2,3-benzofuran.

Most information about the health effects of 2,3-benzofuran comes from studies of animals (rats and mice) exposed by gavage, particularly a study by the National Toxicology Program (NTP 1989). Table 2-l and Figure 2-1 present a summary of studies that provide reliable quantitative data on the toxicity of 2,3-benzofuran following oral exposure. The main conclusions from these studies are discussed below.

TABLE 2-1. Levels of Significant Exposure to 2,3-Benzofuran - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(GO)	14 d 1x/d		250		500 (1/5 females died)	NTP 1989
2	Mouse	(GO)	14 d 1x/d		250			NTP 1989
Systemic								
3	Rat	(GO)	14 d 1x/d	Resp	250	500 (red nasal discharge)		NTP 1989
				Cardio	250			
				Gastro	250			
				Hemato	250			
				Musc/skel	250			
				Hepatic	250			
				Renal	250			
				Derm/oc	250	500 (red ocular discharge)		
				Other	125	250 (decreased body weight in males)		
4	Mouse	(GO)	14 d 1x/d	Resp	250			NTP 1989
				Cardio	250			
				Gastro	250			
				Hemato	250			
				Musc/skel	250			
				Hepatic	250			
				Renal	250			
				Derm/oc	250			
				Other	250			
INTERMEDIATE EXPOSURE								
Death								
5	Rat	(GO)	13 wk 5d/wk 1x/d		125		250 (1/10 females died)	NTP 1989
6	Mouse	(GO)	13 wk 5d/wk 1x/d		125		250 (1/10 males died)	NTP 1989

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Systemic								
7	Rat	(GO)	13 wk 5d/wk 1x/d	Resp	500			NTP 1989
				Cardio	500			
				Gastro	500			
				Hemato	500			
				Musc/skel	500			
				Hepatic		125 (necrosis of hepatocytes in males)		
				Renal	125	250 (tubular nephropathy)		
				Derm/oc	500			
				Other	62.5	125 (reduced body weight in males)		
8	Mouse	(GO)	13 wk 5d/wk 1x/d	Resp	500			NTP 1989
				Cardio	500			
				Gastro	500			
				Hemato	500			
				Musc/skel	500			
				Hepatic	500			
				Renal	125	250 (tubular cell necrosis in males)		
				Derm/oc	500			
				Other	250	500 (reduced body weight in males)		
CHRONIC EXPOSURE								
Death								
9	Rat	(GO)	103 wk 5d/wk 1x/d				30 (decreased survival in males after 1.5 years)	NTP 1989
10	Mouse	(GO)	103 wk 5d/wk 1x/d				120 (decreased survival in females after 1.5 years)	NTP 1989

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Systemic								
11	Rat	(GO)	103 wk 5d/wk 1x/d	Resp	120[b]			NTP 1989
				Cardio		30 (mineralization of pulmonary artery in males)		
				Gastro		30 (forestomach inflammation in males)		
				Hemato	120[b]			
				Musc/skel	120[b]			
				Hepatic	120[b]			
				Renal			30 (severe nephropathy in males)	
				Derm/oc	120[b]			
				Other		30 (reduced body weight in males)		
12	Mouse	(GO)	103 wk 5d/wk 1x/d	Resp		60 (lung hyperplasia in males)		NTP 1989
				Cardio	240[c]			
				Gastro	60	120 (forestomach hyperplasia in females)		
				Hemato	240[c]			
				Musc/skel	240[c]			
				Hepatic		60 (multinuclear hepatocytes in males)		
				Renal	240[c]			
				Derm/oc	240[c]			
				Other		60 (reduced body weight in males)		
Cancer								
13	Rat	(GO)	103 wk 5d/wk 1x/d				120 CEL (kidney adenocarcinoma in females)	NTP 1989

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
14	Mouse	(GO)	103 wk 5d/wk 1x/d				60 CEL (lung, liver and forestomach tumors in males)	NTP 1989

[a]The number corresponds to entries in Figure 2-1.
[b]NOAEL for effect in female rats. NOAEL in male rats is 60 mg/kg/day.
[c]NOAEL for effect in female mice. NOAEL in male mice is 120 mg/kg/day.

Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; (GO) = gavage-oil; Gastro = gastrointestinal; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

FIGURE 2-1. Levels of Significant Exposure to 2,3-Benzofuran – Oral

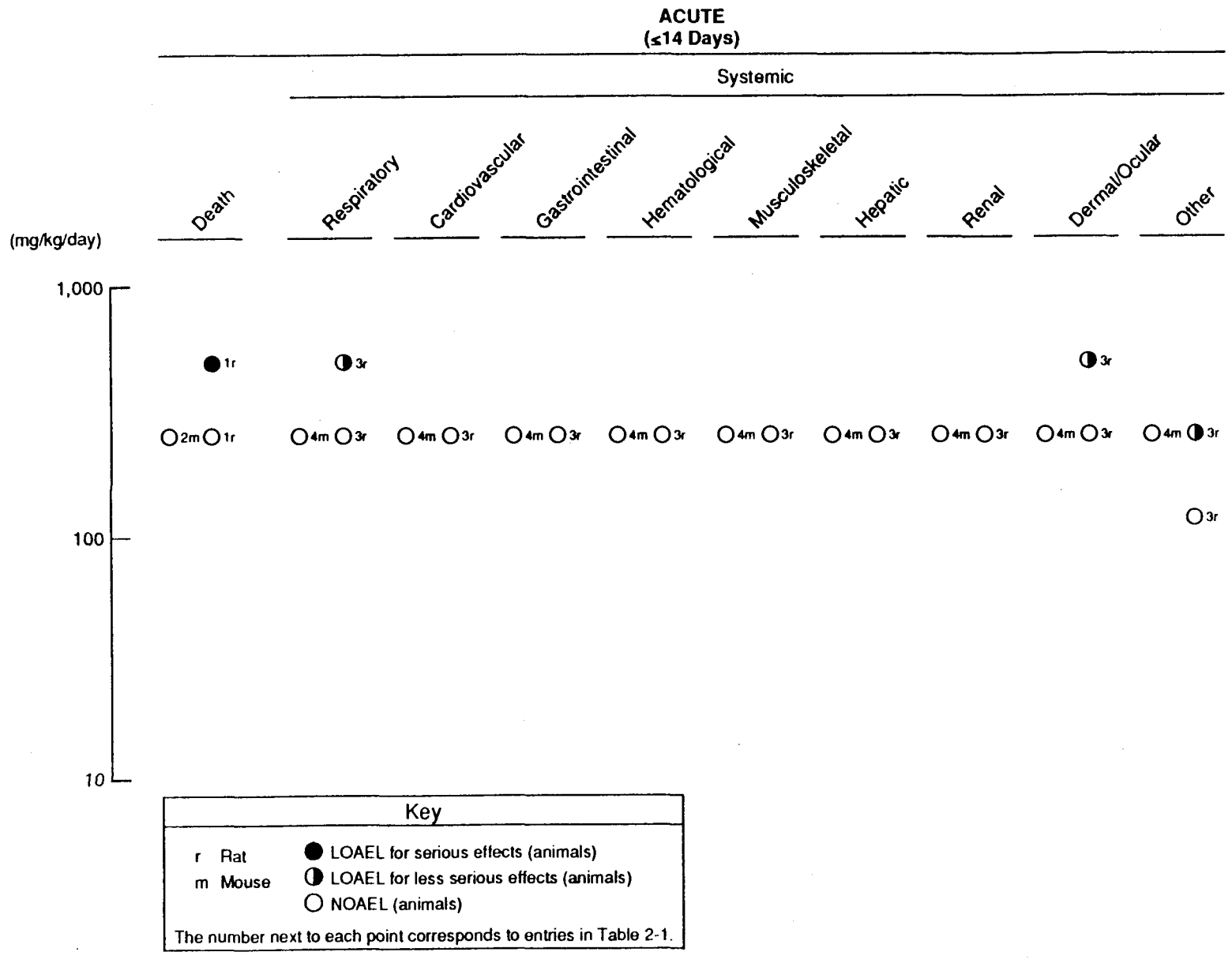


FIGURE 2-1 (Continued)

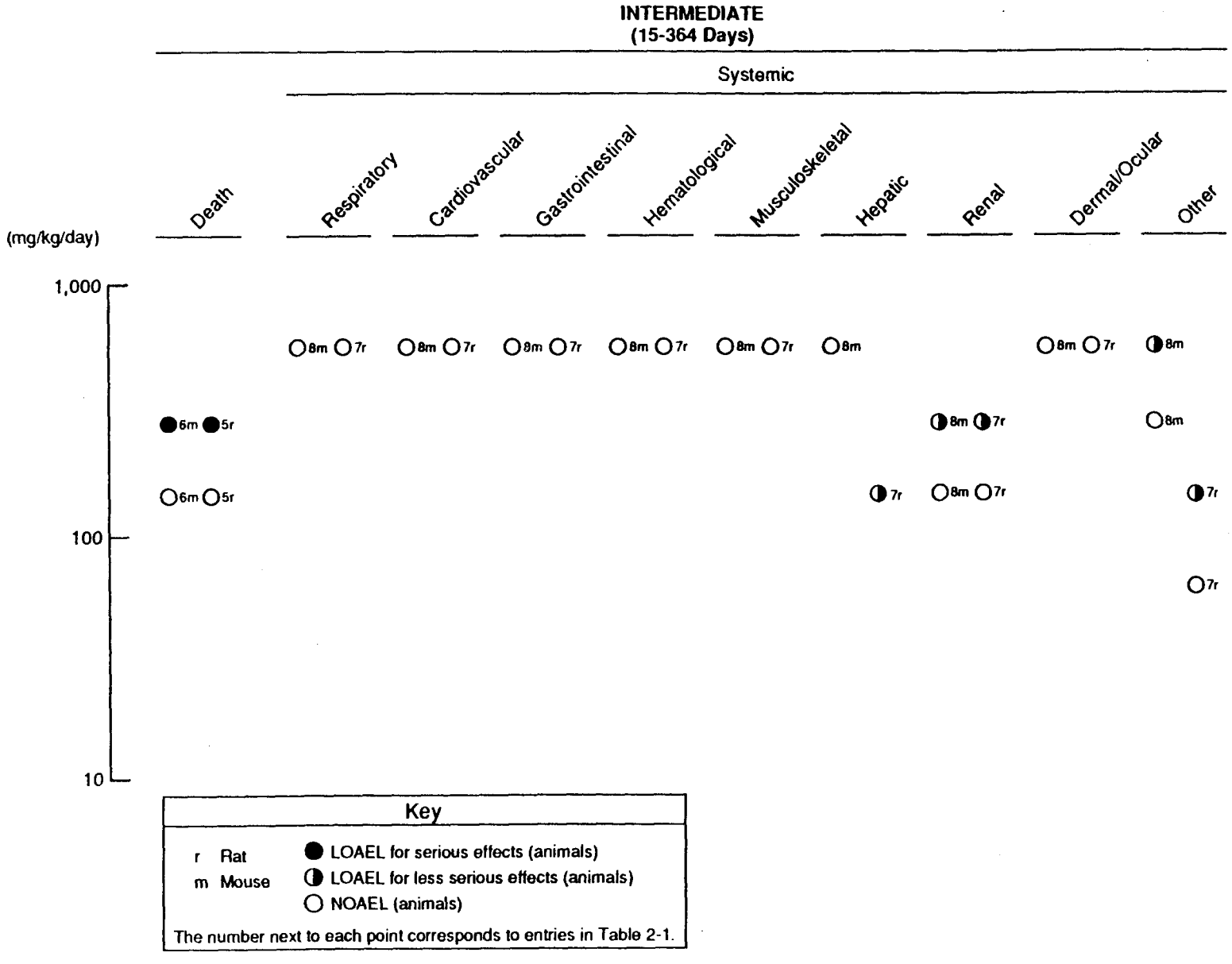
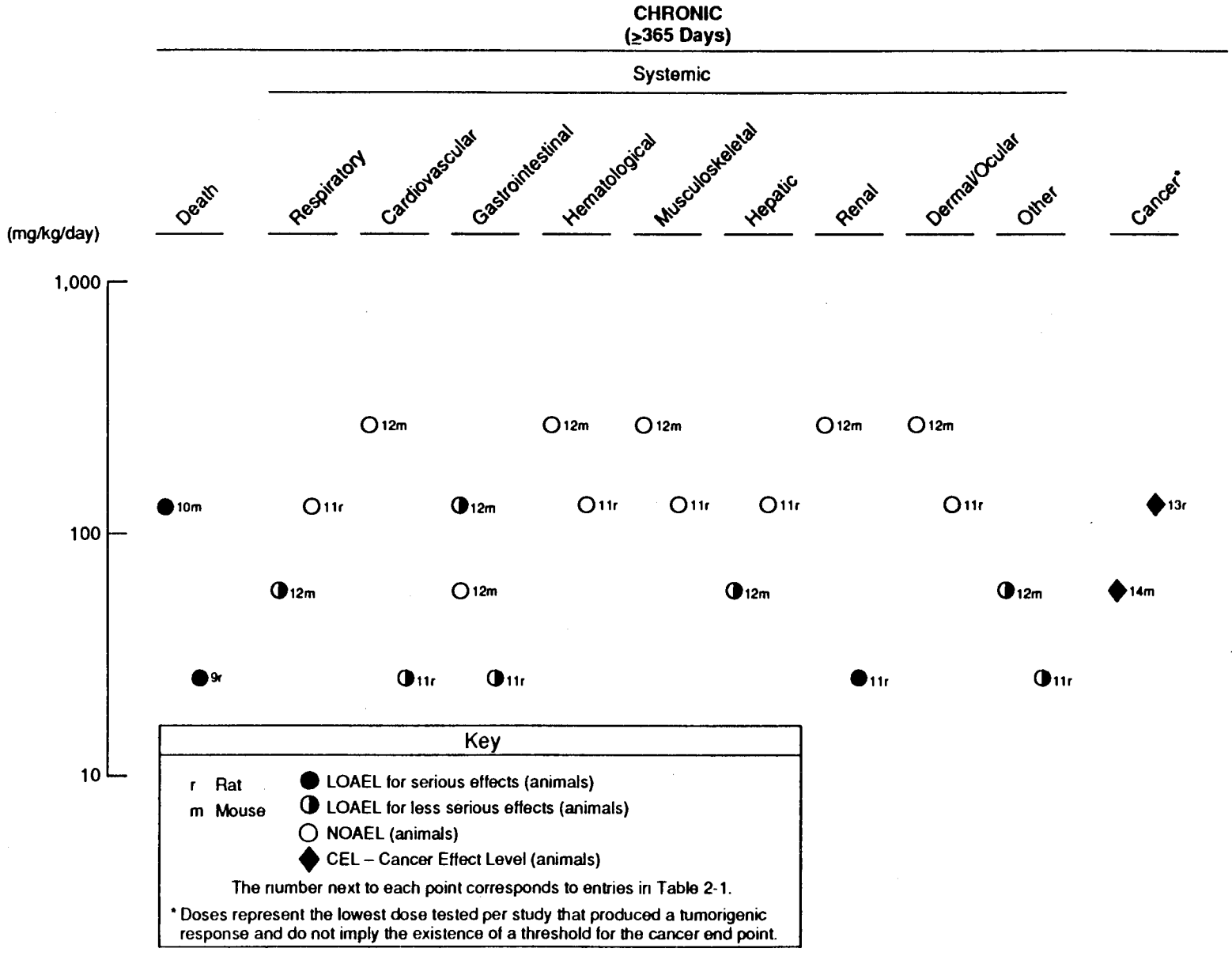


FIGURE 2-1 (Continued)



2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to 2,3-benzofuran. Oral exposure to 2,3-benzofuran can be lethal to animals. One female rat given a dose of 500 mg/kg/day died after 4 days, although 4 other female rats and all 5 male rats given this dose survived for 14 days (NTP 1989). All 10 rats given an oral dose of 1,000 mg/kg/day died within 3 days (NTP 1989). The cause of death was not determined for the rats that died following acute exposure to 2,3-benzofuran (NTP 1989). Some deaths were observed among male and female mice in groups orally exposed for 14 days to doses of 2,3-benzofuran ranging from 31.25 to 250 mg/kg/day (NTP 1989). However, all mice dying early showed evidence of gavage error (oily fluid in the pleural cavity), and the pattern of deaths showed no dose-response relationship (NTP 1989), so that no deaths among mice were attributable to chemical exposure.

Some mortality was seen among animals orally exposed to 2,3-benzofuran for 13 weeks, although the pattern of mortality was somewhat inconsistent. Among rats, l female out of 10 given 250 mg/kg/day died in week 1, 1 female out of 10 given 500 mg/kg/day died in week 5, and no male rats died (NTP 1989). The cause of death was not determined for the rats that died following intermediate-duration exposure to 2,3-benzofuran (NTP 1989). A NOAEL of 125 mg/kg/day and a LOAEL of 250 mg/kg/day is identified for death in rats by this study. Among mice exposed for 13 weeks, discounting deaths attributable to gavage error, 1 out of 10 males given 62.5 mg/kg/day died in week 13, no animals given 125 mg/kg/day died, 1 out of 10 males given 250 mg/kg/day died in week 12, and 4/7 males and 2/9 females given 500 mg/kg/day died in weeks 1 and 3 (NTP 1989). The cause of death was not determined for the mice that died following intermediate-duration exposure to 2,3-benzofuran (NTP 1989). The dose response relationship in this study was inconsistent, but the weight of evidence is compatible with a NOAEL of 125 mg/kg/day and a LOAEL of 250 mg/kg/day for death in mice.

Chronic exposure of male rats to 2,3-benzofuran caused a statistically-significant decrease in survival at doses of 30 and 60 mg/kg/day, attributed to increased severity of kidney damage (NTP 1989). The survival of female rats exposed to 60 and 120 mg/kg/day for 103 weeks was not significantly different from controls (NTP 1989). Female mice exposed to 120 and 240 mg/kg/day had a statistically-significant reduction in survival after 96 weeks, while the survival of male mice exposed to 60 and 120 mg/kg/day for 103 weeks was not different from controls (NTP 1989). When the dose of 2,3-benzofuran was inadvertently increased from 60 to 240 mg/kg/day for male mice in weeks 20-21, 10 out of 50 animals died (NTP 1989). No cause of death was reported for those male mice nor was a cause of decreased survival reported for female mice (NTP 1989). No NOAEL for mortality following chronic-duration exposure to 2,3-benzofuran is identified by this study.

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans after oral exposure to 2,3-benzofuran.

The systemic effects observed in animals after oral exposure to 2,3-benzofuran are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

Respiratory Effects. Rats exposed to oral doses of 500 and 1,000 mg/kg/day of 2,3-benzofuran for up to 14 days exhibited a red nasal discharge, which was not further characterized (NTP 1989). Histological examinations were performed only on animals in the 250 mg/kg/day dose groups (NTP 1989). Histological examination of nasal, larynx, trachea, lung, and bronchial tissues of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years showed compound-related hyperplasia in the lungs and nasal mucosa in chronically-exposed mice (NTP 1989). The lung hyperplasia was seen in all groups of mice exposed for 103 weeks, in males at doses of 60 and 120 mg/kg/day and in females at doses of 120 and 240 mg/kg/day (NTP 1989). The hyperplasia occurred in bronchiolar epithelial cells, often extending into the alveolar ducts (NTP 1989).

Nasal hyperplasia was observed in both control and chemically-treated mice in a 103-week study (NTP 1989). The hyperplasia was associated with inflammation from foreign material (corn oil, hair, and particles of feed and bedding) lodged in the nasal cavity, and the effect of oral 2,3-benzofuran exposure was to increase the inflammatory response to such particles, particularly at the highest dose tested in females, 240 mg/kg/day (NTP 1989).

Cardiovascular Effects. Histological examination of the heart and circulatory system of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years showed a compound-related increase in mineralization of the pulmonary artery in chronically-exposed rats (NTP 1989). The NOAEL values for cardiovascular effects are identified as the highest doses for which histological examinations were performed (250 mg/kg/day for acute-duration exposure and 500 mg/kg/day for intermediate-duration exposure). artery mineralization, Pulmonary nephropathy, which was considered secondary to increased severity of was seen only in the low-dose groups of rats exposed for 103 weeks (30 mg/kg/day in male rats and 60 mg/kg/day in female rats) (NTP 1989). The lack of effect at the higher doses was attributed to reduced survival (NTP 1989).

Gastrointestinal Effects. Histological examination of stomach and intestines of rats and mice with acute- or intermediate-duration exposure to 2,3-benzofuran by gavage showed no compound-related lesions, but chronic exposure caused forestomach hyperplasia in rats and mice (NTP 1989). Male rats exposed for 103 weeks had a significant increase in chronic inflammation of the forestomach at a dose of 30 mg/kg/day, and significant increases in

epithelial hyperplasia and ulcers at a dose of 60 mg/kg/day (NTP 1989). In mice exposed for 103 weeks, forestomach hyperplasia was increased in males at the higher dose (120 mg/kg/day) but not at the lower dose (60 mg/kg/day), and was increased in females in both dose groups (120 and 240 mg/kg/day) (NTP 1989). Only the increase at 120 mg/kg/day in female mice was statistically significant (NTP 1989).

Hematological Effects. Histological examination of tissues from the hematopoietic system of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years showed no compound-related lesions at the highest doses examined (250 mg/kg/day for acute-duration exposure, 500 mg/kg/day for intermediate-duration exposure, and 120 mg/kg/day in rats and 240 mg/kg/day in mice for chronic-duration exposure) (NTP 1989). Effects of oral exposure to 2,3-benzofuran on hemoglobin, hematocrit, red blood cells, white blood cells, or other hematological parameters have not been examined in any reported study. The NOAEL values for hematological effects for each species and duration category are presented in Table 2-l and Figure 2-l.

Musculoskeletal Effects. Histological examination of tissues from the musculoskeletal system of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years showed a compound-related increase in bone degeneration (fibrous osteodystrophy) in chronically-exposed male rats (NTP 1989). The observed increase in bone degeneration, which was not statistically significant at doses of either 30 or 60 mg/kg/day, was not considered a direct effect of 2,3-benzofuran exposure, but as secondary to calcium and phosphate imbalance due to increased severity of nephropathy in male rats caused by 2,3-benzofuran exposure (NTP 1989).

Hepatic Effects. The liver is a common target organ for substituted furan compounds (Boyd 1981). Ten days of oral exposure of female mice to a dose of 591 mg/kg/day of 2,3-benzofuran altered the activity of several hepatic enzymes, decreasing the rate of reactions which activate electrophiles and increasing the rate of reactions which deactivate electrophiles (Cha et al. 1985; Heine et al. 1986). No toxicity was reported in this study (Cha et al. 1985; Heine et al. 1986). Liver damage was seen in rats exposed to 2,3-benzofuran by gavage for 13 weeks and in mice exposed for 103 weeks (NTP 1989). Necrosis of individual hepatocytes was observed after 13 weeks of exposure to 2,3-benzofuran in male rats at doses of 125, 250, and 500 mg/kg/day and in female rats at doses of 250 and 500 mg/kg/day (NTP 1989). No histology was performed on rats exposed at lower doses so confidence in 125 mg/kg/day as a LOAEL for liver damage is low and no NOAEL can be established. Cells resembling normal hepatocytes were found adjacent to and within the pancreatic islets of female rats exposed to 120 mg/kg/day of 2,3-benzofuran for 103 weeks, but these cells were considered to have arisen by transdifferentiation of pancreatic cells (NTP 1989). This metaplasia of the pancreatic islets was not accompanied by any other adverse histologic changes (NTP 1989). The incidence of multinuclear hepatocytes was increased in the livers of male mice exposed to 2,3-benzofuran for 103 weeks at doses of 60 and 120 mg/kg/day (NTP 1989); since this effect was seen at the lowest dose tested, no threshold can be determined.

Renal Effects. The kidney appears to be the organ most consistently affected by 2,3-benzofuran. Male Fisher F344/N rats have a high incidence of spontaneous nephropathy, characterized by degeneration, necrosis, and mineralization of tubular cells, and this nephropathy was made more severe by intermediate- and chronic-duration exposure to 2,3-benzofuran (NTP 1989). The increased severity of nephropathy was accompanied by additional effects in chemically-treated rats, including cortical cysts, bone degeneration, hyperplasia of the parathyroid glands and pelvic epithelium, and mineralization of the pulmonary artery (NTP 1989). Among male rats exposed for 13 weeks, increased severity of nephropathy was seen at a dose of 250 mg/kg/day but not at lower doses. Among male rats exposed for 103 weeks, increased severity of nephropathy contributing to reduced survival was seen at both doses tested, 30 and 60 mg/kg/day.

Female rats had a statistically-significant increase in nephropathy following 13 weeks of exposure to 2,3-benzofuran at doses of 250 and 500 mg/kg/day, but not at 125 mg/kg/day, and exhibited increased severity of nephropathy following 103 weeks of exposure at both doses tested, 60 and 120 mg/kg/day (NTP 1989). Female rats developed renal tubular cell atypical hyperplasia following 103 weeks of exposure to a dose of 120 mg/kg/day (NTP 1989). Male mice exhibited kidney lesions (tubular cell necrosis, inflammation, and focal mineralization) after 13 weeks of 2,3-benzofuran exposure at a dose of 250 mg/kg/day, but not at lower doses for 13 weeks or at doses of 60 or 120 mg/kg/day for 2 years (NTP 1989). No kidney damage was found in female mice at any duration or dose of 2,3-benzofuran, up to 250 mg/kg/day for 14 days, up to 500 mg/kg/day for 13 weeks, or up to 240 mg/kg/day for 2 years (NTP 1989). The highest NOAEL values and all reliable LOAEL values for renal effects for each species and duration category are presented in Table 2-l and Figure 2-l.

Dermal/Ocular Effects. Histological examination of the skin and eyes of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years showed no compound-related lesions at the highest doses examined (250 mg/kg/day for acute-duration exposure, 500 mg/kg/day for intermediate-duration exposure, and 120 mg/kg/day in rats and 240 mg/kg/day in mice for chronic-duration exposure) (NTP 1989). Rats exposed to oral doses of 500 and 1,000 mg/kg/day of 2,3-benzofuran for 3-14 days exhibited a red ocular discharge, but this discharge was not characterized and no histological examinations were performed on animals in these dose groups (NTP 1989).

Other Systemic Effects. Oral 2,3-benzofuran exposure resulted in decreased body weights in some cases (NTP 1989). In rats, reduced body weight was observed after 14 days of exposure of males at doses of 250 and 500 mg/kg/day and of females at a dose of 500 mg/kg/day, after 13 weeks of exposure of males at doses of 125, 250, and 500 mg/kg/day and of females at a dose of 500 mg/kg/day, and after 103 weeks of exposure of males at doses of 30 and 60 mg/kg/day and of females at a dose of 120 mg/kg/day (NTP 1989). In mice, reduced body weight was observed after 13 weeks of exposure of males at a dose of 500 mg/kg/day, and after 103 weeks of exposure of males at a dose of 60 mg/kg/day but not 120 mg/kg/day and of females at doses of 120 and

240 mg/kg/day (NTP 1989). No explanation was provided for the reduction in body weight in male mice in the low dose group but not the high dose group during chronic exposure (NTP 1989). Body weight reduction does not provide specific information concerning toxicity, and often occurs only at doses above those causing other systemic effects. The relative sensitivity to body-weight reduction does appear to parallel the sensitivity to kidney and liver damage: male rats are most sensitive, followed by female rats, male mice, and female mice (NTP 1989).

Rats exposed to 2,3-benzofuran for 13 weeks had an increased incidence of cytoplasmic vacuolization of the adrenal glands, which was observed in 1 out of 10 control males, 2 out of 10 males at a dose of 250 mg/kg/day, and in all 20 males and females at a dose of 500 mg/kg/day (NTP 1989). No adrenal lesions were seen in rats at shorter or longer exposures, and no tests were made to determine the effect on adrenal functioning.

In rats exposed to 2,3-benzofuran for 103 weeks, the occurrence of cystic follicles in the thyroid glands was increased in males at doses of 30 and 60 mg/kg/day but decreased in females at doses of 60 and 120 mg/kg/day (NTP 1989). Parathyroid hyperplasia was increased in male rats exposed for 103 weeks to a dose of 30 mg/kg/day, secondary to increased severity of nephropathy (NTP 1989).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans after oral exposure to 2,3-benzofuran. No abnormalities in lymphatic tissues were detected by histological examination of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years (NTP 1989). However, no examination of lymphocytes or tests of immune system functioning were made, so these studies do not identify a reliable NOAEL for immunological effects.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 2,3-benzofuran. No abnormalities in the nervous systems were detected by histopathologic examination of rats and mice exposed to 2,3-benzofuran for up to 2 years (NTP 1989). However, no neurochemical or neurophysiological parameters were monitored, so these studies do not identify a reliable NOAEL for neurological effects.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to 2,3-benzofuran.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 2,3-benzofuran. No damage to male or female reproductive organs was detected by histological examination of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years (NTP 1989). However, no functional tests of reproductive success have been made, so these studies do not identify a reliable NOAEL for reproductive effects.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to 2,3-benzofuran. Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to 2,3-benzofuran. Chronic gavage exposure to 2,3-benzofuran increases the frequency of tumors in several organs in rats and mice (NTP 1989). In rats, a statistically-significant increase in kidney adenocarcinomas was found in females at a dose of 120 mg/kg/day, but no carcinogenic effects were seen in males, perhaps because of reduced survival (NTP 1989). In mice, increased frequencies of tumors were found in lungs, livers, and forestomachs of both males and females (NTP 1989). Most of these effects showed a dose-response trend and were statistically significant at both doses tested, 60 and 120 mg/kg/day in males and 120 and 240 mg/kg/day in females (NTP 1989). The NTP concluded that the data provided no evidence of carcinogenicity of 2,3-benzofuran to male rats, some evidence of carcinogenicity to female rats, and clear evidence of carcinogenicity to male and female mice (NTP 1989).

Levels of exposure associated with the observed carcinogenic effects of 2,3-benzofuran are indicated in Figure 2-l. Cancer effects could occur at lower exposure levels, but no estimate of the individual human lifetime cancer risks from exposure to 2,3-benzofuran has been made at this time by the EPA.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to 2,3-benzofuran.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to 2,3-benzofuran.

Dermal/Ocular Effects. No skin lesions or dermatitis were reported in an early review of the dermatological problems associated with the manufacture of coumarone-indene resin (a polymer made from 2,3-benzofuran and indene); however, the manufacturing process essentially prevented contact with monomers (Schwartz 1936), so the significance of these negative findings is questionable. Workers continuously exposed to wood varnished with coumarone-indene resin developed dermatitis, but the sensitivity was attributed to the sulfuric acids in the varnish (Schwartz 1936).

No studies were located regarding the following health effects in humans or animals after dermal exposure to 2,3-benzofuran:

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to 2,3-benzofuran. Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to 2,3-benzofuran.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure .

No studies were located regarding absorption in humans or animals after inhalation exposure to 2,3-benzofuran. The partitioning of 2,3-benzofuran between particulate matter and synthetic alveolar surfactant in vitro was reported to depend upon the chemical nature of the particles (Sehnert and Risby 1988). Synthetic lung surfactant was able to dissolve 2,3-benzofuran adsorbed to particles with few active sites, but not 2,3-benzofuran adsorbed to particles with many active sites (Sehnert and Risby 1988). These data indicate that inhalation of particles containing 2,3-benzofuran would result in some absorption, depending on the nature of the particles.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans or animals after oral exposure to 2,3-benzofuran.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to 2,3-benzofuran.

2.3.2 Distribution

No studies were located regarding distribution in humans or animals after exposure to 2,3-benzofuran by the following routes:

2.3.2.1 Inhalation Exposure
2.3.2.2 Oral Exposure
2.3.2.3 Dermal Exposure

2.3.3 Metabolism

No studies were located regarding metabolism of 2,3-benzofuran in humans or animals. However, the metabolism of several other substituted furans has been shown to involve oxidation by P-450, with the unsubstituted double bond of the furan ring converted either to an epoxide (Boyd 1981) or to a dialdehyde (Ravindranath et al. 1984). Pretreatment with inducers and inhibitors of P-450 modified the toxicity of a single intraperitoneal injection of 2,3-benzofuran to male mice (McMurtry and Mitchell 1977). Oral exposure to 2,3-benzofuran altered the activity of P-450 and other enzymes in the livers of female mice (Heine et al. 1986). These experiments indicate that cytochrome P-450 may be involved in the toxicity of 2,3-benzofuran, but do not provide a clear picture of 2,3-benzofuran metabolism.

2.3.4 Excretion

No studies were located regarding excretion in humans or animals after exposure to 2,3-benzofuran by the following routes:

2.3.4.1 Inhalation Exposure
2.3.4.2 Oral Exposure
2.3.4.3 Dermal Exposure

2.4 RELEVANCE TO PUBLIC HEALTH

As discussed in Section 2.2, estimates of levels of exposure to 2,3-benzofuran posing minimal risk to humans (MRLs) were to have been made, where data were believed reliable, for the most sensitive noncancer effect for each route and exposure duration. However, no MRLs could be derived for 2,3-benzofuran. No data were located on effects of acute-duration, intermediate-duration, or chronic-duration inhalation exposure to 2,3-benzofuran in humans or animals. Therefore, no inhalation MRLs were derived. Available information on acute-duration oral exposure in animals does not identify the most sensitive effect or any dose-response relationships (NTP 1989). Available information on intermediate-duration and chronic duration oral exposure to 2,3-benzofuran in animals suggests that the most

sensitive effect may be liver toxicity following intermediate-duration exposure and kidney toxicity following chronic-duration exposure (NTP 1989), but the data do not reliably identify the threshold for liver or kidney damage. Therefore, no oral MRLs were derived. Acute-duration, intermediate duration, and chronic-duration dermal MRLs were not derived for 2,3-benzofuran due to the lack of an appropriate methodology for the development of dermal MRLs.

Essentially nothing is known about the effects of 2,3-benzofuran exposure on humans. The principal adverse health effects noted in animals associated with oral exposure to 2,3-benzofuran are kidney and liver damage (NTP 1989). Intraperitoneal injection of 2,3-benzofuran also causes kidney and liver damage (McMurtry and Mitchell 1977). Inhalation and dermal exposures might also produce adverse effects, although this has not been studied. Because of the limited production and use of 2,3-benzofuran (see Chapter 4), the average person is unlikely to encounter doses high enough to cause kidney or liver damage. However, studies in animals indicate that 2,3-benzofuran exposure may increase the risk of cancer (NTP 1989), and so even low exposure levels may be of concern. Kidney and liver damage, cancer, and other less common effects are discussed in greater detail below.

Death. Large oral doses of 2,3-benzofuran can cause death in rats or mice following acute or intermediate exposure duration, and somewhat lower chronic doses can reduce survival (NTP 1989). No consistent difference in sensitivity between male and females has been observed (NTP 1989). The lethality of 2,3-benzofuran exposure by intraperitoneal injection appears to be greater than that following gavage exposure, as a single intraperitoneal injection of 100 mg/kg caused deaths in some male mice (McMurtry and Mitchell 1977), but 14-day gavage exposure caused no deaths in rats or mice at doses up to 250 mg/kg/day (NTP 1989). The cause of death from 2,3-benzofuran exposure was not reported in these studies except that reduced survival in male rats chronically exposed to 2,3-benzofuran was attributed to increased severity of kidney damage (NTP 1989). An acute dose of 240 mg/kg/day caused death in male mice in a group which had been exposed to 60 mg/kg/day for 20 weeks, but an acute dose of 250 mg/kg/day for 14 days caused no deaths in mice which had not previously been exposed to 2,3-benzofuran (NTP 1989). Although no data were provided concerning the cause of increased lethality of 2,3-benzofuran following prior exposure, cumulative organ damage or altered metabolism are possible explanations. It is unlikely that humans would be exposed to a dose of 2,3-benzofuran sufficient to cause death.

Systemic Effects.

Respiratory Effects. Chronic-duration oral exposure to 2,3-benzofuran causes hyperplasia of nasal mucosa and lung tissue in mice (NTP 1989). In vitro exposure of chicken trachea cells to 2,3-benzofuran results in substantial inhibition of ciliary activity (Pettersson et al. 1982), which may indicate that ciliotoxicity is involved in the respiratory effects seen in mice. Certain other furan derivatives exhibit pulmonary toxicity due to metabolic activation by lung P-450 oxygenases (Boyd 1981), but 2,3-benzofuran

has not been studied specifically. No respiratory effects were seen following acute-, intermediate-, or chronic-duration oral exposure in rats or following acute- or intermediate-duration oral exposure in mice. Thus, respiratory effects are seen fairly infrequently, and only at high doses which also cause liver damage.

Cardiovascular Effects. Chronic-duration oral exposure to 2,3-benzofuran causes mineralization of the pulmonary artery in rats, but this effect was due to mineral imbalances and vascular constriction associated with kidney damage (NTP 1989). No cardiovascular effects were seen following acute-, intermediate-, or chronic-duration oral exposure in mice or following acute- or intermediate-duration oral exposure in rats.

Gastrointestinal Effects. Chronic-duration oral exposure to 2,3-benzofuran causes chronic inflammation of the forestomach in rats and mice (NTP 1989). No gastrointestinal effects were seen following acute- or intermediate-duration oral exposure in rats or mice. The gastrointestinal effects were seen at doses causing severe kidney damage or above doses causing liver damage.

Musculoskeletal Effects. Chronic-duration oral exposure to 2,3-benzofuran causes bone degeneration in rats, but this effect is due to mineral imbalances associated with kidney damage (NTP 1989). No musculoskeletal effects were seen following acute-, intermediate-, or chronic duration oral exposure in mice or following acute- or intermediate-duration oral exposure in rats.

Hepatic Effects. Liver damage is a consistent systemic effect of oral exposure to 2,3-benzofuran (NTP 1989). Intermediate-duration oral exposure causes liver damage in male and female rats and chronic-duration oral exposure causes liver damage in male mice (NTP 1989). Liver damage is also seen following a single intraperitoneal injection of 2,3-benzofuran (McMurtry and Mitchell 1977). The observed liver damage is usually characterized by focal necrosis of hepatocytes after both oral (NTP 1989) and intraperitoneal (McMurtry and Mitchell 1977) exposure. Liver damage was the systemic effect seen at the lowest dose in male rats exposed to 2,3-benzofuran for 13 weeks (NTP 1989).

The toxicity of 2,3-benzofuran to the liver may be associated with activation by P-450 oxygenases. Pretreatment of mice with an inhibitor of P-450 oxygenases, cobaltous chloride, prevents liver damage from intraperitoneal injection of 2,3-benzofuran (McMurtry and Mitchell 1977). Acute-duration oral exposure to 2,3-benzofuran alters the activity of hepatic enzymes in mice, decreasing the cytochrome P-450 content and increasing the activity of several enzymes involved in the deactivation of electrophiles (Cha et al. 1985; Heine et al. 1986). This overall shift in metabolism away from activation of potential carcinogens was taken to suggest that 2,3-benzofuran might have anticarcinogenic activity (Cha et al. 1985; Heine et al. 1986).

However, because chronic-duration exposure to 2,3-benzofuran increases the incidence of cancer in rodents, including liver cancer in mice (NTP 1989), any possible anticarcinogenic action of 2,3-benzofuran is less relevant.

Renal Effects. Intermediate- and chronic-duration oral exposure to 2,3-benzofuran causes kidney damage in male and female rats and intermediate-duration oral exposure causes kidney damage in male mice (NTP 1989). Intraperitoneal injection also causes kidney damage in male mice (McMurtry and Mitchell 1977). Kidney damage involves injury to the tubular cells, with degeneration, necrosis, and mineralization. In male rats (a group predisposed to kidney damage), chronic 2,3-benzofuran exposure increases the severity of the nephropathy to an extent which affects survival at a lifetime dose of 30 mg/kg/day (NTP 1989). Kidney damage seen in rats following chronic-duration oral exposure to 2,3-benzofuran also involved cortical cysts, bone degeneration, hyperplasia of the parathyroid glands and pelvic epithelium, and mineralization of the pulmonary artery (NTP 1989).

Other Systemic Effects. Oral exposure to 2,3-benzofuran causes decreased body weight in rats and mice, and damage to adrenal and thyroid glands in rats (NTP 1989). Reduced body weight is a rather unspecific indicator of toxicity, and was generally not seen except at doses also causing liver or kidney damage. Adrenal and thyroid lesions were seen infrequently, and there was no indication of an effect on organ function (NTP 1989).

The systemic effects caused by 2,3-benzofuran exposure which are most relevant to public health are liver and kidney damage. Other systemic effects, including damage to the adrenal and thyroid glands, lungs, and pancreas, and reduced body weight, are generally seen only at doses above those causing kidney or liver damage. High-level exposure to 2,3-benzofuran would be expected to damage the liver or kidney, and possibly other organs in some individuals.

Immunological Effects. Oral lifetime exposure to 2,3-benzofuran caused no histopathological lesions in lymphatic tissues of rats or mice (NTP 1989). This provides limited evidence that the immunological system may not be a major target for 2,3-benzofuran toxicity, but more definitive conclusions are not possible without further studies.

Neurological Effects. Oral lifetime exposure to 2,3-benzofuran caused no histopathological lesions in tissues of the nervous systems of rats or mice (NTP 1989). However, no tests of neurological function were performed, and so the significance of these negative findings with regard to public health cannot be evaluated.

Developmental Effects. No information is available concerning any effects on development from 2,3-benzofuran exposure.

Reproductive Effects. Oral lifetime exposure to 2,3-benzofuran caused no histopathological lesions in male or female reproductive organs of rats or mice (NTP 1989). However, no studies of organ function or reproductive success have been made, and so the potential effects of 2,3-benzofuran exposure on human reproduction cannot be evaluated.

Genotoxic Effects. No in vivo studies of 2,3-benzofuran genotoxicity were located. The genotoxicity of 2,3-benzofuran has been studied in a number of in vitro systems (Table 2-2). 2,3-Benzofuran was found not to be mutagenic to Salmonella tvphimurium, both with and without exogenous activation (Florin et al. 1980; Haworth et al. 1983; Weill-Thevenet et al. 1981). However 2,3-benzofuran does give positive responses in genotoxicity assays for mutagenicity to mouse lymphoma L5178Y cells (McGregor et al. 1988) and for sister chromatid exchanges in Chinese hamster ovary cells (NTP 1989). Limited evidence suggests that 2,3-benzofuran could be metabolized to an electrophilic epoxide or dialdehyde (see Section 2.3.3), and such an intermediate would be an alkylating agent capable of reacting with DNA. Thus, one possible explanation for the mixed genotoxicity results is differences among the metabolic conditions used in the various tests.

Cancer. 2,3-Benzofuran is carcinogenic to rats and mice (NTP 1989). Chronic oral exposure increased the incidence of kidney tumors in female rats, and increased the incidence of lung, forestomach, and liver tumors in male and female mice (NTP 1989). These findings indicate that chronic exposure to 2,3-benzofuran could be a cause of concern even at low levels; however, without more extensive exposure data, it is not possible to characterize the magnitude of human cancer risk from 2,3-benzofuran exposure.

No information is available concerning the mechanism of carcinogenicity of 2,3-benzofuran. All of the tissues showing a carcinogenic response also exhibited hyperplasia, but there was no evidence that neoplasia was a progression from hyperplasia (NTP 1989). Substituted furans can be activated by cytochrome P-450 to electrophilic intermediates (epoxides or dialdehydes) (Boyd 1981; Ravindranath et al. 1984), and furan and furfural can activate oncogenes in mouse liver (NTP 1989; Reynolds et al. 1987); however, the metabolism of 2,3-benzofuran has not been specifically studied. A possible mechanism for the carcinogenicity of 2,3-benzofuran is electrophilic attack on DNA. The evidence that 2,3-benzofuran has only limited genotoxicity in vitro (see Table 2-2) could be the result of inadequate metabolic activation.

2.5 BIOMARRERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the

TABLE 2-2. Genotoxicity of 2,3-Benzofuran In Vitro

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (plate incorporation)	Gene mutation	-	-	Weill-Thevenet et al. 1981
S. typhimurium (liquid preincubation)	Gene mutation	-	-	Florin et al. 1980
S. typhimurium (liquid preincubation)	Gene mutation	-	-	Haworth et al. 1983
Mammalian cells:				
Mouse lymphoma L5178Y thymidinekinase locus	Gene mutation	No data	+	McGregor et al. 1988
Chinese hamster ovary	Chromosomal aberrations	-	-	NTP 1989
Chinese hamster ovary	Sister chromatid exchange	+	+	NTP 1989

+ = positive result; - = negative result

substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 2,3-benzofuran are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 2,3-benzofuran are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to 2,3-Benzofuran

2,3-Benzofuran has been detected in samples of breast milk (Pellizzari et al. 1982) and in blood from victims who died in fires (Anderson and Harland 1980), but no information was provided by either study on previous exposure to 2,3-benzofuran. No information was located concerning metabolites of 2,3-benzofuran in animals or humans. No information was located concerning the fate of 2,3-benzofuran in animals or humans, so it is not possible to predict how long 2,3-benzofuran remains in the body, or how body levels might correlate with exposure or effects.

2.5.2 Biomarkers Used to Characterize Effects Caused by 2,3-Benzofuran

No information is available concerning the effects of 2,3-benzofuran in humans. Acute oral exposure to 2,3-benzofuran has been shown to alter levels of enzyme activity in the livers of female mice (Heine et al. 1986), but much more work would need to be done to determine whether there is a pattern of enzyme alteration specific to 2,3-benzofuran exposure. Other effects found in animals following oral exposure to 2,3-benzofuran are kidney and liver damage and kidney, lung, liver, and stomach cancer (see Section 2.2.2). Such generalized responses do not suggest the basis for any specific biomarker of clinical or preclinical effects caused by 2,3-benzofuran.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Pretreatment of male mice with compounds that affect cytochrome P-450 oxygenases altered the toxicity of a single intraperitoneal injection of 2,3-benzofuran (McMurtry and Mitchell 1977). However, kidney necrosis was decreased both by phenobarbital, which induces P-450, and by cobaltous chloride and piperonyl butoxide, which inhibit P-450. Also, one of the P-450 inhibitors, cobaltous chloride, decreased lethality while the other, piperonyl butoxide, increased lethality. Differential effects on liver and kidney P-450 systems could explain some of these observations. Compounds which affect P-450 metabolism are likely to alter 2,3-benzofuran toxicity, but the effects on P-450 are not predictive of the specific effects on 2,3-benzofuran toxicity.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Studies of 2,3-benzofuran toxicity in animals reveal differences in susceptibility between sexes and between species, with male rats being the most sensitive (see Section 2.2). Male rats have a high rate of spontaneous kidney disease, and their greater sensitivity to 2,3-benzofuran toxicity may be because the target organ is already damaged. Although no studies provide data concerning human susceptibility, it is reasonable to assume that persons with kidney or liver disease would be more susceptible to the toxic effects of 2,3-benzofuran. In addition, people who have altered P-450 metabolism, due to disease, alcoholism, age, or exposure to drugs or chemicals, would be expected to have altered 2,3-benzofuran toxicity (see Section 2.3.3), but the extent or the direction of the effect (protective or harmful) cannot be predicted.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 2,3-benzofuran. However, because some of the treatment discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 2,3-benzofuran. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Human exposure to 2,3-benzofuran can occur by inhalation, ingestion, or by dermal contact. Also, 2,3-benzofuran has been detected in human milk and can thus be transferred to a nursing infant (Pellizzari et al. 1982). Essentially nothing is known about the effects of 2,3-benzofuran exposure on humans. No information was located on treatment for 2,3-benzofuran specifically, but the sources listed below provided information for the general class of "phenols“ and indicated that this information applied to 2,3-benzofuran exposure; however, it is not known if all of this information applies to 2,3-benzofuran exposure. General recommendations for reducing adsorption following acute exposure have included removal of the chemical with undiluted polyethylene glycol prior to washing with large quantities of water (HSDB 1992). If the eyes have been exposed, irrigation with copious amounts of tepid water has been suggested (HSDB 1992). If ingestion has occurred, gastric lavage may be indicated if performed soon after ingestion, or in patients who are comatose or at risk of convulsing (HSDB 1992). Administration of activated charcoal slurry, aqueous or mixed with saline cathartic or sorbitol has also been suggested (HSDB 1992). Diazepam may be helpful in controlling seizures (HSDB 1992).

Very little data is available on the retention of 2,3-benzofuran. Synthetic lung surfactant was able to dissolve 2,3-benzofuran adsorbed to some particles (Sehnert and Risby 1988), suggesting that it may be absorbed through the lungs. Some substituted furans have been shown to be metabolized by the P-450 enzyme system (Boyd 1981; Ravindranath et al. 1984), suggesting that this is a likely metabolic route for 2,3-benzofuran as well. Certain drugs, such as cobaltous chloride and piperonyl butoxide, inhibit this enzyme system, and were shown to alter the liver and kidney toxicity of 2,3-benzofuran (McMurtry and Mitchell 1977). However, not all treatments with inhibitors and inducers of the P-450 system gave the expected results in this study. One possible explanation for these discrepancies could be the differential effects on the different P-450 systems. It is possible that one or more drugs with this activity could be developed and used to inhibit metabolism of 2,3-benzofuran to more toxic metabolites.

Little is known about the effects of 2,3-benzofuran exposure on humans. The principal adverse health effects noted in animals associated with oral exposure to 2,3-benzofuran are kidney and liver damage (NTP 1989). In the kidney, 2,3-benzofuran causes injury to the tubular cells, with degeneration, necrosis, and mineralization. In the liver, damage due to 2,3-benzofuran is usually characterized by focal necrosis of hepatocytes. However, the mechanism(s) associated with this damage are unknown. A better understanding of the mechanism of action of 2,3-benzofuran may make it possible to develop effective methods to reduce toxic effects caused by exposure.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consulXation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2,3-benzofuran is available. Where adequate information is

not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2,3-benzofuran.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of 2,3-Benzofuran

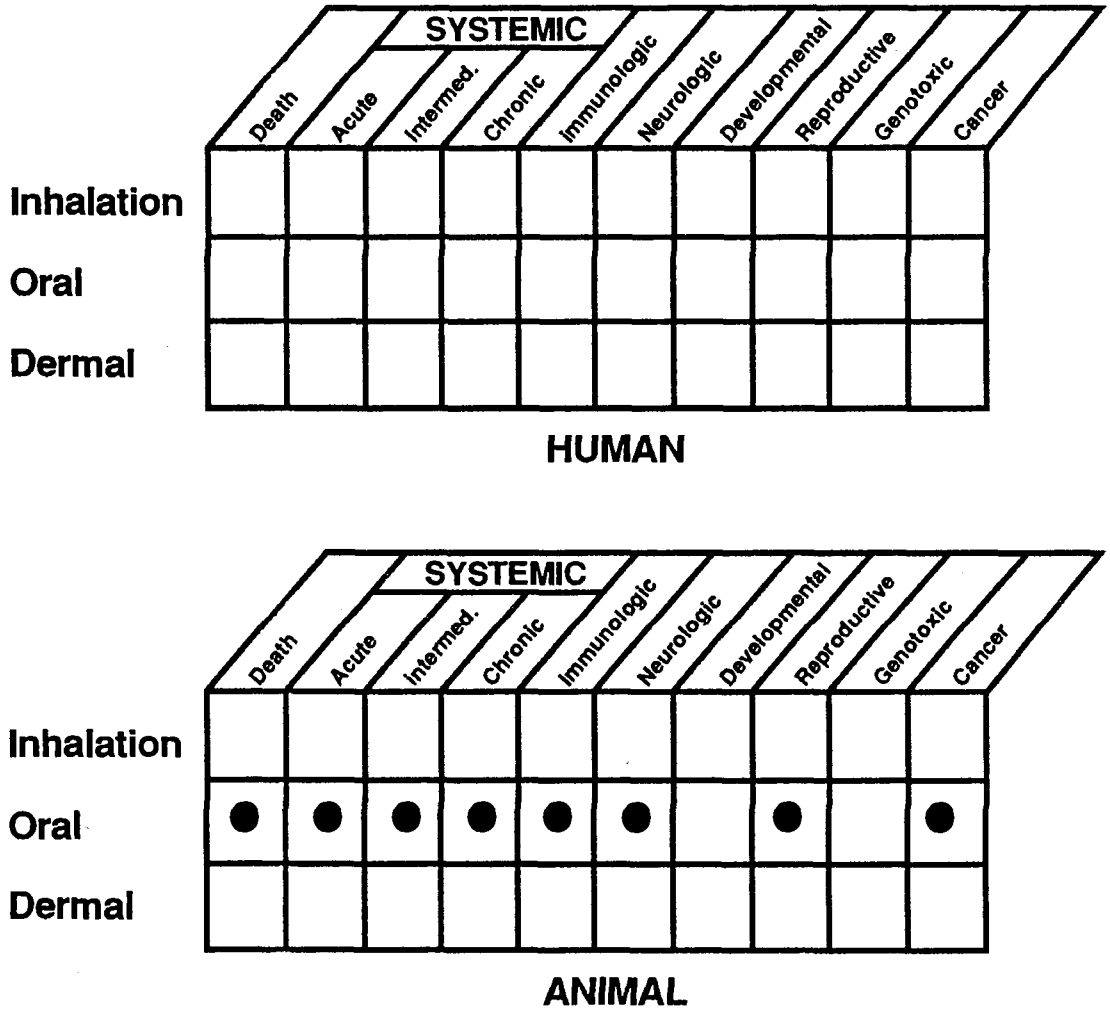
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 2,3-benzofuran are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of 2,3-benzofuran. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

No data exist on the health effects of 2,3-benzofuran in humans. No data exist on the health effects of 2,3-benzofuran in animals following inhalation or dermal exposure. Information on the health effects in rats and mice following oral exposure to 2,3-benzofuran comes primarily from a well-conducted gavage study by NTP of acute-, intermediate-, and chronic-duration (NTP 1989). However, this NTP study was limited to examining histopathological endpoints, so information on immunologic, neurologic and reproductive effects does not include evidence concerning organ or system function. In addition, developmental and *in vivo* genotoxic effects of 2,3-benzofuran exposure have not been studied.

2.9.2 Data Needs

Acute-Duration Exposure. No data are available on the effects of acute-duration exposure to 2,3-benzofuran in humans. No data are available on the effects of 2,3-benzofuran in animals following inhalation and dermal exposure. Lethality in rats was reported in the NTP gavage study but the cause of death was not known. The only systemic effects observed were red ocular and nasal discharges and decreased body weights (NTP 1989). Lethality as well as kidney and liver damage were seen in mice following a single intraperitoneal injection of 2,3-benzofuran (McMurtry and Mitchell 1977). Currently, little or no information is available concerning the target organ or the dose-response of toxicity following inhalation, oral, or dermal exposure, and no oral or inhalation MRLs could be derived. Toxicokinetic data for acute-duration exposure are insufficient to identify targets or to allow conclusions to be made across routes of exposure. Such data are unlikely to become available from human studies, but establishing the end points and levels

FIGURE 2-2. Existing Information on Health Effects of 2,3-Benzofuran



causing toxicity from acute exposure of animals to 2,3-benzofuran by all three routes would be useful to evaluate risk to populations surrounding hazardous waste sites who might be exposed to 2,3-benzofuran for brief periods.

Intermediate-Duration Exposure. No data are available on the effects of intermediate-duration exposure to 2,3-benzofuran in humans. No information is available on the effects of 2,3-benzofuran in animals following inhalation or dermal exposure of intermediate duration, and no inhalation MRL could be derived. Histological evidence of liver damage in male rats exposed to 2,3-benzofuran by gavage for 13 weeks was reported in the lowest dose group examined (125 mg/kg/day) (NTP 1989). Thus, no threshold for liver damage was established by these studies and no oral MRL could be calculated. No renal effects were observed in rats or mice at the dose causing necrosis of liver cells in male rats, but kidney damage was observed at the next higher dose tested, 250 mg/kg/day, in rats and mice (NTP 1989). Studies to establish an oral MRL would be helpful in evaluating risk to populations near hazardous waste sites who might be exposed to 2,3-benzofuran for intermediate durations. Such studies would be valuable if they included examination of liver and kidney function in addition to histopathology. Toxicokinetic data for intermediate-duration exposure are insufficient to identify targets or to allow conclusions to be made across routes of exposure. As for acute-duration exposure, human data are unlikely to become available, but go-day animal studies using several doses and investigating a number of end points would be helpful for assessing the levels which may cause health effects in humans following inhalation or dermal exposure to 2,3-benzofuran.

Chronic-Duration Exposure and Cancer. No data are available on the effects of chronic-duration exposure to 2,3-benzofuran in humans. The NTP study of oral exposure established the kidney as the most sensitive target organ in rats (NTP 1989), but no oral MRL could be derived because the kidney damage in male rats at the lowest dose used, 30 mg/kg/day, was too severe to establish a threshold. Studies using lower doses would establish a LOAEL for less serious effects and a NOAEL, which could also be better defined by tests of kidney function as well as histopathology. Currently, no information is available concerning the target organ or the dose-response of toxicity following inhalation or dermal exposure, and no inhalation MRL could be derived. Toxicokinetic data are insufficient to identify targets or to allow conclusions to be made across routes of exposure. Such information would be useful to evaluate risks to population near hazardous waste sites who might be exposed to 2,3-benzofuran for long periods of time. As for acute- and intermediate-duration exposure, human data are unlikely to become available, but animal studies would help define levels expected to cause adverse health effects in humans chronically exposed to 2,3-benzofuran by oral, inhalation, and dermal routes.

No epidemiologic studies were located concerning the potential human carcinogenicity of 2,3-benzofuran. Lifetime oral exposure increases cancer incidence in female rats and in male and female mice (NTP 1989). The carcinogenicity in both sexes and both species, as well as in multiple organs, strengthens the likelihood of a carcinogenic potential in humans. Studies of

the carcinogenicity of 2,3-benzofuran by inhalation or dermal exposure would be useful if toxicokinetic studies were to show substantial route-specific differences in absorption, distribution, metabolism, or excretion.

Genotoxicity. No data are available on the genotoxicity of 2,3-benzofuran in humans or animals. Genotoxicity results in vitro are mixed, with negative results in the most widely used genotoxicity test, S. tvphimurium mutagenicity (Florin et al. 1980; Haworth et al. 1983; McGregor et al. 1988; NTP 1989; Weill-Thevenet et al. 1981). Other substituted furans appear to be activated by P-450 oxygenases to epoxide (Boyd 1981) or dialdehyde (Ravindranath et al. 1984) intermediates, which are electrophilic and hence likely to react with DNA; however, the metabolism of 2,3-benzofuran has not been studied. The mixed genotoxicity in vitro could reflect inadequate activation, and so additional studies of in vivo metabolism and genotoxicity in animals (e.g., 32P post-labeling to detect DNA adducts following exposure to 2,3-benzofuran) would be useful to confirm or refute the genotoxic potential of 2,3-benzofuran.

Reproductive Toxicity. No data are available on the reproductive toxicity of 2,3-benzofuran in humans. No histopathologic lesions were reported in male or female reproductive organs in rats or mice following acute-, intermediate-, or chronic-duration oral exposure to 2,3-benzofuran (NTP 1989). However, no tests of organ function or reproductive success were done. Thus, limited data indicate that the reproductive system may not be a major target for 2,3-benzofuran toxicity, but further studies in animals by all three routes of exposure examining reproductive organ pathology and organ functions would be useful for assessing the possible effects of 2,3-benzofuran exposure on human reproduction.

Developmental Toxicity. No data are available on the developmental toxicity of 2,3-benzofuran in humans or animals. Thus, a complete investigation of the effects of 2,3-benzofuran on development, studying one rodent and one nonrodent species exposed by all three routes, would be useful to evaluate potential developmental toxicity in humans.

Immunotoxicity. No data are available on the immunotoxicity of 2,3-benzofuran in humans. No histopathologic abnormalities in lymphatic tissues of rats or mice were found following acute-, intermediate-, or chronic-duration oral exposure to 2,3-benzofuran (NTP 1989), indicating that the immune system may not be a target for 2,3-benzofuran toxicity. However, a battery of immune function tests has not been performed. A more thorough investigation could begin by examining peripheral lymphocytes in exposed animals, followed by more detailed studies if effects were found.

Neurotoxicity. No data are available on the neurotoxicity of 2,3-benzofuran in humans. No histopathologic lesions were noted in the nervous systems of rats or mice following acute-, intermediate-, or chronic-duration oral exposure to 2,3-benzofuran (NTP 1989), but no neurochemical or neurophysiological parameters were monitored. It would be helpful to conduct

neurological tests on animals exposed to 2,3-benzofuran by all three routes to establish if the nervous system may be a target for 2,3-benzofuran toxicity.

Epidemiological and Human Dosimetry Studies. No epidemiological or human dosimetry studies on the effects of 2,3-benzofuran were located. Production of coumarone-indene resin involves potential exposure to 2,3-benzofuran (Powers 1980), and so an occupationally exposed subpopulation could be identified. Animal studies suggest that kidney and liver damage and increased risk of cancer would be end points of concern (NTP 1989). Potential difficulties with epidemiological investigations include a small cohort of exposed workers, the difficulty of defining exposure levels, and the possibility that exposure to other chemicals could confound the results. Information from epidemiological and human dosimetry studies would be useful in establishing cause/effect relationships and in planning future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect. The presence of 2,3-benzofuran has been detected in breast milk (Pellizzari et al. 1982) and in blood from victims who died in fires (Anderson and Harland 1980), indicating that the concentration of 2,3-benzofuran in biological samples could serve as a biomarker of exposure. However, more studies on absorption, distribution, metabolism, and excretion would be useful to determine the lifetime of 2,3-benzofuran in the body and to correlate levels with duration and degree of exposure. Indirect evidence suggests that 2,3-benzofuran may be activated by P-450 oxygenases to an epoxide or dialdehyde intermediate which could react with cellular components (Heine et al. 1986; McMurtry and Mitchell 1977). Thus, an assay for adducts of 2,3-benzofuran in proteins or DNA could possibly be developed as a useful marker of exposure to 2,3-benzofuran.

The effects of 2,3-benzofuran exposure in humans are not known. Activities of enzymes in the liver are altered by acute exposure to 2,3-benzofuran in female mice (Heine et al. 1986), which suggests the possibility that there may be a specific response of serum enzyme levels to 2,3-benzofuran exposure that could be developed as a biomarker of effect. Other effects in animals include kidney and liver damage and an increased rate of kidney, lung, liver, and forestomach cancer (NTP 1989). Such effects are too general and severe to serve as biomarkers of 2,3-benzofuran effects.

Absorption, Distribution, Metabolism, and Excretion. No data are available on the absorption, distribution, metabolism, or excretion of 2,3-benzofuran in humans. Limited data suggest the involvement of P-450 oxygenases in the metabolism of 2,3-benzofuran in animals (Heine et al. 1986; McMurtry and Mitchell 1977), and further investigations would be valuable to define the role of organ-specific oxygenases in the toxicity and potential genotoxicity of 2,3-benzofuran. Absorption, distribution, and excretion in animals have not been studied at all via inhalation, oral, or dermal routes. Such information would be valuable because the relative rates and extent of absorption, distribution, metabolism, and excretion following exposure by different routes may account for differences in the toxicity of a chemical administered by different routes. These investigations could start with

monitoring levels as a function of exposure, by the inhalation, oral, and dermal routes, and at acute, intermediate, and chronic durations. It is likely that 2,3-benzofuran exists in the environment primarily adsorbed to particles (see Chapter 5), and the extent of desorption of 2,3-benzofuran by artificial lung surfactant in vitro depends on the nature of the particles (Sehnert and Risby 1988). Thus, studies of absorption would be most useful if they included exposure to 2,3-benzofuran on particles representative of those found in the environment.

Comparative Toxicokinetics. No data are available on toxicokinetics in animals or humans. There is some commonality of target organs (the kidney and liver) between rats and mice (NTP 1989), making it reasonable to assume that both species, and perhaps humans, would handle 2,3-benzofuran similarly. Establishing which animal species serves as the best model for extrapolating results to humans would be a useful first step in investigating comparative toxicokinetics.

Mitigation of Effects. No information was located concerning mitigation of effects of exposure to 2,3-benzofuran. Information on techniques to mitigate low-level, long-term effects would be useful in determining the safety and effectiveness of possible methods for treating 2,3-benzofuran exposed populations in the vicinity of hazardous waste sites.

2.9.3 On-going Studies

No information concerning research projects in progress to investigate 2,3-benzofuran was located.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

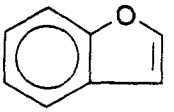
Table 3-l lists common synonyms, trade names, and other pertinent identification information for 2,3-benzofuran.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of 2,3-benzofuran.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of 2,3-Benzofuran

Characteristic	Information	Reference
Chemical name	2,3-Benzofuran	CLPSD 1990
Synonyms	Benzofuran; cumaron; coumarone; benzo(b)furan; benzofurfuran; 1-oxindene	Windholz et al. 1983 Sax 1984
Trade names	No data	
Chemical formula	C_8H_6O	Weast 1985
Chemical structure		Windholz et al. 1983
Identification numbers:		
CAS registry	271-89-6	Sax 1984
NIOSH RTECS	DF6423800	Sax 1984
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	No data	
HSDB	4173	NLM 1989
NCI	C56166	NLM 1989

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of 2,3-Benzofuran

Property	Information	Reference
Molecular weight	118.14	Weast 1985
Color	Colorless	Sax and Lewis 1987
Physical state	Liquid	Sax and Lewis 1987
Melting point	-18°C	Weast 1985
Boiling point	175°C	Weast 1985
Density at 20°C	1.0948	Powers 1980
Odor	Aromatic	Windholz et al. 1983
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	Insoluble	Windholz et al. 1983
Organic solvents	Miscible with benzene, petroleum ether, absolute alcohol and ether	
Partition coefficients:		
Log octanol/water	2.67	Leo et al. 1971
Log K_{oc}	No data	
Vapor pressure at 20°C	No data	
Henry's law constant: at 20°C	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Conversion factors	1 ppm = 4.83 mg/m^3 (calculated) 1 mg/m^3 = 0.21 ppm (calculated)	
Explosive limits	No data	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

2,3-Benzofuran is produced as a component of the crude heavy solvent fraction of the coal-tar light oil formed by the coking of bituminous coal (HSDB 1989; Windholz et al. 1983). 2,3-Benzofuran is not isolated for commercial purposes (HSDB 1989). The fraction of this coal-tar oil distilling at 167-184°C contains small quantities (probably less than 10%) (Powers 1980) of 2,3-benzofuran (also known as coumarone) and also indene (approximately 30%) (NTP 1989), indan, substituted benzenes, and related compounds (CFR 1989a). This fraction of coal oil is used to produce a polymer called coumarone-indene resin (Powers 1980). The polymerization is accomplished by addition of an acid catalyst such as boron trifluoride (NTP 1989) or sulfuric acid (HSDB 1989). Coumarone-indene resin hardens when heated and is used to make floor tiles and other products (HSDB 1989; Morris 1953; NTP 1989). Coumarone-indene resin is produced by the Neville Chemical Company of Neville Island, Pennsylvania (SRI 1989).

No quantitative data were located regarding the production of 2,3-benzofuran or coumarone-indene resin, although it is reported that virtually all of the resin-forming fraction produced by destructive distillation of coal is polymerized (Powers 1980). No information was located concerning the stability or decomposition products of coumarone-indene resin.

4.2 IMPORT/EXPORT

Imports of 2,3-benzofuran in 1977 and 1979 have been reported to be 1,840 metric tons and 0.0009 metric tons, respectively (HSDB 1989). Current information regarding 2,3-benzofuran import was not located.

No data were located regarding the export of 2,3-benzofuran.

4.3 USE

2,3-Benzofuran is not isolated for commercial purposes, and no information was located regarding uses of isolated 2,3-benzofuran. However, the coumarone-indene resin may be used as a coating on grapefruit, lemons, limes, oranges, tangelos, and tangerines (CFR 1989a). Coumarone-indene resin is also used in the production of paints and varnishes for corrosion-resistant coatings (Morris 1953; NTP 1989) and water-resistant coatings on paper products and fabrics (NTP 1989) and as adhesives in food containers (CFR 1989d). Coumarone-indene resin has been used in asphalt floor tiles (Morris 1953; Wilson and McCormick 1960).

No data were located which would indicate the extent to which 2,3-benzofuran or coumarone-indene resin is currently used in these products.

4.4 DISPOSAL

2,3-Benzofuran is not listed as a hazardous waste by the EPA. No data were located regarding rules or regulations which control the disposal of 2,3-benzofuran.

No data were located regarding disposal methods or disposed quantities of waste 2,3-benzofuran.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

2,3-Benzofuran is a colorless organic liquid with an aromatic odor. It is produced by the destructive distillation of coal, and may also be formed during processing of fossil fuels, such as coke production and coal gasification. Limited data indicate that 2,3-benzofuran may partition to soils and sediments from water, but the information available is insufficient to predict the environmental fate of this compound. Substantial bioconcentration in aquatic organisms is not expected based on the physical/chemical properties of 2,3-benzofuran.

Monitoring data on 2,3-benzofuran in environmental media are scarce. Potential human exposure to 2,3-benzofuran may occur by ingestion of foods treated with coumarone-indene resin; however, migration of 2,3-benzofuran from this resin has not been confirmed. Occupational exposure to 2,3-benzofuran may occur in several energy-related industries, and individuals living in the vicinity of hazardous waste sites at which this compound has been detected may also be exposed. The EPA has identified 1,177 NPL sites. 2,3-Benzofuran has been found at 5 of the sites evaluated for the presence of this chemical (View 1989). However, it is not known how many of the 1,177 NPL sites have been evaluated for 2,3-benzofuran. As more sites are evaluated by the EPA, the number may change. The frequency of the sites in the United States at which 2,3-benzofuran was found can be seen in Figure 5-l.

5.2 RELEASES TO THE ENVIRONMENT

2,3-Benzofuran may be released to the environment from production and use of 2,3-benzofuran-containing products, and from coke production, coal gasification, and oil-shale facilities. 2,3-Benzofuran is not listed on the SARA Section 313 Toxics Release Inventory (TRI).

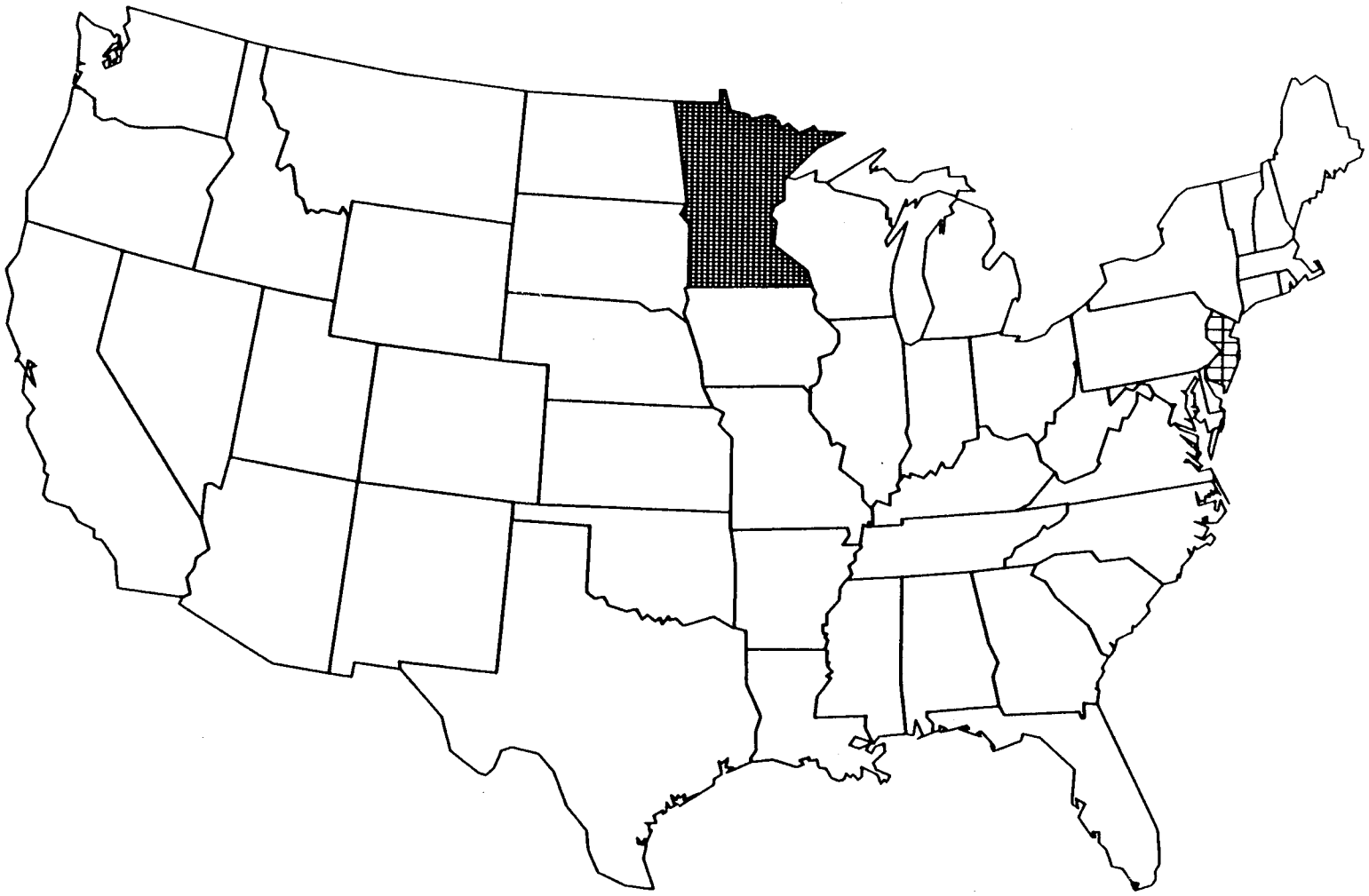
5.2.1 Air

Data on 2,3-benzofuran air emissions are sparse. No information was located regarding 2,3-benzofuran releases from production facilities. However, 2,3-benzofuran was detected in emissions from a Swedish floor finish used on domestic flooring (van Netten et al. 1988), and in emissions from the pyrolysis of silk (Junk and Ford 1980), and in combustor flue gas emissions from fluidized-bed coal combustion at a concentration of 900 ng/g (Hunt et al. 1982). Exhaust produced by an automobile burning simple hydrocarbon fuels contained 2,3-benzofuran at concentrations ranging from less than 0.1 to 2.8 ppm (Seizinger and Dimitriades 1972), but an analysis of air in a highway tunnel in use by both diesel- and gasoline-powered vehicles indicated no 2,3-benzofuran (Hampton et al. 1982).

5.2.2 Water

2,3-Benzofuran may be released to water from coal gasification facilities. 2,3-Benzofuran was detected in coal gasification facility effluents at concentrations ranging from 6 to 267 ppb, but was not detected

FIGURE 5-1. FREQUENCY OF NPL SITES WITH 2,3-BENZOFURAN CONTAMINATION *



* Derived from View 1989

(detection limit 0.1 ppb) in effluents from oil shale processing facilities (Pellizzari et al. 1979). 2,3-Benzofuran was also detected in 1 of 18 waste water concentrates (Lucas 1984). Data from the Contract Laboratory Program (CLP) Statistical Database indicate that 2,3-benzofuran was found at a concentration of 770 ppb in a groundwater sample, but was not found in any surface water samples, taken at one hazardous waste site (CLPSD 1990). It is not known how many hazardous waste sites have been evaluated for 2,3-benzofuran. Note that these data from the CLP Statistical Database represent frequency of occurrence and concentration information for NPL sites only.

5.2.3 Soil

2,3-Benzofuran was found at a concentration of 60 ppb in one soil/sediment sample taken at one hazardous waste site (CLPSD 1990). It is not known how many hazardous waste sites have been evaluated for 2,3-benzofuran. Note that these data from the CLP Statistical Database represent frequency of occurrence and concentration information for NPL sites only.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

No information was located on the transport and partitioning of 2,3-benzofuran in the atmosphere. Based on the high boiling point of 2,3-benzofuran, volatilization would be expected to be slow, but because the vapor pressure of the chemical is unknown, it is not possible to predict how 2,3-benzofuran will partition in the atmosphere.

2,3-Benzofuran is reported not to be soluble in water (Windholz et al. 1983). However, based on its octanol/water partition coefficient (Table 3-2), the solubility of 2,3-benzofuran may be on the order of 200 mg/L, using the empirical regressions of Hassett et al. (1983) for hydrophobic organic chemicals.

2,3-Benzofuran may partition from water to soils and sediments. The extent of adsorption of neutral organic compounds by soils is often correlated with the organic-carbon content of the soil (Hassett et al. 1983). When adsorption is expressed as a function of organic-carbon content, an organic carbon/water partition coefficient (K_{oc}) is generated, and may be used to classify the relative mobility of the chemical in soil. Based on its octanol/water partition coefficient, an estimated K_{oc} for 2,3-benzofuran is about 330, using the empirical regression of Hassett et al. (1983). This K_{oc} implies that 2,3-benzofuran has a medium mobility in soil, using the mobility classifications of Roy and Griffin (1985), and would be most mobile in soils and groundwater where the organic-carbon content is low. No soil adsorption studies on 2,3-benzofuran were located. A coal-tar/water partition coefficient of 912 for 2,3-benzofuran was derived that was similar in magnitude to the octanol/water partition coefficient (Rostad et al. 1985).

Lignite coal is able to adsorb 2,3-benzofuran from aqueous solution (Humenick et al. 1982), which indirectly confirms the expectation that the mobility of the chemical will be influenced by the distribution of organic carbon.

The potential for 2,3-benzofuran to be bioconcentrated by aquatic organisms is likely to be moderate. A bioconcentration factor (BCF) is the ratio of the concentration of a chemical in the tissues of aquatic animals to the concentration of the chemical in the water in which they live. No experimentally measured value for the BCF of 2,3-benzofuran was located, but the octanol-water partition coefficient (K_{OW}) of 2,3-benzofuran has been measured as 468 (Leo et al. 1971). The empirical regressions of Neeley et al. (1974) relate the values of K_{OW}, and BCF for other compounds, and can be used to estimate that the BCF of 2,3-benzofuran is approximately 40. If this estimate is correct, substantial bioconcentration of 2,3-benzofuran by aquatic organisms would not be expected.

5.3.2 Transformation and Degradation

5.3.2.1 Air

No information was located on the transformation or degradation of 2,3-benzofuran in the atmosphere.

5.3.2.2 Water

No information was located on the transformation or degradation of 2,3-benzofuran in water.

5.3.2.3 Soil

No information was located on the transformation or degradation of 2,3-benzofuran in soils, sediments, or waste water treatment processes.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

2,3-Benzofuran was detected, but not quantitated, in 1 of 10 samples of ambient air taken in an industrial area in the Kanawha Valley, West Virginia (Erickson and Pellizzari 1978). No other monitoring data for 2,3-benzofuran in the United States were located. However, one study identified 2,3-benzofuran among pollutants in the air of the Southern Black Forest in Germany (Juttner 1986).

5.4.2 Water

No information was located regarding 2,3-benzofuran in surface water in the United States. 2,3-Benzofuran was detected in contaminated groundwater at a coal-tar distillation and wood-preserving facility in Minnesota (Rostad et al. 1985).

5.4.3 Soil

No studies were located regarding occurrence of 2,3-benzofuran in soils. 2,3-Benzofuran was among those chemicals selected as representative compounds of waste chemicals from energy production for, subsurface transport research (Zachara et al. 1984).

5.4.4 Other Environmental Media

2,3-Benzofuran has not generally been reported in foods. However, 2,3-benzofuran was detected among the volatile constituents of freeze-dried whey powder subjected to accelerated browning (Ferretti and Flanagan 1971). It was also detected in three samples of human milk (Pellizzari et al. 1982) and is reportedly a constituent of cigarette smoke (Curvall et al. 1984; Florin et al. 1980; Schlotzhauer and Chortyk 1987).

Although 2,3-benzofuran is a component of coumarone-indene resin and this resin has been approved by the FDA for use as a coating on citrus fruits, as a component of food-preparation utensils, and as an adhesive in food packages (see Table 7-l), no information was located confirming that coumarone-indene resin is currently used on food in the United States. Furthermore, no data were located to indicate that 2,3-benzofuran migrates from the resin into foodstuffs.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Humans may be exposed to 2,3-benzofuran by inhalation, ingestion, or dermal absorption. Based on the limited data available, exposure of the general population to 2,3-benzofuran does not appear to be substantial. However, since this compound has been detected at hazardous waste sites, is reported to be a component of cigarette smoke, and is one monomer in a resin which may be used as a coating on citrus fruits and in packaging materials for foods, human exposure may be possible from these sources. People in Britain who had died in fires had 2,3-benzofuran in some blood samples, but no source of exposure was identified (Anderson and Harland 1980). 2,3-Benzofuran was detected in human milk (Pellizzari et al. 1982); this indicates possible exposure of the mother and is an exposure source for the infant.

Occupational exposure to 2,3-benzofuran may occur in several energy-related industries. 2,3-Benzofuran is part of the naphtha fraction of coal distillates and exposure is possible in coke production and coal gasification facilities (see Chapter 4). Exposure may also occur during the polymerization process used to produce coumarone-indene resin. 2,3-Benzofuran was not included in the NIOSH National Occupational Hazard Survey or the National Occupational Exposure Survey. However, the naphtha fraction of coal tar is considered in the NIOSH (1978) evaluation of occupational hazards associated with coal gasification.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals occupationally exposed to coal tars or the naphtha fraction of coal-tar distillate have potentially high exposure to 2,3-benzofuran. Persons living near industrial sources or hazardous waste sites contaminated with 2,3-benzofuran may be exposed to 2,3-benzofuran. There are insufficient data to identify any other populations with potentially high exposure to this compound.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2,3-benzofuran is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2,3-benzofuran.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. Measured values of the physical and chemical properties of 2,3-benzofuran necessary to predict the environmental fate and transport of this chemical are not available. Reliable measurements of the vapor pressure, solubility in water, Henry's law constant, and K_{oc} would be useful for more accurate prediction of the behavior of 2,3-benzofuran in environmental media.

Production, Import/Export, Use, and Disposal. No recent quantitative data were located on the production, import/export, use, or disposal of 2,3-benzofuran. Virtually all of the 2,3-benzofuran produced by the destructive distillation of coal is reportedly used in the production of coumarone-indene resin (Powers 1980), but no information was located detailing the current uses of this resin, the composition of this resin, the amount of 2,3-benzofuran emitted from the resin, or the current production volume of the resin. 2,3-Benzofuran is not listed as a hazardous waste by the EPA; therefore, no regulations restricting land disposal apply to this chemical. Data required to assess potential human exposure to this chemical include the amount of production and import/export of 2,3-benzofuran and coumarone-indene resin, and emission rates of 2,3-benzofuran from the resin. If the data indicate that 2,3-benzofuran is emitted from the resin, then current information on the nature and extent of use of the resin will also be

necessary. Data on environmental releases of 2,3-benzofuran from production facilities and disposal methods employed for wastes containing this chemical would also be helpful to assess potential human exposure.

Environmental Fate. The available data on partitioning, transport, and transformation are insufficient to predict the environmental fate of 2,3-benzofuran. Measurements of the rate of photodegradation of 2,3-benzofuran in the atmosphere and determination of the composition and fate of the decay products would be useful to predict the atmospheric fate of this compound. Information regarding the potential for 2,3-benzofuran to photodegrade or oxidize in water or to biodegrade in water or soil, and the rates at which these reactions occur, would be useful in predicting the fate of the compound in these media. Physical/chemical properties suggest that 2,3-benzofuran can partition to soils (Hassett et al. 1983; Roy and Griffin 1985). Verification of this prediction by measurements of the adsorption and desorption of 2,3-benzofuran by soils and sediments, and measurement of the rate of volatilization of the compound from water, would be useful in predicting the transport and partitioning of 2,3-benzofuran among environmental media.

Bioavailability from Environmental Media. The available data are insufficient to assess the bioavailability of 2,3-benzofuran from environmental media. In vitro evidence suggests that 2,3-benzofuran would be less available from organic-rich particles than from organic-poor particles (Sehnert and Risby 1988), but confirmation of this prediction with in vivo studies would be useful. Animal studies have used gavage in oil for exposure to 2,3-benzofuran (NTP 1989) but no quantitative information concerning absorption is available. Additional information on the bioavailability of 2,3-benzofuran would be useful to assess the extent of absorption of 2,3-benzofuran from environmental media.

Food Chain Bioaccumulation. No data were located regarding the bioconcentration of 2,3-benzofuran in plants, aquatic organisms, or animals. Based on physical/chemical properties, substantial bioconcentration of 2,3-benzofuran is not expected (Leo et al. 1971; Neeley et al. 1974). No data on biomagnification in terrestrial or aquatic food chains are available. Data on bioconcentration of this compound in aquatic species would be useful in confirming the predicted low bioconcentration potential of this compound.

Exposure Levels in Environmental Media. Monitoring data for 2,3-benzofuran are sparse and are insufficient to assess the potential for human exposure to this compound, so no estimates of human intake of this substance are available. Since 2,3-benzofuran is a coal-tar product (Powers 1980), monitoring data for this compound in all environmental media in the vicinity of fossil fuel facilities would help to determine the potential for both general population and occupational exposure. In addition, monitoring foods which come in contact with coumarone-indene resin for 2,3-benzofuran would be useful to assess the potential for human exposure from food.

Remedial investigations and feasibility studies at hazardous waste sites are potential sources of information on possible exposures of populations surrounding hazardous waste sites.

Exposure Levels in Humans. 2,3-Benzofuran has been detected in several samples of breast milk (Pellizzari et al. 1982). It is unknown whether the presence of this compound in milk is a result of exposure to 2,3-benzofuran itself, or whether it is a metabolite of other compounds. Biological monitoring of workers in coal gasification or related facilities and of c populations surrounding hazardous waste sites would be useful to evaluate human exposure to this compound.

Exposure Registries. No exposure registries for 2,3-benzofuran were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

No information was located on any on-going studies on the fate, transport, or potential for human exposure to 2,3-benzofuran. Remedial investigations and feasibility studies at hazardous waste sites may provide information on environmental levels, transport, and transformation of 2,3-benzofuran.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring 2,3-benzofuran in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify 2,3-benzofuran. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. No methods approved by federal agencies or other groups specifically for detection of 2,3-benzofuran were located.

Environmental media or biological samples which contain 2,3-benzofuran are also likely to contain numerous other organic compounds with similar chemical and physical properties. Analysis of such samples generally proceeds by first extracting or concentrating some subset of the organic compounds and then separating and identifying them. Techniques for extraction of organic compounds from environmental media or biological samples include absorption onto a polymer and extraction with an organic solvent. Recovery is generally not complete, and so accurate quantification requires using matrix spikes (EPA 1986c). This has not been done in any studies for 2,3-benzofuran. Sensitive and selective techniques for identification of organic compounds in extracts are well established, using high-resolution gas chromatography (HRGC) to separate the compounds and mass spectrometry (MS) to identify them. HRGC achieves higher resolution than standard gas chromatography (GC) by using wall-coated capillary columns rather than packed columns for separation of compounds. Flame ionization detection is not specific enough for the analysis of 2,3-benzofuran in samples containing numerous other compounds, although it has been used to monitor the stability of 2,3-benzofuran in oil for animal feeding studies (NTP 1989). Accurate quantification of the concentration of chemicals in extracts can be achieved with GC/MS by daily calibration using actual and surrogate standards (EPA 1986c), although this has not been done specifically for 2,3-benzofuran.

6.1 BIOLOGICAL MATERIALS

2,3-Benzofuran has been detected, but not quantified, in samples of blood (Anderson and Harland 1980) and breast milk (Pellizzari et al. 1982). In both cases, volatile and semi-volatile organic compounds were purged from the biological fluids by bubbling with an inert gas at an elevated temperature. The compounds were trapped by adsorption onto a Tenax® cartridge. The percent recovery of 2,3-benzofuran by this purge-and-trap collection method was not examined. The Tenax® cartridge was heated to desorb the organic compounds directly into the inlet of the HRGC equipment. Mass spectrometry was used to identify the compounds, including 2,3-benzofuran, by mass fragmentation patterns. The percent recovery or concentration was not quantified in either study (Anderson and Harland 1980; Pellizzari et al. 1982).

Methods for detection of 2,3-benzofuran in biological.materials are summarized in Table 6-1.

TABLE 6-1. Analytical Methods for Determining 2,3-Benzofuran in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Nitrogen purging at 95°C, sorption on Tenax®, thermal desorption	HRGC/MS	No data	No data	Anderson and Harland 1980
Breast milk	Helium purging, sorption on Tenax®, thermal desorption	HRGC/MS	No data	No data	Pellizzari et al. 1982

HRGC = high-resolution gas chromatography; MS = mass spectrometry

6.2 ENVIRONMENTAL SAMPLES

2,3-Benzofuran can be trapped and concentrated from air samples by passing a large volume of air through a Tenax® (Erikson and Pellizzari 1978; Juttner 1986; van Netten et al. 1988) or Chromosorb (Seizinger and Dimitriades 1972) cartridge. The cartridge is then thermally desorbed into an HRGC/MS detection system similar to that used for biological samples. 2,3-Benzofuran can be concentrated from water samples using the purge-and-trap method (Pellizzari et al. 1979), or extraction with dichloromethane (Rostad et al. 1985), and analyzed by HRGC/MS. 2,3-Benzofuran can be extracted from particulate samples with dichloromethane and analyzed by HRGC/MS (Ferretti and Flanagan 1971; Hunt et al. 1982). The percent recovery of 2,3-benzofuran by these extraction methods has not been analyzed. The amount of 2,3-benzofuran in some environmental samples has been quantified (Pellizzari et al. 1979; Seizinger and Dimitriades 1972), but the precision of the quantification was not examined.

Methods for the determination of 2,3-benzofuran in environmental samples are summarized in Table 6-2.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2,3-benzofuran is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2,3-benzofuran.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. The only known biomarker of exposure to 2,3-benzofuran is its presence in blood (Anderson and Harland 1980) or breast milk (Pellizzari et al. 1982). 2,3-Benzofuran was not found in all samples of blood or. breast milk tested, but since existing methods for detection of 2,3-benzofuran in biological samples are not quantitative, it is not possible to assess whether those samples contained no 2,3-benzofuran or whether the method used was not sufficiently sensitive to measure background levels in the population. The levels at which human health effects occur are not known. Only the administered doses, not the target organ concentrations, are known for

TABLE 6-2. Analytical Methods for Determining 2,3-Benzofuran in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Forest air	Sorption on Tenax®, thermal desorption	HRGC/MS	No data	No data	Juttner 1986
Ambient air	Sorption on Tenax®, thermal desorption	HRGC/MS	No data	No data	Erikson and Pellizzari 1978
Indoor air	Sorption on Tenax®, thermal desorption	HRGC/MS	No data	No data	van Netten et al. 1988
Automobile exhaust	Sorption on Chromosorb, thermal desorption	HRGC/MS	0.1 ppm	No data	Seizinger and Dimitriades 1972
Groundwater	Extraction with dichloromethane	HRGC/MS	No data	No data	Rostad et al. 1985
Groundwater and process water	Helium purging, sorption on Tenax®, thermal desorption	HRGC/MS	0.1 ppb	No data	Pellizzari et al. 1979
Whey powder	Extraction with dichloromethane, vacuum distillation	GC/MS	No data	No data	Ferretti and Flanagan 1971
Baghouse filter ash from fluidized-bed coal combustion	Extraction with dichloromethane	HRGC/MS	No data	No data	Hunt et al. 1982

GC = gas chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry

biological effects occurring in animals (NTP 1989), but these doses are relatively high (30 mg/kg/day or greater, see Chapter 2). Based on the general sensitivity of HRGC/MS methods, it is likely that levels of 2,3-benzofuran at which biological effects occur should be achievable with routine quantification procedures. The overall techniques of extraction followed by HRGC/MS analysis can be made precise, accurate, reliable, and specific, so that the opportunity exists to develop methods for sensitive quantitation of 2,3-benzofuran in biological samples. Refinement of existing purge-and-trap extraction techniques and investigation of alternative concentration techniques such as cryotrapping (Pankow and Rosen 1988) and supercritical fluid extraction (King 1989) would be useful. High-performance liquid chromatography as an alternative to HRGC and Fourier transform infrared spectroscopy and photodiode array detectors as alternatives to MS detection might offer advantages. Investigation of possible metabolites of 2,3-benzofuran as biomarkers of exposure would be most useful if accompanied by development of methods for their detection, such as immunoassay techniques and ^{32}P post-labelling for identifying macromolecular adducts.

No known biomarkers of effect were located in the literature. Investigation of biomarkers of effect of 2,3-benzofuran would be most useful if it were also to focus on developing precise, accurate, reliable, and specific methods for measuring background levels of the biomarker of effect in the population and also levels at which adverse effects occur.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The purpose of the analytical methods for 2,3-benzofuran is to identify contaminated areas and to determine if contaminant levels constitute a concern for human health. The media of most concern for human exposure to 2,3-benzofuran are drinking water, soil, and air. It is likely that 2,3-benzofuran exists in these media primarily adsorbed to organic-rich particulates (Hassett et al. 1983). 2,3-Benzofuran has been found relatively infrequently in environmental media, but most samples have excluded particulates. Insufficient work has been done on quantification of 2,3-benzofuran, particularly percent recovery, to determine whether the methods are sensitive enough to measure background levels in the environment (Erikson and Pellizzari 1978; Hunt et al. 1982; Juttner 1986; Pellizzari et al. 1979; Rostad et al. 1985; Seizinger and Dimitriades 1972). The levels of 2,3-benzofuran at which health effects occur in animals are equivalent to 400 ppm in the diet or more (NTP 1989). Existing methods have nominal detection limits of 0.1 ppb (Pellizzari et al. 1979; Seizinger and Dimitriades 1972), indicating that existing methods are probably sensitive enough to detect levels at which health effects occur. The basic techniques of HRGC/MS have the potential for excellent precision, accuracy, reliability, and specificity, with sufficient research and development. One novel technique which may be suitable for in situ monitoring of 2,3-benzofuran in water is surface-enhanced Raman spectroscopy using silver electrodes (Carrabba et al. 1987). No information is available concerning degradation products of 2,3-benzofuran; investigation of 2,3-benzofuran degradation would be most useful if it included development of reliable analytical methods.

6.3.2 On-going Studies

No information was located concerning studies directed towards improving methods for detection of 2,3-benzofuran specifically.

7. REGULATIONS AND ADVISORIES

No regulations or advisories that apply specifically to 2,3-benzofuran were located. 2,3-Benzofuran is one component of coumarone-indene resin and a number of regulations and guidelines have been established for coumaron-eindene resin by various national agencies. These values are summarized in Table 7-l.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to 2,3-Benzofuran[a]

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Food:			
FDA	Coumarone-indene resin as a protective coating on citrus fruit-maximum residue	200 ppm	CFR 1989a (21 CFR 172.215)
	Coumarone-indene resin as a component of adhesives approved for use in food packaging	Yes	CFR 1989c (21 CFR 175.105)
	Coumarone-indene resin as a plasticizer in rubber articles intended for repeated use in contact with food	Yes	CFR 1989d (21 CFR 177.2600)
EPA OPP	Exemption from tolerance Coumarone-indene resin used as coating on citrus fruit	Yes	CFR 1989e (40 CFR 180.1001)

EPA = Environmental Protection Agency; FDA = Food and Drug Administration; OPP = Office of Pesticide Products

[a]There are no regulations or advisories specifically applicable to 2,3-benzofuran. Because 2,3-benzofuran is one component of coumarone-indene resin, the regulations applicable to Coumarone-indene resin are presented in this table.

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*CFR. 1989d. Code of Federal Regulations. 21 CFR Ch. 1, 177.2600.

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed *in* micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves- as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

9. GLOSSARY

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(Lo)}$ (LC_{Lo}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(Lo)}$ (LD_{Lo}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

9. GLOSSARY

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

9. GLOSSARY

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-l

(1). Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

(5). Species The test species, whether animal or human, are identified in this column.

(6). Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "c").

(9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with

increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). Reference The complete reference citation is given in Chapter 8 of the profile.

(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs-for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-l

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

(13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

(18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5	6	7	8	9		10
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
38	Rat	18 mo 5d/wk 7hr/d			20 (CEL, multiple organs)		Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d			10 (CEL, lung tumors, nasal tumors)		NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d			10 (CEL, lung tumors, hemangiosarcomas)		NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

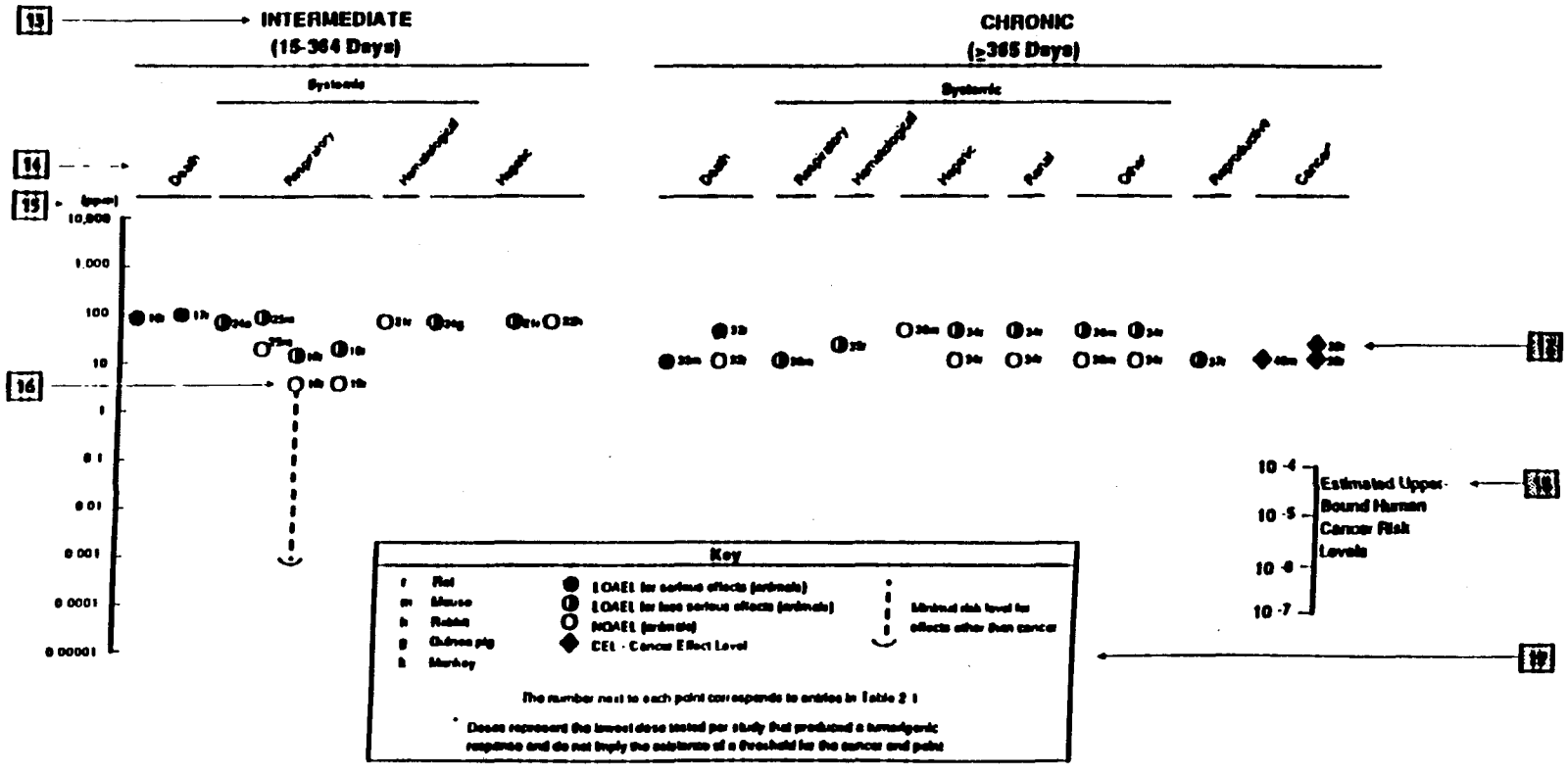

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans), In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCL	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f_1	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
Koc	octanol-soil partition coefficient
Kow	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration low
LC_{50}	lethal concentration 50 percent kill
LD_{Lo}	lethal dose low
LD_{50}	lethal dose 50 percent kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram

APPENDIX B

min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to

APPENDIX B

$<$	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for 2,3-benzofuran. The panel consisted of the following members: Dr. David Warshawsky, Associate Professor, Environmental Health, University of Cincinnati; Dr. Raymond Smith, Instructor, Department of Pathology and Microbiology, University of Nebraska; and Dr. Anthony DeCaprio, Consultant, Albany, New York. These experts collectively have knowledge of 2,3-benzofuran's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. A second panel of reviewers was assembled to review the sections on mitigation of effects. This panel consisted of: Dr. Brent Burton, Medical Director, Oregon Poison Center, Oregon Health Sciences University, Portland, Oregon; Dr. Alan Hall, Private Consultant, Evergreen, Colorado; and Dr. Alan Woolf, Director of Clinical Pharmacology and Toxicology, Massachusetts Poison Control System, The Children's Hospital, Boston, Massachusetts. All reviewers were selected in conformity with the conditions for peer review specified in the Comprehensive Environmental Response, Compensation, and Liability Act of 1986, Section 104.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

*U.S. Government Printing Office: 1992 — 638-236

TOXICOLOGICAL PROFILE FOR ARSENIC

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

August 2007

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Arsenic, Draft for Public Comment was released in September 2005. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-32
Atlanta, Georgia 30333

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Howard Frumkin, M.D., Dr. P.H.
Director
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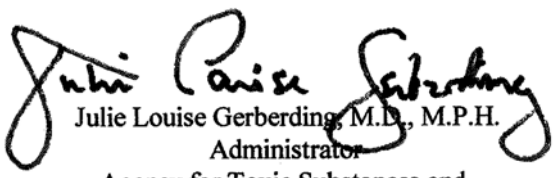
Agency for Toxic Substances and
Disease Registry



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Administrator
Agency for Toxic Substances and
Disease Registry

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014); and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for arsenic. The panel consisted of the following members:

1. Toby Rossman, Ph.D., Professor of Environmental Medicine, New York University School of Medicine, Nelson Institute of Environmental Medicine, Tuxedo, New York;

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These experts collectively have knowledge of arsenic's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about arsenic and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Arsenic has been found in at least 1,149 of the 1,684 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which arsenic is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to arsenic, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS ARSENIC?

Arsenic is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having both properties of a metal and a nonmetal; however, it is frequently referred to as a metal. Elemental arsenic (sometimes referred to as metallic arsenic) is a steel grey solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with

these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic.

Most inorganic and organic arsenic compounds are white or colorless powders that do not evaporate. They have no smell, and most have no special taste. Thus, you usually cannot tell if arsenic is present in your food, water, or air.

Inorganic arsenic occurs naturally in soil and in many kinds of rock, especially in minerals and ores that contain copper or lead. When these ores are heated in smelters, most of the arsenic goes up the stack and enters the air as a fine dust. Smelters may collect this dust and take out the arsenic as a compound called arsenic trioxide (As_2O_3). However, arsenic is no longer produced in the United States; all of the arsenic used in the United States is imported.

Presently, about 90% of all arsenic produced is used as a preservative for wood to make it resistant to rotting and decay. The preservative is copper chromated arsenate (CCA) and the treated wood is referred to as “pressure-treated.” In 2003, U.S. manufacturers of wood preservatives containing arsenic began a voluntary transition from CCA to other wood preservatives that do not contain arsenic in wood products for certain residential uses, such as play structures, picnic tables, decks, fencing, and boardwalks. This phase out was completed on December 31, 2003; however, wood treated prior to this date could still be used and existing structures made with CCA-treated wood would not be affected. CCA-treated wood products continue to be used in industrial applications. It is not known whether, or to what extent, CCA-treated wood products may contribute to exposure of people to arsenic.

In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are added to other metals to form metal mixtures or alloys with improved

properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes.

To learn more about the properties and uses of arsenic, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO ARSENIC WHEN IT ENTERS THE ENVIRONMENT?

Arsenic occurs naturally in soil and minerals and it therefore may enter the air, water, and land from wind-blown dust and may get into water from runoff and leaching. Volcanic eruptions are another source of arsenic. Arsenic is associated with ores containing metals, such as copper and lead. Arsenic may enter the environment during the mining and smelting of these ores. Small amounts of arsenic also may be released into the atmosphere from coal-fired power plants and incinerators because coal and waste products often contain some arsenic.

Arsenic cannot be destroyed in the environment. It can only change its form, or become attached to or separated from particles. It may change its form by reacting with oxygen or other molecules present in air, water, or soil, or by the action of bacteria that live in soil or sediment. Arsenic released from power plants and other combustion processes is usually attached to very small particles. Arsenic contained in wind-borne soil is generally found in larger particles. These particles settle to the ground or are washed out of the air by rain. Arsenic that is attached to very small particles may stay in the air for many days and travel long distances. Many common arsenic compounds can dissolve in water. Thus, arsenic can get into lakes, rivers, or underground water by dissolving in rain or snow or through the discharge of industrial wastes. Some of the arsenic will stick to particles in the water or sediment on the bottom of lakes or rivers, and some will be carried along by the water. Ultimately, most arsenic ends up in the soil or sediment. Although some fish and shellfish take in arsenic, which may build up in tissues, most of this arsenic is in an organic form called arsenobetaine (commonly called "fish arsenic") that is much less harmful.

For more information on how arsenic behaves in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO ARSENIC?

Since arsenic is found naturally in the environment, you will be exposed to some arsenic by eating food, drinking water, or breathing air. Children may also be exposed to arsenic by eating soil. Analytical methods used by scientists to determine the levels of arsenic in the environment generally do not determine the specific form of arsenic present. Therefore, we do not always know the form of arsenic a person may be exposed to. Similarly, we often do not know what forms of arsenic are present at hazardous waste sites. Some forms of arsenic may be so tightly attached to particles or embedded in minerals that they are not taken up by plants and animals.

The concentration of arsenic in soil varies widely, generally ranging from about 1 to 40 parts of arsenic to a million parts of soil (ppm) with an average level of 3–4 ppm. However, soils in the vicinity of arsenic-rich geological deposits, some mining and smelting sites, or agricultural areas where arsenic pesticides had been applied in the past may contain much higher levels of arsenic. The concentration of arsenic in natural surface and groundwater is generally about 1 part in a billion parts of water (1 ppb), but may exceed 1,000 ppb in contaminated areas or where arsenic levels in soil are high. Groundwater is far more likely to contain high levels of arsenic than surface water. Surveys of U.S. drinking water indicate that about 80% of water supplies have less than 2 ppb of arsenic, but 2% of supplies exceed 20 ppb of arsenic. Levels of arsenic in food range from about 20 to 140 ppb. However, levels of inorganic arsenic, the form of most concern, are far lower. Levels of arsenic in the air generally range from less than 1 to about 2,000 nanograms (1 nanogram equals a billionth of a gram) of arsenic per cubic meter of air (less than 1–2,000 ng/m^3), depending on location, weather conditions, and the level of industrial activity in the area. However, urban areas generally have mean arsenic levels in air ranging from 20 to 30 ng/m^3.

You normally take in small amounts of arsenic in the air you breathe, the water you drink, and the food you eat. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, for fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine that is much less harmful. Some seaweeds may

contain arsenic in inorganic forms that may be more harmful. Children are likely to eat small amounts of dust or soil each day, so this is another way they may be exposed to arsenic. The total amount of arsenic you take in from these sources is generally about 50 micrograms (1 microgram equals one-millionth of a gram) each day. The level of inorganic arsenic (the form of most concern) you take in from these sources is generally about 3.5 microgram/day. Children may be exposed to small amounts of arsenic from hand-to-mouth activities from playing on play structures or decks constructed out of CCA-treated wood. The potential exposure that children may receive from playing in play structures constructed from CCA-treated wood is generally smaller than that they would receive from food and water. Hand washing can reduce the potential exposure of children to arsenic after playing on play structures constructed with CCA-treated wood, since most of the arsenic on the children's hands was removed with water.

In addition to the normal levels of arsenic in air, water, soil, and food, you could be exposed to higher levels in several ways, such as the following:

- Some areas of the United States contain unusually high natural levels of arsenic in rock, and this can lead to unusually high levels of arsenic in soil or water. If you live in an area like this, you could take in elevated amounts of arsenic in drinking water. Children may be taking in higher amounts of arsenic because of hand-to-mouth contact or eating soil in areas with higher than usual arsenic concentrations.

- Some hazardous waste sites contain large quantities of arsenic. If the material is not properly disposed of, it can get into surrounding water, air, or soil. If you live near such a site, you could be exposed to elevated levels of arsenic from these media.

- If you work in an occupation that involves arsenic production or use (for example, copper or lead smelting, wood treating, or pesticide application), you could be exposed to elevated levels of arsenic during your work.

- If you saw or sand arsenic-treated wood, you could inhale some of the sawdust into your nose or throat. Similarly, if you burn arsenic-treated wood, you could inhale arsenic in the smoke.

- If you live in a former agricultural area where arsenic was used on crops, the soil could contain high levels of arsenic.

- In the past, several kinds of products used in the home (rat poison, ant poison, weed killer, some types of medicines) had arsenic in them. However, most of these uses of arsenic have ended, so you are not likely to be exposed from home products any longer.

You can find more information on how you may be exposed to arsenic in Chapter 6.

1.4 HOW CAN ARSENIC ENTER AND LEAVE MY BODY?

If you swallow arsenic in water, soil, or food, most of the arsenic may quickly enter into your body. The amount that enters your body will depend on how much you swallow and the kind of arsenic that you swallow. This is the most likely way for you to be exposed near a waste site. If you breathe air that contains arsenic dusts, many of the dust particles settle onto the lining of the lungs. Most of the arsenic in these particles is then taken up from the lungs into the body. You might be exposed in this way near waste sites where arsenic-contaminated soils are allowed to blow into the air, or if you work with arsenic-containing soil or products. If you get arsenic-contaminated soil or water on your skin, only a small amount will go through your skin into your body, so this is usually not of concern.

Both inorganic and organic forms leave your body in your urine. Most of the inorganic arsenic will be gone within several days, although some will remain in your body for several months or even longer. If you are exposed to organic arsenic, most of it will leave your body within several days.

You can find more information on how arsenic enters and leaves your body in Chapter 3.

1.5 HOW CAN ARSENIC AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

Inorganic arsenic has been recognized as a human poison since ancient times, and large oral doses (above 60,000 ppb in water which is 10,000 times higher than 80% of U.S. drinking water arsenic levels) can result in death. If you swallow lower levels of inorganic arsenic (ranging from about 300 to 30,000 ppb in water; 100–10,000 times higher than most U.S. drinking water levels), you may experience irritation of your stomach and intestines, with symptoms such as stomachache, nausea, vomiting, and diarrhea. Other effects you might experience from swallowing inorganic arsenic include decreased production of red and white blood cells, which may cause fatigue, abnormal heart rhythm, blood-vessel damage resulting in bruising, and impaired nerve function causing a "pins and needles" sensation in your hands and feet.

Perhaps the single-most characteristic effect of long-term oral exposure to inorganic arsenic is a pattern of skin changes. These include patches of darkened skin and the appearance of small "corns" or "warts" on the palms, soles, and torso, and are often associated with changes in the blood vessels of the skin. Skin cancer may also develop. Swallowing arsenic has also been reported to increase the risk of cancer in the liver, bladder, and lungs. The Department of Health and Human Services (DHHS) has determined that inorganic arsenic is known to be a human carcinogen (a chemical that causes cancer). The International Agency for Research on Cancer (IARC) has determined that inorganic arsenic is carcinogenic to humans. EPA also has classified inorganic arsenic as a known human carcinogen.

If you breathe high levels of inorganic arsenic, then you are likely to experience a sore throat and irritated lungs. You may also develop some of the skin effects mentioned above. The exposure level that produces these effects is uncertain, but it is probably above 100 micrograms of arsenic

per cubic meter ($\mu g/m^3$) for a brief exposure. Longer exposure at lower concentrations can lead to skin effects, and also to circulatory and peripheral nervous disorders. There are some data suggesting that inhalation of inorganic arsenic may also interfere with normal fetal development, although this is not certain. An important concern is the ability of inhaled inorganic arsenic to increase the risk of lung cancer. This has been seen mostly in workers exposed to arsenic at smelters, mines, and chemical factories, but also in residents living near smelters and arsenical chemical factories. People who live near waste sites with arsenic may have an increased risk of lung cancer as well.

If you have direct skin contact with high concentrations of inorganic arsenic compounds, your skin may become irritated, with some redness and swelling. However, it does not appear that skin contact is likely to lead to any serious internal effects.

Almost no information is available on the effects of organic arsenic compounds in humans. Studies in animals show that most simple organic arsenic compounds (such as methyl and dimethyl compounds) are less toxic than the inorganic forms. In animals, ingestion of methyl compounds can result in diarrhea, and lifetime exposure can damage the kidneys. Lifetime exposure to dimethyl compounds can damage the urinary bladder and the kidneys.

You can find more information on the health effects of inorganic and organic arsenic in Chapters 2 and 3.

1.6 HOW CAN ARSENIC AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Children are exposed to arsenic in many of the same ways that adults are. Since arsenic is found in the soil, water, food, and air, children may take in arsenic in the air they breathe, the water they drink, and the food they eat. Since children tend to eat or drink less of a variety of foods and beverages than do adults, ingestion of contaminated food or juice or infant formula made

with arsenic-contaminated water may represent a significant source of exposure. In addition, since children often play in the soil and put their hands in their mouths and sometimes intentionally eat soil, ingestion of contaminated soil may be a more important source of arsenic exposure for children than for adults. In areas of the United States where natural levels of arsenic in the soil and water are high, or in areas in and around contaminated waste sites, exposure of children to arsenic through ingestion of soil and water may be significant. In addition, contact with adults who are wearing clothes contaminated with arsenic (e.g., with dust from copper- or lead-smelting factories, from wood-treating or pesticide application, or from arsenic-treated wood) could be a source of exposure. Because of the tendency of children to taste things that they find, accidental poisoning from ingestion of pesticides is also a possibility. Thus, although most of the exposure pathways for children are the same as those for adults, children may be at a higher risk of exposure because of normal hand-to-mouth activity.

Children who are exposed to inorganic arsenic may have many of the same effects as adults, including irritation of the stomach and intestines, blood vessel damage, skin changes, and reduced nerve function. Thus, all health effects observed in adults are of potential concern in children. There is also some evidence that suggests that long-term exposure to inorganic arsenic in children may result in lower IQ scores. We do not know if absorption of inorganic arsenic from the gut in children differs from adults. There is some evidence that exposure to arsenic in early life (including gestation and early childhood) may increase mortality in young adults.

There is some evidence that inhaled or ingested inorganic arsenic can injure pregnant women or their unborn babies, although the studies are not definitive. Studies in animals show that large doses of inorganic arsenic that cause illness in pregnant females can also cause low birth weight, fetal malformations, and even fetal death. Arsenic can cross the placenta and has been found in fetal tissues. Arsenic is found at low levels in breast milk.

In animals, exposure to organic arsenic compounds can cause low birth weight, fetal malformations, and fetal deaths. The dose levels that cause these effects also result in effects in the mothers.

You can find more information about how arsenic can affect children in Sections 3.7 and 6.6.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ARSENIC?

If your doctor finds that you have been exposed to substantial amounts of arsenic, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

Many communities may have high levels of arsenic in their drinking water, particularly from private wells, because of contamination or as a result of the geology of the area. The north central region and the western region of the United States have the highest arsenic levels in surface water and groundwater sources, respectively. Wells used to provide water for drinking and cooking should be tested for arsenic. As of January 2006, EPA's Maximum Contaminant Level (MCL) for arsenic in drinking water is 10 ppb. If you have arsenic in your drinking water at levels higher that the EPA's MCL, an alternative source of water should be used for drinking and cooking should be considered.

If you use arsenic-treated wood in home projects, personal protection from exposure to arsenic-containing sawdust may be helpful in limiting exposure of family members. These measures may include dust masks, gloves, and protective clothing. Arsenic-treated wood should never be burned in open fires, or in stoves, residential boilers, or fire places, and should not be composted or used as mulch. EPA's Consumer Awareness Program (CAP) for CCA is a voluntary program established by the manufacturers of CCA products to inform consumers about the proper handling, use, and disposal of CCA-treated wood. You can find more information about this program in Section 6.5. Hand washing can reduce the potential exposure of children to arsenic after playing on play structures constructed with CCA-treated wood, since most of the arsenic on the children's hands was removed with water.

If you live in an area with a high level of arsenic in the water or soil, substituting cleaner sources of water and limiting contact with soil (for example, through use of a dense groundcover or thick lawn) would reduce family exposure to arsenic. By paying careful attention to dust and soil

control in the home (air filters, frequent cleaning), you can reduce family exposure to contaminated soil. Some children eat a lot of soil. You should prevent your children from eating soil. You should discourage your children from putting objects in their mouths. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or engaging in other hand-to-mouth activities. Since arsenic may be found in the home as a pesticide, household chemicals containing arsenic should be stored out of reach of young children to prevent accidental poisonings. Always store household chemicals in their original labeled containers; never store household chemicals in containers that children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center's number by the phone.

It is sometimes possible to carry arsenic from work on your clothing, skin, hair, tools, or other objects removed from the workplace. This is particularly likely if you work in the fertilizer, pesticide, glass, or copper/lead smelting industries. You may contaminate your car, home, or other locations outside work where children might be exposed to arsenic. You should know about this possibility if you work with arsenic.

Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Material safety data sheets (MSDS) for many chemicals used should be found at your place of work, as required by the Occupational Safety and Health Administration (OSHA) in the U.S. Department of Labor. MSDS information should include chemical names and hazardous ingredients, and important properties, such as fire and explosion data, potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in the case of emergencies. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your state OSHA-approved occupational safety and health program or OSHA can answer any further questions and help your employer identify and correct problems with hazardous substances. Your state OSHA-approved occupational safety and health program or

OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to seek safety and health on the job without fear of punishment.

You can find more information about how arsenic can affect children in Sections 3.7 and 6.6.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ARSENIC?

Several sensitive and specific tests can measure arsenic in your blood, urine, hair, or fingernails, and these tests are often helpful in determining if you have been exposed to above-average levels of arsenic in the past. These tests are not usually performed in a doctor's office. They require sending the sample to a testing laboratory.

Measurement of arsenic in your urine is the most reliable means of detecting arsenic exposures that you experienced within the last several days. Most tests measure the total amount of arsenic present in your urine. This can sometimes be misleading, because the nonharmful forms of arsenic in fish and shellfish can give a high reading even if you have not been exposed to a toxic form of arsenic. For this reason, laboratories sometimes use a more complicated test to separate "fish arsenic" from other forms. Because most arsenic leaves your body within a few days, analysis of your urine cannot detect if you were exposed to arsenic in the past. Tests of your hair or fingernails can tell if you were exposed to high levels over the past 6–12 months, but these tests are not very useful in detecting low-level exposures. If high levels of arsenic are detected, this shows that you have been exposed, but unless more is known about when you were exposed and for how long, it is usually not possible to predict whether you will have any harmful health effects.

You can find more information on how arsenic can be measured in your hair, urine, nails, and other tissues in Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for ARSENIC include the following:

The federal government has taken several steps to protect humans from arsenic. First, EPA has set limits on the amount of arsenic that industrial sources can release into the environment. Second, EPA has restricted or canceled many of the uses of arsenic in pesticides and is considering further restrictions. Third, in January 2001, the EPA lowered the limit for arsenic in drinking water from 50 to 10 ppb. Finally, OSHA has established a permissible exposure limit (PEL), 8-hour time-weighted average, of 10 $\mu g/m^3$ for airborne arsenic in various workplaces that use inorganic arsenic.

You can find more information on regulations and guidelines that apply to arsenic in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ARSENIC IN THE UNITED STATES

Arsenic is widely distributed in the Earth's crust, which contains ~3.4 ppm arsenic. In nature, arsenic is mostly found in minerals and only to a small extent in its elemental form. Arsenic is mainly obtained as a byproduct of the smelting of copper, lead, cobalt, and gold ores. Arsenic trioxide is the primary form in which arsenic is marketed and consumed. There has been no domestic production of arsenic since 1985. In 2003, the world's largest producer of arsenic compounds was China, followed by Chile and Peru.

In 2003, the United States was the world's largest consumer of arsenic. Production of wood preservatives, primarily copper chromated arsenate (CCA), CrO_3•CuO•As_2O_5, accounted for >90% of domestic consumption of arsenic trioxide. In response to consumer concerns, U.S. manufacturers of arsenical wood preservative began a voluntary transition from CCA to other wood preservatives for certain residential wood products. This phase-out was completed on December 31, 2003; wood treated prior to this date could still be used and CCA-treated wood products continue to be used in industrial applications.

Other uses for arsenic compounds include the production of agricultural chemicals, as an alloying element in ammunition and solders, as an anti-friction additive to metals used for bearings, and to strengthen lead-acid storage battery grids. High-purity arsenic (99.9999%) is used by the electronics industry for gallium-arsenide semiconductors for telecommunications, solar cells, and space research. Various organic arsenicals are still used in the United States as herbicides and as antimicrobial additives for animal and poultry feed. However, the use of inorganic arsenic compounds in agriculture has virtually disappeared beginning around the 1960s. Arsenic trioxide and arsenic acid were used as a decolorizer and fining agent in the production of bottle glass and other glassware. Arsenic compounds also have a long history of use in medicine, and have shown a re-emergence of late with the recent introduction of arsenic trioxide treatment for acute promyelocytic leukemia.

The principal route of exposure to arsenic for the general population is likely to be the oral route, primarily in the food and in the drinking water. Dietary exposures to total arsenic were highly variable, with a mean of 50.6 μg/day (range of 1.01–1,081 μg/day) for females and 58.5 μg/day (range of 0.21–1,276 μg/day) for males. U.S. dietary intake of inorganic arsenic has been estimated to range from 1 to 20 μg/day, with grains and produce expected to be significant contributors to dietary inorganic arsenic

intake. Drinking water generally contains an average of 2 μg/L of arsenic, although 12% of water supplies from surface water sources in the North Central region of the country and 12% of supplies from groundwater sources in the Western region have levels exceeding 20 μg/L. Arsenic is also widely distributed in surface water, groundwater, and finished drinking water in the United States. Surveys of arsenic concentrations in rivers and lakes indicate that most values are below 10 μg/L, although individual samples may range up to 3,400 μg/L. Arsenic released to the land at hazardous waste sites is likely to be relatively immobile due to a high capacity for soil binding, particularly to iron and manganese oxides. Exposure to arsenic from other pathways is generally small, but may be significant for areas with high levels of arsenic contamination or in occupational settings. For a more complete discussion of possible exposures to arsenic, see Chapter 6 of the profile.

2.2 SUMMARY OF HEALTH EFFECTS

Arsenic is a potent toxicant that may exist in several oxidation states and in a number of inorganic and organic forms. Most cases of arsenic-induced toxicity in humans are due to exposure to inorganic arsenic, and there is an extensive database on the human health effects of the common arsenic oxides and oxyacids. Although there may be some differences in the potency of different chemical forms (e.g., arsenites tend to be somewhat more toxic than arsenates), these differences are usually minor. An exception would be arsine, which is highly toxic. However, because arsine and its methyl derivatives are gases or volatile liquids and are unlikely to be present at levels of concern at hazardous waste sites, health effect data for these compounds are not discussed in this document. Humans may be exposed to organic arsenicals (mainly methyl and phenyl derivatives of arsenic acid) that are used in agriculture and to organic arsenicals found in fish and shellfish (arsenobetaine and arsenocholine). Although the toxicity of organic arsenicals has not been as extensively investigated as inorganic arsenicals, there are sufficient animal data to evaluate the toxicity of methyl arsenates (e.g., monomethylarsonic acid [MMA] and dimethylarsinic acid [DMA]) and roxarsone. The so-called “fish arsenic” compounds (e.g., arsenobetaine) are not thought to be toxic and health effects data are not discussed in this document.

It is generally accepted that the arsenic-carbon bond is quite strong and most mammalian species do not have the capacity to break this bond; thus, inorganic arsenic is not formed during the metabolism of organic arsenicals. In most species, including humans, ingested (or exogenous) MMA(V) and DMA(V) undergo limited metabolism, do not readily enter the cell, and are primarily excreted unchanged in the urine. This is in contrast to inorganic arsenic, which undergoes sequential reduction and methylation reactions leading to the formation of MMA and DMA. Inorganic As(V) is readily reduced to inorganic

As(III), which is taken up by the cell. Within the cell (primarily in the liver), As(III) is methylated to form MMA(V), which is reduced to MMA(III); MMA(III) subsequently undergoes oxidative methylations to form DMA(V). DMA(V) is the primary excretion product in humans. Because inorganic and organic arsenicals exhibit distinct toxicokinetic characteristics, the health effects and MRLs are considered separately.

Inorganic Arsenicals. Exposures of humans near hazardous waste sites could involve inhalation of arsenic dusts in air, ingestion of arsenic in water, food, or soil, or dermal contact with contaminated soil or water. Increased risk of lung cancer, respiratory irritation, nausea, skin effects, and neurological effects have been reported following inhalation exposure. There are only a few quantitative data on noncancer effects in humans exposed to inorganic arsenic by the inhalation route. Animal data similarly identify effects on the respiratory system as the primary noncancer effect of inhaled inorganic arsenic compounds, although only a few studies are available. Only limited data on the effects of inhaled organic arsenic compounds in humans or animals are available; these studies are generally limited to high-dose, short-term exposures, which result in frank effects.

Relatively little information is available on effects due to direct dermal contact with inorganic arsenicals, but several studies indicate that the chief effect is local irritation and dermatitis, with little risk of other adverse effects.

The database for the oral toxicity of inorganic arsenic is extensive, containing a large number of studies of orally-exposed human populations. These studies have identified effects on virtually every organ or tissue evaluated, although some end points appear to be more sensitive than others. The available data from humans identify the skin as the most sensitive noncancer target following long-term oral arsenic exposure. Typical dermal effects include hyperkeratinization of the skin (especially on the palms and soles), formation of multiple hyperkeratinized corns or warts, and hyperpigmentation of the skin with interspersed spots of hypopigmentation. Oral exposure data from studies in humans indicate that these lesions typically begin to manifest at exposure levels of about 0.002–0.02 mg As/kg/day, but one study suggests that lesions may appear at even lower levels. At these exposure levels, peripheral vascular effects are also commonly noted, including cyanosis, gangrene, and, in Taiwanese populations, the condition known as “Blackfoot Disease.” Other reported cardiovascular effects of oral exposure to inorganic arsenic include increased incidences of high blood pressure and circulatory problems. The use of intravenous arsenic trioxide as therapy for acute promyelocytic leukemia has raised further concerns about the cardiovascular effects of arsenic, including alterations in cardiac QT interval and the

development of torsades de pointes. Decrements in lung function, assessed by spirometry, have been reported in subjects exposed to approximately 0.008–0.04 mg As/kg/day in the drinking water who exhibited skin lesions.

In addition to dermal, cardiovascular, and respiratory effects, oral exposure to inorganic arsenic may result in effects on other organ systems. Nausea, vomiting, and diarrhea are very common symptoms in humans following oral exposure to inorganic arsenicals, both after acute high-dose exposure and after repeated exposure to lower doses; these effects are likely due to a direct irritation of the gastrointestinal mucosa. Acute, high-dose exposure can lead to encephalopathy, with clinical signs such as confusion, hallucinations, impaired memory, and emotional lability, while long-term exposure to lower levels can lead to the development of peripheral neuropathy characterized by a numbness in the hands and feet that may progress to a painful "pins and needles" sensation. Recent studies also have reported neurobehavioral alterations in arsenic-exposed children.

Chronic exposure of humans to inorganic arsenic in the drinking water has been associated with excess incidence of miscarriages, stillbirths, preterm births, and infants with low birth weights. Animal data suggest that arsenic may cause changes to reproductive organs of both sexes, including decreased organ weight and increased inflammation of reproductive tissues, although these changes may be secondary effects. However, these changes do not result in a significant impact on reproductive ability. Animal studies of oral inorganic arsenic exposure have reported developmental effects, but generally only at concentrations that also resulted in maternal toxicity.

Arsenic is a known human carcinogen by both the inhalation and oral exposure routes. By the inhalation route, the primary tumor types are respiratory system cancers, although a few reports have noted increased incidence of tumors at other sites, including the liver, skin, and digestive tract. In humans exposed chronically by the oral route, skin tumors are the most common type of cancer. In addition to skin cancer, there are a number of case reports and epidemiological studies that indicate that ingestion of arsenic also increases the risk of internal tumors (mainly of bladder and lung, and to a lesser extent, liver, kidney, and prostate).

The Department of Health and Human Services (DHHS) has concluded that inorganic arsenic is known to be a human carcinogen. The International Agency for Research on Cancer (IARC) cites sufficient evidence of a relationship between exposure to arsenic and human cancer. The IARC classification of arsenic is Group 1. The EPA has determined that inorganic arsenic is a human carcinogen by the

inhalation and oral routes, and has assigned it the cancer classification, Group A. EPA has calculated an oral cancer slope factor of 1.5 $(mg/kg/day)^{-1}$ and a drinking water unit risk of $5x10^{-5}$ $(\mu g/L)^{-1}$ for inorganic arsenic based on human dose-response data. The inhalation unit risk for cancer is calculated to be 0.0043 $(\mu g/m^3)^{-1}$. The unit risk is the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg/L in water or 1 $\mu g/m^3$ in air. EPA is currently revising the assessment for inorganic arsenic; a more detailed discussion of the uncertainties associated with human cancer risk levels for arsenic is presented in Section 3.2.2.7.

The following sections discuss significant effects resulting from exposure to inorganic arsenic in greater detail: dermal, cardiovascular, respiratory, gastrointestinal, neurological, and cancer. Additional information on these effects and on other effects is discussed in Section 3.2.

Dermal Effects. The most characteristic effect of long-term oral exposure to inorganic arsenic compounds is the development of skin lesions; these lesions are often used as diagnostic criteria for arsenicosis. The three lesions most often associated with chronic arsenicosis are hyperkeratinization of the skin (especially on the palms and soles), formation of multiple hyperkeratinized corns or warts, and hyperpigmentation of the skin with interspersed spots of hypopigmentation. Numerous studies of long-term, low-level exposure to inorganic arsenic in humans have reported the presence of these lesions. In general, they begin to manifest at chronic exposure levels >0.02 mg As/kg/day. Chronic oral studies of lower exposure levels, ranging from 0.0004 to 0.01 mg As/kg/day, have generally not reported dermal effects. However, in a study with detailed exposure assessment, all confirmed cases of skin lesions ingested water containing >100 μg/L arsenic (approximately 0.0037 mg As/kg/day) and the lowest known peak arsenic concentration ingested by a case was 0.115 μg/L (approximately 0.0043 mg As/kg/day). Another large study reported increased incidence of skin lesions associated with estimated doses of 0.0012 mg As/kg/day (0.023 mg As/L drinking water). The mechanism(s) by which inorganic arsenic causes dermal effects is not well-understood. Elucidating the mechanism of dermal effects has been particularly difficult because the dermal effects common in humans have not been seen in studies in animals.

Dermal effects have also been reported following inhalation exposures to inorganic arsenic, although they are not as diagnostic as for oral exposure. Several studies of arsenic-exposed workers have reported the development of dermatitis; exposure levels required to produce this condition are not well-established. Altered dermal pigmentation and hyperkeratosis have also been reported in studies of humans exposed to inorganic arsenic by inhalation, although exposure levels have varied considerably. Direct dermal contact

with inorganic arsenicals may cause irritation and contact dermatitis. Usually, the effects are mild (erythema and swelling), but may progress to papules, vesicles, or necrotic lesions in extreme cases; these conditions tend to heal without treatment if exposure ceases.

Cardiovascular Effects. A large number of studies in humans have reported cardiovascular effects following oral exposure to inorganic arsenic compounds. The cardiac effects of arsenic exposure are numerous, and include altered myocardial depolarization (prolonged QT interval, nonspecific ST segment changes), cardiac arrhythmias, and ischemic heart disease. These effects have been seen after acute and long-term exposure to inorganic arsenic in the environment, as well as side effects from intravenous therapy with arsenic trioxide for acute promyelocytic leukemia. Exposure levels for environmental exposures have not been well characterized, but intravenous doses for arsenic trioxide therapy are generally on the order of 0.15 mg As/kg/day.

Chronic exposure to inorganic arsenic has also been shown to lead to effects on the vascular system. The most dramatic of these effects is “Blackfoot Disease,” a disease characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene. Blackfoot Disease is endemic in an area of Taiwan where average drinking water levels of arsenic range from 0.17 to 0.80 ppm, corresponding to doses of about 0.014–0.065 mg As/kg/day. The results of a another study suggested that individuals with a lower capacity to methylate inorganic arsenic to DMA have a higher risk of developing peripheral vascular disease in the Blackfoot Disease-hyperendemic area in Taiwan. Arsenic exposure in Taiwan has also been associated with an increased incidence of cerebrovascular and microvascular diseases and ischemic heart disease. While Blackfoot Disease itself has not been reported outside of Taiwan, other vascular effects are common in areas with high arsenic exposures, and include such severe effects as increases in the incidences of Raynaud's disease and of cyanosis of fingers and toes as well as hypertension, thickening and vascular occlusion of blood vessels, and other unspecified cardiovascular conditions. However, while the majority of human studies have reported cardiovascular effects following exposure to inorganic arsenic, some have found no such effects.

Changes in cardiac rhythm and in some vascular end points have also been reported in animal studies of inorganic arsenicals, but generally only at higher exposure levels and not to the degree of severity seen in humans.

Respiratory Effects. While case reports and small cohort studies have routinely reported an increase in respiratory symptoms of humans exposed occupationally to inorganic arsenic, dose-response data for

these symptoms are generally lacking. The only study that evaluated respiratory effects (changes in chest x-ray or respiratory performance) and reported an exposure estimate did not report significant changes at an exposure level of 0.613 mg As/m^3. Exposed workers often report irritation of the mucous membranes of the nose and throat, which may lead to laryngitis, bronchitis, or rhinitis. Increased mortality due to respiratory disease has been reported in some cohort mortality studies of arsenic-exposed workers, but no conclusive evidence of an association of these diseases with arsenic exposure has been presented. It is not known whether respiratory effects following inhaled inorganic arsenic compounds are due to a direct effect of arsenic on respiratory tissues, general effects of foreign material in the lungs, or an effect of arsenic on the pulmonary vasculature. Similar responses, including rales, labored breathing, and respiratory hyperplasia, have been noted in animal studies of inhaled or instilled inorganic arsenic compounds.

Respiratory effects have also been reported following oral exposure of humans to inorganic arsenic. Acute oral exposure to ≥8 mg As/kg may result in serious respiratory effects, including respiratory distress, hemorrhagic bronchitis, and pulmonary edema; however, it is not clear whether these are primary effects or are the result of damage to the pulmonary vascular system. In general, respiratory effects have not been widely associated with long-term oral exposure to low arsenic doses. However, some studies have reported minor respiratory symptoms, such as cough, sputum, rhinorrhea, and sore throat, in people with repeated oral exposure to 0.03–0.05 mg As/kg/day. More serious respiratory effects, such as bronchitis and sequelae (bronchiectasis, bronchopneumonia) have been observed in patients chronically exposed to arsenic and at autopsy in some chronic poisoning cases. There are few animal data reporting respiratory effects of oral exposure to inorganic arsenic, and those studies generally found effects only at very high dose levels.

Gastrointestinal Effects. Both short-term and chronic oral exposures to inorganic arsenicals have been reported to result in irritant effects on gastrointestinal tissues. Numerous studies of acute, high-dose exposure to inorganic arsenicals have reported nausea, vomiting, diarrhea, and abdominal pain, although specific dose levels associated with the onset of these symptoms have not been identified. Chronic oral exposure to 0.01 mg As/kg/day generally results in similar reported symptoms. For both acute and chronic exposures, the gastrointestinal effects generally diminish or resolve with cessation of exposure. Similar gastrointestinal effects have been reported after occupational exposures to inorganic arsenicals, although it is not known if these effects were due to absorption of arsenic from the respiratory tract or from mucociliary clearance resulting in eventual oral exposure.

Neurological Effects. A common effect following both oral and inhalation exposure to inorganic is the development of peripheral neuropathy. Following occupational exposure to inorganic arsenic in pesticide plants or smelters, exposed workers have shown increased incidence of neurological changes, including altered nerve conduction velocities. One study reported that these effects were seen after 28 years of exposure to 0.31 mg As/m^3. In another study, signs and symptoms of sensory and motor polyneuropathy on both upper and lower extremities were reported in workers at a power station in Slovakia. The average length of exposure was 22.3 years (standard deviation [SD] ±8.4 years) and the average arsenic exposure in inhaled air ranged from 4.6 to 142.7 μg/m^3.

Following high-dose (>2 mg As/kg/day) acute oral exposures to inorganic arsenicals in humans, reported effects include headache, lethargy, mental confusion, hallucination, seizures, and coma. Following longer-term exposure to 0.03–0.1 mg As/kg/day, peripheral neuropathy, characterized initially by numbness of the hands and feet and a "pins and needles" sensation and progressing to muscle weakness, wrist-drop and/or ankle-drop, diminished sensitivity, and altered reflex action. Histological features of the neuropathy include a dying-back axonopathy and demyelination. Following removal from exposure, the neuropathy is only partially reversible and what recovery does occur is generally slow. Reports of neurological effects at lower arsenic levels (0.004–0.006 mg As/kg/day) have been inconsistent, with some human studies reporting fatigue, headache, depression, dizziness, insomnia, nightmare, and numbness while others reported no neurological effects. Some studies also have reported that exposure to arsenic may be associated with intellectual deficits in children. Neurological effects have also been reported in oral studies of arsenic toxicity in animals, although these were generally performed at higher doses (0.4–26.6 mg As/kg/day) than has been reported in exposed human populations. The mechanism(s) of arsenic-induced neurological changes has not been determined.

Cancer. There is clear evidence from studies in humans that exposure to inorganic arsenic by either the inhalation or oral routes increases the risk of cancer. Numerous studies of copper smelters or miners exposed to arsenic trioxide have reported an increased risk of lung cancer. Increased incidence of lung cancer has also been observed at chemical plants where exposure was primarily to arsenate. Other studies suggest that residents living near smelters or arsenical chemical plants may have increased risk of lung cancer, although the reported increases are small and are not clearly detectable in all cases. In general, studies reporting long-term exposure to 0.07 mg As/m^3 or greater have shown an increased incidence of lung cancer, while at lower exposure levels, the association has been less clear or not present.

There is convincing evidence from a large number of epidemiological studies and case reports that ingestion of inorganic arsenic increases the risk of developing skin cancer. The most common tumors seen are squamous cell carcinomas, which may develop from the hyperkeratotic warts or corns commonly seen as a dermal effect of oral inorganic arsenic exposure. Early studies of populations within the United States did not suggest an increased risk of cancer from oral inorganic arsenic exposure. Later studies have found suggestive evidence that the possibility of arsenic-induced skin cancers cannot be discounted based on an association between toenail arsenic levels and incidence of skin cancer.

There is increasing evidence that long-term exposure to arsenic can result in the development of bladder cancer, with transitional cell cancers being the most prevalent. While studies have noted statistical dose-response trends in arsenic-induced bladder cancers, reliable quantitative assessments of dose-response relationships have not been presented. Several studies have also shown that chronic oral exposure to arsenic results in the development of respiratory tumors, making lung cancer an established cause of death from exposure to arsenic in drinking water. Exposure levels in studies evaluating respiratory and bladder cancers have been comparable to those in studies evaluating skin tumors. Studies of U.S. populations have not identified an increased risk of bladder or respiratory tumors following oral exposure to inorganic arsenic.

Animal studies of both inhalation and oral exposure to inorganic arsenicals have not resulted in increased incidence of cancer formation in adult animals. However, a series of studies have shown that inorganic arsenic can induce cancer in the offspring from mice exposed to arsenic during gestation (transplacental carcinogen) and acts as a co-carcinogen with UV light and polycyclic aromatic hydrocarbons (PAHs).

Organic Arsenicals. Humans may be exposed to organic arsenicals via inhalation of dusts, ingestion of organic arsenic in water, food, soil, or dermal contact with contaminated soil, water or plants following pesticide application. There are limited data on the toxicity of organic arsenicals following inhalation exposure in humans and animals and these data do not allow for identification of critical effects. Keratosis was observed in workers exposed to 0.065 mg/m^3 arsanilic acid (i.e., 4-aminophenyl arsenic acid); no alterations in gastrointestinal symptoms or hematological alterations were observed. In animals, very high concentrations (>3,000 mg/m^3) of DMA results in respiratory distress, diarrhea, and erythematous lesions on the feet and ears. No adverse effects were observed in rats exposed to DMA concentrations as high as 100 mg DMA/m^3 for 95 days.

Similarly, the available dermal toxicity data do not allow for identification of critical effects. Contact dermatitis was observed in workers applying DMA (and its sodium salt) and mild dermal irritation was observed in a Draize test in rabbits (adverse effect level not reported). Intermediate duration (21 days) exposure studies in rabbits did not result in systemic toxicity or skin irritation following 5 day/week exposure to 1,000 mg/kg/day MMA or DMA.

The preponderance of toxicity data for organic arsenicals involves oral exposure. Human data are limited to three case reports of individuals intentionally ingesting pesticides containing organic arsenicals. Gastrointestinal irritation (vomiting, nausea, and diarrhea) were consistently reported in these cases. Animal data has primarily focused on the toxicity of MMA, DMA, and roxarsone; these data suggest that the targets of toxicity may differ between the compounds.

MMA. The gastrointestinal tract appears to be the most sensitive target of toxicity for MMA. Diarrhea and tissue damage in the large intestine have been reported in several animal species following dietary, gavage, and capsule exposure. For diarrhea, both the time of onset and incidence appear to be dose-related. In rats, diarrhea was observed in 100% of females exposed to 98.5 mg MMA/kg/day, 55% of females exposed to 33.9 mg MMA/kg/day, and 5.1% of females exposed to 3.9 mg MMA/kg/day. The increased incidence of diarrhea was observed after 3 weeks of exposure to 98.5 mg MMA/kg/day, 4 weeks at 33.9 mg MMA/kg/day, and 18 months at 3.9 mg MMA/kg/day. Histological damage consisting of squamous metaplasia of the epithelial columnar absorptive cells in the cecum, colon, and rectum was observed in rats and mice chronically exposed to 72.4 or 67.1 mg MMA/kg/day, respectively. Hemorrhagic, necrotic, ulcerated, or perforated mucosa were also observed in the large intestine of rats exposed to 67.1 mg MMA/kg/day for 2 years. In rats, the damage to the large intestine resulted in intestinal contents leaking into the abdominal cavity and the development of peritonitis. The available data provide suggestive evidence that there may be some species differences in the sensitivity to gastrointestinal damage; however, some of these differences may be due to the route of administration. The lowest adverse effect levels, regardless of duration of exposure, for gastrointestinal effects in rats, mice, rabbits, and dogs are 25.7, 67.1, 12, and 2 mg MMA/kg/day, respectively; the no adverse effect levels in rats and mice (NOAELs were not identified in rabbits and dogs) were 3.0 and 24.9 mg MMA/kg/day. However, the rabbit and dog studies involved bolus administration (gavage and capsule administration), which may have increased sensitivity; the rat and mouse studies involved dietary exposure.

The kidney also appears to be a sensitive target in rats and mice chronically exposed to MMA. An increase in the severity of progressive glomerulonephropathy was observed in female rats exposed to 33.9 mg MMA/kg/day for 2 years and an increase in the incidence of progressive glomerulonephropathy was observed in male mice exposed to 6.0 mg MMA/kg/day for 2 years. Other adverse effects that have been observed in animals exposed to MMA include hypertrophy of the thyroid follicular cells in rats exposed to 33.9 mg MMA/kg/day in the diet for 2 years, reproductive toxicity, and developmental toxicity. Decreases in pregnancy rate and male fertility index were observed in F_0 and F_1 rats exposed to 76 mg MMA/kg/day for 14 weeks prior to mating and during the mating period; the findings were not significantly different than control values but were considered treatment-related because they were outside the range found in historical controls. This study also reported a decrease in pup survival in the F_1 and F_2 offspring of rats exposed to 76 mg MMA/kg/day; as with the reproductive effects, the incidence was not statistically different from controls but was considered biologically significant because survival in the MMA pups was outside the range found in historical controls. Another study reported impaired fetal growth (decreases in fetal weights and incomplete ossification) and minor skeletal defects (an increase in the number of fetuses with supernumerary thoracic ribs and eight lumbar vertebrae) in rat and rabbit fetuses exposed to 500 or 12mg MMA/kg/day, respectively; maternal toxicity was also observed at these dose levels and the effects may be secondary to maternal stress rather than a direct effect on the developing organisms. A 2-year bioassay did not result in significant increases in the incidence of neoplastic lesions in rats and mice exposed to doses as high as 72.4 and 67.1 mg MMA/kg/day, respectively.

DMA. The most sensitive targets of DMA toxicity in rats are the urinary bladder and kidneys. In the bladder, the effects progress from cytotoxicity to cellular necrosis to regenerative proliferation and hyperplasia. At dietary doses of 11 mg DMA/kg/day, cytotoxicity is observed as early as 6 hours after exposure initiation and cellular proliferation (as evident by increased BrdU labeling) was observed after 2 weeks of exposure. After 10 weeks of exposure, necrosis and hyperplasia were also observed. The lowest adverse effect levels for urinary bladder effects following intermediate or chronic duration exposure were 5 mg DMA/kg/day for evidence of regenerative proliferation and 3.1 mg DMA/kg/day for vacuolar degeneration of urothelium and hyperplasia. Vacuolization of the superficial cells of the urothelium was observed in mice exposed to 7.8 mg DMA/kg/day and higher for 2 years. However, unlike the vacuolar degeneration observed in rats, the vacuolization observed in mice was not associated with cytotoxicity, necrosis, inflammation, or hyperplasia.

Kidney damage characterized by increased urinary calcium levels, calcification, nephrocalcinosis, and necrosis of the renal papillae have been observed in rats following intermediate- or chronic-duration exposure. Increases in urine calcium levels and corticomedullary junction calcification were observed in rats exposed to 5 or 10 mg DMA/kg/day for 10 weeks and cortical degeneration and necrosis were observed in rats exposed to 57 mg DMA/kg/day for 4 weeks. Chronic-duration exposure to 3.1 mg DMA/kg/day resulted in an increased incidence of nephrocalcinosis and necrosis of the renal papillae in rats; these lesions are typical in aged rats, although DMA exposure appeared to exacerbate them. An exacerbation of age-related kidney lesion (progressive glomerulonephropathy and nephrocalcinosis) has also been observed in male mice exposed to 37 or 94 mg DMA/kg/day, respectively, for 2 years. A consistent finding in intermediate and chronic rat studies is an increase in urine volume, which corresponds to an increase in water consumption; the toxicological significance of this finding is not known. The observed decreases in electrolyte levels and specific gravity are likely due to the higher urine volume.

Although gastrointestinal effects have been observed in animals exposed to DMA, it does not appear to be as sensitive a target compared to MMA. Diarrhea has been observed in rats exposed to a lethal dose of 190 mg DMA/kg/day for 4 weeks and in dogs administered via 16 mg DMA/kg/day. No gastrointestinal effects were observed in rats or mice chronically exposed to 7.8 or 94 mg DMA/kg/day.

Other adverse effects that have been observed in animals exposed to organic arsenicals include hypertrophy of thyroid follicular cells in rats exposed to 4.0 mg DMA/kg/day in the diet for 13 weeks and 7.8 mg DMA/kg/day in the diet for 2 years and developmental effects in rats and mice. Decreases in fetal growth and delays in ossification have been observed in rat fetuses exposed to ≥36 mg DMA/kg/day; these alterations typically occur at doses associated with decreases in maternal weight gain. Other developmental effects that have been reported include an increase in the incidences of irregular palatine rugae in rats exposed to 30 mg DMA/kg/day, diaphragmatic hernia in rats exposed to 36 mg DMA/kg/day, and cleft palate in mice exposed to 400 mg DMA/kg/day. No developmental effects were observed in rabbits exposed to 12 mg DMA/kg/day.

The available data provide strong evidence that DMA is carcinogenic in rats. A 2-year exposure to DMA resulted in significant increases in the incidence of neoplastic urinary bladder tumors in rats exposed to 7.8 mg DMA/kg/day in the diet or 3.4 mg DMA/kg/day in drinking water. No increases in neoplastic tumors were observed in mice exposed to doses as high as 94 mg DMA/kg/day for 2 years; however, a

50-week exposure to 10.4 mg DMA/kg/day did result in an increased incidence of lung tumors in A/J mice.

The available data for DMA suggest that there are species differences in terms of the critical effects and sensitivity. In rats, the urinary bladder and kidneys are the most sensitive targets with effects occurring at 5 mg DMA/kg/day following intermediate-duration exposure and 3.1 mg DMA/kg/day following chronic-duration exposure. Although the urinary bladder and kidneys are also sensitive targets in mice with LOAELs of 7.8 and 37 mg DMA/kg/day, respectively, following chronic exposure, the effects are not associated with cytotoxicity or elevated urine calcium levels. In dogs, the most sensitive effect is gastrointestinal tract irritation (diarrhea), which occurs at 16 mg DMA/kg/day.

There is concern that the rat may not be a good model to predict the human risk associated with organic arsenic exposure due to the unique toxicokinetic properties of DMA in rats. In humans and most animal species, DMA is rapidly eliminated from the body; >90% of the dose is excreted 2–3 days after dosing. In contrast, DMA is slowly eliminated in rats. One study estimated that 45% of an initial oral DMA dose was eliminated with a half-time of 13 hours; the remaining 55% of the dose DMA dose had an elimination half-time of 50 days. In rats, DMA has a strong affinity for hemoglobin resulting in an accumulation of DMA in erythrocytes. Species differences in DMA metabolism have also been found. In particular, DMA undergoes further methylation to trimethylarsine oxide (TMAO) in rats. In most animal species, almost the entire oral DMA dose is excreted in the urine unchanged; however, in rats, about half of the dose is excreted in the urine as DMA and the other half as TMAO. During the metabolism of DMA to TMAO, DMA(III) is formed as a metabolic intermediate. The formation of this highly reactive intermediate and the excretion of small amounts of DMA(III) in urine may damage the urinary bladder.

There are limited data on the mode of action of DMA for most end points. Recently, there has been considerable research on the mode of action for the development of neoplastic urinary bladder tumors in rats. Although the mechanisms have not been fully elucidated, it has been proposed that the mode of action involves cytotoxicity leading to necrosis and subsequent regeneration of the urinary bladder urothelium. There is strong evidence to suggest that DMA(III) is the causative agent for the urothelial cytotoxicity. The strongest evidence comes from the finding that urinary concentrations of DMA(III) measured in rats exhibiting urothelial cytotoxicity are equivalent to DMA(III) concentrations that are cytotoxic to urothelial cells *in vitro*. Urothelial cytotoxicity, regenerative urothelial proliferation, and urothelial tumors have not been detected in other animal species. Other animal species, including

humans, only metabolize a small percentage of ingested DMA to TMAO; thus, much lower levels of DMA(III) are produced, suggesting that rats may be very sensitive to toxicity of DMA and therefore are not an appropriate model for human risk assessment.

Roxarsone. The available data on the toxicity of roxarsone suggest that following bolus administration, the gastrointestinal tract, kidney, and nervous system are sensitive end points of roxarsone toxicity. Vomiting and gastrointestinal hemorrhage were observed in dogs receiving a single capsulized dose of 50 mg/kg roxarone; no gastrointestinal effects were observed in rats or mice administered 4 or 42 mg/kg/day roxarsone for 2 years. Kidney effects included increases in kidney weight, minimal tubular epithelial cell degeneration, and focal mineralization in rats exposed to 32 mg roxarsone/kg/day for 13 weeks; no kidney effects were observed at 16 mg/kg/day or in mice exposed to doses as high as 136 mg/kg/day for 13 weeks or 43 mg/kg/day for 2 years. Hyperexcitability, ataxia, and/or trembling were observed in rats exposed to 20 mg/kg/day for 13 weeks or 64 mg/kg/day for 13 weeks. A 14-day study in rats reported slight inactivity in rats exposed to 32 mg/kg/day, but this was not observed in longer-term studies. Neurological effects were observed in mice exposed to doses as high as 136 mg/kg/day for 13 weeks or 43 mg/kg/day for 2 years, although a slight decrease in activity at 42 mg/kg/day was reported in a 14 day study. Pigs appear to be especially sensitive to the neurotoxicity of roxarsone. Muscle tremors have been observed at doses of ≥6.3 mg roxarsone/kg/day and myelin degeneration in the spinal cord was noted at 6.3 mg/kg/day. Both the clinical signs of neuropathy and the myelin degeneration followed a time-related pattern. Mild lethargy and ataxia were observed 7 days after exposure initiation, exercise-induced muscle tremors and clonic seizures were observed at day 11, paraparesis was observed at day 22, and paraplegia was observed at day 33. At day 11, equivocal lesions were observed in the cervical spinal cord, and the severity of these lesions increased with time; myelin degeneration was observed in the peripheral nerves and optic nerve starting at day 32 (2 days after exposure termination). Equivocal evidence of carcinogenicity (a slight increase in the incidence of pancreatic tumors) was found in male rats chronically exposed to roxarsone; no increases in neoplastic tumors were observed in female rats or male and female mice.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for arsenic. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive

health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990i), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inorganic Arsenicals

Inhalation MRLs. No inhalation MRLs were derived for inorganic arsenic. Human data suggest that dermal or respiratory effects may be the most prevalent (Lagerkvist et al. 1986; Mohamed 1998; Perry et al. 1948); respiratory or immunological effects appeared to be the most common following inhalation exposure to inorganic arsenic in animals (Aranyi et al. 1985; Holson et al. 1999). Adequate human studies evaluating dose-response relationships for noncancer end points were not located for inorganic arsenic, and animal data on the health effects of inorganic arsenic following inhalation exposure are limited to studies that did not evaluate a suitable range of health effects. Lacking suitable studies upon which to base the MRLs, no inhalation MRLs were derived for inorganic arsenic.

Oral MRLs

- An MRL of 0.005 mg As/kg/day has been derived for acute-duration (14 days or less) oral exposure to inorganic arsenic.

Mizuta et al. (1956) summarized findings from 220 poisoning cases associated with an episode of arsenic contamination of soy sauce in Japan. The soy sauce was contaminated with approximately 0.1 mg As/mL, probably as calcium arsenate. Arsenic intake in the cases was estimated by the researchers to be 3 mg/day (0.05 mg/kg/day, assuming 55 kg average body weight for this Asian population). The duration of exposure was 2–3 weeks in most cases. The primary symptoms were edema of the face, and gastrointestinal and upper respiratory symptoms initially, followed by skin lesions and neuropathy in

some patients. Other effects included mild anemia and leukopenia, mild degenerative liver lesions and hepatic dysfunction, abnormal electrocardiogram, and ocular lesions. For derivation of the acute oral MRL, facial edema and gastrointestinal symptoms (nausea, vomiting, diarrhea), which were characteristic of the initial poisoning and then subsided, were considered to be the critical effects. The MRL of 0.005 mg As/kg/day was calculated by applying an uncertainty factor of 10 (10 for use of a lowest-observed-adverse-effect level (LOAEL) and 1 for human variability) to the LOAEL of 0.05 mg As/kg/day (see Appendix A for MRL worksheets).

An intermediate-duration oral MRL for inorganic arsenic was not derived due to inadequacy of the database. The lowest LOAEL identified in a limited number of intermediate-duration human studies available was 0.05 mg As/kg/day in a study by Mizuta et al. (1956) (summarized above). While this study was considered appropriate to derive an acute-duration oral MRL for inorganic arsenic, there is considerable uncertainty regarding what the effects and severity might be beyond the relatively short 2–3 weeks of exposure that most subjects experienced. There are numerous studies in animals dosed for intermediate durations, but as indicated in Section 3.5.3, animals are not appropriate models for effects of inorganic arsenic in humans.

- An MRL of 0.0003 mg As/kg/day has been derived for chronic-duration (365 days or more) oral exposure to inorganic arsenic.

Tseng et al. (1968) and Tseng (1977) investigated the incidence of Blackfoot Disease and dermal lesions (hyperkeratosis and hyperpigmentation) in a large number of poor farmers (both male and female) exposed to high levels of arsenic in well water in Taiwan. A control group consisting of 17,000 people, including one group in which arsenic exposure was “undetermined” and which included those villages where arsenic-contaminated wells were no longer used or the level could not be classified, and a control population of 7,500 people who consumed water from wells almost free of arsenic (0.001–0.017 ppm) was also examined. The authors stated that the incidence of dermal lesions increased with dose, but individual doses were not provided. However, incidence data were provided based on stratification of the exposed population into low (<300 μg/L), medium (300–600 μg/L), or high (>600 μg/L) exposure levels. Doses were calculated from group mean arsenic concentrations in well water, assuming the intake parameters described by IRIS (IRIS 2007). Accordingly, the control, low-, medium-, and high-exposure levels correspond to doses of 0.0008, 0.014, 0.038, and 0.065 mg As/kg/day, respectively. The no-observed-adverse-effect level (NOAEL) identified by Tseng (1977) (0.0008 mg As/kg/day) was limited by the fact that the majority of the population was <20 years of age and the incidence of skin lesions increased as a function of age, and because the estimates of water intake and dietary arsenic intake are

highly uncertain. Schoof et al. (1998) estimated that dietary intakes of arsenic from rice and yams may have been 15–211 μg/day (mean=61 μg/day), based on arsenic analyses of foods collected in Taiwan in 1993–1995. Use of the 50 μg/day estimate would result in an approximate doubling of the NOAEL (0.0016 mg/kg/day) (see Appendix A for MRL worksheets). The MRL was derived by applying an uncertainty factor of 3 (for human variability) to the NOAEL of 0.0008 mg/kg/day.

The MRL is supported by a large number of well-conducted epidemiological studies that identify reliable NOAELs and LOAELs for dermal effects. EPA (1981b) identified a NOAEL of 0.006–0.007 mg As/kg/day for dermal lesions in several small populations in Utah. Harrington et al. (1978) identified a NOAEL of 0.003 mg As/kg/day for dermal effects in a small population in Alaska. Guha Mazumder et al. (1988) identified a NOAEL of 0.009 mg As/kg/day and a LOAEL of 0.006 mg As/kg/day for pigmentation changes and hyperkeratosis in a small population in India. Haque et al. (2003) identified a LOAEL of 0.002 mg As/kg/day for hyperpigmentation and hyperkeratosis in a case-control study in India. Cebrián et al. (1983) identified a NOAEL of 0.0004 mg As/kg/day and a LOAEL of 0.022 mg As/kg/day in two regions in Mexico. Borgoño and Greiber (1972) and Zaldívar (1974) identified a LOAEL of 0.02 mg As/kg/day for abnormal skin pigmentation in patients in Chile, and Borgoño et al. (1980) identified a LOAEL of 0.01 mg As/kg/day for the same effect in school children in Chile. Valentine et al. (1985) reported a NOAEL of 0.02 mg As/kg/day for dermal effects in several small populations in California. Collectively, these studies indicate that the threshold dose for hyperpigmentation and hyperkeratosis is approximately 0.002 mg As/kg/day. While many of these studies also identified effects on other end points at these exposure levels, including effects on gastrointestinal (Borgoño and Greiber 1972; Cebrián et al. 1983; Guha Mazumder et al. 1988; Zaldívar 1974), cardiovascular (Tseng et al. 1995, 1996), hepatic (Hernández-Zavala et al. 1998), and neurological end points (Guha Mazumder et al. 1988; Lianfang and Jianzhong 1994; Tsai et al. 2003), the overall database for dermal effects is considerably stronger than for effects on other end points.

Organic Arsenicals

Inhalation MRLs. No inhalation MRLs were derived for organic arsenic. Human data are limited to an occupational exposure study of workers exposed to 0.065 mg/m^3 ansanilic acid (Watrous and McCaughey 1945). The exposed workers more frequently complained of keratosis than nonexposed workers. A limited number of animal studies have examined the toxicity of organic arsenicals following inhalation exposure. Respiratory distress and diarrhea were observed in rats and mice exposed to high concentrations of MMA and DMA (Stevens et al. 1979); at lower concentrations (1,540–3,150 mg DMA/m^3), respiratory irritation, as evidenced by a decrease in respiration rate, was observed in animals

exposed to MMA or DMA (Stevens et al. 1979). The acute-duration studies do not clearly identify the most sensitive targets of inorganic arsenical toxicity; the available studies are of limited scope and none included a comprehensive histological examination.

One study examined the toxicity of DMA in rats following intermediate-duration exposure. This study (Whitman 1994) found an increase in intracytoplasmic eosinophilic globules in the nasal turbinates of rats exposed to 34 or 100 mg/m^3 DMA 6 hours/day, 5 days/week for 67–68 exposures; no other adverse effects were observed in this comprehensive study. As discussed in greater detail in the oral MRL section, the toxicokinetic properties of DMA in rats differ from other species and rats do not appear to be a good model for human exposure. The half-time of DMA in the body is much longer in rats compared to other species, including humans, and DMA is more extensively methylated in rats. In the absence of data to determine whether the observed effect is due to a direct interaction of DMA, derivation of an intermediate-duration MRL using rat data is not recommended at this time.

No studies examined the chronic toxicity of organic arsenicals precluding the derivation of a chronic-duration inhalation MRL.

Oral MRLs

MMA. A limited number of animal studies have examined the acute oral toxicity of MMA. These studies consisted of LD_{50} studies in rats (Gur and Nyska 1990), mice (Kaise et al. 1989), and rabbits (Jaghabir et al. 1988) and developmental toxicity studies in rats (Irvine et al. 2006) and rabbits (Irvine et al. 2006); all studies administered MMA via gavage. Adverse effects reported in the LD_{50} studies included diarrhea in rats at 2,030 mg monosodium methane arsonate (MSMA)/kg (Gur and Nyska 1990), mice at 2,200 mg MMA/kg (Kaise et al. 1989) and rabbits at 60 mg MSMA/kg (Jaghabir et al. 1988) and respiratory arrest in mice at 1,800 mg MMA/kg/day (Kaise et al. 1989). These doses were at or near the LD_{50} levels of 2,449 mg MSMA/kg, 1,800 mg MMA/kg, 100 mg MSMA/kg for the rats, mice, and rabbits, respectively. In the developmental toxicity studies (Irvine et al. 2006), maternal effects included decreases in maternal body weight gain in rats (17% less than controls) and rabbits (70% less than controls) receiving gavage doses of 100 and 12 mg MMA/kg/day, respectively, and loose feces/diarrhea in rabbit does administered 12 mg MMA/kg/day. The NOAELs for maternal effects were 10 and 7 mg MMA/kg/day in the rats and rabbits, respectively. Minor developmental effects (decreased fetal weight, incomplete ossification, and supernumerary ribs) were also observed at the maternally toxic doses in the rats and rabbits (Irvine et al. 2006); these effects were probably secondary to the maternal stress. These

data, coupled with the results of longer-term studies (Arnold et al. 2003; Waner and Nyska 1988), suggest that the gastrointestinal tract is a sensitive target of MMA toxicity. The rabbit developmental toxicity study (Irvine et al. 2006) identified the lowest LOAEL (12 mg MMA/kg/day) for gastrointestinal irritation. However, this study is not suitable for the derivation of an acute-duration oral MRL for MMA because the MMA was administered via bolus doses. It is likely that the observed gastrointestinal effect is a concentration-dependent effect; thus, at a given dose level, effects are more likely to occur following bolus administration. A marked decrease in body weight gain was also observed at this dose level.

- An MRL of 0.1 mg MMA/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to MMA.

Three studies have examined the intermediate-duration toxicity of MMA; two of these are chronic-duration studies reporting diarrhea and decreases in body weight gain after MMA exposure for <1 year. Diarrhea was observed in rats exposed to 30.2 mg MMA/kg/day in the diet (Arnold et al. 2003) and in dogs exposed via a capsule to 2 mg MMA/kg/day (Waner and Nyska 1988). Decreases in body weight were observed at the next highest doses, 106.9 mg MMA/kg/day in rats and 8 mg MMA/kg/day in dogs. In the rat study (Arnold et al. 2003), diarrhea was observed in 16.7 and 40% of the males and females, respectively, exposed to 30.2/35.9 mg MMA/kg/day during the first 52 weeks of the study; diarrhea first occurred after 4 weeks of exposure. At the highest dose level (106.9 mg MMA/kg/day), diarrhea was observed in all exposed male and female rats. In dogs, the increased incidence of diarrhea first occurred during weeks 25–28; at the highest dose tested in the study (35 mg MMA/kg/day), vomiting was also observed. A NOAEL of 3.5 mg MMA/kg/day was identified in the rat study; a NOAEL was not identified in the dog study. The remaining study in the intermediate-duration database is a 2-generation study that reported reproductive (decreased pregnancy rate and male fertility index in F_0 and F_1 generations) and developmental (decreased pup survival in F_1 and F_2 generation) effects in rats exposed to 76 mg MMA/kg/day in the diet (Schroeder 1994). The lowest LOAEL identified in the intermediate-duration database is 2 mg MMA/kg/day for diarrhea in dogs (Waner and Nyska 1988). Although dogs appear to be more sensitive to the gastrointestinal effects of MMA, a direct comparison of the two studies is not possible due to the difference in the routes of exposure. It is possible that the bolus administration of MMA, in the form of a capsule, resulted in increased sensitivity of the dogs. Because the most likely route of exposure for humans would be ingestion and the critical effect appears to be irritation of the gastrointestinal tract, studies involving bolus administration (gavage or capsule) were not considered for derivation of oral MRLs. The Arnold et al. (2003) and Schroeder (1994) studies were considered as the basis for an intermediate-duration MRL. Of these two studies, Arnold et al. (2003) identified the lowest

LOAEL, 30.2 mg MMA/kg/day, for gastrointestinal effects and was selected as the principal study for the intermediate-duration oral MRL.

Arnold et al. (2003) exposed groups of 60 male and 60 female Fischer 344 rats to 0, 50, 400, or 1,300 ppm MMA in the diet for 104 weeks. Using the average doses for weeks 1–50 reported in an unpublished version of this study (Crown et al. 1990), doses of 0, 3.5, 30.2, and 106.9 mg MMA/kg/day and 0, 4.2, 35.9, and 123.3 mg MMA/kg/day were calculated for males and females, respectively. Body weights, food consumption, and water intake were monitored regularly. Blood was taken at 3, 6, and 12 months for clinical chemistry measurements, and urine samples were collected at the same interval. Mortality was increased in high-dose males and females during the first 52 weeks of the study. Body weights were decreased in the mid- and high-dose groups of both sexes; however, at 51 weeks, only the body weight for the high-dose males was <10% of the control weight (14.5%). Food and water consumption was increased in the mid- and high-dose groups. Diarrhea was observed in 100% of the high-dose males and females and in 16.7 and 40% of the mid-dose males and females during the first 52 weeks of exposure. Diarrhea first occurred after 3 weeks of exposure to the high dose and 4 weeks of exposure to the mid-dose group; the severity of the diarrhea was dose-related. The gastrointestinal system was the primary target in animals dying early; numerous macroscopic and histological alterations were observed.

A benchmark dose (BMD) analysis of the incidence data for diarrhea was conducted; details of this analysis are presented in Appendix A. Using the female incidence data, a BMD (BMD_{10}) of 16.17 mg MMA/kg/day, which corresponds to a 10% increase in the incidence of diarrhea, was calculated; the 95% lower confidence limit on the BMD ($BMDL_{10}$) was 12.38 mg MMA/kg/day. The female incidence data were selected over the male data because the females may be more sensitive than the males. Thus, the intermediate-duration oral MRL of 0.1 mg MMA/kg/day is based on the $BMDL_{10}$ of 12.38 mg MMA/kg/day in female rats and an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability).

- An MRL of 0.01 mg MMA/kg/day has been derived for chronic-duration (365 days or longer) oral exposure to MMA.

The available data on the chronic toxicity of MMA in animals (no human data are available) suggest that the gastrointestinal tract and the kidney are the most sensitive targets. Diarrhea has been observed in rats and mice exposed to MMA in the diet for 2 years (Arnold et al. 2003). The NOAEL and LOAEL values for diarrhea are 3.0 and 25.7 mg MMA/kg/day in rats, respectively, and 24.9 and 67.1 mg MMA/kg/day

in mice, respectively. At 72.4 mg MMA/kg/day, necrotic, ulcerated, or perforated mucosa and metaplasia were observed in the cecum, colon, and rectum of rats. Squamous metaplasia was also observed in the cecum, colon, and rectum of mice exposed to 67.1 mg MMA/kg/day. Diarrhea was observed in dogs exposed via capsule to 2 mg MMA/kg/day for 52 weeks (Waner and Nyska 1988). The bolus administration used in the dog study probably increased the dog's sensitivity to MMA. In both the rats and mice, chronic administration of MMA resulted in an exacerbation of chronic progressive nephropathy. In female rats, significant increases in the severity of chronic progressive nephropathy were observed at 33.9 and 98.5 mg MMA/kg/day; the NOAEL was 3.9 mg MMA/kg/day (Arnold et al. 2003). In male mice, there was an increased incidence of slight progressive nephropathy at doses ≥6.0 mg MMA/kg/day; the NOAEL was 1.2 mg MMA/kg/day (Arnold et al. 2003; incidence data reported in Gur et al. 1991). Nephrocalcinosis was also observed in male mice exposed to ≥24.9 mg MMA/kg/day (Arnold et al. 2003). Other effects that have been observed following chronic exposure MMA include decreased weight gain in male and female rats exposed to 25.7/33.9 mg MMA/kg/day and higher (Arnold et al. 2003) and hypertrophy of the thyroid follicular epithelium in female rats exposed to ≥33.9 mg MMA/kg/day (Arnold et al. 2003). A variety of other lesions including peritonitis, pancreatitis, inflammation of the ureter, uterus, prostate, testes, epididymis, and seminal vesicles, hydronephrosis, pyelonephritis, and cortical tubular cystic dilation were also observed in rats; however, these alterations were probably secondary to the ulceration and perforation of the large intestine, which resulted in leaking of gastrointestinal contents into the abdominal cavity. Hyperplasia of the urinary bladder was also observed in rats exposed to 2.1 mg MMA/kg/day as MMA in drinking water for 2 years (Shen et al. 2003). Although hyperplasia of the urinary bladder is commonly observed in rats exposed to DMA, it was not observed in the Arnold et al. (2003) study at doses as high as 72.4 mg MMA/kg/day; thus, the significance of the results of the Shen et al. (2003) study is not known.

The lowest reliable LOAEL identified in the chronic oral MMA database was 6.0 mg MMA/kg/day for an increased incidence of progressive glomerulonephropathy in mice (Arnold et al. 2003). Although the investigators noted that the kidney lesions were consistent with the normal spectrum of spontaneous renal lesions and that there was no difference in character or severity of lesions between groups, ATSDR considers the dose-related increase in glomerulonephropathy to be treatment-related.

In the Arnold et al. (2003) study (incidence data reported in Gur et al. 1991), groups of 52 male and 52 female $B6C3F_1$ mice were exposed to 0, 10, 50, 200, or 400 ppm of MMA in the diet for 104 weeks. The average doses reported in Gur et al. (1991) were 0, 1.2, 6.0, 24.9, and 67.1 mg MMA/kg/day for males and 0, 1.4, 7.0, 31.2, and 101 mg MMA/kg/day for females. Body weights, food consumption, and

water intake were monitored regularly. Blood was taken at 3, 6, 12, 18, and 24 months for white cell counts. At sacrifice, complete necropsies were performed, including histological examination of at least 13 organs. No treatment-related increases in mortality were observed. Significant decreases in body weights were observed in males and females exposed to 67.1 or 101 mg MMA/kg/day, respectively; at week 104, the males and females weighed 17 and 23%, respectively, less than controls. Food consumption was increased in females exposed to 101 mg MMA/kg/day, and water consumption was increased in 67.1 mg MMA/kg/day males and 31.2 and 101 mg MMA/kg/day females. Loose and mucoid feces were noted in mice exposed to 67.1/101 mg MMA/kg/day. No changes were seen in white cell counts of either sex. Small decreases in the weights of heart, spleen, kidney, and liver weights were observed in some animals, but the decreases were not statistically significant. Squamous metaplasia of the cecum, colon, and rectum was observed at 67.1/101 mg MMA/kg/day. The incidence of metaplasia in the cecum, colon, and rectum were 29/49, 14/49, and 39/49 in males and 38/52, 17/52, and 42/52 in females; metaplasia was not observed in other groups of male or female mice. An increased incidence of progressive glomerulonephropathy (incidence of 25/52, 27/52, 38/52, 39/52, and 46/52 in the 0, 1.2, 6.0, 24.9, and 67.1 mg MMA/kg/day males, respectively) was observed in males; the incidence was significantly higher (Fisher Exact Test) than controls at ≥6.0 mg MMA/kg/day. Significant increases in the incidence of nephrocalcinosis was observed in the males at 24.9 and 67.1 mg MMA/kg/day (Fisher Exact Test) (incidences of 25/52, 30/52, 30/52, 45/52, and 45/51 in males and 0/52, 1/52, 1/52, 2/52, and 5/52 in females). A reduction in the incidence of cortical focal hyperplasia in the adrenal gland of male mice exposed to 67.1 mg MMA/kg/day was possibly related to MMA exposure; the toxicological significance of this effect is not known. Thus, this study identifies a NOAEL of 1.2 mg MMA/kg/day and a LOAEL of 6.0 mg MMA/kg/day for progressive glomerulonephropathy in male mice.

As described in greater detail in Appendix A, BMD was applied to the incidence data for progressive glomerulonephropathy in male mice using all available dichotomous models in EPA's Benchmark Dose Software (version 1.4.1) to calculate predicted doses associated with a 10% extra risk. As assessed by the Akaike's Information Criteria (AIC), the log-logistic model provided the best fit to the data. The predicted BMD_{10} and $BMDL_{10}$ are 2.09 and 1.09 mg MMA/kg/day. The $BMDL_{10}$ was selected as the point of departure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive a chronic-duration oral MRL of 0.01 mg MMA/kg/day.

DMA. As discussed in greater detail in Section 2.2, urinary bladder effects characterized by cytotoxicity and regenerative proliferation and hyperplase have been observed in rats, but not in other species. The LOAELs for these effects are lower than the LOAELs for sensitive effects in other species. Additionally,

rats have a much greater capacity than other species to metabolize ingested DMA to form DMA(III) (a reactive intermediate) and TMAO (Cohen et al. 2006; Marafante et al. 1987b; Yoshida et al. 1998). It is likely that DMA(III) is the causative agent for the urothelial cytoxicity observed in rats (Cohen et al. 2006). Thus, rats were not considered a suitable model for humans and these data were not considered for derivation of MRLs for DMA.

There are limited data to assess the acute toxicity of DMA in species other than rats. Diarrhea, increased startle reflex, and ataxia were observed in mice exposed to a lethal gavage dose of 1,757 mg DMA/kg (Kaise et al. 1989); vomiting and diarrhea were also observed during the second week of a 52-week study in dogs exposed via capsule to 16 mg DMA/kg/day (Zomber et al. 1989). The remaining studies in the acute database are developmental toxicity studies in mice and rabbits. Rabbits appear to be more sensitive than mice to maternal and developmental effects. Gavage exposure to 48 mg DMA/kg/day on gestational days 7–19 resulted in maternal weight loss and abortion in approximately 75% of the does; no adverse effects were observed at 12 mg DMA/kg/day (Irvine et al. 2006). In mice, decreases in maternal body weight gain were observed at gavage doses of 200 mg DMA/kg/day on gestational days 7–16 (Rogers et al. 1981), decreases in fetal body weight, delays in ossification, and increased incidence of cleft palate were observed at 400 mg DMA/kg/day on gestational days 7–16 (Rogers et al. 1981) and fetal deaths, decreases in growth, and increased incidence of malformations were observed in mice administered 1,600 mg DMA/kg on gestational day 8 (Kavlock et al. 1985). The acute-duration database for DMA was not considered adequate for derivation of an oral MRL. The database is lacking a comprehensive toxicity study, which would be useful in establishing the critical target of toxicity. In a chronic-duration study in mice (Arnold et al. 2006), vacuolization was observed in the urinary bladder at ≥7.8 mg DMA/kg/day; it is not known if these effects would also be observed after acute-duration exposure. Thus, it is not known if systemic effects would occur at lower doses than the maternal developmental effects observed in rabbits exposed to 48 mg DMA/kg/day (Irvine et al. 2006); an acute-duration oral MRL for DMA is not recommended at this time.

Excluding rat studies, the database on the toxicity of DMA following intermediate-duration oral exposure is limited to a chronic study of dogs exposed to DMA via capsule 6 days/week for 52 weeks (Zomber et al. 1989). Diarrhea and vomiting were observed at 16 and 40 mg DMA/kg/day starting after the first week of exposure. A slight decrease in erythrocyte levels and increase in total leukocyte levels were observed in males exposed to 40 mg DMA/kg/day for 51 weeks. This dog study was not selected as the basis of an MRL because it is likely that bolus administration of DMA would increase sensitivity to the gastrointestinal effects.

- An MRL of 0.02 mg DMA/kg/day has been derived for chronic-duration (365 days or longer) oral exposure to DMA.

Two studies investigated the chronic-duration toxicity of DMA in a species other than rats. In dogs, diarrhea and vomiting were observed after 52 weeks of exposure to 16 or 40 mg As/kg/day (Zomber et al. 1989); no histological alterations were observed. In mice exposed to DMA in the diet for 2 years, vacuolization of the urothelium in the urinary bladder was observed at ≥7.8 mg DMA/kg/day and progressive glomerulonephropathy was observed at ≥37 mg DMA/kg/day (Arnold et al. 2006). As noted in Section 2.2, the vacuolization was not associated with cytotoxicity or proliferation. Because the bladder effects in mice occurred at the lowest adverse effect level for the database, it was selected as the critical effect and Arnold et al. (2006) was selected as the principal study.

In the Arnold et al. (2006) study, groups of 56 male and 56 female B6C3F_1 mice were exposed to 0, 8, 40, 200, or 500 ppm DMA in the diet for 2 years; the results of this study were also reported in an unpublished paper (Gur et al. 1989b) submitted to EPA under Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The investigators reported dietary doses of approximately 0, 1.3, 7.8, 37, and 94 mg DMA/kg/day. The following parameters were used to assess toxicity: clinical observations, body weight, food consumption, water consumption, differential leukocyte levels measured at 12, 18, and 24 months in mice in the control and 94 mg DMA/kg/day groups, organ weights (brain, kidneys, liver, and testes), and histopathological examination of major tissues and organs. No deaths or treatment-related clinical signs were observed. Decreases in body weight gain were observed in the male mice exposed to 94 mg DMA/kg/day; the difference was <10% and not considered adverse. An increase in water consumption was observed in males exposed to 94 mg DMA/kg/day during weeks 60–96. In the female mice exposed to 51 mg As/kg/day, a statistically significant decrease in lymphocytes and an increase in monocytes were observed at 24 months. Treatment related nonneoplastic alterations were observed in the urinary bladder and kidneys. In the urinary bladder, increases in the vacuolization of the superficial cells of the urothelium were observed in males exposed to 37 or 94 mg DMA/kg/day (0/44, 1/50, 0/50, 36/45, 48/48) and in females exposed to 7.8, 37, and 94 mg DMA/kg/day (1/45, 1/48, 26/43, 47/47, 43/43); incidence data reported in Gur et al. (1989b). An increased incidence of progressive glomerulonephropathy was observed in males at 37 mg DMA/kg/day (16/44, 22/50, 17/50, 34/45, 30/50) and an increased incidence of nephrocalcinosis was also observed in male mice at 94 mg DMA/kg/day (30/44, 25/50, 27/50, 29/50, 45/50). Neoplastic alterations were limited to an increased incidence of fibrosarcoma of the skin in females exposed to 94 mg DMA/kg/day (the incidence of 3/56, 0/55, 1/56,

1/56, and 6/56 in the 0, 1.3, 7.8, 37, and 94 mg DMA/kg/day groups, respectively); however, it was concluded that this lesion was not related to DMA exposure.

As described in detail in Appendix A, BMD analysis was applied to the incidence data for vacuolization of the urothelium in the urinary bladder of female mice using all available dichotomous models in EPA's Benchmark Dose Software (version 1.4.1) to calculate predicted doses associated with a 10% extra risk. As assessed by the AIC, the multi-stage model provided the best fit to the data. The predicted BMD_{10} and $BMDL_{10}$ are 2.68 and 1.80 mg DMA/kg/day. The $BMDL_{10}$ was selected as the point of departure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive a chronic-duration oral MRL of 0.02 mg DMA/kg/day.

Roxarsone. A series of three National Toxicology Program (NTP) studies in rats and mice (NTP 1989b) and a study in dogs (Kerr et al. 1963) have examined the acute toxicity of roxarsone; adverse effects have also been reported within the first 2 weeks of a longer-term study in pigs (Rice et al. 1985; Kennedy et al. 1986). A single exposure study reported diarrhea and ataxia in rats and mice exposed to doses that exceeded the LD_{50} (NTP 1989b). In another study, no alterations in hematological parameters (only end point assessed) were found after 10 or 9 days of dietary exposure in rats and mice, respectively (NTP 1989b). In a 14-day study (NTP 1989b), a decrease in body weight gain and slight inactivity were observed in rats exposed to 32 mg roxarsone/kg/day and slight inactivity was observed in mice exposed to 42 mg roxarsone/kg/day; a decrease in body weight gain was also observed in mice exposed to 168 mg roxarsone/kg/day. The dog study was considered inadequate because a small number (n=3) of animals were tested and no control group was used. In a 30-day dietary exposure study in pigs (Rice et al. 1985; Kennedy et al. 1986), mild lethargy and ataxia were observed from day 7 forward and exercise-induced muscle tremors and clonic seizures were observed from day 11 forward in pigs exposed to 6.3 mg roxarsone/kg/day; equivocal evidence of myelin degeneration was also observed in pigs sacrificed after 11 days of exposure. These data clearly identify pigs as the most sensitive species following acute-duration oral exposure; in the absence of data to the contrary, it is assumed that pigs are a good model to predict the toxic potential of roxarsone in humans. Because the lowest dose tested in pigs was a serious LOAEL for neurotoxicity and a NOAEL for this effect was not identified, an acute-duration oral MRL cannot be derived for roxarsone.

As with the acute-duration database, pigs appear to be the most sensitive species; neurotoxicity has been observed at ≥6.3 mg roxarsone/kg/day. In a study reported by Rice et al. (1985) and Kennedy et al. (1986), exercise-induced muscle tremors and clonic convulsions were observed in pigs during the early

part of the study; when the pigs returned to a recumbent position, the seizures and tremors stopped. Paraparesis, evidenced by reluctance to rise and the pigs dragging their hindquarters on the ground, was observed at day 22; paraplegia was observed 2 days after exposure termination. In addition to these clinical signs of neuropathy, histological alterations consisting of myelin degeneration was observed in the spinal cord, peripheral nerves, and optic nerve. The lesions were first detected in the spinal cord on day 15 and in the peripheral nerves and optic nerve 2 days after exposure termination. The Rice et al. (1985) and Kennedy et al. (1986) studies did not identify a NOAEL. Muscle tremors were also observed in pigs exposed to 10 mg roxarsone/kg/day for 28 days (Edmonds and Baker 1986). This study was not designed to assess neurotoxicity and did not include histological examination of the spinal cord or nerves. Trembling, ataxia, and hyperexcitability were also observed in rats exposed to 64 mg roxarsone/kg/day for 13 weeks (NTP 1989b). Other effects that have been observed include tubular degeneration and focal regenerative hyperplasia in the kidney and decreased body weight in rats exposed to 32 mg roxarsone/kg/day for 13 weeks (NTP 1989b) and decreased body weight in mice at 136 mg roxarsone/kg/day for 13 weeks (NTP 1989b). The lowest identified adverse effect level is 6.3 mg roxarsone/kg/day for serious neurological effects in pigs (Kennedy et al. 1986; Rice et al. 1985) and is not suitable for the derivation of an intermediate-duration oral MRL.

The chronic toxicity of roxarsone has been examined in rats (NTP 1989b; Prier et al. 1963), mice (NTP 1989b; Prier et al. 1963), and dogs (Prier et al. 1963) in 2-year dietary exposure studies. None of these studies reported adverse effects at the highest doses tested; the highest NOAELs for each species are 10, 43, and 5 mg roxarsone/kg/day for rats, mice, and dogs, respectively. The results from shorter duration studies suggest that pigs are more sensitive to the neurotoxic effects of roxarsone than rats, mice, or dogs. Because no chronic duration pig studies were identified and deriving an MRL using a potentially less sensitive species may not be protective of human health, a chronic-duration oral MRL is not recommended at this time.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of arsenic. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of arsenic are indicated in Tables 3-1 and 3-3 and Figures 3-1 and 3-3. Because cancer effects could occur at lower exposure levels, Figures 3-1 and 3-3 also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Chemical Forms of Concern. Analysis of the toxic effects of arsenic is complicated by the fact that arsenic can exist in several different oxidation states and many different inorganic and organic compounds. Most cases of human toxicity from arsenic have been associated with exposure to inorganic arsenic, so these compounds are the main focus of this profile.

The most common inorganic arsenical in air is arsenic trioxide (As_2O_3), while a variety of inorganic arsenates (AsO_4^{-3}) or arsenites (AsO_2^{-}) occur in water, soil, or food. A number of studies have noted differences in the relative toxicity of these compounds, with trivalent arsenites tending to be somewhat more toxic than pentavalent arsenates (Byron et al. 1967; Gaines 1960; Maitani et al. 1987a; Sardana et al. 1981; Willhite 1981). However, these distinctions have not been emphasized in this profile, for several reasons: (1) in most cases, the differences in the relative potency are reasonably small (about 2–3-fold), often within the bounds of uncertainty regarding NOAEL or LOAEL levels; (2) different forms of arsenic may be interconverted, both in the environment (see Section 6.3) and the body (see Section 3.4); and (3) in many cases of human exposure (especially those involving intake from water or soil, which are of greatest concern to residents near wastes sites), the precise chemical speciation is not known.

Gallium arsenide (GaAs) is another inorganic arsenic compound of potential human health concern, due to its widespread use in the microelectronics industry. Available toxicokinetic data suggest that although gallium arsenide is poorly soluble, it undergoes slow dissolution and oxidation to form gallium trioxide and arsenite (Webb et al. 1984, 1986). Therefore, the toxic effects of this compound are expected to be attributable to the arsenite that is liberated, plus the additional effects of the gallium species.

It is beyond the scope of this profile to provide detailed toxicity data on other less common inorganic arsenic compounds (e.g., As_2S_3), but these are expected to be of approximately equal or lesser toxicity than the oxycompounds, depending mainly on solubility (see Section 3.4).

Although organic arsenicals are usually viewed as being less toxic than the inorganics, several methyl and phenyl derivatives of arsenic that are widely used in agriculture are of possible human health concerns based on their toxicity in animal species (Arnold et al. 2003, 2006; NTP 1989b). Chief among these are monomethylarsonic acid (MMA) and its salts (monosodium methane arsonate [MSMA] and disodium methane arsonate [DSMA]), dimethylarsinic acid (DMA, also known as cacodylic acid) and its sodium salt (sodium dimethyl arsinite, or sodium cacodylate), and roxarsone (3-nitro-4-hydroxyphenylarsonic acid). However, it should be noted that food is the largest contributor to background intakes of organic arsenicals. Estimates on the concentration of organic arsenicals in the diet were not located; Cohen et al. (2006) estimated that the intake of DMA from food and water is <1 ng/kg/day. As with the inorganic compounds, there are toxicological differences between these various organic derivatives; because of these differences, the discussion of the health effects of MMA, DMA, and roxarsone are discussed separately. As discussed below, animals do not appear to be good quantitative models for inorganic arsenic toxicity in humans, but it is not known if this also applies to toxicity of organic arsenicals.

Several organic arsenicals are found to accumulate in fish and shellfish. These derivatives (mainly arsenobetaine and arsenocholine, also referred to as "fish arsenic") have been studied by several researchers and have been found to be essentially nontoxic (Brown et al. 1990; Cannon et al. 1983; Charbonneau et al. 1978; Kaise et al. 1985; Luten et al. 1982; Siewicki 1981; Tam et al. 1982; Yamauchi et al. 1986). Thus, these compounds are not considered further here.

Arsine (AsH_3) and its methyl derivatives, although highly toxic, are also not considered in this profile, since these compounds are either gases or volatile liquids that are unlikely to be present at levels of concern at hazardous waste sites.

Use of Animal Data. An additional complexity to the analysis of arsenic toxicity is that most laboratory animals appear to be substantially less susceptible to inorganic arsenic than humans. For example, chronic oral exposure of humans to inorganic arsenic at doses of 0.05–0.1 mg/kg/day is frequently associated with neurological (Barton et al. 1992; Goddard et al. 1992; Guha Mazumder et al. 1988; Haupert et al. 1996; Hindmarsh et al. 1977; Huang et al. 1985; Sass et al. 1993; Silver and Wainman 1952; Szuler et al. 1979; Tay and Seah 1975; Valentine et al. 1981) or hematological signs of arsenic toxicity (Glazener et al. 1968; Guha Mazumder et al. 1988; Prasad and Rossi 1995; Sass et al. 1993; Tay and Seah 1975), but no characteristic neurological or hematological signs of arsenism were detected in monkeys, dogs, or rats chronically exposed to arsenate or arsenite at doses of 0.7–2.8 mg As/kg/day (Byron et al. 1967; EPA 1980f; Heywood and Sortwell 1979). This may be because the studies were not conducted for a sufficient length of time, or because too few animals were used. Moreover, while there is good evidence that inorganic arsenic is carcinogenic in humans by both oral and inhalation routes, evidence of inorganic arsenic-induced carcinogenicity in animals is mostly negative, with the exception of studies in mice demonstrating transplacental carcinogenesis. For these reasons, quantitative dose-response data from animals are not judged to be reliable for determining levels of significant human exposure, and will be considered only briefly except when human data are lacking.

3.2.1 Inhalation Exposure

Most information on human inhalation exposure to arsenic derives from occupational settings such as smelters and chemical plants, where the predominant form of airborne arsenic is arsenic trioxide dust. One limitation to this type of study is that exposure data are usually difficult to obtain, especially from earlier time periods when exposure levels were higher than in recent years. This is further complicated by the fact that significant oral and dermal exposures are also likely to occur under these conditions and co exposure to other metals and chemicals is also common. Thus, studies of this type are, like virtually all epidemiological studies, subject to some limitations and uncertainties. Table 3-1 and Figure 3-1 summarize studies that provide the most reliable quantitative data on health effects in humans, along with several studies in animals exposed to arsenic trioxide and other inorganic arsenic compounds by the inhalation route. Data for DMA are shown in Table 3-2 and Figure 3-2. All exposure data are expressed as milligrams of arsenic (as the element) per cubic meter of air (mg As/m^3). These studies and others that provide useful qualitative information on health effects of inorganic and organic arsenicals are discussed below.

Table 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
ACUTE EXPOSURE										
Immuno/ Lymphoret										
1	Mouse (CD-1)	3 hr		0.123 F	0.271 F	(decreased pulmonary bactericidal activity and increased susceptibility to streptococcal infection)			Aranyi et al. 1985 As(+3)	
2	Mouse (CD-1)	5 d 3 hr/d		0.259 F	0.519 F	(decreased pulmonary bactericidal activity and increased susceptibility to streptococcal infection)			Aranyi et al. 1985 As(+3)	
Developmental										
3	Mouse (CFLP)	Gd 9-12 4 hr/d		0.2	2.2	(10% decreased average fetal body weight)	21.6	(increased fetal deaths, skeletal malformations, and retarded growth)	Nagymajtenyi et al. 1985 As(+3)	
INTERMEDIATE EXPOSURE										
Death										
4	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d					20 F	(5/10 dams died)	Holson et al. 1999 As(+3)	
Systemic										
5	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d	Resp	2 F	8 F	(rales, dried red material around nose)			Holson et al. 1999 As(+3)	
			Bd Wt	2 F	8 F	(decreased body weight gain during gestation)				

Table 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
6	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d	Resp	0.9 F	8 F (rales)	20 F (labored breathing, gasping)	Holson et al. 1999 As(+3)	
			Gastro	8 F		20 F (gross gastrointestinal lesions)		
			Bd Wt	8 F		20 F (drastic decrease body weight)		
Immuno/ Lymphoret								
7	Mouse (CD-1)	4 wk 5 d/wk 3 hr/d		0.126 F	0.245 F (decreased pulmonary bactericidal activity)		Aranyi et al. 1985 As(+3)	
Reproductive								
8	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d		8 F			Holson et al. 1999 As(+3)	
9	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d		20 F			Holson et al. 1999 As(+3)	
Developmental								
10	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d		8			Holson et al. 1999 As(+3)	

Table 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
11	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d		8			20	(marked increase in post-implantation loss and marked decrease in viable fetuses)	Holson et al. 1999 As(+3)	
CHRONIC EXPOSURE										
Systemic										
12	Human	23 yr (avg) (occup)	Cardio				0.36 M	(increased incidence of vasospasticity and clinical Raynaud's phenomenon)	Lagerkvist et al. 1986 As(+3)	
13	Human	0.5-50 yr (occup)	Resp	0.613					Perry et al. 1948 As(+3)	
			Dermal		0.078	(mild pigmentation keratosis of skin)	0.613	(gross pigmentation with hyperkeratinization of exposed areas, wart formation)		
Neurological										
14	Human	28 yr (avg) (occup)			0.31 M	(decreased nerve conduction velocity)			Lagerkvist and Zetterlund 1994 As(+3)	
Cancer										
15	Human	1- >30 yr (occup)					0.213 M	(CEL: lung cancer)	Enterline et al. 1987a As(+3)	
16	Human	19.5 yr (avg) (occup)					0.069 M	(CEL: lung cancer)	Enterline et al. 1987b As(+3)	

Table 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
17	Human	3 mo- >30 yr (occup)				0.2 M (CEL: lung cancer)	Jarup and Pershagen 1991 As(+3)	
18	Human	3 mo- >30 yr (occup)				0.05 M (CEL: lung cancer)	Jarup et al. 1989 As(+3)	
19	Human	1- >30 yr (occup)				0.38 M (CEL: lung cancer)	Lee-Feldstein 1986 As(+3)	
20	Human	>25 yr (occup)				0.29 M (CEL: lung cancer)	Lubin et al. 2000 As(+3)	
21	Human	14.8 yr (avg) (occup)				0.3 M (CEL: lung cancer)	Welch et al. 1982 As(+3)	

a The number corresponds to entries in Figure 3-1.

avg = average; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); F = female; Gastro = gastrointestinal; Gd = gestation day; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified; occup = occupational; pmd = pre-mating day; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation

Acute (≤14 days)

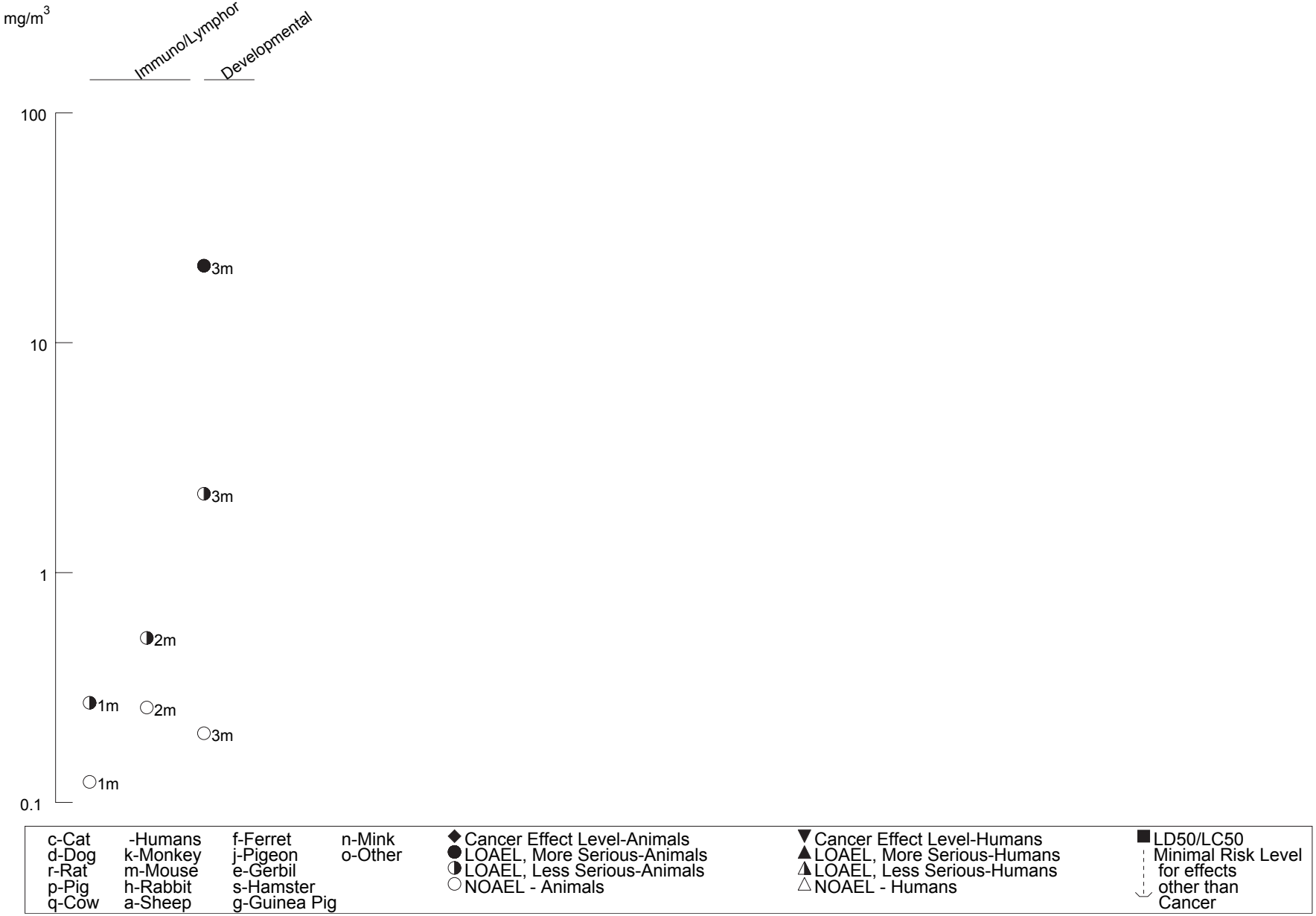


Figure 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation *(Continued)*

Intermediate (15-364 days)

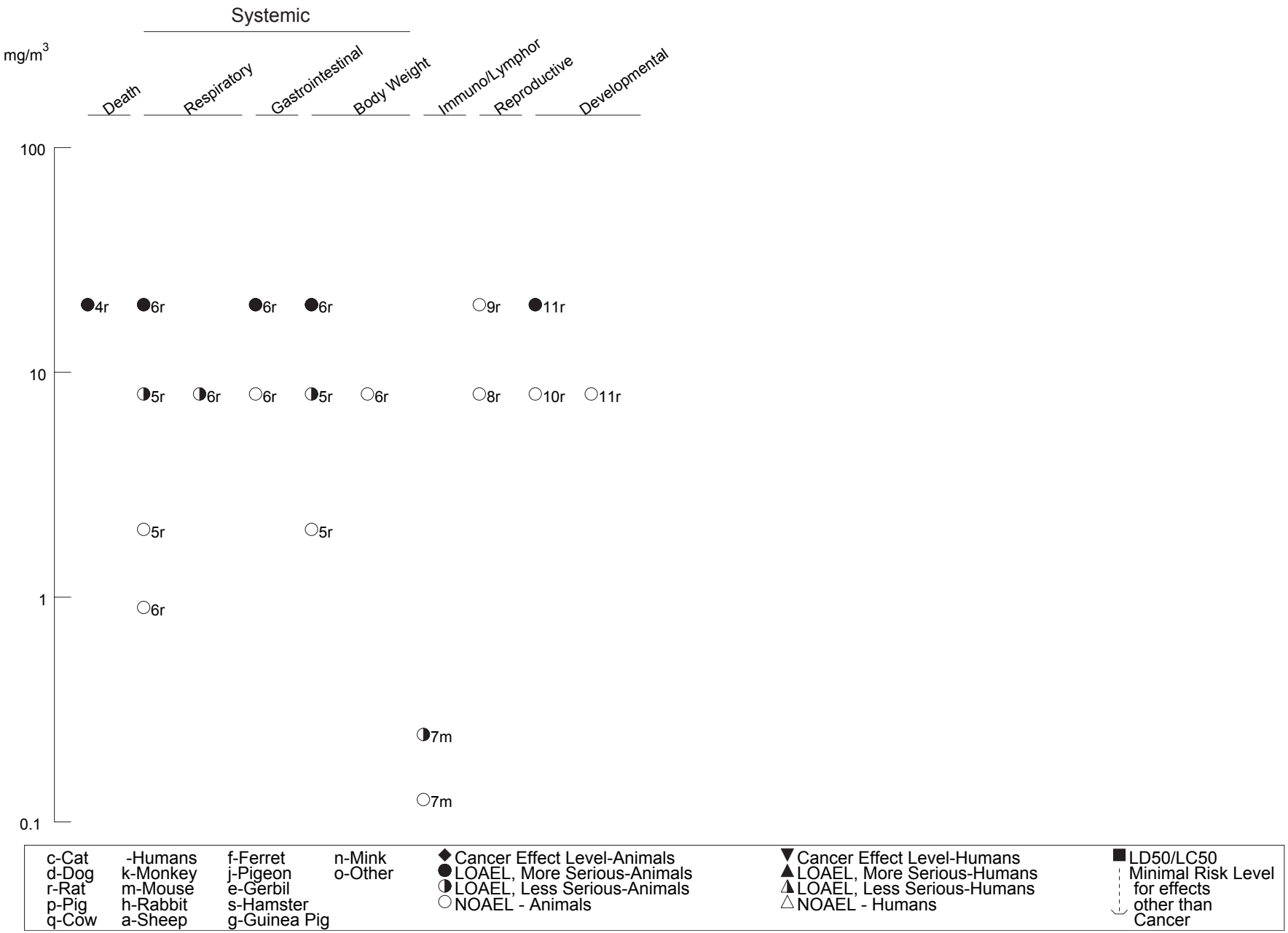


Figure 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation *(Continued)*

Chronic (≥365 days)

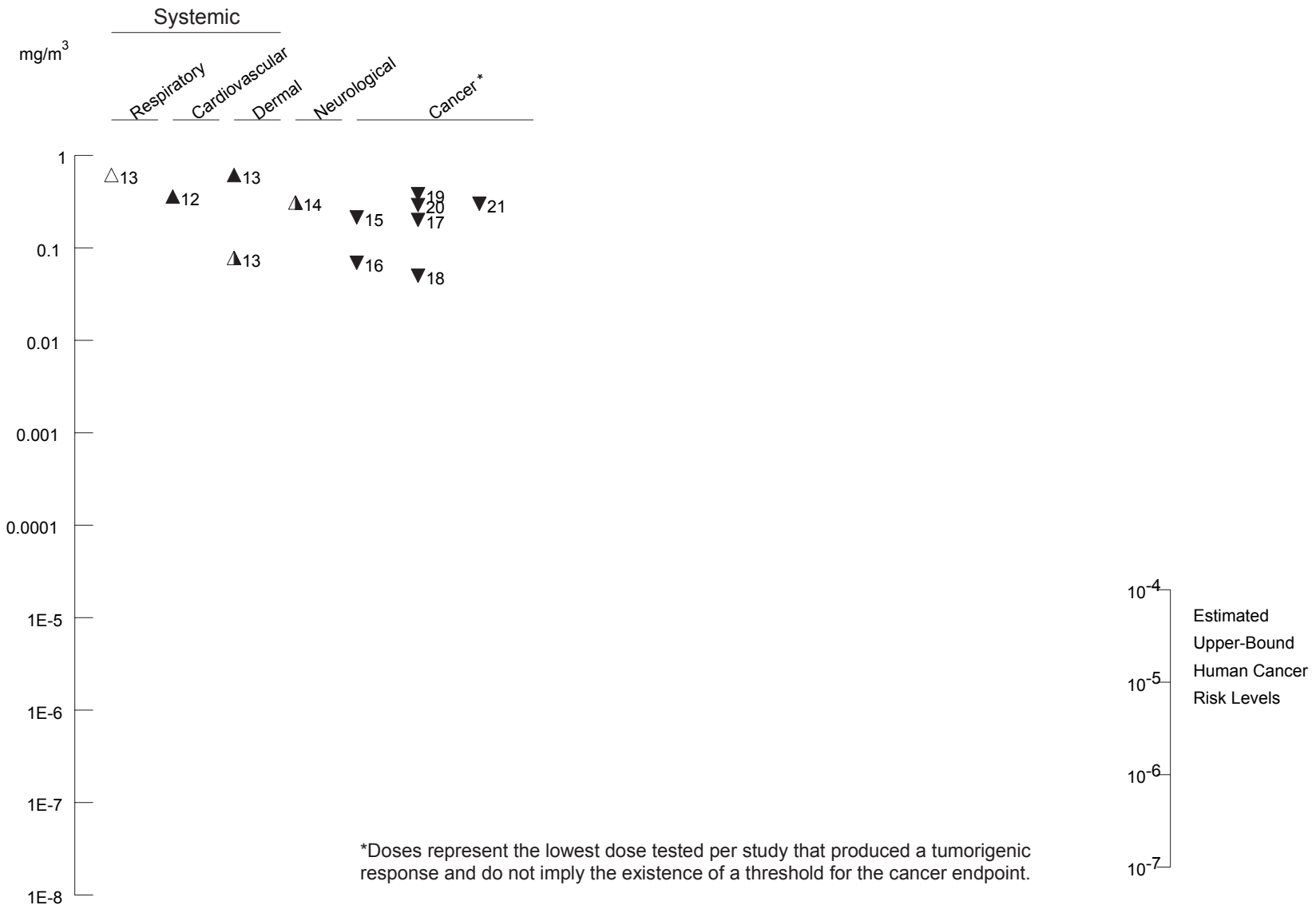


Table 3-2 Levels of Significant Exposure to Dimethylarsinic Acid - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sherman)	2 hr				3900 F (LC50)	Stevens et al. 1979 DMA	
Systemic								
2	Rat (Sherman)	2 hr	Resp			4000 (respiratory distress)	Stevens et al. 1979 DMA	
			Gastro		4000 (diarrhea)			
			Dermal	4100	6900 F (erythematous lesions of ears and feet)			
			Ocular		4000 (eye encrustation)			
			Bd Wt		4000 (unspecified decrease in body weight)			
3	Mouse (Swiss-Webster)	5 min	Resp		3150 M (RD50)		Stevens et al. 1979 DMA	
INTERMEDIATE EXPOSURE								
Systemic								
4	Rat (Sprague-Dawley)	6 hr/d 5 d/wk 67-68 exposures	Resp	10	34 (intracytoplasmic eosinophilic globules in nasal turbinates)		Whitman 1994 DMA	
			Cardio	100				
			Gastro	100				
			Hemato	100				
			Hepatic	100				
			Renal	100				
			Endocr	100				
			Dermal	100				

Table 3-2 Levels of Significant Exposure to Dimethylarsinic Acid - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m^3)	LOAEL			Reference Chemical Form	Comments
					Less Serious (mg/m^3)	Serious (mg/m^3)			
			Bd Wt	100					

a The number corresponds to entries in Figure 3-2.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); DMA = dimethylarsinic acid; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; RD50 = 50% decrease in respiration rate; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Dimethylarsinic Acid - Inhalation

Acute (≤14 days)

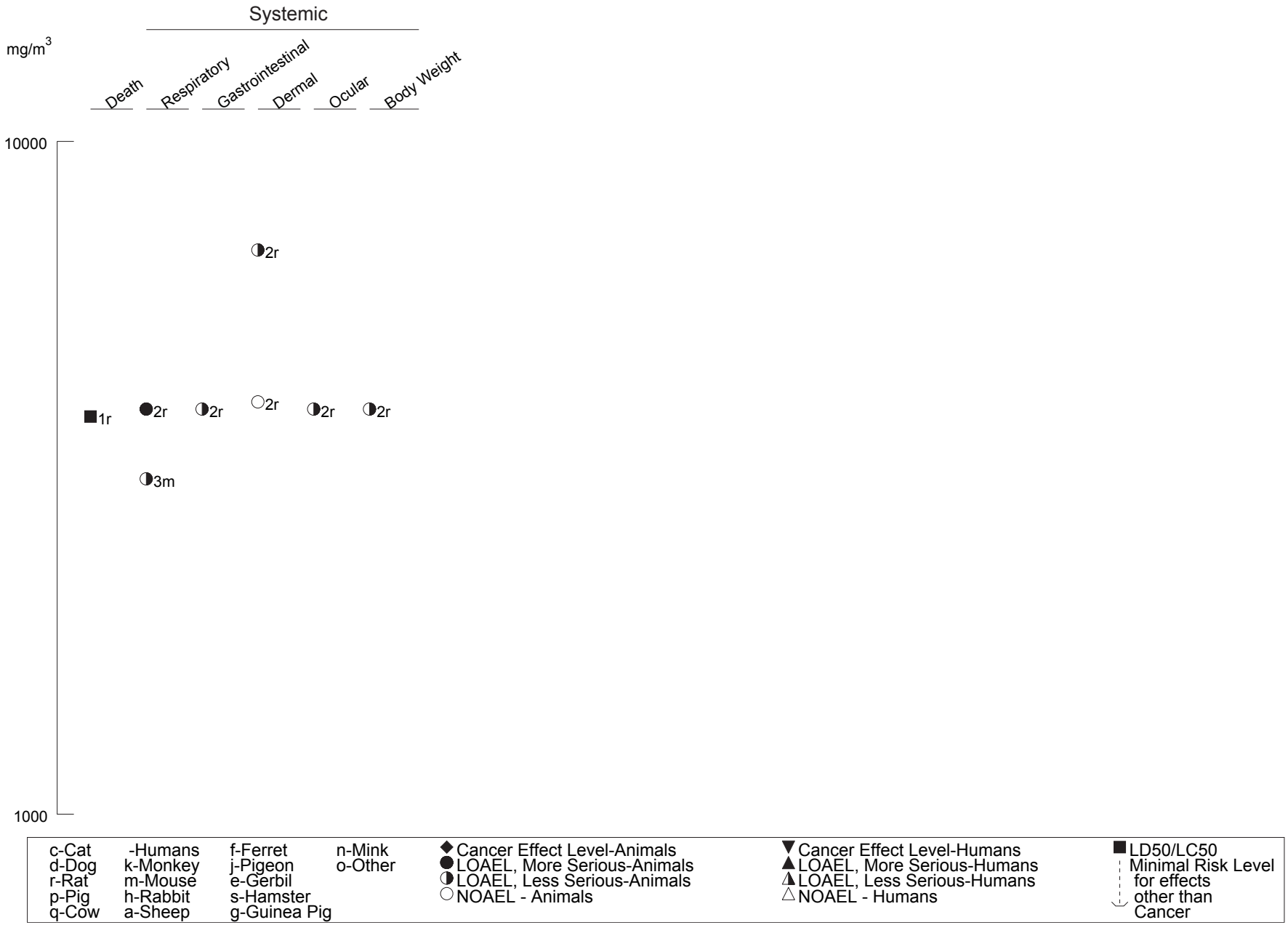
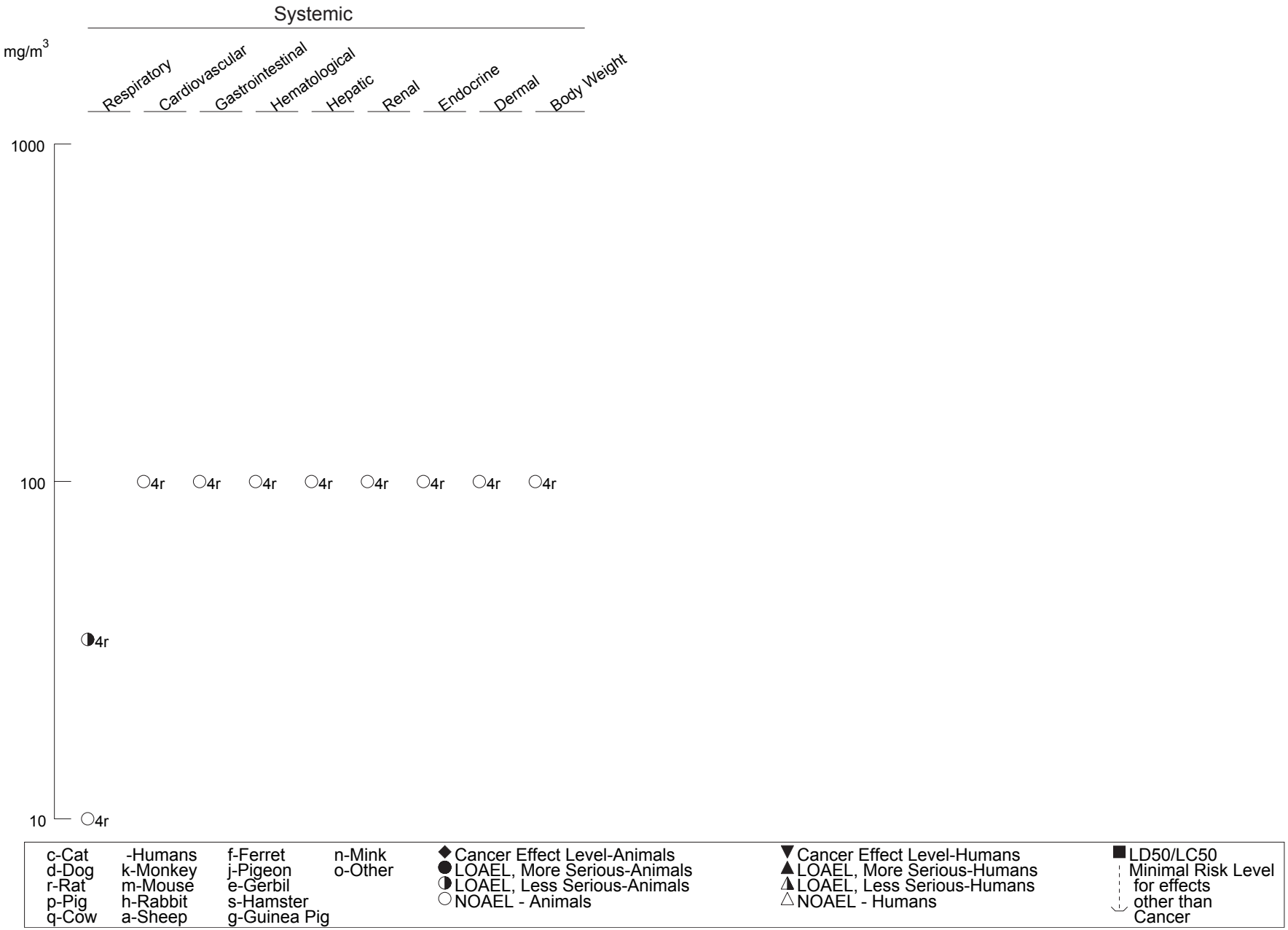


Figure 3-2 Levels of Significant Exposure to Dimethylarsinic Acid - Inhalation *(Continued)*

Intermediate (15-364 days)



3.2.1.1 Death

Inorganic Arsenicals. Although there are many studies of humans exposed to arsenic in air, no cases of lethality from short-term exposure were located. This suggests that death is not likely to be of concern following acute exposure, even at the very high exposure levels (1–100 mg As/m^3) found previously in the workplace (e.g., Enterline and Marsh 1982; Järup et al. 1989; Lee-Feldstein 1986). Delayed lethality from chronic exposure attributable to increased risk of cardiovascular disease or lung cancer is discussed below in Sections 3.2.1.2 and 3.2.1.7, respectively. The only report of a lethal effect of inhaled inorganic arsenic in animals was a developmental toxicology study in which four of nine pregnant rats died, and one rat was euthanized in extremis, between days 12 and 19 of gestation after 30–35 days of exposure to an aerosol of arsenic trioxide at an exposure concentration of 20 mg As/m^3 (Holson et al. 1999). These animals exhibited severe hyperemia and plasma discharge into the intestinal lumen at autopsy. In this same study, there was 100% mortality in groups of 10 pregnant rats after 1 day of exposure to concentrations ≥100 mg/m^3 (76 mg As/m^3).

Organic Arsenicals. No studies were located regarding death in humans after inhalation exposure to organic arsenicals. A 2-hour LC_{50} of 3,900 mg DMA/m^3 was calculated for DMA in female rats (Stevens et al. 1979). This LC_{50} is shown in Table 3-2 and Figure 3-2. Male rats and mice of both sexes were less susceptible, with only a few deaths after 2-hour exposures as high as 6,900 mg DMA/m^3 in rats and 6,400 mg DMA/m^3 in mice (Stevens et al. 1979). The cause of death was not specified, but was probably due to lung injury (see Section 3.2.1.2). No deaths were observed among rats and mice exposed to DSMA (the disodium salt of MMA) at concentrations up to 6,100 mg DSMA/m^3 in rats and 6,900 mg DSMA/m^3 in mice (Stevens et al. 1979). Chamber atmospheres at these high concentrations were so dense that it was difficult to see the animals clearly. These data indicate that there is no significant risk of acute lethality from concentrations of DMA or MMA that might be encountered in the environment or the workplace.

3.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects from inhalation exposure to inorganic arsenicals in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1, while the corresponding data for DMA are shown in Table 3-2 and Figure 3-2.

Respiratory Effects.

Inorganic Arsenicals. Workers exposed to arsenic dusts in air often experience irritation to the mucous membranes of the nose and throat. This may lead to laryngitis, bronchitis, or rhinitis (Dunlap 1921; Morton and Caron 1989; Pinto and McGill 1953), and very high exposures (characteristic of workplace exposures in the past) can cause perforation of the nasal septum (Dunlap 1921; Pinto and McGill 1953; Sandstrom et al. 1989). Despite the known respiratory irritant effects of arsenic, there have been few systematic investigations of respiratory effects in humans exposed to arsenic. Perry et al. (1948) found no difference in chest x-rays or respiratory performance (vital capacity and exercise-tolerance tests) between unexposed and exposed workers in a cross-sectional study at a factory where sodium arsenite was prepared. The NOAEL of 0.613 mg As/m^3 for respiratory effects in this study is shown in Table 3-1 and plotted in Figure 3-1.

Increased mortality due to respiratory disease has been reported in some cohort mortality studies of arsenic-exposed workers, but no conclusive evidence of an association with arsenic has been produced. In studies of workers exposed to arsenic trioxide at the Anaconda copper smelter in Montana, mortality due to noncancer respiratory disease (e.g., emphysema) was significantly increased compared to the general population (Lee-Feldstein 1983; Lubin et al. 2000; Welch et al. 1982). However, the data were not adjusted for smoking (a well-known confounder for respiratory disease), and analysis of the data with respect to arsenic exposure level did not show a clear dose-response. Similarly, Enterline et al. (1995) found a significant excess of nonmalignant respiratory disease mortality in workers at the ASARCO copper smelter in Tacoma, Washington, but only a slight negative relation to cumulative arsenic exposure. Xuan et al. (1993) found an increase in the relative risk of mortality from pneumoconiosis associated with arsenic exposure in a cohort of tin miners in China. However, this finding was based on a small number of observations (n=32), a clear exposure-response relationship with arsenic was not established, and the miners experienced confounding exposures to dust (a known risk factor for pneumoconiosis) and to radon. These studies were all considered to be inconclusive as to the relationship between inhaled inorganic arsenic and respiratory disease.

Respiratory symptoms were observed in a study of developmental effects in rats. Pregnant female rats exposed to arsenic trioxide dust starting 14 days prior to mating and continuing through mating and gestation exhibited rales at 8 mg As/m^3 and labored breathing and gasping at 20 mg As/m^3, with no symptoms at 2 mg As/m^3 (Holson et al. 1999). The lungs were examined by gross necropsy and no lesions were found. Intratracheal instillation of arsenic trioxide (13 mg As/kg) or gallium arsenide (1.5–

52 mg As/kg) can cause marked irritation and hyperplasia in the lungs of rats and hamsters (Goering et al. 1988; Ohyama et al. 1988; Webb et al. 1986, 1987). Since this sort of response is produced by a number of respirable particulate materials, it is likely that the inflammatory response is not specifically due to the arsenic.

Organic Arsenicals. No studies were located regarding respiratory effects in humans exposed to organic arsenicals. Short-term exposure of rats and mice to high concentrations (≥4,000 mg/m^3) of DMA caused respiratory distress, and necropsy of animals that died revealed bright red lungs with dark spots (Stevens et al. 1979). Respiratory distress was also observed in rats and mice exposed to high levels (≥6,100 mg/m^3) of the disodium salt of MMA (Stevens et al. 1979), although none of the MMA-exposed animals died. Respiratory distress appears to be associated with inhalation of very high concentrations of organic arsenicals. In 5-minute whole-body plethysmography trials, DMA and the disodium salt of MMA had RD_{50} (concentration calculated to produce a 50% decrease in respiration rate) values of 3,150 and 1,540 mg/m^3, respectively (Stevens et al. 1979). Based on these RD_{50} values, neither DMA nor MMA is considered to be a potent respiratory irritant. At low concentrations of DMA (34 or 100 mg DMA/m^3), an increase in intracytoplasmic eosinophilic globules were found in the nasal turbinates of rats exposed to DMA 6 hours/day, 5 days/week for 67–68 exposures (Whitman 1994).

Cardiovascular Effects.

Inorganic Arsenicals. There is some evidence from epidemiological studies that inhaled inorganic arsenic can produce effects on the cardiovascular system. Cardiovascular effects following oral exposure to arsenic are well known (see Section 3.2.2.2). A cross-sectional study of workers exposed to an estimated time-weighted average of 0.36 mg As/m^3 (as arsenic trioxide) at the Ronnskar copper smelter in Sweden for an average of 23 years showed that smelter workers had significantly increased incidences of Raynaud's phenomenon (a peripheral vascular disease characterized by spasm of the digital arteries and numbness of the fingers) and showed increased vasospasticity (constriction of blood vessels) in response to cold when tested in the fingers (Lagerkvist et al. 1986). A follow-up study conducted 2–3 years later found that vasospasticity measurements in exposed workers had improved concurrent with a reduction in arsenic exposure levels, although symptoms of peripheral vascular effects (cold hands or feet, white fingers, numbness in fingers or feet) were still common (Lagerkvist et al. 1988). A cross-sectional study including 46 workers in Denmark with varying, unquantified occupational exposure to arsenic in different occupations found that systolic blood pressure was significantly increased in the arsenic workers (median=125 mmHg) compared with controls (median=117 mmHg) (Jensen and Hansen 1998). Diastolic

pressure was also increased in this study (77.9 vs. 74.7 mmHg), although the difference from controls was not statistically significant.

Cohort mortality studies of arsenic-exposed workers at the ASARCO copper smelter in Tacoma, Washington (Enterline et al. 1995), Anaconda copper smelter in Montana (Lee-Feldstein 1983; Welch et al. 1982), Ronnskar copper smelter in Sweden (Wall 1980), orchard workers in Washington state (Tollestrup et al. 1995), and tin miners in China (Qiao et al. 1997; Xuan et al. 1993) have all reported increased risk of mortality from cardiovascular disease, specifically ischemic heart disease and cerebrovascular disease, in the cohorts studied. However, none of these studies provided conclusive evidence that the observed increase in risk was due to arsenic exposure. The studies in the ASARCO and Anaconda copper smelter workers failed to find a clear dose-response relationship with arsenic (Enterline et al. 1995; Welch et al. 1982), while a follow-up study of the Ronnskar smelter workers not only found lack of a dose-response, but also that the risk of cardiovascular disease was no longer elevated in the cohort (Järup et al. 1989). The studies in orchard workers and tin miners were limited by confounding exposures to copper, lead, and radon, respectively (Qiao et al. 1997; Tollestrup et al. 1995). The risk of cardiovascular disease mortality in the tin miners not only showed no dose-response relationship with arsenic exposure, but was positively associated with radon exposure, suggesting that radon may have been responsible for the increased cardiovascular risk in this cohort (Xuan et al. 1993).

The LOAEL for Raynaud's phenomenon and vasospasticity identified by Lagerkvist et al. (1986) is shown in Table 3-1 and Figure 3-1. No studies were located regarding cardiovascular effects in animals after inhalation exposure to inorganic arsenic.

Organic Arsenicals. No studies were located regarding cardiovascular effects in humans after inhalation exposure to organic arsenicals. No histological alterations were observed in the hearts of rats exposed to 100 mg DMA/m^3 for 67–68 exposures (Whitman 1994).

Gastrointestinal Effects.

Inorganic Arsenicals. Several case studies have reported nausea, vomiting, and diarrhea in workers with acute arsenic poisoning following occupational inhalation exposure (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989; Pinto and McGill 1953). Although gastrointestinal effects are not typically associated with arsenic poisoning by inhalation (Pinto and McGill 1953), such effects are a common feature of oral ingestion of high doses of arsenic (see Section 3.2.2.2),

and it is possible that mucociliary transport of arsenic dust from the lungs to the gut could be responsible for the effects in these cases. Exposure levels were not reliably estimated for any of these cases.

The only report of gastrointestinal effects of inhaled inorganic arsenic in animals was a developmental toxicology study in which four of nine pregnant rats died, and one rat was euthanized *in extremis*, between days 12 and 19 of gestation after 30–35 days of exposure to an aerosol of arsenic trioxide at an exposure concentration of 20 mg As/m^3 (Holson et al. 1999). These animals exhibited severe hyperemia and plasma discharge into the intestinal lumen at autopsy. Exposure to 8 mg As/m^3 did not produce gross gastrointestinal lesions.

Organic Arsenicals. Data regarding gastrointestinal effects in people exposed to organic arsenic in the air are limited. The frequency of gastrointestinal complaints was no higher than controls in workers exposed to arsanilic acid (i.e., 4-aminophenyl arsonic acid) at mean concentrations up to 0.17 mg/m^3 in a chemical factory (Watrous and McCaughey 1945). However, this sort of data might easily be biased by workers who chose not to complain about minor symptoms, so no conclusion can be reached. Rats and mice exposed to very high levels (above 3,000 mg/m^3) of MMA (disodium salt) or DMA experienced diarrhea (Stevens et al. 1979). The diarrhea could be due to transport of inhaled particulate material from the lungs to the gastrointestinal system or to direct ingestion of the compound (e.g., from grooming of the fur). No gastrointestinal effects were observed in rats repeatedly exposed to 100 mg DMA/m^3 6 hours/day, 5 days/week for 67–68 exposures (Whitman 1994).

Hematological Effects.

Inorganic Arsenicals. Although anemia is a common feature of arsenic poisoning following oral exposure in humans (see Section 3.2.2.2), case studies of workers with arsenic poisoning from occupational inhalation exposure reported no effects on red blood cell count (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989). The reason for this apparent route specificity is not clear, but might simply be related to dose. No studies were located regarding hematological effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No effect on levels of hemoglobin, red cells, or white cells was detected in the blood of manufacturing workers (323 counts in 35 workers) exposed to airborne arsanilic acid dusts at a mean concentration of 0.17 mg/m^3 in the workplace (Watrous and McCaughey 1945). Controls were an unspecified number of unexposed manufacturing workers with 221 complete blood counts. No

hematological alterations were observed in rats exposed to 100 mg DMA/m^3 for an intermediate duration (Whitman 1994).

Musculoskeletal Effects.

Inorganic Arsenicals. Few data were located regarding musculoskeletal effects associated with inhalation exposure to inorganic arsenic, and none to suggest the existence of any such effects. Electromyographic examination of the calves and feet showed no differences between control and arsenic-exposed workers in a cross-sectional study of workers at the Ronnskar copper smelter in Sweden (Blom et al. 1985). No studies were located regarding musculoskeletal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to organic arsenicals.

Hepatic Effects.

Inorganic Arsenicals. There is no evidence that inhaled inorganic arsenic produces effects on the liver, although few data are available. Case studies of workers with inhalation arsenic poisoning that included liver function tests did not find any evidence of hepatic dysfunction (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988). No studies were located regarding hepatic effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding hepatic effects in humans after inhalation exposure to organic arsenicals. No histological alterations were observed in the livers of rats exposed to 100 mg DMA/m^3 for 67–68 exposures (Whitman 1994).

Renal Effects.

Inorganic Arsenicals. The limited data available do not suggest any relationship between inhalation of inorganic arsenic and kidney effects. A cross-sectional study of renal function parameters in glass factory workers exposed to arsenic (concentrations unknown) found no meaningful differences from controls in urinary levels of several proteins (albumin, retinol binding protein, β_2-microglobulin, brush-border antigen) used as markers of glomerular damage or tubular cell exfoliation (Foà et al. 1987). Routine

clinical urinalysis was normal when included in case studies of workers with inhalation arsenic poisoning (Ide and Bullough 1988; Morton and Caron 1989). No studies were located regarding renal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding renal effects in humans after inhalation exposure to organic arsenicals. No renal effects were reported in rats exposed to 100 mg DMA/m^3 6 hours/day, 5 days/week for 67–68 exposures (Whitman 1994).

Dermal Effects.

Inorganic Arsenicals. Dermatitis has frequently been observed in industrial workers exposed to inorganic arsenic in the air, with the highest rates occurring in the workers with the greatest arsenic exposure (Cöl et al. 1999; Dunlap 1921; Holmqvist 1951; Lagerkvist et al. 1986; Pinto and McGill 1953). Limited quantitative information is available regarding the exposure levels that produce dermatitis, and the high likelihood of co-exposure by the dermal route makes dose-response analysis difficult. A cross-sectional study of workers at a factory where sodium arsenite was prepared found that workers with the highest arsenic exposure (mean air levels ranging from 0.384 to 1.034 mg As/m^3 and estimated to average 0.613 mg As/m^3) tended to be grossly pigmented with hyperkeratinization of exposed skin and to have multiple warts (Perry et al. 1948). In the same study, workers with lower arsenic exposure (estimated to average 0.078 mg As/m^3) were much less affected, but still had a higher incidence of pigmentation keratosis than controls. LOAEL values identified by Perry et al. (1948) and Mohamed (1998) are shown in Table 3-1 and Figure 3-1. NOAEL values for dermal irritation have not been identified. Dermal effects (hyperkeratoses, hyperpigmentation) are also very common in people exposed to inorganic arsenic by the oral route (see Section 3.2.2.2). No studies were located on dermal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. Data regarding dermal effects in people exposed to organic arsenic in the air are limited. Complaints of keratosis were roughly 2-fold higher than unexposed controls in female packaging workers exposed to arsanilic acid at an average concentration of 0.065 mg/m^3 and in male manufacturing workers exposed to an average concentration of 0.17 mg/m^3 in a chemical factory (Watrous and McCaughey 1945). Limitations in study methodology (e.g., alternate sources of effects were not investigated, workers might choose not to report minor complaints to company officials) make the reliability of this observation uncertain. Female rats exposed to DMA at 6,900 mg/m^3 developed erythematous lesions on the feet and ears (Stevens et al. 1979); these lesions did not develop in females

exposed at lower concentrations (4,100 mg/m^3) or males. It seems likely that these effects were due to direct irritation from dermal contact with the dust. No dermal effects were observed in rats repeatedly exposed to lower levels of DMA (100 mg/m^3) (Whitman 1994).

Ocular Effects.

Inorganic Arsenicals. Chemical conjunctivitis, characterized by redness, swelling, and pain, has been observed in workers exposed to arsenic dusts in air, usually accompanied by facial dermatitis (Dunlap 1921; Pinto and McGill 1953). No information was located regarding air levels of arsenic that produce this effect. No studies were located on ocular effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located on ocular effects in humans after inhalation exposure to organic arsenicals. Rats and mice exposed to high concentrations of DMA (≥4,000 mg/m^3) developed an encrustation around the eyes (Stevens et al. 1979). It seems likely that these effects were due to direct irritation from ocular contact with the dust.

Body Weight Effects.

Inorganic Arsenicals. No studies were located on body weight effects in humans after inhalation exposure to inorganic arsenicals. Female rats exposed to arsenic trioxide dust starting 14 days before mating and continuing through mating and gestation showed a marked decrease in body weight and food consumption at 20 mg As/m^3 (preliminary study) and a smaller decrease at 8 mg As/m^3 (definitive study), with no effect at 2 mg As/m^3 (Holson et al. 1999).

Organic Arsenicals. No studies were located on body weight effects in humans after inhalation exposure to organic arsenicals. Rats and mice exposed to high concentrations of DMA (≥4,000 mg/m^3) for 2 hours had an unspecified decrease in body weight gain during the subsequent 14 days (Stevens et al. 1979). No alterations in body weight gain were observed in rats exposed to 100 mg DMA/m^3 for 67–68 exposures (Whitman 1994).

3.2.1.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. A single study was located regarding the immunological and lymphoreticular effects of inhaled inorganic arsenic in humans. Bencko et al. (1988) detected no abnormalities in serum levels of immunoglobins in 47 workers exposed to arsenic (exposure levels not measured) in a coal-burning power plant. However, serum levels of other proteins such as transferrin, orosomucoid, and ceruloplasmin were significantly elevated compared to levels in a group of 27 workers from a different plant in which the arsenic content in the coal was 10 times lower. The investigators suggested that the increased levels of ceruloplasmin might be related to higher cancer mortality rates found among these workers.

The immune effects of inhaled arsenic in animals were studied by Aranyi et al. (1985). Female mice exposed to arsenic trioxide aerosol for 3 hours showed a concentration-related decrease in pulmonary bactericidal activity (presumably as a result of injury to alveolar macrophages) and a corresponding concentration-related increase in susceptibility to introduced respiratory bacterial pathogens. Similar results were found when the exposure was repeated over 1- and 4-week periods. The NOAEL and LOAEL values for this study are shown in Table 3-1 and Figure 3-1.

Intratracheal studies in animals offer some support for an immune effect of inhaled inorganic arsenic. Decreases in humoral response to antigens and in several complement proteins were noted in mice given an intratracheal dose of 5.7 mg As/kg as sodium arsenite (Sikorski et al. 1989), although these changes were not accompanied by any decrease in resistance to bacterial or tumor cell challenges. Animals given an intratracheal dose of GaAs (25 mg As/kg or higher) also displayed a variety of changes in numerous immunological end points (some increased, some decreased) (Burns and Munson 1993; Sikorski et al. 1989). Whether these effects were due to a direct effect on the immune system or were secondary to the inflammatory effect of GaAs on the lung (see Section 3.2.1.2, above) is uncertain.

Organic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.1.4 Neurological Effects

Inorganic Arsenicals. There is evidence from epidemiological studies that inhaled inorganic arsenic can produce neurological effects. A study by Gerr et al. (2000) reported an elevated incidence of peripheral neuropathy in subjects who lived near an arsenic-using pesticide plant (13/85=15.3%; odds ratio

[OR]=5.1, p=0.004), relative to subjects who lived farther from the plant (4/118=3.4%). Concentrations of arsenic in soil and house dust were elevated (~30–300 μg As/g) for residences near the plant, according to 1993–1995 monitoring data. Studies of copper smelter workers at the ASARCO smelter in Tacoma, Washington (Feldman et al. 1979), a power station in Slovakia (Buchancová et al. 1998), and the Ronnskar smelter in Sweden (Blom et al. 1985; Lagerkvist and Zetterlund 1994) have demonstrated peripheral neurological effects in workers associated with arsenic trioxide exposure. At the ASARCO smelter, the prevalence of clinically diagnosed peripheral neuropathy was markedly higher in arsenic-exposed workers (26/61=43%) than controls (4/33=12%), and although the difference in mean nerve conduction velocities (NCV) was not statistically significant, mean peroneal motor NCV was lower in arsenic-exposed workers than controls and all 12 cases of abnormally low NCV occurred in the arsenic group (Feldman et al. 1979). In the study of 70 workers in Slovakia, the investigators described 16 cases of arsenic intoxication. Among these, 13 had signs and symptoms of sensory and motor polyneuropathy on both upper and lower extremities, 10 were diagnosed with pseudoneurasthenic syndrome, and 6 suffered from toxic encephalopathy (Buchancová et al. 1998). The average length of exposure was 22.3 years (SD ±8.4 years) and the average arsenic exposure in inhaled air ranged from 4.6 to 142.7 $\mu g/m^3$. Similar results were observed at the Ronnskar smelter, where Blom et al. (1985) reported significantly increased prevalence of workers with abnormally low NCV in the exposed group, and lower, but not statistically significant, mean NCV in five peripheral nerves. A follow-up study on the Ronnskar workers 5 years later found that the prevalence of abnormally low NCV remained significantly increased in the exposed workers, but that the decrease in mean NCV was now also statistically significant in the tibial (motor) and sural (sensory) nerves (Lagerkvist and Zetterlund 1994). Blood lead was monitored in this study as a potential confounder, but levels were low and not considered likely by the researchers to have had any influence on the results. The follow-up Ronnskar study provided enough information to estimate that mean arsenic exposure was 0.31 mg As/m^3 and lasted an average of 28 years in the exposed group, and this LOAEL is shown in Table 3-1 and Figure 3-1.

The literature also contains several case studies of workers with inhalation arsenic poisoning who developed neurological symptoms. Although these studies do not provide reliable information on exposure levels or conclusive evidence that the observed effects were related to arsenic, the findings are suggestive. Symptoms in these cases included not only indicators of peripheral neuropathy (numbness, loss of reflexes, muscle weakness, tremors) (Ide and Bullough 1988; Morton and Caron 1989), but also frank encephalopathy (hallucinations, agitation, emotional lability, memory loss) (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Morton and Caron 1989). Both peripheral neuropathy and encephalopathy are associated with oral exposure to inorganic arsenic (see Section 3.2.2.4).

The possible association between arsenic in air and neurological effects in children has also been examined. A study by Bencko et al. (1977) reported that children of approximately 10 years of age (n=56) living near a power plant burning coal of high arsenic content showed significant hearing losses (increased threshold) compared to a control group of children (n=51) living outside the polluted area (Bencko et al. 1977). The effect was most marked at low frequencies. The precise site affected within the auditory pathway was not determined and could have been in the periphery, centrally-located, or both. A small study of children in Mexico reported a significant negative correlation between tests of verbal IQ and urinary arsenic in children (n=41) living in an urban area near a smelter complex (Calderón et al. 2001). Exposure concentrations were not available in either study.

No studies were located regarding neurological effects in animals after inhalation exposure to inorganic arsenicals. Mice given a single intratracheal dose of 200 mg/kg of GaAs displayed a decrease in overall activity 6–8 hours later, but no additional neurological evaluations were conducted on these animals (Burns and Munson 1993).

Organic Arsenicals. Data regarding neurological effects in people exposed to organic arsenic in the air are limited to a single study. The frequency of central nervous system complaints was no higher than controls in workers at a chemical factory exposed to arsanilic acid at mean concentrations up to 0.17 mg/m^3 (Watrous and McCaughey 1945). Although peripheral nerve complaints were higher in arsenic packaging workers (mean exposure=0.065 mg/m^3) than in unexposed controls, this was not the case in manufacturing workers with higher arsenic exposure (mean=0.17 mg/m^3). This suggests that the effects on the peripheral nerves in the exposed packaging workers were not due to arsenic. The reliability of these data is limited by shortcomings in the study methodology (e.g., the data might easily be biased by workers who chose not to complain about minor symptoms). No studies were located regarding neurological effects in animals after inhalation exposure to organic arsenicals.

3.2.1.5 Reproductive Effects

Inorganic Arsenicals. No studies were located regarding reproductive effects in humans after inhalation exposure to inorganic arsenicals. Reproductive performance was evaluated in female rats exposed to 0.08–20 mg As/m^3 (preliminary study) or 0.2–8 mg As/m^3 (definitive study) as As_2O_3 6 hours daily from 14 days prior to mating through gestation day 19 (Holson et al. 1999). No changes occurred in the precoital interval (time to mating), mating index (percentage of rats mated), or fertility index (percentage

of matings resulting in pregnancy). The NOAEL values for this study are shown in Table 3-1 and Figure 3-1.

Organic Arsenicals. No studies were located regarding reproductive effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.1.6 Developmental Effects

Inorganic Arsenicals. Developmental effects associated with occupational and environmental exposure to airborne arsenic have been investigated in a series of studies at the Ronnskar copper smelter in northern Sweden (Nordström et al. 1978a, 1978b, 1979a, 1979b). In comparison to a northern Swedish reference population, female employees of the smelter had a significantly increased incidence of spontaneous abortion (Nordström et al. 1979a), and their children had a significantly increased incidence of congenital malformations (Nordström et al. 1979b) and significantly decreased average birth weight (Nordström et al. 1978a). Increased incidence of spontaneous abortion and decreased average birth weight of children were also found in populations living in close proximity to the smelter (Nordström et al. 1978a, 1978b, 1979b). While these data are suggestive of developmental effects associated with occupational and environmental exposure from the smelter, the reported effects are not large, the analyses include only limited consideration of potential confounders (e.g., smoking), and there are no data relating the apparent effects specifically to arsenic exposure.

Ihrig et al. (1998) conducted a case-control study of stillbirths in the vicinity of a Texas arsenic pesticide factory that included estimation of environmental arsenic exposures using atmospheric dispersion modeling and multiple regression analysis considering arsenic exposure, race/ethnicity, maternal age, median income, and parity as explanatory variables. There was a statistically significant increase in the risk of stillbirth in the highest exposure category (>100 ng As/m^3, midpoint=682 ng/m^3). Further analysis showed that this increase in risk was limited to people of Hispanic descent, who the researchers speculated may be an especially sensitive population due to a genetic impairment in folate metabolism. Interpretation of this study is limited by small numbers of cases and controls in the high exposure group, lack of data on smoking, potential confounding exposures to other chemicals from the factory, and failure to take into account previous years of deposition in the exposure estimates.

Arsenic has been shown to produce developmental effects by inhalation exposure in laboratory animals, although it is unclear whether or not the effects occur only at maternally toxic doses. Mice exposed to

22 mg As/m^3 (as As_2O_3) for 4 hours on days 9–12 of gestation had serious developmental effects (significant increases in the percentage of dead fetuses, skeletal malformations, and the number of fetuses with retarded growth), while those exposed to 2.2 mg As/m^3 had only a 10% decrease in average fetal body weight, and those exposed to 0.20 mg As/m^3 had no effects (Nagymajtényi et al. 1985). The study was limited by failure to quantify malformations on a litter basis, discuss the nature and severity of the observed malformations, or report on the occurrence of maternal effects. No increases in fetal resorptions, fetal mortality, or malformations, and no decreases in fetal body weight occurred when rats were exposed to 0.2–8 mg As/m^3 (as As_2O_3), 6 hours daily from 14 days prior to mating through gestation day 19 (Holson et al. 1999). At the 8 mg/m^3 exposure level, toxicity was observed in the dams, including rales, a dried red exudate at the nose, and lower gains in net body weight than controls. In a preliminary dose-range study, there was a marked significant increase in postimplantation loss (primarily early resorptions) and consequent marked significant decrease in viable fetuses per litter at 20 mg As/m^3, a concentration that also produced severe maternal effects including mortality (Holson et al. 1999).

The NOAEL and LOAEL values for increased risk of stillbirth in humans identified by Ihrig et al. (1998) and those for developmental effects in rodents found by Nagymajtényi et al. (1985) and Holson et al. (1999) are shown in Table 3-1 and Figure 3-1.

Organic Arsenicals. No studies were located regarding developmental effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.1.7 Cancer

Inorganic Arsenicals. There is convincing evidence from a large number of epidemiological studies that inhalation exposure to inorganic arsenic increases the risk of lung cancer. Most studies involved workers exposed primarily to arsenic trioxide dust in air at copper smelters (Axelson et al. 1978; Brown and Chu 1982, 1983a, 1983b; Enterline and Marsh 1982; Enterline et al. 1987a, 1987b, 1995; Ferreccio et al. 1996; Järup and Pershagen 1991; Järup et al. 1989; Lee and Fraumeni 1969; Lee-Feldstein 1983, 1986; Lubin et al. 2000; Mazumdar et al. 1989; Pinto et al. 1977, 1978; Sandstrom et al. 1989; Viren and Silvers 1999; Wall 1980; Welch et al. 1982) and mines (Liu and Chen 1996; Qiao et al. 1997; Taylor et al. 1989; Xuan et al. 1993), but increased incidence of lung cancer has also been observed at chemical plants where exposure was primarily to arsenate (Bulbulyan et al. 1996; Mabuchi et al. 1979; Ott et al. 1974; Sobel et al. 1988). In addition, several studies suggest that residents living near smelters or arsenical chemical plants may also have increased risk of lung cancer (Brown et al. 1984; Cordier et al. 1983; Matanoski et

al. 1981; Pershagen 1985), although the increases are small and are not clearly detectable in all cases (e.g., Frost et al. 1987). The strongest evidence that arsenic is responsible for the observed lung cancer comes from quantitative dose-response data relating specific arsenic exposure levels to lung cancer risk. These data are available for arsenic-exposed workers at the ASARCO copper smelter in Tacoma, Washington (Enterline and Marsh 1982; Enterline et al. 1987a, 1995; Mazumdar et al. 1989), the Anaconda copper smelter in Montana (Lee-Feldstein 1986; Welch et al. 1982), eight other U.S. copper smelters (Enterline et al. 1987b), and the Ronnskar copper smelter in Sweden (Järup and Pershagen 1991; Järup et al. 1989). A common limitation of these studies is confounding exposure to other chemicals, such as sulfur dioxide, and cigarette smoking.

Enterline and Marsh (1982) reported a significant increase in respiratory cancer mortality (standard mortality ratio [SMR]=189.4) based on 104 observed respiratory cancer deaths and only 54.9 expected over the years 1941–1976 in a cohort of 2,802 male workers employed for ≥1 year between 1940 and 1964 at the ASARCO smelter. When the cohort was separated into low and high arsenic exposure groups, with mean estimated time-weighted average arsenic exposures of 0.054 and 0.157 mg As/m^3, respectively (based on work history, historical urinary arsenic measurements, and an experimentally derived relationship between urinary and inhaled arsenic), respiratory cancer mortality was significantly increased in both groups in a concentration-related fashion (SMR=227.7 and 291.4 in the low and high groups, respectively). Enterline et al. (1987a) re-analyzed these data using improved exposure estimates that incorporated historical measurements of arsenic in the ambient air and personal breathing zone of workers. Respiratory cancer mortality was significantly increased in a concentration-related fashion in the low (SMR=213.0), medium (SMR=312.1), and high (SMR=340.9) arsenic exposure groups, which had mean estimated time-weighted average arsenic exposures of 0.213, 0.564, and 1.487 mg As/m^3, respectively. An alternative analysis of these data by Mazumdar et al. (1989) produced similar results. Enterline et al. (1995) extended the mortality follow-up from 1976 to 1986, but reported findings similar to the earlier study in a less thorough analysis. The CEL from Enterline et al. (1987a), the most complete analysis of the ASARCO cohort with the best exposure estimates, is presented in Table 3-1 and Figure 3-1.

Respiratory cancer mortality was significantly increased (SMR=285) based on 302 observed respiratory deaths between 1938 and 1977 in a cohort of 8,045 white male workers employed for at least 1 year between 1938 and 1956 at the Anaconda smelter (Lee-Feldstein 1986). When workers were categorized according to cumulative arsenic exposure and date of hire, lung cancer mortality was significantly increased in all groups hired between 1925 and 1947. Workers in the lowest cumulative exposure group

(<10 mg-mo/m^3) were reported to have had <2 years of exposure at an average arsenic concentration of 0.38 mg/m^3. An alternative analysis of a subset of the Anaconda cohort (n=1,800, including all 277 employees with heavy arsenic exposure and 20% of the others) that included information on smoking and other occupational exposures was performed by Welch et al. (1982). This analysis showed that lung cancer mortality increased with increasing time-weighted average arsenic exposure, with a small nonsignificant increase in the low group (SMR=138) exposed to 0.05 mg/m^3 and significant increases in the medium (SMR=303), high (SMR=375), and very high (SMR=704) groups exposed to 0.3, 2.75, and 5.0 mg/m^3, respectively. Cohort members were more likely to be smokers than U.S. white males, but smoking did not differ among the arsenic exposure groups. Exposure-response analysis of smokers was similar to the analysis based on the full subcohort, while analysis of nonsmokers (limited by small group sizes) also showed a similar pattern, but with lower SMRs. In a followup analysis of the same cohort, Lubin et al. (2000) re-weighted the exposure concentrations based on duration and time of exposure and re-evaluated the effects of exposure. Relative risks for respiratory cancer increased with increasing duration in each arsenic exposure area (light, medium, and heavy) after adjustment for duration in the other two exposure areas. SMRs were significantly elevated following exposure to 0.58 mg/m^3 (medium; SMR=3.01, 95% CI=2.0–4.6) or 11.3 mg/m^3 (high; SMR=3.68, 95% CI=2.1–6.4) for 10 or more years, and following exposure to 0.29 mg/m^3 (low; SMR=1.86, 95% CI=1.2–2.9) for 25 or more years. The CELs from the analyses of the Anaconda cohort are presented in Table 3-1 and Figure 3-1.

Enterline et al. (1987b) studied the mortality experience from 1949 to 1980 of a cohort of 6,078 white males who had worked for 3 years or more between 1946 and 1976 at one of eight U.S. copper smelters in Arizona, Utah, Tennessee, and Nevada. Lung cancer mortality was significantly increased only in the Utah smelter (SMR=226.7), which had the highest average arsenic exposure concentration (0.069 mg/m^3 vs. 0.007–0.013 mg/m^3 in the other smelters) and also contributed the largest number of cohort members (n=2,288 vs. 189–965 from the other smelters). A nested case-control study showed that arsenic exposure and cigarette smoking were significant risk factors for lung cancer in the smelter workers. Smoking was lower in the Utah smelter workers than in the other smelter workers, but still higher than in the referent Utah population, suggesting that the risk attributable to arsenic in this study population is somewhat lower than indicated by the SMR reported above. The CEL from this study is presented in Table 3-1 and Figure 3-1.

Järup et al. (1989) reported significantly increased lung cancer mortality (SMR=372, 95% confidence interval [CI]=304–450) based on 106 lung cancer deaths in a cohort of 3,916 male workers employed for ≥3 months between 1928 and 1967 at the Ronnskar smelter and followed for mortality through 1981.

Workers were separated into low, medium, and high arsenic exposure groups with mean time-weighted average exposure estimates of 0.05, 0.2, and 0.4 mg/m^3, respectively. Lung cancer mortality was significantly increased in all three exposure groups in a concentration-related fashion (SMR=201, 353, and 480, respectively). A nested case-control analysis of 102 lung cancer cases and 190 controls from the cohort showed that lung cancer risk increased with increasing arsenic exposure in nonsmokers, light smokers, and heavy smokers (Järup and Pershagen 1991). The results demonstrated that arsenic is a risk factor for lung cancer in the smelter workers, but also suggested a greater-than-additive interaction between smoking and arsenic exposure. In this analysis, in contrast to the cohort study, lung cancer risk due to arsenic was increased only in the higher arsenic-exposure groups. Potential explanations for this difference between the cohort and case-control analyses include a higher proportion of smokers in the smelter workers than in the regional referent population in the cohort study, and limited power to detect increased risk in the case-control study due to small group sizes in the dose-response analysis. The CELs from both the cohort and case-control studies are presented in Table 3-1 and Figure 3-1.

Several researchers have examined the histological cell types of lung cancer (epidermoid carcinoma, small cell carcinoma, adenocarcinoma) in arsenic-exposed workers (e.g., Axelson et al. 1978; Newman et al. 1976; Pershagen et al. 1987; Qiao et al. 1997; Wicks et al. 1981). Although the incidence of the various cell types varied from population to population, all studies found an increase in several tumor types. This indicates that arsenic does not specifically increase the incidence of one particular type of lung cancer.

The studies of the ASARCO cohort (Enterline and Marsh 1982; Enterline et al. 1987a, 1995) noted a supralinear exposure-response relationship (i.e., steeper at lower doses) between arsenic exposure and lung cancer mortality. Hertz-Picciotto and Smith (1993) extended this observation to several other occupationally exposed cohorts with quantitative exposure information. The authors suggest that neither toxicokinetic mechanisms nor confounding from age, smoking, or other workplace carcinogens that differ by exposure level are likely explanations for the curvilinearity. Plausible explanations offered include: (1) synergism (with smoking), which varies in magnitude according to the level of arsenic exposure, (2) long-term survivorship at higher exposures among the healthier, less susceptible individuals, and (3) exposure estimate errors that were more prominent at higher-exposure levels as a result of past industrial hygiene sampling or worker protection practices.

Quantitative risk estimates for inhaled inorganic arsenic have been derived using the exposure-response data. EPA derived a unit risk estimate (the excess risk of lung cancer associated with lifetime exposure to

1 μg/m^3) of 4.3x10^{-3} per (μg/m^3) based on the dose-response relationships between arsenic exposure and excess lung cancer mortality in workers at the Anaconda smelter in Montana (Brown and Chu 1982, 1983a, 1983b; Lee-Feldstein 1983; and an unpublished paper by Higgins and associates) and the ASARCO smelter in Tacoma, Washington (Enterline and Marsh 1982; EPA 1984a; IRIS 2007). In some cases, calculations of exposure, as well as the procedures for generating quantitative risk estimates, are quite complex and the interested reader is referred to the EPA documents (EPA 1981c, 1984a, 1987e, 1996b; IRIS 2007) for a detailed description. Viren and Silvers (1994) re-evaluated the unit risk estimate using the same methods as EPA, but incorporating updated results from the ASARCO smelter (Enterline et al. 1987a; Mazumdar et al. 1989) and the findings from the Swedish smelter (Järup et al. 1989). Their analysis yielded a revised unit risk of 1.28x10^{-3} per (μg/m^3) that, when pooled with the earlier estimate from the Montana smelter cohort, yielded a composite unit risk of 1.43x10^{-3} per (μg/m^3). This unit risk estimate is a factor of 3 smaller than the EPA's current estimate of 4.3x10^{-3} per (μg/m^3). Figure 3-1 shows the air concentrations that correspond to excess lifetime cancer risks of 10^{-4}–10^{-7} based on the EPA unit risk estimate.

There have been occasional reports of other types of cancer (i.e., nonrespiratory cancer) potentially associated with inhalation exposure to inorganic arsenic, but there is no strong evidence for any of them. For example, Enterline et al. (1995) found significantly increased mortality due to cancer of the large intestine and bone cancer in the ASARCO cohort. However, neither cancer showed any relation to cumulative arsenic exposure, and the purported increase in bone cancer risk was based on a very small number of observations. Pesch et al. (2002) reported an increase in nonmelanoma skin cancers resulting from exposure from a Slovakian coal-burning power plant, but exposure levels associated with the lesions were not presented. Bencko et al. (2005) also reported an increase in the incidence of nonmelanoma skin cancer among workers of a power plant burning coal of a high arsenic content and in the population living in the vicinity of the power plant. Bulbulyan et al. (1996) reported an increase in risk of stomach cancer among workers exposed to the highest average arsenic concentrations at a Russian fertilizer plant, but this finding, which was based on a small number of observations and was only marginally statistically significant, was confounded by exposure to nitrogen oxides, which were more convincingly associated with stomach cancer in this study. Wingren and Axelson (1993) reported an association between arsenic exposure and stomach and colon cancer in Swedish glass workers, but this result was confounded by concomitant exposure to other metals. Lee-Feldstein (1983) observed a small, marginally significant increase in digestive tract cancer (SMR=125) in one study of the Anaconda cohort, but this was not found in other studies of this cohort (Lee and Fraumeni 1969; Lee-Feldstein 1986; Welch et al. 1982). Wulff et al. (1996) observed an apparent increase in the risk of childhood cancer (all types combined) in the

population living within 20 km of the Ronnskar smelter, but the apparent increase was based on a small number of cases (13 observed vs. 6.7 expected) and was not statistically significant, and exposure to arsenic was confounded by exposure to lead, copper, cadmium, sulfur dioxide, and possibly other emissions such as nickel and selenium. A retrospective study of deaths due to unspecified types of malignancies among workers of power plants found no significant differences in death rate between two groups whose exposure levels to arsenic had a difference of one order of magnitude (Bencko et al. 1980). However, the mean age of those deceased due to cancer in the high-exposure group was 55.9 years compared to 61.2 years in the low-exposure group, and this difference was statistically significant ($p<0.05$). Also, when the workers were stratified by exposure-duration, there was a significantly higher frequency of tumors in the high-exposure group after shorter employment periods (<5 or 6–10 years) than after a longer employment period (≥11 years). No information was provided regarding specific types of cancer. Various case reports have implicated occupational arsenic exposure as a potential contributing factor in workers who developed sinonasal cancer (Battista et al. 1996), hepatic angiosarcoma (Tsai et al. 1998a), and skin cancer (Cöl et al. 1999; Tsuruta et al. 1998), but provide no proof that inhaled arsenic was involved in the etiology of the observed tumors. Wong et al. (1992) found no evidence that environmental exposure to airborne arsenic produced skin cancer in residents living near the Anaconda smelter or an open pit copper mine.

No studies were located regarding cancer in animals after inhalation exposure to inorganic arsenicals, although several intratracheal instillation studies in hamsters have provided evidence that both arsenite and arsenate can increase the incidence of lung adenomas and/or carcinomas (Ishinishi et al. 1983; Pershagen and Björklund 1985; Pershagen et al. 1984; Yamamoto et al. 1987). These data support the conclusion that inhalation of arsenic may lead to lung cancer in humans.

Organic Arsenicals. No studies were located regarding cancer effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.2 Oral Exposure

There are a large number of studies in humans and animals on the toxic effects of ingested arsenic. In humans, most cases of toxicity have resulted from accidental, suicidal, homicidal, or medicinal ingestion of arsenic-containing powders or solutions or by consumption of contaminated food or drinking water. In some cases, the chemical form is known (e.g., the most common arsenic medicinal was Fowler's solution, which contained 1% potassium arsenite or arsenic trioxide), but in many cases (e.g., exposures through

drinking water), the chemical form is not known. In these cases, it is presumed that the most likely forms are either inorganic arsenate [As(+5)], inorganic arsenite [As(+3)], or a mixture. Table 3-3 and Figure 3-3 summarize a number of studies that provide reliable quantitative data on health effects in humans and animals exposed to inorganic arsenicals by the oral route. Similar data for MMA, DMA, and roxarsone are listed in Tables 3-4, 3-5, and 3-6, and shown in Figures 3-4, 3-5, and 3-6, respectively. All exposure data are expressed as milligrams of arsenic (as the element) per kilogram body weight per day (mg As/kg/day). These studies and others that provide useful qualitative information are summarized below.

3.2.2.1 Death

Inorganic Arsenicals. There are many case reports of death in humans due to ingestion of high doses of arsenic. In nearly all cases, the most immediate effects are vomiting, diarrhea, and gastrointestinal hemorrhage, and death may ensue from fluid loss and circulatory collapse (Levin-Scherz et al. 1987; Saady et al. 1989; Uede and Furukawa 2003). In other cases, death may be delayed and result from the multiple tissue injuries produced by arsenic (Campbell and Alvarez 1989). Some accounts of fatal arsenic poisoning describe both gastrointestinal effects soon after ingestion and extensive damage to multiple organ systems prior to death (Quatrehomme et al. 1992). A precise estimate of the ingested dose is usually not available in acute poisonings, so quantitative information on lethal dose in humans is sparse. The lethal doses ranged from 22 to 121 mg As/kg in four cases where known amounts were ingested as a single bolus (Civantos et al. 1995; Hantson et al. 1996; Levin-Scherz et al. 1987; Quatrehomme et al. 1992). Two people in a family of eight died from ingestion of water containing about 110 ppm of arsenic for a week (Armstrong et al. 1984). This corresponded to a dose of about 2 mg As/kg/day. Based on a review of clinical reports in the older literature, Holland (1904) estimated the minimum lethal dose to be about 130 mg (also about 2 mg/kg). A similar estimate of 70–180 mg (about 1–3 mg/kg) was provided by Vallee et al. (1960). Death due to chronic arsenic exposure has been reported at lower concentrations. Five children between the ages of 2 and 7 years died from late sequelae of chronic arsenic poisoning after drinking contaminated water throughout their lives at estimated average doses of 0.05–0.1 mg As/kg/day (Zaldívar and Guillier 1977). A 22-year-old man with chronic arsenical dermatosis died from arsenic-related effects after lifetime exposure to an estimated average dose of 0.014 mg As/kg/day in the drinking water (Zaldívar et al. 1981). Systematic studies of lethality from chronic exposure attributable to increased risk of cardiovascular disease or cancer are discussed below in Sections 3.2.2.2 and 3.2.2.7, respectively.

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Human	1 wk (W)				2 (death)	Armstrong et al. 1984 NS	
2	Human	once (IN)				121 M (death)	Civantos et al. 1995 As(+5)	
3	Human	once (IN)				108 M (death)	Hantson et al. 1996 As(+3)	
4	Human	once (IN)				22 M (death)	Levin-Scherz et al. 1987 As(+3)	
5	Human	once (IN)				93 M (death)	Quatrehomme et al. 1992 As(+3)	
6	Rat (wild Norway)	once (G)				104 (LD50)	Dieke and Richter 1946 As(+3)	
7	Rat (Sherman)	once (G)				112 F (LD50)	Gaines 1960 As(+5) calcium arsenate	
8	Rat (Sherman)	once (G)				44 F (LD50)	Gaines 1960 As(+3)	
9	Rat (Sherman)	once (G)				175 F (LD50)	Gaines 1960 As(+5) lead arsenate	
10	Rat (Sprague-Dawley)	once (GW)				15 M (LD50)	Harrisson et al. 1958 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
11	Rat (Sprague-Dawley)	once (F)				145 M (LD50)	Harrisson et al. 1958 As(+3)	
12	Rat (CD)	once Gd 9 (GW)				23 F (7/25 dams died)	Stump et al. 1999 As(+3)	
13	Mouse (Swiss-Webster)	once (GW)				39 M (LD50)	Harrisson et al. 1958 As(+3)	
14	Mouse (C57H46)	once (GW)				26 M (LD50)	Harrisson et al. 1958 As(+3)	
15	Mouse (Dba2)	once (GW)				32 M (LD50)	Harrisson et al. 1958 As(+3)	
16	Mouse (C3H)	once (GW)				26 M (LD50)	Harrisson et al. 1958 As(+3)	
17	Mouse (ddY)	once (GW)				26 M (LD50)	Kaise et al. 1985 As(+3)	
18	Rabbit (New Zealand)	Gd 6-18 1 x/d (GW)				1.49 F (7/20 dams died)	Nemec et al. 1998 As(+5)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
19	Human	1 wk (W)	Gastro		0.2 (vomiting, diarrhea, abdominal pain)	2 M (diffuse inflammation of the GI tract)	Armstrong et al. 1984 NS	
			Hemato			0.2 (pancytopenia, leukopenia)		
			Hepatic			0.4 (hepatitis)		
			Renal			0.2 (nephropathy)		
			Ocular		0.2 (periorbital swelling)			
20	Human	once (IN)	Resp			121 M (respiratory distress, lung hemmorhage and edema)	Civantos et al. 1995 As(+5)	
			Cardio			121 M (hypotension, ventricular fibrillation, cardiac arrest)		
			Gastro			121 M (ulceration of upper gastrointestinal tract)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Human	once (IN)	Cardio			19 F (tachycardia)	Cullen et al. 1995 As (+5)	
			Gastro			19 F (profuse vomiting and diarrhea)		
			Hemato	19 F				
			Hepatic	19 F				
			Renal	19 F				
22	Human	once (NS)	Resp			8 M (hemorrhagic bronchitis, pulmonary edema)	Fincher and Koerker 1987 As(+3)	
			Cardio			8 M (hypotension, tachycardia, massive cardiomegaly)		
			Gastro			8 M (gastrointestinal bleeding)		
			Hemato			8 M (hemolysis)		
			Musc/skel			8 M (marked atrophy of distal muscle groups)		
			Renal			8 M (acute renal failure)		
			Dermal		8 M (truncal macular rash)			
23	Human	1 or 2 x (W)	Gastro		0.05 (occasional nausea, diarrhea, and abdominal cramps)		Franzblau and Lilis 1989 As(+3) As(+5)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
24	Human	once (W)	Gastro			120 M (vomiting and diarrhea)	Goebel et al. 1990 NS	
			Renal			120 M (anuria)		
			Dermal		120 M (hyperkeratosis)			
25	Human	once (IN)	Gastro		2 F (vomiting)		Hantson et al. 1996 As(+3)	
			Hepatic		2 F (slight increase in serum bilirubin)			
			Renal		2 F (altered renal function tests)			
26	Human	once (IN)	Gastro			13 M (frequent vomiting, diarrhea)	Kamijo et al. 1998 As(+3)	
			Hepatic			13 M (large increase in serum bilirubin, ALT, AST, LDH)		
			Dermal		13 M (erythematous eruption)			
			Ocular		13 M (constricted vision)			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
27	Human	once (IN)	Resp			22 M (tachypnea, respiratory failure)	Levin-Scherz et al. 1987 As(+3)	
			Cardio			22 M (cyanosis, hypotension, tachycardia, ventricular fibrillation)		
			Gastro			22 M (abdominal pain, nausea, diarrhea, massive vomiting, dysphagia, hemorrhage)		
			Hepatic			22 M (large increase in serum AST and LDH)		
			Renal			22 M (large increase in serum creatinine and BUN indicating acute renal failure)		
28	Human	once pregnancy wk 30 (IN)	Cardio			6 F (hypotension, rapid pulse)	Lugo et al. 1969 As(+3)	
			Gastro			6 F (abdominal pain, vomiting)		
			Hemato		6 F (high leukocyte count, low hematocrit)			
			Renal			6 F (acute renal failure)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Human	2-3 wk (F)	Resp		0.05 (sore throat, rhinorrhea, cough, sputum)		Mizuta et al. 1956 As(+5)	
			Cardio			0.05 (abnormal electrocardiogram)		
			Gastro			0.05[b] (nausea, vomiting, diarrhea, occult blood in feces and gastric and duodenal juice)		
			Hemato		0.05 (mild anemia, leukopenia)			
			Musc/skel		0.05 (tender calf muscle)			
			Hepatic		0.05 (mild hepatomegaly, impaired liver function, degenerative lesions)			
			Renal	0.05				
			Dermal		0.05 (pigmentation, itching, desquamation, exanthema)			
			Ocular		0.05 (edema of eyelids, conjunctivitis, central scotoma, neuro-retinitis)			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Human	once (IN)	Resp	11 M		43 M (shortness of breath, decreased oxygen saturation)	Moore et al. 1994a As(+3)	
			Cardio	11 M		43 M (hypotension, asystolic cardiac arrest)		
			Gastro			11 M (profuse diarrhea and vomiting, severe abdominal pain)		
			Hemato	43 M				
			Renal		11 M (increased serum creatinine)	43 M (acute renal failure)		
31	Human	once (IN)	Resp			93 M (pulmonary edema)	Quatrehomme et al. 1992 As(+3)	
			Gastro			93 M (ulcero-necrotic hemorrhagic gastritis)		
			Hepatic			93 M (hepatomegaly, diffuse fatty degeneration)		
			Renal			93 M (glomerular congestion)		
			Dermal			93 M (dermoepidermic separation)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
32	Monkey (Rhesus)	13 d 1 x/d (IN)	Gastro	3		6 (vomiting, unformed stool, "loss of condition")	Heywood and Sortwell 1979 As(+5)	
			Hepatic	3	6 (decreased liver glycogen, vacuolation of hepatocytes)			
			Renal	3	6 (dilation of proximal tubules)			
33	Rat (Wistar-Barby)	4-14 d 5 d/wk 1 x/d (G)	Cardio	2 F	11 F (decreased vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)	
			Gastro	2 F		11 F (diarrhea, bloody stools)		
34	Rat (Sprague-Dawley)	2 x (GW)	Resp	14 F			Brown and Kitchin 1996 As(+3)	
			Hepatic		0.9 F (slight increased ornithine decarboxylase and heme oxygenase activity in liver)			
			Dermal	14 F				
35	Rat (Sprague-Dawley)	2 x (GW)	Hepatic	8 F	24 F (increased heme oxygenase activity in liver)		Brown et al. 1997c As(+5)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Rat (Sprague-Dawley)	1 x/d 15 d (G)	Bd Wt	10 M	20 M (20-25% decreased body weight)		Rodriguez et al. 2001 As(+3)	
37	Rat (CD)	once Gd 9 (GW)	Bd Wt	15 F	23 F (decreased body weight gain)		Stump et al. 1999 As(+3)	
38	Mouse (CD-1)	Gd 6-15 1 x/d (GW)	Bd Wt	12 F	24 F (decreased body weight gain during gestation)		Nemec et al. 1998 As(+5)	
39	Mouse (B6C3F1)	1 or 4 d 1 x/d (GW)	Hemato	3 M	6 M (decreased polychromatic erythrocytes in bone marrow)		Tice et al. 1997 As(+3)	
40	Gn Pig	1 x/d 8 d (G)	Cardio		3.8 M (prolongation of QT interval)		Chiang et al. 2002 As2O3	
41	Rabbit (New Zealand)	Gd 6-18 1 x/d (GW)	Bd Wt	0.37 F	1.49 F (loss of body weight during treatment during gestation)		Nemec et al. 1998 As(+5)	
Neurological								
42	Human	1 wk (W)				2 (encephalopathy, peripheral neuropathy)	Armstrong et al. 1984 NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
43	Human	once (IN)				121 M (confusion, brain edema)	Civantos et al. 1995 As(+5)	
44	Human	once (IN)				19 F (lethargy)	Cullen et al. 1995 As (+5)	
45	Human	once (NS)				8 M (severe, persistent encephalopathy and peripheral neuropathy)	Fincher and Koerker 1987 As(+3)	
46	Human	once (W)				120 M (severe polyneuropathy)	Goebel et al. 1990 NS	
47	Human	once (IN)				216 M (peripheral neuropathy)	Hantson et al. 1996 As(+3)	
48	Human	once (IN)				13 M (peripheral neuropathy)	Kamijo et al. 1998 As(+3)	
49	Human	once (IN)				22 M (agitation, disorientation, paranoia, violent reactions)	Levin-Scherz et al. 1987 As(+3)	
50	Human	2-3 wk (F)				0.05 (hypesthesia in legs, abnormal patellar reflex)	Mizuta et al. 1956 As(+5)	
51	Human	once (IN)		43 M			Moore et al. 1994a As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
52	Human	once (IN)				93 M (encephalopathy)	Quatrehomme et al. 1992 As(+3)	
53	Monkey (Rhesus)	13 d 1 x/d (IN)		3		6 (marked salivation, uncontrolled head shaking)	Heywood and Sortwell 1979 As(+5)	
54	Rat (Sprague-Dawley)	1 x/d 15 d (G)		10 M	20 M (altered spontaneous locomotor activity)		Rodriguez et al. 2001 As(+3)	
55	Rabbit (New Zealand)	Gd 6-18 1 x/d (GW)		0.37 F		1.49 F (prostration, ataxia)	Nemec et al. 1998 As(+5)	
Developmental								
56	Human	once pregnancy wk 30 (IN)				6 (severe pulmonary hemorrhage that may have contributed to death in premature neonate)	Lugo et al. 1969 As(+3)	
57	Rat (CD)	once Gd 9 (GW)		15		23 (increased post-implantation loss and decreased viable fetuses)	Stump et al. 1999 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
58	Mouse (CD-1)	once Gd 8-15 (GW)		11		23	(increased fetal mortality, exencephaly)	Baxley et al. 1981 As(+3)	
59	Mouse (CD-1)	once Gd 7-15 (GW)				48	(increased fetal death, decreased fetal weight, gross and skeletal malformations)	Hood et al. 1978 As(+5)	
60	Mouse (CD-1)	Gd 6-15 1 x/d (GW)		12		24	(increased resorptions per litter, decreased live fetuses per litter, decreased mean fetal weight)	Nemec et al. 1998 As(+5)	
61	Hamster (Lak:LVG [SYR])	once Gd 8-12 (GW)		11		14	(increased fetal mortality, decreased fetal weight)	Hood and Harrison 1982 As(+3)	
62	Rabbit (New Zealand)	Gd 6-18 1 x/d (GW)		0.37		1.49	(increased resorptions per litter, decreased live fetuses per litter)	Nemec et al. 1998 As(+5)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Cancer								
63	Mouse C3H	10 d (W)				9.55 M (CEL: liver and adrenal tumors)	Waalkes et al. 2003 As(+3)	
						19.13 F (CEL: ovarian and lung tumors)		
INTERMEDIATE EXPOSURE								
Systemic								
64	Human	3 mo (W)	Gastro			0.1 (severe nausea, diarrhea, pain, cramps, vomiting, traces of blood in stool)	Franzblau and Lilis 1989 As(+3) As(+5)	
			Hemato			0.1 (anemia, leukopenia)		
			Hepatic			0.1 (large increased AST and ALT)		
			Dermal		0.1 (diffuse erythematous and scaly rash)			
			Ocular		0.1 (swelling and irritation of the eyes, impaired peripheral vision)			
65	Human	0.5-14 yr (W)	Dermal			0.05 (hyperpigmentation with keratosis, possibly pre-cancerous)	Huang et al. 1985 NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
66	Human	4 mo (W)	Gastro			0.06 F (nausea, vomiting, diarrhea)	Wagner et al. 1979 NS	
			Hemato			0.06 F (anemia, leukopenia, erythroid hyperplasia of bone marrow)		
			Dermal			0.06 F (persistent extensive hyperkeratosis of palms and soles)		
			Bd Wt			0.06 F (40 lb weight loss)		
67	Rat (Wistar-Barby)	4 wk 5 d/wk 1 x/d (GW)	Cardio		11 F (decreased vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)	
68	Rat (Sprague-Dawley)	6 wk (W)	Renal		4.7 M (increased relative kidney weight, impaired renal mitochondrial respiration, ultrastructural changes in proximal tubule)		Brown et al. 1976 As(+5)	
			Bd Wt	9.4 M	10.9 M (decreased body weight gain)			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
69	Rat (Wistar)	1 x/d 28 d (G)	Bd Wt	0.14 F			Chattopadhyay et al. 2001 As(+3)	
70	Rat (CD)	6 wk (W)	Hepatic	3 M	6 M (ultrastructural changes in hepatocytes, impaired liver mitochondrial respiration)		Fowler et al. 1977 As(+5)	
			Bd Wt	6 M		12 M (final body weight 28% lower than controls)		
71	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d (GW)	Gastro	4 F		8 F (stomach adhesions, eroded luminal epithelium in the stomach)	Holson et al. 2000 As(+3)	
			Hepatic	2 F	4 F (increased liver weight)			
			Renal	4 F	8 F (increased kidney weight)			
			Bd Wt	4 F	8 F (decreased body weight gain)			
72	Rat (NS)	16 wk (W)	Hemato		0.92 M (decreased erythrocyte and leukocyte numbers)		Kannan et al. 2001 As(+3)	
			Hepatic	2.3 M				

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
73	Rat (Sprague-Dawley)	4 wk (W)	Hemato	0.12	0.3 (increased platelet aggregation)		Lee et al. 2002 As(+3)	
74	Rat (NS)	1 x/d 30 d (G)	Endocr		2.3 M (decreased islet cells in pancreas, increased pancreatic SOD and catalase)		Mukherjee et al. 2003 As2O3	
75	Rat (Wistar)	1 x/d 5 d/wk 12 wk (G)	Resp	19 M			Schulz et al. 2002 As(+3)	
			Renal	19 M				
			Bd Wt	9.5 M	19 M (~17% decreased body weight gain)			
76	Mouse (C57BL)	6 wk (W)	Hepatic	5 M	10 M (ultrastructural changes in hepatocytes, impaired liver mitochondrial respiration)		Fowler and Woods 1979 As(+5)	
			Bd Wt	5 M	10 M (decreased body weight gain)			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
77	Mouse (C57BL/6 B6)	14 wk (W)	Hepatic	25 M			Kerkvliet et al. 1980 As(+5)	
			Renal	25 M				
78	Gn Pig (NS)	16 wk (W)	Hemato		0.69 M (decreased erythrocyte number and leukocyte number, decreased ALAD levels)		Kannan et al. 2001 As(+3)	
			Hepatic		0.69 M (increased ALAS activity)			
79	Dog (Beagle)	26 wk ad lib (F)	Hemato	1.9 F			Neiger and Osweiler 1989 As(+3)	
			Hepatic		0.8 F (mild increased serum ALT/AST)			
			Renal	1.9 F				
			Bd Wt	0.8 F	1.5 F (decreased body weight gain)	1.9 F (25% decrease in body weight)		
Immuno/ Lymphoret								
80	Mouse (C57BL/6 B6)	14 wk (W)		25 M			Kerkvliet et al. 1980 As(+5)	
Neurological								
81	Human	3 mo (W)				0.1 (paresthesia of hands and feet; confusion, disorientation and mental sluggishness)	Franzblau and Lilis 1989 As(+3) As(+5)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
82	Human	4 mo (W)				0.06 F (weakness, paresthesia)	Wagner et al. 1979 NS	
83	Rat (NS)	16 wk (W)		0.92 M	2.3 M (decreased brain neurotransmitter levels)		Kannan et al. 2001 As(+3)	
84	Rat (Wistar)	1 x/d 5 d/wk 12 wk (G)		19 M			Schulz et al. 2002 As(+3)	
85	Gn Pig (NS)	16 wk (W)		0.69 M	1.7 M (changes in brain neurotransmitter levels)		Kannan et al. 2001 As(+3)	
Reproductive								
86	Rat (Wistar)	1 x/d 28 d (G)			0.14 F (changes in uterine and ovarian weights, decreased estradiol)		Chattopadhyay et al. 2001 As(+3)	
87	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d (GW)		8 F			Holson et al. 2000 As(+3)	
88	Mouse (CD)	3 gen (W)				1 (decreased litter size)	Schroeder and Mitchener 1971 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
89	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d (GW)		4	8 (decreased fetal body weight, increased skeletal variations)		Holson et al. 2000 As(+3)	
90	Rat (Sprague-Dawley)	Gd 15 or pnd 1-4 mo (W)			2.93 M (impaired performance in postnatal neurobehavioral tests)		Rodriguez et al. 2002 As(+3)	
91	Mouse (CD)	3 gen (W)				1 (decreased litter size)	Schroeder and Mitchener 1971 As(+3)	
CHRONIC EXPOSURE								
Death								
92	Human	2-7 yr children (W)				0.05 (death)	Zaldivar and Guillier 1977 NS	
93	Human	22 yr (W)				0.014 M (death)	Zaldivar et al. 1981 NS	Cause of death was liver tumor.
94	Monkey (Rhesus)	1 yr (IN)				3 (2/7 died)	Heywood and Sortwell 1979 As(+5)	
95	Rat (Wistar)	27 mo (F)				30 (increased mortality)	Kroes et al. 1974 As(+5) lead arsenate	
96	Mouse (CD)	2 yr (W)				1 (increased mortality, decreased life span)	Schroeder and Balassa 1967 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
97	Dog (Beagle)	2 yr (F)				2.4	(6/6 died)	Byron et al. 1967 As(+3)	
98	Dog (Beagle)	2 yr (F)				2.4	(1/6 died)	Byron et al. 1967 As(+5)	
Systemic									
99	Human	NS (W)	Resp	0.032	(cough)			Ahmad et al. 1997 NS	
			Dermal			0.032	(melanosis, keratosis, hyperkeratosis, and depigmentation)		
			Ocular			0.032	(chronic conjunctivitis)		
100	Human	>8 yr (W)	Dermal	0.0012	(increased risk of premalignant skin lesions)			Ahsan et al. 2006 (NS)	
101	Human	4 yr (IN)	Dermal			0.1 F	(de-pigmentation with hyperkeratosis, possibly pre-cancerous)	Bickley and Papa 1989 As(+3)	
102	Human	NS (W)	Cardio			0.014	(gangrene of feet)	Biswas et al. 1998 NS	
			Dermal			0.014	(melanosis and keratosis of hand palms and foot soles)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
103	Human	12 yr (W)	Cardio				0.02	(Raynaud's disease, gangrene of toes)	Borgono and Greiber 1972 NS	
			Gastro		0.02	(diarrhea, abdominal pain)				
			Dermal				0.02	(abnormal pigmentation with hyperkaratosis, possibly pre-cancerous)		
104	Human	11-15 yr (W)	Dermal		0.01	(hypo- and hyperpigmentation)			Borgono et al. 1980 NS	
105	Human	NS (W)	Gastro	0.0004	0.022	(gastrointestinal irritation, diarrhea, nausea)			Cebrian et al. 1983 As(+5)	
			Dermal	0.0004			0.022	(pigmentation changes with hyperkeratosis, possibly pre-cancerous)		
106	Human	1-11 yr (W)	Hepatic		0.046	(hepatomegaly)			Chakraborty and Saha 1987 NS	
			Dermal				0.046	(pigmentation changes with keratosis, possibly pre-cancerous)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
107	Human	NS (W)	Cardio			0.064	(Blackfoot disease)	Chen et al. 1988b NS	
108	Human	>10 yr (W)	Cardio	0.0008		0.022	(increased risk of ischemic heart disease mortality)	Chen et al. 1996 NS	
109	Human	NS (W)	Cardio			0.002	(increased prevalence of cerebrovascular disease and cerebral infarction)	Chiou et al. 1997 NS	
110	Human	>5 yr (W)	Hemato	0.006[c] M 0.007 F				EPA 1981b NS	
			Dermal	0.0009[c] M 0.001 F					
111	Human	3-7 yr (W)	Cardio			0.05	(Blackfoot disease)	Foy et al. 1992 NS	
			Dermal			0.05	(melanosis with hyperkeratosis, possibly pre-cancerous)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
112	Human	2-6 yr (IN)	Hepatic			0.08 M (cirrhosis, ascites)	Franklin et al. 1950 As(+3)	
			Dermal			0.08 M (pigmentation with hyperkeratosis, possibly pre-cancerous)		
113	Human	1-15 yr (W)	Hepatic		0.16 (portal fibrosis of the liver)		Guha Mazumder 2005 (NS)	
114	Human	NS (W)	Hepatic	0.004		0.014 (hepatomegaly)	Guha Mazumder et al. 1988 NS	
			Dermal	0.004		0.014 (pigmentation changes with hyperkaratosis, possibly pre-cancerous)		
115	Human	1-20 yr (W)	Gastro		0.06 (abdominal pain)		Guha Mazumder et al. 1988 NS	
			Hemato		0.06 (anemia)			
			Hepatic			0.06 (hepatomegaly, fibrosis)		
			Dermal			0.06 (hyperpigmentation with hyperkeratosis, possibly pre-cancerous)		
116	Human	NS (W)	Dermal	0.0016		0.009 (hyperpigmentation with keratosis, possibly pre-cancerous)	Guha Mazumder et al. 1998a NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
117	Human	(W)	Dermal		0.0014 (arsenical dermatosis)		Guo et al. 2001a (NS)	
118	Human	NS (W)	Dermal		0.0043 (hyperkeratosis, hyperpigmentation)		Haque et al. 2003 (NS)	dose listed is that associated with lowest known peak As concentration ingested by a case with complete water history
119	Human	10 yr (W)	Gastro	0.0046			Harrington et al. 1978 NS	
			Hemato	0.0046				
			Dermal	0.0046				
120	Human	NS (W)	Hepatic	0.0008	0.006 (increased serum alkaline phosphatase and bilirubin)		Hernandez-Zavala et al. 1998 NS	
121	Human	lifetime (W)	Hemato		0.002 F (anemia during pregnancy)		Hopenhayn et al. 2006 (NS)	
122	Human	NS (W)	Cardio			0.067 (ischemic heart disease)	Hsueh et al. 1998b NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
123	Human	0.5-14 yr (W)	Dermal			0.05	(hyperpigmentation with keratosis, possibly pre-cancerous)	Huang et al. 1985 NS	
124	Human	15 yr (IN)	Gastro			0.03 M	(hematemesis, hemoperitoneum, melena)	Lander et al. 1975 As(+3)	
			Dermal			0.03 M	(hyperkeratosis - possibly pre-cancerous)		
125	Human	NS (W)	Cardio	0.004		0.005	(cyanosis of extremities, palpitations/chest discomfort)	Lianfang and Jianzhong 1994 NS	
			Dermal	0.004		0.005	(keratosis, hyperpigmentation, depigmentation)		
126	Human	3-22 yr (IN)	Gastro			0.05 M	(gastrointestinal hemorrhages)	Morris et al. 1974 As(+3)	
			Hepatic			0.05 M	(vascular fibrosis, portal hypertension)		
			Dermal			0.05 M	(hyperpigmentation with keratoses, possibly pre-cancerous)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
127	Human	15 yr (IN)	Hepatic			0.05 F (central fibrosis)	Piontek et al. 1989 As(+3)	
			Dermal			0.05 F (hyperkeratosis, possibly pre-cancerous)		
128	Human	NS (W)	Endocr			0.11 (diabetes mellitus)	Rahman et al. 1998 NS	
129	Human	NS (W)	Cardio	0.018	0.055 (hypertension)		Rahman et al. 1999 NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
130	Human	28 mo (IN)	Cardio	0.06 F			Silver and Wainman 1952 As(+3)	
			Gastro		0.06 F (intermittent, progressively severe nausea, cramps, and diarrhea)			
			Hemato	0.06 F				
			Hepatic		0.06 F (hepatomegaly, fatty liver)			
			Renal	0.06 F				
			Dermal			0.06 F (melanosis with hyperkeratosis, possibly pre-cancerous)		
			Ocular		0.06 F (conjunctival injection, periocular edema)			
131	Human	55 yr (IN)	Hepatic			0.03 M (portal fibrosis and hypertension, bleeding from esophageal varices)	Szuler et al. 1979 As(+3)	
			Dermal			0.03 M (hyperpigmentation with hyperkeratosis, possibly pre-cancerous)		
132	Human	45 yr (W)	Cardio			0.014 (Blackfoot disease)	Tseng 1977 NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
133	Human	NS (W)	Cardio			0.014 (Blackfoot disease)	Tseng 1989 NS	
134	Human	>45 yr (W)	Dermal	0.0008[d] M	0.014 M (hyperkeratosis and hyperpigmentation)		Tseng et al. 1968 NS	
135	Human	>30 yr (W)	Cardio		0.064 M (deficits in cutaneous microcirculation of the toes)		Tseng et al. 1995 As(+3)	
136	Human	52.6 yr (avg) (W)	Cardio	0.016		0.031 (peripheral vascular disease)	Tseng et al. 1996 NS	
137	Human	16 mo (IN)	Resp	0.1 M			Wade and Frazer 1953 As(+3)	
			Cardio	0.1 M				
			Hemato	0.1 M				
			Hepatic		0.1 M (liver enlargment)			
			Dermal			0.1 M (hyperkeratosis, hyperpigmentation with hyperkeratosis, possibly pre-cancerous)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
138	Human	30-33 yr (W)	Dermal			0.015 M (hyperkeratosis of foot, possibly pre-cancerous)	Zaldivar 1974 NS	
139	Human	12 yr (W)	Resp		0.015[c] M (bronchitis, bronchiectasis)		Zaldivar 1974 NS	
					0.018 F (bronchitis, bronchiectasis)			
			Cardio			0.015[c] M (Raynaud's disease, thrombosis)		
						0.018 F		
			Gastro		0.015[c] M (diarrhea)			
					0.018 F (diarrhea)			
			Dermal		0.015[c] M (scaling of skin, hyperkeratosis, leukoderma, melanoderma)			
					0.018 F			
			Bd Wt		0.015[c] M (unspecified decreased body weight)			
					0.018 F (unspecified decreased body weight)			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
140	Human	NS (W)	Dermal			0.063 (hyperpigmentation with keratoses, possibly pre-cancerous)	Zaldivar 1977 NS	
141	Human	2-7 yr children (W)	Resp			0.08 (inflammation of bronchi and larynx, bronchopneumonia)	Zaldivar and Guillier 1977 NS	
			Cardio			0.05 (vascular spasms, thrombosis, ischemia, hypotension, cardiac failure)		
			Gastro			0.05 (nause, vomiting, diarrhea, intestinal hemorrhage)		
			Hemato			0.05 (anemia)		
			Hepatic			0.08 (cirrhosis)		
			Renal		0.08 (cloudy swelling in kidneys)			
			Dermal			0.05 (hyperkeratosis of palms and soles, melanoderma, leukoderma)		
142	Human	1-39 yr (W)	Cardio			0.06 (arterial thickening, Raynaud's disease)	Zaldivar and Guillier 1977 NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
143	Rat (Osborne-Mendel)	2 yr (F)	Resp	20			Byron et al. 1967 As(+3)	
			Cardio	20				
			Gastro	20				
			Hemato	9	20 (slight transient decrease in Hb and Hct values)			
			Hepatic	4		9 (enlarged bile duct, bile duct proliferation)		
			Renal	9	20 (pigmentation)			
			Bd Wt	2	4 (decreased body weight gain)			
144	Rat (Osborne-Mendel)	2 yr (F)	Resp	30			Byron et al. 1967 As(+5)	
			Cardio	30				
			Gastro	30				
			Hemato	30				
			Hepatic	9	20 (enlarged bile duct)			
			Renal	9	20 (pigmentation, cysts)			
			Bd Wt		2 (decreased body weight gain in females)			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
145	Rat (Wistar)	27 mo (F)	Resp	7			Kroes et al. 1974 As(+5)	
			Cardio	7				
			Gastro	7				
			Hemato	7				
			Musc/skel	7				
			Hepatic	7				
			Renal	7				
			Endocr	7				
			Bd Wt		7 (decreased body weight gain)			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
146	Rat (Wistar)	27 mo (F)	Resp	30			Kroes et al. 1974 As(+5) lead arsenate	
			Cardio	30				
			Gastro	30				
			Hemato	7	30 (slight anemia)			
			Musc/skel	30				
			Hepatic	7		30 (enlarged bile duct with extensive dilation and inflammation)		
			Renal	30				
			Endocr	30				
			Bd Wt	7	30 (decreased body weight gain)			
147	Rat (Long-Evans)	3 yr (W)	Resp	0.6			Schroeder et al. 1968 As(+3)	
			Cardio	0.6				
			Hepatic	0.6				
			Renal	0.6				
			Dermal	0.6				
			Bd Wt	0.6				

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
148	Mouse (NS)	48 wk (W)	Hepatic	11.1			Liu et al. 2000 As(+3)	
			Renal		5.6 (histological alterations of the kidney)			
			Bd Wt	11.1				
149	Mouse (NS)	48 wk (W)	Hepatic	18.5			Liu et al. 2000 As (+5)	
			Renal		18.5 (increased relative kidney weight)			
			Bd Wt	18.5				
150	Mouse (BALB/c)	15 mo (W)	Hepatic		0.7 M (increased liver weight, altered liver histopathology, decreased hepatic enzymes in serum)		Santra et al. 2000 (NS)	
			Bd Wt		0.7 M (13-17% decreased body weight)			
151	Mouse (CD)	2 yr (W)	Bd Wt		1 (decreased body weight gain after the first 6 months of the study)		Schroeder and Balassa 1967 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
152	Dog (Beagle)	2 yr (F)	Resp	2.4			Byron et al. 1967 As(+3)	
			Cardio	2.4				
			Gastro	1		2.4 (bleeding in the gut)		
			Hemato	1	2.4 (slight to moderate anemia)			
			Hepatic	1	2.4 (hemosiderin deposits in hepatic macrophages)			
			Renal	2.4				
			Bd Wt	1		2.4 (44-61% weight loss)		
153	Dog (Beagle)	2 yr (F)	Resp	2.4			Byron et al. 1967 As(+5)	
			Cardio	2.4				
			Gastro	2.4				
			Hemato	1	2.4 (mild anemia)			
			Hepatic	1	2.4 (pigmentation in hepatic macrophages)			
			Renal	2.4				
			Bd Wt	1		2.4 (marked decreased weight gain)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
154	Human	>5 yr (W)		0.006[c] M 0.007 F			EPA 1981b NS	
155	Human	3-7 yr (W)				0.11 F (wrist weakness)	Foy et al. 1992 NS	
156	Human	1-20 yr (W)			0.06 (tingling of hands and feet)		Guha Mazumder et al. 1988 NS	
157	Human	10 yr (W)		0.0046			Harrington et al. 1978 NS	
158	Human	NS (W)		0.0014		0.04 (functional denervation)	Hindmarsh et al. 1977 NS	
159	Human	NS (W)		0.004	0.005 (fatigue, headache, dizziness, insomnia, nighmare, numbness)		Lianfang and Jianzhong 1994 NS	
160	Human	28 mo (IN)				0.06 F (paresthesia)	Silver and Wainman 1952 As(+3)	
161	Human	55 yr (IN)			0.03 M (absent ankle jerk reflex and vibration sense in legs)		Szuler et al. 1979 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
162	Human	NS (W)			0.0017 (decreased performance in neurobehavioral tests)		Tsai et al. 2003 (NS)	
163	Human	lifetime continuous (W)			0.005 (decreased performance in neurobehavioral tests)		Wasserman et al. 2004 (NS)	
164	Human	lifetime		0.0008	0.003 (decreased score in Performance domain of an intelligence scale)		Wasserman et al. 2007 (NS)	
Reproductive								
165	Human	NS (W)				0.008 F (increased frequencies for spontaneous abortion, stillbirth, and preterm birth rates)	Ahmad et al. 2001 (NS)	98% of the exposed group drank water containing 0.1 mg As/L or more.
166	Human	lifetime (W)				0.006 F (increased incidence of spontaneous abortion)	Milton et al. 2005 (NS)	
167	Human	lifetime (W)				0.02 F (increased risk of stilbirth)	von Ehrenstein et al. 2006 (NS)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
168	Human	continuous (W)			0.002 (reduced birth weight)		Hopenhayn et al. 2003a (NS)	
169	Human	>1 yr 1 x/d (W)				0.03 (increased SMR for malignant and non-malignant lung disease)	Smith et al. 2006 (NS)	
170	Human	lifetime (W)		0.008			von Ehrenstein et al. 2006 (NS)	NOAEL is for no increase in risk of neonatal mortality or overall infant mortality.
Cancer								
171	Human	NS (W)				0.022 (CEL: skin cancer)	Cebrian et al. 1983 As(+5)	
172	Human	NS (W)				0.064 (CEL: bladder, lung and liver cancers)	Chen et al. 1986 NS	
173	Human	NS (W)				0.064 (CEL: malignant neoplasms of the bladder, skin, lung and liver)	Chen et al. 1988b NS	
174	Human	NS (W)				0.003 (CEL: bladder cancer)	Chiou et al. 2001 (NS)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
175	Human	2 wk- 12 yr (IN)				3.67	(CEL: bladder cancer risk)	Cuzick et al.1992 As(+3)	
176	Human	NS (W)				0.0011	(CEL: lung cancer)	Ferreccio et al. 1998 NS	
177	Human	NS (W)				0.0017	(CEL: lung cancers)	Ferreccio et al. 2000 (NS)	
178	Human	NS (W)				0.018	(CEL: lung cancer mortality)	Guo 2004 (NS)	
179	Human	NS (W)				0.018	(CEL: bladder cancer)	Guo and Tseng 2000 (NS)	
180	Human	NS (W)				0.052	(CEL: increased incidence of transitional cell carcinomas of the bladder, kidney, ureters, and all urethral cancer)	Guo et al. 1997 NS	
181	Human	NS (W)				0.0049[c] M	(CEL: squamous cell carcinoma of the skin)	Guo et al. 2001b (NS)	
						0.0094 F			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
182	Human	>1 yr (W)				0.0075	(CEL: basal or squamous skin carcinoma)	Haupert et al. 1996 NS	
183	Human	16 yr (avg) (IN)				0.04 M	(CEL: basal cell and squamous cell carcinomas of the skin, small cell and squamous cell carcinoma of the lung)	Luchtrath 1983 As(+5)	
184	Human	60 yr (W)				0.038	(CEL: intraepidermal carcinoma)	Tseng 1977 NS	
185	Human	>45 yr (W)				0.014	(CEL: squamous cell carcinoma of the skin)	Tseng et al. 1968 NS	
186	Human	~5 yr (W)				0.033	(CEL: lung, urinary tract cancer)	Tsuda et al. 1995a As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
187	Human	12 yr (W)				0.015[c] M (CEL: squamous cell carcinoma of the skin)	Zaldivar 1974 NS	
						0.018 F (CEL: squamous cell carcinoma of the skin)		
188	Human	22-34 yr (W)				0.014 M (CEL: basal cell and squamous cell carcinomas of the skin, hemangioendothelioma of the liver)	Zaldivar et al. 1981 NS	

a The number corresponds to entries in Figure 3-3.

b Used to derive provisional acute oral minimal risk level (MRL) of 0.005 mg/kg/day; dose divided by an uncertainty factor of 10 (for extrapolation from a LOAEL to a NOAEL).

c Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

d Used to derive chronic oral minimal risk level (MRL) of 0.0003 mg/kg/day; dose divided by an uncertainty factor of 3 (for human variability).

avg = average; ALAD = delta-aminolevulinic acid dehydratase; ALAS = delta-aminolevulinic acid synthetase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; GI = gastrointestinal; (GW) = gavage in water; gen = generation; Gd = gestation day; Gn pig = guinea pig; Hemato = hematological; Hb = hemoglobin; Hct = hematocrit; Hemato = hematological; hr = hour(s); (IN) = ingestion; LD50 = lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; pmd = pre-mating day; pnd = post-natal day; Resp = respiratory; SMR =standardized mortality ratio; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

Acute (≤14 days)

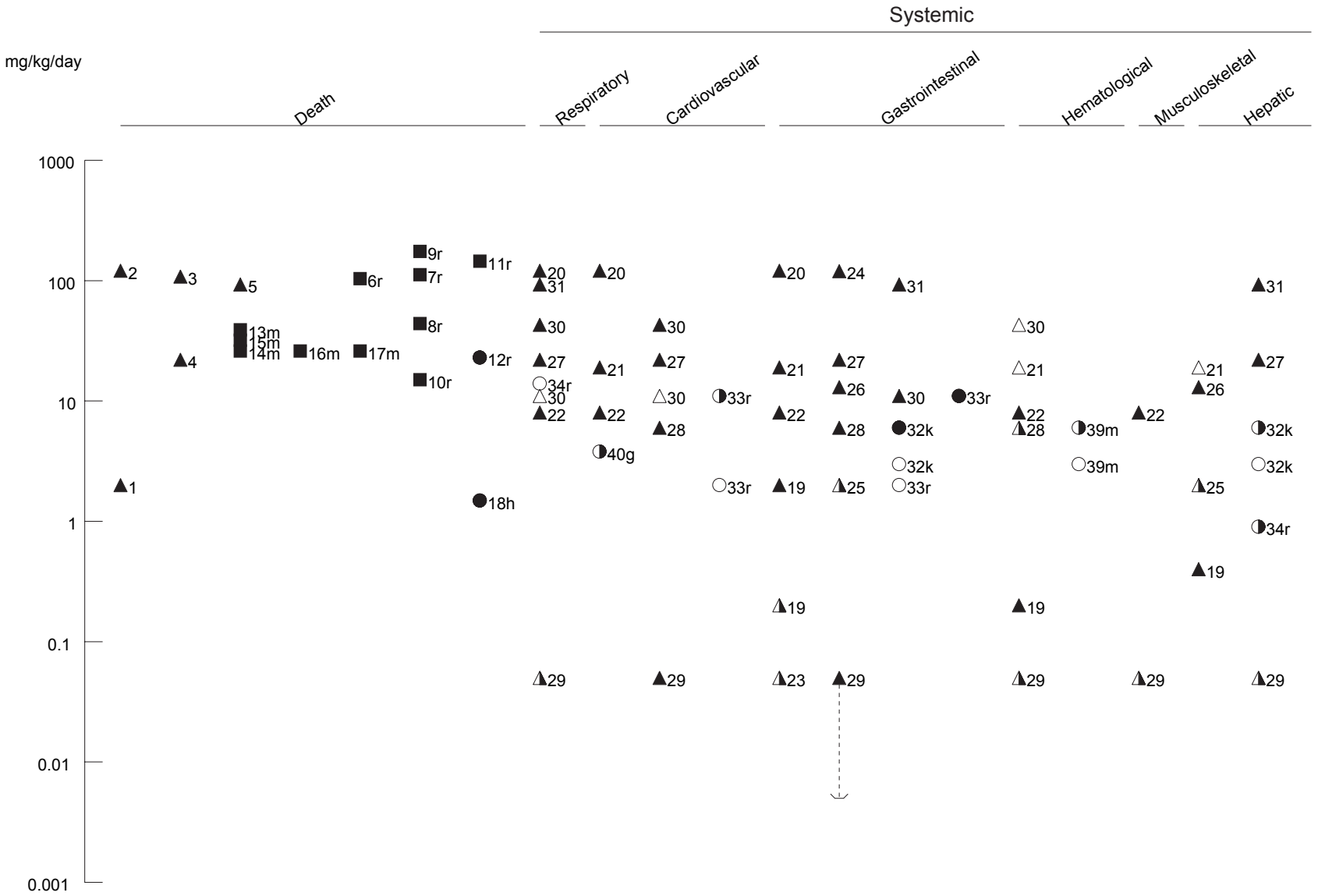
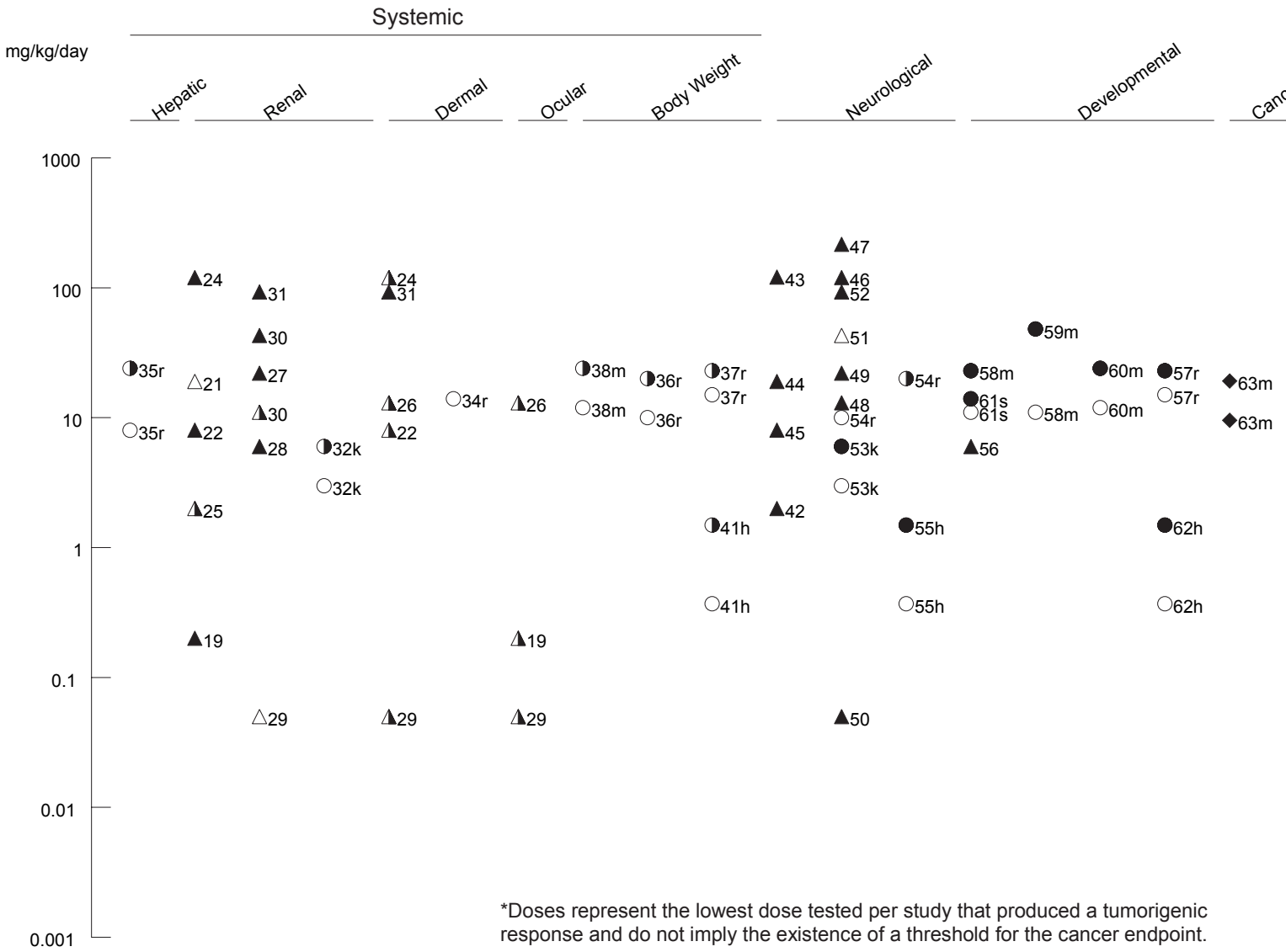


Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral *(Continued)*

Acute (≤14 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◮ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral *(Continued)*

Intermediate (15-364 days)

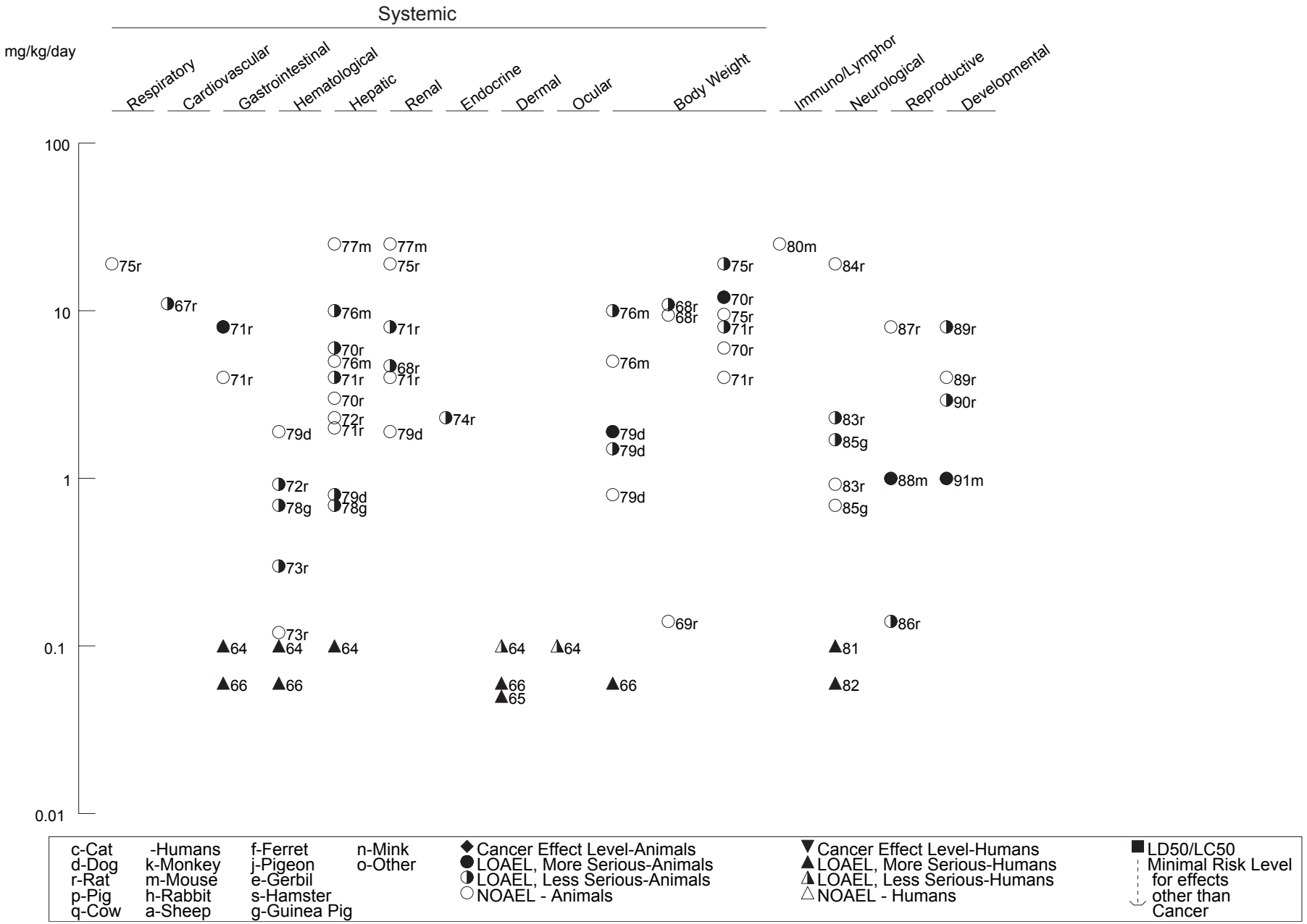


Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral *(Continued)*

Chronic (≥365 days)

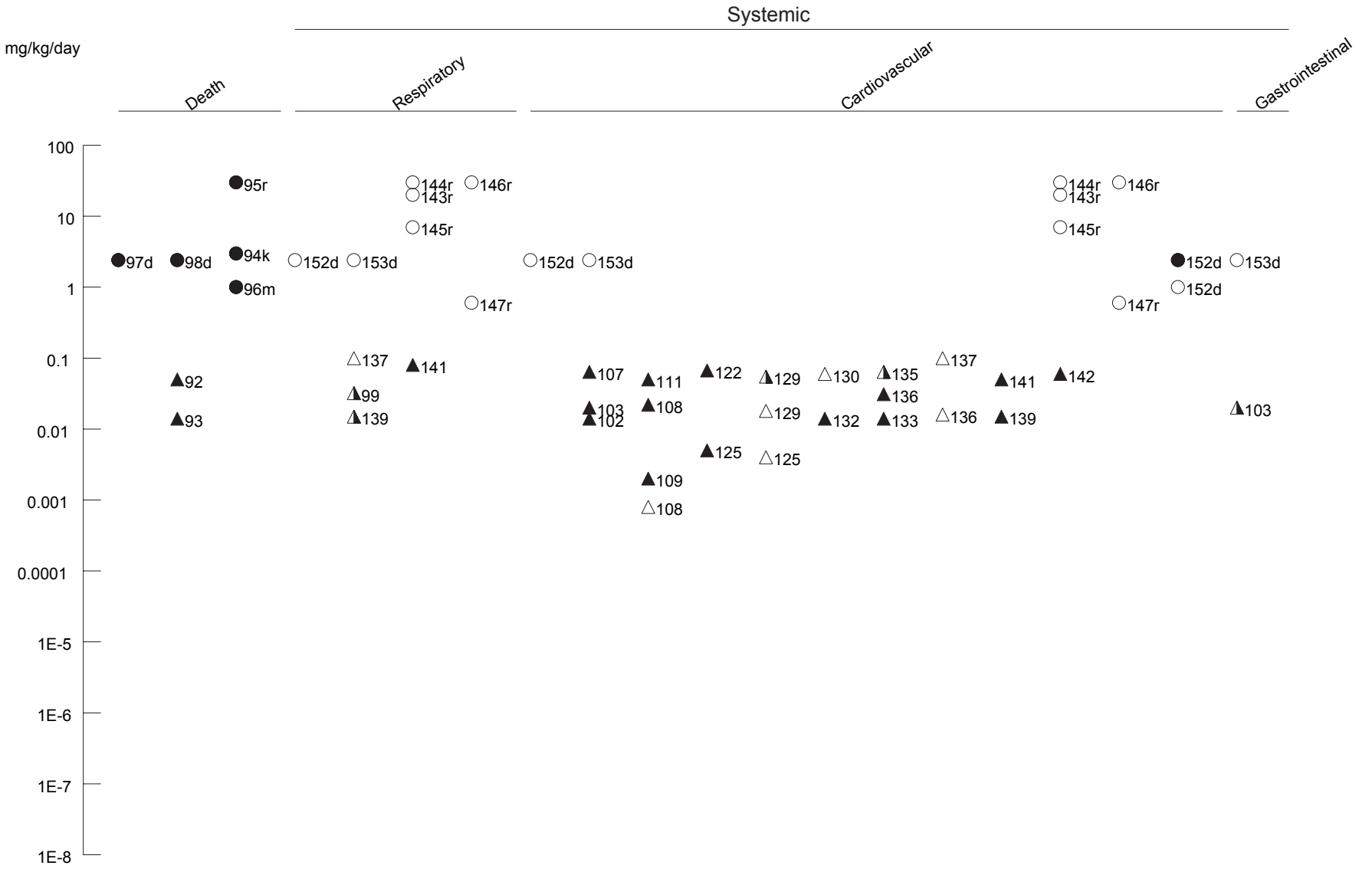


Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral *(Continued)*

Chronic (≥365 days)

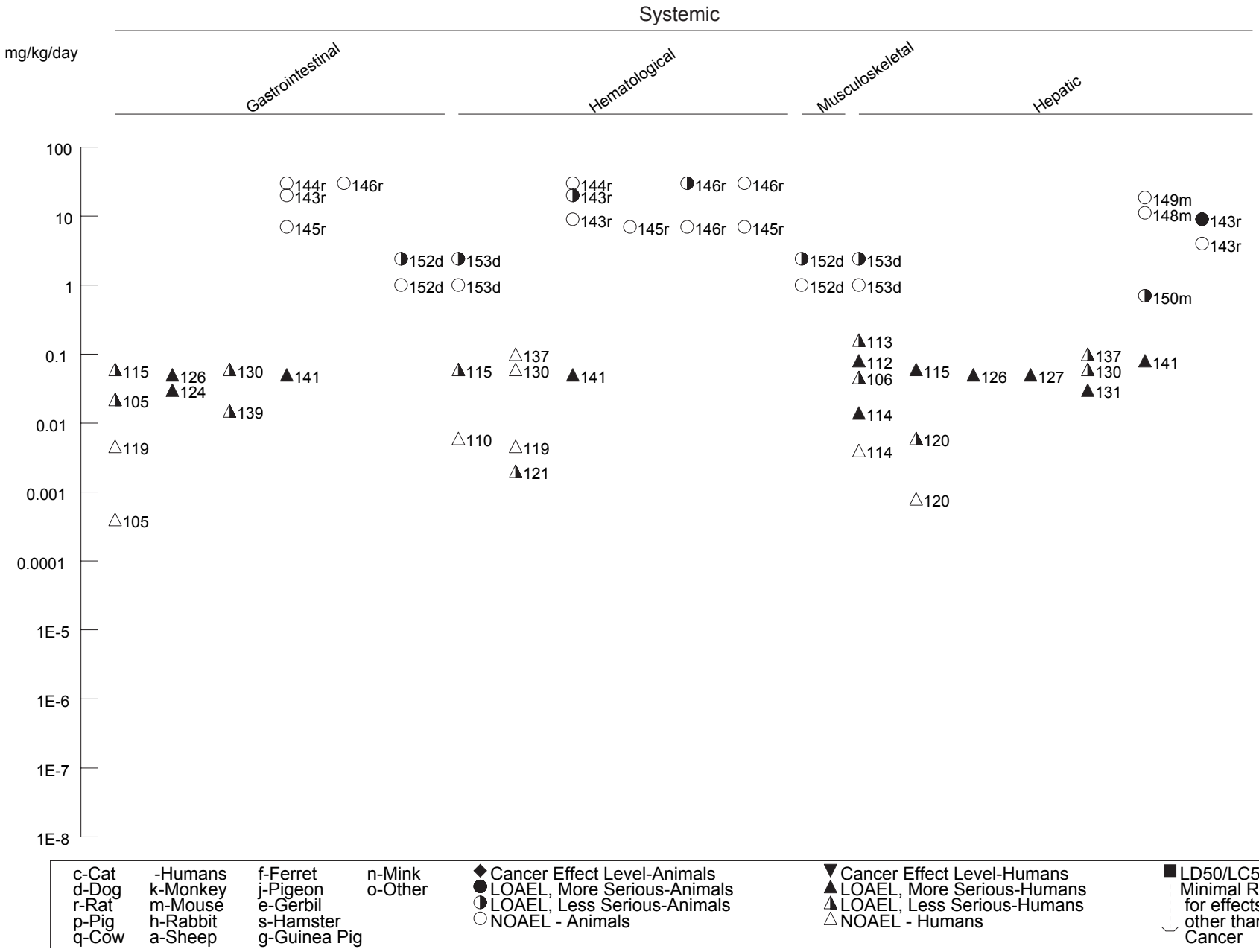
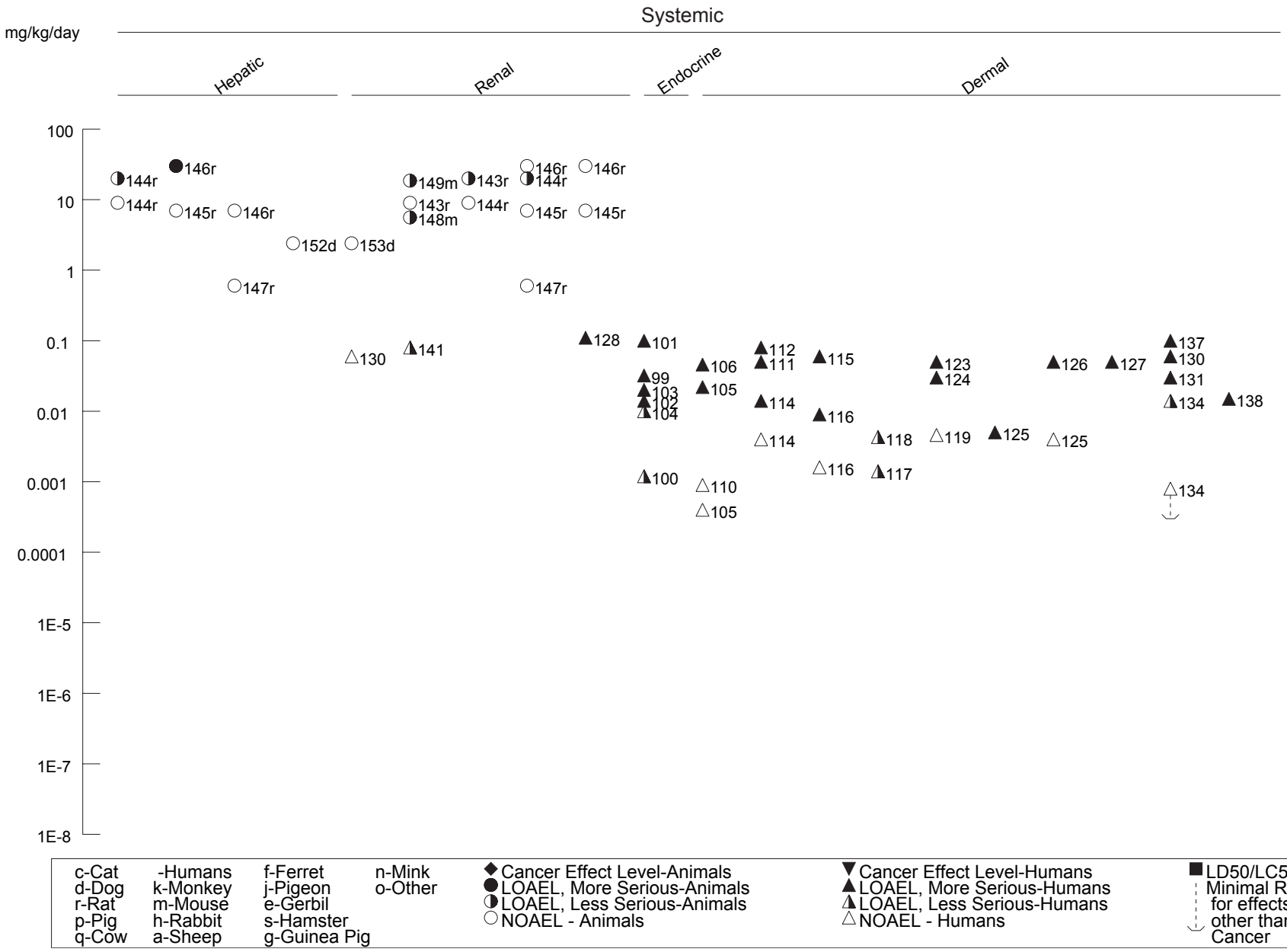


Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral *(Continued)*

Chronic (≥365 days)



c-Cat, d-Dog, r-Rat, p-Pig, q-Cow
-Humans, k-Monkey, m-Mouse, h-Rabbit, a-Sheep
f-Ferret, j-Pigeon, e-Gerbil, s-Hamster, g-Guinea Pig
n-Mink, o-Other

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral *(Continued)*

Chronic (≥365 days)

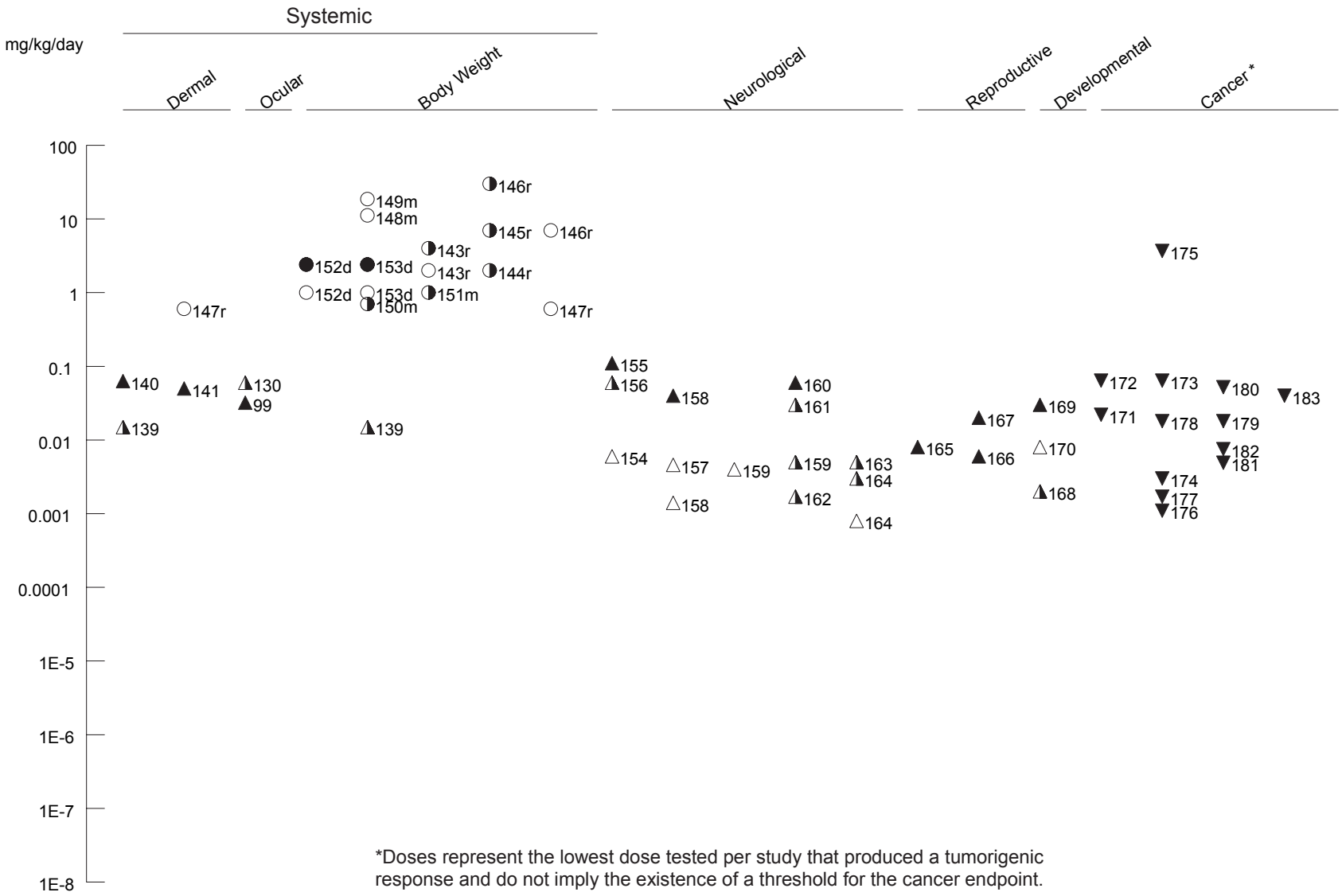


Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral *(Continued)*

Chronic (≥365 days)

*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (GW)				3184 M (LD50) 2449[b] F (LD50)	Gur and Nyska 1990 MSMA	
2	Mouse (ddY)	once (GW)				1800 M (LD50)	Kaise et al. 1989 MMA	
3	Rabbit (New Zealand)	once (GW)				102 M (LD50)	Jaghabir et al. 1988 MSMA	
Systemic								
4	Rat (Sprague-Dawley)	once (GW)	Gastro		2030 (mucoid feces and diarrhea)		Gur and Nyska 1990 MSMA	
			Bd Wt	2030				
5	Rat (Sprague-Dawley)	Gd 6-15 (GW)	Bd Wt	10 F	100 F (17% decrease in maternal body weight gain)	500 F (40% decrease in maternal body weight gain)	Irvine et al. 2006 MMA	
6	Mouse (ddY)	once (GW)	Resp			1800 M (respiratory arrest)	Kaise et al. 1989 MMA	
			Gastro		2200 M (diarrhea, slight congestion of the small intestine)			

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
7	Rabbit (New Zealand)	Gd 7-19 (GW)	Gastro	7 F	12 F (loose feces/diarrhea in 7/14 pregnant rabbits)		Irvine et al. 2006 MMA	
			Bd Wt	7 F		12 F (67% decrease in maternal body weight gain)		
8	Rabbit (New Zealand)	once (GW)	Gastro		60 M (diarrhea)		Jaghabir et al. 1988 MSMA	
Developmental								
9	Rat (Sprague-Dawley)	Gd 6-15 (GW)		100	500 (decreased fetal weight and increased fetal incidence of imcomplete ossification of thoracic vertebrae)		Irvine et al. 2006 MMA	
10	Rabbit (New Zealand)	Gd 7-19 (GW)		7	12 (supernumerary thoracic ribs and eight lumbar vertebrae)		Irvine et al. 2006 MMA	
INTERMEDIATE EXPOSURE								
Death								
11	Rat (Fischer- 344)	52 wk (F)				106.9 M (increased mortality)	Arnold et al. 2003 MMA	

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
12	Rat (Fischer- 344)	52 wk (F)	Gastro	3.5[c] M	30.2 M (diarrhea)		Arnold et al. 2003 MMA	
			Bd Wt	30.2 M	106.9 M (14% decrease in body weight)			
13	Rat (Sprague-Dawley)	146-171 d pre-mating, mating, gestation, and lactation (F)	Bd Wt	76			Schroeder 1994 MMA	
14	Dog (Beagle)	52 wk (C)	Gastro		2 M (diarrhea)		Waner and Nyska 1988 MMA	
			Bd Wt	2 F	8 F (decrease in body weight)			
Reproductive								
15	Rat (Sprague-Dawley)	146-171 d pre-mating, mating, gestation, and lactation (F)		22	76 (decreased pregnancy rate and male fertility index in F0 and F1)		Schroeder 1994 MMA	
16	Mouse (Swiss)	19 d 3 d/wk (GW)			119 M (reduced fertility)		Prukop and Savage 1986 MSMA	

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
17	Rat (Sprague-Dawley)	146-171 d pre-mating, mating, gestation, and lactation (F)		22	76 (decreased pup survival F1 and F2)		Schroeder 1994 MMA	
CHRONIC EXPOSURE								
Death								
18	Rat (Fischer- 344)	104 wk (F)				72.4 M (increased mortality)	Arnold et al. 2003 MMA	

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
19	Rat (Fischer- 344)	104 wk (F)	Gastro	3 M	25.7 M (diarrhea)	72.4 M (necrosis, ulceration, perforation in large intestine)	Arnold et al. 2003 MMA	
			Hemato	72.4 M				
			Musc/skel	72.4 M				
			Hepatic	72.4 M				
			Renal	3.9 F	33.9 F (increased absolute kidney weight and progressive glomerulonephropathy)			
			Endocr	3.9 F	33.9 F (hypertrophy of thyroid follicular epithelium, decreased absolute thyroid weight)			
			Dermal	72.4 M				
			Ocular	72.4 M				
			Bd Wt	3 M	25.7 M (15% decrease in body weight)	33.9 F (30% decrease in body weight)		

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
20	Rat (Fischer- 344)	104 wk (W)	Hemato	8.4 M			Shen et al. 2003 MMA	
			Hepatic	2.1 M	8.4 M (increased GST-P-positive foci)			
			Renal		2.1 M (hyperplasia of the bladder)			
			Bd Wt	8.4 M				
21	Mouse (B6C3F1)	104 wk (F)	Cardio	67.1 M			Arnold et al. 2003 MMA	
			Gastro	24.9 M	67.1 M (loose and mucoid feces, metaplasia of the cecum and colon)			
			Musc/skel	67.1 M				
			Hepatic	67.1 M				
			Renal	1.2[d] M	6 M (increased incidence of progressive glomeruloephropathy)			
			Dermal	67.1 M				
			Ocular	67.1 M				
			Bd Wt	24.9 M	67.1 M (17% decrease in body weight)			

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
22	Dog (Beagle)	52 wk (C)	Resp	35			Waner and Nyska 1988 MMA	
			Gastro		2 M (diarrhea)			
			Hemato	35				
			Hepatic	35				
			Renal		8 (increased urine specific gravity; increased kidney weight)			
			Ocular	35				
			Bd Wt	2 F		8 F (42% decrease in body weight)		
Neurological								
23	Dog (Beagle)	52 wk (C)		35			Waner and Nyska 1988 MMA	
Reproductive								
24	Dog (Beagle)	52 wk (C)		35 M 8 F	35 F (decrease in estrus)		Waner and Nyska 1988 MMA	Histological examination of reproductive tissues.

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Cancer								
25	Rat (Fischer- 344)	104 wk (W)		8.4 M			Shen et al. 2003 MMA	

a The number corresponds to entries in Figure 3-4.

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-4. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c The intermediate-duration oral MRL of 0.1 mg MMA/kg/day was calculated using a benchmark dose analysis. The BMDL10 of 12.38 mg MMA/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability)

d The chronic-duration oral MRL of 0.01 mg MMA/kg/day was calculated using a benchmark dose analysis. The BMDL10 of 1.09 mg MMA/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability)

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = female; Gastro = gastrointestinal; (GO) = gavage in oil; (GW) = gavage in water; Gd = gestation day; GST-P = glutathione S-transferase placental form; Hemato = hematological; IN = ingestion; LD50 = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MMA = monomethylarsonic acid; MSMA = monosodium methane arsonate; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s)

Figure 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

Acute (≤14 days)

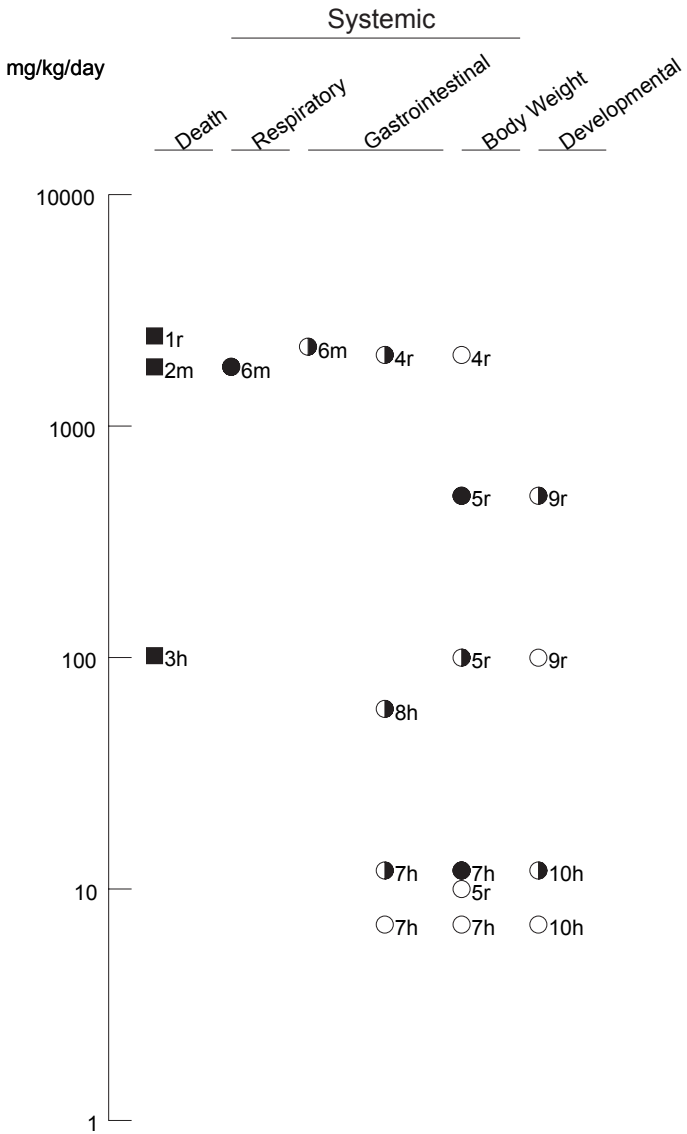


Figure 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral *(Continued)*

Intermediate (15-364 days)

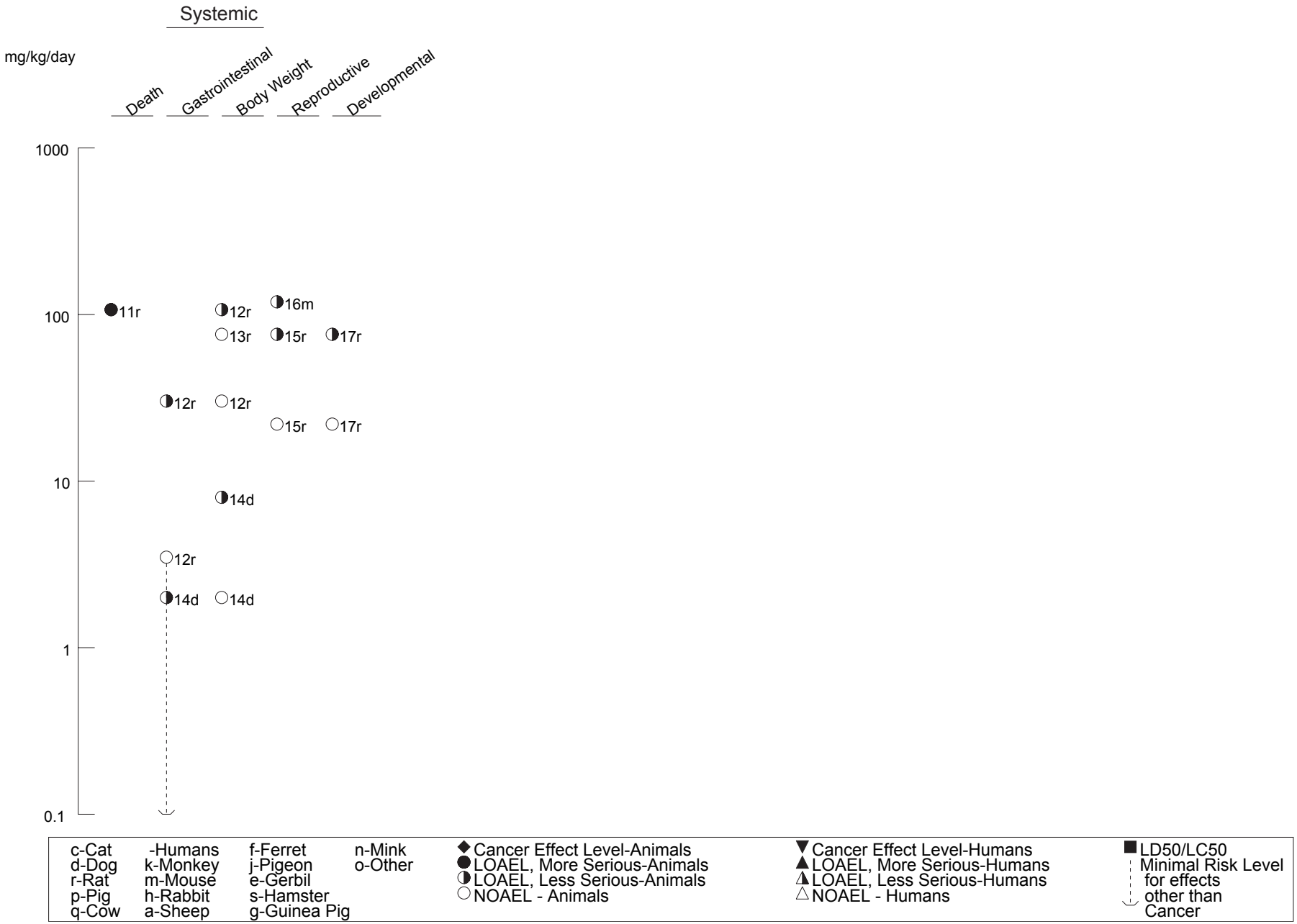


Figure 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral *(Continued)*

Chronic (≥365 days)

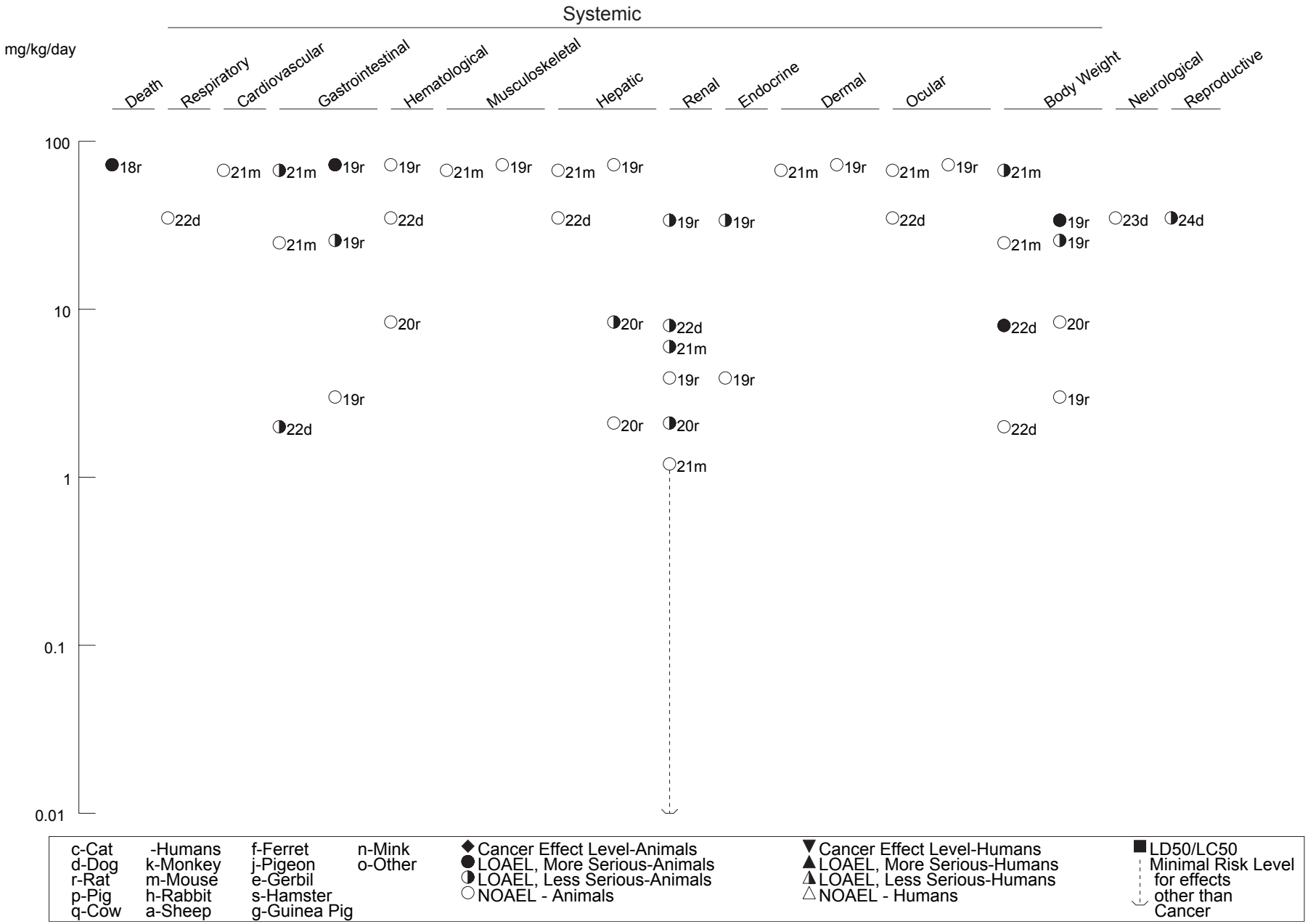


Figure 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral *(Continued)*

Chronic (≥365 days)

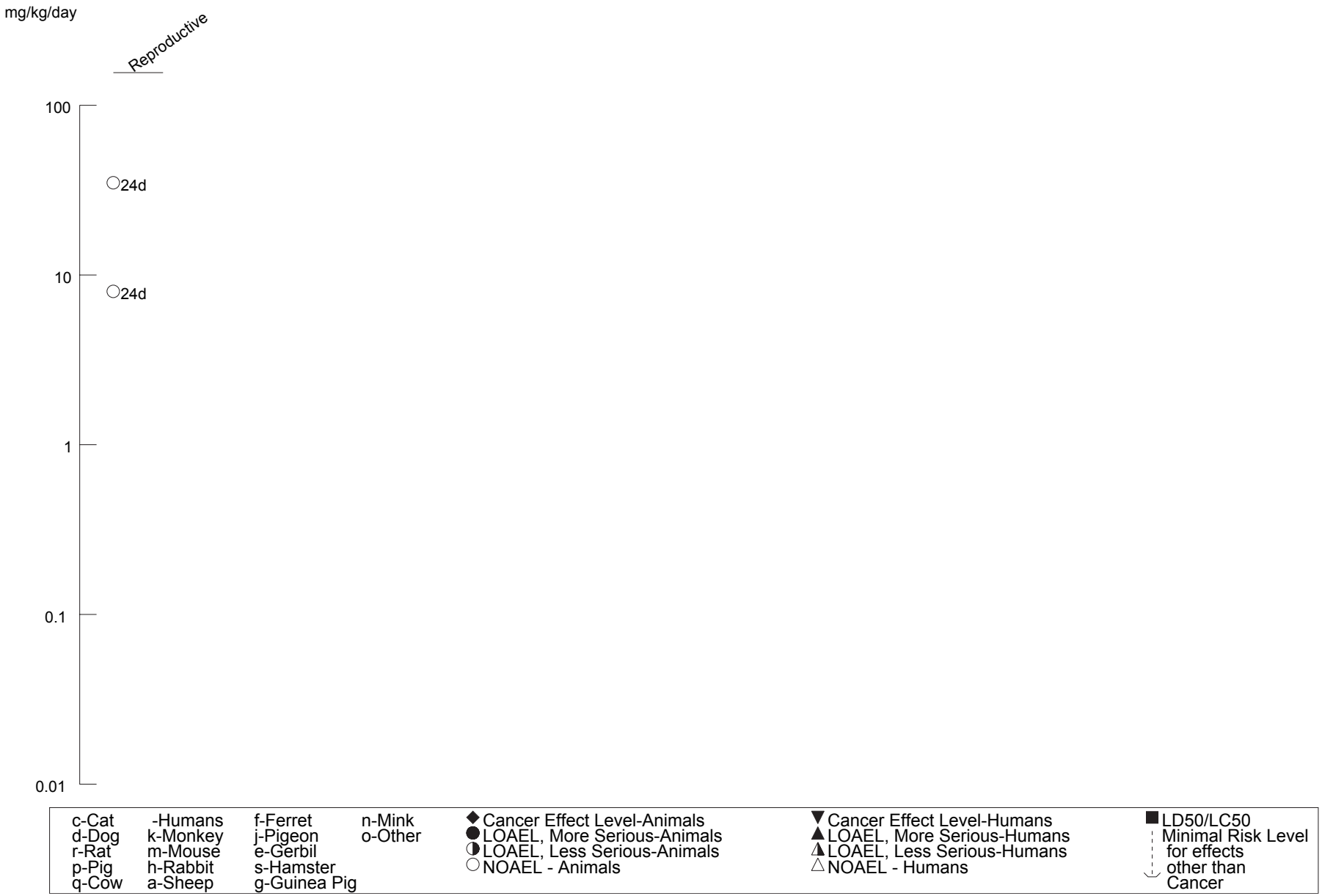


Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Fischer- 344)	13 wk (F)				475 M (100% mortality during first 2 weeks of study)	Crown et al. 1987 DMA	
2	Rat (CD)	10 d Gd 7-16 1 x/d (GW)				60 F (67% mortality)	Rogers et al. 1981 DMA	
3	Mouse (ddY)	once (GW)				1200 M (LD50)	Kaise et al. 1989 DMA	
4	Mouse (CD-1)	10 d Gd 7-16 1 x/d (GW)				600 F (59% mortality)	Rogers et al. 1981 DMA	
Systemic								
5	Rat (Fischer- 344)	2 wk (F)	Renal		11 F (altered bladder cell surface characteristics)		Cohen et al. 2001 DMA	
			Bd Wt	11 F				
6	Rat (Fischer- 344)	13 wk (F)	Gastro		475 M (diarrhea and congestion and hemorrhagic contents in gastrointestinal tract in rats dying during first 2 weeks)		Crown et al. 1987 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
7	Rat (Sprague-Dawley)	Gd 6-15 (GW)	Bd Wt	12 F	36 F (decreased maternal body weight gain)		Irvine et al. 2006 DMA	
8	Rat (CD)	10 d Gd 7-16 1 x/d (GW)	Bd Wt			40 F (27% decreased maternal weight gain)	Rogers et al. 1981 DMA	
9	Mouse (B6C3F1)	24 hr 1 or 2 x (GW)	Resp		720 F (decreased lung ODC)		Ahmad et al. 1999a DMA	
			Hepatic		720 F (decreased liver GSH, GSSG, CYP-450 and ODC; increased serum ALT)			
10	Mouse (ddY)	once (GW)	Resp			900 M (respiratory arrest)	Kaise et al. 1989 DMA	
			Gastro		1757 M (diarrhea, slight congestion of the intestion)			
11	Mouse (CD-1)	10 d Gd 7-16 1 x/d (GW)	Bd Wt			200 F (26% decreased maternal weight gain)	Rogers et al. 1981 DMA	
12	Dog (Beagle)	52 wk (C)	Gastro	6.5	16 (vomiting and diarrhea)		Zomber et al. 1989 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
13	Rabbit (New Zealand)	Gd 7-19 (GW)	Gastro	12 F	48 F (fluid gastrointestinal tract contents)		Irvine et al. 2006 DMA	
			Bd Wt	12 F		48 F (maternal weight loss)		
Neurological								
14	Mouse (ddY)	once (GW)				1757 M (increased startle reflex; ataxia)	Kaise et al. 1989 DMA	
Developmental								
15	Rat (Sprague-Dawley)	GD6-15 (GW)			40 F (decreased fetal body weight)		Chernoff et al. 1990 DMA	
16	Rat (Sprague-Dawley)	Gd 6-15 (GW)		12	36 (decreases in number of live fetuses and fetal weight; increases in fetuses with diaphragmatic hernia; delayed ossification)		Irvine et al. 2006 DMA	
17	Rat (CD)	10 d Gd 7-16 1 x/d (GW)		15		30 (malformed palates in 15%)	Rogers et al. 1981 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Mouse (CD-1)	Gd 8 (GW)				1600 F (fetal deaths, decreased fetal weight, delayed ossification, skeletal malformations)	Kavlock et al. 1985 DMA	
19	Mouse (CD-1)	10 d Gd 7-16 1 x/d (GW)		200		400 (18% decrease in fetal weight, delayed ossification, cleft palate in 12/28; irregular palatine rugae in 4.8%)	Rogers et al. 1981 DMA	
20	Rabbit (New Zealand)	Gd 7-19 (GW)		12			Irvine et al. 2006 DMA	
INTERMEDIATE EXPOSURE								
Death								
21	Rat (Fischer- 344)	13 wk (F)				190 M (100% mortality during first 4 weeks of study)	Crown et al. 1987 DMA	
22	Rat (Fischer- 344)	4 wk 5 d/wk 1 x/d (G)				57 (50% survival in males; 20% survival in females)	Murai et al. 1993 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
23	Rat (Fischer- 344)	8 wk (W)				17 M (10/10 died)	Wanibuchi et al. 1996 DMA	
Systemic								
24	Rat (Fischer- 344)	10 or 20 wk (F)	Renal	1 F	10 M (necrosis in bladder epithelium)		Arnold et al. 1999 DMA	
					5 F[b] (increased kidney weight, calcification at corticomedullary junction; increased bladder weight and increased BrdU labelling in bladder epithelium)			
			Bd Wt	10				
25	Rat (Fischer- 344)	10 wk (F)	Renal		11 F (increased bladder and kidney weights, hyperplasia and necrosis of bladder epithelium)		Cohen et al. 2001 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
26	Rat (Fischer- 344)	13 wk (F)	Resp	43.2 M			Crown et al. 1987 DMA	
			Cardio	43.2 M				
			Gastro	43.2 M	190 M (diarrhea and congestion and hemorrhagic contents in gastrointestinal tissues)			
			Hemato	0.44 F	4.5 F (decreased hemoglobin and erythrocyte levels)			
			Hepatic	23.5 M				
			Renal	0.4 M	4 M (increased urine volume and decreased specific gravity)			
			Endocr	0.4 M	4 M (hypertrophy of thyroid follicle epithelium)			
			Bd Wt	43.2 M				
27	Rat (Fischer- 344)	4 wk 5 d/wk 1 x/d (G)	Renal			57 (papillary necrosis and hyperplasia; cortical degeneration and necrosis)	Murai et al. 1993 DMA	
			Bd Wt		57 (decreased body weight)			

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
28	Rat (Sprague-Dawley)	10 wk pre-mating, gestation and lactation periods (F)	Resp	16.5			Rubin et al. 1989 DMA	
			Cardio	16.5				
			Hemato	0.34 M	2.3 M (decreased mean corpscular hemoglobin concentration)			
			Hepatic	16.5				
			Renal	16.5				
			Endocr	2.3 F	16.5 F (hypertrophy of thyroid follicle epithelium)			
			Bd Wt	16.5				
29	Rat (Sprague-Dawley)	42 d (F)	Hemato	3.7 M			Siewicki 1981 DMA	
			Hepatic	3.7 M				
			Renal	3.7 M				
			Bd Wt	3.7 M				

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Dog (Beagle)	6 d/wk 52 wk (C)	Gastro	6.5	16 (vomiting and diarrhea)		Zomber et al. 1989 DMA	
			Hemato	16 M	40 M (decreased erythrocyte and increased leukocyte levels)			
Reproductive								
31	Rat (Sprague-Dawley)	10 wk pre-mating, gestation and lactation periods (F)		16.5			Rubin et al. 1989 DMA	
Cancer								
32	Mouse A/J	50 wk ad lib (W)				10.4 M (CEL: lung tumors)	Hayashi et al. 1998 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
33	Rat (Fischer- 344)	daily 2 yr (F)	Resp	7.8			Arnold et al. 2006 DMA	
			Cardio	7.8				
			Gastro	7.8				
			Hemato	7.8				
			Musc/skel	7.8				
			Hepatic	7.8				
			Renal	0.77 M	3.1 M (nephrocalcinosis)			
				0.77 F	3.1 F (urothelial vacular degeneration and hyperplasia of urothelial cells in urinary bladder)			
			Endocr	3.1	7.8 (hypertrophy of thyroid follicle epithelium)			
			Dermal	7.8				
			Ocular	7.8				
			Bd Wt	7.8				
34	Rat (Fischer- 344)	104 wk (W)	Renal	0.75 M	3.4 M (nodular or papillary hyperplasia in urinary bladder)		Wei et al. 1999, 2002 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
35	Mouse (B6C3F1)	daily 2 yr (F)	Resp	94			Arnold et al. 2006 DMA	
			Cardio	94				
			Gastro	94				
			Hemato	94 F	94 F (decreased lymphocytes and increased monocytes)			
			Musc/skel	94				
			Hepatic	94				
			Renal	1.3[c] F	37 M (progressive glomerulonephropathy)			
					7.8[b] F (vacuolization of superficial cells of urotheliumin urinary bladder)			
			Dermal	94				
			Ocular	94				
			Bd Wt	94				

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Dog (Beagle)	6 d/wk 52 wk (C)	Resp	40			Zomber et al. 1989 DMA	
			Cardio	40				
			Gastro	6.5	16 (vomiting and diarrhea)			
			Hepatic	40				
			Renal	40				
Reproductive								
37	Rat (Fischer- 344)	daily 2 yr (F)		7.8			Arnold et al. 2006 DMA	Histological examination of reproductive tissues.
38	Mouse (B6C3F1)	daily 2 yr (F)		94			Arnold et al. 2006 DMA	Histological examination of reproductive tissues.
Cancer								
39	Rat (Fischer- 344)	daily 2 yr (F)				7.8 (CEL: urothelial cell papillomas and carcinomas in urinary bladder)	Arnold et al. 2006 DMA	
40	Rat (Fischer- 344)	104 wk (W)				3.4 M (CEL: urinary bladder tumors)	Wei et al. 1999, 2002 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
41	Mouse knockout	continuous 18 mo (W)				11.8 M (CEL)	Salim et al. 2003 DMA	

a The number corresponds to entries in Figure 3-5.

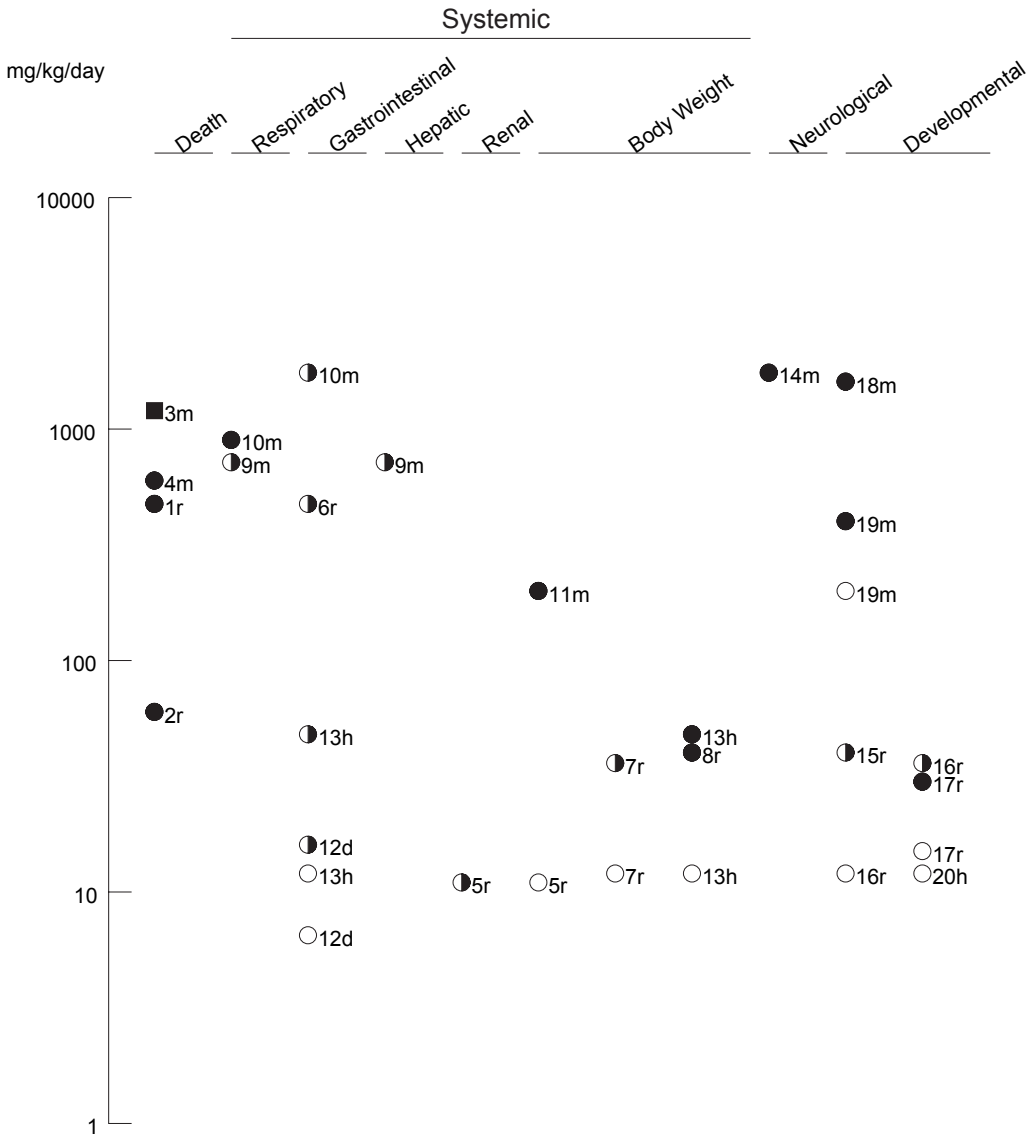
b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-5. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c The chronic-duration oral MRL of 0.02 mg DMA/kg/day was calculated using a benchmark dose analysis. The BMDL10 of 1.80 mg DMA/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability)

ad lib = ad libitum; ALT = alanine aminotransferase; Bd Wt = body weight; BrdU = bromodeoxyuridine; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CYP = cytochrome p; d= day(s); DMA = dimethylarsinic acid; Endocr = endocrine; (F) = feed; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; GSH = reduced glutathione; GSSG = oxidized glutathione; (GW) = gavage in water; Hemato = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; ODC = ornithine decarboxylase; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

Acute (≤14 days)



c-Cat, d-Dog, r-Rat, p-Pig, q-Cow
-Humans, k-Monkey, m-Mouse, h-Rabbit, a-Sheep
f-Ferret, j-Pigeon, e-Gerbil, s-Hamster, g-Guinea Pig
n-Mink, o-Other

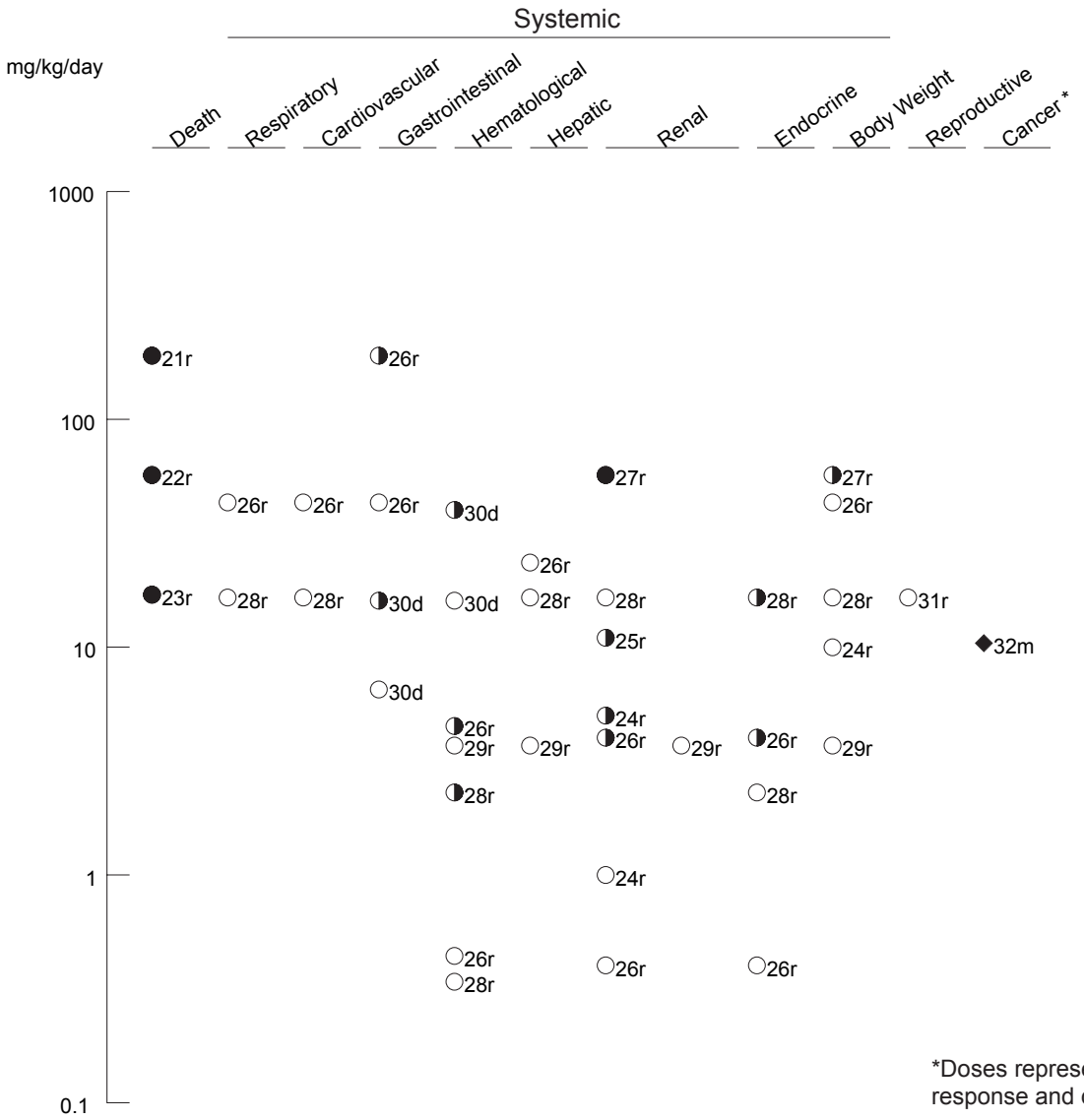
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral *(Continued)*

Intermediate (15-364 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

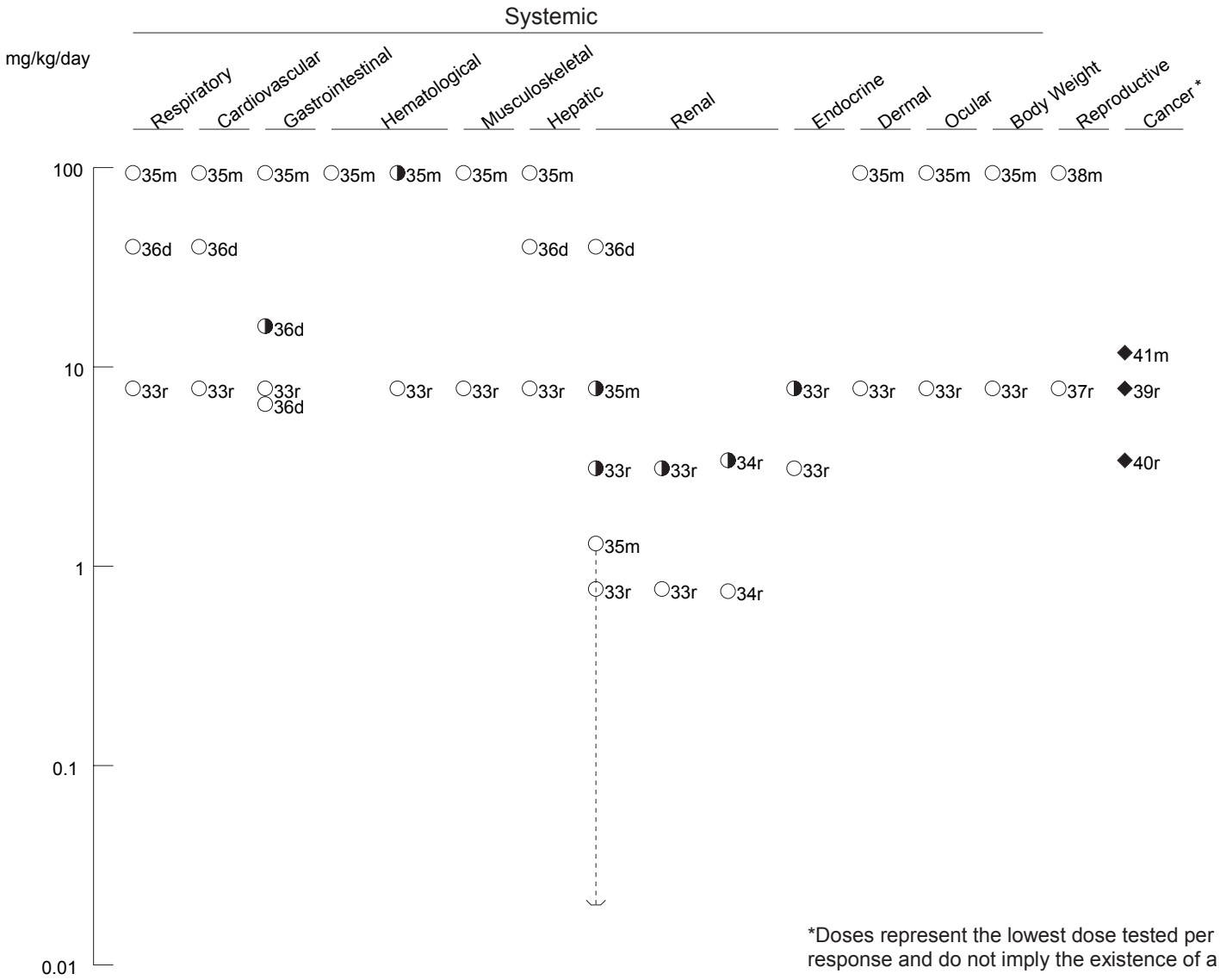
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	-Humans	f-Ferret	n-Mink
d-Dog	k-Monkey	j-Pigeon	o-Other
r-Rat	m-Mouse	e-Gerbil	
p-Pig	h-Rabbit	s-Hamster	
q-Cow	a-Sheep	g-Guinea Pig	

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Holtzman)	once (GW)				155 (LD50)	Kerr et al. 1963 ROX	
2	Rat (Fischer- 344)	once (GO)				150 M (5/5 died) 81[b] F (LD50)	NTP 1989b ROX	
3	Rat (Fischer- 344)	14 d (F)				128[b] M (3/5 died) 144 F (5/5 died)	NTP 1989b ROX	
4	Mouse (B6C3F1)	once (GO)				300 M (5/5 died) 244[b] F (LD50)	NTP 1989b ROX	
5	Mouse (B6C3F1)	14 d (F)				168 F (5/5 died)	NTP 1989b ROX	
Systemic								
6	Rat (Fischer- 344)	14 d (F)	Bd Wt	16 M	32 M (22% reduced body weight)		NTP 1989b ROX	
7	Mouse (B6C3F1)	14 d (F)	Bd Wt	84		168 (34% decrease in body weight)	NTP 1989b ROX	
Neurological								
8	Rat (Fischer- 344)	14 d (F)		16 M	32 M (slight inactivity)		NTP 1989b ROX	

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
9	Mouse (B6C3F1)	14 d (F)		20	42 (slight inactivity; ruffled fur)		NTP 1989b ROX	
10	Pig (Landrace)	30 d ad lib (F)				6.3 (muscle tremors and clonic convulsions)	Rice et al. 1985; Kennedy et al. 1986 ROX	
INTERMEDIATE EXPOSURE								
Death								
11	Rat (Holtzman)	13 wk (F)				20 (10/12 died)	Kerr et al. 1963 ROX	
12	Rat (Fischer- 344)	13 wk ad lib (F)				64 M (3/10 died)	NTP 1989b ROX	
13	Mouse (B6C3F1)	13 wk ad lib (F)				136 (6/10 males and 8/10 females died)	NTP 1989b ROX	

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
14	Rat (Fischer- 344)	31 or 90 d ad lib (F)	Hemato	32 M			NTP 1989b ROX	
			Hepatic	9 F	36 F (decreased absolute and relative liver weight)			
			Renal	8 M	32 M (increased kidney weight; minimal tubular degeneration)			
			Bd Wt	8 M		32 M (27% decrease in body weight)		

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
15	Rat (Fischer- 344)	13 wk ad lib (F)	Resp	64 M			NTP 1989b ROX	
			Cardio	64 M				
			Gastro	64 M				
			Musc/skel	64 M				
			Hepatic	4 M	8 M (increased relative liver weight)			
			Renal	16 M	32 M (interstitial inflammation, focal regenerative hyperplasia of tubular cell epithelium and mineralization)			
			Endocr	64 M				
			Dermal	64 M				
			Bd Wt	8 M	16 M (14% decreased body weight)	32 M (26% decreased body weight)		

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Mouse (B6C3F1)	13 wk ad lib (F)	Cardio	136			NTP 1989b ROX	
			Gastro	136				
			Musc/skel	136				
			Hepatic	136				
			Renal	136				
			Endocr	136				
			Dermal	136				
			Bd Wt		136 (18% decreased body weight in males; 11% decreased body weight in females)			
17	Mouse (B6C3F1)	29 or 91 d ad lib (F)	Hemato	68			NTP 1989b ROX	
			Hepatic	68				
			Renal	68				
Neurological								
18	Rat (Fischer- 344)	13 wk ad lib (F)		32 M		64 M (trembling, ataxia, hyperexcitability, slight inactivity, ruffled fur)	NTP 1989b ROX	

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
19	Pig	28 d (F)				10	(muscle tremors)	Edmonds and Baker 1986 ROX	
20	Pig (Landrace)	30 d ad lib (F)				6.3	(paraplegia, myelin degeneration in spinal cord, peripheral nerves, optic nerve)	Rice et al. 1985; Kennedy et al. 1986 ROX	
CHRONIC EXPOSURE									
Systemic									
21	Rat (Fischer- 344)	103 wk ad lib (F)	Resp	4				NTP 1989b ROX	
			Cardio	4					
			Gastro	4					
			Musc/skel	4					
			Hepatic	4					
			Renal	4					
			Endocr	4					
			Dermal	4					
			Ocular	4					
			Bd Wt	4					
22	Mouse (Fischer- 344)	103 wk ad lib (F)	Resp	43 M				NTP 1989b ROX	
			Cardio	43 M					
			Gastro	43 M					
			Musc/skel	43 M					
			Hepatic	43 M					

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
			Renal	43 M				
			Endocr	43 M				
			Dermal	43 M				
			Ocular	43 M				
			Bd Wt	43 F				

a The number corresponds to entries in Figure 3-6.

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-6. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; Gastro = gastrointestinal; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; LC50 = lethal concentration, 50% kill, LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; occup = occupational; Resp = respiratory; wk = week(s)

Figure 3-6 Levels of Significant Exposure to Roxarsone - Oral

Acute (≤14 days)

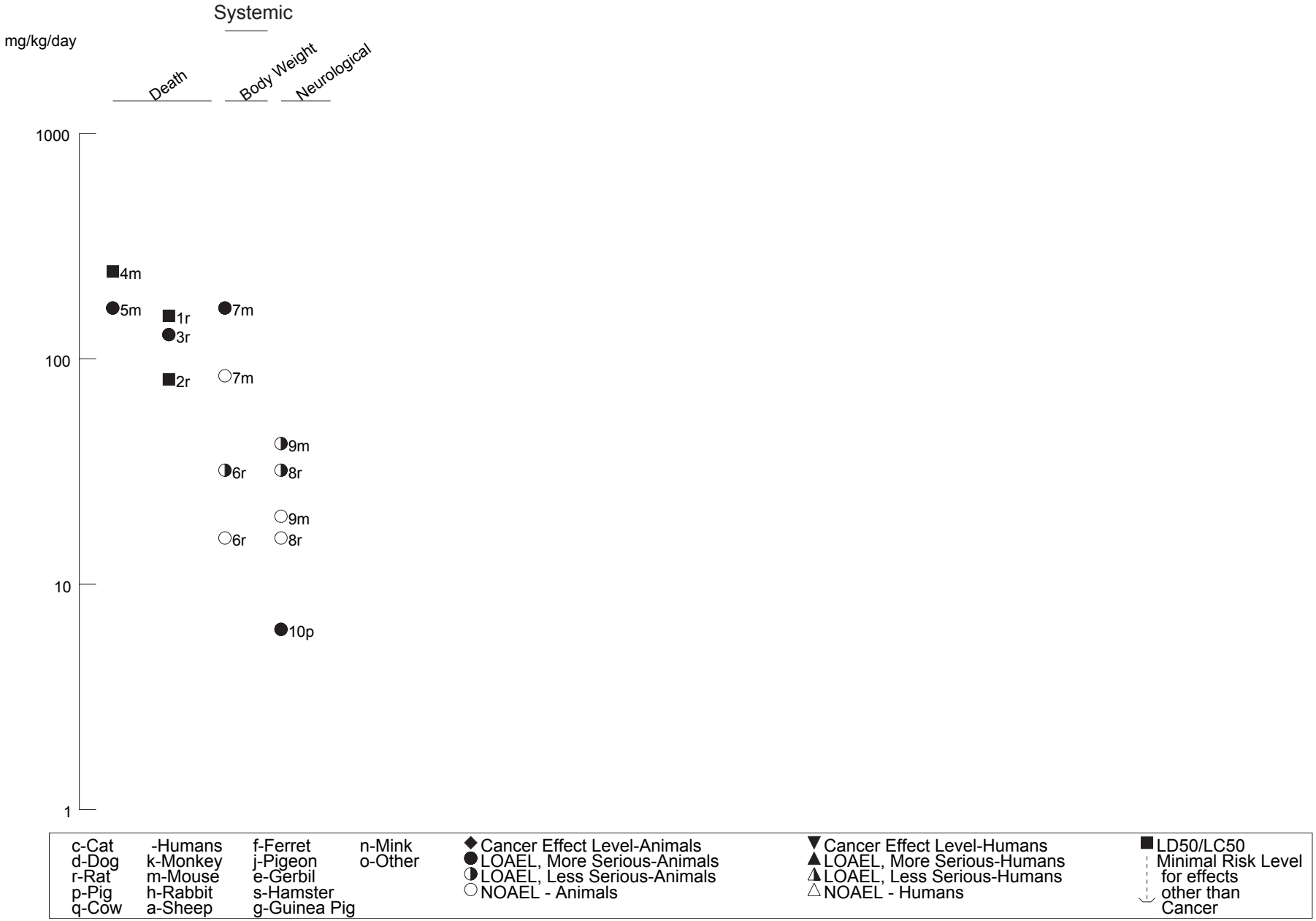


Figure 3-6 Levels of Significant Exposure to Roxarsone - Oral *(Continued)*

Intermediate (15-364 days)

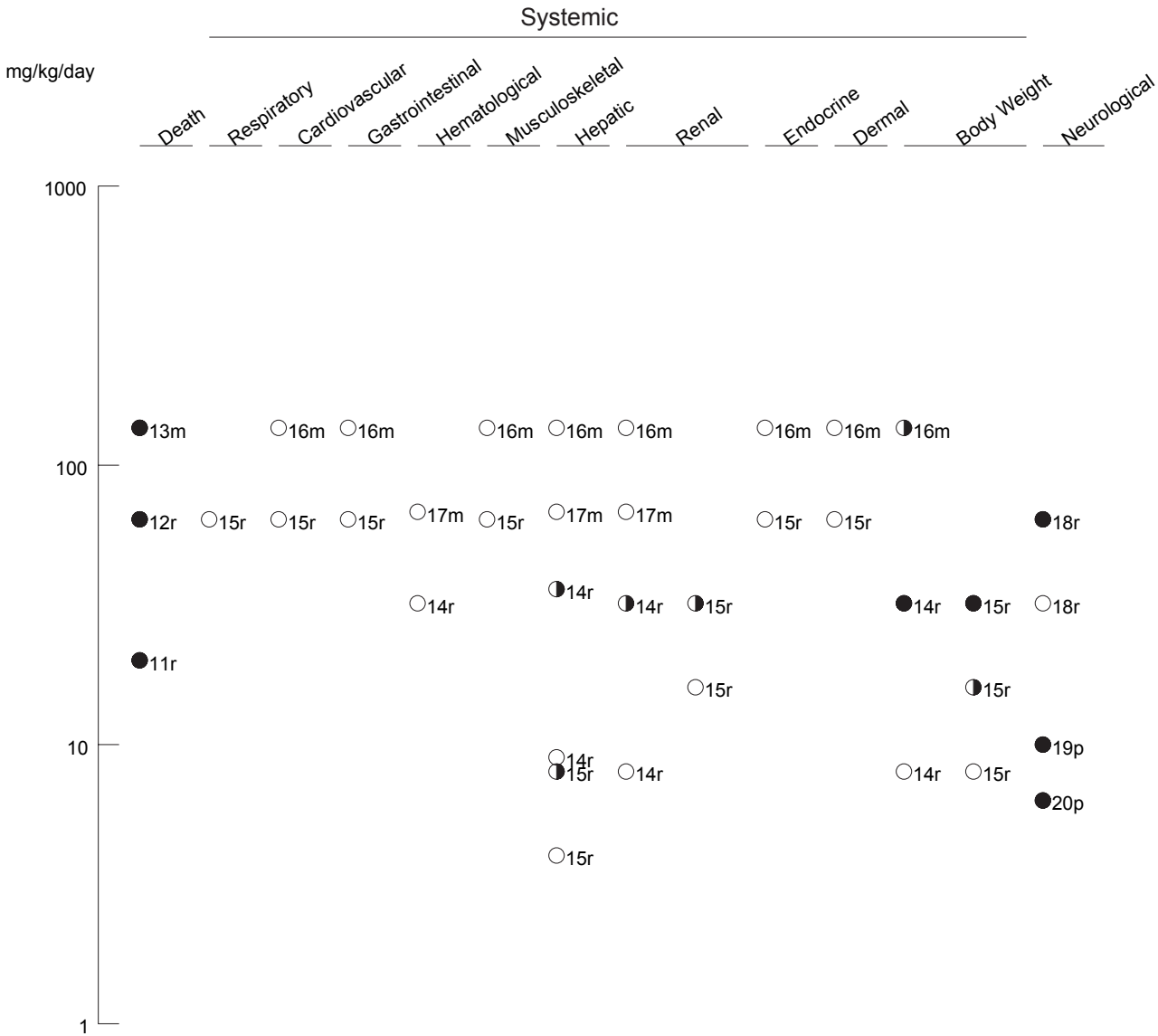
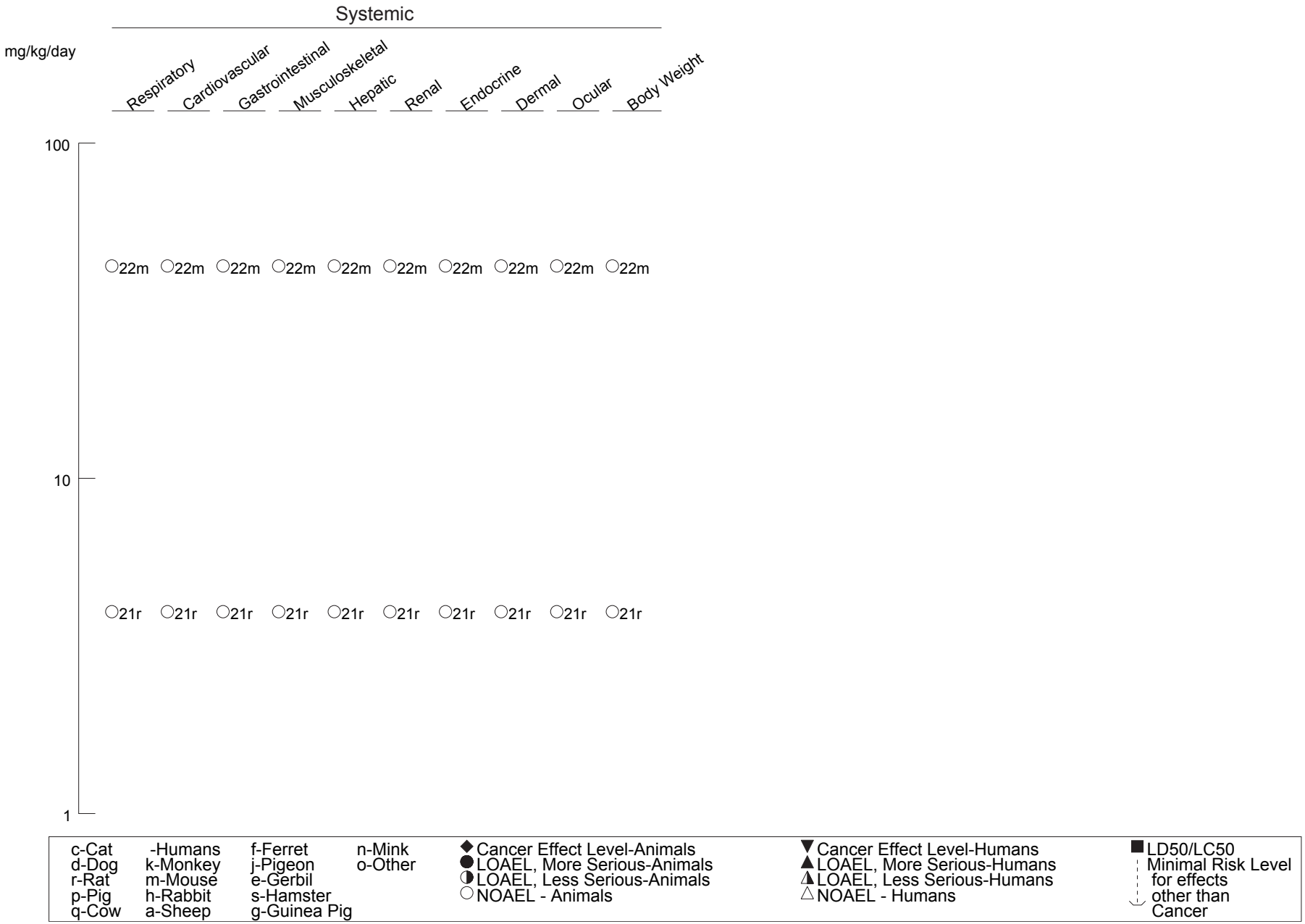


Figure 3-6 Levels of Significant Exposure to Roxarsone - Oral *(Continued)*

Chronic (≥365 days)



Available LD_{50} values for arsenate and arsenite in rats and mice range from 15 to 175 mg As/kg (Dieke and Richter 1946; Gaines 1960; Harrisson et al. 1958; Kaise et al. 1985). The variability can be attributed to differences based on species, strain, specific route of exposure (feed vs. gavage), specific compound tested, and testing laboratory. Most deaths occurred within 1 day of exposure, but details regarding cause of death were not generally reported. Seven of 25 pregnant rats given a single gavage dose of 23 mg As/kg as arsenic trioxide on day 9 of gestation died soon after dosing, while no deaths occurred at doses of 4–15 mg As/kg (Stump et al. 1999). Data on lethality from repeated exposure studies in animals are relatively sparse. Seven of 20 pregnant rabbits died from repeated gavage doses of 1.5 mg As/kg/day as arsenic acid during gestation, while none died at 0.1–0.4 mg As/kg/day (Nemec et al. 1998). Chronic studies observed treatment-related mortality in monkeys exposed to 3 mg As/kg/day as arsenate (Heywood and Sortwell 1979), dogs exposed to 2.4 mg As/kg/day as arsenite or arsenate (Byron et al. 1967), mice exposed to 1 mg As/kg/day as arsenite (Schroeder and Balassa 1967), and rats exposed to 30 mg As/kg/day as lead arsenate (Kroes et al. 1974).

Reliable LOAEL and LD_{50} values for lethality from oral exposure to inorganic arsenicals in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Organic Arsenicals. No studies were located regarding death in humans after oral exposure to organic arsenicals, but the acute lethality of MMA, DMA, and roxarsone have been investigated in several animal studies. The LD_{50} values for MMA (including MSMA), DMA, and roxarsone are 102–3,184 mg/kg MMA or MSMA (Gur and Nyska 1990; Jaghabir et al. 1988; Kaise et al. 1989), 1,200 mg DMA/kg/day (Kaise et al. 1989), and 14.2–69.5 mg DMA/kg/day (Kerr et al. 1963; NTP 1989b), respectively. The cause of death was not investigated in any of these studies. Intermediate-duration exposure to MMA, DMA, or roxarsone resulted in increased mortality in laboratory animals exposed to 106.9 mg MMA/kg/day (Arnold et al. 2003), 17–190 mg DMA/kg/day (Crown et al. 1987; Murai et al. 1993; Wanibuchi et al. 1996) or 20–64 mg/kg/day roxarsone (Edmonds and Baker 1986; Kerr et al. 1963; NTP 1989b), respectively. Increased mortality was also observed in rats chronically exposed to 72.4 mg MMA/kg/day (Arnold et al. 2003).

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects from oral exposure in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3. Similar data for

oral exposure to MMA, DMA, and roxarsone are shown in Tables 3-4, 3-5, and 3-6, and shown in Figures 3-4, 3-5, and 3-6, respectively.

Respiratory Effects.

Inorganic Arsenicals. Serious respiratory effects, including respiratory distress, hemorrhagic bronchitis, and pulmonary edema, have been reported in some cases of acute oral arsenic poisoning at doses of 8 mg As/kg and above (e.g., Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Moore et al. 1994b; Quatrehomme et al. 1992). These effects may be secondary to injury to the pulmonary vasculature (see Cardiovascular Effects, below). In addition, bronchitis and sequelae (bronchiectasis, bronchopneumonia) have been observed in patients and at autopsy in some chronic poisoning cases (Guha Mazumder et al. 2005; Milton and Rahman 2002; Rosenberg 1974; Tsai et al. 1999; Zaldívar 1974; Zaldívar and Guillier 1977). Bronchopneumonia secondary to arsenic-induced bronchitis was considered to be the cause of death in one young child who died after several years of exposure to an average dose of 0.08 mg As/kg/day (Zaldívar and Guillier 1977). Decrements in lung function, measured as decreased FEV_1, FVC, and $FEF_{25–75}$ have also been reported in subjects exposed to 0.1–0.5 mg As/L in the drinking water and exhibiting skin lesions (von Ehrenstein et al. 2005). In general, however, respiratory effects have not been widely associated with repeated oral ingestion of low arsenic doses. Nevertheless, a few studies have reported minor respiratory symptoms, such as cough, sputum, rhinorrhea, and sore throat, in people with repeated oral exposure to 0.03–0.05 mg As/kg/day (Ahmad et al. 1997; Mizuta et al. 1956).

There are few data regarding respiratory effects in animals following acute oral exposure to inorganic arsenic. An infant Rhesus monkey that died after 7 days of oral exposure to a complex arsenate salt at a dose of 3 mg As/kg/day exhibited bronchopneumonia with extensive pulmonary hemorrhage, edema, and necrosis (Heywood and Sortwell 1979). Two other monkeys in this treatment group survived a 1-year exposure period and had no gross or microscopic pulmonary lesions at sacrifice. Increased relative lung weights were seen in rats exposed to 6.66 mg As/kg/day as sodium arsenite 5 days/week for 12 weeks (Schulz et al. 2002). Chronic oral studies in dogs and rats treated with arsenate or arsenite failed to find respiratory lesions (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968).

One study utilizing gallium arsenide included limited investigation of respiratory function. Respiration rate was significantly decreased in rats following ingestion of a single dose of gallium arsenide at 1,040 mg As/kg, but was unaffected at a dose of 520 mg As/kg (Flora et al. 1997a). Respiration rate was measured 1, 7, and 15 days after dosing, but the decrease was most noticeable after 15 days.

Organic Arsenicals. No respiratory effects were noted after acute human ingestion of 1,714 mg MSMA/kg (Shum et al. 1995). Mice exhibited respiratory arrest after a single oral dose of 1,800 mg MMA/kg (Kaise et al. 1989) or 900 mg DMA/kg (Kaise et al. 1989) and lung ornithine decarboxylase activity was reduced after ingestion of one or two doses of 720 mg DMA/kg (Ahmad et al. 1999a). Localized lung hemorrhage was observed in dogs after a single oral dose of 14.2 mg/kg roxarsone in a capsule (Kerr et al. 1963). No respiratory effects were seen after intermediate or chronic exposure of rats, mice, or dogs exposed to 35 mg MMA/kg/day (Waner and Nyska 1988), 7.8–94 mg DMA/kg/day (Arnold et al. 2006; Crown et al. 1987; Rubin et al. 1989; Zomber et al. 1989), or 4–136 mg/kg/day roxarsone (NTP 1989b).

Cardiovascular Effects.

Inorganic Arsenicals. A number of studies in humans indicate that arsenic ingestion may lead to serious effects on the cardiovascular system. Characteristic effects on the heart from both acute and long-term exposure include altered myocardial depolarization (prolonged QT interval, nonspecific ST segment changes) and cardiac arrhythmias (Cullen et al. 1995; Glazener et al. 1968; Goldsmith and From 1986; Heyman et al. 1956; Little et al. 1990; Mizuta et al. 1956; Moore et al. 1994b; Mumford et al. 2007). A significant dose-related increase in the prevalence of cardiac electrophysiologic abnormalites was observed in residents of Inner Mongolia, China; the incidences of QT prolongation were observed in 3.9, 11.1, and 20.6% of the residents with drinking water levels of <21, 110–300, and 430–690 μg/L, respectively (Mumford et al. 2007). Hypertrophy of the ventricular wall was observed at autopsy after acute exposure to 93 mg of arsenic (Quatrehomme et al. 1992). Long-term, low-level exposures may also lead to damage to the vascular system. The most dramatic example of this is "Blackfoot Disease," a condition that is endemic in an area of Taiwan where average drinking water levels of arsenic range from 0.17 to 0.80 ppm (Tseng 1977), corresponding to doses of about 0.014–0.065 mg As/kg/day (IRIS 2007). The disease is characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene (Chen et al. 1988b; Ch'i and Blackwell 1968; Tseng 1977, 1989; Tseng et al. 1968, 1995, 1996). Several researchers have presented evidence that other factors besides arsenic (e.g., other water contaminants, dietary deficits) may play a role in the etiology of this disease (Ko 1986; Lu et al. 1990; Yu et al. 1984). While this may be true, the clear association between the occurrence of Blackfoot Disease and the intake of elevated arsenic levels indicates that arsenic is at least a contributing factor. The results of a recent study suggested that individuals with a lower capacity to methylate

inorganic arsenic to DMA have a higher risk of developing peripheral vascular disease in the Blackfoot Disease-hyperendemic area in Taiwan (Tseng et al. 2005).

Arsenic exposure in Taiwan has also been associated with an increased incidence of cerebrovascular and microvascular diseases (Chiou et al. 1997; Wang et al. 2002, 2003) and ischemic heart disease (Chang et al. 2004; Chen et al. 1996; Hsueh et al. 1998b; Tsai et al. 1999; Tseng et al. 2003). Moreover, effects of arsenic on the vascular system have also been reported in a number of other populations. For example, hypertension, defined as a systolic blood pressure of ≥140 mm Hg in combination with a diastolic blood pressure of ≥90 mm Hg, was associated with estimated lifetime doses of approximately 0.055 mg As/kg/day (0.25 mg/L in water) in a study of people in Bangladesh (Rahman et al. 1999); no significant association was found with estimated doses of 0.018 mg As/kg/day (0.75 mg/L in water). Wang et al. (2003) found an increased incidence of microvascular and macrovascular disease among subjects in Taiwan living in an arseniasis-endemic area in which the water of artesian wells had arsenic concentrations >0.35 mg/L (estimated doses of >0.03 mg As/kg/day). An additional study of Taiwanese subjects reported a significant increase in incidence of hypertension associated with concentrations of arsenic in the water >0.7 mg/L (estimated doses of >0.06 mg As/kg/day) (Chen et al. 1995). Studies in Chile indicate that ingestion of 0.6–0.8 ppm arsenic in drinking water (corresponding to doses of 0.02–0.06 mg As/kg/day, depending on age) increases the incidence of Raynaud's disease and of cyanosis of fingers and toes (Borgoño and Greiber 1972; Zaldívar 1974, 1977; Zaldívar and Guillier 1977). Autopsy of five children from this region who died of apparent arsenic toxicity showed a marked thickening of small and medium sized arteries in tissues throughout the body, especially the heart (Rosenberg 1974). In addition, cardiac failure, arterial hypotension, myocardial necrosis, and thrombosis have been observed in children who died from chronic arsenic ingestion (Zaldívar 1974), as well as adults chronically exposed to arsenic (Dueñas et al. 1998). Likewise, thickening and vascular occlusion of blood vessels were noted in German vintners exposed to arsenical pesticides in wine and in adults who drank arsenic-contaminated drinking water (Roth 1957; Zaldívar and Guillier 1977). A survey of Wisconsin residents using private wells for their drinking water found that residents exposed for at least 20 years to water concentrations of >10 μg As/L had increased incidences of cardiac bypass surgery, high blood pressure, and circulatory problems as compared with residents exposed to lower arsenic concentrations (Zierold et al. 2004). Similarly, Lewis et al. (1999) reported increased mortality from hypertensive heart disease in both men and women among a cohort exposed to arsenic in their drinking water in Utah, as compared with the general population of Utah. Limitations in the study included lack of evaluation of smoking as a confounder and of other dietary sources of arsenic, and the lack of a dose-response for hypertensive heart disease. Another ecological study (Engel and Smith 1994) found significant increases in deaths from

arteriosclerosis, aortic aneurysm, and all other diseases of the arteries, arterioles, and capillaries among U.S. residents with arsenic drinking waters of >20 μg/L; the increase in deaths from congenital anomalies of the heart and other anomalies of the circulatory system also observed in this subpopulation limits the interpretation of the findings.

Similar alterations in vascular reactivity have been noted in rats given repeated oral doses of arsenic trioxide (11 mg As/kg/day) for several weeks (Bekemeier and Hirschelmann 1989), although no histological effects could be detected in the hearts of rats or dogs exposed to up to 30 mg As/kg/day as arsenate or arsenite for 2 years (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). Acute exposure of rats to gallium arsenide at a dose of 1,040 mg As/kg resulted in an increase in blood pressure and heart rate, while 520 mg As/kg had no effect (Flora et al. 1997a). Guinea pigs exposed to arsenic trioxide for 1 day (0, 7.6, 22.7, or 37.9 mg As/kg) or 8 days (0 or 3.8 mg As/kg/day) showed prolongation of the cardiac QT interval and action potential duration (Chiang et al. 2002).

Organic Arsenicals. No adverse cardiovascular effects were noted after acute human ingestion of 1,714 mg MSMA/kg (Shum et al. 1995). However, sinus tachycardia was noted after acute ingestion of 73 mg DMA/kg (as dimethyl arsenic acid and dimethyl arsenate) (Lee et al. 1995). No cardiovascular effects were seen after intermediate or chronic exposure of laboratory animals to 35–67.1 mg MMA/kg/day (Arnold et al. 2003; Waner and Nyska 1988), 7.8–94 mg DMA/kg/day (Arnold et al. 2006; Crown et al. 1987; Rubin et al. 1989; Zomber et al. 1989), or 4–136 mg/kg/day roxarsone (NTP 1989b).

Gastrointestinal Effects.

Inorganic Arsenicals. Clinical signs of gastrointestinal irritation, including nausea, vomiting, diarrhea, and abdominal pain, are observed in essentially all cases of short-term high-dose exposures to inorganic arsenic (e.g., Armstrong et al. 1984; Bartolome et al. 1999; Campbell and Alvarez 1989; Chakraborti et al. 2003a; Cullen et al. 1995; Fincher and Koerker 1987; Goebel et al. 1990; Kingston et al. 1993; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994b; Muzi et al. 2001; Uede and Furukawa 2003; Vantroyen et al. 2004). Similar signs are also frequently observed in groups or individuals with longer-term, lower-dose exposures (e.g., Borgoño and Greiber 1972; Cebrián et al. 1983; Franzblau and Lilis 1989; Guha Mazumder et al. 1988, 1998a; Haupert et al. 1996; Holland 1904; Huang et al. 1985; Mizuta et al. 1956; Nagai et al. 1956; Silver and Wainman 1952; Wagner et al. 1979; Zaldívar 1974), but effects are usually not detectable at exposure levels below about 0.01 mg As/kg/day (Harrington et al. 1978; Valentine et al. 1985). These symptoms generally decline within a short time after exposure ceases.

Gastrointestinal irritation symptoms form the basis (in part) for the acute oral MRL of 0.005 mg/kg/day for inorganic arsenic, as described in footnote b in Table 3-3. More severe symptoms (hematemesis, hemoperitoneum, gastrointestinal hemorrhage, and necrosis) have been reported in some cases with acute exposure to 8 mg As/kg or more (Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Quatrehomme et al. 1992), and also in some people with long-term ingestion of 0.03–0.05 mg As/kg/day as a medicinal preparation (Lander et al. 1975; Morris et al. 1974).

Clinical signs of gastrointestinal irritation were observed in monkeys and rats given repeated oral doses of arsenic (6 and 11 mg As/kg/day, respectively) for 2 weeks (Bekemeier and Hirschelmann 1989; Heywood and Sortwell 1979). Hemorrhagic gastrointestinal lesions have also been reported in animal studies. A monkey that died after repeated oral treatment with 6 mg As/kg/day for approximately 1 month was found to have acute inflammation and hemorrhage of the small intestine upon necropsy (Heywood and Sortwell 1979). This lesion was not found in other monkeys that died in this study, or in the survivors. Two pregnant mice that died after repeated gavage treatment with 24 mg As/kg/day as arsenic acid had hemorrhagic lesions in the stomach (Nemec et al. 1998). Gross gastrointestinal lesions (stomach adhesions, eroded luminal epithelium in the stomach) were seen frequently in rats treated by gavage with 8 mg As/kg/day as arsenic trioxide starting before mating and continuing through the end of gestation (Holson et al. 2000). The lesions were not found in rats treated with 4 mg As/kg/day in this study. No histological evidence of gastrointestinal injury was detected in rats exposed to arsenate or arsenite in the feed for 2 years at doses up to 30 mg As/kg/day, but dogs fed a diet containing 2.4 mg As/kg/day as arsenite for 2 years had some bleeding in the gut (Byron et al. 1967; Kroes et al. 1974).

Organic Arsenicals. Vomiting was noted after ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) in a suicide attempt (Shum et al. 1995). Ingestion of 78 mg DMA/kg (as dimethyl arsenic acid and dimethyl arsenate) induced vomiting, abdominal pain, hyperactive bowel, and diarrhea (Lee et al. 1995).

The gastrointestinal tract appears to be the critical target of toxicity following oral exposure to MMA. Diarrhea/loose feces has been reported in mice and rabbits following a single gavage dose of 2,200 mg MMA/kg or 60 mg MSMA/kg, respectively (Jaghabir et al. 1988; Kaise et al. 1989), pregnant rabbits administered 12 mg MMA/kg/day via gavage (Irvine et al. 2006), rats exposed to 30.2 mg MMA/kg/day in the diet during the first year of a 2-year study (Arnold et al. 2003), dogs administered 2 mg MMA/kg/day via capsule for 52 weeks (Waner and Nyska 1988), rats fed diets containing 25.7 mg MMA/kg/day for 2 years (Arnold et al. 2003), and mice exposed to 67.1 mg MMA/kg/day in the diet for

2 years (Arnold et al. 2003). However, the increased incidence of diarrhea is not always accompanied by macroscopic or histological alterations in the gastrointestinal tissues. For example, in the 2-year rat study (Arnold et al. 2003; incidence data reported in Crown et al. 1990), an increased incidence of diarrhea was observed at 25.7 mg MMA/kg/day; macroscopic or histological alterations were observed in some animals, but the incidence was similar to controls. At the next highest dose level (72.4 mg MMA/kg/day), thickened wall and edema and hemorrhagic, necrotic, ulcerated, or perforated mucosa were observed in the large intestine and significant increases in the incidence of squamous metaplasia of the epithelial columnar absorptive cells were found in the cecum, colon, and rectum. Squamous metaplasia was also observed in the cecum and colon of mice chronically exposed to 67.1 mg MMA/kg/day (Arnold et al. 2003; incidence data reported in Gur et al. 1991).

There are some reports of gastrointestinal effects in rats and dogs exposed to DMA; however, the LOAELs for these effects are higher than the LOAELs for MMA and most rodent studies do not report effects at nonlethal doses. Diarrhea with congestion and hemorrhagic gastrointestinal contents were observed in rats exposed to a lethal dose of 190 mg DMA/kg/day in the diet for 4 weeks (Crown et al. 1987) and diarrhea and vomiting were reported in dogs administered 16 mg DMA/kg/day via capsule 6 days/week (Zomber et al. 1989). No gastrointestinal effects were observed in rats or mice chronically exposed to 7.8 or 94 mg DMA/kg/day, respectively (Arnold et al. 2006).

Vomiting and gastrointestinal hemorrhage were observed in dogs after a single capsulized dose of 50 mg/kg roxarsone (Kerr et al. 1963), although slightly higher doses administered for 13 weeks to rats and mice had no effect (NTP 1989b). No gastrointestinal effects were seen after chronic exposure of rats (4 mg/kg/day) or mice (43 mg/kg/day) to roxarsone (NTP 1989b).

Hematological Effects.

Inorganic Arsenicals. Anemia and leukopenia are common effects of arsenic poisoning in humans, and have been reported following acute (Armstrong et al. 1984; Goldsmith and From 1986; Mizuta et al. 1956; Muzi et al. 2001; Westhoff et al. 1975), intermediate (Franzblau and Lilis 1989; Heyman et al. 1956; Nagai et al. 1956; Wagner et al. 1979), and chronic oral exposures (Chakraborti et al. 2003a; Glazener et al. 1968; Guha Mazumder et al. 1988; Hopenhayn et al. 2006; Kyle and Pease 1965; Tay and Seah 1975) at doses of 0.002 mg As/kg/day or more. These effects may be due to both a direct cytotoxic or hemolytic effect on the blood cells (Armstrong et al. 1984; Fincher and Koerker 1987; Goldsmith and From 1986; Kyle and Pease 1965; Lerman et al. 1980) and a suppression of erythropoiesis (Kyle and

Pease 1965; Lerman et al. 1980). However, hematological effects are not observed in all cases of arsenic exposure (EPA 1981b; Harrington et al. 1978; Huang et al. 1985; Silver and Wainman 1952) or even all acute poisoning cases (Cullen et al. 1995; Moore et al. 1994b).

In an acute animal study, Tice et al. (1997) found that there was a decrease in polychromatic erythrocytes in the bone marrow of mice treated with 6 mg As/kg/day for 1 or 4 days. There was no effect at 3 mg As/kg/day. Long-term studies found mild anemia in dogs fed arsenite or arsenate for 2 years at 2.4 mg As/kg/day, but no hematological effect in dogs fed 1 mg As/kg/day for 2 years or 1.9 mg As/kg/day for 26 weeks (Byron et al. 1967; Neiger and Osweiler 1989). Chronic rat studies found little or no evidence of anemia at doses up to 30 mg As/kg/day, even with co-exposure to lead (Byron et al. 1967; Kroes et al. 1974). No hematological effects were found in monkeys exposed to arsenic doses of 3–6 mg As/kg/day for 1 year (Heywood and Sortwell 1979).

Rats exposed to arsenate for 6 weeks had decreased activities of several enzymes involved in heme synthesis, but data were not provided on whether this resulted in anemia (Woods and Fowler 1977, 1978). Exposure of rats to ≥5 ppm of arsenic (0.30 mg As/kg/day as sodium arsenite) in the drinking water for 4 weeks resulted in increased platelet aggregation, while 10 or 25 ppm (0.60 or 1.5 mg As/kg/day) was associated with increased P-selectin-positive cells and decreased occlusion time (Lee et al. 2002), representing a change in platelet function. Similarly, exposure of rats or guinea pigs to 10 or 25 ppm of arsenic as arsenite (approximate doses of 0, 0.92, or 2.3 mg As/kg/day for rats and 0, 0.69, or 1.7 mg As/kg/day for guinea pigs) in the drinking water for 16 weeks (Kannan et al. 2001) resulted in decreases in erythrocyte and leukocyte numbers (rats and guinea pigs), increased blood mean corpuscular volume and corpuscular hemoglobin mass (guinea pigs only), and decreased mean corpuscular hemoglobin concentration (rats only). Gallium arsenide also disrupts heme synthesis in rats, although the evidence suggests that this effect is due primarily to the gallium moiety (Flora et al. 1997a).

Organic Arsenicals. No adverse hematological effects were noted in a man who ingested 78 mg/kg as dimethyl arsenic acid and dimethyl arsenate (Lee et al. 1995). No hematological effects were observed in rats exposed to 8.4 or 72.4 mg MMA/kg/day for 2 years (Arnold et al. 2003; Shen et al. 2003) or dogs administered 35 mg MMA/kg/day for 52 weeks (Waner and Nyska 1988); additionally, no alterations in total or differential leukocyte levels were observed in mice exposed to 67.1 mg MMA/kg/day for 2 years (Arnold et al. 2003). Although some studies have reported hematological alterations following oral exposure to DMA, this is not a consistent finding. Observed alterations include decreased mean corpuscular hemoglobin concentration in rats exposed to 2.3 mg DMA/kg/day for 10 weeks (Rubin et al.

1989), decreased hemoglobin and erythrocyte levels in rats exposed to 4.5 mg DMA/kg/day for 13 weeks (Crown et al. 1987), decreased erythrocyte levels and increased leukocyte levels in dogs administered capsules containing 40 mg DMA/kg/day for 52 weeks (Zomber et al. 1989), and decreased lymphocyte and increased monocyte levels were observed in mice chronically exposed to 94 mg DMA/kg/day (Arnold et al. 2006). No hematological alterations have been observed in rats exposed to 7.8 mg DMA/kg/day for 2 years (Arnold et al. 2006). Similarly, no hematological effects were observed in rats (Kerr et al. 1963; NTP 1989b), mice (NTP 1989b), or dogs (Prier et al. 1963) exposed to 20–32, 68, or 5 mg/kg/day roxarsone, respectively, for intermediate or chronic durations

Musculoskeletal Effects.

Inorganic Arsenicals. No studies were located regarding musculoskeletal effects in humans or animals after oral exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding musculoskeletal effects in humans after oral exposure to organic arsenicals. No musculoskeletal effects were seen after intermediate or chronic exposure of rats and mice to MMA (Arnold et al. 2003), DMA (Arnold et al. 2006), or roxarsone (NTP 1989b).

Hepatic Effects.

Inorganic Arsenicals. A number of studies in humans exposed to inorganic arsenic by the oral route have noted signs or symptoms of hepatic injury. Clinical examination often reveals that the liver is swollen and tender (Chakraborty and Saha 1987; Franklin et al. 1950; Guha Mazumder et al. 1988, 1998a; Liu et al. 2002; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953; Zaldívar 1974), and analysis of blood sometimes shows elevated levels of hepatic enzymes (Armstrong et al. 1984; Franzblau and Lilis 1989; Guha Mazumder 2005; Hernández-Zavala et al. 1998). These effects are most often observed after repeated exposure to doses of 0.01–0.1 mg As/kg/day (Chakraborty and Saha 1987; Franklin et al. 1950; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953), although doses as low as 0.006 mg As/kg/day have been reported to have an effect following chronic exposure (Hernández-Zavala et al. 1998). Hepatic effects have also been reported in acute bolus poisoning cases at doses of 2 mg As/kg/day or more (Hantson et al. 1996; Kamijo et al. 1998; Levin-Scherz et al. 1987; Quatrehomme et al. 1992; Vantroyen et al. 2004), although acute exposure to 19 mg As/kg did not cause hepatic effects in an infant (Cullen et al. 1995).

Histological examination of the livers of persons chronically exposed to similar doses has revealed a consistent finding of portal tract fibrosis (Guha Mazumder 2005; Guha Mazumder et al. 1988; Morris et al. 1974; Piontek et al. 1989; Szuler et al. 1979), leading in some cases to portal hypertension and bleeding from esophageal varices (Szuler et al. 1979); cirrhosis has also been reported at an increased frequency in arsenic-exposed individuals (Tsai et al. 1999). Several researchers consider that these hepatic effects are secondary to damage to the hepatic blood vessels (Morris et al. 1974; Rosenberg 1974), but this is not directly established.

Acute exposure of monkeys to 6 mg As/kg/day resulted in vacuolization of the hepatocytes (Heywood and Sortwell 1979). Studies in dogs or mice have not detected clinically significant hepatic injury following exposure to either arsenite or arsenate (Byron et al. 1967; Fowler and Woods 1979; Kerkvliet et al. 1980; Neiger and Osweiler 1989; Schroeder and Balassa 1967), although enlargement of the common bile duct was noted in rats fed either arsenate or arsenite in the diet for 2 years (Byron et al. 1967; Kroes et al. 1974) and lipid vacuolation and fibrosis were seen in the livers of rats exposed to 12 mg As/kg/day as arsenate in the drinking water for 6 weeks (Fowler et al. 1977). Similarly, fatty changes and inflammatory cell infiltration were seen in the livers of both normal and metallothionein-null mice exposed to 5.6 mg arsenic/kg/day in the drinking water for 48 weeks (Liu et al. 2000). Increases in liver zinc and copper concentrations were noted in rats receiving a single oral dose of 10 mg As/kg as sodium arsenite (Flora and Tripathi 1998) and hepatic levels of malondialdehyde were increased and glutathione levels were decreased in livers of rats receiving 200 mg As/kg as GaAs (Flora et al. 1998). An increase in indices of peroxidation was reported in rats dosed with approximately 0.02 mg As/kg/day for 60 days from drinking water containing 2.5 mg sodium arsenite/L (Bashir et al. 2006); absolute liver weight was also increased at this dose level. Elevated levels of serum aspartate aminotransferase (AST) were observed in rats administered a single oral dose of 100 mg As/kg as GaAs (Flora et al. 1998). Exposure of guinea pigs to 0.69 or 1.7 mg As/kg/day in the drinking water for 16 weeks, but not in rats exposed to 0.92 or 2.3 mg As/kg/day, resulted in increases in delta-aminolevulinic acid synthetase (ALAS) levels (Kannan et al. 2001). Exposure of BALB/C mice to 0.7 mg arsenic/kg/day in the drinking water for 15 months resulted in increased liver weights, changes in liver enzymes (glutathione S-transferase, glutathione reductase, catalase, glucose-6-phosphate dehydrogenase, glutathione peroxidase), fatty liver, and fibrosis (Santra et al. 2000).

Organic Arsenicals. No adverse hepatic effects were noted after ingestion of 1,714 mg/kg MSMA or 78 mg DMA/kg (as dimethyl arsenic acid and dimethyl arsenate) in a suicide attempt (Lee et al. 1995; Shum et al. 1995). No other studies of the hepatic effects of organic arsenicals in humans were located.

Histological examination of livers from rabbits given repeated oral doses of MMA showed diffuse inflammation and hepatocellular degeneration (Jaghabir et al. 1989), but the lesions were not severe. Male rats exposed to a time-weighted average (TWA) dose of 72.4 mg MMA/kg/day for 104 weeks showed a decrease in absolute liver weight, while females exposed to 98.5 mg MMA/kg/day showed histiocytic proliferation of the liver (Arnold et al. 2003); however, these effects were probably due to a decrease in body weight and secondary complications of perforation and ulceration of the gastrointestinal effect, respectively. Shen et al. (2003) reported increases in and the number of GST-P-positive foci in the livers of rats exposed to average concentrations of 8.4 mg MMA/kg/day in the diet for 104 weeks. No effects were observed in rats exposed to DMA (Siewicki 1981), but mice exposed to one or two oral doses of 720 mg DMA/kg had decreased liver glutathione and cytochrome P-450 content and serum ornithine decarboxylase activity (Ahmad et al. 1999a). Generalized icterus was reported in dogs after acute exposure to roxarsone (Kerr et al. 1963). Some small fluctuations in liver weight have been noted in rats and mice after intermediate oral exposure to roxarsone, but the toxicological significance of this is not clear and is not observed after chronic exposure of rats and mice to lower doses (NTP 1989b).

Renal Effects.

Inorganic Arsenicals. Most case studies of acute and chronic arsenic toxicity do not report clinical signs of significant renal injury, even when other systems are severely impaired (e.g., Cullen et al. 1995; Franzblau and Lilis 1989; Jenkins 1966; Kersjes et al. 1987; Mizuta et al. 1956; Silver and Wainman 1952). In some cases, elevated serum levels of creatinine or bilirubin have been noted (Armstrong et al. 1984; Levin-Scherz et al. 1987; Moore et al. 1994b), and mild proteinuria may occur (Armstrong et al. 1984; Glazener et al. 1968; Tay and Seah 1975). Acute renal failure in some bolus poisoning episodes (e.g., Fincher and Koerker 1987; Goebel et al. 1990; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994b) is probably a result of fluid imbalances or vascular injury (Rosenberg 1974; Zaldívar 1974). Glomerular congestion has been observed after an acute exposure to high doses (Quatrehomme et al. 1992).

Studies in animals also indicate that the kidney is not a major target organ for inorganic arsenic (Byron et al. 1967; Schroeder and Balassa 1967; Woods and Southern 1989), although some effects have been reported at high exposure levels. Mild histological changes in the renal tubules of monkeys exposed to arsenate for 2 weeks were noted by Heywood and Sortwell (1979), and some mild alterations in renal mitochondria in rats exposed to arsenate for 6 weeks were noted by Brown et al. (1976). Mild proteinuria

(Flora et al. 1998) and an increase in kidney zinc concentration (Flora and Tripathi 1998) have also been noted in rats exposed orally to a single dose of 100 mg As/kg as GaAs or 10 mg As/kg as sodium arsenite, respectively. These data suggest that the kidney is relatively less sensitive to arsenic than most other organ systems, and renal effects are unlikely to be of concern except secondary to fluid imbalances or cardiovascular injury.

Organic Arsenicals. No adverse renal effects were noted after ingestion of 1,714 mg MSMA/kg in a suicide attempt (Shum et al. 1995). Animal studies have reported renal and urinary bladder effects following oral exposure to organic arsenicals; the available data suggest that the urinary system is a more sensitive target for DMA, than for MMA or roxarsone. A decrease in urine volume was observed in rabbits following a single gavage dose of 30 mg MSMA/kg/day (Jaghabir et al. 1988) and a decrease in urine volume (35 mg MMA/kg/day) and an increase in urine specific gravity (8 mg MMA/kg/day) were observed in dogs administered MMA via capsule for 52 weeks (Waner and Nyska 1988). However, these effects may be indicative of dehydration due to diarrhea rather than a direct effect on the kidney. In a 2-year study in rats (Arnold et al. 2003), an increase in the severity of progressive glomerulonephropathy was observed in females at 33.9 mg MMA/kg/day. Hydronephrosis, pyelonephritis, cystitis, and decreases in urine volume and pH were also observed 72.4 mg MMA/kg/day; however, the investigators noted that these lesions probably resulted from urinary tract obstruction, which was secondary to peritonitis caused by gastrointestinal tract ulcerations. An increased incidence of progressive glomerulonephropathy was also observed in male mice exposed to ≥6.0 mg MMA/kg/day in the diet for 2 years (Arnold et al. 2003; incidence data reported in Gur et al. 1991); the investigators (Gur et al. 1991) noted that the kidney lesions were consistent with the normal spectrum of spontaneous lesions and that there were no differences in character or severity of the lesions between the different groups.

Exposure to DMA has resulted in kidney effects in rats and mice exposed to at least 3.1 or 37 mg DMA/kg/day, respectively; no renal effects were observed in dogs exposed to doses as high as 40 mg As/kg/day for 52 weeks (Zomber et al. 1989). In rats, the renal damage is characterized by increased urine volume and pH, decreased urine osmolarity and electrolyte (sodium, potassium, chlorine) levels, increased urinary calcium levels, and increased organ weight, nephrocalcinosis, and necrosis in the renal papillae and/or cortex; an increase in water consumption is also typically observed. The LOAELs for these effects are 5–57 mg DMA/kg/day in intermediate-duration studies (Arnold et al. 1999; Crown et al. 1987; Murai et al. 1993) and 3.1 mg DMA/kg/day in a chronic-duration study (Arnold et al. 2006). Another study did not find renal effects in rats exposed to 16.5 mg DMA/kg/day (Rubin et al. 1989). This study involved exposure to Sprague-Dawley rats compared to Fischer 344 rats used in the studies with

positive results; it is not known if this reflects a difference in strain sensitivity. In mice, progressive glomerulonephropathy was observed at 37 mg DMA/kg/day and nephrocalcinosis was observed at 94 mg DMA/kg/day (Arnold et al. 2006).

Increased kidney weights and minimal tubular epithelial cell degeneration, tubular casts, and focal mineralization were observed in rats exposed to 32 mg/kg/day roxarsone for 13 weeks (NTP 1989b). No adverse effects were observed in rats at doses as high as 20 mg/kg/day (Kerr et al. 1963; NTP 1989b) for 13 weeks or 10 mg/kg/day for 2 years (NTP 1989b; Prier et al. 1963). No adverse renal effects have been observed in mice exposed to roxarsone doses as high as 136 mg/kg/day (NTP 1989b) or 43 mg/kg/day (NTP 1989b; Prier et al. 1963) for intermediate or chronic durations, respectively, or in dogs exposed to 5 mg/kg/day for a chronic duration (Prier et al. 1963).

Damage to the urinary bladder has been observed in several studies in which rats were exposed to DMA. The observed effects include altered bladder cell surface characteristics in rats exposed to 11 mg DMA/kg/day in the diet for 2 weeks (Cohen et al. 2001), increased bladder weight and regenerative proliferation (measured as an increase in BrdU labeling) in bladder epithelium at 5 mg DMA/kg/day for 10 weeks (Arnold et al. 1999), necrosis of bladder epithelium at 10 mg DMA/kg/day for 10 weeks (Arnold et al. 1999), nodular or papillar hyperplasia at 3.4 mg DMA/kg/day for 2 years (Wei et al. 2002), and urothelial vacuolar degeneration and hyperplasia of urothelial cells at 3.1 mg DMA/kg/day for 2 years (Arnold et al. 2006). Vacuolization of the urothelium in the urinary bladder have also been observed in mice exposed to 7.8 mg DMA/kg/day in the diet for 2 years (Arnold et al. 2006). Inconsistent results were found for MMA. Hyperplasia was observed in the bladders of rats exposed to 1 mg As/kg/day as MMA in drinking water for 2 years (Shen et al. 2003), but bladder effects were not observed in another 2-year study (Arnold et al. 2003) in which rats were exposed to doses as high as 34.8 mg As/kg/day as MMA in the diet. No urinary bladder effects were found in rats and mice exposed to 64 or 136 mg/kg/day roxarsone for 13 weeks (NTP 1989b) or 4 or 43 mg/kg/day roxarsone for 2 years (NTP 1989b).

Endocrine Effects.

Inorganic Arsenicals. Very little has been written about the effects of oral exposure to arsenic on endocrine glands. In a report of the autopsies of five children who died in Chile after chronic exposure to arsenic in the drinking water, arterial thickening in the pancreas was noted (Rosenberg 1974). An association has been demonstrated between exposure to arsenic in drinking water and an increased

incidence of diabetes mellitus (Lai et al. 1994; Rahman et al. 1998; Tsai et al. 1999; Tseng et al. 2000; Wang et al. 2003), although dose-response relationships are not available.

Exposure of rats to 2.3 mg As/kg/day as arsenic trioxide for 30 days resulted in reductions in the number of islet cells in the pancreas, as well as significant reductions in pancreatic superoxide dismutase (SOD) and catalase enzyme levels and increases in the production of nitric oxide and malondialdehyde (Mukherjee et al. 2004).

Organic Arsenicals. No studies of effects of organic arsenic compounds on endocrine glands in humans were found. Hypertrophy of thyroid epithelium was observed in rats exposed to 33.9 mg MMA/kg/day in the diet for 2 years (Arnold et al. 2003), 4.0 mg DMA/kg/day in the diet for 13 weeks (Crown et al. 1987), 16.5 mg DMA/kg/day in the diet for at least 10 weeks (Rubin et al. 1989), and 7.8 mg DMA/kg/day in the diet for 2 years (Arnold et al. 2006). No other biologically significant effects were observed in other endocrine tissues following exposure to MMA or DMA. No adverse effects were seen in the adrenal or pituitary glands, thyroid, or pancreas after intermediate or chronic exposure of rats (20–64 or 4 mg/kg/day, respectively) and mice (136 or 43 mg/kg/day, respectively) to roxarsone (NTP 1989b).

Dermal Effects.

Inorganic Arsenicals. One of the most common and characteristic effects of arsenic ingestion is a pattern of skin changes that include generalized hyperkeratosis and formation of hyperkeratotic warts or corns on the palms and soles, along with areas of hyperpigmentation interspersed with small areas of hypopigmentation on the face, neck, and back. These and other dermal effects have been noted in a large majority of human studies involving repeated oral exposure (e.g., Ahmad et al. 1997, 1999b; Ahsan et al. 2000; Bickley and Papa 1989; Borgoño and Greiber 1972; Borgoño et al. 1980; Cebrián et al. 1983; Chakraborti et al. 2003a, 2003b; Chakraborty and Saha 1987; Foy et al. 1992; Franklin et al. 1950; Franzblau and Lilis 1989; Guha Mazumder et al. 1988, 1998a, 1998b, 1998c; Guo et al. 2001a; Haupert et al. 1996; Huang et al. 1985; Lander et al. 1975; Liu et al. 2002; Lüchtrath 1983; Milton et al. 2004; Mizuta et al. 1956; Morris et al. 1974; Nagai et al. 1956; Piontek et al. 1989; Rosenberg 1974; Saha and Poddar 1986; Silver and Wainman 1952; Szuler et al. 1979; Tay and Seah 1975; Tseng et al. 1968; Wade and Frazer 1953; Wagner et al. 1979; Wong et al. 1998a, 1998b; Zaldívar 1974, 1977). In cases of low-level chronic exposure (usually from water), these skin lesions appear to be the most sensitive indication of effect, so this end point is considered to be the most appropriate basis for establishing a chronic oral MRL. This is supported by the finding that other effects (hepatic injury, vascular disease, neurological

effects) also appear to have similar thresholds. As shown in Table 3-3 and Figure 3-3, numerous studies in humans have reported dermal effects at chronic dose levels generally ranging from about 0.01 to 0.1 mg As/kg/day (Ahmad et al. 1997; Bickley and Papa 1989; Borgoño and Greiber 1972; Borgoño et al. 1980; Cebrián et al. 1983; Chakraborty and Saha 1987; Foy et al. 1992; Franklin et al. 1950; Guha Mazumder et al. 1988; Huang et al. 1985; Lüchtrath 1983; Piontek et al. 1989; Silver and Wainman 1952; Tseng et al. 1968; Zaldívar 1974, 1977). However, in a study with detailed exposure assessment, all confirmed cases of skin lesions ingested water containing >100 µg/L arsenic (approximately 0.0037 mg As/kg/day) and the lowest known peak arsenic concentration ingested by a case was 0.115 µg/L (approximately 0.0043 mg As/kg/day) (Haque et al. 2003). Another large study reported increased incidence of skin lesions associated with estimated doses of 0.0012 mg As/kg/day (0.023 mg As/L drinking water) (Ahsan et al. 2006). Several epidemiological studies of moderately sized populations (20–200 people) exposed to arsenic through drinking water have detected no dermal or other effects at average chronic doses of 0.0004–0.01 mg As/kg/day (Cebrián et al. 1983; EPA 1981b; Guha Mazumder et al. 1988; Harrington et al. 1978; Valentine et al. 1985), and one very large study detected no effects in any person at an average total daily intake (from water plus food) of 0.0008 mg As/kg/day (Tseng et al. 1968). This value has been used to calculate a chronic oral MRL for inorganic arsenic of 0.0003 mg/kg/day, as described in footnote c in Table 3-3.

Another prominent dermal effect associated with chronic ingestion of inorganic arsenic is skin cancer. As discussed in greater detail in Section 3.2.2.7 (below), some of these skin cancers may evolve from the hyperkeratotic corns or warts, while the areas of altered pigmentation are not considered to be precancerous (EPA 1988d).

Dermal lesions similar to those observed in humans have not been noted in oral exposure studies in monkeys (Heywood and Sortwell 1979), dogs (Byron et al. 1967), or rodents (Schroeder et al. 1968). However, a hyperplastic response to oral arsenic exposure was reported in arsenic-exposed mice (Rossman et al. 2004).

Organic Arsenicals. No studies were located regarding dermal effects in humans after oral exposure to organic arsenicals. No gross or histological skin alterations were observed in rats or mice following intermediate- or chronic-duration exposure to MMA (Arnold et al. 2003; as reported in Crown et al. 1990; Gur et al. 1991), DMA (Arnold et al. 2006; as reported in Gur et al. 1989a, 1989b), or roxarsone (NTP 1989b)

Ocular Effects.

Inorganic Arsenicals. Periorbital swelling was reported in people drinking contaminated well water at an approximate dose of 0.2 mg As/kg for 1 week (Armstrong et al. 1984). Facial edema, generally involving the eyelids, was a prominent feature of arsenic poisoning among 220 cases associated with an episode of arsenic contamination of soy sauce in Japan (Mizuta et al. 1956). Exposure was to an estimated dose of 0.05 mg/kg/day and lasted for up to 2–3 weeks. The edema developed soon after the initial exposure and then subsided. This effect forms the basis (in part) for the acute oral MRL of 0.005 mg/kg/day for inorganic arsenic, as described in footnote b in Table 3-3. Nemec et al. (1998) noted the appearance of dried red material around the eyes of mice receiving daily oral doses of 24 mg As/kg as arsenic acid for 10 days during gestation.

Organic Arsenicals. No studies were located regarding ocular effects in humans or animals after oral exposure to organic arsenicals. No gross or histological alterations in the eye were observed in rats or mice following intermediate- or chronic-duration exposure to MMA (Arnold et al. 2003; as reported in Crown et al. 1990; Gur et al. 1991), DMA (Arnold et al. 2006; as reported in Gur et al. 1989a, 1989b), or roxarsone (NTP 1989b).

Body Weight Effects.

Inorganic Arsenicals. A 41-year old woman exposed to arsenic in the drinking water for 4 months at an approximate dose of 0.06 mg As/kg/day reported losing 40 pounds (18 kg) of body weight before seeking treatment (Wagner et al. 1979). Weight loss was also among the effects observed in a series of 475 chronic arsenism patients hospitalized in Antofagasto, Chile after receiving approximate doses of 0.02 mg As/kg/day in the drinking water for an unspecified number of years (Zaldívar 1974).

Reductions in body weight gain are commonly seen in animal studies of ingested arsenic. In pregnant rats, body weight gain was reduced by gavage treatment with 23 mg As/kg/day as arsenic trioxide on day 9 of gestation (NOAEL=15 mg As/kg/day, Stump et al. 1999), and by repeated gavage treatment with 8 mg As/kg/day as arsenic trioxide from 2 weeks prior to mating through gestation (NOAEL=4 mg As/kg/day, Holson et al. 2000). Exposure of rats by gavage to 26.6 mg As/kg/day as sodium arsenite, but not 13.3 mg As/kg/day or lower, 5 days/week for 4 weeks resulted in a significant decrease in body weight (Schulz et al. 2002). In 6-week rat studies, body weight gain was decreased at 11–12 mg As/kg/day, but not at 6–9 mg As/kg/day (Brown et al. 1976; Fowler et al. 1977). In a 12-week oral

gavage study, rats dosed with 1.5 mg/kg/day sodium arsenite had a median final body weight 18% lower than controls Dhar et al. (2005). A 60-day rat study with sodium arsenite in the drinking water reported a 13% reduction in final body weight in rats dosed with approximately 0.02 mg As/kg/day (Bashir et al. 2006). In chronic rat studies of arsenate and arsenite, body growth decreases were found at doses as low as 2 mg As/kg/day in feeding studies (Byron et al. 1967; Kroes et al. 1974), while rats exposed to lower levels of sodium arsenite in the drinking water (0.6 mg As/kg/day) throughout their lifetimes grew normally (Schroeder et al. 1968). Rats given a single oral dose of 100 mg As/kg as GaAs exhibited a 15% reduction in body weight compared to controls 7 days after exposure (Flora et al. 1998). Body weight gain was decreased in mice at 24 mg As/kg/day in a gestation exposure study (Nemec et al. 1998), 10 mg As/kg/day in a 6-week study (Fowler and Woods 1979), and 1 mg As/kg/day in a 2-year study (Schroeder and Balassa 1967). Growth was unaffected in mice that received 12 mg As/kg/day in the gestation exposure study (Nemec et al. 1998), 5 mg As/kg/day in the 6-week study (Fowler and Woods 1979), or 0.7–0.8 mg As/kg/day in 1–3 month arsenate drinking water studies (Healy et al. 1998). Dogs chronically treated with 2.4 mg As/kg/day as sodium arsenite lost 44–61% of their starting body weight and died, while lower doses had no effect on growth (Byron et al. 1967). Weight depression was also reported in dogs chronically treated with 2.4 mg As/kg/day as sodium arsenate (Byron et al. 1967). Feed consumption and body weight gain were significantly reduced in a dose-related manner in dogs fed 1.5 or 1.9 mg As/kg/day as sodium arsenite in the diet (Neiger and Osweiler 1989). Dogs in the high-dose group lost 25% of their body weight over the 17-week study period. Pair-fed controls lost weight at the same rate as high-dose dogs, showing that the effect on body weight was due to reduced feed consumption, rather than a direct effect of arsenic.

Organic Arsenicals. No studies were located regarding body weight effects in humans after oral exposure to organic arsenicals. In animal studies of organic arsenicals, decreases in body weight gain were observed in rats and mice after acute, intermediate, and chronic duration exposure to MMA (Arnold et al. 2003; Waner and Nyska 1988), DMA (Murai et al. 1993), and roxarsone (NTP 1989b); decreases in body weight gain have also been reported in pregnant rats and rabbits exposed to MMA (Irvine et al. 2006) or DMA (Irvine et al. 2006; Rogers et al. 1981). For MMA, the decreases in body weight gain were observed following intermediate-duration exposure of rats and dogs to 106.9 or 8 mg MMA/kg/day (Arnold et al. 2003; Waner and Nyska 1988), respectively, and following chronic-duration exposure of rats, mice, and dogs to 25.7, 67.1, or 8 mg MMA/kg/day, respectively (Arnold et al. 2003; Waner and Nyska 1988). The decreases in body weight gain occurred at doses that were associated with diarrhea and histological alterations in the gastrointestinal tract (Arnold et al. 2003; Waner and Nyska 1988). One DMA study in nonpregnant animals reported decreases in body weight gain in rats administered 57 mg

DMA/kg/day via gavage 5 days/week for 4 weeks (Murai et al. 1993); other DMA studies have not reported decreases in body weight gain in rats following exposure to 11 mg DMA/kg/day for acute durations (Cohen et al. 2001), 3.7–60 mg DMA/kg/day for intermediate durations (Arnold et al. 1999; Crown et al. 1987; Rubin et al. 1989; Siewicki 1981; Wanibuchi et al. 1996; Yamamoto et al. 1995), or 0.77 mg DMA/kg/day for chronic durations (Arnold et al. 2006). No alterations in body weight gain were observed in mice exposed to 94 mg DMA/kg/day for 2 years (Arnold et al. 2006). The lowest doses of roxarsone to produce a decrease in growth were 32 and 16 mg/kg/day in rats following acute- or intermediate-duration exposure, respectively, and 168 and 136 mg/kg/day in mice following acute or intermediate exposure (NTP 1989b); at the highest dose tested in chronic studies, no significant alterations in body weight gain were observed in rats at 4 mg/kg/day or in mice at 43 mg/kg/day (NTP 1989b).

3.2.2.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to inorganic arsenicals. No evidence of immunosuppression was detected in mice exposed to arsenate at levels up to 100 ppm (20 mg As/kg/day) in drinking water (Kerkvliet et al. 1980). This NOAEL is shown in Table 3-3 and Figure 3-3. Gallium arsenide at doses of 52–260 mg As/kg/day produced significant, dose-related decreases in relative spleen weight, spleen cellularity, humoral immune response (antibody forming cell response to sheep RBC), and delayed type hypersensitivity in rats (Flora et al. 1998). However, it is not clear to what extent these effects are due to the arsenic moiety.

Organic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans or animals after oral exposure to organic arsenicals. No histological alterations were observed in immunological or lymphoreticular tissues following intermediate-duration exposure of rats to 43.2 mg DMA/kg/day in the diet (Crown et al. 1987) or rats and mice to 18.23 or 38.7 mg As/kg/day as roxarsone, respectively (NTP 1989b) or following chronic-duration exposure of rats and mice to 72.4 or 67.1 mg MMA/kg/day (Arnold et al. 2003), 7.8 or 94 mg DMA/kg/day (Arnold et al. 2006), or 4 or 43 mg/kg/day roxarsone (NTP 1989b). No studies examined immune function following oral exposure to organic arsenicals.

3.2.2.4 Neurological Effects

Inorganic Arsenicals. A large number of epidemiological studies and case reports indicate that ingestion of inorganic arsenic can cause injury to the nervous system. Acute, high-dose exposures (2 mg As/kg/day or above) often lead to encephalopathy, with signs and symptoms such as headache, lethargy, mental confusion, hallucination, seizures, and coma (Armstrong et al. 1984; Bartolome et al. 1999; Civantos et al. 1995; Cullen et al. 1995; Danan et al. 1984; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Quatrehomme et al. 1992; Uede and Furukawa 2003; Vantroyen et al. 2004). Repeated exposures to lower levels (0.03–0.1 mg As/kg/day) are typically characterized by a symmetrical peripheral neuropathy (Chakraborti et al. 2003a, 2003b; Foy et al. 1992; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Hindmarsh et al. 1977; Huang et al. 1985; Lewis et al. 1999; Mizuta et al. 1956; Muzi et al. 2001; Silver and Wainman 1952; Szuler et al. 1979; Wagner et al. 1979). This neuropathy usually begins as numbness in the hands and feet, but later may develop into a painful "pins and needles" sensation. Both sensory and motor nerves are affected, and muscle weakness often develops, sometimes leading to wrist-drop or ankle-drop (Chhuttani et al. 1967; Heyman et al. 1956). Diminished sensitivity to stimulation and abnormal patellar reflexes have also been reported (Mizuta et al. 1956). Histological examination of nerves from affected individuals reveals a dying-back axonopathy with demyelination (Goebel et al. 1990; Hindmarsh and McCurdy 1986). Some recovery may occur following cessation of exposure, but this is a slow process and recovery is usually incomplete (Fincher and Koerker 1987; Le Quesne and McLeod 1977; Murphy et al. 1981). Peripheral neuropathy is also sometimes seen following acute high-dose exposures, with or without the previously described encephalopathy (Armstrong et al. 1984; Baker et al. 2005; Fincher and Koerker 1987; Goebel et al. 1990; Hantson et al. 1996; Kamijo et al. 1998). Neurological effects were not generally found in populations chronically exposed to doses of 0.006 mg As/kg/day or less (EPA 1981b; Harrington et al. 1978; Hindmarsh et al. 1977), although fatigue, headache, dizziness, insomnia, nightmare, and numbness of the extremities were among the symptoms reported at 0.005, but not 0.004 mg As/kg/day in a study of 31,141 inhabitants of 77 villages in Xinjiang, China (Lianfang and Jianzhong 1994), and depression was reported in some Wisconsin residents exposed to 2–10 µg As/L in the drinking water for 20 years or longer (Zierold et al. 2004).

There is emerging evidence suggesting that exposure to arsenic may be associated with intellectual deficits in children. For example, Wasserman et al. (2004) conducted a cross-sectional evaluation of intellectual function in 201 children 10 years of age whose parents were part of a larger cohort in Bangladesh. Intellectual function was measured using tests drawn from the Wechsler Intelligence Scale for Children; results were assessed by summing related items into Verbal, Performance, and Full-Scale

raw scores. The mean arsenic concentration in the water was 0.118 mg/L. The children were divided into four exposure groups, representing <5.5, 5.6–50, 50–176, or 177–790 μg As/L drinking water. After adjustment for confounding factors, a dose-related inverse effect of arsenic exposure was seen on both Performance and Full-Scale subset scores; for both end points, exposure to ≥50 μg/L resulted in statistically significant differences (p<0.05) relative to the lowest exposure group (<5.5 μg/L). In a later report, the same group of investigators examined 301 6-year-old children from the same area (Wasserman et al. 2007). In this case, the children were categorized into the following quartiles based on water arsenic concentration: 0.1–20.9, 21–77.9, 78–184.9, and 185–864 μg/L. After adjustment for water Mn, blood lead, and sociodemographic features known to contribute to intellectual function, water arsenic was significantly negatively associated with both Performance and Processing speed raw scores. Analyses of the dose-response showed that compared to the first quartile, those in the second and third categories had significantly lower Performance raw scores (p<0.03 and p=0.05, respectively). Those in the fourth category had marginally significantly lower Full-Scale and Processing Speed raw scores. It should be mentioned, however, that in general, arsenic in the water explained <1% of the variance in test scores. Water arsenic made no contribution to IQ outcomes. A study of 351 children age 5–15 years from West Bengal, India, found significant associations between urinary arsenic concentrations and reductions in scores of tests of vocabulary, object assembly, and picture completion; the magnitude of the reductions varied between 12 and 21% (von Ehrenstein et al. 2007). In this cohort, the average lifetime peak arsenic concentration in well water was 0.147 mg/L. However, no clear pattern was found for increasing categories of peak arsenic water concentrations since birth and children's scores in the various neurobehavioral tests conducted. Furthermore, using peak arsenic as a continuous variable in the regression models also did not support an adverse effect on the tests results. Exposure to arsenic *in utero* also did not suggest an association with the tests scores. Von Ehrestein et al. (2007) concluded that the study provided little evidence for an effect of long-term arsenic concentrations in drinking water and that the lack of findings with past exposures via drinking water may be due to incomplete assessment of past exposure, particularly exposure originating from food. Wasserman's results are consistent with those of ecological studies in children in Taiwan (Tsai et al. 2003) and in China (Wang et al. 2007). In the former, adolescents exposed to low (0.0017–0.0018 mg As/kg/day; n=20) levels of inorganic arsenic in the drinking water showed decreased performance in the switching attention task, while children in the high exposure group (0.0034–0.0042 mg As/kg/day; n=29) showed decreased performance in both the switching attention task and in tests of pattern memory, relative to unexposed controls (n=60). In the study in China (age 8– 12 years), 87 children whose mean arsenic concentration in the drinking water was 0.190 mg/L had a mean IQ score of 95 compared with 101 for children (n=253) with 0.142 mg/L arsenic in the water and 105 for control children (n=196) with 0.002 mg/L arsenic in the drinking water (Wang et

al. 2007). The differences in IQ scores between the two exposure groups and the control group were statistically significant.

Neurological effects have also been observed in animal studies. Rodriguez et al. (2001) evaluated neurobehavioral changes in male Sprague-Dawley rats exposed to 0, 5, 10, or 20 mg As/kg/day as sodium arsenite by gavage for 2 or 4 weeks; significant effects were seen in spontaneous locomotor activity and the food pellet manipulation test in the high-dose animals, while no effects were seen in the low- or mid-dose rats. Decreased performance in open field tests were also seen in rats exposed to 26.6 mg As/kg/day, but not to 13.3 mg/kg/day or less, as sodium arsenite for 4 weeks (Schulz et al. 2002); curiously, the behavioral changes were no longer present at 8 and 12 weeks of exposure, which may suggest an adaptive response. Heywood and Sortwell (1979) reported salivation and uncontrolled head shaking in two monkeys given several doses of 6 mg As/kg/day as arsenate, while no such effects were noted in monkeys given 3 mg As/kg/day for 2 weeks. Nemec et al. (1998) observed ataxia and prostration in pregnant female rabbits treated with 1.5 mg As/kg/day repeatedly during gestation, but not in rabbits treated with 0.4 mg As/kg/day. Some changes in levels of neurotransmitters (dopamine, norepinephrine, and 5-hydroxytryptamine) were seen in rats exposed to 2.3 mg As/kg/day as sodium arsenite and guinea pigs exposed to 1.7 mg As/kg/day as sodium arsenite in the drinking water for 16 weeks (Kannan et al. 2001) or in rats exposed to 0.14 mg As/kg/day as sodium arsenite by gavage for 28 days (Chattopadhyay et al. 2001), but the functional significance of these changes is not clear.

The highest NOAEL values and all reliable LOAEL values for neurological effects from inorganic arsenic in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Organic Arsenicals. Numbness and tingling of the fingertips, toes, and circumoral region were reported by a women exposed to an unspecified amount of organic arsenic in bird's nest soup. Discontinuation of exposure resulted in the disappearance of symptoms (Luong and Nguyen 1999). Decreased absolute brain weights were seen in male rats exposed to 25.7 mg MMA/kg/day and female rats exposed to ≥33.9 mg MMA/kg/day, but decreased body weight also occurred at these exposure levels, and relative brain weights were increased in the males at 25.7 mg MMA/kg/day and the females at ≥33.9 mg MMA/kg/day in this study (Arnold et al. 2003). No neurological clinical signs or brain lesions were observed following chronic exposure of rats to 72.4 mg MMA/kg/day or mice to 67.1 mg MMA/kg/day (Arnold et al. 2003). Decreased spontaneous motility, increased startle response, and ataxia were observed in mice receiving a single gavage dose of 1,757 mg DMA/kg/day (Kaise et al. 1989); no other evidence (clinical signs or histological alterations) were observed in chronic studies of DMA in which

rats and mice were exposed to 7.8 or 94 mg DMA/kg/day, respectively (Arnold et al. 2006). Two studies in pigs indicate that repeated oral doses of roxarsone (6.3–20 mg/kg/day for 1 month) can cause significant neurotoxicity (Edmonds and Baker 1986; Kennedy et al. 1986; Rice et al. 1985). The main signs were time-dependent degenerations of myelin and axons (Kennedy et al. 1986; Rice et al. 1985). Evidence of neurological effects (hyperexcitability, ataxia, trembling) was noted in some rat and mouse studies (Kerr et al. 1963; NTP 1989b). Reliable NOAELs and LOAELs are presented in Tables 3-4, 3-5, and 3-6, and Figures 3-4, 3-5, and 3-6.

3.2.2.5 Reproductive Effects

Inorganic Arsenicals. Exposure to arsenic in drinking water has been associated with adverse reproductive outcomes in some studies. For example, a study of 96 women in Bangladesh who had been drinking water containing ≥0.10 mg As/L (approximately 0.008 mg As/kg/day) for 5–10 years reported a significant increase in spontaneous abortions (p=0.008), stillbirth (p=0.046), and preterm birth (p=0.018) compared to a nonexposed group (Ahmad et al. 2001). Similar results were reported by Milton et al. (2005) who found a significant association between concentrations of arsenic in the water >0.05 mg/L (approximately 0.006 mg As/kg/day) and spontaneous abortion (odds ratio [OR]=2.5; 95% CI=1.5–4.3) in a study of 533 women, also from Bangladesh. A study of 202 women from West Bengal, India, reported that exposure to arsenic concentrations of arsenic ≥0.2 mg/L in drinking water (approximately 0.02 mg As/kg/day) during pregnancy were associated with a 6-fold increased risk of stillbirth (OR=6.1; 95% CI=1.54–24.0) after adjustment for confounders (von Ehrenstein et al. 2006). No association was found between arsenic exposure and risk of spontaneous abortion (OR=1.01; 95% CI=0.73–10.8). An earlier study of 286 women in the United States also found no significant association between arsenic in the drinking water (0.0016 mg/L; approximately 0.00005 mg As/kg/day) and spontaneous abortion (OR=1.7; 95% CI=0.7–4.2) (Aschengrau et al. 1989).

Lugo et al. (1969) reported a case of a 17-year-old mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison) at week 30 of pregnancy. Twenty-four hours after ingestion of approximately 30 mL of arsenic trioxide (0.39 mg As/kg), she was admitted for treatment of acute renal failure. She went into labor and delivered a live female infant weighing 2 pounds, 7 ounces with a 1-minute Apgar score of 4. The infant's clinical condition deteriorated and she died at 11 hours of age.

Reproductive performance was not affected in female rats that received gavage doses of 8 mg As/kg/day (as As_2O_3) from 14 days prior to mating through gestation day 19 (Holson et al. 2000). Reproductive

indices that were evaluated included the precoital interval (time to mating), mating index (percentage of rats mated), and fertility index (percentage of matings resulting in pregnancy). In a 3-generation study in mice given sodium arsenite in drinking water at an average dose of 1 mg As/kg/day, there was a significant increase in the incidence of small litters and a trend toward a decreased number of pups per litter in all three generations of the treated group (Schroeder and Mitchener 1971). This finding is consistent with the results of developmental toxicity studies reported in Section 3.2.2.6. Female rats exposed to 0.24 mg As/kg/day (as arsenite) for 28 days showed changes in several reproductive system end points, including decreases in wet weights of the ovary and uterus, inhibition of steroidogenic enzymes, decreased ovarian and uterine peroxidase activities, and decreased estradiol levels relative to controls (Chattopadhyay et al. 2001). NOAEL and LOAEL values from these studies are shown in Table 3-3 and Figure 3-3.

Organic Arsenicals. No studies were located regarding reproductive effects in humans after oral exposure to organic arsenicals. No histological alterations in male or female reproductive tissues were observed in laboratory animals following exposure to MMA (Arnold et al. 2003), DMA (Arnold et al. 2006), or roxarsone (NTP 1989b) and no alterations in sperm parameters were observed in male rats exposed to 76 mg MMA/kg/day for at least 14 weeks (Schroeder 1994). However, some functional alterations have been reported in animals exposed to MMA or DMA. A decrease in estrus was observed in dogs exposed to 35 mg MMA/kg/day for 52 weeks (Waner and Nyska 1988); decreases in body weight gain (terminal body weight was 59% lower than controls) were also observed at this dose level and the effect may have been secondary to systemic toxicity. Decreases in pregnancy rate and male fertility index were observed in F_0 and F_1 rats exposed to 76 mg MMA/kg/day for 14 weeks prior to mating and during the mating, gestation, and lactation periods (Schroeder 1994). In the F_0 animals, the pregnancy rate and male fertility index were not statistically different from controls; however, the values were below historical controls and the investigators considered the effect to be treatment-related. In the F_1 animals, the male fertility index was statistically different from controls but the pregnancy rate was not; both parameters were within the range found in historical controls, but the investigators considered the effect to be treatment-related due to the consistency of the findings in the F_0 and F_1 animals. Impaired fertility, as evidenced by a decreased number of litters, was observed in male mice dosed with MSMA (119 mg/kg/day) during a 19-day mating period with unexposed females (Prukop and Savage 1986); the poor reporting of the study protocol and results precludes drawing conclusions from this study. An increase in the number of does with aborted fetuses was observed in rabbits exposed to 48 mg DMA/kg/day as DMA (Irvine et al. 2006); severe maternal toxicity (weight loss, reduced food intake, and

diarrhea) was also observed at this dose level. No reproductive effects were observed in a 2-generation rat study in which rats were exposed to 16.5 mg DMA/kg/day (Rubin et al. 1989).

3.2.2.6 Developmental Effects

Inorganic Arsenicals. Whether ingestion of inorganic arsenic may cause developmental effects in humans has not been extensively investigated. Lugo et al. (1969) reported a case of a mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison) at 30 weeks of gestation. Twenty-four hours after ingestion, she went into labor and delivered a live female infant weighing 2 pounds, 7 ounces with a 1-minute Apgar score of 4. The infant's clinical condition deteriorated with frequent episodes of apnea and bradycardia; subsequent venous blood gas determinations documented hypoxia, hypercapnea, and acidosis. The infant died at 11 hours of age. Autopsy performed 8 hours after death showed organ immaturity, generalized petechial hemorrhages, and hyaline membrane disease. Severe intra-alveolar pulmonary hemorrhage was remarkable. High arsenic levels were found in the infant's liver, kidney, and brain, demonstrating easy passage of inorganic arsenic across the placenta. The authors considered most of the findings in the neonate to be attributable to immaturity, but suggested that arsenic may have played a role in the severe intra-alveolar hemorrhaging that contributed to death.

Chronic exposure of women to arsenic in the drinking water has been associated with infants with low birth weights in Taiwan (Yang et al. 2003) and Chile (Hopenhayn et al. 2003a). Similar associations have been made between late fetal mortality, neonatal mortality, and postneonatal mortality and exposure to high levels of arsenic in the drinking water (up to 0.86 mg/L during over a decade), based on comparisons between subjects in low- and high-arsenic areas of Chile (Hopenhayn-Rich et al. 2000). More recently, von Ehrenstein et al. (2006) reported no significant association between exposure to concentrations of ≥0.1 mg/L arsenic in drinking water (approximately 0.008 mg As/kg/day) (n=117; 29 women were exposed to ≥0.5 mg/L) and increased risk for neonatal death or infant mortality during the first year of life in a study of a population in West Bengal, India. The same group of investigators reported significantly increased SMRs for lung cancer and bronchiectasis among subjects in a city in Chile who had probable exposure *in utero* (maternal exposure) or during childhood to high levels of arsenic (near 0.9 mg/L) in the drinking water (Smith et al. 2006). For those exposed in early childhood, the SMR for lung cancer was 7.0 (95% CI=5.4–8.9, $p<0.001$) and for bronchiecstasis 12.4 (95% CI=3.3–31.7, $p<0.001$). For those born during the high-exposure period, the corresponding SMRs were 6.1 (95% CI=3.5–9.9, $p<0.001$) and 46.2 (95% CI=21.1–87.7, $p<0.001$). The mortality data analyzed were for the age range 30–49 years.

No overall association between arsenic in drinking water and congenital heart defects was detected in a case-control study in Boston (Zierler et al. 1988), although an association with one specific lesion (coarctation of the aorta) was noted (OR=3.4, 95% CI=1.3–8.9). A study of 184 women with neural tube defects in the offspring living in a Texas county bordering Mexico found that exposure to levels of arsenic in the drinking water >0.010 mg/L (range or upper limit not specified) did not significantly increase the risk for neural tube defects (OR=2.0, 95% CI=0.1–3.1) (Brender et al. 2006).

Studies in animals, however, suggest that ingested inorganic arsenic may produce developmental effects at high doses that also produce overt maternal toxicity. Rats treated with a single gavage dose of 23 mg As/kg as arsenic trioxide on day 9 of gestation had a significant increase in postimplantation loss and a decrease in viable fetuses per litter, while those treated with 15 mg As/kg showed no effects (Stump et al. 1999). Rats treated by daily gavage with 8 mg As/kg/day starting 14 days before mating and continuing through gestation had significantly reduced fetal body weights and significantly increased incidences of several skeletal variations (unossified sternebrae #5 or #6, slight or moderate sternebrae malalignment, 7th cervical ribs) that the researchers considered to be consequences of developmental growth retardation (Holson et al. 2000). No developmental effects were found at 4 mg As/kg/day in this study. Exposure of rats to 2.93–4.20 mg As/kg/day throughout gestation and for 4 months postnatally resulted in alterations in neurobehavioral parameters in the offspring, including increased spontaneous locomotor activity and number of errors in a delayed alternation task; maternal behavior was not affected (Rodriguez et al. 2002). Studies in mice found increased fetal mortality, decreased fetal body weight, a low incidence of gross malformations (primarily exencephaly), and an increase in skeletal malformations in mice given single gavage doses of 23–48 mg As/kg during gestation (Baxley et al. 1981; Hood et al. 1978), with no effects at 11 mg As/kg. Similarly, in mice treated with 24 mg As/kg/day as arsenic acid on days 6–15 of gestation, there was a significant increase in the number of resorptions per litter (42% vs. 4% in controls) and significant decreases in the number of live pups per litter (6.6 vs. 12.3 in controls) and mean fetal weight (1.0 g vs. 1.3 g in controls), while no developmental effects were found at 12 mg As/kg/day (Nemec et al. 1998). Hamsters treated with a single gavage dose of 14 mg As/kg during gestation also had increased fetal mortality and decreased fetal body weight (Hood and Harrison 1982), with no effect at 11 mg As/kg. However, the most sensitive species was the rabbit, which had increased resorptions and decreased viable fetuses per litter at 1.5 mg As/kg/day and a developmental NOAEL of 0.4 mg As/kg/day, following repeated gavage dosing with arsenic acid during gestation (Nemec et al. 1998). In each of these studies (except Hood et al. 1978, which failed to report maternal effects), overt maternal toxicity, including death in some cases, was found at the same or lower doses as the developmental

effects (Baxley et al. 1981; Holson et al. 2000; Hood and Harrison 1982; Nemec et al. 1998; Stump et al. 1999).

It is noteworthy that the effect in the 3-generation reproduction study in mice by Schroeder and Mitchener (1971), decreased pups per litter (all generations), is consistent with the findings of many of these shorter-term studies (Baxley et al. 1981; Hood and Harrison 1982; Hood et al. 1978; Nemec et al. 1998; Stump et al. 1999). The dose in this long-term study was 1 mg As/kg/day; in a 2-year study by these researchers, this dose produced effects such as decreased body weight gain and increased mortality (Schroeder and Balassa 1967).

A series of studies presented evidence that inorganic arsenic may be a transplacental carcinogen in animals. Waalkes et al. (2003, 2004a, 2004b, 2004c) exposed timed-pregnant AJ mice to 0, 42.5, or 85 ppm of sodium arsenite in the drinking water from gestation day 8 through 18 and observed the offspring for 90 weeks following birth; the study authors estimated daily doses at 9.55 and 19.3 mg As/kg/day. A dose-related increase was reported in the incidence of hepatocellular carcinomas and adrenal tumors in the male offspring from both treatment levels, while male offspring from high-dose animals showed an increase in total number of tumors. In female offspring, an increase in uterine hyperplasia was seen in the offspring of both treated groups while the offspring of high-dose animals showed increased incidence of lung carcinomas. For both exposed groups, regardless of gender, the offspring showed a significant increase in the number of malignant tumors (Waalkes et al. 2003). More recent studies from the same group of investigators have suggested that aberrant estrogen signaling, potentially through inappropriate estrogen receptor-α (ER-α), may play a role in arsenic-induced liver tumors in male offspring (Waalkes et al. 2006a) and in arsenic-induced uterine and bladder carcinoma in female offspring (Waalkes et al. 2006b). The latter was based on the observation of over-expression of ER-α and *pS*2, an estrogen-regulated gene, in the respective tissues.

These studies (shown in Table 3-3 and Figure 3-3) indicate that the fetus may be affected by ingested arsenic.

Organic Arsenicals. No studies were located regarding developmental effects in humans after oral exposure to organic arsenicals. The developmental toxicity of organic arsenicals has been investigated in rats and rabbits for MMA and in rats, mice, and rabbits for DMA. Decreased fetal weights and an increased incidence of fetuses with incomplete ossification of thoracic vertebrae were observed in the offspring of rats administered via gavage 500 mg MMA/kg/day on gestational days 6–15; no

developmental effects were observed at 100 mg MMA/kg/day (Irvine et al. 2006). Decreases in maternal body weight gain were observed at 100 and 500 mg MMA/kg/day. A decrease in pup survival was observed in F_1 and F_2 offspring of rats exposed to 76 mg MMA/kg/day (Schroeder 1994); although pup survival was not statistically different from controls, the investigators considered the effect to be biologically significant because survival in the MMA pups was outside the lower range of survival in historical controls. Increases in the number of fetuses with supernumerary thoracic ribs and eight lumbar vertebrae were observed in the offspring of rabbits administered to 12 mg MMA/kg/day on gestational days 7–19 (Irvine et al. 2006); the investigators noted that these effects were probably secondary to maternal stress.

No developmental effects were observed in the offspring of rats administered via gavage 15 mg DMA/kg/day on gestational days 7–16 (Rogers et al. 1981). At 30 mg DMA/kg/day, there was an increase in the percentage of fetuses with irregular palatine rugae; no maternal effects were observed at this dose level (Rogers et al. 1981). The investigators noted that the functional significance of aberrant rugae in rats is not known. Doses of ≥36 mg DMA/kg/day resulted in decreases in fetal weights and delays in ossification (Chernoff et al. 1990; Irvine et al. 2006; Rogers et al. 1981); decreases in maternal body weight gain were often observed at the same dose levels. Irvine et al. (2006) also reported an increase in the occurrence of diaphragmatic hernia in the offspring of rats exposed to 36 mg DMA/kg/day as DMA on gestational days 6–15. Mice appear to be less sensitive than rats to the developmental toxicity of DMA. No developmental effects were observed in the offspring of mice administered 200 mg DMA/kg/day on gestational days 7–16 (Rogers et al. 1981); at higher doses, decreases in fetal body weight, delays in ossification, and cleft palate were observed (Kavlock et al. 1985; Rogers et al. 1981). In rabbits, a NOAEL of 12 mg DMA/kg/day was identified (Irvine et al. 2006); at 48 mg DMA/kg/day, there were increased maternal deaths and abortions.

3.2.2.7 Cancer

Inorganic Arsenicals. There is convincing evidence from a large number of epidemiological studies and case reports that ingestion of inorganic arsenic increases the risk of developing skin cancer (Alain et al. 1993; Beane Freeman et al. 2004; Bickley and Papa 1989; Cebrián et al. 1983; Chen et al. 2003; Guo et al. 2001a; Haupert et al. 1996; Hsueh et al. 1995; Lewis et al. 1999; Lüchtrath 1983; Mitra et al. 2004; Morris et al. 1974; Piontek et al. 1989; Sommers and McManus 1953; Tay and Seah 1975; Tsai et al. 1998a, 1999; Tseng 1977; Tseng et al. 1968; Zaldívar 1974; Zaldívar et al. 1981). Lesions commonly observed are multiple squamous cell carcinomas, some of which appear to develop from the

hyperkeratotic warts or corns described in Section 3.2.2.2. In addition, multiple basal cell carcinomas may occur, typically arising from cells not associated with hyperkeratinization. In most cases, skin cancer develops only after prolonged exposure, but one study has reported skin cancer in people exposed for <1 year (Reymann et al. 1978). Although both types of skin cancer can be removed surgically, they may develop into painful lesions that may be fatal if left untreated (Shannon and Strayer 1989).

A number of studies that identify CELs in exposed humans are summarized in Table 3-3 and shown in Figure 3-3. The EPA reviewed the studies that provided dose-response data on the risk of skin cancer (EPA 1988d) and concluded that the most useful study for the purposes of quantitative risk assessment was the ecologic epidemiology study by Tseng et al. (1968). In this study, the incidence of skin cancer was measured as a function of exposure level in over 40,000 people residing in 37 villages in Taiwan, and compared to a control group of over 7,500 people. Beyond the very large sample size, other strengths of this study include excellent case ascertainment (physical examination), inclusion of both males and females, and lifetime exposure duration. Weaknesses and uncertainties include poor nutritional status of the exposed populations, their genetic susceptibility, their exposure to inorganic arsenic from nonwater sources, and the applicability of extrapolating data from Taiwanese to the U.S. population because of different background rates of cancer, possibly genetically determined, and differences in diet other than arsenic (e.g., low protein and fat and high carbohydrate) (EPA 1988d). Because of a lack of information on the amount of individual exposure, subjects were classified into three exposure groups (i.e., high, medium, and low). Based upon pooled data for skin cancer incidence and average well concentrations for each village in the Tseng et al. (1968) study, the EPA calculated a unit risk (the upper-bound excess cancer risk from lifetime exposure to water containing 1 μg As/L) of $5x10^{-5}$ (IRIS 2007). The average daily doses (expressed as mg As/kg/day) that correspond to excess cancer risks of $1x10^{-4}$–$1x10^{-7}$ are shown in Figure 3-3.

The use of a cancer risk estimate derived from the Tseng et al. (1968) study for a U.S. population has been the source of intense debate. Some have argued and have provided data in support of the view that there is persuasive evidence that inorganic arsenic is a cause of human cancer at several sites (i.e., Smith et al. 1992, 1995, 2002). On the other hand, a number of concerns have been raised regarding the strength, or lack of strength, of the database, including: the adequacy of the model used by EPA and the accuracy and reliability of the exposure data (Brown et al. 1997a, 1997b); a number of host and environmental factors among the Taiwanese not applicable elsewhere (Carlson-Lynch et al. 1994); a possible threshold for arsenic carcinogenicity and nonlinearities in the dose-response curve (Abernathy et al. 1996; Slayton et al. 1996); differences in health and nutrition between Taiwan and the United States

that might increase cancer risk in Taiwan (Beck et al. 1995); the possibility that lower doses of arsenic may be beneficial role in some physiological processes (EPA 1988d; FNB/IOM 2001; NRC 1999, 2001); and the possibility of significant exposure to arsenic from sources other than the well water (Chappell et al. 1997). Many of these factors were recognized by EPA (1988d). A report by NRC (2001) suggested that the risks calculated based on increases in incidence of lung and bladder cancers may be greater than those calculated by the EPA based on incidences of skin cancer.

Several early epidemiological studies performed in the United States did not report an increased frequency of skin cancer in small populations consuming water containing arsenic at levels of around 0.1–0.2 ppm (EPA 1981b; Goldsmith et al. 1972; Harrington et al. 1978; Morton et al. 1976). These early data suggested that arsenic-associated skin cancer is not a common problem in this country, but these studies lacked sufficient statistical power to detect small increases in skin cancer incidence that might have occurred at these low doses (EPA 1983g). Later studies in exposed U.S. populations from Utah (Lewis et al. 1999) and Iowa (Beane Freeman et al. 2004) have suggested that arsenic-exposed individuals within the United States may have increased incidence or risk of mortality from some skin cancers, melanoma in particular; however, exposure data from these studies are generally insufficient for dose-response analysis. Another study found a suggestion of an arsenic-induced effect on the development of skin cancer, but the association did not achieve statistical significance (Karagas et al. 2001). Therefore, the risk of arsenic-induced skin cancers in U.S. populations, while it may appear to be less than in some other evaluated populations, may be the reflection that, in most studies, exposures were lower.

In addition to the risk of skin cancer, there is mounting evidence that ingestion of arsenic may increase the risks of internal cancers as well. Many case studies have noted the occurrence of internal tumors of the liver and other tissues in patients with arsenic-induced skin cancer (Falk et al. 1981b; Kasper et al. 1984; Koh et al. 1989; Lander et al. 1975; Regelson et al. 1968; Sommers and McManus 1953; Tay and Seah 1975; Zaldívar et al. 1981). These studies are supported by large-scale epidemiological studies, where associations and/or dose response trends have been detected for tumors of the bladder, kidney, liver, lung, and prostate (Chen and Wang 1990; Chen et al. 1985, 1986, 1988a, 1988b, 1992; Chiou et al. 1995; Cuzick et al. 1992; Ferreccio et al. 1998; Guo et al. 1997; Hopenhayn-Rich et al. 1998; Kurttio et al. 1999; Lewis et al. 1999; Moore et al. 2002; Rivara et al. 1997; Smith et al. 1998; Tsuda et al. 1995a; Wu et al. 1989). The EPA has not yet calculated a unit risk value or slope factor for arsenic-induced internal tumors.

There is increasingly convincing evidence that long-term exposure to arsenic can result in the development of bladder cancer (Bates et al. 2004; Chen et al. 1992, 2003; Chiou et al. 1995, 2001; Cuzick et al. 1992; Guo et al. 2001b; Karagas et al. 2004; Lamm et al. 2004; Michaud et al. 2004; Steinmaus et al. 2003), with transitional cell cancers being the most prevalent. Chiou et al. (1995) reported a dose-response relationship between long-term arsenic exposure from drinking artesian well water and the incidence of lung cancer, bladder cancer, and cancers of all sites combined (after adjustment for age, sex, and cigarette smoking) in four townships in Taiwan exposed to inorganic arsenic in drinking water (0–1.14 mg/L). In a later followup study of the same cohort, the increase in bladder cancer was found to be statistically significant only in subjects exposed for 40 years or longer (Chiou et al. 2001). Cuzick et al. (1992) evaluated a cohort treated with Fowler's solution (potassium arsenite) in Lancashire, England, during the period 1945–1969 and followed through 1991; the cohort of 478 patients showed a significant excess of bladder cancer, but no excess for other causes of death. Of a subcohort of 142 patients examined for signs of arsenicism around 1970 (Cuzick et al. 1992), all 11 subsequent cancer deaths occurred in those with signs of arsenicism (p=0.0009). Hopenhayn-Rich et al. (1996a) investigated bladder cancer mortality for the years 1986–1991 in the 26 counties of Cordoba, Argentina, and reported that bladder cancer SMRs were consistently higher in counties with documented arsenic exposure; a later case-control study by the same authors (Bates et al. 2004) did not report statistically significant increases in bladder cancers resulting from arsenic exposure, except in individuals exposed for 50 years or longer. Guo et al. (2001a) reported significantly increased rate differences for bladder cancer in men and women in Taiwan exposed to 0.64 mg arsenic/L in the drinking water, but not at lower exposure levels. The arsenic-induced bladder tumors do not appear to be histologically different than similar bladder tumor types of nonarsenic origin (Chow et al. 1997), although they tended to be more pronounced. In contrast, Michaud et al. (2004) reported no correlation between arsenic levels in toenails and the incidence of bladder cancers in Finnish workers. Among evaluated U.S. cohorts, there has generally been no association between arsenic exposure (~60–100 μg As/L) and the incidence of mortality from bladder cancers (Lamm et al. 2004; Steinmaus et al. 2003), although it is possible that smoking may render individuals more susceptible to arsenic-induced bladder tumors (Karagas et al. 2004; Steinmaus et al. 2003).

Studies have also suggested that chronic oral exposure to arsenic may result in the development of respiratory tumors and increased incidence of lung cancer (Ferreccio et al. 2000; Guo 2004; Nakadaira et al. 2002; Smith et al. 1998; Viren and Silvers 1999). A study of arsenic-exposed individuals in northern Chile reported significantly increased odds ratios for lung cancer among subjects with ≥30 μg As/L of drinking water (Ferreccio et al. 2000), although when adjusted for socioeconomic status, smoking, and

other factors, the increase was only significant at 60 μg As/L or greater. Guo (2004) reported significantly increased rates differences (RD) for lung cancer for Taiwanese men and women exposed to 0.64 mg As/L or greater, with those subjects >50 years of age being particularly at risk. Nakadaira et al. (2002) suggested that even comparatively short exposure durations (≤5 years) may be sufficient for the development of arsenic-induced lung cancer.

Studies in U.S. populations exposed to arsenic in drinking water (EPA 1981b; Lamm et al. 2004; Lewis et al. 1999; Morton et al. 1976; Steinmaus et al. 2003; Valentine et al. 1992) have not yielded the cancer incidences and health effects noted in Taiwan, Mexico, and Chile. Whether this difference is due to a smaller population of subjects compared to Taiwan, to overall lower doses in exposed U.S. populations, or to differences in nutritional or socioeconomic conditions has not been resolved. It should be noted that exposed populations in Mexico and Chile are also smaller than those in Taiwan.

Most studies of animals exposed to arsenate or arsenite by the oral route have not detected any clear evidence for an increased incidence of skin cancer or other cancers (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). Arsenic has sometimes been called a “paradoxical” human carcinogen because of this lack of animal data (Jager and Ostrosky-Wegman 1997). The basis for the lack of tumorigenicity in animals is not known, but could be related to species-specific differences in arsenic distribution, and induction of cell proliferation (Byrd et al. 1996) (see Section 3.5). As discussed in Section 3.5 below, the carcinogenic effects of arsenic may partially result from its function as a cocarcinogen, which would not manifest in most animal carcinogenicity studies.

One mouse study using transgenic mice (which carry the v-Ha-ras oncogene) administered 48 mg As/kg/day as sodium arsenite in drinking water for 4 weeks followed by dermal application of 12-O-tetradecanoylphorbol-13-acetage (TPA) to shaved back skin twice a day for 2 weeks showed an increase in the incidence of skin papillomas when compared to transgenic mice receiving only TPA treatment, only arsenic, or to wild-type mice receiving both TPA and arsenic (Germolec et al. 1998); arsenic treatment alone did not result in increased papilloma incidence. Increases in mRNA transcripts for the growth factors transforming growth factor-α (TGF-α) and granulocyte/ macrophage-colony stimulating factor (GM-CSF) were detected in the epidermis of the arsenic-treated mice.

A few studies in mice have noted that arsenic ingestion may actually decrease the incidence of some tumor types. For example, arsenic exposure caused decreased incidence of urethane-induced pulmonary tumors (Blakley 1987), spontaneous mammary tumors (Schrauzer and Ishmael 1974; Schrauzer et al.

1976), and tumors resulting from injection of mouse sarcoma cells (Kerkvliet et al. 1980). However, arsenic also increased the growth rate of the tumors that did occur, resulting in a net decrease in survival time in tumor-bearing animals (Kerkvliet et al. 1980; Schrauzer and Ishmael 1974). These observations suggest that arsenic may affect different types of neoplastic cells differently, perhaps acting mainly as a tumor promoter (Schrauzer and Ishmael 1974; Shirachi et al. 1983), although some studies have suggested that arsenic's actions are not consistent with tumor promotion (Baroni et al. 1963; Boutwell 1963).

There is evidence suggesting that inorganic arsenic can induce cancer in the offspring from mice exposed to arsenic during gestation (transplacental carcinogen) (Waalkes et al. 2003, 2004a, 2004b, 2004c, 2006a, 2006b). These studies are summarized in Section 3.2.2.6, Developmental Effects.

Organic Arsenicals. No studies were located regarding cancer in humans after oral exposure to organic arsenicals. Two lifetime carcinogenicity studies with MMA did not find significant increases in tumors in rats exposed to 72.4 mg MMA/kg/day in the diet for 2 years (Arnold et al. 2003) or 8.4 mg MMA/kg/day in drinking water for 2 years (Shen et al. 2003). No significant increases in neoplastic lesions were observed in mice exposed to 67.1 mg MMA/kg/day in the diet for 2 years (Arnold et al. 2003).

In contrast, significant increases in the incidence of urinary bladder tumors have been observed in rats exposed for 2 years to 7.8 mg DMA/kg/day in the diet (Arnold et al. 2006) or 3.4 mg DMA/kg/day in drinking water (Wei et al. 1999, 2002). The incidence of bladder tumors was similar to controls in the rats exposed to 0.77 mg DMA/kg/day (Arnold et al. 2006) or 0.75 mg DMA/kg/day (Wei et al. 1999, 2002). Neither study reported significant increases in the incidence of neoplastic lesions in other tissues. Arnold et al. (2006) did not find increases in the incidence of neoplastic lesions in mice exposed to doses as high as 94 mg DMA/kg/day in the diet for 2 years. Hayashi et al. (1998) reported that exposure of A/J mice (a strain susceptible to lung tumorigenesis) to 10.4 mg DMA/kg/day (but not 1.3 or 5.2 mg DMA/kg/day) in drinking water for 50 weeks resulted in an increased incidence of papillary adenomas and/or adenocarcinomas and an increased number of lung tumors per mouse.

The incidence of basophilic foci (believed to be a precancerous lesion) in the liver of rats initiated with diethylnitrosamine was increased by subsequent 6-month drinking water exposure to 11 mg DMA/kg/day, suggesting that this compound could act as a cancer promoter (Johansen et al. 1984). Additional evidence for the possible role of DMA as a promoter comes from Yamamoto et al. (1995), who reported that 15 or 60 mg DMA/kg/day in the drinking water for 24 weeks significantly enhanced the tumor induction in the

urinary bladder, kidney, liver, and thyroid gland in male F344 rats treated with a series of initiators. Wanibuchi et al. (1996) reported that treatment of F344 rats for 32 weeks with up to 14.3 mg DMA/kg/day DMA in the drinking water did not result in increased incidences of urinary bladder papillomas or carcinomas, but that incidence of these tumors was elevated if the animals were first pretreated with an initiating compound (BBN). A later study by Li et al. (1998) reported that NBR rats (which do not synthesize $\alpha_{2\mu}$-globulin) exposed to an initiator for 4 weeks followed by DMA for 32 weeks, similar to the Wanibuchi et al. (1996) study, showed a statistically significant increase in simple hyperplasia and papillary or nodular hyperplasia of the bladder. A study by Salim et al. (2003) suggested that DMA primarily exerts its carcinogenic effects on spontaneous tumor development.

No increases in tumor incidence were observed in rats, mice, or dogs exposed to 10, 13, or 5 mg/kg/day roxarsone, respectively, in the diet for 2 years (Prier et al. 1963). Similarly, no evidence of carcinogenicity was observed in female rats or male or female mice exposed to 4 or 43 mg/kg/day as roxarsone in the diet for 2 years (NTP 1989b). However, a slight increase in pancreatic tumors was noted in male rats exposed to 4 mg/kg/day (NTP 1989b); this was considered to constitute equivocal evidence of carcinogenicity.

3.2.3 Dermal Exposure

Adverse effects from dermal exposure to inorganic or organic arsenicals have not been extensively investigated. Table 3-7 summarizes studies in animals and humans that provide quantitative data on dermal exposure-effect relationships for inorganic arsenicals. No quantitative data on dermal exposure to organic arsenicals were located. Available quantitative and qualitative data are discussed in greater detail below.

3.2.3.1 Death

Inorganic Arsenicals. No studies were located regarding death in humans after dermal exposure to inorganic arsenicals. In rats, no deaths resulted from dermal exposure to arsenate or arsenite at doses up to 1,000 mg As/kg (Gaines 1960). These data indicate that dermal exposure to inorganic arsenic compounds is very unlikely to result in death.

Organic Arsenicals. No studies were located regarding death in humans after dermal exposure to organic arsenicals. No deaths were observed in rabbits receiving daily dermal applications of 540 mg As/kg as

Table 3-7 Levels of Significant Exposure to Inorganic Arsenic - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
ACUTE EXPOSURE							
Immuno/ Lymphoret							
Gn Pig (Hartley)	once		580 mg/L			Wahlberg and Boman 1986 As(+3)	
Gn Pig (Hartley)	once		4000 mg/L			Wahlberg and Boman 1986 As(+5)	
INTERMEDIATE EXPOSURE							
Systemic							
Mouse (Rockland)	30 wk 11 x/wk	Dermal		6 F mg/kg/day (gross hyperplasia, ulceration)		Boutwell 1963 As(+3)	

F = female; Gn pig = guinea pig; Immuno/Lymphoret = immunological/lymphoreticular; wk = week(s); x = time(s)

MMA 5 days/week for 21 days (Margitich and Ackerman 1991b) or 1,000 mg DMA/kg/day 5 days/week for 21 days (Margitich and Ackerman 1991a).

3.2.3.2 Systemic Effects

No studies were located that have associated respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular, or body weight effects in humans or animals with dermal exposure to inorganic arsenicals.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to organic arsenicals. No histological effects were observed in the respiratory tracts of rabbits following dermal application of 1,000 mg/kg/day MMA or DMA 5 days/week for 21 days (Margitich and Ackerman 1991a, 1991b).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to organic arsenicals. No histological effects were observed in the hearts of rabbits following dermal application of 1,000 mg/kg/day MMA or DMA 5 days/week for 21 days (Margitich and Ackerman 1991a, 1991b).

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to organic arsenicals. No treatment-related hematological alterations were observed in rabbits receiving dermal applications of 1,000 mg MMA/kg/day (Margitich and Ackerman 1991a) or 1,000 mg DMA/kg/day 5 days/week for 21 days (Margitich and Ackerman 1991b).

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to organic arsenicals. No significant alterations in blood clinical chemistry, liver weights, or histopathology were observed in rabbits dermally exposed to 1,000 mg/kg/day MMA or DMA 5 days/week for 21 days (Margitich and Ackerman 1991a, 1991b).

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to organic arsenicals. No significant alterations in urinalysis, kidney weights, or histopathology were observed in rabbits following dermal exposure to 1,000 mg MMA/kg/day (Margitich and Ackerman 1991a) or 1,000 mg DMA/kg/day 5 days/week for 21 days (Margitich and Ackerman 1991b).

Endocrine Effects. No studies were located regarding endocrine effects in humans after dermal exposure to organic arsenicals. No alterations in adrenal gland weight or histopathology of the adrenal glands, pancreas, pituitary gland, thyroid gland, and parathyroid gland were observed in rabbits following dermal application of 1,000 mg/kg/day MMA or DMA 5 days/week for 21 days (Margitich and Ackerman 1991a, 1991b).

Dermal Effects.

Inorganic Arsenicals. Several studies of humans exposed to arsenic dusts in the workplace have reported that inorganic arsenic (usually arsenic trioxide) can cause contact dermatitis (Holmqvist 1951; Pinto and McGill 1953). Typical responses included erythema and swelling, with papules and vesicles in more severe cases (Holmqvist 1951). The dermal contact rates that cause these effects in humans have not been quantified, but a similar direct irritation of the skin has been noted in mice exposed to 4 mg As/kg/day as potassium arsenite for 30 weeks (Boutwell 1963). In contrast, no significant dermal irritation was noted in guinea pigs exposed to aqueous solutions containing 4,000 mg As/L as arsenate or 580 mg As/L as arsenite (Wahlberg and Boman 1986). These studies indicate that direct contact may be of concern at high exposure levels, but do not suggest that lower levels are likely to cause significant irritation.

Studies on possible dermal sensitization by inorganic arsenicals are discussed in Section 3.2.3.3 below.

Organic Arsenicals. Contact dermatitis was reported in workers involved in the application of an organic arsenical herbicide, which is a mixture of DMA and its sodium salt (Peoples et al. 1979).

Application of an unspecified amount of MMA to the skin of rabbits was reported to result in mild dermal irritation in a Draize test (Jaghabir et al. 1988). No dermal irritation was reported in rabbits repeatedly exposed to 1,000 mg MMA/kg/day (Margitich and Ackerman 1991a) or 1,000 mg DMA/kg/day 5 days/week for 21 days (Margitich and Ackerman 1991b).

Ocular Effects. No studies were located regarding ocular effects in humans or animals after dermal exposure to organic arsenicals.

Body Weight Effects. No studies were located regarding body weight effects in humans after dermal exposure to organic arsenicals. No significant alterations in body weight gain were observed in rabbits

following a 5 day/week exposure to 1,000 mg/kg/day MMA or DMA for 21 days (Margitich and Ackerman 1991a, 1991b).

3.2.3.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. Examination of workers exposed to arsenic trioxide dusts in a copper smelter led Holmqvist (1951) to suspect that repeated dermal contact could lead to dermal sensitization. In support of this, Holmqvist (1951) found a positive patch test in 80% of the exposed workers compared to 30% in a control population. These data do suggest that workers may be sensitized to arsenic, but the high response rate in controls seems unusual. A much lower response rate (0.5%) was noted in another patch test study of dermal sensitization (Wahlberg and Boman 1986), and the few positive responses seemed to be due to a cross-reactivity with nickel. Mohamed (1998) evaluated 11 male workers at a tin smelting factory where arsenic trioxide levels ranged from 5.2 to 14.4 mg/m^3. The workers experienced symptoms of generalized itch, dry and hyperpigmented skin, folliculitis, and superficial ulcerations. The authors concluded that arsenic-containing dust collected on the sweat on the workers' skin, causing contact dermatitis. Studies in guinea pigs did not yield evidence of a sensitization reaction to inorganic arsenic (Wahlberg and Boman 1986).

Organic Arsenicals. Support for sensitization to DMA is provided in a case report of a 26-year-old woman who was occupationally exposed to DMA and experienced eczema on her face (Bourrain et al. 1998). Patch testing confirmed an allergic reaction to DMA, and avoidance of DMA resulted in disappearance of the symptoms. No studies were located regarding immunological or lymphoreticular effects in animals after dermal exposure to organic arsenicals.

No studies were located that have associated any of the following effects in humans or animals with dermal exposure to inorganic or organic arsenicals:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

Inorganic Arsenicals. No studies were found that have associated cancer in humans with dermal exposure to arsenic. Application of arsenic acid to the skin of mice pretreated with dimethylbenz-

anthracene did not result in any skin tumors (Kurokawa et al. 1989), suggesting that arsenic does not act as a promoter in this test system.

Organic Arsenicals. No studies were located regarding cancer in humans or animals after dermal exposure to organic arsenicals.

3.3 GENOTOXICITY

Inorganic Arsenicals. There have been a large number of studies of the genotoxic effects of arsenic. Tables 3-8 and 3-9 summarize a number of reports on the *in vitro* and *in vivo* genotoxicity of inorganic arsenicals, respectively. In general, *in vitro* studies in prokaryotic organisms have been negative for gene mutations (Lantzsch and Gebel 1997; Löfroth and Ames 1978; Nishioka 1975; Rossman et al. 1980; Ulitzur and Barak 1988). Studies in human fibroblasts, lymphocytes, and leukocytes, mouse lymphoma cells, Chinese hamster ovary cells, and Syrian hamster embryo cells demonstrate that *in vitro* arsenic exposure can induce chromosomal aberrations and sister chromatid exchange (see Table 3-8 for citations). *I vitro* studies in human, mouse, and hamster cells have also been positive for DNA damage and repair and enhancement or inhibition of DNA synthesis.

Studies of humans have detected a higher-than-average incidence of chromosomal aberrations in peripheral lymphocytes, both after inhalation exposure (Beckman et al. 1977; Nordenson et al. 1978) and oral exposure (Burgdorf et al. 1977; Nordenson et al. 1979). These studies must be interpreted with caution, since in most cases, there were only a small number of subjects and a number of other chemical exposures were possible (EPA 1984a). Human and animal data are available indicating that inhaled inorganic arsenic is clastogenic. Workers exposed to unspecified concentrations of arsenic trioxide at the Ronnskar copper smelter in Sweden were found to have a significant increase in the frequency of chromosomal aberrations in peripheral lymphocytes (Beckman et al. 1977; Nordenson et al. 1978). This result is supported by an animal study that found increased chromosomal aberrations in the livers of fetuses from pregnant mice exposed to 22, but not 2.2 or 0.20, mg As/m^3 as arsenic trioxide on days 9–12 of gestation (Nagymajtényi et al. 1985). Workers in the arsenic-based glass making industry in southern India had a significantly increased frequency of micronuclei in buccal cells and increased DNA damage in leukocytes compared to a control group (Vuyyuri et al. 2006). Exposure levels were not available, but the concentration of arsenic in the blood from workers was approximately 5 times higher than in the reference group.

Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:					
As^{+3}	*Escherichia coli*	Reverse mutation	No data	+	Nishioka 1975
As^{+3}	*E. coli* PQ37	Gene mutation	No data	–	Lantzsch and Gebel 1997
As^{+3}	*E. coli* (six strains)	Reverse mutation	No data	–	Rossman et al. 1980
As^{+3}	*Salmonella typhimurium*	Gene mutation	No data	–	Löfroth and Ames 1978
As^{+3}	*Photobacterium fischeri*	Gene mutation	No data	–	Ulitzur and Barak 1988
As^{+5}	*S. typhimurium*	Gene mutation	No data	–	Löfroth and Ames 1978
As^{+5}	*P. fischeri*	Gene mutation	No data	+	Ulitzur and Barak 1988
Eukaryotic organisms:					
	Fungi:				
As^{+3}; As^{+5}	*Saccharomyces cerevisiae*	Gene mutation	No data	–	Singh 1983
	Mammalian cells:				
As^{+3}	Human fibroblasts	DNA repair inhibition	No data	+	Okui and Fujiwara 1986
As^{+3}	Human fibroblasts	DNA repair and mutant frequencies	+	+	Wiencke et al. 1997
As^{+3}	Human fibroblasts	DNA repair inhibition	+	+	Hartwig et al. 1997
As^{+3}	Human fibroblasts (MRC5CV1)	DNA migration	No data	+	Hartmann and Speit 1996
As^{+3}	Human fibroblasts (HFW cells)	Cytotoxicity	No data	+	Lee and Ho 1994
As^{+3}	Human skin fibroblasts (HFW)	Chromosome endoreduplication	No data	+	Huang et al. 1995
As^{+3}	Human skin fibroblasts	Chromosomal aberrations	No data	+	Yih et al. 1997
As^{+3}	Human fetal lung fibroblasts	DNA strand breaks	No data	+	Dong and Luo 1993
As^{+3}	Human fetal lung fibroblasts (2BS cells)	DNA damage and repair	No data	+	Dong and Luo 1994
As^{+3}; As^{+5}	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
As^{+3}	Diploid human fibroblasts	Morphological transformation	No data	+	Landolph 1994

Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As^{+3}	Human leukocytes	Chromosomal aberration	No data	+	Nakamuro and Sayato 1981
As^{+3}	Human lymphocytes	DNA protein cross-links	–	–	Costa et al. 1997
As^{+3}, As^{+5}	Human lymphocytes	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1993a
As^{+3}, As^{+5}	Human lymphocytes	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1993b
As^{+3}, As^{+5}	Human lymphocytes	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1994
As^{+3}	Human lymphocytes	Hyperdiploidy and chromosomal breakage	No data	(+)	Rupa et al. 1997
As^{+3}	Human lymphocytes	Hyperdiploid nuclei	No data	+	Ramirez et al. 1997
As^{+3}	Human lymphocytes	Chromosomal aberration	No data	+	Beckman and Nordenson 1986
As^{+3}	Human lymphocytes	Chromosomal aberrations and sister chromatid exchange	No data	+	Nordenson et al. 1981
As^{+3}	Human lymphocytes	Chromosomal aberration	No data	+	Sweins 1983
As^{+3}	Human lymphocytes	Chromosomal aberrations	No data	+	Yager and Wiencke 1993
As^{+3}	Human lymphocytes	Chromosomal aberrations	No data	+	Vega et al. 1995
As^{+3}	Human lymphocytes	Chromosomal aberrations	No data	+	Wan et al. 1982
As^{+3}	Human lymphocytes	Chromosomal aberrations and sister chromatic exchange	No data	+	Wiencke and Yager 1992
As^{+3}	Human lymphocytes	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As^{+3}	Human lymphocytes	Sister chromatid exchange	No data	+	Gebel et al. 1997
As^{+5}	Human lymphocytes	Sister chromatid exchange	No data	–	Gebel et al. 1997
As^{+3}	Human lymphocytes	Sister chromatid exchange	No data	+	Hartmann and Speit 1994
As^{+3}	Human lymphocytes	Sister chromatid exchange	No data	+	Jha et al. 1992
As^{+3}	Human lymphocytes	Sister chromatid exchange	No data	+	Rasmussen and Menzel 1997

Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As^{+3}; As^{+5}	Human T-cell lymphoma-derived cell line (Molt-3)	PARP activity inhibition	No data	+	Yager and Wiencke 1997
As^{+3}	Human cervix carcinoma HeLa and cisplatin-resistant HeLa/CPR variant cells	DNA repair modification	+	+	Chao 1996
As^{+3}	Human cervix carcinoma cells (HeLa)	DNA damage recognition	No data	-	Hartwig et al. 1998
As^{+3}	Human osteosarcoma cells (HOS)	DNA repair	No data	+	Hu et al. 1998
As^{+3}	Human osteosarcoma cells (HOS)	Cell transformation	No data	+	Mure et al. 2003
As^{+3}	Human-hamster hybrid A_1 cells	DNA adducts	No data	+	Kessel et al. 2002
As^{+3}	Mouse lymphoma cells	Enhanced viral forward mutation	No data	(+)	Oberly et al. 1982
As^{+3}; As^{+5}	Mouse lymphoma cells [L5178Y/$TK^{+/-}$ (-3.7.2C)]	Chromosomal mutations	No data	+	Moore et al. 1997a
As^{+3}	Mouse lymphoma cells [L5178Y $tk^{+/-}$ (3.7.sc)]	Mutagenicity	No data	+	Oberly et al. 1996
As^{+3}; As^{+5}	Mouse lymphoma cells	Chromosomal aberrations	No data	+	Moore et al. 1994a
As^{+3}	Mouse lymphoma cells	Chromosomal aberrations	No data	+	Sofuni et al. 1996
As^{+3}	Mouse 3T6 cells	Gene amplification	No data	+	Lee et al. 1988
As^{+3}	Mouse embryo fibroblasts (C3H/10T/2 Cl8)	Morphological transformation	No data	+	Landolph 1994
As^{+3}	Chinese hamster V79 cells	Gene mutation	No data	–	Li and Rossman 1991
As^{+3}	Chinese hamster V79 cells	Gene mutation	No data	–	Rossman et al. 1980
As^{+3}	Chinese hamster V79 cells	DNA damage, DNA-protein cross-linking, micronucleus induction	No data	+	Gebel et al. 1998a
As^{+3}	Chinese hamster V79 cells	DNA repair and mutant frequencies	No data	+	Li and Rossman 1991
As^{+3}	Chinese hamster V79 cells	Intrachromosomal homologous recombination	No data	+	Helleday et al. 2000
As^{+3}	Chinese hamster ovary cells (CHO-AL)	Gene mutation	No data	+	Hei et al. 1998
As^{+3}	Chinese hamster ovary cells (CHO-AS52)	Mutagenicity	No data	+	Meng and Hsie 1996

Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As^{+3}	Chinese hamster ovary cells	Gene mutation	No data	+	Yang et al. 1992
As^{+3}	Chinese hamster ovary cells	DNA repair inhibition	No data	+	Lee-Chen et al. 1993
As^{+3}	Chinese hamster ovary cells	DNA repair inhibition	No data	–	Lee-Chen et al. 1992
As^{+3}	Chinese hamster ovary cells (CHO-K1)	DNA strand breaks	+	+	Lee-Chen et al. 1994
As^{+3}	Chinese hamster ovary cells (CHO-K1)	DNA strand breaks	No data	+	Lynn et al. 1997
As^{+3}	Chinese hamster ovary cells	Aberrant metaphases	No data	+	Jan et al. 1986
As^{+3}	Chinese hamster ovary cells	Aberrant metaphases	No data	+	Lee et al. 1986
As^{+3}	Chinese hamster ovary cells	Chromosomal aberrations	+	+	Huang et al. 1992
As^{+3}	Chinese hamster ovary cells (CHO-K1)	Chromosomal aberrations	No data	+	Huang et al. 1993
As^{+3}; As^{+5}	Chinese hamster ovary cells (CHO-K1)	Chromosomal aberrations and sister chromatid exchange	No data	+	Kochhar et al. 1996
As^{+3}	Chinese hamster ovary cells	Chromosomal aberrations and sister chromatid exchange	+	+	Lin and Tseng 1992
As^{+3}	Chinese hamster ovary cells	Chromosomal aberrations and sister chromatid exchange	No data	+	Wan et al. 1982
As^{+3}	Chinese hamster ovary cells	Sister chromatid exchange and micronucleus induction	No data	+	Fan et al. 1996
As^{+3}	Chinese hamster ovary cells	Cell-killing and micronucleus induction	No data	+	Wang and Huang 1994
As^{+3}	Chinese hamster ovary cells	Micronuclei	No data	+	Liu and Huang 1997
As^{+3}	Chinese hamster ovary cells	Micronuclei formation	No data	+	Yee-Chien and Haimei 1996
As^{+3}	Chinese hamster ovary cells	Micronuclei induction	No data	+	Wang et al. 1997
As^{+3}	Chinese hamster ovary cells	Cytotoxicity	No data	–	Lee and Ho 1994
As^{+3}	Syrian hamster embryo cells	Gene mutation	No data	–	Lee et al. 1985

Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As^{+3}	Syrian hamster embryo cells	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As^{+3}	Syrian hamster embryo cells	Chromosomal aberration	No data	+	Lee et al. 1985
As^{+3}	Syrian hamster embryo cells	Sister chromatid exchange	No data	+	Lee et al. 1985
As^{+3}	Syrian hamster embryo cells	Micronuclei induction	No data	–	Gibson et al. 1997
As^{+3}	Syrian hamster embryo cells	Micronuclei induction	No data	–	Gibson et al. 1997
As^{+3}	Syrian hamster embryo cells	Morphological transformation	No data	+	Kerckaert et al. 1996
As^{+3}	Syrian hamster embryo cells	Morphological transformation	No data	+	Lee et al. 1985
As^{+3}	Syrian hamster embryo cells	Morphological transformation	No data	+	Casto et al. 1979
As^{+5}	Human fibroblasts	DNA repair inhibition	No data	–	Okui and Fujiwara 1986
As^{+5}	Human leukocytes	Chromosomal aberrations	No data	(+)	Nakamuro and Sayato 1981
As^{+5}	Human lymphocytes	Chromosomal aberrations	No data	–	Nordenson et al. 1981
As^{+5}	Human lymphocytes	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As^{+5}	Human lymphocytes	Sister chromatid exchange	No data	–	Rasmussen and Menzel 1997
As^{+5}	Human peripheral lymphocytes	Sister chromatid exchange	No data	+	Zanzoni and Jung 1980
As^{+5}	Human keratinocyte line SCC-9 cells	Keratinocyte programming and transcriptional activity	No data	+	Kachinskas et al. 1997
As^{+5}	Mouse lymphoma cells	Gene mutation	No data	–	Amacher and Paillet 1980
As^{+5}	Mouse lymphoma cells	Gene mutation	No data	–	Amacher and Paillet 1980
As^{+5}	Chinese hamster ovary cells	Chromosomal aberrations	No data	+	Wan et al. 1982
As^{+5}	Syrian hamster embryo cells	Gene mutation	No data	–	Lee et al. 1985
As^{+5}	Syrian hamster embryo cells	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981

Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As^{+5}	Syrian hamster embryo cells	Chromosomal aberrations	No data	+	Lee et al. 1985
As^{+5}	Syrian hamster embryo cells	Sister chromatid exchange	No data	+	Lee et al. 1985
As^{+5}	Syrian hamster embryo cells	Morphological transformation	No data	+	Lee et al. 1985
As^{+5}	Syrian hamster embryo cells	Morphological transformation	No data	+	DiPaolo and Casto 1979

(+) = weakly positive or marginal result; – = negative result; + = positive result; DNA = deoxyribonucleic acid

Table 3-9. Genotoxicity of Inorganic Arsenic *In Vivo*

Valence	Exposure route	Species (test system)	End point	Results	Reference
Nonmammalian					
As^{+3} As^{+5}	Injection	*Drosophila melanogaster*	Somatic mutations and mitotic recombination	+	Ramos-Morales and Rodriguez-Arnaiz 1995
As^{+3} As^{+5}	Larval feeding	*D. melanogaster*	Somatic mutations and mitotic recombination	+	Ramos-Morales and Rodriguez-Arnaiz 1995
As^{+5}	Larvae	*D. melanogaster*	Mitotic recombinations	+	de la Rosa et al. 1994
Mammalian					
As^{+3}	Inhalation	Human (lymphocytes)	Chromosomal aberrations	–	Beckman et al. 1977
As^{+3}	Inhalation	Human (lymphocytes)	Chromosomal aberrations	+	Nordenson et al. 1978
As^{+3}	Oral	Human (lymphocytes)	Chromosomal aberrations	–	Burgdorf et al. 1977
No data	Oral	Human (lymphocytes)	Chromosomal aberrations	–	Vig et al. 1984
No data	Oral	Human (skin)	DNA adducts	+	Matsui et al. 1999
As^{+3}	Oral	Human (lymphocytes)	Sister chromatid exchange	–	Burgdorf et al. 1977
As^{+3}	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Hsu et al. 1997
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Lerda 1994
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Liou et al. 1999
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Mahata et al. 2003
As^{+3}	Oral	Human (lymphocytes)	Sister chromatid exchange	–	Nordenson et al. 1978
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	–	Vig et al. 1984
No data	Oral	Human skin carcinoma	Mutation and overexpression of p53	+	Hsu et al. 1999
As^{+3}	Oral	Exfoliated human epithelial cells	Micronuclei	+	Moore et al. 1996
As^{+3}	Oral	Exfoliated human epithelial cells	Micronuclei	+	Tian et al. 2001
No data	Oral	Human (bladder cells)	Micronuclei	+	Moore et al. 1995
No data	Oral	Human (lymphocytes)	Micronuclei	+	Martínez et al. 2004
No data	Oral	Human (lymphocytes)	Micronuclei	+	Basu et al. 2004
No data	Oral	Human (oral mucosa cells)	Micronuclei	+	Basu et al. 2004

Table 3-9. Genotoxicity of Inorganic Arsenic *In Vivo*

Valence	Exposure route	Species (test system)	End point	Results	Reference
No data	Oral	Human (urothelial cells)	Micronuclei	+	Basu et al. 2004
As^{+5}	Oral	Rat (bone marrow cells)	Chromosomal aberrations	+	Datta et al. 1986
As^{+3}	Inhalation	Mouse (fetal liver)	Chromosomal aberrations	(+)	Nagymajtényi et al. 1985
As^{+3}	Oral	Mouse (bone marrow cells)	Chromosomal aberrations	+	Das et al. 1993
As^{+3}	Oral	Mouse (bone marrow cells)	Chromosomal aberrations	+	Poddar et al. 2000
As^{+3}	Oral	Mouse (bone marrow cells)	Chromosomal breaks, exchanges	–	Poma et al. 1987
As^{+3}	Oral	Mouse (spermatogonia)	Chromosomal aberrations	–	Poma et al. 1987
As^{+3}	Oral	Mouse (leukocytes)	Chromosomal breaks	+	McDorman et al. 2002
As^{+3}	Intraperitoneal	Mouse (bone marrow cells)	Chromosomal breaks, exchanges	–	Poma et al. 1981
As^{+3}	Intraperitoneal	Mouse (bone marrow cells)	Micronuclei	+	DeKnudt et al. 1986
As^{+3}	Intraperitoneal	Mouse (spermatogonia)	Spermatongonia	–	Poma et al. 1981
As^{+3}	Intraperitoneal	Mouse (spermatogonia)	Sperm morphology	–	DeKnudt et al. 1986
As^{+3}	Intraperitoneal	Mouse (spermatogenesis)	Dominant lethal mutations	–	DeKnudt et al. 1986

(+) = weakly positive or marginal result; – = negative result; + = positive result; DNA = deoxyribonucleic acid

Investigations of genotoxic effects of ingested arsenic have yielded mixed results possibly due to the different types of cells examined and the different exposure levels experienced by the populations studied. A study of p53 mutations in arsenic-related skin cancers from patients in Taiwan exposed to arsenic from drinking water found a high rate of p53 mutations and different types of p53 mutations compared with those seen in UV-induced skin cancers (Hsu et al. 1999); similar results have been found in mice (Salim et al. 2003). In humans exposed to Fowler's solution (potassium arsenite, usually taken at a dose of about 0.3 mg As/kg/day [Holland 1904]), increased sister chromatid exchanges, but no increase in chromosomal aberrations, was reported in one study (Burgdorf et al. 1977), while just the converse (increased aberrations but no increase in sister chromatid exchange) was reported in another (Nordenson et al. 1979). Moore et al. (1997a) reported an exposure-dependent increase in the occurrence of micronucleated cells in epithelial cells from the bladder in a male population in northern Chile chronically exposed to high and low arsenic levels in their drinking water (average concentrations, 600 and 15 μg As/L, respectively), and noted that chromosome breakage was the major cause of micronucleus (MN) formation. Similar results were reported by Martínez et al. (2004) who evaluated micronuclei formation in peripheral lymphocytes from people in northern Chile exposed to up to 0.75 mg As/L in their drinking water. In contrast, Martínez et al. (2005) did not find a significant increase in micronuclei in buccal cells from subjects from the same area relative to a low exposure group. Vig et al. (1984) found no significant differences in the frequency of chromosomal aberrations or sister chromatid exchanges between two populations in Nevada with differing levels of arsenic in their drinking water (mean concentrations of 5 and 109 μg/L). In animal studies, an increased incidence of chromosomal abnormalities was detected in rats given oral doses of sodium arsenate (4 mg As/kg/day) for 2–3 weeks (Datta et al. 1986), but no consistent increase in chromosomal aberrations was detected in bone marrow cells or spermatogonia from mice given sodium arsenite (about 50 mg As/kg/day) for up to 8 weeks (Poma et al. 1987). These studies suggest that ingested arsenic may cause chromosomal effects, but these data are too limited to draw a firm conclusion.

Organic Arsenicals. The genotoxicity of the organic arsenicals has been investigated in a number of studies (see Table 3-10). Several tests indicate that DMA and roxarsone may be able to cause chromosome aberrations, mutations, and deoxyribonucleic acid (DNA) strand breaks; *in vitro* studies with MMA did not find significant increases in the occurrence of chromosome aberrations, forward or reverse mutations, unscheduled DNA synthesis (Chun and Killeen 1989a, 1989b, 1989c, 1989d). An increased number of DNA strand breaks were detected in lung and other tissues of mice and rats given oral doses of ~1,500 mg/kg DMA (Okada and Yamanaka 1994; Yamanaka et al. 1989a); this effect appeared to be related to the formation of some active oxygen species. These breaks were largely repaired within 24 hours, so the relevance with respect to health risk is uncertain.

Table 3-10. Genotoxicity of Organic Arsenic

Chemical form	Species (test system)	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms (*in vitro*):					
MMA	*Salmonella typhimurium*	Gene mutation	–	–	Chun and Killeen 1989c
DMA	*Escherichia coli*	Gene mutation	No data	+	Yamanaka et al. 1989b
Roxarsone	*S. typhimurium*	Gene mutation	–	–	NTP 1989b
Eukaryotic organisms (*in vitro*):					
MMA	Chinese hamster ovary cells	Chromosome aberrations	–	–	Chun and Killeen 1989a
MMA	Mouse lymphoma cells ($L5178Y/TK^{+/-}$)	Forward mutation	–	–	Chun and Killeen 1989b
MMA	Rat heptocytes	Unscheduled DNA synthesis	No data	–	Chun and Killeen 1989d
DMA	Human peripheral lymphocytes	Mitogenesis inhibited	No data	–	Endo et al. 1992
DMA	Human lymphocytes	Sister chromatid exchange	No data	–	Rasmussen and Menzel 1997
DMA	Human alveolar (L-132) cells	Lung-specific DNA damage	No data	+	Kato et al. 1994
DMA	Human alveolar type II (L-132) cells	DNA single-strand breaks	+	+	Kawaguchi et al. 1996
DMA	Human diploid L-132 epithelial cells	DNA single-strand breaks	No data	+	Rin et al. 1995
DMA	Human alveolar type II (L-132) cells	DNA strand breaks	No data	+	Tezuka et al. 1993
DMA	Human embryonic cell line of type II alveolar epithelial cells (L-132)	DNA single-strand breaks and DNA-protein crosslinks	No data	+	Yamanaka et al. 1993
DMA	Human alveolar epithelial (L-132) cells	DNA single-strand breaks and DNA-protein crosslinks	No data	+	Yamanaka et al. 1995
DMA	Human pulmonary epithelial (L-132) cells	DNA single-strand breaks	No data	+	Yamanaka et al. 1997
DMA	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
DMA	Mouse lymphoma cells ($L5178Y/TK^{+}/^{-}$ -3.7.2C)	Chromosomal mutations	No data	+	Moore et al. 1997a
DMA	Chinese hamster lung and diploid cells (V79)	Mitotic arrest and tetraploid formation	No data	+	Endo et al. 1992

Table 3-10. Genotoxicity of Organic Arsenic

Chemical form	Species (test system)	End point	Results		Reference
			With activation	Without activation	
DMA	Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Ueda et al. 1997
DMA	Chinese hamster lung and diploid cells (V79)	Chromosomal aberrations	No data	+	Kitamura et al. 2002
DMA	Chinese hamster lung and diploid cells (V79)	Chromosomal aberrations	+	+	Kuroda et al. 2004
DMA	Chinese hamster V79 cells	Tetraploids and mitotic arrest	No data	+	Eguchi et al. 1997
MMA	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
MMA	Chinese hamster V79 cells	Tetraploids and mitotic arrest	No data	+	Eguchi et al. 1997
Roxarsone	*Drosophila melanogaster*	Sex linked recessive	No data	–	NTP 1989b
Roxarsone	Rat hepatocyte	DNA double-strand breaks	No data	+	Storer et al. 1996
Roxarsone	A31-1-13 clone of BALB/c-3T3 cells	Transformation response and mutagenicity	No data	–	Matthews et al. 1993
Roxarsone	Mouse lymphoma (L5178Y) cells	Trifluorothymidine resistance	No data	+	NTP 1989b
Eukaryotic organisms (*in vivo*):					
DMA	Rat (oral exposure)	DNA single-stand breaks in lung	No data	+	Yamanaka and Okada 1994
DMA	Mouse (oral exposure)	DNA strand breaks in tissues	No data	+	Yamanaka et al. 1989b
DMA	Mouse (oral exposure)	DNA single-stand breaks in lung	No data	+	Yamanaka et al. 1993
DMA	Mouse (oral exposure)	DNA single-strand breaks in lung	No data	–	Yamanaka et al. 1989a
DMA	Mouse (oral exposure)	DNA adduct formation	No data	+	Yamanaka et al. 2001
DMA	Mouse (injection)	Aneuploidy in bone marrow cells	No data	+	Kashiwada et al. 1998

– = negative result; + = positive result; DMA = dimethylarsinic acid; DNA = deoxyribonucleic acid; MMA = monomethylarsonic acid

3.4 TOXICOKINETICS

There is an extensive database on the toxicokinetics of inorganic arsenic. Most studies have been performed in animals, but there are a number of studies in humans as well. These studies reveal the following main points:

- Both arsenate and arsenite are well absorbed by both the oral and inhalation routes. Absorption by the dermal route has not been well characterized, but is low compared to the other routes. Inorganic arsenic in soil is absorbed to a lesser extent than solutions of arsenic salts.
- The rate of absorption of arsenic in highly insoluble forms (e.g., arsenic sulfide, lead arsenate) is much lower than that of more soluble forms via both oral and inhalation routes.
- Once absorbed, arsenites are oxidized to arsenates and methylated. This process may then be repeated to result in dimethylated arsenic metabolites.
- Distribution of arsenic in the rat is quite different from other animal species, suggesting that the rat is probably not an appropriate toxicokinetic model for distribution, metabolism, or excretion of arsenic by humans.
- The As(+3) form undergoes enzymic methylation primarily in the liver to form MMA and DMA. The rate and relative proportion of methylation production varies among species. The rate of methylation varies considerably among tissues.
- Most arsenic is promptly excreted in the urine as a mixture of As(+3), As(+5), MMA, and DMA; DMA is usually the primary form in the urine. Smaller amounts are excreted in feces. Some arsenic may remain bound to tissues, depending inversely on the rate and extent of methylation.

Less information is available for the organic arsenicals. It appears that both MMA and DMA are well absorbed, but are rapidly excreted in the urine and feces. MMA may be methylated to DMA, but neither MMA nor DMA are demethylated to yield inorganic arsenic.

A review of the evidence that supports these conclusions is presented below.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Inorganic Arsenicals. Since arsenic exists in air as particulate matter, absorption across the lung involves two processes: deposition of the particles onto the lung surface, and absorption of arsenic from the deposited material. In lung cancer patients exposed to arsenic in cigarette smoke, deposition was

estimated to be about 40% and absorption was 75–85% (Holland et al. 1959). Thus, overall absorption (expressed as a percentage of inhaled arsenic) was about 30–34%. In workers exposed to arsenic trioxide dusts in smelters, the amount of arsenic excreted in the urine (the main route of excretion; see Section 3.4.4) was about 40–60% of the estimated inhaled dose (Pinto et al. 1976; Vahter et al. 1986). Absorption of arsenic trioxide dusts and fumes (assessed by measurement of urinary metabolites) correlated with time weighted average arsenic air concentrations from personal breathing zone air samplers (Offergelt et al. 1992). Correlations were best immediately after a shift and just before the start of the next shift. Although the percent deposition was not measured in these cases, it seems likely that nearly all of the deposited arsenic was absorbed. This conclusion is supported by intratracheal instillation studies in rats and hamsters, where clearance of oxy compounds of arsenic (sodium arsenite, sodium arsenate, arsenic trioxide) from the lung was rapid and nearly complete (60–90% within 1 day) (Marafante and Vahter 1987; Rhoads and Sanders 1985). In contrast, arsenic sulfide and lead arsenate were cleared more slowly (Marafante and Vahter 1987), indicating that the rate of absorption may be lower if the inhaled arsenic is in a highly insoluble form. There are no data to suggest that absorption of inhaled arsenic in children differs from that in adults.

Organic Arsenicals. No studies were located regarding absorption of organic arsenicals in humans or animals after inhalation exposure. However, DMA instilled in the lungs of rats was absorbed very rapidly (half-time of 2.2 minutes) and nearly completely (at least 92%) (Stevens et al. 1977). This indicates that organic arsenicals are likely to be well absorbed by the inhalation route.

3.4.1.2 Oral Exposure

Inorganic Arsenicals. Several studies in humans indicate that arsenates and arsenites are well absorbed across the gastrointestinal tract. The most direct evidence is from a study that evaluated the 6-day elimination of arsenic in healthy humans who were given water from a high-arsenic sampling site (arsenic species not specified) and that reported approximately 95% absorption (Zheng et al. 2002). A similar absorption efficiency can be estimated from measurements of fecal excretion in humans given oral doses of arsenite, where <5% was recovered in the feces (Bettley and O'Shea 1975). This indicates absorption was at least 95%. These results are supported by studies in which urinary excretion in humans was found to account for 55–87% of daily oral intakes of arsenate or arsenite (Buchet et al. 1981b; Crecelius 1977; Kumana et al. 2002; Mappes 1977; Tam et al. 1979b). In contrast, ingestion of arsenic triselenide (As_2Se_3) did not lead to a measurable increase in urinary excretion (Mappes 1977), indicating that

gastrointestinal absorption may be much lower if highly insoluble forms of arsenic are ingested. There are no data to suggest that absorption of arsenic from the gut in children differs from that in adults.

These observations in humans are supported by a number of studies in animals. Fecal excretion of arsenates and arsenites ranged from 2 to 10% in monkeys and mice, with 70% or more appearing in urine (Charbonneau et al. 1978; Roberts et al. 2002; Vahter 1981; Vahter and Norin 1980). Oral absorption of [^{73}As] labeled sodium arsenate in mice was unaffected by dose (0.0005–5 mg/kg) as reflected in percentage of dose excreted in feces over 48 hours (Hughes et al. 1994). Absorption ranged from 82 to 89% at all doses. Gonzalez et al. (1995) found that the percentage of arsenate that was absorbed in rats decreased as the dose increased from 6 to 480 μg, suggesting saturable, zero-order absorption of arsenate in this species. Hamsters appear to absorb somewhat less than humans, monkeys, and mice, since fecal excretion usually ranges from 10 to 40% (Marafante and Vahter 1987; Marafante et al. 1987a; Yamauchi and Yamamura 1985). Rabbits also appear to absorb less arsenate than humans, monkeys, or mice after oral exposure (Freeman et al. 1993). After a gavage dose of 1.95 mg/kg sodium arsenate, 45% of the arsenate was recovered in feces in males and 52% in females. As in humans, when highly insoluble arsenic compounds are administered (arsenic trisulfide, lead arsenate), gastrointestinal absorption is reduced 20–30% (Marafante and Vahter 1987).

Bioavailability of arsenic was measured in rabbits ingesting doses of smelting soils that contained arsenic primarily in the form of sulfides (Freeman et al. 1993). Bioavailability was assessed by comparing the amounts of arsenic that was excreted after ingestion of the soil to that excreted after an intravenous dose of sodium arsenate. The bioavailability of the arsenic in the ingested soil was 24±3.2% and that of sodium arsenate in the gavage dose was 50±5.7%. Approximately 80% of the arsenic from ingested soil was eliminated in the feces compared with 50% of the soluble oral dose and 10% of the injected dose. In another study, rabbits dosed with sodium arsenite (0.8 mg As/kg) had 5 times greater blood arsenic concentrations than rabbits dosed with arsenic-containing soil (2.8 mg As/kg), suggesting a lower bioavailability of the arsenic in soil (Davis et al. 1992).

Studies of the bioavailability of arsenic suggest that absorption of arsenic in ingested dust or soil is likely to be considerably less than absorption of arsenic from ingested salts (Davis et al. 1992, 1996; EPA 1997g; Freeman et al. 1993, 1995; Pascoe et al. 1994; Roberts et al. 2002, 2007; Rodriguez et al. 1999). Oral absorption of arsenic in a group of three female Cynomolgus monkeys from a soluble salt, soil, and household dust was compared with absorption of an intravenous dose of sodium arsenate (Freeman et al. 1995). Mean absolute percentage bioavailability based on urine arsenic excretion was reported at

67.6±2.6% (gavage), 19.2±1.5% (oral dust), and 13.8±3.3% (oral soil). Mean absolute percentage bioavailability based on blood arsenic levels was reported at 91.3±12.4% (gavage), 9.8±4.3% (oral dust), and 10.9±5.2% (oral soil). The arsenic in the dust and soil was approximately 3.5–5-fold (based on levels in the urine) and 8–9-fold (based on levels in the blood) less bioavailable than arsenic in solution. Two other studies in monkeys reported relative bioavailability of arsenic in soil from a number of locations (electrical substation, wood preserving sites, pesticide sites, cattle-dip sites, volcanic soil, and mining sites) ranged from 5 to 31% (Roberts et al. 2002, 2007). A study in beagle dogs fed with soil containing As_2O_5 or treated with intravenous soluble arsenic found that compared to injection the bioavailability of arsenic from ingested soil was 8.3±2.0% (Groen et al. 1993). The bioavailability of arsenic in soil has been studied in juvenile swine that received daily oral doses of soil or sodium arsenate (in food or by gavage) for 15 days (EPA 1997g). The soils were obtained from various mining and smelting sites and contained, in addition to arsenic at concentrations of 100–300 μg/g, lead at concentrations of 3,000–14,000 μg/g. The arsenic doses ranged from 1 to 65.4 μg/kg/day. The fraction of the arsenic dose excreted in urine was measured on days 7 and 14 and the relative bioavailability of the soil-borne arsenic was estimated as the ratio of urinary excretion fractions, soil arsenic:sodium arsenate. The mean relative bioavailability of soil-borne arsenic ranged from 0 to 98% in soils from seven different sites (mean±SD, 45%±32). Estimates for relative bioavailability of arsenic in samples of smelter slag and mine tailings ranged from 7 to 51% (mean±SD, 35%±27). Rodriguez et al. (1999) used a similar approach to estimate the relative bioavailability of arsenic in mine and smelter wastes (soils and solid materials) in juvenile swine. Samples included iron slag deposits and calcine deposits and had arsenic concentrations that ranged from 330 to 17,500 μg/g. Relative bioavailability (waste:sodium arsenate) ranged from 3 to 43% for 13 samples (mean, 21%) and was higher in iron slag wastes (mean, 25%) than in calcine wastes (mean, 13%).

Bioavailability of arsenic from soil is reduced by low solubility and inaccessibility due to the presence of secondary reaction products or insoluble matrix components (Davis et al. 1992). This is supported by studies conducted with *in vitro* simulations of the gastric and/or intestinal fluids (Hamel et al. 1998; Pouschat and Zagury 2006; Rodriguez et al. 1999; Ruby et al. 1996, 1999; Williams et al. 1998). When soils containing arsenic are incubated in simulated gastrointestinal fluids, only a fraction of the arsenic becomes soluble. Estimates of the soluble, or bioaccessible, arsenic fraction have ranged from 3 to 50% for various soils and mining and smelter waste materials (Pouschat and Zagury 2006; Rodriguez et al. 1999; Ruby et al. 1996); these estimates are similar to *in vivo* estimates of the relative bioavailability of arsenic in these same materials (Ruby et al. 1999).

Organic Arsenicals. Based on urinary excretion studies in volunteers, it appears that both MMA and DMA are well absorbed (at least 75–85%) across the gastrointestinal tract (Buchet et al. 1981a; Marafante et al. 1987b). This is supported by studies in animals, where at least 75% absorption has been observed for DMA (Marafante et al. 1987b; Stevens et al. 1977; Vahter et al. 1984; Yamauchi and Yamamura 1984) and MMA (Hughes et al. 2005; Yamauchi et al. 1988). In mice, the relative bioavailability of MMA appears to be dose-dependent; 81% was absorbed following a single gavage dose of 0.4 mg MMA/kg/day compared to 60% following administration of 4 mg MMA/kg/day (Hughes et al. 2005).

3.4.1.3 Dermal Exposure

Inorganic Arsenicals. No quantitative studies were located on absorption of inorganic arsenicals in humans after dermal exposure. Percutaneous absorption of [^{73}As] as arsenic acid (H_3AsO_4) alone and mixed with soil has been measured in skin from cadavers (Wester et al. 1993). Labeled arsenic was applied to skin in diffusion cells and transit through the skin into receptor fluid measured. After 24 hours, 0.93% of the dose passed through the skin and 0.98% remained in the skin after washing. Absorption was lower with [^{73}As] mixed with soil: 0.43% passed through the skin over 24 hours and 0.33% remained in the skin after washing.

Dermal absorption of arsenic has been measured in Rhesus monkeys (Lowney et al. 2005; Wester et al. 1993). After 24 hours, 6.4% of [^{73}As] as arsenic acid was absorbed systemically, as was 4.5% of [^{73}As] mixed with soil (Wester et al. 1993). Similarly, 2.8% of soluble arsenic in water was detected in the urine 24 hours after exposure (Lowney et al. 2005). However, arsenic from soil was poorly absorbed; 0.12% was detected in the urine after 24 hours. Differences between the Wester et al. (1993) and Lowney et al. (2005) studies in terms of uptake from soil may be due to the differences in forms of arsenic in the soil. In the Wester et al. (1993) study, soil was mixed with radiolabelled arsenic acid in water; Lowney et al. (2005) used soil samples from a pesticide manufacturing facility that historically manufactured arsenical pesticides (the arsenic was primarily in the iron oxide and iron silicate mineral phases). Lowney et al. (2005) also measured urinary levels of arsenic following dermal application of CCA residues and found that the levels did not increase from background. Uptake of arsenic into blood or tissues was undetectable for up to 24 hours in rats whose tails were immersed in solutions of sodium arsenate for 1 hour. However, arsenic began to increase in blood, liver, and spleen over the next 5 days (Dutkiewicz 1977). The rate of uptake was estimated to be 1–33 μg/cm^2/hour. These findings suggest that dermal exposure leads initially to arsenic binding to skin, and that the bound arsenic may slowly be taken up into the blood, even after exposure ends.

Organic Arsenicals. No studies were located on absorption of organic arsenicals in humans or animals after dermal exposure.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Inorganic Arsenicals. No studies were located on the distribution of arsenic in humans or animals after inhalation exposure, but intratracheal administration of arsenic trioxide to rats resulted in distribution of arsenic to the liver, kidney, skeleton, gastrointestinal tract, and other tissues (Rhoads and Sanders 1985). This is consistent with data from oral and parenteral studies (below), which indicate that absorbed arsenic is distributed throughout the body.

Organic Arsenicals. No studies were located regarding the distribution of organic arsenicals in humans or animals after inhalation exposure. However, DMA administered to rats by the intratracheal route was distributed throughout the body (Stevens et al. 1977), suggesting that inhalation of organic arsenicals would also lead to widespread distribution.

3.4.2.2 Oral Exposure

Inorganic Arsenicals. Analysis of tissues taken at autopsy from people who were exposed to background levels of arsenic in food and water revealed that arsenic is present in all tissues of the body (Liebscher and Smith 1968). Most tissues had about the same concentration level (0.05–0.15 ppm), while levels in hair (0.65 ppm) and nails (0.36 ppm) were somewhat higher. This indicates that there is little tendency for arsenic to accumulate preferentially in any internal organs. However, exposure levels may not have been high enough to cause elevated levels in tissues. Arsenic exposure may have been low enough that the methylation process in the body resulted in limited accumulation in internal organs. Tissue analysis of organs taken from an individual following death from ingestion of 8 g of arsenic trioxide (about 3 g of arsenic) showed a much higher concentration of arsenic in liver (147 μg/g) than in kidney (27 μg/g) or muscle, heart, spleen, pancreas, lungs, or cerebellum (11–12 μg/g) (Benramdane et al. 1999a). Small amounts were also found in other parts of the brain (8 μg/g), skin (3 μg/g), and hemolyzed blood (0.4 μg/g). Many studies have been performed where arsenic levels in hair and nails have been measured and correlations with exposure analyzed. Some of these studies are discussed in Section 3.8, Biomarkers of Exposure.

Inorganic arsenic passes easily through the placenta. High levels of arsenic were found in the liver, kidney, and brain during autopsy of an infant prematurely born to a young mother who had ingested inorganic arsenic at week 30 of gestation (Lugo et al. 1969). Arsenic was detected in human breast milk at concentrations of 0.00013–0.00082 ppm in a World Health Organization study (Somogyi and Beck 1993). Arsenic concentrations were 0.0001–0.0044 ppm in human milk sampled from 88 mothers on the Faroe Islands whose diets were predominantly seafood (Grandjean et al. 1995). Exposures to arsenic from the seafood diet in this population was most likely to organic "fish arsenic." In a population of Andean women exposed to high concentrations (about 200 ppb) of inorganic arsenic in drinking water, concentrations of arsenic in breast milk ranged from about 0.0008 to 0.008 ppm (Concha et al. 1998b).

Studies in mice and hamsters given oral doses of arsenate or arsenite have found elevated levels of arsenic in all tissues examined (Hughes et al. 2003; Vahter and Norin 1980; Yamauchi and Yamamura 1985), including the placenta and fetus of pregnant females (Hood et al. 1987, 1988). Inorganic arsenic crosses the placental barrier and selectively accumulates in the neuroepithelium of the developing animal embryo (Hanlon and Ferm 1977; Lindgren et al. 1984). In mice, radiolabel from orally administered 74-As was widely distributed to all tissues, with the highest levels in skin, kidney, and liver (Hughes et al. 2003). No obvious differences between As(+3) and As(+5) were found, although residual levels after 24 hours tended to be higher for As(+3) than As(+5) (Vahter and Norin 1980). However, *in vitro* studies have found that the cellular uptake of As(+3) was higher than that of As(+5) (Bertolero et al. 1987; Dopp et al. 2004); in mouse cells, the difference was 4-fold (Bertolero et al. 1987). In hamsters, increases in tissue levels were noted after oral treatment with As(+3) for most tissues (hair, kidney, liver, lung, skin, muscle), with the largest increases in liver and lung (Yamauchi and Yamamura 1985). Liver and kidney arsenic concentrations increased with dose in dogs fed arsenite in the diet for 6 months (Neiger and Osweiler 1992). A study examining the speciation of arsenic following a single dose exposure to sodium arsenate to mice (Kenyon et al. 2005) found that the levels of inorganic arsenic and DMA were similar in the blood, liver, and kidney; much lower levels of MMA were found in these tissues. The concentration of DMA in the lungs exceeded inorganic arsenic and the levels of inorganic arsenic and MMA were similar; the DMA concentration was about 6 times higher than that of inorganic arsenic.

Inorganic arsenic crosses the placental barrier and selectively accumulates in the neuroepithelium of the developing animal embryo (Hanlon and Ferm 1977; Lindgren et al. 1984). Following maternal exposure to arsenite or arsenate throughout gestation and lactation, inorganic arsenic and DMA were detected in the

newborn mouse brains (Jin et al. 2006). The levels of inorganic arsenic in the brain were similar to those in the newborn livers; however, the levels of DMA in the brain were about twice as high as in the liver.

Organic Arsenicals. No studies were located on the distribution of organic arsenicals in humans following oral exposure. Studies in animals found MMA and DMA distributed to all tissues after acute oral doses (Hughes et al. 2005; Stevens et al. 1977; Vahter et al. 1984; Yamauchi and Yamamura 1984; Yamauchi et al. 1988). In mice, MMA is rapidly distributed throughout the body with peak tissue concentrations occurring between 0.25 and 4 hours after administration of a single gavage dose of 0.4 or 4 mg MMA/kg (Hughes et al. 2005). The peak levels of MMA in the bladder, kidneys, and lungs were higher than blood, with the highest levels occurring in the bladder. The terminal half-lives of MMA were 4.2–4.9 hours in the liver, lung, and blood, 9.0 hours in the urinary bladder, and 15.9 hours in the kidney in mice dosed with 0.4 mg MMA/kg; similar half-lives were measured in the 4.0 mg MMA/kg mice. Two hours after dosing, most of the methylated arsenic in the tissues was in the form of MMA. In rats exposed to 100 mg/kg DMA in the diet for 72 days, high levels of arsenic was detected in the blood (Lu et al. 2004a). The arsenic was primarily found in the erythrocyte; the concentration in the erythrocyte was 150 times higher than the arsenic concentration in the plasma.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of inorganic or organic arsenicals in humans or animals after dermal exposure.

3.4.2.4 Other Routes of Exposure

Inorganic Arsenicals. Studies in mice, rabbits, and monkeys injected intravenously with solutions of arsenite or arsenate confirm that arsenic is widely distributed throughout the body (Lindgren et al. 1982; Marafante and Vahter 1986; Vahter and Marafante 1983; Vahter et al. 1982). Shortly after exposure, the concentration of arsenic tends to be somewhat higher in liver, kidney, lung, and gastrointestinal epithelium (Hughes et al. 2000; Lindgren et al. 1982; Vahter and Marafante 1983; Vahter et al. 1982), but levels tend to equilibrate over time. Arsenate shows a tendency to deposit in skeletal tissue that is not shared by arsenite (Lindgren et al. 1982, 1984), presumably because arsenate is an analog of phosphate.

The distribution of arsenic in the rat is quite different from other animal species. Following intramuscular injection of carrier-free radio-arsenate in rats, most of the injected arsenic became bound to hemoglobin in red blood cells, and very little reached other tissues (Lanz et al. 1950). However, similar experiments

in dogs, mice, guinea pigs, rabbits, and chicks found very little uptake of arsenic into the blood in these species (cats gave intermediate results).

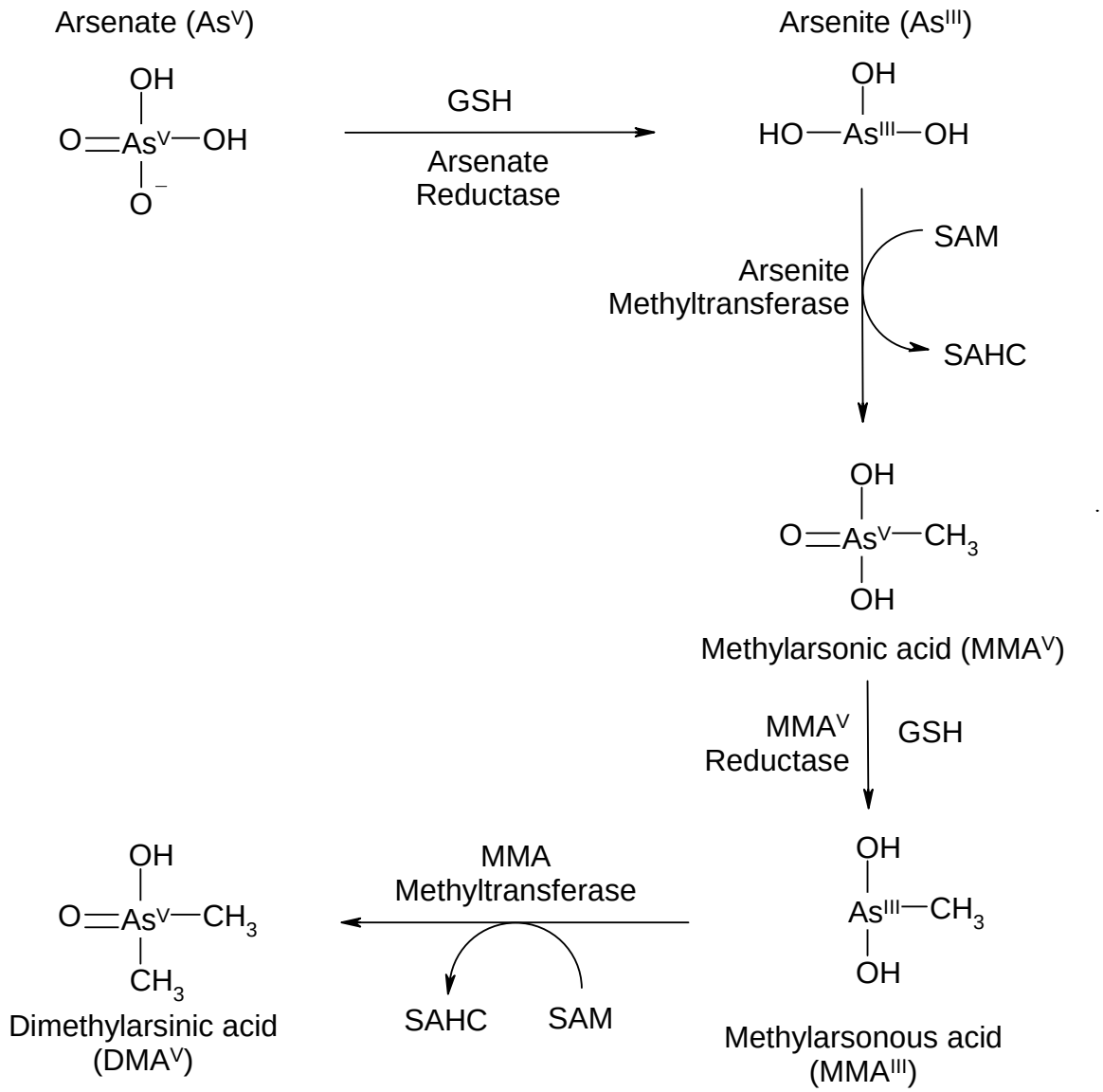
Organic Arsenicals. Following intravenous administration of DMA in mice, DMA is rapidly distributed throughout the body (Hughes et al. 2000). In the blood, the DMA was initially detected in the plasma, but fairly rapidly equilibrated between the plasma and erythrocytes. Blood, plasma, erythrocyte, liver, and kidney distribution and elimination of DMA did not differ in groups of mice administered 1.11 or 111 mg DMA/kg. However, a significant difference in DMA elimination from the lungs was observed; the elimination half-time increased from 91 minutes in the 1.11 mg DMA/kg group to 6,930 minutes in the 111 mg DMA/kg group.

3.4.3 Metabolism

Inorganic Arsenicals. The metabolism of inorganic arsenic has been extensively studied in humans and animals, and is diagrammed in Figure 3-7. Two basic processes are involved: (1) reduction/oxidation reactions that interconvert As(III) and As(V), and (2) methylation reactions, which convert arsenite to MMA and DMA. The resulting series of reactions results in the reduction of inorganic arsenate to arsenite (if necessary), methylation to MMA(V), reduction to MMA(III), and methylation to DMA(V). These processes appear to be similar whether exposure is by the inhalation, oral, or parenteral route. The human body has the ability to change inorganic arsenic to organic forms (i.e., by methylation) that are more readily excreted in urine. In addition, inorganic arsenic is also directly excreted in the urine. It is estimated that by means of these two processes, >75% of the absorbed arsenic dose is excreted in the urine (Marcus and Rispin 1988), although this may vary with the dose and exposure duration. This mechanism is thought to have an upper-dose limit which, when overwhelmed, results in a higher incidence of arsenic toxicity. This is supported by a case report of an individual who died 3 days after ingesting 8 g of arsenic trioxide (about 3 g of arsenic) (Benramdane et al. 1999a). Only 20% of the total arsenic in all tissues analyzed was methylated (14% MMA, 6% DMA), while 78% remained as arsenite and 2% as arsenate.

The majority of the evidence characterizing the metabolic pathways of arsenic is derived from analysis of urinary excretion products. Exposure of humans to either arsenates or arsenites results in increased levels of inorganic As(+3), inorganic As(+5), MMA, and DMA in urine (Aposhian et al. 2000a, 2000b; Buchet et al. 1981a, 1981b; Concha et al. 1998a, 1998b; Crecelius 1977; Kurttio et al. 1998; Lovell and Farmer

Figure 3-7. Inorganic Arsenic Biotransformation Pathway



SAHC = S-adenosylhomocysteine; SAM = S-adenosylmethionine

Source: adapted from Aposhian et al. 2000b

1985; Smith et al. 1977; Tam et al. 1979b; Vahter 1986). Similar results are obtained from studies in mice (Vahter 1981; Vahter and Envall 1983), hamsters (Hirata et al. 1988; Marafante and Vahter 1987; Takahashi et al. 1988), and rabbits (Maiorino and Aposhian 1985; Marafante et al. 1985; Vahter and Marafante 1983). Historically, little distinction was made between MMA(V) and MMA(III) in the urine in most studies, and the assumption was that the majority of MMA in the urine was MMA(V); however, Aposhian et al. (2000a, 2000b) demonstrated that the methylated arsenic atom may be in either valance state.

The relative proportions of As(+3), As(+5), MMA, and DMA in urine can vary depending upon the chemical administered, time after exposure, route of exposure, dose level, and exposed species. In general, however, DMA is the principal metabolite following long-term exposure, with lower levels of inorganic arsenic [As(+3) and As(+5)] and MMA. In humans, the relative proportions are usually about 40–75% DMA, 20–25% inorganic arsenic, and 15–25% MMA (Buchet et al. 1981a; Hopenhayn et al. 2003b; Loffredo et al. 2003; Mandal et al. 2001; Smith et al. 1977; Tam et al. 1979b; Tokunaga et al. 2002; Vahter 1986). With relatively constant exposure levels, these metabolic proportions remain similar over time (Concha et al. 2002), and appear to be similar among family members (Chung et al. 2002). One study of groups of women and children in two villages in Argentina showed that children ingesting large amounts of arsenic in their drinking water (200 μg/L) excreted about 49% inorganic arsenic and 47% DMA (Concha et al. 1998b). This compared to 32% inorganic arsenic and 66% DMA for the women in the study. This may indicate that metabolism of arsenic in children is less efficient than in adults. The rabbit has a ratio of metabolites similar to human adults (Maiorino and Aposhian 1985), suggesting that this may be a good animal model for toxicokinetics in humans. Mice may also be a good human toxicokinetic model based on the similarity of arsenic metabolism and deposition (Vahter et al. 2002). In contrast, the guinea pig, marmoset, and tamarin monkey do not methylate inorganic arsenic (Healy et al. 1998; Vahter and Marafante 1985; Vahter et al. 1982; Zakharyan et al. 1996); thus, they may be poor models for humans.

Reduction of arsenate to arsenite can be mediated by glutathione (Menzel et al. 1994). Scott et al. (1993) showed that glutathione forms complexes with both arsenate and arsenite *in vitro*, and that glutathione is oxidized (and arsenate reduced) in the glutathione-arsenate reaction. Studies *in vitro* indicate that the substrate for methylation is As(+3), and that As(+5) is not methylated unless it is first reduced to As(+3) (Buchet and Lauwerys 1985, 1988; Lerman et al. 1983). The main site of methylation appears to be the liver, where the methylation process is mediated by enzymes that utilize S-adenosylmethionine as cosubstrate (Buchet and Lauwerys 1985, 1988). Under normal conditions, the availability of methyl

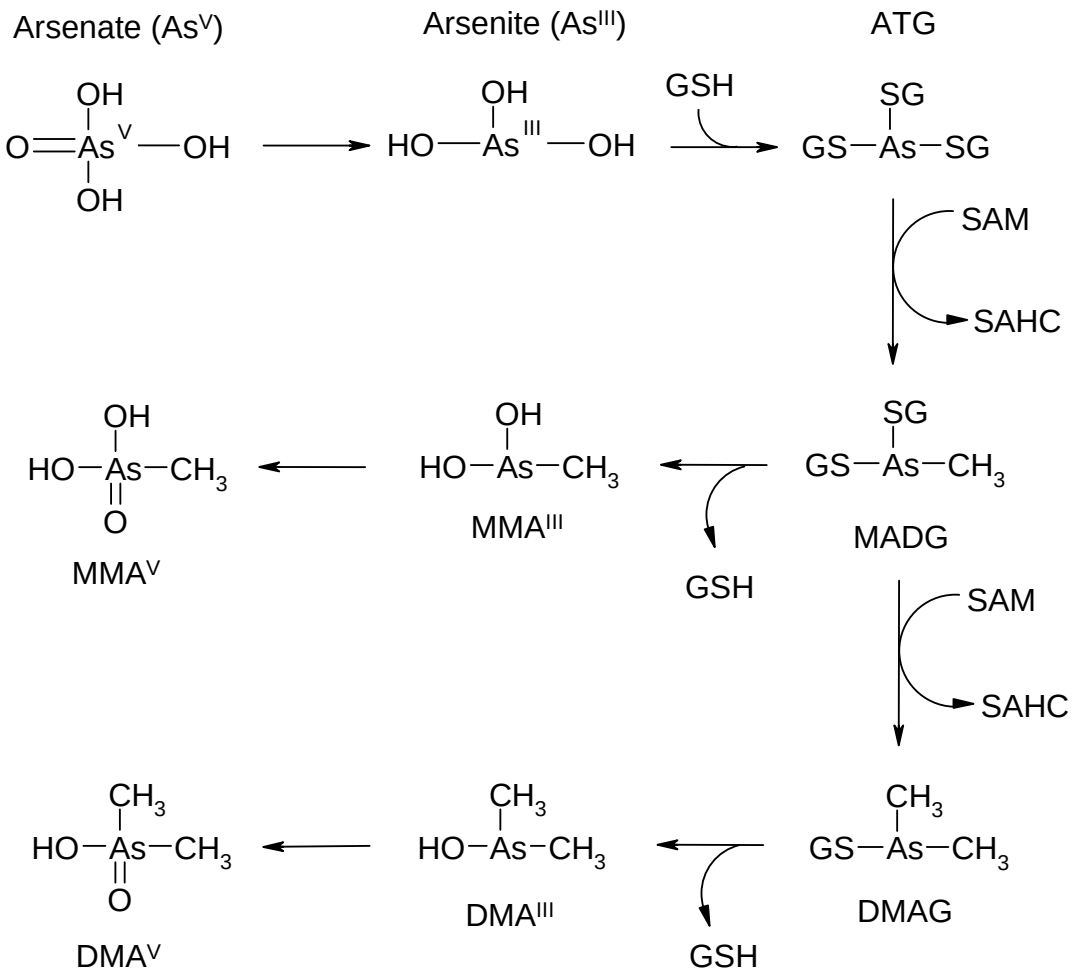
donors (e.g., methionine, choline, cysteine) does not appear to be rate limiting in methylating capacity, either in humans (Buchet et al. 1982) or in animals (Buchet and Lauwerys 1987; Buchet et al. 1981a). However, severe dietary restriction of methyl donor intake can result in significant decreases in methylating capacity (Buchet and Lauwerys 1987; Vahter and Marafante 1987).

Arsenic methyltransferase and MMA methyltransferase activities have been purified to homogeneity from cytosol of rabbit liver (Zakharyan et al. 1995), Rhesus monkey liver (Zakharyan et al. 1996), and rat liver (Thomas et al. 2004). It appears that a single protein catalyzes both activities. This activity transfers a methyl group from S-adenosylmethionine to As(+3) yielding MMA, which is then further methylated to DMA. Reduced glutathione is probably a co-factor *in vivo*, but other thiols can substitute *in vitro* (L-cysteine, dithiothreitol). The substrate saturation concentration for rabbit arsenite methyltransferase is 50 μM, for MMA methyltransferase it is 1,000 μM. The purified activity is specific for arsenite and MMA; selenite, selenate, selenide, and catechols do not serve as substrates. Thomas et al. (2004) reported cloning the gene for an S-adenosylmethionine-dependent methyltransferase from rat liver cytosol that catalyzes the conversion of arsenic to methylated and dimethylated species. It bears a high similarity to translations of *cyt19* genes in both the mouse and the human; both this gene and protein are now termed arsenic (+3 oxidation state) methyltransferase (AS3MT).

Studies in mice indicate that exposure to arsenic does not induce arsenic methylation activity (Healy et al. 1998). Mice receiving up to 0.87 mg As/kg/day as sodium arsenate in drinking water for 91 days had the same arsenic methylating activity as unexposed controls. Specific activities were highest in testis (1.45 U/mg) followed by kidney (0.70 U/mg), liver (0.40 U/mg), and lung (0.20 U/mg). None were affected by arsenic exposure.

An alternative biotransformation pathway (Figure 3-8) has recently been proposed for arsenic (Hayakawa et al. 2005) based on the nonenzymatic formation of glutathione complexes with arsenite resulting in the formation of arsenic triglutathione. The arsenic triglutathione is subsequently methylated by AS3MT to form monomethyl arsenic glutathione. At low glutathione levels (1 mM), the monomethyl arsenic glutathione is hydrolyzed to form MMA(III). At high glutathione levels (5 mM), the monomethyl arsenic glutathione is methylated to dimethylarsinic glutathione by AS3MT. Dimethylarsinic glutathione is quickly hydrolyzed to form DMA(III) (Hayakawa et al. 2005; Thomas et al. 2007). In the classical inorganic arsenic biotransformation pathway (Figure 3-7), MMA(V) is converted to the more toxic MMA(III); in contrast, in the alternative pathway, MMA(III) is converted to the less toxic MMA(V).

Figure 3-8. Alternative Inorganic Arsenic Biotransformation Pathway



ATG = arsenic triglutathione; DMAG = dimethylarsinic glutathione; GSH = glutathione; MADG = monomethyl arsenic glutathione; SAHC = S-adenosylhomocysteine; SAM = S-adenosylmethionine

Source: Hayakawa et al. 2005; Thomas et al. 2007

Since methylation tends to result in lower tissue retention of inorganic arsenic (Marafante and Vahter 1984, 1986; Marafante et al. 1985; Vahter and Marafante 1987), the methylation process is usually viewed as a detoxification mechanism. However, several studies showing an elevated toxicity of MMA(III) relative even to As(III) in cultured human liver cells (Petrick et al. 2000, 2001) have called this assumption into question. Because methylation is an enzymic process, an important issue is the dose of arsenic that saturates the methylation capacity of an organism, resulting in a possible increased level of the more toxic As(III) in tissues, or whether or not such a dose exists. Limited data from studies in humans suggest that methylation may begin to become limiting at doses of about 0.2–1 mg/day (0.003–0.015 mg/kg/day) (Buchet et al. 1981b; Marcus and Rispin 1988). However, these observations are relatively uncertain since they are based on data from only a few subjects, and the pattern of urinary excretion products in humans who ingested high (near lethal) oral doses or were exposed to elevated levels in the workplace is not much different from that in the general population (Lovell and Farmer 1985; Vahter 1986). Furthermore, the nutrient intakes reported by Engel and Receveur (1993) were sufficient to accommodate the body stores of methyl groups needed for arsenic biomethylation. At the highest arsenic level reported in the endemic area, the biomethylation process required only a few percent of the total daily methyl intake (Mushak and Crocetti 1995). Thus, the dose rate at which methylation capacity becomes saturated cannot be precisely defined with current data.

Organic Arsenicals. With the exception of arsenosugars, which may undergo extensive metabolism, organic arsenicals appear to undergo little metabolism. Humans who ingested a dose of MMA converted a small amount (about 13%) to DMA (Buchet et al. 1981a). Similarly, in mice and hamsters, DMA and MMA are primarily excreted unchanged in the urine (Hughes et al. 2005; Marafante et al. 1987b; Vahter et al. 1984). In mice, a small percentage of MMA is methylated to DMA and some is further methylated to trimethylarsine oxide (TMAO) (Hughes et al. 2005). In contrast, administration of MMA(III) to mice resulted in the excretion of mostly DMA(V) and smaller amounts of MMA(V), MMA(III), and DMA(III) (Hughes et al. 2005). As with MMA, only a small percentage (<10%) of the DMA is methylated to TMAO (Hughes et al. 2005; Marafante et al. 1987b; Yamauchi and Yamamura 1984; Yamauchi et al. 1988).

MMA and DMA are more extensively methylated in rats compared to other animal species. After 1 week of exposure to 100 mg As/kg/day as MMA in drinking water, rats excreted 50.6% of the total arsenic in urine as MMA, 19.0% as DMA, 6.9% as TMAO, and 0.4% as tetramethylarsonium (Yoshida et al. 1998). In contrast, mice exposed to a single dose of 40 mg As/kg as MMA excreted 89.6% of the dose as MMA, 6.2% as DMA, and 1.9% as TMAO (Hughes et al. 2005). Similarly, 24 hours after administration of a

single oral dose of 50 mg As/kg as MMA in hamsters, 26.9% was excreted in urine as MMA, 1.43% as DMA, and 0.07% as trimethylarsenic compound (Yamauchi et al. 1988). As with MMA, oral exposure of mice and hamsters to DMA results in most of the dose being excreted in the urine in the form of DMA (or DMA complex) (Marafante et al. 1987b); in rats, the levels of DMA and TMAO are about equal (Yoshida et al. 1998).

The available data suggest that the methylarsenates are not demethylated to inorganic arsenic either in humans (Buchet et al. 1981a; Marafante et al. 1987b) or in animals (rats and hamsters) (Stevens et al. 1977; Yamauchi and Yamamura 1984; Yoshida et al. 2001).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Inorganic Arsenicals. As noted previously (see Section 3.4.1.1), urinary excretion of arsenic appears to account for 30–60% of the inhaled dose (Holland et al. 1959; Pinto et al. 1976; Vahter et al. 1986). Since the deposition fraction usually ranges from about 30 to 60% for most respirable particles (EPA 1989b), this suggests that nearly all arsenic that is deposited in the lung is excreted in the urine. The time course of excretion in humans exposed by inhalation has not been thoroughly investigated, but urinary arsenic levels in workers in a smelter rose within hours after they came to work on Monday and then fell over the weekend (Vahter et al. 1986). This implies that excretion is fairly rapid, and this is supported by intratracheal studies in rats (Rhoads and Sanders 1985) and hamsters (Marafante and Vahter 1987), where whole-body clearance of administered arsenate or arsenite occurred with a half-time of 1 day or less. However, the study in rats (Rhoads and Sanders 1985) found that the clearance of arsenic trioxide was biphasic, with 95% cleared with a half-time of 29 minutes and the remaining arsenic cleared with a half-time of 75 days. For sodium arsenate and sodium arsenite, <0.1% of the dose was retained in the lung 3 days after exposure of hamsters; 1.3% of the arsenic trisulfide dose was retained after 3 days (Marafante and Vahter 1987). The Marafante and Vahter (1987) study suggested that lung clearance was influenced by compound solubility. The primary forms of arsenic found in the urine of inhalation-exposed humans are DMA and MMA, with inorganic arsenic comprising <25% of the total urinary arsenic (Apostoli et al. 1999).

Organic Arsenicals. No studies were located regarding the excretion of organic arsenicals by humans or animals after inhalation exposure. However, rats that were given a single intratracheal dose of DMA

excreted about 60% in the urine and about 8% in the feces within 24 hours (Stevens et al. 1977). This indicates that organic arsenicals are likely to be promptly excreted after inhalation exposure.

3.4.4.2 Oral Exposure

Inorganic Arsenicals. Direct measurements of arsenic excretion in humans who ingested known amounts of arsenite or arsenate indicate that very little is excreted in the feces (Bettley and O'Shea 1975), and that 45–85% is excreted in urine within 1–3 days (Apostoli et al. 1999; Buchet et al. 1981a; Crecelius 1977; Mappes 1977; Tam et al. 1979b). At low exposure levels, urinary arsenic levels generally increase linearly with increasing arsenic intake (Calderon et al. 1999). During lactation, a very small percent of ingested arsenic may also be excreted in the breast milk (Concha et al. 1998a). A similar pattern of urinary and fecal excretion is observed in hamsters (Marafante and Vahter 1987; Yamauchi and Yamamura 1985) and mice (Vahter and Norin 1980); this pattern is typically modeled as a biphasic process (e.g., Hughes et al. 2003). Generally, whole body clearance is fairly rapid, with half-times of 40–60 hours in humans (Buchet et al. 1981b; Mappes 1977). Clearance is even more rapid in mice and hamsters, with 90% removed in 2 days (Hughes et al. 2003; Marafante and Vahter 1987; Vahter 1981; Vahter and Norin 1980).

A study in pregnant women exposed to elevated levels of inorganic arsenic in drinking water found that most of the ingested arsenic was excreted in the urine as DMA (79–85%), with smaller amounts excreted as inorganic arsenic (8–16%) or MMA (5–6%) (Christian et al. 2006). Similarly, in mice, arsenate is primarily excreted in the urine as DMA, with lesser amounts of inorganic arsenic and MMA (Kenyon et al. 2005). Following a single oral dose of 10 μmol/kg sodium arsenate, 78.4% was excreted as DMA, 20.2% as inorganic arsenic, and 1.45% as MMA; at a 10-fold higher dose, the ratio of DMA to inorganic arsenic decreased (57.7% DMA, 39.8% inorganic arsenic, and 2.59% MMA).

Arsenic is also excreted in the bile via the formation of two arsenic-glutathione complexes (arsenic triglutathione and methylarsenic diglutathione) (Kala et al. 2000). In rats administered 5.0 mg/kg sodium arsenite, equal amounts of arsenic triglutathione and methylarsenic diglutathione were found in the bile 18–20 minutes after exposure. At a lower arsenic dose (0.5 mg/kg), only methylarsenic diglutathione was found. As discussed in Section 3.4.4.4, biliary excretion of arsenic has also been detected in mice, hamsters, guinea pigs, and rabbits following parenteral exposure (Csanaky and Gregus 2002).

Organic Arsenicals. Studies in humans indicate that ingested MMA and DMA are excreted mainly in the urine (75–85%), and this occurs mostly within 1 day (Buchet et al. 1981a; Marafante et al. 1987b). This is supported by studies in rats, mice, and hamsters, although in animals, excretion is more evenly distributed between urine and feces (Hughes et al. 2005; Marafante et al. 1987b; Stevens et al. 1977; Yamauchi and Yamamura 1984; Yamauchi et al. 1988). In mice administered 40 mg As/kg as DMA, 56.4% was excreted in the urine as DMA, 7.7% as a DMA complex, and 3.5% as TMAO during a 48-hour period after dosing; in the feces, 24.3% was DMA and 4.9% as DMA complex (Marafante et al. 1987b). In hamsters, 38.7% was DMA, 11.2% as DMA complex, and 6.4% as TMAO in the urine; in the feces, 37.3% as DMA and 4.9% as DMA complex. As with DMA, most MMA is excreted in the urine and feces as parent compound. In the urine of mice administered 0.4 mg As/kg as MMA, 98.2% of the urinary arsenicals was in the form of MMA(V) and 1.8% as MMA(III) (Hughes et al. 2005); at a 10-fold higher dose, 89.6% was excreted as MMA(V), 1.2% as MMA(III), 6.2% as DMA(V), 1.1% as DMA(III), and 1.9% as TMAO. As discussed previously, exposure of rats to MMA or DMA results in the excretion of a higher percentage of metabolites. After 1 week exposure to MMA, 50.6% of the dose was excreted as MMA, 19.0% as DMA, and 6.9% of TMAO (Yoshida et al. 1998). A 1-week exposure to DMA, 44.9% was excreted as DMA in the urine and 40.0% as TMAO (Yoshida et al. 1998). A longer-term exposure to DMA (>7 months) resulted in a higher percentage of the amount of parent compound excreted; 56–65% as DMA and 23–35% as TMAO (Li et al. 1998; Wanibuchi et al. 1996; Yoshida et al. 1998).

In mice and hamsters, DMA and MMA are rapidly cleared from the body (Hughes et al. 2005; Marafante et al. 1987b; Vahter et al. 1984). In mice, 85% of the initial oral dose of DMA was eliminated from the body with a half-life of 2.5 hours (Vahter et al. 1984). In contrast to the mouse data, 45% on the initial DMA dose to rats was eliminated with a half-time of 13 hours and the remaining 55% had an elimination half-time of 50 days (Vahter et al. 1984).

3.4.4.3 Dermal Exposure

Inorganic Arsenicals. No studies were located regarding excretion of inorganic arsenicals in humans or animals following dermal exposure. In rats, arsenic absorbed through the tail was excreted approximately equally in urine and feces, similar to the excretion pattern following oral exposure (Dutkiewicz 1977).

Organic Arsenicals. No studies were located regarding excretion of organic arsenicals in humans or animals following dermal exposure.

3.4.4.4 Other Routes of Exposure

Inorganic Arsenicals. Excretion of arsenate and arsenite following parenteral exposure of animals is similar to that seen following oral exposure. In rabbits and mice, urinary excretion within 8 hours usually accounts for about 50–80% of the dose (Maehashi and Murata 1986; Maiorino and Aposhian 1985; Vahter and Marafante 1983). Somewhat lower levels (30–40%) are excreted in the urine of marmoset monkeys (Vahter and Marafante 1985; Vahter et al. 1982), probably because of the absence of methylation in this species. Whole-body clearance studies in mice indicate that arsenate is over 65% removed within 24 hours, while arsenite is about 86% removed at 24 hours (Lindgren et al. 1982). A relatively small proportion of an injected dose of arsenic V (10% for rats, 4% for mice, and <2% for hamsters, guinea pigs, and rabbits) was found to be excreted into the bile within the first 2 hours postinjection (Csanaky and Gregus 2002). Following arsenic III injection, a much greater percentage (92% for guinea pigs and 75% for rats) of the arsenic was found in the bile in the first 2 hours after administration (Csanaky and Gregus 2002). Similarly, approximately 40% of an intravenous dose of sodium arsenite was excreted into the bile of rats, most of it occurring during the first hour after exposure (Kala et al. 2000). Kala et al. (2000) determined that the biliary transport of arsenic was dependent on the formation of arsenic-glutathione complexes, which were transported out of hepatocytes by multidrug resistance associated protein 2 (MRP2/cMOAT); most of the arsenic in bile was in the form of arsenic triglutathione or methylarsenic diglutathione.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and

Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

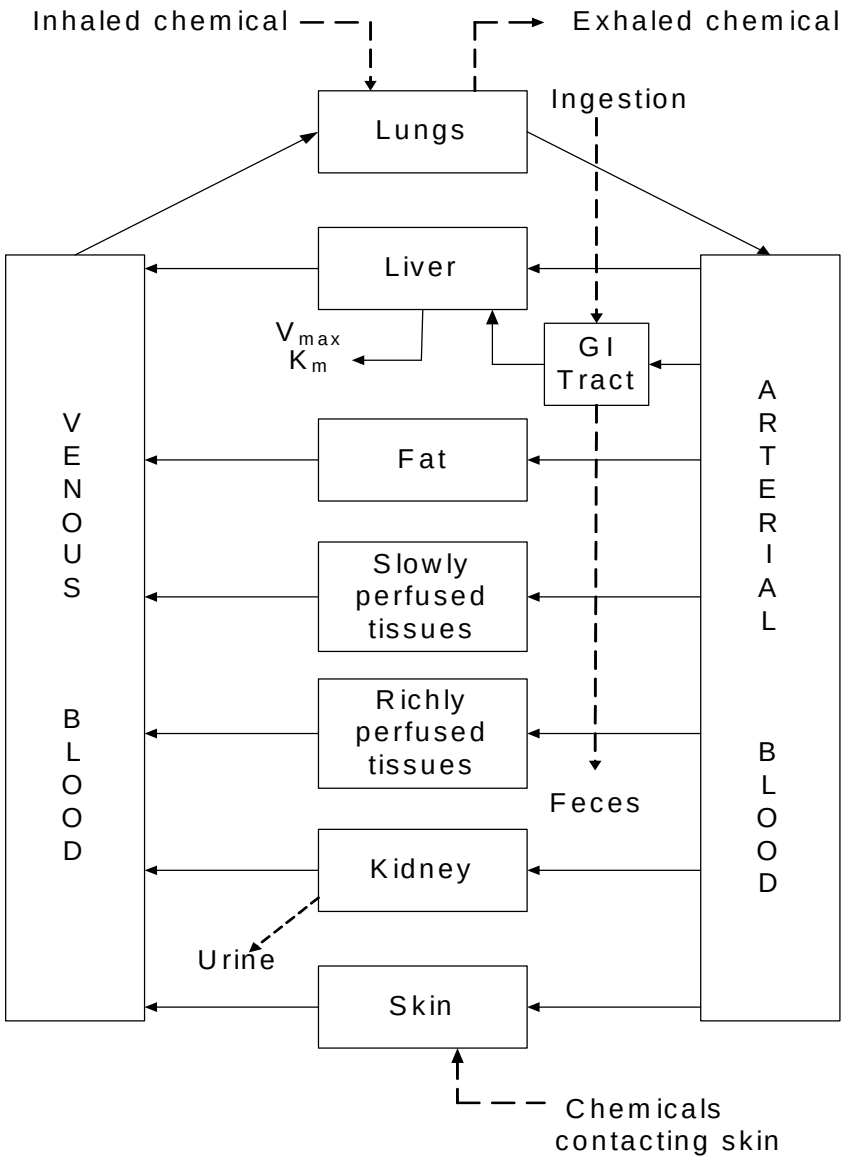
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-9 shows a conceptualized representation of a PBPK model.

If PBPK models for arsenic exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Figure 3-9. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

Several PBPK models have been developed for inorganic arsenic; the Mann, Yu, and Menzel models are discussed below. A joint research effort between the Chemical Industry Institute of Toxicology (CIIT) Centers for Health Research, EPA, ENVIRON International, and the Electric Power Research Institute (EPRI) is underway to develop a biologically based dose response model of carcinogenicity. Part of this effort involves refining the existing PBPK models (Clewell et al. 2007).

3.4.5.1 Summary of PBPK Models

The Mann model (Gentry et al. 2004; Mann et al. 1996a, 1996b), Yu model (Yu 1998a, 1998b; Yu 1999a, 1999b), and Menzel model (Menzel et al. 1994) are the PBPK models for arsenic currently available. The Mann model simulates the absorption, distribution, metabolism, elimination, and excretion of As(+3), As(+5), MMA, and DMA after oral and inhalation exposure in mice, hamsters, rabbits, and humans. The Yu model simulates the absorption, distribution, metabolism, elimination, and excretion of As(+3), As(+5), MMA, and DMA after oral exposure to inorganic arsenic in mice, rats, or humans. The Menzel model is a preliminary model that predicts internal organ burden of arsenic during specific oral exposures, simulating the metabolism, distribution to organs and binding to organs in mice, rats, and humans.

3.4.5.2 Arsenic PBPK Model Comparison

The Mann model is a well-derived model, consisting of multiple compartments and metabolic processes, and modeling four chemical forms of arsenic (two organic and two inorganic), which has been validated using experimental data. The Yu model has more compartments than the Mann model, also models metabolism and fate of four forms of arsenic, and has likewise been validated using experimental data. The Menzel model is still preliminary and has not been validated.

3.4.5.3 Discussion of Models

The Mann Model

Risk assessment. The Mann model was not used for risk assessment.

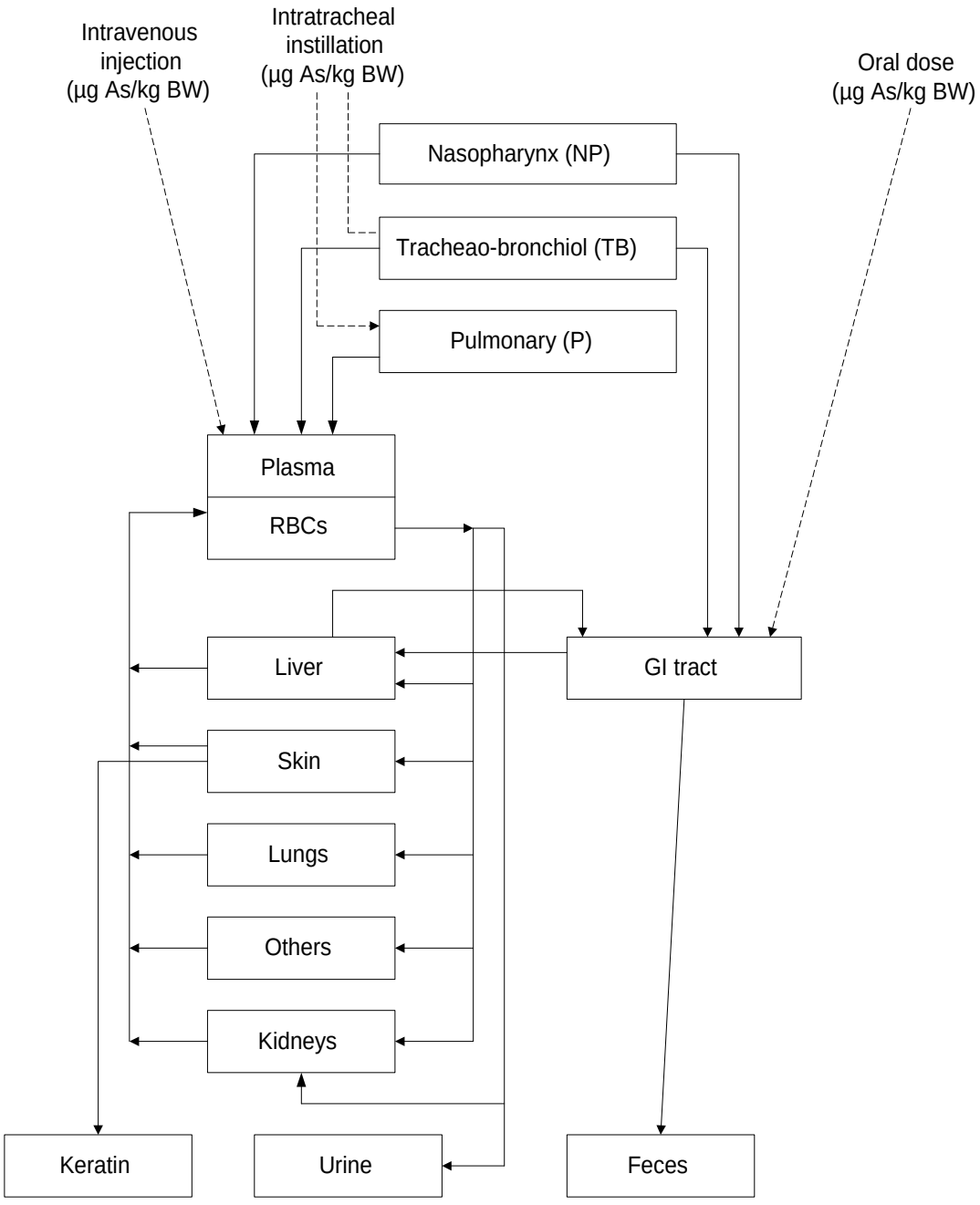
Description of the model. The Mann model was initially developed to simulate oral, intratracheal, and intravenous exposure to arsenic in rabbits and hamsters (Mann et al. 1996a). In a companion paper, the model was expanded to include inhalation exposure and extrapolated and applied to humans (Mann et al. 1996b). A subsequent paper further expanded the model to include mice (Gentry et al. 2004).

The model consists of six tissue compartments: blood, liver, kidneys, lungs, skin, and other tissues. The blood compartment is divided into plasma and red blood cell subcompartments, considered to be at equilibrium. Three routes of exposure are considered in the model. Oral exposure is considered to enter the liver from the gastrointestinal tract via first-order kinetics. Intratracheal exposure results in deposition into the pulmonary and tracheo-bronchial regions of the respiratory tract. Uptake into blood from the pulmonary region is considered to be via first order kinetics into plasma, uptake from the tracheo-bronchial region is by both transfer into plasma and transport into the gastrointestinal tract. Intravenous injection results in a single bolus dose into the plasma compartment.

Metabolism in the model consists of oxidation/reduction and two methylation reactions. The oxidation/reduction of inorganic arsenic was modeled as a first order process in the plasma, with reduction also included in the kidneys. Methylation of As(+3) was modeled as a two-step process occurring in the liver according to Michaelis-Menton kinetics.

Most physiological parameters were derived by scaling to body weight. In cases where parameters were not available (absorption rates, tissue affinity, biotransformation), estimates were obtained by fitting. This was done by duplicating the initial conditions of published experiments in the model, varying the unknown parameters and comparing the results of the simulation to the reported results. Tissue affinity constants were estimated using reported arsenic levels in tissues at various times after exposure. Metabolic rate constants and absorption rate constants were estimated using data for excretion of arsenic metabolites in urine and feces. Figure 3-10 shows the animal model and Tables 3-11, 3-12, 3-13, and 3-14 provide the parameters used in the animal model. The human model is similar to the animal models with adjustments for body weight and absorption and metabolic rates. A naso-pharynx compartment is included in the human model, which was not present in the animal models. Penetration and deposition in the respiratory tract are based on the log-normal particle size distribution of the aerosol. Metabolic and absorption rate constants were fitted using experimental data on urinary excretion of arsenic following a single oral dose of As(+3) (Buchet et al. 1981a) or As(+5) (Tam et al. 1979b) in volunteers. The lung absorption rate constant was obtained by fitting the total urinary excretion of arsenic as predicted with the model to experimental data obtained from occupational exposure to arsenic trioxide (Offergelt et al. 1992). Figure 3-11 shows the human model, and Tables 3-15 and 3-16 provide the data and constants used in the human model.

Figure 3-10. Parameters Used in the Mann PBPK Model for Animals



Source: Mann et al. 1996b

Table 3-11. Parameters Used in the Mann PBPK Model for Animals

Physiological parameter	Rabbit (body weight=3.5 kg)	Hamster (body weight=0.100 kg)
Blood volume (mL)	253	7.0
Organ weight (g)		
Liver	121	4.8
Kidneys	25	1.2
Lungs	31	1.0
Skin	420	17.1
Organ volume (mL)		
Others	2,386	62.0
Lumen volume (mL)		
Stomach	15	0.5
Small intestine	20	0.6
Blood flow (mL/minute)		
Cardiac output	556	38.3
Liver, hepatic	25	1.2
Liver, splanchic	98	6.0
Kidneys	100	7.0
Lungs	13	0.7
Skin	38	2.6
Others	282	20.8
Clearance (mL/minute)		
Glomerular Filtration Rate	10	0.6
Small intestine length (cm)	180	56.0
Total capillary surface area (cm^2)	93,835	2,681.0

PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996a

Table 3-12. Tissue Affinity Constants (K_{ij}) Obtained for the Mann PBPK Model for Animals by Fitting for Rabbits and Hamsters

	K_{ij} (unitless)			
Tissue (*i*)	As(V)	As(III)	MMA	DMA
Liver	1	200	10	1
Kidneys	40	20	100	5
Lungs	1	1	1	20
Skin	1	60	50	1
Others	10	40	1	1

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996a

Table 3-13. Metabolic Rate Constants for the Mann PBPK Model for Animals Obtained by Fitting for Rabbits and Hamsters

Oxidation/reduction	First order	Rabbit	Hamster
Reduction	(1/hour)	3,000.00	100.00
Oxidation	(1/hour)	6,000.00	400.00
Kidney reduction	(1/hour)	30.00	1.00
Methylation	Michaelis–Menten		
1st step	$K_{M_{MMA}}$ (µmol/mL)	0.05	0.12
	$V_{MAX_{MMA}}$ (µmol/mL-hour)	4.00	0.12
2nd step	$K_{M_{DMA}}$ (µmol/mL)	0.90	0.08
	$V_{MAX_{DMA}}$ (µmol/mL-hour)	1.50	0.12

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996a

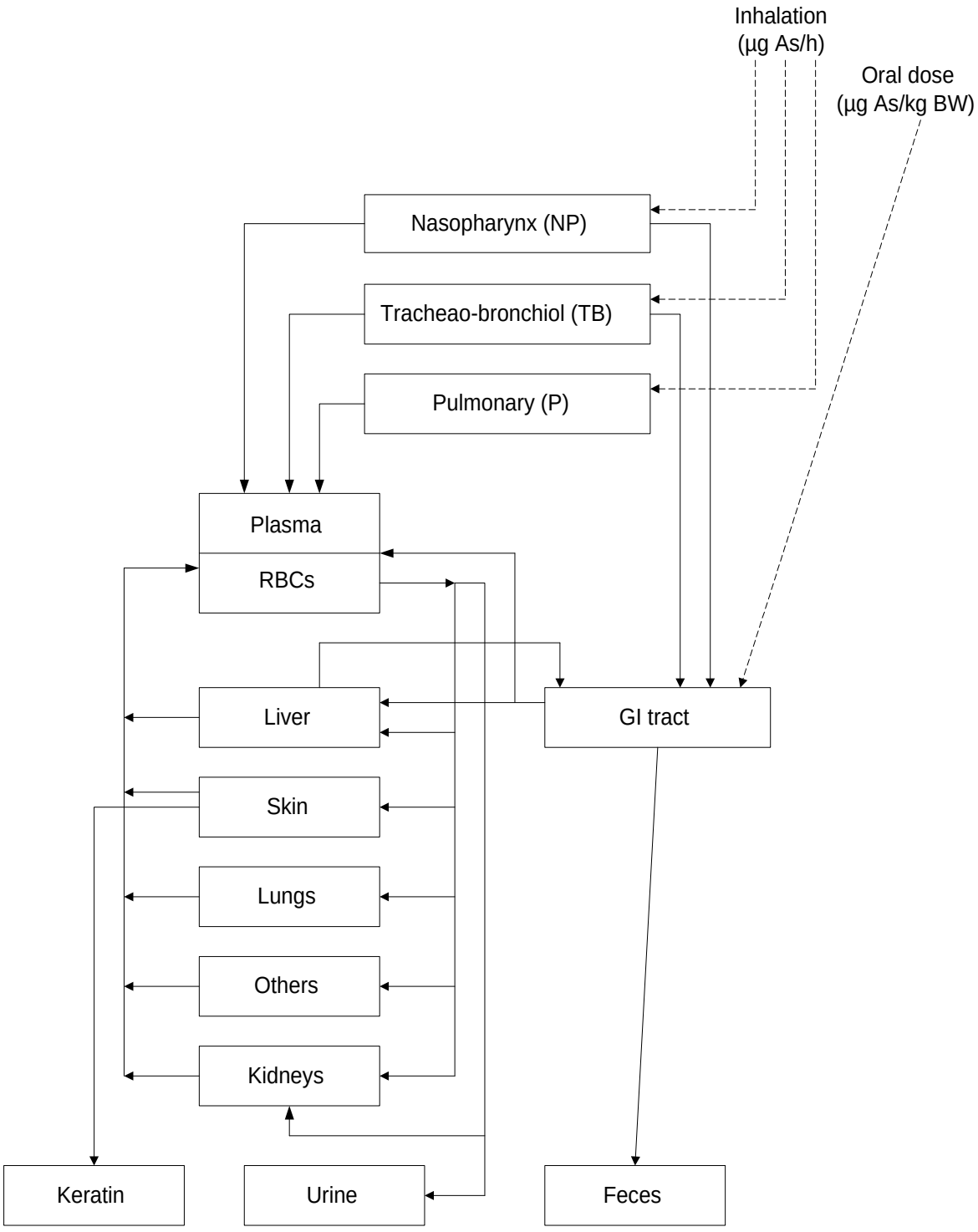
Table 3-14. Fitted Gastrointestinal Tract and Lung Absorption Half-time for the Hamster for the Mann PBPK Model

	Absorption, half-time (hour)	
Arsenic compound	Gastrointestinal tract	Lung
As(V)		
$Na_3(AsO_4)$	0.08	12
$Pb_3(AsO_4)$	0.39	690
As_2O_5	0.28	—
As(III)		
$NaAsO_2$	0.08	12
As_2S_3	0.48	12
As_2O_3	0.02	—
DMA	0.09	—

DMA = dimethylarsinic acid; PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996a

Figure 3-11. Parameters Used in the Mann PBPK Model for Humans



Source: Mann et al. 1996b

Table 3-15. Physiological Data Used in the Mann PBPK Model for Humans

Physiological parameter	Organ	Units	Human (body weight=70 kg)
Blood volume		mL	5,222
Organ weight	Liver	g	1,856
	Kidneys	g	314
	Lungs	g	584
	Skin	g	6,225
	Others	g	55,277
Lumen volume	Stomach	mL	274
	Small intestine	mL	393
Blood flow	Cardiac output	L/minute	5.29
	Liver, hepatic	L/minute	0.32
	Liver, splanchic	L/minute	1.02
	Kidneys	L/minute	0.95
	Lungs	L/minute	0.16
	Skin	L/minute	0.35
	Others	L/minute	2.49
Creatinine			
Male		g/day	1.7
Female		g/day	1.0
Clearance			
Glomerular filtration rate		mL/minute	156
Small intestine length		cm	481
Nasopharynx area		cm^2	177
Tracheobronchial area		cm^2	5,036
Pulmonary area		cm^2	712,471
Total capillary surface area		cm^2	$1,877x10^6$

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996b

Table 3-16. Tissue Affinity Constants (K_{ij}) Obtained by Fitting the Mann PBPK Animal Model for Use with Humans

	K_{ij} (unitless)			
Tissue (i)	As(V)	As(III)	MMA	DMA
Liver	1	200	10	1
Kidneys	40	20	100	5
Lungs	1	1	1	20
Skin	1	60	50	1
Red blood cells	0.2	1.5	0.2	0.2
Others	10	40	1	1

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996b

Validation of the model. The model was generally successful in describing the disposition of an intravenous dose of sodium arsenate in rabbits over a 24-hour period (Marafante et al. 1985). Discrepancies included a 6–7-fold overestimation of levels in skin at 24 hours and underestimation of As(+5) in plasma in the hour following injection. A statistical assessment of how well the model fit the empirical data was not presented. In hamsters, the model was also generally predictive of oral and intratracheal exposures (Marafante and Vahter 1987). Generally, predictions were better for the exposures to As(+5) than for those to As(+3).

The human model was validated using data from studies of repeated oral intake of sodium arsenite in volunteers (Buchet et al. 1981b), occupational exposure to arsenic trioxide and elemental arsenic (Vahter et al. 1986), and community exposure to As(+5) via drinking water (Harrington et al. 1978; Valentine et al. 1979). Simulations were generally in good agreement with the experimental data.

The predictions of tissue distribution, metabolism, and elimination of arsenic compounds from the mouse model were compared with experimental data, and showed generally good agreement. The model tended to overpredict the concentration of organic arsenicals in the lungs, and to a lesser extent in the kidneys and liver, while for inorganic arsenic, the model overpredicted the levels of arsenic (V) present in the urine of acutely-exposed mice.

Target tissues. Levels in skin were not well predicted by this model in animals. Results for the lung were not presented, except for the mouse model, which tended to overpredict lung levels. The human model was only used to predict urinary metabolites.

Species extrapolation. Species extrapolation was not attempted in this model. However, tissue affinities derived for the rabbit and hamster models were used in the human model.

Interroute extrapolation. Interroute extrapolation was not attempted in this model.

The Menzel Model

Risk assessment. The Menzel model was not used for risk assessment.

Description of the model. The Menzel model was developed to simulate oral exposure to arsenic from drinking water and food. Inhalation of arsenic in the particulate phase or as arsine gas is not considered. The chemical species in drinking water is assumed to be As(+5).

The model consists of two sets of compartments: those in which the pools of arsenic are not influenced by blood perfusion, and those in which blood perfusion does determine arsenic burden. The former set of compartments includes the gut, feces, hair, bladder, and urine. The latter set of compartments included lung, liver, fat, skin, kidney, and other tissues. Oral exposure is considered to enter the liver from the gastrointestinal tract.

The model followed that of Andersen and coworkers (Andersen et al. 1987; Ramsey and Andersen 1984). Data from mice were used to test predictions of absorption. Excretion is considered to be rapid and complete into the urine, with no reabsorption from the kidney. Fecal arsenic content accounts for unabsorbed arsenic excreted in the bile, and complex arsenic species from food. Metabolism includes reduction by glutathione and methylation. Arsenic accumulation in the skin, hair and nails was included by assuming that arsenic binds irreversibly to protein sulfide groups in hair and nails.

Validation of the model. The model was preliminary and has not been validated.

Target tissues. Target tissues have not yet been modeled.

Species extrapolation. Species extrapolation was not attempted in this model.

Interroute extrapolation. Interroute extrapolation was not attempted in this model.

The Yu Model

Risk assessment. The Yu model was not used for risk assessment.

Description of the model. The Yu model was developed to simulate oral exposure to arsenic in mice and rats (Yu 1998a, 1998b), and was later adapted for oral exposures in humans (Yu 1999a, 1999b). Inhalation of arsenic in the particulate phase or as arsine gas is not considered. As(+3), As(+5), MMA, and DMA were all considered in the model, though the movements of MMA and DMA were not considered.

The model consists of eight tissue compartments: intestine, skin, muscle, fat, kidney, liver, lung, and vessel-rich group (VRG, e.g., brain); in the human model, the VRG and kidney compartments were combined. Only oral exposure was considered. Absorption is based on absorption to the stomach, which then passes the arsenic to the gastrointestinal tract. From the gastrointestinal tract, arsenic is either transferred to the blood or excreted in the feces.

The physiological parameters for the model were obtained from published values in the literature. Tissue/blood partition coefficients were based on the postmortem blood and tissue concentrations from a fatal human poisoning case study (Saady et al. 1989). Tissue volumes and blood flow rates were based on published values from a number of sources (EPA 1988e; Reitz et al. 1990). Absorption and excretion rate constants were based on experimental observations of blood concentrations and urinary and fecal excretion following oral administration of inorganic arsenic (Odanaka et al. 1980; Pomroy et al. 1980). Metabolic rate constants for the methylation and dimethylation of inorganic arsenic were also based on experimental observations (Buchet et al. 1981a; Crecelius 1977). Figure 3-12 shows the model and Table 3-17 provides the parameters used for each species.

Validation of the model. The model was generally successful at predicting the urinary excretion 48 hours after administration of 5 mg/kg inorganic arsenic in both rats and mice. After 48 hours, the observed/predicted ratios associated with excreted doses ranged from 0.78 to 1.11 for the mouse and from 0.85 to 0.93 for the rat. However, the model overpredicted the amount of inorganic arsenic found in the feces of mice at 24 and 48 hours, and overpredicted the amount of DMA formed by exposed mice at 48 hours. In rats, the model overestimated the urinary and fecal excretion of inorganic arsenic at 24 hours postexposure, though at 48 hours, measured values all fell within the predicted ranges. The human model was also generally successful at predicting the urinary excretion of arsenic compounds following oral exposure, based on results of controlled human exposure studies (Buchet et al. 1981a; Vahter 1983). In general, however, the model underpredicts excretion at early time points and overpredicts at later time points, with 24 hours being the time at which its predictive capabilities agreed most strongly with available data.

The ability of the model to predict tissue burdens was not compared to actual data for any species.

Figure 3-12. Parameters Used in the Yu PBPK Model for Animals

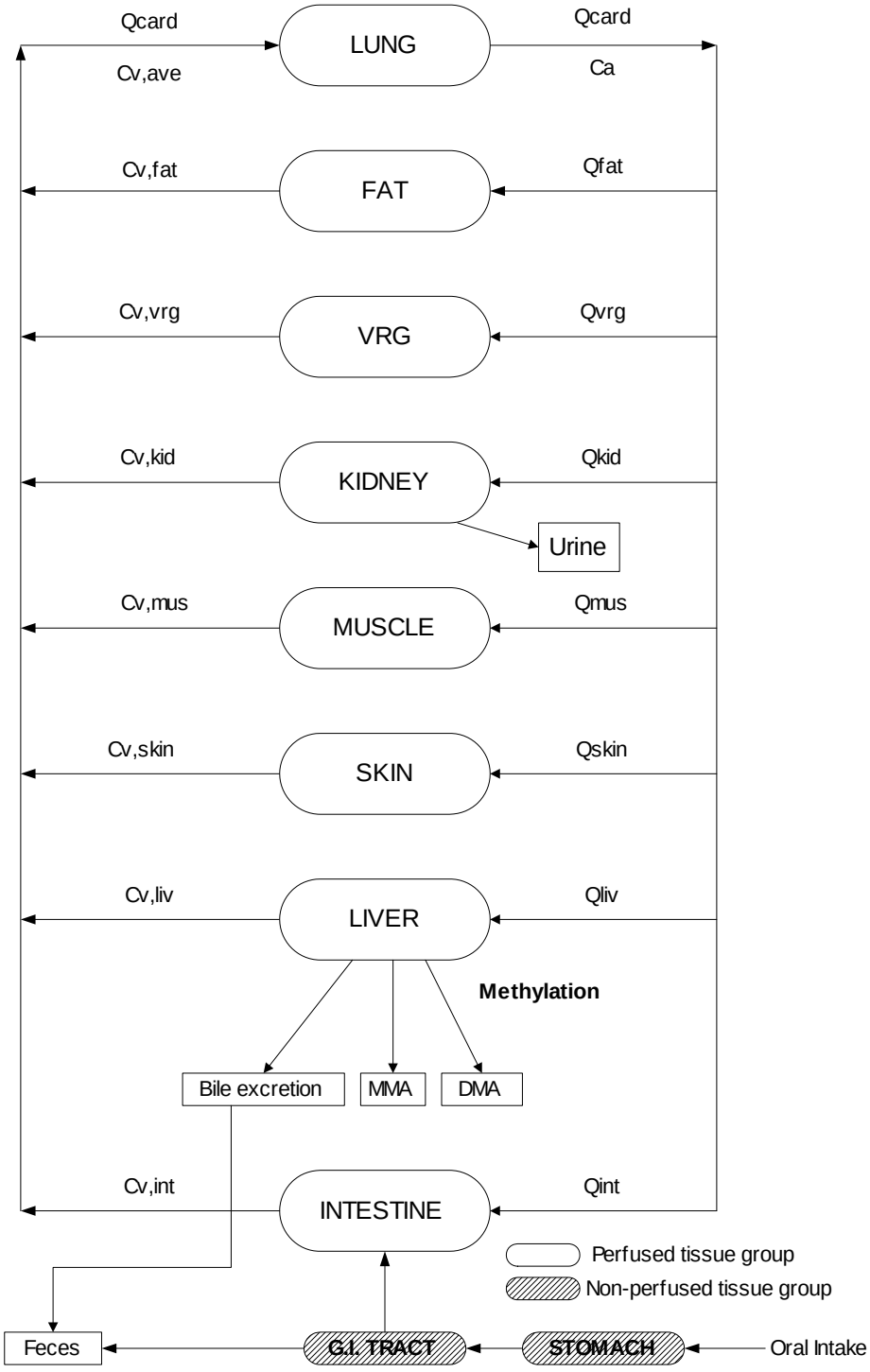


Table 3-17. Parameters Used in the Yu PBPK Model

	Mouse	Rat	Human
Partition coefficients			(As^{III}/As^{V}/MMA/DMA)
Intestine	6.0	6.0	2.8/2.8/1.2/1.4
Skin	5.0	5.0	2.5/2.5/1.25/1.25
VRG	6.0	6.0	Combined with kidney
Muscle	5.0	10.0	2.6/2.6/1.8/2.8
Fat	—	0.5	0.3/0.3/0.3/0.3
Kidney	8.5	7.5	4.15/4.15/1.8/2.075
Liver	10.0	10.0	5.5/5.3/2.35/2.65
Lung	4.0	4.0	4.15/4.15/1.8/2.075
Blood flow rate (mL/hour)			
Intestine	100	528	1,810
Skin	7.68	37.8	130
VRG	157	960	N/A
Muscle	153	1,260	25,850
Fat	—	253.2	6,467
Kidney	255	255	45,240
Liver	255	1,260	32,320
Lung	N/R	N/R	129,000
Tissue volume (mL)			
Intestine	1.94	6.9	558
Skin	1.83	15.4	606
VRG	0.81	23.0	N/A
Muscle	19.9	162	6,989
Fat	—	14.5	2,328
Kidney	0.484	1.63	248
Liver	1.67	5.82	422
Lung	0.124	1.0	400
Metabolism constants			
$Vmax_{(MMA)}$ (µmol/hour)	0.45	0.15	11.25
$Vmax_{(DMA)}$ (µmol/hour)	0.375	0.06	22.25
$Km_{(MMA)}$ (µmol/hour)	1.0	0.2	0.01
$Km_{(DMA)}$ (µmol/hour)	0.2	0.2	0.01

Table 3-17. Parameters Used in the Yu PBPK Model

	Mouse	Rat	Human
First-order rate constants			(As^{III}/As^{V}/MMA/DMA)
K_{SI} ($hour^{-1}$)	0.3	0.3	-/1.2/-/-
K_{AI} ($hour^{-1}$)	1.5	3.6	-/1.2/-/-
K_{fecal} ($hour^{-1}$)	0.33	0.048	-/0.0012/0.0/0.0
$K_{urinary}$ ($hour^{-1}$)	1.32	0.9	0.05/0.075/0.07/0.04
$K_{biliary}$ ($hour^{-1}$)	0.33	0.3	-/0.018/-/-

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; N/A = not applicable; N/R = not reported

Source: Yu 1998a, 1998b, 1999a, 1999b

Target tissues. Model predictions of tissue burdens were not compared to actual data. The model accurately predicted, with a few exceptions, the urinary and fecal excretion of inorganic arsenic and its metabolites in rats, mice, and humans.

Species extrapolation. Species extrapolation beyond rats and mice was not attempted using this model. The human model has not been compared to, or linked with, either of the rodent models.

Interroute extrapolation. Interroute extrapolation was not attempted using this model.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Arsenic absorption depends on its chemical form. In humans, As(+3), As(+5), MMA, and DMA are orally absorbed ≥75%. Arsenic is also easily absorbed via inhalation. Absorption appears to be by passive diffusion in humans and mice, although there is evidence (Gonzalez et al. 1995) for a saturable carrier-mediated cellular transport process for arsenate in rats (for review, see Rosen 2002). Dermal absorption appears to be much less than by the oral or inhalation routes. Bioavailability of arsenic from soil appears to be lower via the oral route than it is for sodium salts of arsenic. Arsenic in soil may form water insoluble compounds (e.g., sulfides), which are poorly absorbed.

Arsenic and its metabolites distribute to all organs in the body; preferential distribution has not been observed in human tissues at autopsy or in experiments with animal species other than rat (in which arsenic is concentrated in red blood cells). Since the liver is a major site for the methylation of inorganic arsenic, a “first-pass” effect is possible after gastrointestinal absorption; however, this has not been investigated in animal models.

Arsenic and its metabolites are largely excreted via the renal route. This excretion mechanism is not likely to be saturated within the dose range expected from human exposure. Excretion can also occur via feces after oral exposure; a minor excretion pathway is nails and hair. The methylation of inorganic arsenic is the major metabolism pathway. The proportion of metabolites recovered in urine (As(+3), As(+5), MMA, DMA) are roughly consistent in humans regardless of the exposure scenario. However, interindividual variation is great enough that it cannot be determined if capacity limitation may occur in some individuals.

The manifestation of arsenic toxicity depends on dose and duration of exposure. Single oral doses in the range of 2 mg As/kg and higher have caused death in humans. Doses as low as 0.05 mg As/kg/day over longer periods (weeks to months) have caused gastrointestinal, hematological, hepatic, dermal, and neurological effects. These effects appear to be a result of direct cytotoxicity. Long-term exposure (years) to drinking water at levels as low as 0.001 mg As/kg/day have been associated with skin diseases and skin, bladder, kidney, and liver cancer. Long-term inhalation exposure to arsenic has also been associated with lung cancer at air levels as low as 0.05–0.07 mg/m^3. It is not clear at this time why long-term toxicity is different between the oral and inhalation routes, given that arsenic is easily absorbed into the systemic circulation by both routes.

Studies in mice and rats have shown that arsenic compounds induce metallothionein, a metal-binding protein thought to detoxify cadmium and other heavy metals, *in vivo* (Albores et al. 1992; Hochadel and Waalkes 1997; Kreppel et al. 1993; Maitani et al. 1987a). The potency of arsenic compounds in inducing metallothionein parallels their toxicity (i.e., As(+3) > As(+5) > MMA > DMA). For cadmium, it is thought that metallothionein binds the metal, making it biologically inactive. For arsenic, however, only a small percentage of the administered arsenic is actually bound to metallothionein (Albores et al. 1992; Kreppel et al. 1994; Maitani et al. 1987a). *In vitro* studies have shown that affinity of arsenic for metallothionein is much lower than that of cadmium or zinc (Waalkes et al. 1984). It has been proposed that metallothionein might protect against arsenic toxicity by acting as an antioxidant against oxidative injury produced by arsenic (NRC 1999).

3.5.2 Mechanisms of Toxicity

Mechanisms of arsenic-induced toxicity and carcinogenicity have not been clearly identified. However, recent efforts to elucidate mechanisms of arsenic toxicity and carcinogenicity have resulted in numerous *in vitro* and *in vivo* reports. Whereas these mechanistic studies typically employed relatively high arsenic exposure levels, some of the most recent studies were performed using more environmentally-relevant exposure levels. Due to the extremely large amount of mechanistic data for arsenic, it is not feasible to include all pertinent primary studies that address issues concerning proposed mechanisms of arsenic toxicity and carcinogenicity. Therefore, the following discussion of mechanisms of arsenic toxicity represents a summary of information from several recent review articles (Chen et al. 2004, 2005; Florea et al. 2005; Hughes 2002; Kitchin 2001; Lantz and Hays 2006; Navas-Acien et al. 2005; Rossman 2003; Roy and Saha 2002; Thomas et al. 2007; Vahter 2002).

It is becoming increasingly evident that the toxicity and carcinogenicity of arsenic is likely to be closely associated with metabolic processes. Absorbed pentavalent arsenic (AsV) is rapidly reduced to trivalent arsenic (AsIII) at least partially in the blood. Much of the formed AsIII is distributed to tissues and taken up by cells (particularly hepatocytes). Many cell types appear to accumulate AsIII more rapidly than AsV. Because AsIII (as arsenite) is known to be more highly toxic than AsV (as arsenate), the reduction step may be considered bioactivation rather than detoxification. Glutathione appears to play a role in the reduction of AsV to AsIII, which is required prior to methylation. Methylation of arsenic ultimately forms relatively less toxic MMA and DMA; this process is accomplished by alternating between the reduction of AsV to AsIII and the addition of a methyl group; S-adenosylmethionine is considered to be the source of the methyl group. Both MMA and DMA are less reactive with tissue constituents than inorganic arsenic and both are readily excreted in the urine. The methylation process appears to include multiple intermediates, some of which are more reactive than inorganic arsenic. For example, reactive trivalent metabolites, MMAIII and DMAIII, have been detected in the urine of human subjects chronically exposed to arsenic in drinking water, and *in vitro* studies have demonstrated MMAIII to be more toxic than arsenite or arsenate to human hepatocytes, epidermal keratinocytes, and bronchial epithelial cells. Additional *in vitro* studies have demonstrated genotoxic and DNA damaging properties of both MMAIII and DMAIII.

AsV (as arsenate) has been demonstrated to: (1) replace phosphate in glucose-6-phosphate and 6-phosphogluconate *in vitro*, (2) replace phosphate in the sodium pump and the anion exchange transport system of human red blood cells, (3) diminish the *in vitro* formation of adenosine-t′-triphosphate (ATP) by replacing phosphate in enzymatic reactions, and (4) deplete ATP in some cellular systems, but not in human erythrocytes. However, it is becoming more apparent that the major source of arsenic toxicity and carcinogenicity is related to its reduction to arsenite.

AsIII (as arsenite) is known to react with thiol-containing molecules such as glutathione and cysteine *in vitro*. Methylated trivalent arsenics such as MMAIII are potent inhibitors of glutathione reductase and thioredoxin reductase. It has been suggested that binding of arsenite and methylated trivalent arsenicals to critical thiol groups could lead to the inhibition of essential biochemical reactions, alteration of cellular redox status, and eventual cytotoxicity. Binding of MMAIII and DMAIII to protein has also been demonstrated *in vitro*. Arsenite inhibits pyruvate dehydrogenase (PDH), a complex that oxidizes pyruvate to acetyl-CoA, a precursor to intermediates of the citric acid cycle that provides reducing equivalents to the electron transport system for ATP production. This property may explain the depletion of carbohydrates in arsenite-treated rats.

Evidence that arsenic may induce alterations in nitric oxide metabolism and endothelial function includes findings that persons exposed to high levels of arsenic in drinking water had decreased serum and urine concentrations of nitric oxide metabolites, which was reversed upon intervention with drinking water containing lower levels of arsenic. Urinary arsenic levels have been inversely associated with nitric oxide production in activated monocytes. Arsenite concentrations of 1–25 μM inhibited endothelial nitric oxide synthase activity and resulting decreased cell growth in human endothelial cells, although lower concentrations up-regulated the expression of constitutive nitric oxide synthase 3, which might serve as an explanation for observed arsenic-induced cell growth and angiogenesis.

Although epidemiological studies demonstrate the carcinogenicity of arsenic in humans, early animal cancer bioassays failed to demonstrate a carcinogenic effect following lifetime exposure to inorganic arsenic. However, more recent focus has resulted in the development of animal models that exhibit carcinogenic activity in skin, urinary bladder, liver, and lung, tissues implicated in arsenic-induced cancer in humans. This concordance in target sites among animal models and humans indicates that common mechanisms of action may be applicable to humans and laboratory animals.

Several modes of action have been proposed to explain, at least in part, the carcinogenicity of arsenic. It is likely that multiple mechanisms are involved, some of which may relate to noncancer effects as well.

Oxidative Stress. Mechanistic studies of arsenic toxicity have suggested a role of the generation of reactive oxygen species in the toxicity of inorganic arsenic. Results of both *in vivo* and *in vitro* studies of arsenic-exposed humans and animals suggest the possible involvement of increased lipid peroxidation, superoxide production, hydroxyl radical formation, blood nonprotein sulfhydrals, and/or oxidant-induced DNA damage. Reduction of cellular oxidant defense by treatment with glutathione-depleting agents results in an increased sensitivity of cells to arsenic toxicity. Support for mechanisms of toxicity that involves arsenic-induced oxidative stress includes findings that inhaled arsenic can predispose the lung to oxidative damage, chronic low-dose arsenic alters genes and proteins that are associated with oxidative stress and inflammation, and major transcriptional regulators of altered genes are redox sensitive.

Genotoxicity. Collectively, *in vitro* and *in vivo* genotoxicity assays have demonstrated that arsenics cause single strand breaks, formation of apurinic/apyrimidinic sites, DNA base and oxidative base damage, DNA-protein crosslinks, chromosomal aberrations, aneuploidy, sister chromatid exchanges, and micronuclei. Chromosomal aberrations, characterized by chromatid gaps, breaks and fragmentation,

endoreduplication, and chromosomal breaks, are dose-dependent and arsenite is more potent than arsenate. Both MMAIII and DMAIII are directly genotoxic and are many times more potent than arsenite at inducing DNA damage. Inorganic arsenic can potentiate the mutagenicity observed with other chemicals, although arsenic itself does not appear to induce point mutations. Arsenic-induced genotoxicity may involve oxidants or free radical species.

Altered Growth Factors→Cell Proliferation→Promotion of Carcinogenesis. Increased concentrations of growth factors can lead to cell proliferation and eventual promotion of carcinogenesis. Arsenic-induced cell death can also lead to compensatory cell regeneration and carcinogenesis. Altered growth factors, cell proliferation, and promotion of carcinogenesis have all been demonstrated in one or more systems exposed to arsenics. Altered growth factors and mitogenesis were noted in human keratinocytes. Cell death was observed in human hepatocytes and rat bladder epithelium. Cell proliferation was demonstrated in human keratinocytes and intact human skin and rodent bladder cells. Promotion of carcinogenesis was noted in rat bladder, kidney, liver, and thyroid, and mouse skin and lung.

Additional Mechanisms of Toxicity Data. Inorganic arsenic exposure has been shown to modify the expression of a variety of genes related to cell growth and defense, including the tumor suppressor gene p53, as well as to alter the binding of nuclear transcription factors. Carcinogenic effects of arsenic may result from a cocarcinogenic effect. Whereas arsenic exposure alone did not elicit skin tumors in mice, co-exposure to arsenic and ultraviolet light resulted in skin tumors that were greater in number and larger in size than those produced by ultraviolet light alone. Arsenate and arsenite enhanced the amplification of a gene that codes for the enzyme dihydrofolate reductase, arsenate being more potent than arsenite. Furthermore, inhibition of DNA repair has been demonstrated in arsenic-treated cells.

3.5.3 Animal-to-Human Extrapolations

The usefulness of animal models for toxicity studies with arsenic is significantly limited by two major factors. First and most importantly, no animal model exists for the health effect of greatest concern for human exposure: carcinogenicity in skin and other organs after oral exposure. Second, the pattern of metabolism in humans (significant excretion of the methylated forms of arsenic) is unlike that of most other mammalian species (the mouse and rabbit may be exceptions). The ratios of inorganic to organic arsenic excreted also vary between species. The rat sequesters arsenic in its erythrocytes and is not a suitable model for human toxicity.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997h). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

There is little evidence to suggest that arsenic functions as an endocrine disruptor. An association has been demonstrated between exposure to arsenic in drinking water and increased incidence of diabetes mellitus (Rahman et al. 1998; Tsai et al. 1999; Tseng et al. 2000; Wang et al. 2003), although dose-response relationships are not available and the mechanism of action for this response has not been characterized. Studies by Waalkes and coworkers (Waalkes et al. 2006a, 2006b) have suggested that in

mice, arsenic may interact with estrogens to enhance production of female urogenital cancers and male hepatocellular cancer following exposure to arsenic *in utero*. The mechanism by which this might happen has not been elucidated. No other relevant data were located in humans or animals. Data on general effects of arsenic compounds on the endocrine system are presented in Sections 3.2.1.2 and 3.2.2.2 above.

In vitro studies provide suggestive evidence that arsenic may act as an endocrine disruptor. Studies by Bodwell et al. (2004, 2006) and Davey et al. (2007) demonstrate that arsenic can alter gene regulation of steroid hormone receptors for glucocorticoids, mineralocorticoids, progesterone, and estrogen.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek

1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Arsenic has been recognized as a human toxicant for many centuries, and the symptoms of acute poisoning are well known. Children who are exposed to high levels of arsenic exhibit symptoms similar to those seen in adults, including respiratory, cardiovascular, dermal, and neurological effects, and vomiting if the arsenic is ingested (Borgoño et al. 1980; Foy et al. 1992; Kersjes et al. 1987; Muzi et al. 2001; Rosenberg 1974; Zaldívar 1974; Zaldívar and Guillier 1977). Arterial thickening of the pancreas was observed in five children who died in Chile after chronic exposure to arsenic (Rosenberg 1974). Foy et al. (1992) described systemic effects of chronic arsenic exposure in children in a village near a tin and tungsten mining operation in Thailand. The arsenic concentration in water samples from 35 shallow wells averaged 0.82 mg As/L (range, 0.02–2.7 mg As/L). Piped water (available in some homes) had a concentration of 0.07 mg As/L. A survey of skin manifestations of arsenic poisonings was conducted in the autumn of 1987. The case reports of four children were presented. All of the children had hyperkeratosis and hyperpigmentation of the extremities, including tibia, palms, and soles. In addition, one child had developed weakness 3 years previously and had anorexia and a chronic cough for 1 year. She had been held back twice in school as a slow learner. On examination, she had a runny nose and

weakness of her wrist joints. The liver was about 4 finger-breadths below the right costal margin with a sharp but tender edge. Blood arsenic levels ranged from 0.087 to 0.46 μg/mL and the arsenic level in hair ranged from 14.4 to 20 μg/g. The authors concluded that the finding of typical skin manifestations of chronic arsenic poisoning suggests that it may take a considerably shorter period of time to develop these manifestations than previously thought. However, it is not known what effect co-exposure to tin and tungsten might have had on skin manifestations in these children. Exposure to high arsenic levels during gestation and/or during early childhood also was associated with significant increases in SMRs for lung cancer and bronchiectasis during adulthood in a study of residents in a city in Chile with high arsenic levels in the drinking water (near 0.9 mg/L) during several years (Smith et al. 2006).

As previously mentioned in Sections 3.2.1.4 and 3.2.2.4, exposure of children to arsenic also has been associated with neurological deficits in children. Studies by Wasserman et al. (2004, 2007) of 6- and 10-year-old children from Bangladesh reported small but significant decreases in some tests of cognitive function associated with levels of arsenic in the water ≥0.05 mg/L. A study of pre-school age children in West Bengal, India, reported an association between current urinary arsenic concentrations, but not long-term water arsenic, and small decrements in intellectual tests (von Ehrenstein et al. 2007). Similar results were reported in a study of children in Taiwan (Tsai et al. 2003) and in China (Wang et al. 2007). Neurological effects have also been associated with elevated levels of arsenic in the air. For example, Bencko et al. (1977) reported that children of approximately 10 years of age living near a power plant burning coal of high arsenic content showed significant hearing losses (increased threshold) compared to a control group of children living outside the polluted area (Bencko et al. 1977). Also, in a study of Mexican children, Calderón et al. (2001) reported that children living near a smelter complex had poor performance on tests evaluating verbal IQ than children who lived farther from the smelter. Thus, the limited data available suggest that exposure of children to inorganic arsenic may result in detrimental effects on neurobehavioral parameters.

Wulff et al. (1996) conducted a retrospective study of a cohort of children born between 1961 and 1990 in the municipality of Skelleftea, Sweden, where a smelter released arsenic and other pollutants including lead, copper, cadmium, and sulfur dioxide. Childhood cancer incidences among children born in the vicinity of the smelter (i.e., within 20 km) and distant from the smelter (>20 km) were compared with expected incidences based on Swedish national statistics. There appeared to be an increased risk of childhood cancer (all types combined) among children born in the vicinity of the smelter (SIR=195, 95% CI=88–300, based on 13 cases observed and 6.7 expected), but the increase was not statistically significant, and in any event, the role of arsenic in any finding from this study is confounded by the

presence of other metals. The number of cases (n=42) was very close to the expected number (n=41.8) among children born distant from the smelter. Similar results were reported in a study by Moore et al. (2002), which did not find increased incidence ratios for all childhood cancers or for childhood leukemias in children from an area of Nevada with high arsenic exposures.

Inorganic arsenic has been characterized as a developmental toxicant. It is known to cross the placental barrier and selectively accumulate in the neuroepithelium of the developing animal embryo (Hanlon and Ferm 1977; Lindgren et al. 1984). Studies in animals have also revealed that various fetal malformations occur after embryonic exposure to arsenic *in vitro*; neural tube defects are the predominant and consistent malformation in these studies (Chaineau et al. 1990; Mirkes and Cornel 1992; Morrissey and Mottet 1983; Mottet and Ferm 1983; Tabacova et al. 1996; Willhite and Ferm 1984; Wlodarczyk et al. 1996). *In vivo* studies have shown that high doses of ingested arsenic can produce developmental effects (fetal mortality, skeletal defects), but generally only at maternally toxic doses (Baxley et al. 1981; Holson et al. 1999, 2000; Hood and Harrison 1982; Hood et al. 1978; Nemec et al. 1998; Stump et al. 1999). A series of studies showed an increased incidence of tumors in the offspring of mice exposed to arsenic from gestational day 8 through day 18(Waalkes et al. 2003, 2004a, 2004b, 2004c, 2006a, 2006b) (see Section 3.2.2.6 for further details). In humans, acute prenatal exposure to high doses of inorganic arsenic can result in miscarriage and early neonatal death (Bolliger et al. 1992; Lugo et al. 1969). Although several studies have reported marginal associations between prolonged low-dose human arsenic exposure and adverse reproductive outcomes, including spontaneous abortion, stillbirth, developmental impairment, and congenital malformation (Ahmad et al. 2001; Aschengrau et al. 1989; Chakraborti et al. 2003c; Hopenhayn-Rich et al. 2000; Nordström et al. 1978a, 1979b; Yang et al. 2003; Zierler et al. 1988), none of these studies have provided convincing evidence for such effects or information concerning possible dose-response relationships.

There is no evidence for differences in absorption of arsenic in children and adults. Ingestion of arsenic in dirt may be an important route of exposure for young children. A study that used a synthetic gastric juice designed to mimic gastric conditions in a 2-year-old child found that absorption of arsenic from contaminated soil was likely to be up to 5 times lower than the total concentration of arsenic in the soil (Williams et al. 1998). As previously mentioned, arsenic crosses the placenta and preferentially accumulates in the embryonic neuroepithelium. In addition, arsenic is known to be present in breast milk at low concentrations. Arsenic concentrations were low in human milk sampled from 88 mothers in the Faroe Islands (0.0001–0.0044 ppm), where the diet is predominantly seafood (exposures were primarily to “fish arsenic” [Grandjean et al. 1995]), in a population of Andean women (0.0008–0.008 ppm) exposed

to high concentrations of inorganic arsenic in drinking water (Concha et al. 1998b), and in a World Health Organization survey (0.00013–0.00082 ppm) (Somogyi and Beck 1993). There is no information in the literature describing storage of arsenic in maternal tissues. There is some evidence that metabolism of arsenic in children is less efficient than in adults. Children in two villages in Argentina ingesting large amounts of arsenic in their drinking water (200 μg/L) excreted about 49% inorganic arsenic and 47% DMA, compared to 32% inorganic arsenic and 66% DMA for the women in the study (Concha et al. 1998b). No PBPK models specifically targeted at fetuses, infants, or children, or pregnant or lactating women were found in the literature. There are no biomarkers that have been specifically identified for children exposed to arsenic. In addition, no unique interactions of arsenic with other chemicals have been identified in children.

The mechanism of toxic action of arsenic in the mammalian cell may involve inhibition of proliferation of cells (Dong and Luo 1993; Jha et al. 1992; Petres et al. 1977). In addition, high-dose arsenic impairs assembly and disassembly of microtubules, thus interfering with mitotic spindle formation and embryonal cell division (Léonard and Lauwerys 1980; Li and Chou 1992; Mottet and Ferm 1983). Arsenic compounds also cause chromosomal aberrations (Jha et al. 1992; Léonard and Lauwerys 1980), which may disrupt cell cycling. The direct toxic effects of high levels of arsenic in the developing embryo result not from a difference in the mechanism of toxicity during development, but rather from the existence of a unique target tissue, the neuroepithelium. The process of neurulation involves cell shape changes, cytokinesis, and cell adhesion, which are dependent upon cytoskeletal elements that are functionally affected by arsenic (Dallaire and Béliveau 1992; Edelman 1992; Gunn et al. 1992; Li and Chou 1992; Moriss-Kay et al. 1994; Schoenwolf and Smith 1990; Taubeneck et al. 1994). However, since arsenic is known to affect vasculature, and since altered placental and/or embryonal vasculature has been suggested as a mechanism leading to neural tube defects, the embryo may be sensitive to this manifestation of arsenic toxicity.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic

substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to arsenic are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by arsenic are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Arsenic

Arsenic levels in blood, urine, hair, and nails have all been investigated and used as biological indicators of exposure to arsenic. Since arsenic is cleared from blood within a few hours (Tam et al. 1979b; Vahter 1983), measurements of blood arsenic reflect exposures only within the very recent past. Typical values in nonexposed individuals are <1 μg/L (Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al.

1979). Consumption of medicines containing arsenic is associated with blood values of 100–250 μg/L, while blood levels in acutely toxic and fatal cases may be 1,000 μg/L or higher (Driesback 1980).

However, blood levels do not appear to be reliable indicators of chronic exposure to low levels of arsenic. For example, there was no correlation between the level of arsenic in blood of residents and the level of arsenic in drinking water in several U.S. communities where water levels ranged from about 6 to 125 μg/L (Valentine et al. 1979, 1981). Consequently, measurement of blood arsenic is not generally considered to be a reliable means of monitoring human populations for arsenic exposure.

As discussed in Section 3.4.4, most arsenic that is absorbed from the lungs or the gastrointestinal tract is excreted in the urine, mainly within 1–2 days. For this reason, measurement of urinary arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure, and this approach has proved useful in identifying above-average exposures in populations living near industrial point sources of arsenic (e.g., Milham and Strong 1974; Polissar et al. 1990). By the inhalation route, several researchers have found that there is a good quantitative correlation between the concentration of arsenic in workplace air (C_{air}, $\mu g/m^3$) and the concentration in the urine (C_{urine}, μg/L) of exposed workers. For example, Pinto et al. (1976) found a linear relationship for exposures ranging up to 150 $\mu g/m^3$, given by the following equation:

$$C_{air}=0.3\ C_{urine}$$

Enterline et al. (1987a) reinvestigated this relationship over a wider range of exposures (up to 3,500 $\mu g/m^3$), and found that the curve tended to be concave upward, as given by the following equation:

$$C_{air}=0.0064\ (C_{urine})^{1.94}$$

This indicates that at higher exposure levels, a higher fraction of the dose is excreted in urine, although the toxicokinetic basis for this is not certain. Numerous studies have used above-average urinary levels (i.e., higher than about 100 μg/L) as evidence of recent arsenic ingestion (e.g., Borgoño et al. 1980; Fincher and Koerker 1987; Franzblau and Lilis 1989; Goldsmith and From 1986; Kyle and Pease 1965; Valentine et al. 1981). Calderon et al. (1999) found a quantitative correlation between the log of the mean total urinary arsenic concentration/creatinine (TAs/c, μg/mg) of people living in areas with arsenic-contaminated drinking water sources and the log of the inorganic arsenic concentration in the drinking water (InAs, μg/L). The equation for the regression line is:

$$TAs/c=10^{-2.57} \times (InAs)^{0.63}$$

where -2.57 and 0.63 are the intercept and slope, respectively, for the regression of the log10-transformed data. Mixed model regression analysis showed that the log of estimated arsenic intake from drinking water (µg/day) is also a good predictor of TAs/c excretion (Calderon et al. 1999).

There is some indication that speciation of urinary arsenic may indicate the extent of past cumulative exposure to arsenic. Hsueh et al. (1998a) reported higher levels of DMA and MMA in the urine of individuals with higher cumulative past exposure to inorganic arsenic. Speciated urinary arsenic is also a recommended biomarker for recent inorganic arsenic exposure. Walker and Griffin (1998) used the EPA Exposure Assessment Model and a number of site-specific data covering environmental and biological factors to predict total and speciated urinary arsenic concentrations for children living near high levels of arsenic-contaminated soil. There was reasonable agreement between the measured and predicted speciated urinary arsenic concentrations.

An important limitation to the use of total urinary arsenic as a biomarker of exposure is that arsenobetaine is excreted (unmetabolized) in urine after ingestion of certain seafoods (Brown et al. 1990; Kalman 1987; Tam et al. 1982). Since "fish arsenic" is essentially nontoxic, analytical methods based on total urinary arsenic content may overestimate exposures to arsenic species that are of health concern. As discussed in Section 7.1, there are adequate methods for distinguishing arsenobetaine from other forms of arsenic in urine (inorganic, MMA, DMA), although these are not convenient to use as a routine screening method.

Arsenic tends to accumulate in hair and nails, and measurement of arsenic levels in these tissues may be a useful indicator of past exposures. Normal levels in hair and nails are 1 ppm or less (Choucair and Ajax 1988; Franzblau and Lilis 1989). These values may increase from several-fold to over 100-fold following arsenic exposure (Agahian et al. 1990; Bencko 2005; Bencko et al. 1986; de Peyster and Silvers 1995; EPA 1977a, 1981b; Karagas et al. 1996; Milham and Strong 1974; Valentine et al. 1979; Yamauchi et al. 1989) and remain elevated for 6–12 months (Choucair and Ajax 1988). Minimum exposure levels that produce measurable increases in arsenic levels in hair and nails have not been precisely defined. For hair, ingestion of 50–120 ppb of arsenic in drinking water produced only a marginal effect, but a clear increase was noted at 393 ppb (Valentine et al. 1979). A study of children living in a region polluted with arsenic derived from a power plant burning coal with a high arsenic content found a significant correlation between arsenic levels in hair and distance from the source of emission (Bencko and Symon 1977).

Inhalation exposure of workers to about 0.6 μg/m^3 of arsenic in air significantly increased average levels in nails (Agahian et al. 1990), although there was wide variation between individuals.

Analysis of hair may yield misleading results due to the presence of arsenic adsorbed to the external surface, but this can be minimized by collecting samples from close to the scalp or from unexposed areas and by washing the hair before analysis (e.g., Paschal et al. 1989). Similarly, extensive washing of nails is required to remove exogenous contamination (Agahian et al. 1990). The relationship between consumption of food items and levels of arsenic in toenails has been evaluated by MacIntosh et al. (1997) using standard multivariate regression models. This approach does not appear to be highly reliable, but may be sufficient for exploring associations between diet and disease. Kurttio et al. (1998) used linear regression models to show that there is a good association between arsenic concentration in hair (mg/kg) and total arsenic concentration in urine (μg/L), arsenic concentration in drinking water (μg/L) or daily intake of arsenic (μg/day). A 10 μg/L increase in the drinking water concentration or a 10–20 μg/day increase in daily arsenic intake corresponded to a 0.1 mg/kg increase in the arsenic concentration in hair. It is also important to note that the measurement of arsenic in hair and fingernails is a process not readily accessible to many clinical offices.

3.8.2 Biomarkers Used to Characterize Effects Caused by Arsenic

As discussed in Section 3.2, the characteristic pattern of skin changes caused by arsenic (hyperkeratinization, hyperpigmentation) is probably the most sensitive and diagnostic clinical indicator of chronic exposure to arsenic. However, no means has been developed for detecting these effects except by routine dermatological examination.

Peripheral neuropathy is another characteristic effect of arsenic exposure, and several researchers have investigated decreased nerve conduction velocity or amplitude as a biomarker for peripheral neuropathy. While effects can usually be detected in individuals with clinical signs of neuropathy (e.g., Goebel et al. 1990; Jenkins 1966; Le Quesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981), effects are only marginal (EPA 1977a; Hindmarsh et al. 1977; Valentine et al. 1981) or undetectable (EPA 1981b; Kreiss et al. 1983) in exposed populations without obvious clinical signs of toxicity. This indicates that this approach is probably not sufficiently sensitive to detect neurological effects earlier than by standard neurological examination (Hindmarsh and McCurdy 1986). Also, decreases in nerve conduction velocity or amplitude are not specific for arsenic-induced neuropathy.

Arsenic is known to affect the activity of a number of enzymes, and some of these may have potential as biomarkers of effect. Most promising is the spectrum of effects caused by arsenic on the group of enzymes responsible for heme synthesis and degradation, including inhibition of coproporphyrinogen oxidase and heme synthetase (Woods and Fowler 1978; Woods and Southern 1989) and activation of heme oxygenase (Sardana et al. 1981). Menzel et al. (1998) has examined the *in vitro* induction of human lymphocyte heme oxygenase 1(HO1) as a biomarker of arsenite exposure. Arsenite did induce *de novo* synthesis of HO1 in human lymphoblastoid cells, but it has not been determined if the same response is induced *in vivo*. It has been shown in animals that these arsenic-induced enzymic changes result in increased urinary levels of uroporphyrin, coproporphyrin, and bilirubin (Albores et al. 1989; Woods and Fowler 1978), and it has been shown that these effects can be detected in the urine of arsenic-exposed humans (García-Vargas and Hernández-Zavala 1996). Therefore, altered urinary levels of these heme-related compounds could serve as a biomarker of effect. However, it is known that numerous other toxic metals also have similar effects on heme metabolism (Albores et al. 1989; Sardana et al. 1981; Woods and Southern 1989), so it is likely that these effects would not be specific for arsenic.

For more information on biomarkers for renal and hepatic effects of chemicals, see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (Agency for Toxic Substances and Disease Registry 1990b) and for information on biomarkers for neurological effects, see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

A number of researchers have found that arsenic compounds tend to reduce the effects of selenium (Hill 1975; Howell and Hill 1978; Kraus and Ganther 1989; Levander 1977; Miyazaki et al. 2003; Moxon et al. 1945; Schrauzer 1987; Schrauzer et al. 1978). Likewise, selenium can decrease the effects of arsenic, including clastogenicity (Beckman and Nordenson 1986; Biswas et al. 1999; Sweins 1983), delayed mutagenesis (Rossman and Uddin 2004), cocarcinogenesis (Uddin et al. 2005), cytotoxicity (Babich et al. 1989; Rössner et al. 1977; Styblo and Thomas 2001), and teratogenicity (Holmberg and Ferm 1969). The mechanism of this mutual inhibition of effects is not known, but may be related to the formation of a selenium-arsenic complex (seleno-bis [S-gluthionyl] arsinium ion; Gailer et al. 2002) that is excreted more rapidly than either arsenic or selenium alone (Cikrt et al. 1988; Hill 1975; Levander 1977; Levander and Baumann 1966) or due to selenium-induced changes in arsenic methylation (Styblo and Thomas 2001; Walton et al. 2003). There is little direct evidence that variations in selenium exposure in humans lead to significant increases or decreases in arsenic toxicity, although copper smelter workers who developed lung cancer had lower tissue levels of selenium than workers who did not develop lung tumors

(Gerhardsson et al. 1985, 1988). This suggests that selenium deficiency could significantly increase the risk of lung cancer following inhalation exposure to arsenic, but it is difficult to distinguish cause from effect in such a study. However, there is evidence that administration of selene can facilitate recovery from arsenic poisoning. In residents living in an area of Inner Mongolia with high levels of arsenic in drinking water, administration of 100–200 μg selenium/day in the form of selenium yeast and exposure to arsenic-free water for 14 months resulted in a greater improvement in clinical signs and symptoms, liver function, and EKG readings as compared to residents administered arsenic-free water only (Wuyi et al. 2001; Yang et al. 2002). An improvement in skin lesions was observed in 67 and 21% of the subjects in the selenium-supplemented and control groups (Yang et al. 2002). Additionally, the levels of arsenic in blood, hair, and urine were significantly lower after the 14-month period only in the selenium supplemented group.

The interaction between cigarette smoking, inhalation of arsenic, and the risk of lung cancer has not been extensively investigated. Smoking appeared to increase lung cancer risk synergistically (multiplicatively) in one study of smelter workers (Pershagen et al. 1981), although the data are not adequate to exclude a simple additive interaction (Thomas and Whittemore 1988). Cigarette smoking has been shown to increase the occurrence of lung cancer in people with high levels of arsenic in the drinking water (Chiou et al. 1995; Tsuda et al. 1995a). Suggestive evidence of a positive interaction between arsenic and benzo(a)pyrene has also been noted for induction of lung adenocarcinomas in hamsters (Pershagen et al. 1984).

Co-exposure to ethanol and arsenic may exacerbate the toxic effects of arsenic. Simultaneous exposure of rats to ethanol (10% in drinking water) and arsenic (dose not stated) for 6 weeks produced a significant increase in the concentration of arsenic in the kidney, a nonsignificant increase of arsenic in the liver and a significant increase in the concentration of glutathione in the liver, compared to rats treated with either ethanol or arsenic alone (Flora et al. 1997a, 1997b). Histological damage to the liver, but not the kidneys, was increased in rats treated with both ethanol and arsenic compared to those receiving only arsenic.

Studies of rats exposed to arsenic, lead, and cadmium, alone or in combination, have revealed mainly additive or subadditive effects on body weight, hematological parameters, and enzymes of heme synthesis (Mahaffey and Fowler 1977; Mahaffey et al. 1981). Similarly, studies of the tissue levels of arsenic in rats fed arsenic with or without lead or cadmium revealed only limited evidence of any toxicokinetic interactions (Mahaffey et al. 1981). Pretreatment of rats with a nontoxic dose of cadmium had no effect on the lethality of a high dose of arsenic and did not reduce arsenic-induced hepatotoxicity (Hochadel and

Waalkes 1997). These data do not suggest that arsenic toxicity is likely to be significantly influenced by concomitant exposure to these metals. However, supplementation with zinc or chromium may be useful in reducing chronic arsenism. Arsenic has been shown to cause an increase in total plasma cholesterol; co-administration of chromium(III) counteracts this effect (Aguilar et al. 1997). Pretreatment of mice with zinc, at least 24 hours before injection with arsenic-73, reduced arsenic retention compared to controls that did not receive the zinc pretreatment or received it only a short time before the administration of arsenic (Kreppel et al. 1994). Zinc is an inducer of metallothionein, but this induction does not appear to be the mechanism that reduces arsenic toxicity because other inducers of metallothionein did not reduce arsenic toxicity and arsenic elimination was increased by the zinc pretreatment.

Since methylation of arsenic is a detoxification mechanism, it is possible that chemicals that interfere with the methylation process could increase toxicity. This is supported by studies in animals in which reagents that inhibit methylation enzymes (e.g., periodate-oxidized adenosine) caused an increase in tissue levels of inorganic arsenic (Marafante and Vahter 1986; Marafante et al. 1985). Similarly, cellular glutathione levels appear to play a role in the methylation process, and treatment with reagents (e.g., phorone) that decrease glutathione levels increases arsenic toxicity (Buchet and Lauwerys 1987). Inadequate dietary intake of methionine, choline, or protein may also exacerbate arsenic toxicity. Rabbits pretreated with diets low in choline, methionine, or protein showed a significant increase in tissue retention of arsenic and a significant decrease in the excretion of dimethylarsinic acid (Vahter and Marafante 1987). The increased retention of arsenic in rabbits fed these deficient diets is likely to be due to a reduction in arsenic methylation. Thus, the toxic effects of chronic arsenic ingestion may be increased in populations that are also subject to malnutrition.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to arsenic than will most persons exposed to the same level of arsenic in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of arsenic, or compromised function of organs affected by arsenic. Populations who are at greater risk due to their unusually high exposure to arsenic are discussed in Section 6.7, Populations with Potentially High Exposures.

No studies were located that identified an unusual susceptibility of any human subpopulation to arsenic. Several studies have evaluated possible sex-related differences in arsenic toxicity and carcinogenesis (Aposhian et al. 2000a, 2000b; Calderon et al. 1999; Loffredo et al. 2003; Mandal et al. 2001; Watanabe et al. 2001), but have not consistently identified differences. However, since the degree of arsenic toxicity may be influenced by the rate and extent of its methylation in the liver (see Section 3.4.3), it seems likely that some members of the population might be especially susceptible because of lower than normal methylating capacity. Studies of exposed humans in Taiwan suggested that subjects with lower secondary methylation indices have an increased risk of bladder cancer (Chen et al. 2003) and peripheral vascular disease (Tseng et al. 2005), particularly in subjects with high exposure levels. Reduced hepatic methylation could result from dietary deficiency of methyl donors such as choline or methionine (Buchet and Lauwerys 1987; Vahter and Marafante 1987), although this is unlikely to be a concern for most people in the United States. There is evidence that methylation capacity can vary greatly among individuals (e.g., Buchet et al. 1981a; Foà et al. 1984; Hopenhayn-Rich et al. 1996b; Tam et al. 1979b), but the basis of this variation and its impact on human susceptibility have not been fully established. There is some evidence that low dietary protein intake and possibly other nutritional deficiencies can decrease arsenic methylation (Steinmaus et al. 2005a). Recently, Heck et al. (2007) examined whether the capacity to methylate arsenic differs by nutrient intake in a cohort of 1,016 Bangladeshi adults exposed to arsenic in drinking water. The results showed that higher intakes of cysteine, methionine, calcium, protein, and vitamin B-12 were associated with lower percentages of inorganic arsenic and higher ratios of MMA to inorganic arsenic in urine. In addition, higher intakes of niacin and choline were associated with higher DMA/MMA ratios, after adjustment for sex, age, smoking, total urinary arsenic, and total energy intake. The issue of increased susceptibility to arsenic due to poor nutrition was discussed by NRC (2001), it was concluded that, with regard to skin effects, studies of cohorts from India, Bangladesh, and Taiwan suggest that nutrition plays an important role in arsenic toxicity. On the other hand, studies in other regions of the world (i.e., Chile) involving populations with much better nutrition argue against poor nutrition having a major impact on arsenic toxicity.

Various genetic polymorphisms also seem to play a role in arsenic-induced toxicity. For example, a study of 85 lung cancer patients and 108 healthy controls in northern Chile reported that there was a nonstatistically significant difference for the frequency of the GSTM1 null genotype between the healthy and lung cancer patients stratified by gender and smoking status. The same results were observed for the MspI CYP450 1A1 polymorphism (Adonis et al. 2005). Hsueh et al. (2005) examined the association of four polymorphisms: NAD(P)H oxidase, manganese superoxide dismutase (MnSOD), catalase, and endothelial nitric oxide synthase (eNOS) with arsenic related hypertension risk among 79 hypertensive

cases and 213 controls in an arseniasis-hyperendemic area in Taiwan. The results showed that MnSOD polymorphism significantly increased the risk of hypertension regardless of exposure to arsenic. NAD(P)H oxidase and eNOS polymorphisms were significantly associated with increased risk of hypertension in subjects with higher cumulative arsenic exposure (≥10.5 mg/L x year), whereas catalase polymorphism was not associated with hypertension. The results also showed that the association between MnSOD, NAD(P)H oxidase, and eNOS polymorphisms and risk of hypertension were more pronounced in subjects with high triglyceride level. A study of a population of West Bengal, India, exposed to arsenic via drinking water reported that the frequencies of null genotype in GSTT1 were 13.52 and 12.92% in skin-symptomatic and skin-asymptomatic individuals, and GSTM1 null genotype were 13.90 and 22.47% in skin-symptomatic and skin-asymptomatic individuals, respectively (Ghosh et al. 2006). Compared to those with GSTM1 null genotype, subjects with GST1-positive (at least one allele) had significantly higher risk of arsenic-induced skin lesions. Recently, Steinmaus et al. (2007) investigated urinary arsenic methylation patterns and genetic polymorphisms in methylenetetrahydro-folate reductase (MTHFR) and GST in 170 subjects (139 males) from an arsenic-exposed region in Argentina. MTHFR is a key enzyme in the metabolism of folate and has been linked to arsenic metabolism and toxicity (NRC 1999). Steinmaus et al. (2007) found that subjects with the TT/AA variant of MTHFR 677/1298 (associated with lower MTHFR activity) excreted a significantly higher proportion on ingested arsenic as inorganic arsenic and a smaller proportion as DMA(V). The study also reported that women with null genotype of GSTM1 excreted a significantly higher proportion of arsenic as monomethylarsenate than women with the active genotype. The study also found no association between polymorphisms in GSTT1 and arsenic methylation.

There is a report that described severe arsenic-induced neuropathy that developed only in a 5,10-methylenetetrahydrofolate-reductase (MTHFR) deficient member of a family that had been exposed to arsenic (Brouwer et al. 1992). The authors suggest that the MTHFR deficiency in this girl might explain the fact that of all the family members exposed to arsenic, only she developed severe clinical signs of arsenic poisoning. Liver disease does not appear to decrease methylation capacity in humans, at least at low levels of arsenic exposure (Buchet et al. 1982; Geubel et al. 1988).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to arsenic. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to arsenic. When specific

exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to arsenic:

Tintinalli JE, Ruiz E, Krone RL, eds. 1996. Emergency medicine. A comprehensive study. American College of Emergency Physicians. 4th ed. New York, NY: The McGraw-Hill Companies, Inc.

Goldfrank RL, Flomenbaum NE, Lewin NA, et al., eds. 1998. Goldfrank's toxicologic emergencies. 6th ed. Stamford, CT: Appleton and Lange.

Ellenhorn MJ. 1997. Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning. Baltimore, MD: Williams & Wilkins.

3.11.1 Reducing Peak Absorption Following Exposure

No data were located regarding the reduction of absorption after inhalation exposure to arsenic.

There are a number of methods for reducing absorption of arsenic following oral exposure. In cases of acute high-dose exposure, the removal of arsenic from the gastrointestinal tract may be facilitated by gastric lavage, stomach intubation, induced emesis, or use of cathartics (saline, sorbitol) within a few hours after ingestion (Agency for Toxic Substances and Disease Registry 1990a; Aposhian and Aposhian 1989; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barceloux 1988; EPA 1989e; Haddad and Winchester 1990; Kamijo et al. 1998; Stutz and Janusz 1988). However, the efficacy of several of these methods has been questioned by some authors, and in some cases, the treatments may be contraindicated. For example, vomiting and diarrhea often occur soon after ingesting arsenic, and therefore, use of an emetic or cathartic may not be necessary. Also, emesis should not be induced in obtunded, comatose, or convulsing patients (Campbell and Alvarez 1989; Ellenhorn and Barceloux 1988; EPA 1989e), and saline cathartics should be used with caution in patients with impaired renal function (Campbell and Alvarez 1989). Vantroyen et al. (2004) described a case of a massive arsenic trioxide overdose that was successfully treated by continuous gastric irrigation with sodium bicarbonate, forced diuresis, and administration of BAL and DMSA. Treatments of this sort are unlikely to be required following low-level exposures.

Another possible approach for reducing absorption following oral exposure is to administer substances that bind the arsenic in the gastrointestinal tract. For example, activated charcoal is sometimes used for this purpose (Campbell and Alvarez 1989; EPA 1989e; Stutz and Janusz 1988), although the effectiveness of this treatment is not well established. Because pentavalent arsenic is a phosphate analogue,

administration of phosphate-binding substance such as aluminum hydroxide might possibly be useful, but this has not been investigated. Sulfhydryl compounds might be given to bind trivalent arsenic, but it seems unlikely that these would be effective under the acid conditions in the stomach, and it is not clear that such complexes would have reduced gastrointestinal absorption.

Following dermal or ocular exposure to arsenic, several measures can be taken to minimize absorption. All contaminated clothing should be removed, and contacted skin should be immediately washed with soap and water. Eyes that have come in contact with arsenic should be flushed with copious amounts of clean water (EPA 1989e; Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

Acute arsenic intoxication may require treatment with chelating agents such as dimercaprol (BAL) and D-penicillamine. Although body burden is not necessarily reduced, these chelators bind free arsenic and serve to reduce the body's pool of biologically active arsenic. Chelation therapy is most effective when instituted within a few hours after exposure, and efficacy decreases as time after exposure increases (Agency for Toxic Substances and Disease Registry 1990a; Kamijo et al. 1998; McFall et al. 1998; Peterson and Rumack 1977).

In general, chelating agents should be used with caution, since they may have serious side effects such as pain, fever, hypotension, and nephrotoxicity (Ellenhorn and Barceloux 1988). Some water-soluble and less toxic analogues of BAL such as dimercaptosuccinic acid (DMSA), dimercaptopropyl phthalamadic acid (DMPA), and dimercaptopropane sulfonic acid (DMPS) are currently under investigation and may prove to be promising treatments for arsenic poisoning (Agency for Toxic Substances and Disease Registry 1990a; Aposhian and Aposhian 1989; Aposhian et al. 1997; Guha Mazumder 1996; Kreppel et al. 1995). However, a randomized placebo trial of 2,3-dimercaptosuccinic acid as a therapy for chronic arsenosis due to drinking contaminated water found no significant difference between patients treated with 2,3-dimercaptosuccinic acid and those treated with a placebo (Guha Mazumder et al. 1998a). N-acetylcysteine has been used in animals to chelate arsenic (Haddad and Winchester 1990), and a human case study reported N-acetylcysteine to be successful in treating a case of arsenic poisoning that was not responding well to BAL treatment (Martin et al. 1990). Vantroyen et al. (2004) described a case of a massive arsenic trioxide overdose that was successfully treated by continuous gastric irrigation with sodium bicarbonate, forced diuresis, and administration of BAL and DMSA.

As discussed in Section 3.4.3, once arsenic has been absorbed into the blood stream, it undergoes methylation to yield MMA and DMA. These forms of arsenic are less toxic than inorganic arsenic and are cleared from the body by excretion in the urine. Therefore, if it were possible to enhance arsenic methylation, both body burden and toxicity of arsenic might be reduced. However, experimental evidence in animals and humans suggests that arsenic methylation is not enhanced to any significant degree by supplementation with methylation cofactors (Buchet and Lauwerys 1987; Buchet et al. 1982), presumably because it is enzyme level and not cofactor availability that is rate limiting in arsenic methylation.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

It is generally thought that trivalent arsenic exerts its toxic effects mainly by complexing with sulfhydryl groups in key enzymes within the body, thereby inhibiting critical functions such as gluconeogenesis and DNA repair (Aposhian and Aposhian 1989; Li and Rossman 1989). Therefore, administration of sulfhydryl-containing compounds soon after exposure could provide alternative target molecules for arsenic, and prevent inhibition of enzyme functions. In fact, many of the chelating agents discussed above (BAL, DMSA, DMPA, DMPS, N-acetylcysteine) contain sulfhydryl groups, and this may account for their efficacy.

The mechanism by which pentavalent arsenic acts is less certain. Since pentavalent arsenic is reduced in the body to the trivalent state, pentavalent arsenic may act in a similar manner as described above for trivalent arsenic. If this is the case, efforts to inhibit the reduction of pentavalent arsenic would decrease its toxicity. However, no methods are currently recognized for blocking this reduction. Pentavalent arsenic may also exert effects by acting as a phosphate analogue. As a phosphate analogue, pentavalent arsenic could potentially affect a number of biological processes, including ATP production, bone formation, and DNA synthesis. However, any effort to interfere in normal phosphate metabolism could produce serious side effects, and no method is known for selectively interfering with arsenate metabolism.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the

initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of arsenic.

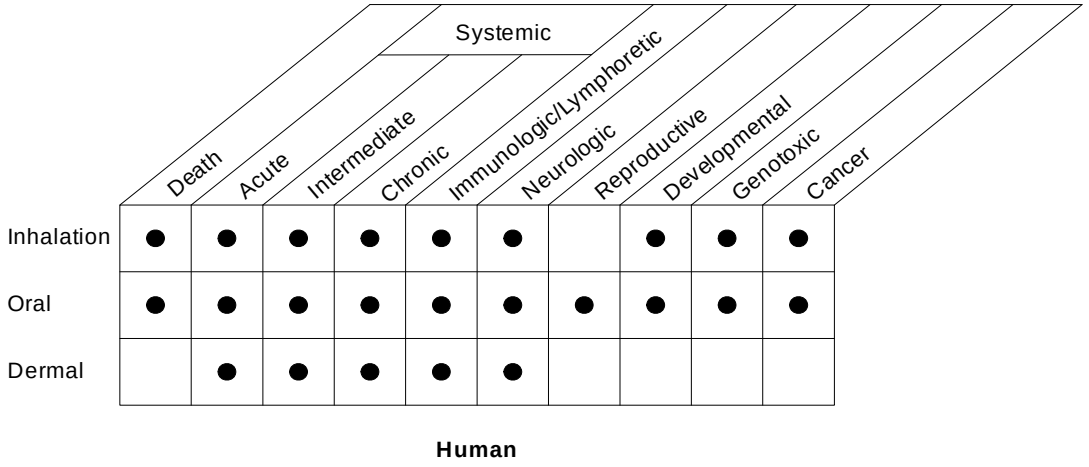
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Arsenic

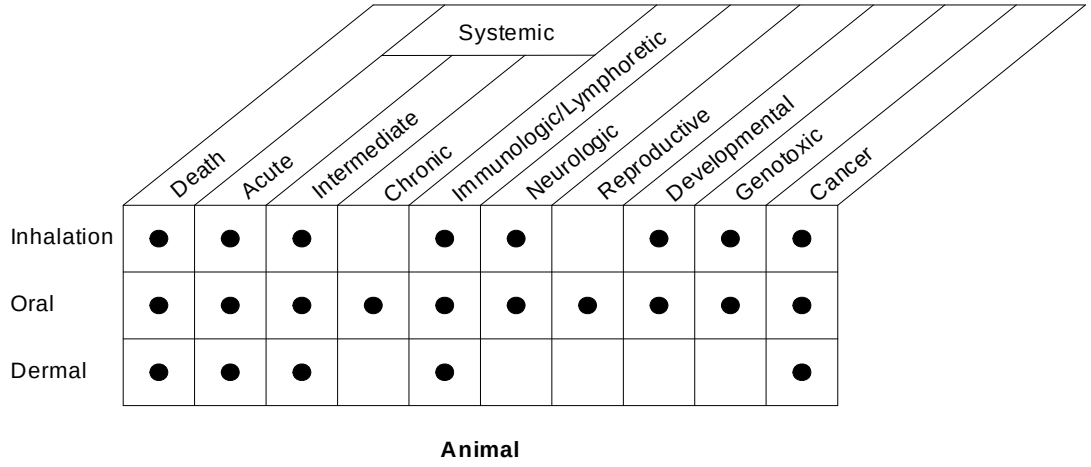
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to inorganic and organic arsenic are summarized in Figures 3-13 and 3-14, respectively. The purpose of this figure is to illustrate the existing information concerning the health effects of arsenic. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As shown in Figure 3-13, there is a substantial database on the toxicity of inorganic arsenicals, both in humans and in animals. The oral route has been most thoroughly investigated, and reports are available on most end points of concern following acute, intermediate, and chronic exposure. The inhalation route has also been studied extensively, mainly in humans, with special emphasis on lung cancer. A number of noncancer end points have also been studied following inhalation exposure, but information on these effects is less extensive. Limited information on the effects of dermal exposure is also available in both humans and animals, focusing mainly on direct irritancy and dermal sensitization reactions. The absence of studies on other effects of inorganic arsenic following dermal exposure is probably not a critical data need, since dermal uptake of inorganic arsenic appears to be sufficiently limited that other routes of exposure (oral or inhalation) would almost always be expected to be of greater concern.

Figure 3-13. Existing Information on Health Effects of Inorganic Arsenic



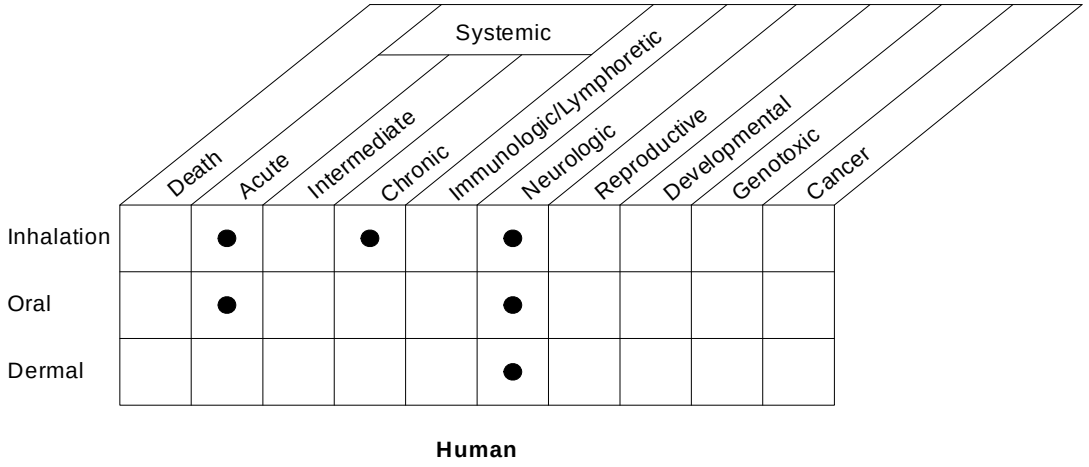
Human



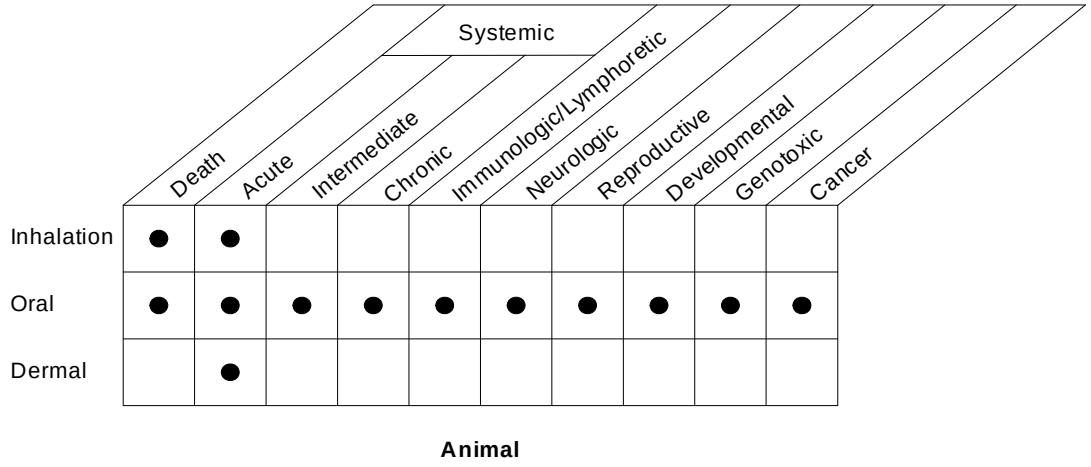
Animal

● Existing Studies

Figure 3-14. Existing Information on Health Effects of Organic Arsenic



Human



Animal

● Existing Studies

As shown in Figure 3-14, very little information is available on the effects of organic arsenic compounds in humans, although there are a number of studies in animals. These studies mainly involve the oral route, since all of these compounds are nonvolatile solids, although a few acute inhalation studies have been performed. Limited information is available on acute dermal lethality and dermal irritancy of some organic arsenicals, but data are lacking on other effects of organic arsenicals following dermal exposure. As discussed previously, in evaluating the adequacy of the database on arsenic, it is important to keep in mind that most studies in animals indicate that they are quantitatively less sensitive to arsenic than humans. For this reason, data from animal studies should be used to draw inferences about effects in humans only with caution.

3.12.2 Identification of Data Needs

Acute-Duration Exposure.

Inorganic Arsenicals. There is only limited information on the effects of acute inhalation exposure to arsenic in humans, but the chief symptoms appear to be irritation of the respiratory and gastrointestinal tracts (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Dunlap 1921; Ide and Bullough 1988; Morton and Caron 1989; Pinto and McGill 1953). Quantitative data are lacking, but effects generally appear to be mild even at high-exposure levels. On this basis, it seems that risks of acute effects are probably low for inhalation exposures in the environment or near waste sites. Research to obtain a quantitative acute inhalation NOAEL value that could be used to derive an acute inhalation MRL would, therefore, be useful but not critical. There are numerous case studies in humans on the acute oral toxicity of arsenic, and the main end points (gastrointestinal irritation, pancytopenia, hepatic injury, neuropathy) are well characterized (Armstrong et al. 1984; Fincher and Koerker 1987). An acute oral MRL of 0.005 mg As/kg/day was derived for inorganic arsenic based on a LOAEL for gastrointestinal symptoms and facial edema reported by Mizuta et al. (1956). Additional studies to define an acute oral NOAEL would be useful to reduce uncertainty in the MRL derivation. Acute dermal exposure is unlikely to cause serious systemic injury, but it can lead to contact dermatitis and skin sensitization (Holmqvist 1951; Pinto and McGill 1953). However, available data do not permit a quantitative estimate of the concentration of arsenic on the skin or in air, dust, soil, or water that causes these effects. Further research would be valuable to obtain a quantitative NOAEL for direct dermal effects, since humans may have dermal contact with contaminated soil or water near hazardous waste sites.

Organic Arsenicals. Information on the acute toxicity of organic arsenicals in humans is limited to reports of gastrointestinal irritation in individuals ingesting pesticides containing organic arsenicals (Lee et al. 1995; Shum et al. 1995); these case reports provide limited dosing information. Acute lethality and systemic toxicity data exist for several compounds by inhalation, oral, and dermal exposure of animals. Inhalation data are limited to a lethality study of rats and mice exposed to MMA or DMA that reported respiratory and ocular irritation (Stevens et al. 1979). The oral acute studies consist of lethality studies for MMA (Gur and Nyska 1990; Jaghabir et al. 1988; Kaise et al. 1989), DMA (Kaise et al. 1989), and roxarsone (Kerr et al. 1963; NTP 1989b), systemic toxicity studies (or longer-term studies reporting effects within the first 2 weeks of exposure) for MMA (Irvine et al. 2006), DMA (Ahmad et al. 1999a; Chernoff et al. 1990; Cohen et al. 2001; Crown et al. 1987; Irvine et al. 2006; Kavlock et al. 1985; Rogers et al. 1981; Zomber et al. 1989), or roxarsone (NTP 1989b). For MMA, the available data suggest that the gastrointestinal tract may be the most sensitive target of toxicity; however, the study identifying the lowest LOAEL (Irvine et al. 2006) involved bolus administration and this is not an appropriate exposure route to estimate human risk for gastrointestinal effects following environmental exposure to MMA. The available animal studies for DMA have examined urinary bladder (Cohen et al. 2001) and developmental toxicity (Chernoff et al. 1990, Irvine et al. 2006; Kavlock et al. 1985; Rogers et al. 1981). For DMA, acute-duration studies in rats suggest that the urinary bladder is the most sensitive target of toxicity in rats (Cohen et al. 2001); however, there is evidence from longer-term studies that rats may be more sensitive than humans and other species for bladder effects. Thus, rat data were not considered as the basis of an acute-duration oral MRL for DMA. Other effects observed following acute exposure to DMA include developmental and maternal effects in mice (Kavlock et al. 1985; Rogers et al. 1981) and rabbits (Irvine et al. 2006) and diarrhea and vomiting in dogs receiving a bolus dose of DMA (Zomber et al. 1989). An acute-duration oral MRL was not derived for DMA because it is not known if systemic effects would occur at lower doses than the developmental effects. For roxarsone, the available data suggest that the most sensitive effect following acute oral exposure is neuropathy observed in pigs (Kennedy et al. 1986; Rice et al. 1985). At the only dose tested in this study, tremors, clonic convulsions, and equivocal evidence of myelin degeneration were observed; these were considered serious effects and not suitable for the derivation of an acute-duration oral MRL for roxarsone. Additional studies are needed for MMA, DMA, and roxarsone that examine a variety of end points in several species; studies for roxarsone should also include examination of neurological end points, which would be useful for identifying the critical targets of toxicity and establishing dose-response relationships.

Intermediate-Duration Exposure.

Inorganic Arsenicals. Intermediate-duration inhalation exposure of humans to arsenic appears to result in respiratory tract irritation (occasionally including perforation of the nasal septum) and mild gastrointestinal tract irritation (Ide and Bullough 1988). Quantitative data are too limited (only one study, of one individual) to derive an intermediate-duration inhalation MRL. Further studies to define the NOAEL for intermediate-duration inhalation exposure of humans would be valuable, since humans could be exposed to arsenic-containing airborne dusts near smelters, chemical plants, or waste sites. Effects of intermediate-duration oral exposure are similar to those of acute oral exposure, but may also include development of vascular injury and a characteristic group of skin changes (Franzblau and Lilis 1989; Holland 1904; Wagner et al. 1979). Most studies indicate that these effects occur at doses of about 0.05 mg As/kg/day or higher, but the data do not provide a firm basis for identifying the intermediate-duration NOAEL. For this reason, no intermediate-duration oral MRL has been derived. Further studies to establish the NOAEL would be valuable, since humans could have intermediate-duration oral exposures to arsenic through ingestion of contaminated soil or water near smelters, chemical factories, or waste sites. Since dermal effects appear to be restricted to acute irritancy, intermediate-duration dermal studies are probably not essential.

Organic Arsenicals. No information was located on the intermediate-duration toxicity of organic arsenicals in humans. Several studies have examined the intermediate-duration oral toxicity of MMA; dietary exposure studies in rats and mice (Arnold et al. 2003) identify the gastrointestinal tract as the most sensitive target. Diarrhea and lesions in the cecum, colon, and rectum have been observed. The rat 13-week study (Arnold et al. 2003) was used as the basis of the MRL. Because rats appear to be more sensitive to the toxicity of DMA, rat studies were not considered for MRL derivation. The only non-rat study was a chronic-duration dog study reporting effects during the first 51 weeks of exposure (Zomber et al. 1989); these effects included diarrhea and vomiting. However, because DMA was administered via capsule, this study was not considered adequate for derivation of an MRL. Additional studies are needed for DMA to identify critical targets of toxicity and establish dose-response relationships in non-rat species. The available data for roxarsone suggest that neurotoxicity in pigs is the most sensitive end point. One of the two available neurotoxicity studies in pigs (Edmonds and Baker 1986) did not include sensitive tests of toxicity and was not considered for MRL derivation; the other study identified a serious LOAEL at the only dose tested and thus, was not suitable for MRL derivation. Several comprehensive studies examined the toxicity of roxarsone in rats and mice (NTP 1989b). Renal tubular damage in rats was the most sensitive end point (NTP 1989b); however, the LOAEL for this effect was 9 times higher

than the dose associated with neurotoxicity in pigs. Additional studies are needed to establish a no effect level for neurotoxicity in pigs, which could be used to derive an intermediate duration MRL for roxarsone. Further studies on the intermediate-duration inhalation and dermal toxicity of these compounds would be valuable, especially in humans, since people may be exposed to organic arsenicals during their manufacture or use, or from materials deposited in waste sites.

Chronic-Duration Exposure and Cancer.

Inorganic Arsenicals. The target tissues of chronic-duration exposure of humans to inorganic arsenic are the same as for intermediate-duration exposure for both the oral and inhalation routes. Effects of dermal exposure appear to be restricted to direct irritation of exposed surfaces. Therefore, chronic-duration studies are probably not essential for the dermal route. Quantitative data from one study identify an inhalation exposure level of about 0.1 mg As/m^3 as the LOAEL for skin changes (Perry et al. 1948), but because there are no additional supporting studies and a NOAEL is not clearly established, a chronic-duration inhalation MRL has not been derived. Additional studies in humans to define the chronic inhalation NOAEL for dermal or other effects would be valuable, since humans may be chronically exposed to arsenic dusts in air near smelters, chemical factories, or waste sites. Chronic oral exposure data from studies in humans indicate that the LOAEL for skin lesions and other effects is probably about 0.01–0.02 mg As/kg/day (10–20 μg As/kg/day), and that the NOAEL is probably between 0.0004 and 0.0009 mg As/kg/day (0.4–0.9 μg As/kg/day) (Cebrián et al. 1983; EPA 1981b; Hindmarsh et al. 1977; Tseng 1977; Tseng et al. 1968). The NOAEL of 0.0008 mg As/kg/day from the study by Tseng et al. (1968) is appropriate for derivation of a chronic-duration oral MRL, but an uncertainty factor of 3 was required to account for the fact that the population that constituted the no-effect group were relatively young (possibly decreasing the ability to detect dermal or other effects that increase in prevalence with age). Another issue that needs to be acknowledged, which is common to ecological studies and contributes to uncertainty, is the fact that individual doses were not available and were calculated from group mean arsenic concentrations in well water using estimated water intake parameters. For this reason, further epidemiological studies that do not rely on an ecological-based exposure assessment that would provide additional support for the threshold dose for arsenic in humans would be valuable.

There are numerous studies in humans that support the carcinogenic effects of inorganic arsenic from inhalation exposure (Enterline et al. 1987a, 1987b, 1995; Järup and Pershagen 1991; Järup et al. 1989; Lee-Feldstein 1986; Welch et al. 1982) and oral exposure (Chen et al. 1986, 1988b, 1992; Chiou et al. 1995; Ferreccio et al. 1996; Hsueh et al. 1995; Lander et al. 1975; Liu and Chen 1996; Lüchtrath 1983;

Smith et al. 1992; Tseng 1977; Tseng et al. 1968; Yu et al. 1992; Zaldívar 1974; Zaldívar et al. 1981). Quantitative slope factors have been derived for both routes. There is a noticeable absence, however, of 2-year animal carcinogenicity studies for either the inhalation or oral route of exposure (Chan and Huff 1997). In light of the ongoing controversy over the reasons for the absence of a carcinogenic effect in animals, it seems prudent to firmly establish a negative effect in a 2-year study. The carcinogenic effects of chronic dermal exposure to inorganic arsenicals have not been studied, but dermal exposure is a relatively minor route of exposure, and these studies would not be a top priority.

The mechanism of arsenic carcinogenicity is not known, although the current view is that it functions mainly as a promoter or cocarcinogen. Further studies on the mechanism of arsenic toxicity would be particularly valuable to improve our ability to evaluate human cancer risks from inhalation or oral exposures that might occur near waste sites. Also, mechanistic studies could help in the evaluation of cancer risks from organic derivatives (see below).

Organic Arsenicals. There is very little information on the chronic toxicity of organic arsenicals in humans. One study of workers exposed to arsanilic acid did not identify any adverse effects, but no systematic, clinical, or toxicological examinations of exposed people were performed (Watrous and McCaughey 1945). Chronic toxicity studies are available for rats, mice, and dogs exposed to MMA (Arnold et al. 2003; Waner and Nyska 1988), DMA (Arnold et al. 2006; Zomber et al. 1989), and roxarsone (NTP 1989b; Prier et al. 1963). Chronic exposure to MMA results in diarrhea in rats, mice, and dogs (Arnold et al. 2003; Waner and Nyska 1988) and an increase in progressive nephropathy in rats and mice (Arnold et al. 2003). The increased incidence of progressive nephropathy was used as the basis of the chronic-duration oral MRL for MMA. For DMA, chronic exposure also resulted in an increased incidence of diarrhea and vomiting in dogs (Zomber et al. 1989) and an increased incidence of vacuolization in the urinary bladder and progressive nephropathy in mice (Arnold et al. 2006). The vacuolization in the urinary bladder was used as the basis of a chronic-duration oral MRL for DMA. The available data for chronic-exposure to roxarsone were considered inadequate for derivation of an MRL. The highest doses tested in the rat, mouse, and dog studies (NTP 1989b; Prier et al. 1963) were NOAELs. Intermediate-duration studies identify neurotoxicity in pigs as the most sensitive end point; this has not been adequately examined following chronic exposure and studies are needed.

No information was located on carcinogenic effects of organic arsenicals in humans. The carcinogenic potential of MMA (Arnold et al. 2003), DMA (Arnold et al. 2006), and roxarsone (NTP 1989b) following oral exposure has been investigated in rats and mice. No evidence of carcinogenicity was observed

following oral exposure to MMA (Arnold et al. 2003) and equivocal evidence of carcinogenicity was found in male rats, with no evidence of carcinogenicity in female rats or in male or female mice orally exposed to roxarsone (NTP 1989b). Oral exposure to DMA resulted in an increased incidence of urinary bladder tumors in rats and no evidence of carcinogenicity in mice (Arnold et al. 2006). However, there is concern that the rat is not a good model to assess the carcinogenic potential of DMA in humans due to species differences in the toxicokinetic properties of DMA. No information was located on the carcinogenicity of organic arsenicals following inhalation or dermal exposure. Studies of humans exposed in the workplace would provide valuable information on the carcinogenic potential of organic arsenicals, particularly DMA. Studies on cancer risk following inhalation and dermal exposure to organic arsenicals are would be useful since these are possible routes of exposure for humans.

Genotoxicity.

Inorganic Arsenicals. There are several studies that suggest that inorganic arsenic may cause genotoxicity (mainly chromosomal effects) in exposed humans (Burgdorf et al. 1977; Nordenson et al. 1978), and this is supported by numerous studies in animals (Datta et al. 1986; DeKnudt et al. 1986; Nagymajtényi et al. 1985) and cultured cells (Beckman and Nordenson 1986; Casto et al. 1979; DiPaolo and Casto 1979; Lee et al. 1985; Nakamuro and Sayato 1981; Nishioka 1975; Oberly et al. 1982; Okui and Fujiwara 1986; Sweins 1983; Ulitzur and Barak 1988; Zanzoni and Jung 1980). The mechanism of genotoxicity is not known, but may be due to the ability of arsenite to interfere with DNA repair (Li and Rossman 1989) or to alter apoptosis (Pi et al. 2005) or the ability of arsenate to act as a phosphate analog. Further studies to improve our understanding of the mechanism of genotoxicity would be valuable, since this could aid in the understanding of arsenic-induced cancer risk.

Organic Arsenicals. For organic arsenicals, *in vitro* genotoxicity studies are available for arsenobetaine (Eguchi et al. 1997; Oya-Ohta et al. 1996), MMA (Chun and Killeen 1989a, 1989b, 1989c, 1989d; Eguchi et al. 1997; Oya-Ohta et al. 1996), DMA (Eguchi et al. 1997; Endo et al. 1992; Kato et al. 1994; Kawaguchi et al. 1996; Kitamura et al. 2002; Kuroda et al. 2004; Moore et al. 1997a; Oya-Ohta et al. 1996; Rasmussen and Menzel 1997; Rin et al. 1995; Tezuka et al. 1993; Ueda et al. 1997; Yamanaka et al. 1989b, 1993, 1995, 1997), and roxarsone (Matthews et al. 1993; NTP 1989b; Storer et al. 1996) and *in vivo* studies are available for DMA (Kashiwada et al. 1998; Yamanaka and Okada 1994; Yamanaka et al. 1989a, 1989b, 1993, 2001). The results of these studies suggest that DMA and roxarsone are clastogenic and can cause DNA strand breaks. Additional *in vivo* studies are needed to evaluate the genotoxic potential of MMA and roxarsone.

Reproductive Toxicity.

Inorganic Arsenicals. Several studies have examined reproductive function in populations living in Bangladesh or India exposed to high levels of arsenic in drinking water and found increases in spontaneous abortions/stillbirths or preterm births (Ahmad et al. 2001; von Ehrenstein et al. 2006); another study in U.S. women did not find an increase in adverse reproductive outcomes (Aschengrau et al. 1989). Available animal studies did not find evidence for reproductive effects following inhalation or oral exposure (Holson et al. 1999, 2000), except for a trend toward decreased pups per litter in mice in a 3-generation study (Schroeder and Mitchener 1971) that is consistent with embryolethality observed in developmental studies of inorganic arsenic. Studies on spermatogenesis and reproductive success in arsenic-exposed workers would be valuable in evaluating whether there are significant reproductive risks of arsenic in humans, and this could be further strengthened by studies including histopathological examination of reproductive tissues (which was not done in the existing studies) in animals.

Organic Arsenicals. No information was located on reproductive effects of organic arsenicals in humans and no inhalation or dermal exposure animal studies were located. Intermediate- and chronic-duration oral studies for MMA (Arnold et al. 2003), DMA (Arnold et al. 2006), and roxarsone (NTP 1989b) have not reported histological damage to reproductive tissues. Decreases in pregnancy rate and male fertility index were observed in a two-generation study in rats (Schroeder 1994) and a single generation study in mice (Prukop and Savage 1986) exposed to MMA; the poor reporting in the Prukop and Savage (1986) study limits its usefulness in assessing reproductive toxicity. However, in the two-generation study, the differences between control and exposed rats were not statistically different; the effect was considered biologically significant because effects observed in the exposed rats were outside the range found in historical controls. Another reproductive performance study to confirm these results would be useful. No reproductive effects were observed in a two generation study in rats exposed to DMA (Rubin et al. 1989).

Developmental Toxicity.

Inorganic Arsenicals. There are several epidemiological studies that suggest that inhalation (Ihrig et al. 1998; Nordström et al. 1978a, 1978b, 1979a, 1979b) or oral (Hopenhayn et al. 2003a; Yang et al. 2003) exposure to inorganic arsenic might increase the risk of low birth weight, congenital defects, or abortion in exposed women. These studies do not establish that arsenic was responsible, since all involved exposures to other chemicals or risk factors, but do suggest that additional studies on developmental

parameters in humans exposed to arsenic would be valuable in determining whether this is an effect of concern. Other human studies have not found significant associations between arsenic levels in drinking water and increased neonatal deaths or infant mortality (von Ehrenstein et al. 2006) or the increase in congenital heart defects (Zierler et al. 1988) or neural tube defects (Brender et al. 2006). Studies in animals support the view that oral, inhalation, and parenteral exposure to inorganic arsenic can all increase the incidence of fetotoxicity and teratogenicity, although this appears to occur only at doses that are toxic or even lethal to the dams (Baxley et al. 1981; Beaudoin 1974; Carpenter 1987; Ferm and Carpenter 1968; Ferm et al. 1971; Hanlon and Ferm 1986; Holson et al. 1999, 2000; Hood and Bishop 1972; Hood and Harrison 1982; Hood et al. 1978; Mason et al. 1989; Nagymajtényi et al. 1985; Nemec et al. 1998; Stump et al. 1999; Willhite 1981). There are also some data to suggest that it may increase the risk of transplacental cancer in humans (Smith et al. 2006) and animals (Waalkes et al. 2003). Thus, additional studies in animals may be useful in defining the mechanisms of these developmental effects and in identifying the time of maximum susceptibility of the fetus, but such studies probably will not help identify a safe exposure level for humans.

Organic Arsenicals. No information was located regarding developmental effects in humans after oral or inhalation exposure to organic arsenicals. Animal studies conducted in rats (Chernoff et al. 1990; Irvine et al. 2006; Rogers et al. 1981), mice (Kavlock et al. 1985; Rogers et al. 1981), and rabbits (Irvine et al. 2006) have examined the developmental toxicity of organic arsenicals. Decreases in fetal body weights and delays in ossification were commonly reported at maternally toxic (decreases in body weight gain) doses of DMA (Irvine et al. 2006; Kavlock et al. 1985; Rogers et al. 1981). However, one study found increases in the percentage of fetuses with irregular palatine rugae at DMA doses not associated with maternal toxicity (Rogers et al. 1981). This effect has not been reported in other studies and additional developmental studies are needed to confirm the finding. In view of the apparent differences in susceptibility between animals and humans, it would be valuable to investigate whether there are any measurable effects on development in humans exposed to organic arsenicals in the workplace or the environment.

Immunotoxicity.

Inorganic Arsenicals. No studies were located on immunotoxic effects in humans after oral exposure to inorganic arsenic. One inhalation study in humans (Bencko et al. 1988), an inhalation study in animals (Aranyi et al. 1985), one oral study in animals (Kerkvliet et al. 1980), and one intratracheal instillation study in animals (Sikorski et al. 1989) suggest that arsenic causes little or no functional impairment of the

immune system, but one inhalation study in animals found decreased pulmonary bactericidal activity and increased susceptibility to streptococcal infection in exposed mice (Aranyi et al. 1985). Additional studies (both in humans and animals) would be valuable to investigate this end point further. Dermal exposure of humans to high levels of arsenic dusts may cause dermal sensitization (Holmqvist 1951), but the dose and time dependence of this phenomenon are not known. Studies to determine whether dermal sensitization occurs in people with low level dermal exposures to arsenic in dust or soil, such as might occur for residents near an arsenic-containing waste site, would be valuable in assessing the significance of this effect to nonoccupationally exposed populations.

Organic Arsenicals. No information was located on the effect of organic arsenicals exposure in humans or animals on immune function. Since there are suggestions that inorganic arsenic may cause some changes in the immune system, studies on possible immune effects of the common organic arsenicals might be helpful.

Neurotoxicity.

Inorganic Arsenicals. There is convincing evidence from studies in humans that inorganic arsenic can cause serious neurological effects, both after inhalation (Beckett et al. 1986; Bencko et al. 1977; Blom et al. 1985; Buchancová et al. 1998; Calderón et al. 2001; Danan et al. 1984; Feldman et al. 1979; Gerr et al. 2000; Lagerkvist and Zetterlund 1994; Morton and Caron 1989) and oral exposure (Armstrong et al. 1984; Bartolome et al. 1999; Chakraborti et al. 2003a, 2003b; Civantos et al. 1995; Cullen et al. 1995; Danan et al. 1984; EPA 1977a; Feldman et al. 1979; Fincher and Foy et al. 1992; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Hindmarsh et al. 1977; Huang et al. 1985; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Lewis et al. 1999; Mizuta et al. 1956; Muzi et al. 2001; Quatrehomme et al. 1992; Silver and Wainman 1952; Szuler et al. 1979; Tsai et al. 2003; Uede and Furukawa 2003; Vantroyen et al. 2004; Wagner et al. 1979). This is based mainly on clinical observations and neurological examinations of exposed persons. Available studies provide a reasonable estimate of LOAEL and NOAEL values by the oral route, but similar data are lacking for the inhalation route. Further studies designed to identify the threshold for neurological effects in humans exposed by the inhalation route would be valuable, since humans may be exposed to arsenic dusts in air from smelters, chemical factories, or waste sites. Adult animals appear to be much less susceptible than humans to the neurological effects of inorganic arsenic, so studies in adult animals would probably not help in estimation of a safe exposure limit. However, in light of recent findings of possible associations between arsenic in drinking water and neurobehavioral alterations in children (Tsai et al. 2003; von Ehrenstein et

al. 2007; Wang et al. 2007; Wasserman et al. 2004, 2007), studies in animals, in which confounding can be eliminated, may be warranted.

Organic Arsenicals. Information on neurological effects of organic arsenicals in humans is limited to an occupational study that did not find increases in the frequency of central or peripheral nervous system complaints (Watrous and McCaughey 1945) and a case report of a women of a women reporting numbness and tingling of the fingertips, toes, and circomoral region who was exposed to organic arsenic in soup (Luong and Nguyen 1999). Neurological effects have also been observed in some animal studies. Decreases spontaneous motility, ataxia, and increased startle response were observed in mice exposed to a single high dose of DMA (Kaise et al. 1989). Degeneration of myelin and axons were observed in several studies involving oral exposure of pigs to roxarsone (Edmonds and Baker 1986; Kennedy et al. 1986; Rice et al. 1985). Hyperexcitability, ataxia, and trembling have also been observed in rats and mice orally exposed to roxarsone (Kerr et al. 1963; NTP 1989b). These findings suggest that more extensive investigations of the neurotoxic potential of roxarsone and other organic arsenicals would be valuable to determine the potential human health risk from these compounds, since humans could be exposed during the manufacture or use of these compounds, or near waste sites where they have been deposited.

Epidemiological and Human Dosimetry Studies. Numerous epidemiologic studies of humans exposed to inorganic arsenic by the oral and inhalation routes constitute the database on arsenic-related cancer and noncancer human health effects. As with virtually all epidemiologic investigations, these studies are limited by possible confounding from factors such as smoking, exposure to other chemicals, and differences in population characteristics (e.g., nutritional state, metabolism, and toxicokinetics) that inhibit extrapolation of study results to a wider population. Moreover, many of these studies lack good dose estimates for study participants. Some studies lack quantitative data altogether. For this reason, improved data on confounding factors and improved methods of human dosimetry would be valuable in any further human epidemiologic studies of arsenic, either in the workplace or in the general environment. Recent work has broadened the qualitative dose-response information beyond the highly exposed Taiwanese population, but additional studies of persons with lower exposure levels would be especially valuable for risk assessments for the U.S. population. From a public health standpoint, well designed studies of common noncancer health outcomes (e.g., cardiovascular disease and diabetes) could be more important than additional studies of cancer. Availability of methods for biomonitoring of exposure are discussed below.

Biomarkers of Exposure and Effect.

Exposure. There are sensitive and specific methods for measuring arsenic in blood, urine, hair, nails, and other tissues, and this is the approach normally employed for measuring arsenic exposure in humans. Usually total arsenic is measured, but methods are available for measuring inorganic arsenic and each of the organic derivatives separately. Urinary levels are generally considered to be the most reliable indication of recent exposures (Enterline et al. 1987a; Milham and Strong 1974; Pinto et al. 1976; Polissar et al. 1990), but if a high urinary level is present, care must be taken to account for the presence of nontoxic forms of arsenic from the diet. Blood levels are sometimes used to evaluate the status of acutely poisoned individuals (Driesback 1980; Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al. 1979, 1981), but this approach is not generally useful for biomonitoring of long-term exposure to low levels. Hair and nails provide a valuable indication of exposures that occurred 1–10 months earlier (Agahian et al. 1990; Bencko et al. 1986; Choucair and Ajax 1988; EPA 1977a, 1981b; Milham and Strong 1974; Valentine et al. 1979; Yamauchi et al. 1989), although care must be taken to exclude external contamination of these samples. Cumulative urinary arsenic levels may be used to derive a quantitative estimate of exposure (Enterline et al. 1987a; Pinto et al. 1976), but data on the quantitative relation between exposure and arsenic levels in nails and hair were not located. Efforts to establish an algorithm for estimating past exposure levels from hair or nail levels would be valuable in quantifying average long-term exposure levels in people where repeated urinary monitoring is not feasible.

Effect. The effects of arsenic are mainly nonspecific, but the combined presence of several of the most characteristic clinical signs (e.g., nausea, diarrhea, peripheral neuropathy, anemia, vascular lesions, hyperkeratinization, hyperpigmentation) is usually adequate to suggest arsenic intoxication. Although there are standard clinical methods for detecting and evaluating each of these effects, there are no recognized methods for identifying early (preclinical) effects in exposed persons. Neurophysiological measurements of nerve conduction velocity or amplitude have been investigated (Goebel et al. 1990; Jenkins 1966; Le Quesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981), but at present, this approach does not seem to offer much advantage over a standard neurological examination. Changes in urinary excretion levels of several heme-related metabolites appear to be a good indication of preclinical effects of arsenic toxicity in animals (Albores et al. 1989; Sardana et al. 1981; Woods and Fowler 1978; Woods and Southern 1989), but this has not been established in humans and is not specific for arsenic-induced effects. Further efforts to develop these approaches and to identify other more specific biochemical or physiological indicators of arsenic-induced effects would be very valuable in monitoring the health of persons exposed to low levels of arsenic in the environment or near waste sites.

Absorption, Distribution, Metabolism, and Excretion. Available data from toxicokinetic studies in humans reveal that arsenates and arsenites are well absorbed following both oral and inhalation exposure. Data on distribution are limited, but it appears that arsenic is transported to nearly all tissues. Metabolism involves mainly reduction-oxidation reactions that interconvert As(+5) and As(+3) and methylation of As(+3) to yield MMA and DMA. Most arsenic is rapidly excreted in the urine as a mixture of inorganic arsenics, MMA, and DMA, although some may remain bound in tissues (especially skin, hair, and fingernails). These findings are strongly supported by numerous studies in animals. Because methylation represents a detoxification pathway, an area of special interest is the capacity of the human body to methylate inorganic arsenic. Limited data suggest that the methylation system might begin to become saturated at intakes of about 0.2–1 mg As/day (Buchet et al. 1981b; Marcus and Rispin 1988), but this is uncertain. Further studies to define the rate and saturation kinetics of whole-body methylation in humans would be especially helpful in evaluating human health risk from the low levels of arsenic intake that are usually encountered in the environment. Along the same line, further studies to determine the nature and magnitude of individual variations in methylation capacity and how this depends on diet, age, and other factors would be very useful in understanding and predicting which members of a population are likely to be most susceptible.

The toxicokinetics of dermal exposure have not been studied. It is usually considered that dermal uptake of arsenates and arsenites is sufficiently slow that this route is unlikely to be of health concern (except that due to direct irritation), but studies to test the validity of this assumption would be valuable. Also, dermal uptake of organic arsenicals could be of concern, and quantitative data on the rate and extent of this would be helpful in evaluating risks from application of arsenical pesticides or exposures to organic arsenicals in waste sites.

Comparative Toxicokinetics. Available toxicity data indicate that arsenic causes many of the same effects in animals that are observed in humans, but that animals are significantly less sensitive. The basis for this difference in susceptibility is not certain but is probably mainly a result of differences in absorption, distribution, metabolism, or excretion. For example, rats strongly retain arsenic in red blood cells (Lanz et al. 1950), while humans (and most other species) do not. Similarly, marmoset monkeys do not methylate inorganic arsenic (Vahter and Marafante 1985; Vahter et al. 1982), while humans and other animal species do. Because of these clear differences in toxicity and toxicokinetics between species, further comparative toxicokinetic studies that focus on the mechanistic basis for these differences would be very valuable. At a minimum, this would help clarify which laboratory species are the most useful

models for humans and could ultimately lead to development of a PBPK model that would permit reliable extrapolation of observations across species.

Methods for Reducing Toxic Effects. There are a number of general methods for reducing the absorption of arsenic in the gastrointestinal tract and skin, but there are currently no methods for reducing the absorption of arsenic from the lungs. The removal of arsenic from the gastrointestinal tract is usually facilitated by the use of emetics, cathartics, lavages, or activated charcoal (Agency for Toxic Substances and Disease Registry 1990a; Aposhian and Aposhian 1989; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barceloux 1988; EPA 1989e; Haddad and Winchester 1990; Mitra et al. 2004; Stutz and Janusz 1988). Studies that investigate the effects of phosphate-binding chemicals (aluminum hydroxide) and nonabsorbable sulfhydryl compounds on the absorption of pentavalent and trivalent arsenic, respectively, may be useful in developing treatments that are more specific to arsenic intoxication. Once arsenic is in the body, treatment usually involves the use of one or more chelators, such as BAL or penicillamine. However, these agents often exhibit adverse side effects (Agency for Toxic Substances and Disease Registry 1990a; Ellenhorn and Barceloux 1988), and are generally only applied following high-dose acute exposure. Further studies investigating the efficacy of less toxic arsenic chelators, such as DMSA, DMPA, DMPS, and N-acetyl cysteine, may lead to the development of safer treatment methods. Studies on the efficacy of chelators and agents to enhance methylation and elimination in treatment of chronic arsenic exposure would also be helpful, as available treatment methods for chronic arsenic exposure are limited. Trivalent arsenic is generally believed to exert toxic effects by binding to the vicinal sulfhydryl group of key enzymes, thereby interfering with a number of biological processes, such as gluconeogenesis and DNA repair (Li and Rossman 1989; Szinicz and Forth 1988). Since pentavalent arsenic may need to be reduced in the body to the trivalent state before it can exert toxic effects, studies that investigate methods for blocking this conversion may lead to a method for interfering with the mechanism of action for pentavalent arsenic. The insufficient intake of calcium, animal protein, folate, selenium, and fiber may enhance the toxic effects of inorganic arsenic (Mitra et al. 2004), but it is not known if dietary supplementation will prove effective in patients who already show arsenic-induced symptoms.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

A majority of the data on the effects of exposure of humans to arsenic has focused on adults. Although a few studies of acute poisoning and chronic exposure specifically describe children (Borgoño et al. 1980; Concha et al. 1998a, 1998b, 1999; Foy et al. 1992; Kersjes et al. 1987; Rosenberg 1974; Zaldívar 1974; Zaldívar and Guillier 1977), in general, data are lacking. Specifically, although there is a substantial database on the effect of arsenic on animal development, there are few data describing developmental effects in humans. Additional research in this area, using populations in areas of endemic arsenic exposure, would be useful.

Although there is no reason to suspect that the pharmacokinetics of arsenic differs in children and adults, there are few data available on this topic. Research on absorption, distribution, metabolism, and excretion in children would aid in determining if children are at an increased risk, especially in areas where chronic exposure to an environmental source occurs. With regard to exposure during development, additional research on maternal kinetics, and transfer via breast milk would be useful in obtaining a more complete picture of prenatal and neonatal development, especially with regard to neural development and the possible development of childhood cancer.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

A number of researchers are continuing to investigate the toxicity and toxicokinetics of arsenic. Table 3-18 summarizes studies being sponsored by agencies of the U.S. federal government (FEDRIP 2007). Additional research is being sponsored by industry groups and other agencies, and research is also ongoing in a number of foreign countries.

Table 3-18. Ongoing Studies on Health Effects of Arsenic, Federally Funded

Investigator	Affiliation	Title	Sponsor
Ahsan, H	Columbia University, New York, New York	Chemoprevention of arsenic-induced skin cancer	NCI
Ahsan, H	Columbia University, New York, New York	Genetic susceptibility to arsenic-induced skin cancer	NCI
Andrew, A	Darmouth College, Hanover, New Hampshire	Bladder cancer prognostic indicators	NCI
Beckman, K	Children's Hospital and Research Center, Oakland, California	Fetal arsenic-nutrient interaction in adult-onset cancer	NIEHS
Bodwell, J	Darmouth College, Hanover, New Hampshire	Arsenic effects on glucocorticoid receptor action	NIEHS
Calderon, R	EPA, Research Triangle Park, North Carolina	Arsenic-induced skin conditions identified in Southwest United States	HEERL
Christiani, D	Harvard University, Boston, Massachusetts	Arsenic and health in Bangladesh	NIEHS
Dong, Z	University of Minnesota, Minneapolis, Minnesota	Molecular basis of arsenic-induced cell transformation	NCI
Finnell, R	Texas A & M University College Station, Texas	Sensitive genotypes to arsenic as a model environmental toxicant	NIEHS
Frenkel, K	New York University, New York, New York	Metal induced inflammatory factors, oxidative stress, and suppression	NIEHS
Futscher, B	University of Arizona, Tucson, Arizona	Epigenetic remodeling by environmental arsenicals	NCI
Gamble, M	Columbia University, New York, New York	Nutritional influences on arsenic toxicity	NIEHS
Germolec, D	NIH, Research Triangle Park, North Carolina	The role of growth factors and inflammatory mediators in arsenic-induced dermatotoxicity	NIEHS
Guallar, E	Johns Hopkins University, Baltimore, Maryland	Mercury, arsenic, and carotid atherosclerosis	NIEHS
He, K	Northwestern University, Chicago, Illinois	Trace elements and CVD risks factors among young adults	NHLBI
Hei, T	Columbia University, New York, New York	Mechanisms of arsenic carcinogenesis	NIEHS
Huang, C	New York University, New York, New York	Effects of arsenic on PI-3K signaling pathway	NCI
Hudgens, E	EPA, Research Triangle Park, North Carolina	Study of individuals chronically exposed to arsenic in drinking water	HEERL
Hughes, M	EPA, Research Triangle Park, North Carolina	Biomarkers of exposure: a case study with inorganic arsenic	HEERL
Hughes, M	EPA, Research Triangle Park, North Carolina	Tissue dosimetry, metabolism, and excretion of pentavalent arsenic	HEERL
Jing, Y	New York University, New York, New York	Arsenic trioxide and acute myeloid leukemia	NCI

Table 3-18. Ongoing Studies on Health Effects of Arsenic, Federally Funded

Investigator	Affiliation	Title	Sponsor
Jung, M	Georgetown University, Washington, DC	Epigenetic regulation by poly(ADP-ribose) in response to arsenite	NIEHS
Karin, M	University of California San Diego, La Jolla, California	Interaction of heavy metal ions with the human genome	NIEHS
Kelsey, K	Harvard University, Boston, Massachusetts	Arsenic mode of action in cancer—models of epigenetic mechanism	NIEHS
Liu, K	University of New Mexico, Albuquerque, New Mexico	Oxidative mechanisms of arsenic-induced carcinogenesis	NIEHS
Markowski, V	University of Southern Maine, Portland, Maine	Developmental arsenic exposure produces cognitive impairment	NIEHS
Martin, M	Georgetown University, Washington, DC	Arsenic and epigenetic regulation of gene expression	NIEHS
Muscarella, D	Cornell University Ithaca, Ithaca, New York	Arsenite effects on CD40 signaling and B-cell apoptosis	NIEHS
Nichols, R	Dartmouth College, Hanover, New Hampshire	Effect of arsenic on cytochrome P450	NIEHS
Nriagu, J	University of Michigan, Ann Harbor, Michigan	Arsenic exposure and bladder cancer in Michigan	NCI
Rosen, B	Wayne State University, Detroit, Michigan	Mechanisms of arsenical transport	NIGMS
Rosen, B	Wayne State University, Detroit, Michigan	Metal binding domains in metallo-regulatory proteins	NIAID
Rosenblatt, A	University of Miami, Coral Gables, Florida	Environmental arsenic and androgen receptor regulation	NIEHS
Rossman, T	New York University, New York, New York	Investigation and genetic analysis of the human arsenite efflux pump	NIEHS
Schwartz, J	Harvard University, Boston Massachusetts	Epigenetic effects of particles and metals on cardiac health of an aging cohort	NIEHS
Self, W	University of Central Florida, Orlando, Florida	Impact of arsenicals on selenoprotein synthesis	NIEHS
Sens, D	University of North Dakota, Grand Forks, North Dakota	Metallothionein isoform-3 urinary marker bladder cancer	NIEHS
Sheldon, L	Dartmouth College, Hanover, New Hampshire	Arsenic, histone modification, and transcription	NIEHS
Shi, X	University of Kentucky, Lexington, Kentucky	Mechanism of arsenic-induced carcinogenesis	NCI
Smith, A	University of California, Berkeley, California	Arsenic biomarker epidemiology	NIEHS
Spallholz, J	Texas Tech University, Lubbock, Texas	Selenium against arsenic toxicity and skin lesions	NCI
States, C	University of Louisville, Louisville, Kentucky	Arsenic induced miotic arrest associated apoptosis	NIEHS
Styblo, M	University of North Carolina, Chapel Hill, North Carolina	Metabolism and toxicity of arsenic in human liver	NIEHS

Table 3-18. Ongoing Studies on Health Effects of Arsenic, Federally Funded

Investigator	Affiliation	Title	Sponsor
Taylor, P	Division of Cancer Epidemiology and Genetics, NCI, Bethesda, Maryland	Biologic specimen bank for early lung cancer markers in Chinese tin miners	NCI
Taylor, B	University of Louisville, Louisville, Kentucky	Arsenite inhibition of mitotic progression	NIEHS
Vaillancourt, R	University of Arizona, Tucson, Arizona	Modulation of Prostaglandins by Arsenic	NIEHS
Willett, W	Harvard University, Boston, Massachusetts	Prospective studies of diet and cancer in men and women	NCI
Wright, R	Brigham and Women's Hospital, Boston, Massachusetts	Metal mixtures and neurondevelopment	NIEHS
Zhang, D	University of Arizona, Tucson, Arizona	The protective role of Nrf2 in arsenic-induced toxicity and carcinogenicity	NIEHS

EPA = Environmental Protection Agency; NHEERL = National Health and Environmental Effects Research Laboratory; NCI = National Cancer Institute; NHLBI = National Heart, Lung, and Blood Institute; NIEHS = National Institute of Environmental Health Sciences; NIAID= National Institute of Allergy and Infectious Diseases; NIGMS = National Institute of General Medical Sciences; NIH = National Institute of Health

Source: FEDRIP 2007

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of arsenic and some common inorganic and organic arsenic compounds are located in Tables 4-1 and 4-2, respectively.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of arsenic and some common inorganic and organic arsenic compounds is located in Tables 4-3 and 4-4, respectively.

Arsenic appears in Group 15 (V) of the periodic table, below nitrogen and phosphorus. Arsenic is classified chemically as a metalloid, having both properties of a metal and a nonmetal; however, it is frequently referred to as a metal. Elemental arsenic, which is also referred to as metallic arsenic, (As(0)) normally occurs as the α-crystalline metallic form, which is a steel gray and brittle solid. The β-form is a dark gray amorphous solid. Other allotropic forms of arsenic may also exist. In compounds, arsenic typically exists in one of three oxidation states, -3, +3, and +5 (Carapella 1992). Arsenic compounds can be categorized as inorganic, compounds without an arsenic-carbon bond, and organic, compounds with an arsenic-carbon bond.

Table 4-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds[a]

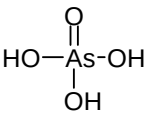
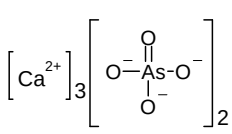
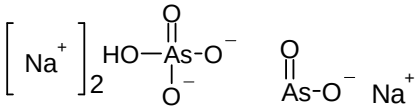
Characteristic	Arsenic	Arsenic acid	Arsenic pentoxide	Arsenic trioxide
Synonym(s)	Arsenic black; colloidal arsenic; gray arsenic, metallic arsenic	Orthoarsenic acid	Arsenic(V) oxide; arsenic acid anhydride; diarsenic pentoxide	Arsenic(III) oxide; arsenious acid; arsenious oxide; white arsenic
Registered trade name(s)	No data	Zotox; Hi-Yield Desiccant H-10; Desiccant L-10; Crab Grass Killer	No data	White Arsenic; Arsenicum Album
Chemical formula	As	H_3AsO_4	As_2O_5	As_2O_3
Chemical structure	As		$[As^{5+}]_2\,[O^{2-}]_5$	$[As^{3+}]_2\,[O^{2-}]_3$
Identification numbers:				
CAS registry	7440-38-2	7778-39-4	1303-28-2	1327-53-3
NIOSH RTECS[b]	CG0525000	CG0700000	CG2275000	CG3325000
EPA hazardous waste	D004	D004, P010	D004, P011	D004, P012
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMDG shipping	UN1558/IMDG 6.1	UN1553 (liquid)/ UN1554 (solid)/ IMDG 6.1 (liquid and solid)	UN1559/IMDG 6.1	UN1561/ IMDG 6.1
HSDB	509	431	429	419
EINECS	231-148-6	231-901-9	215-116-9	215-481-4
NCI	No data	No data	No data	No data

Table 4-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds[a]

Characteristic	Calcium arsenate	Gallium arsenide	Sodium arsenate	Sodium arsenite
Synonym(s)	Calcium ortho-arsenate; arsenic acid, calcium salt	Gallium mono-arsenide	Disodium arsenate, dibasic; disodium hydrogen arsenate; arsenic acid, disodium salt	Arsenenous acid, sodium salt; sodium meta-arsenite
Registered trade name(s)	Pencal; Security; Turf-Cal; Chip-Cal; SPRA-Cal	No data	No data	Atlas "A"; Penite; Kill-All; Chem-Sen 56; Chem Pels C; Progalumnol Double
Chemical formula	$Ca_3(AsO_4)_2$	GaAs	Na_2HAsO_4	$NaAsO_2$
Chemical structure		Ga:As		
Identification numbers:				
CAS registry	7778-44-1	1303-00-0	7778-43-0	7784-46-5
NIOSH RTECS[b]	CG0830000	LW8800000	CG0875000	CG3675000
EPA hazardous waste	D004	D004	D004	D004
OHM/TADS	No data	No data	No data	7800057
DOT/UN/NA/IMDG shipping	UN1573/IMDG 6.1	UN 2803; Gallium/ IMDG 8.0; Gallium	UN 1685/IMDG 6.1	UN1686 (aqueous solution)/UN2027 (solid)/IMDG 6.1
HSDB	1433	4376	1675	693
EINECS	233-287-8	215-114-8	231-902-4	232-070-5
NCI	No data	No data	No data	No data

[a]All information obtained from HSDB 2007 and CHEMIDplus 2007, except where noted.
[b]RTECS 2007

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Chemical Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Chemical Identity of Selected Organic Arsenic Compounds[a]

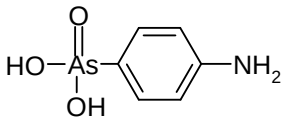
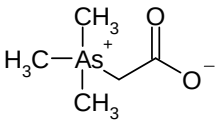
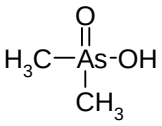
Characteristic	Arsanilic acid	Arsenobetaine	Dimethylarsinic acid
Synonym(s)	(4-Aminophenyl)arsonic acid; antoxylic acid; atoxylic acid, Pro-Gen	Arsonium, (carboxymethyl)-trimethyl-, hydroxide, inner salt	Cacodylic acid; hydroxydimethyl-arsine oxide; DMA; DMAA
Registered trade name(s)	No data	No data	510; Arsan; Phytar 560; Rad-E-Cate 35
Chemical formula	$C_6H_8AsNO_3$	$C_5H_{11}AsO_2$	$C_2H_7AsO_2$
Chemical structure			
Identification numbers:			
CAS registry	98-50-0	64436-13-1	75-60-5
NIOSH RTECS[b]	CF7875000	CH9750000	CH7525000
EPA hazardous waste	D004	No data	U136/D004
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	UN1572/IMDG 6.1
HSDB	432	No data	360
EINECS	202-674-3	No data	200-883-4
NCI	No data	No data	No data

Table 4-2. Chemical Identity of Selected Organic Arsenic Compounds[a]

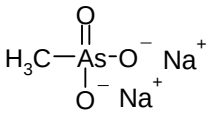
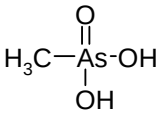
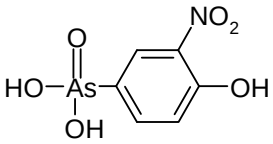
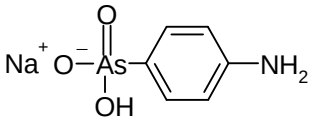
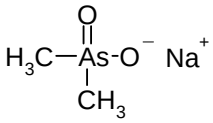
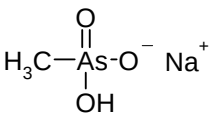
Characteristic	Disodium methane-arsonate	Methanearsonic acid	3-Nitro-4-hydroxy-phenyl-arsonic acid
Synonym(s)	DSMA; disodium monomethane arsonate	Arsonic acid, methyl-; monomethylarsonic acid	Roxarsone; 3-nitro-4-hydroxyphenylarsonic acid; 3-Nitro-10
Registered trade name(s)	Ansar 8100; Arrhenal; Ansar DSMA Liquid; Dinate; Crab-E-Rad; Chipco Crab Kleen; Arsinyl; Sodar; Methar; Drexel DSMA Liquid; Di-Tac; Ansar 184; Weed-E-Rad; Versar DSMA-LQ; Calar-E-Rad; Dal-E-Rad; Jon-Trol; Namate	No data	No data
Chemical formula	$CH_3AsO_3Na_2$	CH_5AsO_3	$C_6H_6AsNO_6$
Chemical structure			
Identification numbers:			
CAS registry	144-21-8	124-58-3	121-19-7
NIOSH RTECS[b]	PA2275000	PA1575000	CY5250000
EPA hazardous waste	D004	D004	D004
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	1701	845	4296
EINECS	205-620-7	204-705-6	204-453-7
NCI	No data	No data	C5608

Table 4-2. Chemical Identity of Selected Organic Arsenic Compounds[a]

Characteristic	Sodium arsanilate	Sodium dimethylarsinate	Sodium methanearsonate
Synonym(s)	(4-Aminophenyl)arsonic acid sodium salt; arsanilic acid sodium salt; arsamin; atoxyl; soamin; trypoxyl	Sodium cacodylate; cacodylic acid, sodium salt; sodium dimethylarsonate	Arsonic acid, methyl-, monosodium salt; monosodium acid metharsonate; MSMA
Registered trade name(s)	No data	Ansar 160; Ansar 560; Bolls-Eye; Chemaid; Phytar 560, component of (with 012501); Rad-E-Cate 25.	Ansar 529; Ansar 170; Target MSMA; Phyban H.C.; Deconate; Mesamate; Bueno; Monate Merge 823; Dal-E-Rad; Weed-S-Rad; Arsanote liquid; Silvisar 550.
Chemical formula	$C_6H_7AsNO_3Na$	$C_2H_6AsO_2Na$	CH_4AsO_3Na
Chemical structure			
Identification numbers:			
CAS registry	127-85-5	124-65-2	2163-80-6
NIOSH RTECS[b]	CF9625000	CH7700000	PA2625000
EPA hazardous waste	D004	D004	D004
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	UN2473/IMDG 6.1	UN1688/IMDG 6.1	No data
HSDB	5189	731	754
EINECS	204-869-9	204-708-2	218-495-9
NCI	C61176	No data	C60071

[a]All information obtained from HSDB 2007 and CHEMIDplus 2007, except where noted.
[b]RTECS 2007

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Dept. of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Chemical Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds[a]

Property	Arsenic	Arsenic acid	Arsenic pentoxide	Arsenic trioxide
Molecular weight	74.9216	141.944	229.840	197.841
Color	Silver-gray or tin-white	White[b]	White	White
Physical state	Solid	Solid[b]	Solid	Solid
Melting point	817 °C (triple point)	35 °C	Decomposes at ~300 °C	313 °C (claudetite) 274 °C (arsenolite)
Boiling point	614 °C sublimes	Loses H_2O at 160 °C [b]	No data	460 °C
Density	5.778 g/cm^3 at 25 °C	~2.2 g/cm^3	4.32 g/cm^3	3.865 g/cm^3 (cubes) 4.15 g/cm^3 (rhombic crystals)
Odor	Odorless	No data	No data	Odorless
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	302 g/L at 12.5 °C[b]	2,300 g/L at 20 °C	17 g/L at 16 °C
Organic solvent(s)	No data	Soluble in alcohol, glycerol[b]	Soluble in alcohol	Practically insoluble in alcohol, chloroform, ether; soluble in glycerol
Other	Insoluble in caustic and nonoxidizing acids	No data	Soluble in acid, alkali	Soluble in dilute hydrochloric acid, alkali hydroxide, carbonate solution
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
pK_a	No data	pK_{a1}=2.22; pK_{a2}=6.98 pK_{a3}=11.53[c]	No data	No data
Vapor pressure	7.5x10^{-3} mmHg at 280 °C	No data	No data	2.47x10^{-4} mmHg at 25 °C
Autoignition temperature	No data	No data	No data	Not flammable
Flashpoint	No data	No data	No data	No data
Flammability limits in air	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

Table 4-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds[a]

Property	Calcium arsenate	Gallium arsenide	Disodium arsenate	Sodium arsenite
Molecular weight	398.072	144.64	185.91	130.92
Color	Colorless	Dark gray	Colorless[d]	White to gray-white
Physical state	Solid	Solid	Solid[d]	Solid
Melting point	Decomposes on heating	1,238 °C	57 °C[d]	No data
Boiling point	No data	No data	No data	No data
Density	3.620 g/cm^3	5.3176 g/cm^3 at 25 °C	1.87 g/cm[d]	1.87 g/cm^3
Odor	Odorless	Garlic odor	Odorless[d]	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	0.13 g/L at 25 °C	<1 mg/mL at 20 °C	Soluble 1:3 parts in water[d]	Freely soluble in water
Organic solvents	Insoluble	<1 mg/mg dimethyl sulfoxide, ethanol, methanol, acetone	Slightly soluble in alcohol; soluble in glycerol[d]	Slightly soluble in alcohol
Other	Soluble in dilute acids	Soluble in hydrochloric acid	Slightly soluble in alkaline solution[d]	No data
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
pK_a	No data	No data		
Vapor pressure	~0 mmHg at 20 °C	No data	No data	No data
Autoignition temperature	Not combustible	No data	No data	Not combustible
Flashpoint	No data	No data	No data	No data
Flammability limits in air	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

[a]All information from HSDB 2007, except where noted.
[b]Value for arsenic acid hemihydrate
[c]NRC 1999
[d]Value for disodium arsenate heptahydrate

Table 4-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds[a]

Property	Arsenilic acid	Arsenobetaine	Dimethylarsinic acid
Molecular weight	217.06	196.1[b]	138.00
Color	White	No data	Colorless
Physical state	Solid	Solid[b]	Solid
Melting point	232 °C	203–210 °C (decomposes)[b]	195 °C
Boiling point		No data	>200 °C
Density	1.9571 g/cm^3 at 10 °C	No data	No data
Odor	Practically odorless	No data	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Slightly soluble in cold water; soluble in hot water	No data	2,000 g/L at 25 °C
Organic solvent(s)	Slightly soluble in alcohol; soluble in amyl alcohol; insoluble in ether, acetone, benzene, chloroform	No data	Soluble in alcohol; insoluble in diethyl ether
Acids	Slightly soluble in acetic acid; soluble in alkaki carbonates; moderately soluble in concentrated mineral acids; insoluble in dilute mineral acids	No data	Soluble in acetic acid
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
pK_a	No data	2.2[c]	1.57
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	No data	No data	Nonflammable
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds[a]

Property	Methanearsonic acid	3-Nitro-4-hydroxy-phenylarsonic acid	Sodium arsanilate
Molecular weight	139.97	263.03	239.04
Color	White	Pale yellow	White or creamy white
Physical state	Solid	Solid	Solid
Melting point	160.5 °C	No data	No data
Boiling point	No data	No data	No data
Density	No data	No data	No data
Odor	No data	No data	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	256 g/L at 20 °C	Slightly soluble in cold water; soluble in about 30 parts boiling water	Soluble 1 part in 3 parts water
Organic solvents	Soluble in ethanol	Soluble in methanol, ethanol, acetone; insoluble in ether, ethyl acetate	Soluble 1 part in 150 parts alcohol; practically insoluble in chloroform, ether
Acids	No data	Soluble in acetic acid, alkalies; sparingly soluble in dilute mineral acids	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
pK_a	pK_{a1}=4.1; pK_{a2}=9.02	No data	No data
Vapor pressure at 25 °C	$<7.5x10^{-8}$ mmHg	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds[a]

Property	Disodium methanearsonate	Sodium dimethylarsinate	Sodium methanearsonate
Molecular weight	183.93	159.98	161.95
Color	White	Colorless to light yellow	White
Physical state	Solid	Solid	Solid
Melting point	>355 °C	200 °C	130–140 °C
Boiling point	No data	No data	No data
Density	1.04 g/cm^3	>1 g/cm^3 at 20 °C	1.55 g/mL[d]
Odor	No data	Odorless	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	432 g/L at 25 °C	200 g/L at 25 °C	580 g/L at 20 °C
Organic solvents	Soluble in methanol; practically insoluble in most organic solvents	No data	Insoluble in most organic solvents
Acids	No data	No data	No data
Partition coefficients:			
Log K_{ow}	<1	No data	-3.10
Log K_{oc}	No data	No data	No data
pK_a	pK_{a1}=4.1; pK_{a2}=8.94	6.29	pK_{a1}=4.1; pK_{a2}=9.02
Vapor pressure at 25 °C	10^{-7} mmHg	No data	$7.8x10^{-8}$ mmHg
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	Nonflammable	No data	Nonflammable
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

[a]All information from HSDB 2007, except where noted.
[b]Cannon et al. 1981 (arsenobetaine as monohydrate)
[c]Teräsahde et al. 1996
[d]Value for Ansar 6.6

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Arsenic is presently obtained as a byproduct of the smelting of copper, lead, cobalt, and gold ores. Arsenic trioxide is volatilized during smelting and accumulates in the flue dust, which may contain up to 30% arsenic trioxide. The crude flue dust is further refined by mixing with small amounts of galena or pyrite to prevent the formation of arsensites and roasting to yield arsenic trioxide of 90–95% purity. By successive sublimations, a purity of 99% can be obtained. Elemental arsenic can be prepared by the reduction of arsenic oxide with charcoal. Demand for elemental arsenic is limited and thus, about 95% of arsenic is marketed and consumed in combined form, principally as arsenic trioxide, which is subsequently converted to arsenic acid (Carapella 1992; Hanusch et al. 1985; USGS 2006a).

Since 1985, when the ASARCO smelter in Tacoma, Washington ceased operation, there has been no domestic production of arsenic trioxide or elemental arsenic and consequently, the United States remains entirely dependent on imports (U.S. Bureau of Mines 1988, 1990; USGS 2006a). Prior to its cessation, U.S. production of arsenic trioxide had been 7,300 metric tons in 1983, 6,800 metric tons in 1984, and 2,200 metric tons in 1985 (U.S. Bureau of Mines 1988). In 2005, arsenic trioxide was obtained from the treatment of nonferrous ores or concentrates in 14 countries. In 2005, the world's largest producer of arsenic trioxide was China, followed by Chile and Peru. China is the world leader in the production of commercial-grade arsenic followed by Japan. The United States, with an apparent demand of 8,800 metric tons in 2005, is the world's leading consumer of arsenic, mainly for CCA. This is an increase over 2004 with an apparent demand of 6,800 metric tons, but far less than that of 2003, 21,600 metric tons (USGS 2006a).

Tables 5-1 and 5-2 list facilities in each state that manufacture or process arsenic and arsenic compounds, respectively, as well as the intended use and the range of maximum amounts of arsenic or arsenic compounds that are stored on site. In 2004, there were 58 and 361 reporting facilities that produced, processed, or used arsenic and arsenic compounds, respectively, in the United States. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI04 2006). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list. Current U.S. manufacturers of selected arsenic compounds are given in Table 5-3.

Table 5-1. Facilities that Produce, Process, or Use Arsenic

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	1,000,000	9,999,999	1, 13
AL	18	0	9,999,999	1, 2, 3, 5, 7, 8, 11, 12, 13, 14
AR	4	1,000	999,999	7, 8
AZ	9	0	99,999	1, 3, 4, 5, 8, 12, 13
CA	31	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
CO	8	0	999,999	2, 7, 8, 11, 12
FL	10	1,000	999,999	1, 3, 5, 7, 8, 11, 12
GA	16	100	49,999,999	2, 3, 4, 6, 7, 8, 11, 12, 13, 14
HI	1	10,000	99,999	8
IA	4	100	99,999	6, 7, 8
ID	7	0	49,999,999	1, 2, 3, 5, 6, 7, 9, 12, 13
IL	16	0	999,999	1, 3, 4, 5, 6, 7, 8, 12, 14
IN	17	0	999,999	1, 3, 5, 6, 7, 8, 9, 12, 13
KY	9	0	999,999	1, 2, 3, 5, 6, 7, 8, 11
LA	8	0	999,999	1, 2, 3, 7, 8, 12, 13
MA	5	1,000	999,999	3, 7, 8
MD	9	0	999,999	1, 2, 4, 5, 6, 7, 8
MI	10	0	999,999	3, 7, 8, 12, 13
MN	5	100	99,999	1, 7, 8, 13
MO	6	100	999,999	1, 2, 3, 4, 5, 6, 7, 8
MS	9	1,000	49,999,999	2, 3, 4, 7, 8, 9
NC	21	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
ND	2	0	99,999	8
NE	1	0	99	8
NJ	9	0	99,999	1, 2, 3, 5, 7, 8, 9
NM	2	10,000	999,999	7, 12
NV	6	1,000	99,999,999	1, 2, 4, 5, 6, 7, 8, 11, 12, 13
NY	4	0	99,999	7, 8, 12
OH	15	0	999,999	1, 2, 3, 4, 5, 8, 9, 12, 13
OK	9	0	99,999	1, 2, 5, 6, 7, 9, 11, 12, 13
OR	6	10,000	999,999	1, 5, 7, 8, 12
PA	24	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
PR	3	1,000	99,999	8, 11
SC	9	0	9,999,999	1, 2, 3, 5, 6, 8, 12
SD	1	10,000,000	49,999,999	1, 7, 11, 13
TN	11	0	999,999	1, 2, 3, 6, 7, 8, 11, 12, 14
TX	29	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
VA	8	0	999,999	2, 3, 7, 8, 10

Table 5-1. Facilities that Produce, Process, or Use Arsenic

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WA	3	0	99,999	5, 7, 8
WI	9	0	99,999	1, 2, 3, 4, 5, 6, 7, 8, 12
WV	19	100	999,999	1, 2, 3, 5, 7, 8, 10, 11, 12
WY	1	100	999	1, 13

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI04 2006 (Data are from 2004)

Table 5-2. Facilities that Produce, Process, or Use Arsenic Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	6	1,000	49,999,999	1, 5, 7, 12, 13, 14
AL	37	0	499,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13
AR	20	1,000	99,999,999	1, 2, 3, 7, 8, 9, 11, 12, 13, 14
AZ	29	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	40	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
CO	9	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
DE	1	10,000	99,999	1, 5, 9
FL	30	0	999,999	1, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
GA	50	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
HI	6	1,000	99,999	7, 8, 11
IA	22	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
ID	6	10,000	9,999,999	1, 3, 5, 6, 7, 8, 9, 12, 13
IL	44	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	54	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
KS	14	0	999,999	1, 3, 4, 5, 6, 7, 8, 12, 13, 14
KY	29	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	32	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
MA	9	0	999,999	1, 4, 5, 6, 7, 8
MD	19	0	999,999	1, 4, 5, 7, 8, 9, 11, 12, 13
ME	2	1,000	99,999	7
MI	32	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
MN	13	0	999,999	1, 3, 4, 5, 7, 8, 9, 11, 12, 13
MO	32	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
MS	28	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
MT	8	1,000	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 12, 13, 14
NC	65	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	11	1,000	99,999	1, 5, 8, 9, 11, 12, 13, 14
NE	6	1,000	999,999	1, 2, 3, 4, 5, 6, 8, 9, 12, 13
NH	2	1,000	99,999	8, 11
NJ	35	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
NM	11	1,000	499,999,999	1, 5, 7, 12, 13
NV	31	1,000	10,000,000,000	1, 2, 3, 5, 6, 7, 9, 11, 12, 13, 14
NY	27	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13
OH	50	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
OK	14	100	9,999,999	1, 2, 3, 4, 5, 6, 8, 12, 13, 14
OR	12	100	99,999	1, 2, 3, 7, 8, 12
PA	53	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
PR	8	1,000	99,999	1, 2, 3, 5, 8, 11
RI	7	100	99,999	7, 8

Table 5-2. Facilities that Produce, Process, or Use Arsenic Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
SC	34	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
SD	6	1,000	99,999,999	1, 5, 6, 7, 8, 11, 12, 13
TN	29	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
TX	54	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
UT	23	0	499,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
VA	24	0	499,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
WA	14	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13
WI	13	100	99,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11
WV	26	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
WY	9	1,000	99,999	1, 3, 4, 5, 7, 8, 9, 12, 13

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI04 2006 (Data are from 2004)

Table 5-3. Current U.S. Manufacturers of Selected Arsenic Compounds[a]

Company	Location(s)
Arsenic acid	
Arch Wood Protection, Inc.	Conley, Georgia
Osmose Wood Preserving, Inc.	Millington, Tennessee
Arsanilic acid	
Fleming Laboratories, Inc.	Charlotte, North Carolina
Copper Chromated Arsenic (CCA)	
Arch Wood Protection, Inc.	Conley, Georgia; Kalama, Washington; Smyrna, Georgia[b]; Valparaiso, Indiana
Chemical Specialties, Inc.[b]	Charlotte, North Carolina
Osmose Wood Preserving, Inc.[b]	Buffalo, New York
Calcium acid methanearsonate (CAMA)	
Drexel Chemical Company (formulator)[c]	No information provided
Disodium methanearsonate (DSMA)	
Drexel Chemical Company	Tunica, Mississippi
Monosodium methyl arsonate (MSMA)	
Drexel Chemical Company	Tunica, Mississippi
Gallium arsenide	
Atomergic Chemetals Corporation	Farmingdale, New York

[a]Derived from Stanford Research Institute (SRI 2006), except where otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed.
[b]USGS 2006a
[c]Meister et al. 2006

5.2 IMPORT/EXPORT

Since U.S. production ceased in 1985, all arsenic consumed in the United States is imported. Imports of arsenic (metal and compounds combined) have increased substantially since the mid-1980s, reaching 8,810 metric tons (as arsenic content) in 2005, of which 812 metric tons was as elemental arsenic. In 2005, 11,000 metric tons of arsenic trioxide was imported into the United States. China is the major import source for elemental arsenic from 2001 to 2004, supplying 81%, followed by Japan (15%) and Hong Kong (2%). China is also the major import source in 2001–2004 for arsenic trioxide, supplying 59% to the United States, followed by Morocco (22%), Chile (7%), and Mexico (5%) (USGS 2006a, 2006b).

U.S. exports of elemental arsenic were 220 metric tons in 2004 and are estimated to be 200 metric tons in 2005 (USGS 2006b). In 2005, U.S. import of arsenic was approximately $8.1x10^5$ kilograms (810 metric tons) (ITA 2007a, 2007b).

5.3 USE

In 2003, the United States was the world's largest consumer of arsenic, with an apparent demand of 21,600 metric tons. In 2005, the Unites States was still the world's largest consumer of arsenic, mainly for CCA. Production of wood preservatives, primarily CCA, CrO_3•CuO•As_2O_5, accounted for >90% of domestic consumption of arsenic trioxide prior to 2004. In 2005, about 65% of domestic consumption of arsenic trioxide was used for the production of CCA. The remainder was used for the production of agricultural chemicals, including herbicides, and insecticides. The major U.S. producers of CCA in 2005 included Arch Wood Protection, Inc., Smyrna Georgia; Chemical Specialties Inc., Charlotte, North Carolina; and Osmose Wood Preserving, Inc., Buffalo, New York (USGS 2006a). CCA is the most widely used wood preservative in the world. Wood treated with CCA is referred to as 'pressure treated' wood (American Wood Preservers Association 2007; Page and Loar 1993). In 1997, approximately 727.8 million cubic feet (20.6 million cubic meters) of wood products were pressure treated in the United States. CCA is a water-based product that protects several commercially available species of western lumber from decay and insect attack. It is widely used in treating utility poles, building lumber, and wood foundations. CCA comes in three types, A, B, and C, which contain different proportions of chromium, copper, and arsenic oxides. Type C, the most popular type, contains CrO_3, CuO, and As_2O_5 in the proportions 47.5, 18.5, and 34.0%, respectively. The retention levels are 0.25 pounds per cubic feet (pcf) for above ground use such as fencing and decking, 0.40 pcf for lumber used in ground contact such as

fence posts and deck posts, and 0.60 pcf for all weather wood foundations (Chicago Flameproof 2000; Permapost 2000). Piling used for fresh and saltwater contact should contain 0.80 and 2.5 pcf of CCA, respectively. Ammoniacal copper zinc arsenate (ACZA) is another arsenic containing preservative used to treat wood; however, it is not as widely used as CCA–C (Lebow et al. 2000).

In 2003, U.S. manufacturers of arsenical wood preservatives began a voluntary transition from CCA to other wood preservatives in wood products for certain residential uses, such as play structures, picnic tables, decks, fencing, and boardwalks. This phase out was completed on December 31, 2003; wood treated prior to this date could still be used and structures made with CCA-treated wood would not be affected. CCA-treated wood products continue to be used in industrial applications (EPA 2003a).

Elemental arsenic is used as an alloying element in ammunition and solders, as an anti-friction additive to metals used for bearings, and to strengthen lead-acid storage battery grids. In the past, the predominant use of arsenic was in agriculture. The uses of lead arsenate as a growth regulator on citrus, calcium arsenate as an herbicide on turf, sodium arsenite as a fungicide on grapes, and arsenic acid as a desiccant on okra for seed and cotton were voluntarily cancelled in the late 1980s and the early 1990s (EPA 2006). The herbicides, MSMA and DSMA, are registered for weed control on cotton, for turf grass and lawns, and under trees, vines, and shrubs; calcium acid methanearsonate (CAMA) is registered for postemergent weed control on lawns. Cacodylic acid, a defoliant and herbicide, is registered for weed control under nonbearing citrus trees, around buildings and sidewalks, and for lawn renovation (EPA 2006). Approximately 3 million pounds of MSMA or DSMA, and 100,000 pounds of cacodylic acid are applied in the U.S. annually based on EPA's Screening Level Use Analysis data. Data were not available for CAMA. Application to cotton and turf (residential and golf courses) are the major uses of organic arsenical herbicides. Currently, there are approximately 90, 25, 4, and 35 end-use products containing MSMA, DSMA, CAMA, and cacodylic acid, respectively (EPA 2006).

Other organic arsenicals used in agriculture include arsanilic acid, sodium arsanilate, and 3-nitro-4-hydroxyphenylarsonic acid (roxarsone), which are antimicrobials used in animal and poultry feeds (Beerman 1994). While the U.S. Food and Drug Administration (FDA) has authorized the used of these compounds as medicinal feed additives, only one of the arsenical compounds may be used at a time as the sole source of organic arsenic in the feed (EPA 1998k). In 1999–2000, about 70% of the broiler industry added roxarsone to broiler poultry feed; concentrations of roxarsone in feed range from 22.7 to 45.4 g/ton (Garbarino et al. 2003).

From the mid-nineteenth century to the introduction of organic pesticides in the 1940s, inorganic arsenic compounds were the dominant pesticides available to farmers and fruit growers. Calcium arsenate was formerly used to control the boll weevil and cotton worm and was used as an herbicide. Lead arsenate was used on apple and other fruit orchards as well as on potato fields. Sodium arsenite was used to control weeds on railroad right-of-ways, potato fields, and in industrial areas, as well as in baits and to debark trees. Sodium arsenate had some application in ant traps. The use of inorganic arsenic compounds in agriculture has virtually disappeared beginning around the 1960s (Azcue and Nriagu 1994; Meister 1987; Merwin et al. 1994; Sanok et al. 1995). Food uses were voluntarily cancelled in 1993 as was the use of arsenic acid as a defoliant on cotton plants; inorganic arsenic's remaining allowable uses are in ant baits and wood preservatives (EPA 1999h). In 1987, EPA issued a preliminary decision to cancel the registration of most inorganic arsenicals used as nonwood pesticides (Loebenstein 1994) (see Chapter 8). According to the California Department of Pesticide Regulation, arsenic acid, arsenic pentoxide, and arsenic trioxide are registered currently as pesticides in the United States; there are no active registrants listed for calcium arsenate, lead arsenate, or sodium arsenite (NPIRS 2007).

High-purity arsenic (99.9999%) is used by the electronics industry for gallium-arsenide semiconductors for telecommunications, solar cells, and space research (USGS 2006b). Arsenic trioxide and arsenic acid were used as a decolorizer and fining agent in the production of bottle glass and other glassware (Carapella 1992).

Arsenic compounds have a long history of use in medicine. Inorganic arsenic was used as a therapeutic agent through the mid-twentieth century, primarily for the treatment of leukemia, psoriasis, and chronic bronchial asthma; organic arsenic antibiotics were extensively used in the treatment of spirochetal and protozoal disease (NRC 1999). The availability of inorganic arsenicals in Western medicines ended in the 1970s, although they may still be encountered in non-Western traditional medicines. By the 1980s, the only remaining medicinal organic arsenical was melarsoprol for treatment of the meningoencephalitic stage of African trypanosomiasis. There has been renewed interest in arsenic as a therapeutic agent, namely the use of arsenic trioxide in the treatment of acute promyelocytic leukemia (APL) (Gallagher 1998; Kroemer and de Thé 1999; Miller 1998; Wang 2001). In 2000, the FDA approved arsenic trioxide for this use (FDA 2000).

5.4 DISPOSAL

Wastes containing arsenic are considered hazardous wastes, and as such, their treatment, storage, and disposal are regulated by law (see Chapter 8). The main route of disposal of solid wastes containing arsenic is landfilling. EPA has promulgated rules and treatment standards for landfilling liquid arsenical wastes (EPA 1990e). Arsenic-containing electronic components such as relays, switches, and circuit boards are disposed of at hazardous waste sites, and the elemental arsenic is not reclaimed. Process water at wood treatment plants that contained arsenic contained was reused. Gallium-arsenide scrap from the manufacture of semiconductor devices was reprocessed for arsenic recovery. Arsenic was not recovered from arsenical residues and dusts at domestic nonferrous smelters (USGS 2006b).

CCA-treated wood is classified as nonhazardous waste under the Federal Resource Conservation and Recovery Act (RCRA). CCA-treated wood is disposed of with regular municipal trash (i.e., municipal solid waste, not yard waste). It should not be burned in open fires, stoves, residential boilers, or fire places and should not be composted or used as mulch. Treated wood from commercial or industrial applications may only be burned in commercial or industrial incinerators in accordance with state and federal regulations (Adobe Lumber 2002; EPA 2005a).

Arsenic is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995c). Disposal of wastes containing arsenic is controlled by a number of federal regulations (see Chapter 8).

6. POTENTIAL FOR HUMAN EXPOSURE

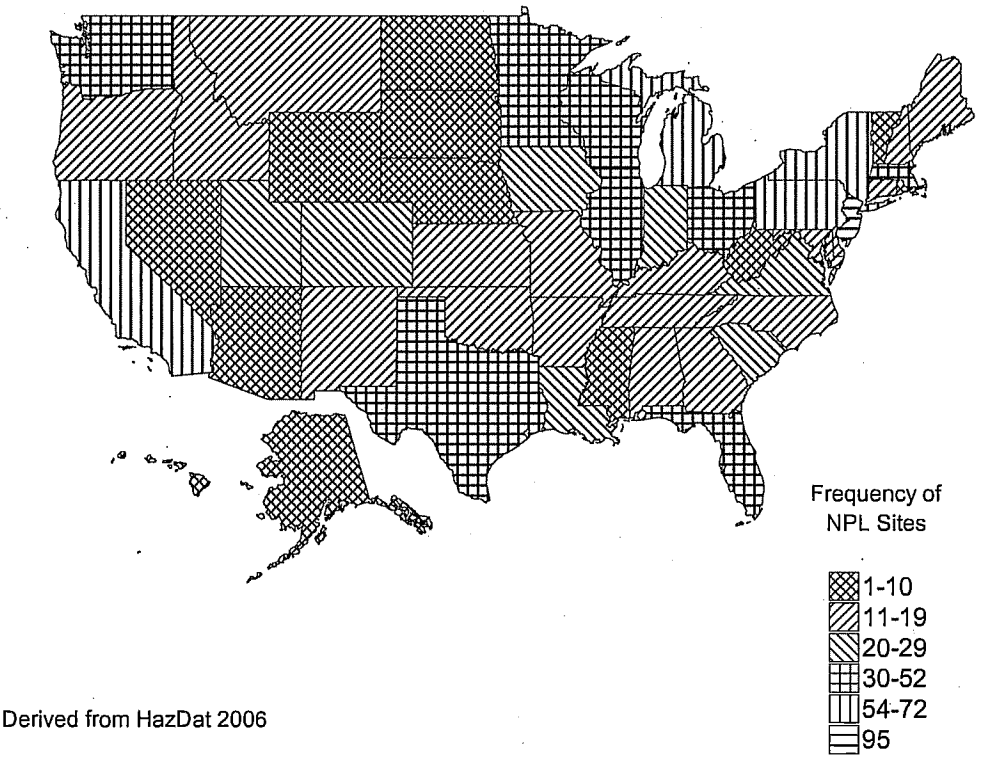
6.1 OVERVIEW

Arsenic has been identified in at least 1,149 of the 1,684 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2006). However, the number of sites evaluated for arsenic is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 1,134 are located within the United States and 11, 2, and 2 are located in the Commonwealth of Puerto Rico, the Virgin Islands, and Guam (not shown).

Arsenic is widely distributed in the Earth's crust, which contains about 3.4 ppm arsenic (Wedepohl 1991). It is mostly found in nature in minerals, such as realgar (As_4S_4), orpiment (As_2S_3), and arsenolite (As_2O_3), and only found in its elemental form to a small extent. There are over 150 arsenic-bearing minerals (Budavari et al. 2001; Carapella 1992). While arsenic is released to the environment from natural sources such as wind-blown soil and volcanoes, releases from anthropogenic sources far exceed those from natural sources. Anthropogenic sources of arsenic include nonferrous metal mining and smelting, pesticide application, coal combustion, wood combustion, and waste incineration. Most anthropogenic releases of arsenic are to land or soil, primarily in the form of pesticides or solid wastes. However, substantial amounts are also released to air and water.

Arsenic found in soil either naturally occurring or from anthropogenic releases forms insoluble complexes with iron, aluminum, and magnesium oxides found in soil surfaces, and in this form, arsenic is relatively immobile. However, under reducing conditions, arsenic can be released from the solid phase, resulting in soluble mobile forms of arsenic, which may potentially leach into groundwater or result in runoff of arsenic into surface waters. In aquatic systems, inorganic arsenic occurs primarily in two oxidation states, As(V) and As(III). Both forms generally co-exist, although As(V) predominates under oxidizing conditions and As(III) predominates under reducing conditions. Arsenic may undergo a variety of reactions in the environment, including oxidation-reduction reactions, ligand exchange, precipitation, and biotransformation (EPA 1979, 1984a; Pongratz 1998; Welch et al. 1988). These reactions are influenced by Eh (the oxidation-reduction potential), pH, metal sulfide and sulfide ion concentrations, iron concentration, temperature, salinity, and distribution and composition of the biota (EPA 1979; Wakao et al. 1988). Much of the arsenic will adsorb to particulate matter and sediment. Arsenic released to air exists mainly in the form of particulate matter. Arsenic released from combustion processes will

Figure 6-1. Frequency of NPL Sites with Arsenic Contamination



generally occur as highly soluble oxides. These particles are dispersed by the wind and returned to the earth in wet or dry deposition. Arsines that are released to the atmosphere as a result of microbial action are oxidized to nonvolatile species that settle back to the ground.

Because arsenic is a natural component of the Earth's crust, low levels of the element are found in all environmental media. Atmospheric levels of arsenic in remote locations (away from human releases) range from 1 to 3 ng/m^3, while concentrations in urban areas may range from 20 to 100 ng/m^3. Concentrations in water are usually <10 μg/L, although higher levels may occur near natural mineral deposits or anthropogenic sources. Natural levels of arsenic in soil usually range from 1 to 40 mg/kg, with a mean of 5 mg/kg, although much higher levels may occur in mining areas, at waste sites, near high geological deposits of arsenic-rich minerals, or from pesticide application. Arsenic is also found in many foods, at concentrations that usually range from 20 to 140 μg/kg. Total arsenic concentrations may be substantially higher in certain seafoods. However, the general consensus in the literature is that about 85–>90% of the arsenic in the edible parts of marine fish and shellfish is organic arsenic (e.g., arsenobetaine, arsenochloline, dimethylarsinic acid) and that approximately 10% is inorganic arsenic (EPA 2003b). Drinking water in the United States generally contains an average of 2 μg/L of arsenic (EPA 1982c), although 12% of water supplies from surface water sources in the north Central region of the United States and 12% of supplies from groundwater sources in the western region have levels exceeding 20 μg/L (Karagas et al. 1998). In January 2001, EPA adopted a new standard that arsenic levels in drinking water were not to exceed 10 μg/L, replacing the previous standard of 50 μg/L. The date for compliance with the new MCL was January 23, 2006 (EPA 2001).

For most people, diet is the largest source of exposure to arsenic. Mean dietary intakes of total arsenic of 50.6 μg/day (range of 1.01–1,081 μg/day) and 58.5 μg/day (range of 0.21–1,276 μg/day) has been reported for females and males (MacIntosh et al. 1997). U.S. dietary intake of inorganic arsenic has been estimated to range from 1 to 20 μg/day, with grains and produce expected to be significant contributors to dietary inorganic arsenic intake (Schoof et al. 1999a, 1999b). The predominant dietary source of arsenic is generally seafood. Inorganic arsenic in seafood sampled in a market basket survey of inorganic arsenic in food ranged from <0.001 to 0.002 μg/g (Schoof et al. 1999a, 1999b). Intake of arsenic from air and soil are usually much smaller than that from food and water (Meacher et al. 2002).

People who produce or use arsenic compounds in occupations such as nonferrous metal smelting, pesticide manufacturing or application, wood preservation, semiconductor manufacturing, or glass production may be exposed to substantially higher levels of arsenic, mainly from dusts or aerosols in air.

Exposure at waste sites may occur by a variety of pathways, including inhalation of dusts in air, ingestion of contaminated soil or water, or through the food chain. The magnitude of the exposures can only be evaluated on a site-by-site basis; however, exposures generally do not exceed background intakes from food and drinking water.

Tables 4-1, 4-2, 4-3, and 4-4 summarize all of the names, abbreviations, and structures of the various arsenic compounds that are discussed in Chapter 6.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005k). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005k).

6.2.1 Air

Estimated releases of 4,800 pounds (~2.2 metric tons) of arsenic to the atmosphere from 58 domestic manufacturing and processing facilities in 2004, accounted for about 0.52% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). Estimated releases of 0.13 million pounds (~59 metric tons) of arsenic compounds to the atmosphere from 361 domestic manufacturing and processing facilities in 2004, accounted for about 0.11% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases for arsenic and arsenic compounds are summarized in Table 6-1 and 6-2, respectively.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	1	51	162	0	110,264	0	110,425	52	110,477
AR	2	0	0	No data	0	0	No data	0	0
AZ	2	10	0	0	20,717	0	20,727	0	20,727
CA	3	13	14	0	5,482	0	13	5,497	5,510
FL	2	4	0	0	0	4,950	4	4,950	4,954
GA	4	8	10	0	1,603	5	13	1,613	1,626
IA	1	0	1	0	0	0	0	1	1
ID	1	39	0	0	361,252	0	361,291	0	361,291
IL	2	250	129	0	14,087	0	379	14,087	14,466
IN	1	5	5	0	13,250	250	5	13,505	13,510
KS	1	0	0	No data	0	0	No data	0	0
KY	1	0	1	0	0	6	1	6	7
MI	2	0	5	0	0	750	5	750	755
MN	1	15	47	0	14,504	0	15	14,551	14,566
MO	1	5	0	0	0	4,040	5	4,040	4,045
MS	2	0	0	0	0	0	0	0	0
NC	4	35	8	0	1	1	43	2	45
NV	1	0	0	0	0	0	0	0	0
NY	4	0	1	0	26,525	1	26,401	126	26,527
OH	2	13	0	0	0	0	13	0	13
OR	1	0	0	0	92,606	0	92,606	0	92,606
PA	5	166	8	0	14,362	26,140	199	40,477	40,676
SC	3	10	10	0	0	1,002	15	1,007	1,022
TN	3	3,988	0	0	0	0	3,988	0	3,988
TX	5	139	376	168,563	12,600	0	181,636	42	181,678

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WI	2	15	0	0	760	0	15	760	776
WV	1	0	0	0	10,135	0	10,135	0	10,135
Total	58	4,766	778	168,563	698,149	37,145	807,935	101,466	909,401

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	511	0	1,400,000	1,200,000	0	2,600,511	0	2,600,511
AL	19	4,299	18,127	0	853,469	7,555	875,876	7,574	883,450
AR	12	0	0	0	133	26,435	0	26,568	26,568
AZ	5	5,421	0	0	402,335	422	394,749	13,429	408,178
CA	5	65	14	0	355,660	86,396	160,673	281,461	442,134
CO	1	11	0	0	4,094	0	4,105	0	4,105
CT	1	0	0	0	0	0	No data	0	0
FL	15	3,208	503	0	343,508	4,057	346,310	4,966	351,276
GA	23	8,643	7,823	0	422,124	5,127	437,496	6,221	443,717
HI	1	0	0	0	0	0	No data	0	0
IA	4	1,291	482	0	0	35,324	1,773	35,324	37,097
ID	3	332	20	0	1,056,904	0	1,057,256	0	1,057,256
IL	11	3,960	3,110	0	96,093	21,038	71,819	52,382	124,202
IN	21	13,786	8,282	0	768,297	42,808	632,704	200,470	833,174
KS	4	924	0	0	12,082	1	13,006	1	13,007
KY	18	14,406	8,427	0	616,074	95,285	578,080	156,112	734,192
LA	7	265	23	0	25,426	0	25,563	151	25,714
MA	1	0	0	0	0	500	0	500	500
MD	8	1,870	291	0	34,130	114,115	2,661	147,745	150,406
MI	10	1,123	2,310	68,924	101,857	1,059	77,505	97,769	175,274
MN	2	10	130	0	19,270	0	19,410	0	19,410
MO	6	462	116	0	27,855	936	10,026	19,343	29,369
MS	6	61	121	0	11,676	46	11,228	676	11,904
MT	3	630	0	0	2,138,190	37	2,138,820	37	2,138,857
NC	15	5,626	4,732	0	168,030	2,429	178,388	2,429	180,818
ND	6	6,326	5	0	318,175	0	137,961	186,545	324,506
NE	2	180	0	0	11,000	0	11,180	0	11,180
NJ	2	0	1	0	0	8	0	9	9
NM	2	130	0	0	18,326	0	18,456	0	18,456
NV	10	3,041	30,017	0	98,894,564	0	98,927,328	294	98,927,622
NY	3	67	36	0	27,059	802	27,141	823	27,964
OH	17	8,595	8,352	81,024	741,730	274	668,157	171,818	839,975
OK	4	115	13	0	25,000	4,202	115	29,215	29,330
OR	4	0	5	0	0	4,012	5	4,012	4,017
PA	23	18,963	2,166	0	666,753	69,053	403,582	353,353	756,935
PR	3	0	0	0	0	0	No data	0	0
RI	1	0	8	0	0	1,006	8	1,006	1,014

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
SC	13	2,178	1,443	0	25,817	22,705	29,438	22,705	52,143
SD	1	0	0	0	0	0	No data	0	0
TN	13	3,379	25,878	0	292,914	17,219	258,643	80,746	339,389
TX	17	4,616	199	33,148	196,385	31,557	226,751	39,155	265,906
UT	5	6,715	4,500	0	6,368,500	3,500	6,379,715	3,500	6,383,215
VA	11	1,911	2,773	0	160,154	8,463	164,789	8,512	173,301
WA	4	0	0	0	0	0	No data	0	0
WI	4	94	21	0	1,313	9,216	223	10,421	10,644
WV	12	2,693	2,417	0	536,628	10,000	441,237	110,501	551,738
WY	2	3,300	0	0	10,800	0	14,100	0	14,100
Total	361	129,205	132,347	1,583,096	116,952,326	625,588	117,346,787	2,075,775	119,422,562

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

Arsenic naturally occurs in soil and will be present in the atmosphere as airborne dust. It is also emitted from volcanoes and in areas of dormant volcanism (e.g., fumaroles). Gaseous alkyl arsenic compounds may be released from soil that has been treated with inorganic arsenic compounds as a result of biogenic processes (Schroeder et al. 1987; Tamaki and Frankenberger 1992). Arsenic naturally occurs in sea water and vegetation and is released into the atmosphere in sea salt spray and forest fires. Anthropogenic sources of arsenic include nonferrous metal smelting, coal, oil and wood combustion, and municipal waste incineration. Arsenic naturally occurs in coal and oil and therefore, coal- and oil-fired power plants release arsenic to the atmosphere in their emissions (Pacyna 1987). Arsenic's use in agriculture and industrial processes also contributes to its emissions. One important source of arsenic emissions is cotton ginning in which the cotton seeds are removed from the raw cotton.

The National Air Toxics Assessment reported that total anthropogenic emissions for arsenic compounds in the United States in 1996 were 355 tons/year (EPA 2005b). EPA conducted a modeling study with the Assessment System for Population Exposure Nationwide (ASPEN) in which estimates of emissions of hazardous air pollutants were used to estimate air quality (Rosenbaum et al. 1999). Using 1990 data, the total emissions of arsenic in the conterminous 48 states, excluding road dust or windblown dust from construction or agricultural tilling was estimated to be 3.0 tons/day with 90% of emissions coming from point sources and 5% each from area and mobile sources. U.S. emissions of arsenic to the atmosphere were estimated as 3,300 metric tons per year between 1979 and 1986 (Pacyna et al. 1995). There is evidence that anthropogenic emissions, at least from smelters, are lower than they had been in the early 1980s. It is likely that air releases of arsenic decreased during the 1980s due to regulations on industrial emissions (EPA 1986f), improved control technology for coal-burning facilities, and decreased use of arsenical pesticides.

Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated worldwide emissions of arsenic to the atmosphere for 1983. Estimates of yearly emissions from anthropogenic sources ranged from 12,000 to 25,600 metric tons with a median value of 18,800 metric tons. Natural sources contributed 1,100–23,500 metric tons annually. Chilvers and Peterson (1987) estimated global natural and anthropogenic arsenic emissions to the atmosphere as 73,500 and 28,100 metric tons per year, respectively. Copper smelting and coal combustion accounted for 65% of anthropogenic emissions. A U.S. Bureau of Mines study on the flow of mineral commodities estimated that global emissions of arsenic from metal smelting, coal burning, and other industrial uses ranged from 24,000 to 124,000 metric tons per year compared to natural releases, mostly from volcanoes, ranging from 2,800 to 8,000 metric tons per year (Loebenstein 1994).

Pirrone and Keeler (1996) compared trends of trace element emissions from major anthropogenic sources in the Great Lakes region with ambient concentrations observed in urban areas of the region. They found that arsenic emissions increased about 2.8% per year from 1982 to 1988 and then decreased steadily by about 1.4% per year to 1993. Coal combustion in electric utilities and in residential, commercial, and industrial facilities was an important source of arsenic in the region, accounting for about 69% of the total emissions. Iron-steel manufacturing accounted for about 13% of the region wide arsenic emissions and nonferrous metals production for 17%.

Arsenic in the particulate phase is the predominant (89–98.6%) form of arsenic in the troposphere (Matschullat 2000). Inorganic species, most commonly trivalent arsenic, is the dominant form of arsenic in the air over emission areas; methylated forms of arsenic are probably of minor significance. Arsenic-containing air samples of smelter or coal-fired power plant origin consist largely of trivalent arsenic in both vapor and particulate form (Pacyna 1987). Oxides are the primary species evolved from fossil fuel and industrial processes. Additionally, arsenic trisulfide has also been reported from coal combustion, organic arsines from oil combustion, and arsenic trichloride from refuse incineration.

Arsenic has been identified in 59 air samples collected from 1,684 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2006).

6.2.2 Water

Estimated releases of 780 pounds (~0.35 metric tons) of arsenic to surface water from 58 domestic manufacturing and processing facilities in 2004, accounted for about 0.09% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). Estimated releases of 1.3x105 pounds (~59 metric tons) of arsenic compounds to surface water from 361 domestic manufacturing and processing facilities in 2004, accounted for about 0.11% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases for arsenic and arsenic compounds are summarized in Tables 6-1 and 6-2, respectively.

Arsenic may be released to water from the natural weathering of soil and rocks, and in areas of vulcanism. Arsenic may also leach from soil and minerals into groundwater. Anthropogenic sources of arsenic releases to water include mining, nonferrous metals, especially copper, smelting, waste water, dumping of sewage sludge, coal burning power plants, manufacturing processes, urban runoff, atmospheric deposition and poultry farms (Garbarino et al. 2003; Nriagu and Pacyna 1988; Pacyna et al. 1995). A contributory

part of mining and coal burning power plants is leaching from abandoned mine tailing and fly ash waste piles. Significant amounts of arsenic are released in liquid effluents from gold-milling operations using cyanide (Environment Canada 1993). Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated global anthropogenic inputs of arsenic into rivers, lakes, and oceans for 1983; annual estimated inputs ranged from 11,600 to 70,300 metric tons with a median value of 41,800 metric tons. Arsenic was detected in 58% of samples of urban storm water runoff from 8 of 15 cities surveyed in the National Urban Runoff Program at concentrations ranging from 1 to 50.5 μg/L (Cole et al. 1984).

Leaching of arsenic from soil, landfills, or slag deposits is a source of arsenic in groundwater (Francis and White 1987; Wadge and Hutton 1987). The arsenic in soil may be naturally-occurring or a result of the application of arsenic-containing pesticides or sludge. Wood treated with CCA is used in piers, piling and bulkheads and arsenic can leach from the treated wood (Breslin and Adler-Ivanbrook 1998; Brooks 1996; Cooper 1991; Sanders et al. 1994; Weis et al. 1998). Ammoniacal copper zinc arsenate (ACZA) is another arsenic-containing waterborne preservative; however, it is not as widely used as CCA (Lebow et al. 2000).

Arsenic has been identified in 846 groundwater and 414 surface water samples collected from 1,684 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2006).

6.2.3 Soil

Estimated releases of 0.70 million pounds (~320 metric tons) of arsenic to soils from 58 domestic manufacturing and processing facilities in 2004, accounted for about 77% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). An additional 0.17 million pounds (~77 metric tons), constituting about 19% of the total environmental emissions, were released via underground injection (TRI04 2006). Estimated releases of 117 million pounds (~5.3x104 metric tons) of arsenic compounds to soils from 361 domestic manufacturing and processing facilities in 2004, accounted for about 98% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). An additional 1.6 million pounds (~720 metric tons), constituting about 1.3% of the total environmental emissions, were released via underground injection (TRI04 2006). These releases for arsenic and arsenic compounds are summarized in Tables 6-1 and 6-2, respectively.

The soil receives arsenic from a variety of anthropogenic sources, including ash residue from power plants, smelting operations, mining wastes, and municipal, commercial, and industrial waste. Ash from

power plants is often incorporated into cement and other materials that are used for roads and construction. Arsenic may be released from such material into soil. Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated global anthropogenic inputs of arsenic into soil for 1983. Excluding mine tailings and smelter slag, annual estimated inputs ranged from 52,000 to 112,000 metric tons with a median value of 82,000 metric tons. Mine tailings and smelter slag were estimated to add an additional 7,200–11,000 and 4,500–9,000 metric tons, respectively. Old abandoned mine tailings undoubtedly contribute still more. Wood treated with CCA used in foundations or posts could potentially release arsenic into the surrounding soil. CCA preservatives have been shown to leach to varying degrees from wood, as well as through soils in both field and laboratory studies (Chirenje et al. 2003a; Hingston et al. 2001; Lebow et al. 2000; Rahman et al. 2004; Stilwell and Graetz 2001; USDA/USDT 2000). Arsenic may also be released on land through the application of pesticides and fertilizer. Senesi et al. (1999) reported the range of arsenic in 32 fertilizers as 2.2–322 ng/g. Roxarsone (3-nitro-4-hydroxyphenyl-arsonic acid), which was used to treat poultry feed in approximately 70% of the broiler poultry operations in 1999–2000, is excreted unchanged in the manure. Poultry litter (manure and bedding) is routinely used as fertilizer to cropland and pasture. In 2000, assuming 70% of the 8.3 billion broiler poultry produced in the United States were fed roxarsone-treated feed, the resulting manure would contain approximately $2.5x10^5$ kg of arsenic (Garbarino et al. 2003). Land application of sewage sludge is another source of arsenic in soil. Arsenic was detected in sewage sludge samples from 23 cities at concentrations of 0.3–53 μg/g (Mumma et al. 1984).

Arsenic has been identified in 758 soil and 515 sediment samples collected from 1,684 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2006).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Arsenic in soil may be transported by wind or in runoff or may leach into the subsurface soil. However, because many arsenic compounds tend to partition to soil or sediment under oxidizing conditions, leaching usually does not transport arsenic to any great depth (EPA 1982c; Moore et al. 1988; Pantsar-Kallio and Manninen 1997; Welch et al. 1988). Arsenic is largely immobile in agricultural soils; therefore, it tends to concentrate and remain in upper soil layers indefinitely. Downward migration has been shown to be greater in a sandy soil than in a clay loam (Sanok et al. 1995). Arsenic from lead arsenate that was used for pest control did not migrate downward below 20 cm in one fruit orchard; in another orchard, 15 years after sludge amendments and deep plowing, essentially all arsenic residues

remained in the upper 40 cm of soil (Merwin et al. 1994). Leaching of arsenic in polluted wetland soil was low; leaching was correlated with the amount of dissolved organic matter in the soil (Kalbitz and Wennrich 1998). The effect of soil characteristics, namely pH, organic matter content, clay content, iron oxide content, aluminum oxide content, and cation exchange capacity (CEC), on the adsorption of various metals, including the metalloid arsenic, to 20 Dutch surface soils was assessed by regression analysis (Janssen et al. 1997). The most influential parameter affecting arsenic adsorption was the iron content of the soil.

Arsenic that is adsorbed to iron and manganese oxides may be released under reducing conditions, which may occur in sediment or flooding conditions (LaForce et al. 1998; McGeehan 1996; Mok and Wai 1994). In addition to reductive dissolution, when nutrient levels are adequate, microbial action can also result in dissolution (LaForce et al. 1998). Interestingly, drying of the previously flooded soil increases arsenic adsorption, possibly due to alterations in iron mineralogy (McGeehan et al. 1998).

Darland and Inskeep (1997) conducted a study to determine the effects of pH and phosphate competition on the transport of arsenate ($H_xAsO_4^{x-3}$) through saturated columns filled with sand containing free iron oxides. At pH 4.5 and 6.5, arsenate transport was strongly retarded, while at pH 8.5, it was rapid. The enhanced transport of arsenate at pH 8 is consistent with the pH dependence of surface complexation reactions describing arsenate sorption by metal oxide minerals that can be categorized as a ligand exchange mechanism. Phosphate was shown to compete effectively with arsenate for adsorption sites on the sand, but the competition was not sufficient to desorb all of the arsenate in batch column experiments, even when the applied phosphate exceeded the column adsorption capacity by a factor of two. The researchers concluded that arsenate desorption kinetics may play an important role in the transport of arsenate through porous media. In a study looking at the effect of competing anions on the adsorption of arsenite and arsenate on ferrihydrite, the effect of phosphate on arsenate adsorption was greater at higher pH than at low pH and the opposite trend was observed for arsenite. While sulfate did not change the affinity of arsenate for ferrihydrite, sulfate reduced the adsorption of arsenite at pHs below 7.0 (Jain and Loeppert 2000).

Smith et al. (1999) investigated the sorption properties of both As(V) and As(III) in 10 Australian soils of widely different chemistry and mineralogy at commonly found arsenic levels. Adsorption of both arsenate and arsenite was rapid (1 hour). The amount of As(V) sorbed varied widely (1.7–62.0 L/kg); soils with lower amounts of oxidic material adsorbed much less arsenic than those with higher amounts of these minerals. Arsenate sorption was highly correlated with the iron oxide content of the soil and this

factor probably accounts for much of the variation in soil adsorptivity. Considerable leaching of arsenic occurred at a separate site where cattle were treated with a dip containing arsenic (cattle dip site) and that contained similar soil properties to that studied by Smith et al. (1999). Arsenite adsorption, which was investigated in four of the Australian soils, was sorbed to a lesser extent than was arsenate. This was attributed to soil minerology and the species of As(V) (arsenate) and As(III) (arsenite) present in solution; at pH 5–7, the dominant As(V) species are $H_2AsO_4^-$ and $HAsO_4^{2-}$ and neutral H_3AsO_3 is the dominant As(III) species. For soils containing low amounts of oxidic minerals, pH had little effect on As(V) sorption, while for oxidic soils, a decrease in sorption was evident as the pH increased. In contrast, As(III) sorption increased with increasing pH (Smith et al. 1999). Jain et al. (1999) reported similar results where arsenite were both found to bind strongly to iron oxides; however, the adsorption of arsenate decreases with increasing pH, while the adsorption of arsenite increases with increasing pH (Jain et al. 1999). As(III), which exists in a neutral form as arsenous acid, H_3AsO_3 (pK_a=9.23, 12.13, 13.4), is less strongly adsorbed on mineral surfaces than the oxyanions of arsenic acid, H_3AsO_4, (pK_a=2.22, 6.98, 11.53) (NRC 1999). Based on its pK_a values, arsenic acid would exist as a mixture of arsenate anions, $H_2AsO_4^-$ and $HAsO_4^{2-}$, under most environmental conditions (pH 5–9).

The practice of liming to remediate contaminated soils and mine tailings has the potential to mobilize arsenic. Experiments performed by Jones et al. (1997) indicate that the increased mobility appears to be consistent with the pH dependence of sorption reactions of arsenic on iron oxide minerals rather than dissolution-precipitation reactions involving arsenic. They recommend that remediation of acidic mine tailings or other arsenic-contaminated soils be carefully evaluated with respect to potential arsenic mobilization, especially at contaminated sites hydraulically connected to surface or groundwaters.

Transport and partitioning of arsenic in water depends upon the chemical form (oxidation state and counter ion) of the arsenic and on interactions with other materials present. Soluble forms move with the water, and may be carried long distances through rivers (EPA 1979). However, arsenic may be adsorbed from water onto sediments or soils, especially clays, iron oxides, aluminum hydroxides, manganese compounds, and organic material (EPA 1979, 1982c; Welch et al. 1988). Under oxidizing and mildly reducing conditions, groundwater arsenic concentrations are usually controlled by adsorption rather than by mineral precipitation. The extent of arsenic adsorption under equilibrium conditions is characterized by the distribution coefficient, K_d, which measures the equilibrium partitioning ratio of adsorbed to dissolved contaminant. The value of K_d depends strongly upon the pH of the water, the arsenic oxidation state, and the temperature. In acidic and neutral waters, As(V) is extensively adsorbed, while As(III) is relatively weakly adsorbed. Trivalent inorganic arsenic exists predominantly as arsenous acid (H_3AsO_3)

at environmental pH and is not strongly adsorbed to suspended solids and sediments in the water column. Pentavalent inorganic arsenic exists predominantly as $H_2AsO_4^-$ and $HAsO_4^{2-}$ in most environmental waters, which has considerably greater adsorption characteristics than arsenous acid. While in acidic and neutral waters, As(V) is more strongly adsorbed relative to As(III), in high-pH waters (pH >9) aquifer K_d values are considerably lower for both oxidation states (Mariner et al. 1996). Sediment-bound arsenic may be released back into the water by chemical or biological interconversions of arsenic species (see Section 6.3.2).

Arsenic enters rivers from where mining operations occurred and is transported downstream, moving from water and sediment into biofilm (attached algae, bacterial, and associated fine detrital material), and then into invertebrates and fish. The source of arsenic in the water column may be resuspended sediment. While arsenic bioaccumulates in animals, it does not appear to biomagnify between tropic levels (Eisler 1994; Farag et al. 1998; Williams et al. 2006).

Most anthropogenic arsenic emitted to the atmosphere arises from high temperature processes (e.g., coal and oil combustion, smelting operations, and refuse incineration) and occurs as fine particles with a mass median diameter of about 1 μm (Coles et al. 1979; Pacyna 1987). These particles are transported by wind and air currents until they are returned to earth by wet or dry deposition. Their residence time in the atmosphere is about 7–9 days, in which time the particles may be transported thousands of kilometers (EPA 1982b; Pacyna 1987). Long-range transport was evident in analyzing deposition of arsenic in countries like Norway; there was no indication that the marine environment contributed significantly to the deposition (Steinnes et al. 1992). Atmospheric fallout can be a significant source of arsenic in coastal and inland waters near industrial areas. Scudlark et al. (1994) determined the average wet depositional flux of arsenic as 49 μg As/m^2/year for two sites in Chesapeake Bay, Maryland from June 1990 to July 1991. They found a high degree of spatial and temporal variability. The elemental fluxes derived predominantly from anthropogenic sources. Golomb et al. (1997) report average total (wet + dry) deposition rates to Massachusetts Bay of 132 μg/m^2/year, of which 21 μg/m^2/year was wet deposition during the period September 15, 1992–September 16, 1993. Hoff et al. (1996) estimated the following arsenic loadings into the Great Lakes for 1994 (lake, wet deposition, dry deposition): Superior, 11,000 kg/year, 3,600 kg/year; Michigan, 5,000 kg/year, 1,800 kg/year; Erie, 5,500 kg/year, 1,800 kg/year; and Ontario, 3,000 kg/year, 580 kg/year. The measured dry deposition fluxes of arsenic at four sampling sites around Lake Michigan ranged approximately from 0.01 to 1.5 μg As/m^2/day; estimated inputs of arsenic into Lake Michigan were reported to be $1.4x10^3$ kg/year (Shahin et al. 2000).

Terrestrial plants may accumulate arsenic by root uptake from the soil or by absorption of airborne arsenic deposited on the leaves, and certain species may accumulate substantial levels (EPA 1982b). Yet, even when grown on highly polluted soil or soil naturally high in arsenic, the arsenic level taken up by the plants is comparatively low (Gebel et al. 1998b; Pitten et al. 1999). Kale, lettuce, carrots, and potatoes were grown in experimental plots surrounding a wood preservation factory in Denmark where waste wood was incinerated to investigate the amount and pathways for arsenic uptake by plants (Larsen et al. 1992). On incineration, the arsenate in the wood preservative was partially converted to arsenite; the arsenic emitted from the stack was primarily particle bound. Elevated levels of inorganic arsenic were found in the test plants and in the soil around the factory. Statistical analyses revealed that the dominating pathway for transport of arsenic from the factory to the leafy vegetables (kale) was by direct atmospheric deposition, while arsenic in the root crops (potatoes and carrots) was a result of both soil uptake and atmospheric deposition. Arsenic accumulation by plants is affected by arsenic speciation. Uptake of four arsenic species (arsenite, arsenate, methylarsonic acid, and dimethylarsinic acid) by turnips grown under soilless culture conditions showed that while uptake increased with increasing arsenic concentration in the nutrient, the organic arsenicals showed higher upward translocation than the inorganic arsenical (Carbonell-Barrachina et al. 1999). The total amount of arsenic taken up by the turnip plants (roots and shoots) followed the trend methylarsenate (MMA)<dimethylarsinic acid (DMA) <arsenite<arsenate. In a similar experiment, conducted with tomato plants, the total amount of arsenic taken up by the tomato plants followed the trend DMA<MMA<arsenate≈arsenite, with arsenic concentrations in the plants increasing with increasing arsenic concentration in the nutrient solution. Arsenic was mainly accumulated in the root system (85%) with smaller amounts translocating to the fruit (1%). However, plants treated with MMA and DMA had higher arsenic concentrations in the shoots and fruit than those treated with arsenite or arsenate (Burlo et al. 1999). Terrestrial plants growing on land bordering arsenic-contaminated waters show relatively little arsenic content, even though the sediments have arsenic concentrations as high as 200 μg/g (Tamaki and Frankenberger 1992). Arsenic concentrations in vegetables grown in uncontaminated soils and contaminated soils containing arsenic, as well as other metals and organic contaminants, were generally <12 μg/kg wet weight. A maximum arsenic concentration of 18 μg/kg wet weight was found in unpeeled carrots grown in soil, which contained a mean arsenic concentration of 27 mg/kg dry weight (Samsøe-Petersen et al. 2002).

In a study by Rahman et al. (2004), CCA-treated lumber was used to construct raised garden beds to determine how far the components of CCA migrated in the soil and the uptake of these components by crops grown in the soil. Arsenic was found to diffuse laterally into the soil from the CCA-treated wood, with the highest concentrations found at 0–2 cm from the treated wood and a steady decline in

concentration with increased distance. The highest average arsenic concentrations found in soil closest (0–2 cm) to the CCA-treated wood were 56 and 46 μg/g in loamy sand and sandy loam soils, respectively. At a distance of 30–35 cm from the CCA-treated wood, arsenic concentrations were approximately 7 μg/g in both soils. All samples were of the top 0–15 cm of soil. Crops grown in both soil types within 0–2 cm of the CCA-treated wood contained higher concentrations of arsenic, 0.186 and 10.894 μg/g for carrots without peal and bean leaves and stems, respectively, than those grown at 1.5 m from the CCA-treated wood, 0.006 and 0.682 μg/g for bean pods and bean leaves and stems, respectively. However, based on FDA guidelines on tolerance limits, these crops would be considered approved for human consumption. Studies by Chirenje et al. (2003a) also showed that elevated arsenic concentrations were found in surface (0–5 cm) soils immediately surrounding, within the first 0.3 m, of utility poles, fences, and decks made with CCA-treated wood. Factors such as the preservative formula, fixation temperature, post treatment handling, and timber dimensions of CCA-treated wood, as well as the pH, salinity, and temperature of the leaching media can affect the leach rates from CCA-treated wood (Hingston et al. 2001). Studies of leaching of the components of CCA- and ACZA-treated wood used to construct a boardwalk in wetland environments reported elevated arsenic levels in soil and sediment below and adjacent to these structures. Generally, these levels decreased with increasing distance from the structure (Lebow et al. 2000). Increased concentrations of arsenic were also observed under CCA-treated bridges. Arsenic levels declined with distance from the bridge and were near background levels at 1.8–3 m from the bridge's perimeter (USDA/USDT 2000).

In a study by Lebow et al. (2003), the use of a water repellent finish on CCA-treated wood significantly reduces the amount of arsenic, as well as copper and chromium, in the run-off water. It was also observed the exposure to UV radiation caused a significant increase in leaching from both finished and unfinished samples of CCA-treated wood. Small amounts of arsenic can be transferred from CCA-treated wood to skin from touching CCA-treated wood surfaces (Hemond and Solo-Gabriele 2004; Kwon et al. 2004; Shalat et al. 2006; Ursitti et al. 2004; Wang et al. 2005).

Breslin and Adler-Ivanbrook (1998) examined the leaching of the copper, chromium, and arsenic from CCA-treated wood in laboratory studies using samples of treated southern yellow pine in solutions simulating estuarine waters. The tank leaching solutions were frequently sampled and replaced to approximate field conditions. Initial 12-hour fluxes ranging from $0.2x10^{-10}$ to $5.2x10^{-10}$ mol/mm^2 d was reported for arsenic. After 90 days, arsenic fluxes decreased to $0.5x10^{-11}$–$3.1x10^{-11}$ mol/mm^2 d. A study by Cooper (1991) demonstrated that the buffer system used in leaching studies of components from CCA-treated wood can significantly change the amount arsenic released from treated wood. Samples of four

species of CCA-treated wood were exposed to four acidic leaching solutions. In the samples exposed to water adjusted to pHs of 3.5, 4.5, and 5.5, losses of arsenic after 13 days were generally <7%. However, when a leaching solution of sodium hydroxide and citric acid buffer (pH 5.5) was used, the percent of arsenic leached ranged from 27.4 to 46.7% (Cooper 1991).

Arsenic bioaccumulation depends on various factors, such as environmental setting (marine, estuarine, freshwater), organism type (fish, invertebrate), trophic status within the aquatic food chain, exposure concentrations, and route of uptake (Williams et al. 2006). Bioaccumulation refers to the net accumulation of a chemical by aquatic organisms as a result of uptake from all environmental sources, such as water, food, and sediment, whereas bioconcentration refers to the uptake of a chemical by an aquatic organism through water (EPA 2003b). Biomagnification in aquatic food chains does not appear to be significant (EPA 1979, 1982b, 1983e, 2003b; Mason et al. 2000; Williams et al. 2006).

Bioconcentration of arsenic occurs in aquatic organisms, primarily in algae and lower invertebrates. Both bottom-feeding and predatory fish can accumulate contaminants found in water. Bottom-feeders are readily exposed to the greater quantities of metals, including the metalloid arsenic, which accumulate in sediments. Predators may bioaccumulate metals from the surrounding water or from feeding on other fish, including bottom-feeders, which can result in the biomagnification of the metals in their tissues. An extensive study of the factors affecting bioaccumulation of arsenic in two streams in western Maryland in 1997–1998 found no evidence of biomagnification since arsenic concentrations in organisms tend to decrease with increasing tropic level (Mason et al. 2000). Arsenic is mainly accumulated in the exoskeleton of invertebrates and in the livers of fish. No differences were found in the arsenic levels in different species of fish, which included herbivorous, insectivorous, and carnivorous species. The major bioaccumulation transfer is between water and algae, at the base of the food chain and this has a strong impact on the concentration in fish. National Contaminant Biomonitoring data produced by the Fish and Wildlife Service were used to test whether differences exist between bottom-feeders and predators in tissue levels of metals and other contaminants. No differences were found for arsenic (Kidwell et al. 1995). The bioconcentration factors (BCFs) of bryophytes, invertebrates, and fish (livers) in Swedish lakes and brooks impacted by smelter emissions were 8,700, 1,900–2,200, and 200–800, respectively (Lithner et al. 1995). EPA (2003b) assessed a large dataset of bioaccumulation data for various fish and invertebrate species. BCF values in this dataset ranged from 0.048 to 1,390.

Williams et al. (2006) reviewed 12 studies of arsenic bioaccumulation in freshwater fish, and proposed that BCF and bioaccumulation factor (BAF) values are not constant across arsenic concentrations in

water. BCF or BAF values from these 12 studies ranged from 0.1 to 3,091. Williams et al. (2006) found that BCF and BAF values appear to be the highest within the range of ambient arsenic concentrations, and decline steeply to relatively low levels as the arsenic concentrations in water increase. Based on this analysis, arsenic concentrations in tissue and BAF values may be a power function of arsenic concentrations in water. EPA (2007b) also reported that for many nonessential metals, including arsenic, accumulation is nonlinear with respect to exposure concentration.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Arsenic is released into the atmosphere primarily as arsenic trioxide or, less frequently, in one of several volatile organic compounds, mainly arsines (EPA 1982b). Trivalent arsenic and methyl arsines in the atmosphere undergo oxidation to the pentavalent state (EPA 1984a), and arsenic in the atmosphere is usually a mixture of the trivalent and pentavalent forms (EPA 1984a; Scudlark and Church 1988). Photolysis is not considered an important fate process for arsenic compounds (EPA 1979).

6.3.2.2 Water

Arsenic in water can undergo a complex series of transformations, including oxidation-reduction reactions, ligand exchange, precipitation, and biotransformation (EPA 1979, 1984a; Sanders et al. 1994; Welch et al. 1988). Rate constants for these various reactions are not readily available, but the factors most strongly influencing fate processes in water include Eh, pH, metal sulfide and sulfide ion concentrations, iron concentrations, temperature, salinity, distribution and composition of the biota, season, and the nature and concentration of natural organic matter (EPA 1979; Farago 1997; Redman et al. 2002; Wakao et al. 1988). Organic arsenical pesticides, such as MSMA, DSMA, and DMA do not degrade by hydrolysis or by aquatic photolysis (EPA 2006). No formation of arsine gas from marine environments has been reported (Tamaki and Frankenberger 1992).

Inorganic species of arsenic are predominant in the aquatic environment. In the pH range of natural waters, the predominant aqueous inorganic As(V) species are the arsenate ions, $H_2AsO_4^-$ and $HAsO_4^{2-}$; the predominant inorganic As(III) species is $As(OH)_3$ (Aurillo et al. 1994; EPA 1982c). As(V) generally dominates in oxidizing environments such as surface water and As(III) dominates under reducing conditions such as may occur in groundwater containing high levels of arsenic. However, the reduction of arsenate to arsenite is slow, so arsenate can be found in reducing environments. Conversely, the oxidation of arsenite in oxidizing environments is moderately slow (half-life, 0.4–7 days in coastal

systems) and therefore, arsenite can be found in oxidizing environments (Mariner et al. 1996; Sanders et al. 1994). The main organic species in fresh water are MMA and DMA; however, these species are usually present at lower concentrations than inorganic arsenic species (Eisler 1994). (The toxicities of MMA and DMA are discussed in Chapter 3.) Aquatic microorganisms may reduce the arsenate to arsenite, as well as methylate arsenate to its mono- or dimethylated forms (Aurillo et al. 1994; Benson 1989; Braman and Foreback 1973; Edmonds and Francesconi 1987; Sanders et al. 1994). Methylated species are also produced by the biogenic reduction of more complex organoarsenic compounds like arsenocholine or arsenobetaine. Water samples from a number of lakes and estuaries, mostly in California, show measurable concentrations of methylated arsenic (equivalent to 1–59% of total arsenic) (Anderson and Bruland 1991). Within the oxic photic zone, arsenate and DMA were the dominant species. A seasonal study of one lake demonstrated that DMA was the dominant form of arsenic in surface waters during late summer and fall. Methylated species declined and arsenate species increased when the lake turned over in late fall. Mono Lake, a highly alkaline body of water, and four rivers did not have measurable concentrations of methylated arsenic. It was hypothesized that the reason why methylated forms were not detected in Mono Lake was that the extremely high inorganic arsenic concentrations in the lake, 230 μM (17 mg/L), could overwhelm the analysis of small amounts of organic forms. Other possibilities are that the high alkalinity or very high phosphate levels in the water, 260 μM (25 mg/L), are not conducive to biogenic methylation (Anderson and Bruland 1991). Both reduction and methylation of As(V) may lead to increased mobilization of arsenic, since As(III), dimethylarsinates, and monomethylarsonates are much less particle-reactive than As(V) (Aurillo et al. 1994). In the estuarial Patuxet River, Maryland, arsenate concentrations peaked during the summer, at 1.0 μg/L in 1988–1989 (Sanders et al. 1994). In contrast, winter to spring levels were around 0.1 μg/L. Arsenite concentrations were irregularly present at low levels during the year. Peaks of DMA occurred at various times, particularly in the winter and late spring and appeared to be linked with algal blooms. The DMA peak declined over several months that was followed by a rise in MMA. The MMA was thought to be occurring as a degradation product of DMA. A similar seasonal pattern of arsenic speciation was observed in Chesapeake Bay. Arsenite methylation took place during the warmer months leading to changes down the main stem of the bay; arsensite production dominated the upper reaches of the bay and methylated species dominated the more saline lower reaches. In coastal waters, reduced and methylated species are present in lower concentrations, around 10–20% of total arsenic (Sanders et al. 1994). In groundwater, arsenic generally exists as the oxyanion of arsenate ($H_xAsO_4^{3-x}$) or arsenite ($H_xAsO_3^{3-x}$), or both; however, the distribution between arsenite and arsenate is not always predictable based on oxidation-reduction potential (Robertson 1989; Welch et al. 1988).

6.3.2.3 Sediment and Soil

In soil, arsenic is found as a complex mixture of mineral phases, such as co-precipitated and sorbed species, as well as dissolved species (Roberts et al. 2007). The degree of arsenic solubility in soil will depend on the amount of arsenic distributed between these different mineral phases. The dissolution of arsenic is also affected by particle size. The distribution between these phases may reflect the arsenic source (e.g., pesticide application, wood treatment, tanning, or mining operations), and may change with weathering and associations with iron and manganese oxides and phosphate minerals in the soil (Roberts et al. 2007; Ruby et al. 1999). Davis et al. (1996) reported that in soil in Anaconda, Montana, a smelting site from 1860 to 1980, contained arsenic that is only in a sparingly soluble form, consisting of primarily arsenic oxides and phosphates.

The arsenic cycle in soils is complex, with many biotic and abiotic processes controlling its overall fate and environmental impact. Arsenic in soil exists in various oxidation states and chemical species, depending upon soil pH and oxidation-reduction potential. Under most environmental conditions, inorganic As(V) will exist as a mixture of arsenate anions, $H_2AsO_4^-$ and $HAsO_4^{2-}$, and inorganic As(III) will exist as H_3AsO_3. The arsenate and arsenite oxyanions have various degrees of protonation depending upon pH (EPA 1982b; McGeehan 1996). As(V) predominates in aerobic soils, and As(III) predominates in slightly reduced soils (e.g., temporarily flooded) or sediments (EPA 1982b; Sanders et al. 1994). As(III) commonly partitions to the aqueous phase in anoxic environments, and would be more mobile. As(V) usually remains bound to minerals, such as ferrihydrite and alumina, limiting its mobility and bioavailability (Rhine et al. 2006).

Arsenite is moderately unstable in the presence of oxygen; however, it can be found under aerobic conditions as well (Sanders et al. 1994). While arsenate is strongly sorbed by soils under aerobic conditions, it is rapidly desorbed as the system becomes anaerobic. Once it is desorbed, arsenate can be reduced to arsenite, which exhibits greater mobility in soils (McGeehan 1996). Transformations between the various oxidation states and species of arsenic occur as a result of biotic or abiotic processes (Bhumbla and Keefer 1994). While degradation of an organic compound is typically considered complete mineralization, in the case of organic arsenic compounds, the element arsenic itself cannot be degraded. However, the organic portion of the molecule can be metabolized (Woolson 1976).

Arsenicals applied to soils may be methylated by microorganisms to arsines, which are lost through volatilization, and organic forms may be mineralized to inorganic forms. Gao and Burau (1997) reported

that the overall percentage of DMA and MMA minerialized after 70 days ranged from 3 to 87% in air-dry soil and a soil near saturation, respectively. The rate of demethylation of DMA increased with soil moisture. Over the same 70-day period, arsenic losses as volatile arsines were much lower than minerialization, ranging from 0.001 to 0.4%. Arsine evolution rates followed the order: DMA>MMA>arsenite=arsenate (Gao and Burau 1997). Woolson and Kearney (1973) reported that ^{14}C-labeled DMA degraded differently in soils under aerobic and anaerobic conditions. Under anaerobic conditions, 61% of the applied DMA was converted to a volatile alkyl arsine after 24 weeks, and lost from the soil system. Under aerobic conditions, 35% was converted to a volatile organo-arsenic compound, possibly dimethyl arsine, and 41% was converted to $^{14}CO_2$ and arsenate after 24 weeks. Similar to microorganisms in soils, Reimer (1989) reported that microorganisms found in natural marine sediments and sediments contaminated with mine-tailings are also capable of methylating arsenic under aerobic and anaerobic conditions. Von Endt et al. (1968) reported that the degradation of ^{14}C-labelled monosodium methanearsonate (MSMA) was found to range from 1.7 to 10% in Dundee silty clay loam soil and Sharkey clay soil after 60 days, respectively. MSMA decomposition to CO_2 was a slow process without a lag period. Sterilized soils were found to produce essentially no $^{14}CO_2$ (0.7%) after 60 days, indicating that soil bacteria contributed to the decomposition of MSMA (Von Endt et al. 1968). Akkari et al. (1986) studied the degradation of MSMA in various soils. At 20% water content, half-lives of 144, 88, and 178 days were reported in Sharkey clay, Taloka silt loam, and Steele-Crevasse sand loam, respectively. The Sharkey soil with the highest clay content was expected to have the greatest adsorptive capacity for both water and MSMA, reducing the amount of MSMA available in the soil solution to microorganisms that degrade the MSMA. The half-lives were 25, 41, and 178 days under anaerobic (flooded) conditions in Sharkey clay, Taloka silt loam, and Steele-Crevasse sand loam, respectively. Under flooded conditions, MSMA degradation occurs by reductive methylation to form arsinite and alkylarsine gas. The authors attributed the longer half-lives for MSMA degradation in the Steele-Crevasse sand loam soil to its low organic matter content, which may have supported fewer microbial populations needed for oxidation demethylation under aerobic conditions. Under flooded conditions, anaerobiosis is expected to be slowest in low organic matter sandy loam soils (Akkari et al. 1986).

Organic arsenical pesticides, such as MSMA, DSMA, and DMA, do not degrade by hydrolysis or by soil photolysis (EPA 2006).

Roxarsone (3-nitro-4-hydroxyphenylarsonic acid) used in poultry feed is found excreted unchanged in poultry litter (bedding and manure). Roxarsone found in poultry litter, which is used to amend agricultural soil, was found to degrade to arsenate in approximately 3–4 weeks upon composting

(Garbarino et al. 2003). In addition, the arsenic in poultry litter was found to be easily mobilized by water; however, its leach rate from amended soils was slow enough that it accumulated in soils (Rutherford et al. 2003).

A sequential fractionation scheme was used to assess the chemical nature, and thus the potential bioavailability, of arsenic at cattle dip sites in Australia where sodium arsenite was used extensively in cattle dips from the turn of the century until the early 1950s (McLaren et al. 1998). Most sites contained substantial amounts, 13% on the average, of arsenic in the two most labile fractions indicating a high potential for bioaccessibility and leaching. The bulk of the arsenic appeared to be associated with amorphous iron and aluminum minerals in soil. Similarly, arsenic in soil and mine waste in the Tamar Valley in England was found to be concentrated in a fraction associated with iron and organic-iron (Kavanagh et al. 1997). Laboratory studies were performed to assess the phase partitioning of trace metals, including the metalloid arsenic, to sediment from the Coeur d'Alene River, a mining area of Idaho, and the release of metals under simulated minor and major flooding events (LaForce et al. 1998). Arsenic was primarily associated with the iron and manganese oxides as seen by its large release when these oxides were reduced. Arsenic levels were comparatively low in the organic fraction and remaining residual fraction and negligible in the extractible fractions.

6.3.2.4 Other Media

Carbonell-Barrachina et al. (2000) found the speciation and solubility of arsenic in sewage sludge suspensions to be affected by pH and Eh. Under oxidizing conditions, the solubility of arsenic was low, with a major portion of the soluble arsenic present as organic arsenic compounds, mainly dimethylarsinic acid (approximately 74% of the total arsenic in solution). Under moderately reducing conditions (0–100 mV), inorganic arsenic accounted for the majority (90%) of the total arsenic in solution, and the solubility of arsenic was increased due to dissolution of iron oxyhydroxides. Under strongly reducing conditions (-250 mV), arsenic solubility was decreased by the formation of insoluble sulfides. The pH of the solution was also found to influence the speciation and solubility of arsenic. At neutral pH, the solubility of arsenic was at its maximum, and decreased under acidic or alkaline conditions. Inorganic arsenic species were the dominant species at pH 5.0; at pH 6.5, the major soluble forms were organic arsenic species. The biomethylation of arsenic was limited at acidic pH, and was at its maximum at near neutral pH (Carbonell-Barrachina et al. 2000).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to arsenic depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of arsenic in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on arsenic levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring arsenic in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Arsenic in ambient air is usually a mixture of particulate arsenite and arsenate; organic species are of negligible importance except in areas of substantial methylated arsenic pesticide application or biotic activity (EPA 1984a). Mean levels in ambient air in the United States have been reported to range from <1 to 3 ng/m^3 in remote areas and from 20 to 30 ng/m^3 in urban areas (Davidson et al. 1985; EPA 1982c; IARC 1980; NAS 1977a). EPA conducted a modeling study with the Assessment System for Population Exposure Nationwide (ASPEN) in which estimates of emissions of hazardous air pollutants were used to estimate ambient concentrations (Rosenbaum et al. 1999). Using 1990 data to estimate total emissions of arsenic in the conterminous 48 states, excluding road dust or windblown dust from construction or agricultural tilling, the 25th percentile, median, and 75th percentile arsenic concentration were estimated to be 9, 20, and 30 ng/m^3, respectively. Maps illustrating the amount of toxic air pollutant emissions, including arsenic compounds, by county in 1996 for the 48 coterminous states of the United States as well as Puerto Rico and the Virgin Islands are available on the internet at http://www.epa.gov/ttn/atw/-nata/mapemis.html, as of March 2005. Schroeder et al. (1987) listed ranges of arsenic concentrations in air of 0.007–1.9, 1.0–28, and 2–2,320 ng/m^3 in remote, rural, and urban areas, respectively. The average annual arsenic concentration in air at Nahant, Massachusetts, just north of Boston, between September 1992 and September 1993, was 1.2 ng/m^3; 75% of the arsenic was associated with fine (<2.5 μm) particles. The long-term means of the ambient concentrations of arsenic measured in urban areas of the Great Lakes region from 1982 to 1993 ranged from 4.2 to 9.6 ng/m^3 (Pirrone and Keeler 1996). Large cities generally have higher arsenic air concentrations than smaller ones due to emissions from coal-fired power plants (IARC 1980), but maximum 24-hour concentrations generally are <100 ng/m^3 (EPA 1984a). In the spring of 1990, aerosols and cloud water that were sampled by aircraft at an altitude of 1.2–3 km above the Midwestern United States had a mean mixed layer arsenic concentration of 1.6±0.9 ng/m^3 (Burkhard et al. 1994). A mean arsenic concentration of 1.0±0.5 ng/m^3 was reported at

Mayville, New York, a site 400 km to the northwest of the sampling area and directly downwind on most days.

Arsenic was monitored at an application site in the San Joaquin Valley, California and at four sites in nearby communities in 1987 where sodium arsenite was used as a fungicide on tokay grapes (Baker et al. 1996). The maximum arsenic concentration measured 15–20 meters from the edge of the field was 260 ng/m^3. The maximum arsenic concentration at four community sites in the area was 76 ng/m^3. The concentration at an urban background site was 3 ng/m^3 (Baker et al. 1996). Sodium arsenite is no longer registered in California (Baker et al. 1996). The highest historic arsenic levels detected in the atmosphere were near nonferrous metal smelters, with reported concentrations up to 2,500 ng/m^3 (IARC 1980; NAS 1977a; Schroeder et al. 1987).

Arsenic air concentrations measured in several indoor public places (e.g., cafeteria, coffee house, music club, Amtrak train, and several restaurants) with environmental tobacco smoke (ETS) ranged from <0.1 to 1 ng/m^3, with a mean of 0.4±0.3 ng/m^3. Sites that were ETS-free (university office and library) had arsenic concentrations <0.13 ng/m^3 (Landsberger and Wu 1995). The Toxic Exposure Assessment at Columbia/Harvard (TEACH) study measured levels of various toxics in New York City air in 1999. Exposures were assessed in a group of 46 high school students in West Central Harlem. Mean arsenic concentrations in summer home outdoor, home indoor, and personal air of the participants were 0.37, 0.40, and 0.45 ng/m^3, respectively (Kinney et al. 2002). Detected arsenic concentrations in indoor and outdoor air collected as part of the National Human Exposure Assessment Survey (NHEXAS) in Arizona ranged from 3.4 to 22.3 and from 3.5 to 25.7 ng/m^3, respectively, with 71 and 68% below the detection limit (1.8–14.3 ng/m^3) (O'Rourke et al. 1999).

6.4.2 Water

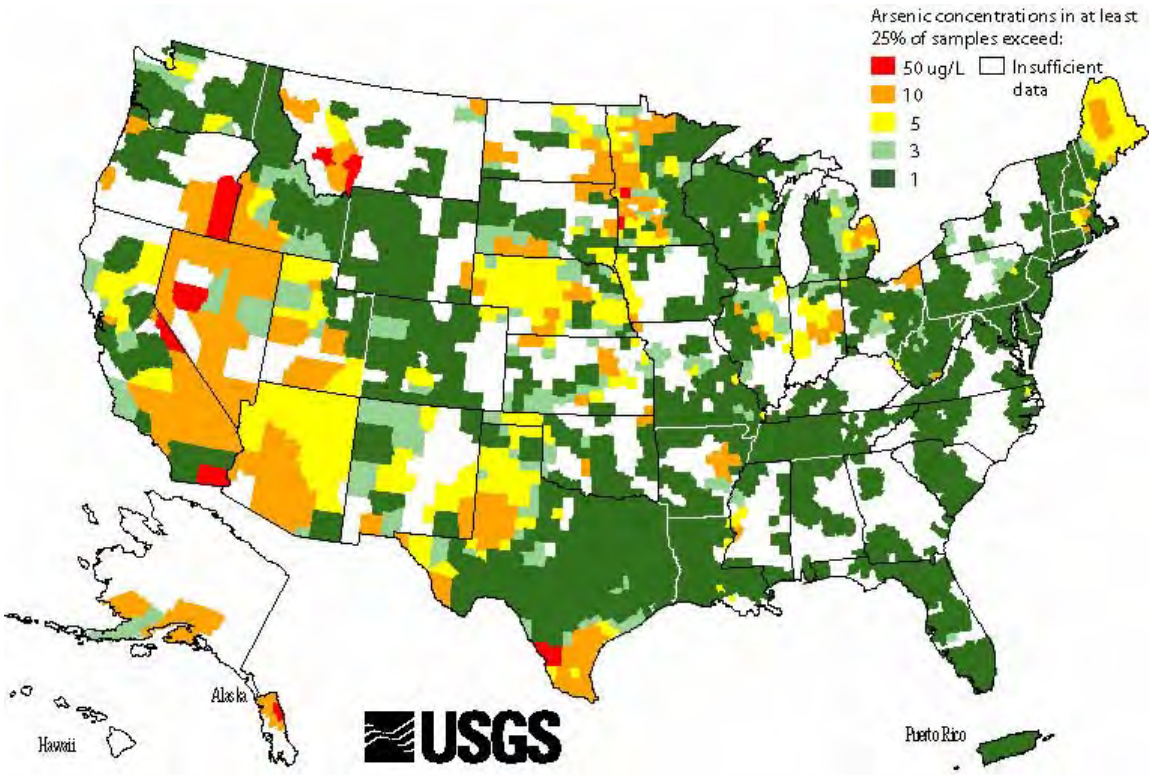
Arsenic is widely distributed in surface water, groundwater, and finished drinking water in the United States. A survey of 293 stations in two nationwide sampling networks on major U.S. rivers found median arsenic levels to be 1 μg/L; the 75th percentile level was 3 μg/L (Smith et al. 1987). Arsenic was detected in 1,298 of 3,452 surface water samples recorded in the STORET database for 2004 at concentrations ranging from 0.138 to 1,700 μg/L in samples where arsenic was detected (EPA 2005c). Two streams in western Maryland that were the focus of a major bioaccumulation study in 1997–1998 had arsenic concentrations of 0.370±0.200 and 0.670±0.460 μg/L (Mason et al. 2000). Surface water will be impacted by runoff from polluted sites. An average arsenic concentration of 5.12 μg/L was reported in

water from Moon Lake, a Mississippi River alluvial floodplain in northwest Mississippi. Intensive cultivation has occurred in this area, including cotton, soybeans, and rice (Cooper and Gillespie 2001). Hard-rock mining activities occurred in the southern part of Colorado and New Mexico north of Taos since the latter part of the 19th century until recently, which have impacted the Rio Grande and its tributaries. A mean arsenic concentration of approximately 0.8 μg/L was reported for the main stem of the Rio Grande sampled in June and September 1994. Arsenic concentrations in the Alamosa River, Colorado were 0.11 and 0.14 μg/L in June and September 1994, respectively, and 1.4 μg/L in Big Arsenic Spring, New Mexico in September 1994 (Taylor et al. 2001). Arsenic concentrations in water from watersheds in Black Hills, South Dakota, an area impacted by gold mining activities ranged from 2.5 to 55 μg/L and from 1.7 to 51 μg/L in unfiltered and filtered samples, respectively; concentrations from reference areas ranged from 1.1 to 3.4 μg/L and from 0.9 to1.9 μg/L in unfiltered and filtered samples, respectively (May et al. 2001). Arsenic concentrations ranged from 0.29 to 34.0 μg/L in water samples from Wakulla River and St. Joseph Bay North, along the Florida Panhandle; arsenic contamination in this area is likely to result from nonpoint source pollution (Philp et al. 2003).

Data on total arsenic in surface water from a number of seas and oceans show levels of <1 μg/L, except in the Antarctic Ocean and Southwest Pacific Oceans where the levels are 1.1 and 1.2 μg/L, respectively. Levels in coastal waters and estuaries are generally somewhat higher, in the range of 1–3 μg/L. However, estuarine water in Salinas, California had arsenic levels of 7.42 μg/L (Francesconi et al. 1994). The dissolved arsenic concentration in water at 40 sites in the Indian River Lagoon System in Florida ranged from 0.35 to 1.6 μg/L with a mean of 0.89±0.34 μg/L (Trocine and Trefry 1996). Thermal waters generally have arsenic levels of 20–3,800 μg/L, although levels as high as 276,000 μg/L have been recorded (Eisler 1994).

Arsenic levels in groundwater average about 1–2 μg/L, except in some western states with volcanic rock and sulfidic mineral deposits high in arsenic, where arsenic levels up to 3,400 μg/L have been observed (IARC 1980; Page 1981; Robertson 1989; Welch et al. 1988). In western mining areas, groundwater arsenic concentrations up to 48,000 μg/L have been reported (Welch et al. 1988). Arsenic concentrations in groundwater samples collected form 73 wells in 10 counties in southeast Michigan in 1997 ranged from 0.5 to 278 μg/L, with an average of 29 μg/L. Most (53–98%) of the arsenic was detected as arsenite (Kim et al. 2002). The U.S. Geological Survey mapped concentrations of arsenic in approximately 31,350 groundwater samples collected between 1973 and 2001; the counties in which at least 25% of wells exceed various levels are shown in Figure 6-2 (USGS 2007a). Most arsenic in natural waters is a

Figure 6-2. Counties in Which at Least 25% of Wells Exceed Different Arsenic Levels



Source: USGS 2007a

mixture of arsenate and arsenite, with arsenate usually predominating (Braman and Foreback 1973; EPA 1982c, 1984a). Methylated forms have also been detected in both surface water and groundwater, at levels ranging from 0.01 to 7.4 μg/L (Braman and Foreback 1973; Hood 1985), with most values below 0.3 μg/L (Hood 1985). In a survey of shallow groundwater quality in the alluvial aquifer beneath a major urban center, Denver, Colorado, arsenic levels in the 30 randomly-chosen wells sampled had median levels of <1 μg/L; the maximum level was 33 μg/L (Bruce and McMahon 1996). Arsenic levels in groundwater sometimes exceeded the EPA maximum contaminant level (MCL), which was 50 μg/L at the time, in the Willamette Valley, Oregon and a nine-county region of southeastern Michigan (USGS 1999b, 1999c).

Arsenic has also been detected in rainwater at average concentrations of 0.2–0.5 μg/L (Welch et al. 1988). This range is consistent with that found in a 1997–1998 study in western Maryland, which was the focus of a major bioaccumulation study (Mason et al. 2000). Arsenic levels in wet deposition in the watershed as well as throughfall into the two streams were 0.345±0.392, 0.400±0.400, and 0.330±0.250 μg/L, respectively. Median arsenic concentrations in 30-day rainwater composite samples collected May-September 1994 from eight arctic catchments in northern Europe at varying distances and wind directions from the emissions of a Russian nickel ore mining, roasting, and smelting industry on the Kola Peninsula ranged from 0.07 to 12.3 μg/L (Reimann et al. 1997). Rain and snow samples were collected during the fall of 1996 and winter of 1997 at eight locations in a semi-circular pattern radiating out (2–15 km) in the direction of the prevailing wind from the Claremont incinerator located in New Hampshire. This incinerator processes 200 tons of solid waste per day. Arsenic concentrations in rainwater and snow ranged from 0.020 to 0.079 μg/L and from 0.80 to 1.28 μg/L, respectively (Feng et al. 2000).

Drinking water is one of the most important sources of arsenic exposure. Surveys of drinking water in the United States have found that >99% of public water supplies have arsenic concentrations below the EPA MCL, which was 50 μg/L at the time (EPA 1984a). In an EPA study of tap water from 3,834 U.S. residences, the average value was 2.4 μg/L (EPA 1982c).

Before the MCL for arsenic in drinking water was lowered from 50 to 10 μg/L, studies were undertaken to ascertain how different standards would affect compliance. One such survey sponsored by the Water Industry Technical Action Fund was the National Arsenic Occurrence Survey (NAOS). NAOS was based on a representational survey of public water systems defined by source type, system size, and geographical location. Additionally, it included a natural occurrence factor, a stratifying variable that could qualitatively describe the likelihood of arsenic occurrence in the supply. To predict finished water

arsenic concentrations, data on the water treatment options, efficiency, and frequency of use were factored in. The results of the NAOS are presented in Table 6-3. The NAOS results are in general agreement with two older and more limited national surveys, EPA's National Inorganics and Radionuclides Survey (NIRS) and the Metropolitan Water District of Southern California Survey (MWDSC). The percentages of water systems that would be out of compliance are estimated to be 1.7, 3.6, 9.3, and 20.7% for arsenic MCLs of 20, 10, 5, and 2 μg/L, respectively. Arsenic concentrations were determined in drinking in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin) as part of the NHEXAS; mean arsenic concentration in flushed and standing tap water were both 1.1 μg/L (Thomas et al. 1999). A review by Frost et al. (2003) of existing data from the EPA Arsenic Occurrence and Exposure Database, as well as additional data from state health and environmental departments and water utilities found that 33 counties in 11 states had estimated mean drinking water arsenic concentrations of 10 μg/L or greater. Eleven counties had mean arsenic concentrations of ≥20 μg/L, and two counties had mean arsenic concentrations of ≥50 μg/L (Frost et al. 2003).

The north central region and the western region of the United States have the highest arsenic levels in surface water and groundwater sources, respectively. In a study of drinking water from New Hampshire, arsenic concentrations ranged from <0.01 to 180 μg/L in the 793 households tested. More than 10% of the private wells had arsenic concentrations >10 μg/L, and 2.5% had levels >50 μg/L (Karagas et al. 1998). In New Hampshire, 992 randomly selected household water samples were analyzed for arsenic levels and the results for domestic well users were compared with those for users of municipal water supplies (Peters et al. 1999). The concentrations ranged from <0.0003 to 180 μg/L, with water from domestic wells containing significantly more arsenic than water from municipal supplies; the median concentration of the former was about 0.5 μg/L and the latter was 0.2 μg/L. None of the municipal supplies exceeded an arsenic concentration of 50 μg/L, and 2% of the domestic wells were found to have arsenic concentrations that exceeded 50 μg/L. Approximately 2% of the municipal water users have water with arsenic levels exceeding 10 μg/L compared with 13% of domestic wells. Twenty-five percent of domestic wells and 5% of municipal supplies were found to have arsenic concentrations exceeding 2 μg/L. The highest arsenic levels in New Hampshire are associated with bedrock wells in the south eastern and south central part of the state (Peters et al. 1999). In a study of arsenic in well water supplies in Saskatchewan, Canada, 13% of samples were >20 μg/L and one sample exceeded 100 μg/L (Thompson et al. 1999). It was noted that the samples with high arsenic levels were derived from sites that were in near proximity to each other, indicating the presence of 'hot spots' with similar geological characteristics. As part of an epidemiological study, Engel and Smith (1994) investigated the levels of arsenic in drinking

Table 6-3. Regional Occurrence of Arsenic in U.S. Water Sources and Finished Drinking Water

	Arsenic concentration in µg/L			
Geographical region	<1	1–5	5–20	>20
Occurrence in U.S. surface water sources				
Region 1. New England	50	50	0	0
Region 2. Mid-Atlantic	84	12	4	0
Region 3. South East	93	7	0	0
Region 4. Midwest	24	76	0	0
Region 5. South Central	32	55	13	0
Region 6. North Central	33	22	33	0
Region 7. Western	42	58	0	0
Occurrence in U.S. groundwater sources				
Region 1. New England	71	21	7	0
Region 2. Mid-Atlantic	81	4	11	4
Region 3. South East	82	14	2	0
Region 4. Midwest	40	40	15	5
Region 5. South Central	68	27	15	0
Region 6. North Central	30	40	30	0
Region 7. Western	24	34	28	14
Occurrence in U.S. finished surface water supplies				
Region 1. New England	88	12	0	0
Region 2. Mid-Atlantic	92	8	0	0
Region 3. South East	100	0	0	0
Region 4. Midwest	73	27	0	0
Region 5. South Central	74	19	7	0
Region 6. North Central	44	44	0	12
Region 7. Western	42	58	0	0
Occurrence in U.S. finished groundwater supplies				
Region 1. New England	79	21	0	0
Region 2. Mid-Atlantic	81	4	11	4
Region 3. South East	94	4	2	0
Region 4. Midwest	58	27	12	3
Region 5. South Central	61	27	12	0
Region 6. North Central	40	50	10	0
Region 7. Western	20	40	22	12

Source: National Arsenic Occurrence Survey (Frey and Edwards 1997)

water throughout the United States between 1968 and 1984. They found that 30 counties in 11 states had mean arsenic levels of >5 μg/L, with a range of 5.4–91.5 μg/L; 15 counties had mean levels from 5 to 10 μg/L; 10 counties had mean levels from 10 to 20 μg/L; and 5 counties had levels >20 μg/L. The highest levels were found in Churchill County, Nevada, where 89% of the population was exposed to a mean arsenic concentration of 100 μg/L and 11% to a mean of 27 μg/L. A study by Frost et al. (2003) identified 33 counties from 11 states in which the average arsenic concentration of at least 75% of public wells was >10 μg/L. Arsenic concentrations in drinking water from these counties ranged from 10.3 to 90.0 μg/L in Pinal, Arizona and Churchill, Nevada, respectively (Frost et al. 2003).

Many communities have high levels of arsenic in their drinking water because of contamination or as a result of the geology of the area. In Millard County, Utah, seven towns had median and maximum arsenic levels of 18.1–190.7 and 125–620 μg/L, respectively, in their drinking water (Lewis et al. 1999). The mean arsenic concentration in tap water from homes in Ajo, Arizona, about 2 miles from an open pit copper mine and smelter was 90 μg/L (Morse et al. 1979). The town's water was supplied from five deep wells.

Countries such as Mexico, Bangladesh, India, Chile, Argentina, and Vietnam have highly elevated levels of arsenic in drinking water in some regions (Bagla and Kaiser 1996; Berg et al. 2001; Tondel et al. 1999; WHO 2001; Wyatt et al. 1998a, 1998b). In Bangladesh and West Bengal, the soil naturally contains high levels of arsenic, which leaches into the shallow groundwater that is tapped for drinking water. In West Bengal, India, it is estimated that more than one million Indians are drinking arsenic-laced water and tens of millions more could be at risk in areas that have not been tested for contamination. Analysis of 20,000 tube-well waters revealed that 62% have arsenic at levels above the World Health Organization (WHO) permissible exposure limit (PEL) in drinking water of 10 μg/L, with some as high as 3,700 μg/L (Bagla and Kaiser 1996). Analysis of 10,991 and 58,166 groundwater samples from 42 and 9 arsenic-affected districts in Bangladesh and West Bengal were found to have arsenic levels that were 59 and 34%, respectively, above 50 μg/L (Chowdhury et al. 2000). Berg et al. (2001), studied the arsenic contamination of the Red River alluvial tract in Hanoi, Vietnam and the surrounding rural areas. Arsenic concentrations in groundwater from private small-scale tube-wells averaged 159 μg/L, ranging from 1 to 3,050 μg/L. Arsenic concentrations ranged from 37 to 320 μg/L in raw groundwater pumped from the lower aquifer for the Hanoi water supply (Berg et al. 2001). Several investigators have noticed a correlation between high levels of arsenic and fluoride in drinking water (Wyatt et al. 1998a, 1998b). Arsenic concentrations in drinking water from four villages in Bangladesh ranged from 10 to 2,040 μg/L (Tondel et al. 1999).

6.4.3 Sediment and Soil

Arsenic is widely distributed in the Earth's crust, which contains about 3.4 ppm arsenic (Wedepohl 1991). It is mostly found in nature minerals, such as realgar (As_4S_4), orpiment (As_2S_3), and arsenolite (As_2O_3), and only found in its elemental form to a small extent. There are over 150 arsenic-bearing minerals (Budavari et al. 2001; Carapella 1992). Arsenic concentrations in soils from various countries can range from 0.1 to 50 μg/g and can vary widely among geographic regions. Typical arsenic concentrations for uncontaminated soils range from 1 to 40 μg/g, with the lowest concentrations in sandy soils and soils derived from granites. Higher arsenic concentrations are found in alluvial soils and soils with high organic content (Mandal and Suzuki 2002). Arsenic in soil may originate from the parent materials that form the soil, industrial wastes, or use of arsenical pesticides. Geological processes that may lead to high arsenic concentrations in rock and subsequently the surrounding soil include hydrothermic activity and pegmatite formation (Peters et al. 1999). In the first case, thermal activity results in the dissolution and transport of metals, including the metalloid arsenic, which are precipitated in fractures in rocks. In the second process, cooling magmas may concentrate metals that are injected into rocks, crystallizing as pegmatites. Areas of volcanic activity include large areas of California, Hawaii, Alaska, Iceland, and New Zealand.

The U.S. Geological Survey reports the mean and range of arsenic in soil and other surficial materials as 7.2 and <0.1–97 μg/g, respectively (USGS 1984). The concentrations of arsenic in 445 Florida surface soils ranged from 0.01 to 50.6 μg/g (Chen et al. 1999). The median, arithmetic mean, and geometric mean were 0.35, 1.34±3.77, and 0.42±4.10 μg/g, respectively. Chirenje et al. (2003b) reported a geometric mean arsenic concentrations of 0.40 (0.21–660) and 2.81 (0.32–110) μg/g in surface soil samples (0–20 cm) collected in May–June 2000 from Gainesville and Miami, Florida, respectively. The geometric mean arsenic concentration in 50 California soils was 2.8 μg/g (Chen et al. 1999). In the Florida surface soils, arsenic was highly correlated (α=0.0001) with the soil content of clay, organic carbon, CEC, total iron, and total aluminum. Arsenic tends to be associated with clay fractions and iron and manganese oxyhydroxides. Soils of granitic origin are generally low in arsenic, about 4 μg/g, whereas arsenic in soils derived from sedimentary rocks may be as high as 20–30 μg/g (Yan-Chu 1994). Soils overlying arsenic-rich geologic deposits, such as sulfide ores, may have soil concentrations two orders of magnitude higher (NAS 1977a).

Soils in mining areas or near smelters may contain high levels of arsenic. Arsenic concentrations up to 27,000 μg/g were reported in soils contaminated with mine or smelter wastes (EPA 1982b). Soils at an abandoned mining site in the Tamar Valley in southwest England have arsenic concentrations that may exceed 50,000 μg/g (Erry et al. 1999). The average arsenic levels in the top 2 cm of different soil types in the vicinity of a former copper smelter in Anaconda, Montana, ranged from 121 to 236 μg/g; levels were significantly related to proximity and wind direction to the smelter site (Hwang et al. 1997a). Smelter fallout can contaminate land miles from the source. Soils in mainland southern King County were studied for the presence of arsenic and lead (WSDOE 2005). Soil samples were collected in the fall of 1999 and the spring of 2001 from locations around the ASARCO smelter, which operated in Ruston from the 1890s to 1986. The study area ran roughly from the I-90 corridor south to the King-Pierce county line, from the Puget Sound shore to the Cascade foothills. Almost all of the contamination was found was in the 0–6-inch depths of the cores samples; 62 of the 75 samples were found to have arsenic levels above 20 ppm (WSDOE 2005).

Soil on agricultural lands treated with arsenical pesticides may retain substantial amounts of arsenic. One study reported an arsenic concentration of 22 μg/g in treated soil compared to 2 μg/g for nearby untreated soil (EPA 1982b). Arsenic was measured in soil samples taken from 10 potato fields in Suffolk County on Long Island, New York, where sodium arsenite had been used for vine control and fall weed control for many years. Lead arsenate also may have been used as an insecticide in certain areas. The mean arsenic levels taken at a depth of 0–18 cm from each of the 10 fields ranged from 27.8±5.44 μg/g dry weight (n=10) to 51.0±7.40 μg/g dry weight (n=10). These levels were markedly higher than the level of 2.26±0.33 μg/g (n=10) for untreated control soils (Sanok et al. 1995). A survey was conducted in 1993 to determine the concentrations of arsenic and lead in soil samples from 13 old orchards in New York State. Lead arsenate was used for pest control in fruit orchards for many years, mainly from the 1930s to 1960s, and residues remain in the soil. Concentrations of arsenic ranged from 1.60 to 141 μg/g dry weight (Merwin et al. 1994). Arsenic and lead concentrations were also measured in former orchard soils contaminated by lead arsenate from the Hanford site in Washington State. The mean arsenic concentration in surface (5–10 cm) and subsurface (10–50 cm) soils were 30 (2.9–270) and 74 (32–180) μg/g dry weight, respectively (Yokel and Delistraty 2003). Average arsenic concentration of 5.728, 5.614, and 6.746 μg/g were reported in soils, lake sediments, and wetland sediments, respectively, from Moon Lake, a Mississippi River alluvial floodplain in northwest Mississippi. Intensive cultivation has occurred in this area, including cotton, soybeans, and rice (Cooper and Gillespie 2001). A geometric mean arsenic concentration of 20.6 mg/kg (range 4.6–340 mg/kg) was reported soil collected during the

summer and fall of 2003 from 85 homes in Middleport, New York, where historical pesticide manufacturing was associated with arsenic in the soil (Tsuji et al. 2005).

The Washington State Area-wide Soil Contamination Project provides various data on arsenic contamination in soils across Washington State (Washington State 2006). Arsenic concentrations within areas affected by area-wide soil contamination are highly variable, ranging from natural background levels to >3,000 ppm in smelter areas. Generally, average arsenic concentrations in soil at developed properties are <100 ppm. Areas affected by smelter emissions in King, Pierce, Snohomish, and Stevens Counties have a higher likelihood of arsenic soil contamination than other areas of the State due to historical emissions from metal smelters located in Tacoma, Harbor Island, Everett, Northport, and Trail, British Columbia. Areas where apples and pears were historically grown, such as Chelan, Spokane, Yakima, and Okanogan Counties, also have a higher likelihood of arsenic soil contamination than other areas due to the past use of lead arsenate pesticides. Generally, arsenic contamination in soils from historical smelter emissions and historical use of lead-arsenate pesticides is found in the upper 6–18 inches of soil (Washington State 2006).

The New Jersey Department of Environmental Protection (Historic Pesticide Contamination Task Force 1999) reported on the analysis of soil samples collected from 18 sites for various pesticide residues, including arsenic, from current and former agricultural sites in New Jersey in order to assess contamination from historic pesticide use. Arsenic was detected in all 463 samples, with concentrations ranging from 1.4 to 310 ppm.

Natural concentrations of arsenic in sediments are usually <10 μg/g dry weight, but can vary widely around the world (Mandal and Suzuki 2002). Sediment arsenic concentrations reported for U.S. rivers, lakes, and streams range from about 0.1 to 4,000 μg/g (Eisler 1994; Heit et al. 1984; NAS 1977a; Welch et al. 1988). During August through November 1992 and August 1993, bed sediment in the South Platte River Basin (Colorado, Nebraska, and Wyoming) was sampled and analyzed for 45 elements, including arsenic. The range of arsenic found was 2.8–31 μg/g dry weight and the geometric mean (n=23) was 5.7 μg/g (Heiny and Tate 1997). The arsenic concentration in surface sediment (0–2 cm) at 43 sites in the Indian River Lagoon System in Florida ranged from 0.6 to 15 μg/g dry weight with a mean of 5.0±3.9 μg/g (Trocine and Trefry 1996). Arsenic levels were well correlated with those of aluminum. Correlation with aluminum levels is used to normalize sediment level concentrations to natural levels in Florida estuaries. Surficial sediments collected from 18 locations in 3 major tributaries to Newark Bay, New Jersey, were analyzed for 7 toxic metals, including arsenic (Bonnevie et al. 1994). The highest

concentrations of arsenic were found in the Rahway River adjacent to a chemical plant, 58 μg/g dry weight, and in the Hackensack River adjacent to a coal-fired power plant, 49 μg/g. The average arsenic concentration for all sediments was 17±16 μg/g. Sediments collected from seven sites in Baltimore Harbor, Maryland, at five seasonal periods between June 1987 and June 1988 had a geometric mean maximum of 7.29 μg/g dry weight and a geometric mean minimum of 1.25 μg/g (Miles and Tome 1997). This harbor is one of two sub-tributaries of the Chesapeake Bay where contaminants have been discharged on a large scale.

The upper Clark Fork River basin in western Montana is widely contaminated by metals from past mining, milling, and smelting activities. In a 1991 study, arsenic levels were determined in sediment along the river and in a reservoir 205 km downstream. Total arsenic in sediments from Clark Fork River decreased from 404 μg/g dry weight at the farthest upstream sampling station to 11 μg/g, 201 km downstream. Sediment samples from the Milltown Reservoir had arsenic concentrations ranging from 6 to 56 μg/g (Brumbaugh et al. 1994). Total recoverable arsenic in nonfiltered pore water from the Clark Fork River decreased from 1,740 μg/L at the farthest upstream sampling station to 31 μg/L at the 201 km station (Brumbaugh et al. 1994). The Coeur d'Alene river basin in northern Idaho has been contaminated with heavy metals from mining and smelting operations since 1885 (Farag et al. 1998). A 1994 study determined the metal content of sediment, biofilm, and invertebrates at 13 sites in the basin, 10 with historic mining activity and 3 reference sites. The mean arsenic levels in sediment at the mining sites ranged from 8.3 to 179.0 μg/g dry weight, compared to 2.4–13.1 μg/g dry weight at the reference sites. The mean arsenic levels in biofilm adhering to rock in the water at the mining sites ranged from 7.5 to 155.8 μg/g dry weight, compared to 7.2–27.3 μg/g dry weight at the reference sites. In Whitewood Creek, South Dakota, where as much as 100 million tons of mining and milling waste derived from gold mining activities were discharged between 1876 and 1977, mean and maximum sediment arsenic concentrations were 1,920 and 11,000 μg/g, respectively (USGS 1987). Uncontaminated sediment had mean arsenic levels of 9.2 μg/g. Arsenic concentrations in surface (0–5 cm) sediments from watersheds in Black Hills, South Dakota, an area impacted by gold mining activities, ranged from 23 to 1,951 μg/g dry weight; concentrations from reference areas ranged from 10 to 58 μg/g dry weight (May et al. 2001). Swan Lake, a sub-bay of Galveston Bay in Texas is a highly industrial area that received runoff from a tin smelter in the 1940s and 1950s. Surface sediments at 17 sites where oysters and mussels were collected ranged from 4.53 to 103 μg/g (Park and Presley 1997). A site in the channel leading from the old smelter had arsenic levels of 568 μg/g. Surface sediment was less contaminated than deeper sediment, indicating less arsenic input recently than in the past as a result of the smelter closing.

It has been suggested that the wood preservative most commonly used in dock pilings and bulkheads, CCA, can be toxic to estuarine organisms. Wendt et al. (1996) measured arsenic in surface sediments and oysters from creeks with high densities of docks and from nearby reference creeks with no docks. The average concentrations in the sediments ranged from 14 to 17 μg/g throughout the study area, which is within the range of natural background levels. Weis et al. (1998) sampled sediments along a 10-m transect from CCA-treated wood bulkheads from four Atlantic coast estuaries. Arsenic concentrations were highest in the fine-grained portion of the sediments near the CCA-treated bulkhead (0–1 m); arsenic concentrations were generally at reference levels at distances >1 m from the bulkheads (Weis et al. 1998).

Soils below and around play structures constructed from CCA-treated wood in the City of Toronto, Canada were sampled and analyzed for inorganic arsenic (Ursitti et al. 2004). A mean arsenic concentration of 2.1 μg/g (range 0.5–10 μg/g) was reported in soil samples taken within 1 m of the CCA-treated wood for all play structures. Soil samples that were collected 10 m from the play structures served as a background had arsenic concentration of 2.4 μg/g (range 0.5–13 μg/g). A mean arsenic concentration of 6.2 μg/g (range 0.5–47.5 μg/g) was reported in soil samples taken below CCA-treated wood for all play structures. Of the 217 play structures in the study, 32 had arsenic concentrations under the play structures that exceeded the Canadian federal soil guidelines with arsenic concentrations ranging from 12.4 to 47.5 μg/g. From this study, the authors concluded that arsenic does not migrate laterally, but does accumulate in soil under elevated platforms constructed from CCA-treated wood (Ursitti et al. 2004).

6.4.4 Other Environmental Media

Low levels of arsenic are commonly found in food; the highest levels are found in seafood, meats, and grains. Typical U.S. dietary levels of arsenic in these foods range from 0.02 mg/kg in grains and cereals to 0.14 mg/kg in meat, fish, and poultry (Gartrell et al. 1986). Shellfish and other marine foods contain the highest arsenic concentrations and are the largest dietary source of arsenic (Gunderson 1995a; Jelinek and Corneliussen 1977; Tao and Bolger 1999). Arsenic levels in various fish and shellfish are presented in Table 6-4. In the U.S. Food and Drug Administration (FDA) Total Diet Study, 1991–1997, seafood contained the highest levels of arsenic, followed by rice/rice cereal, mushrooms, and poultry. Concentrations in canned tuna (in oil), fish sticks, haddock (pan-cooked), and boiled shrimp were 0.609–1.470, 0.380–2.792, 0.510–10.430, and 0.290–2.681 mg/kg, respectively (Tao and Bolger 1999). Typically, arsenic levels in foods in the Total Diet Study, 1991–1996 were low, <0.03 mg/kg; only 63 of the 264 foods contained arsenic above this level. Similar results were reported in the Total Diet Study,

Table 6-4. Levels of Arsenic in Fish and Shellfish—Recent Studies

Sample type	Arsenic concentration[a] (µg/g)	Comments	Reference
Yellowtail flounder		Samples collected from Northwest Atlantic 1993	Hellou et al. 1998
Muscle (n=8)	8–37		
Liver (n=6)	7–60		
Gonad (n=6)	1.2–9.4		
Marine organisms		Belgian fish markets in 1991; inorganic arsenic ranged from 0.003 to 0.2 µg/g	Buchet and Lison 1998
Ray (n=8)	16.4		
Cod (n=8)	4.7		
Plaice (n=8)	19.8		
Sole (n=8)	5.1		
Sea-bream (n=8)	2.4		
Mussell (n=8)	3.5		
Bluefin tuna (*Thunnus thynus*) (n=14)	3.2	Virgin Rocks, Grand Banks of Newfoundland, Canada, 1990	Hellou et al. 1992
Fish		National Contaminant Biomonitoring Program, 1984–1985, 112 stations	Kidwell et al. 1995
Bottom feeding (n=2,020)	0.16±0.23 wet weight		
Predatory (n=12)	0.16±0.140 wet weight		
Oysters		South Carolina, private residential docks on tidal creeks, 1994	Wendt et al. 1996
<1 m from docks (n=10)	8.3±1.1		
>10 m from docks (n=10)	7.6±0.9		
Reference (no docks) (n=10	8.4±1.3		
Clams (n=22)	12±1.1	Indian River Lagoon, Florida, 22 sites, 1990	Trocine and Trefry 1996
Marine organisms		Swan Lake, Galveston Bay, Texas, 1993	Park and Presley 1997
Snails	13.3±17.0		
Blue crab	6.61		
Fish	0.82		
Shrimp	1.37±0.64		
Whole crab	5.35±2.51		
Oysters (n=10, pooled)	7.28±1.32		
Mussels (n=7, pooled)	7.75±2.15		
Marine organisms		GPNEP, 1992, Galveston Bay, Texas	Park and Presley 1997
Blue crab	2.31±2.15		
Fish	2.46		
Oysters, two areas		NOAA NS&T Program, 1986–1990	Park and Presley 1997
n=78, pooled	4.50±1.08	Galveston Bay	
n=874, pooled	9.67±7.00	Gulf of Mexico	

Table 6-4. Levels of Arsenic in Fish and Shellfish—Recent Studies

Sample type	Arsenic concentration[a] (µg/g)	Comments	Reference
Marine crustaceans			
Parapenaeus longirostris (pink shrimp) (n=826, 10 pools	34.84±19.21 (12.01–62.60)	Commercial crustaceans from the Mediterranean Sea (Italy)	Storelli and Marcotrigiano 2001
Aristeus antennatus (red shrimp) (n=387, 8 pool)	17.09±3.49 (10.45–20.82)		
Plesionika martia (shrimp) (n=456, 7 pools)	40.82±2.50 (36.37–44.06)		
Nephrops norvegicus (Norway lobster) (n=270, 5 pools)	43.48±14.21 (35.63–69.15)		
Freshwater fish			
Sabalo (*Brycon melanopterus)* (n=3)	0.015–0.101	Fish samples (muscle) were collected in August 1997 from the Candamo River, Peru; a pristine rainforest valley prior to the start of oil-drilling activities	Gutleb et al. 2002
Huazaco (*Hoplias malabaracus)* (n=4)	nd–0.005		
Bagre (*Pimelodus ornatus*) (n=8)	nd–0.201		
Boquichio (*Prochilodus nigricans)* (n=1)	0.063		
Doncello (*Pseudo-platystoma sp.*) (n=1)	0.055		
Freshwater fish			
Bowfin (n=59)	0.32±0.04 wet weight	Savannah River, along and below the Department of Energy's Savannah River Site (SRS); samples analyzed were edible fillets	Burger et al. 2002
Bass (n=47)	0.03±0 wet weight		
Channel catfish (n=50)	0.09±00.02 wet weight		
Chain pickerel (n=19)	0.05±0.01 wet weight		
Yellow perch (n=51)	0.05±0.01 wet weight		
Black crappie (n=52)	0.04±0.01 wet weight		
American eel (n=24)	0.04±0.01 wet weight		
Shellcracker n=52)	0.06±0 wet weight		
Bluegill (n=52)	0.05±0.02 wet weight		
Redbreast (n=43)	0.07±0.01 wet weight		
Spotted sucker (n=35)	0.03±0 wet weight		

Table 6-4. Levels of Arsenic in Fish and Shellfish—Recent Studies

Sample type	Arsenic concentration[a] (µg/g)	Comments	Reference
Horseshoe crabs			
Apodeme (n=74)	7.034±0.65 wet weight	Overall mean in tissues of crabs collected from New Jersey in 2000	Burger et al. 2003
Egg (n=63)	5.924±0.345 wet weight		
Leg (n=74)	14.482±0.685 wet weight		
Apodeme (n=40)	7.513±0.835 wet weight	Overall mean in tissues of crabs collected from Delaware in 2000	
Egg (n=35)	6.766±0.478 wet weight		
Leg (n=40)	18.102±1.489 wet weight		

[a]Concentrations are means±standard deviation, unless otherwise stated. Concentrations are in a dry weight basis, unless otherwise stated.

GM = geometric mean; GPNEP = Galveston Bay National Estuary Program; nd = not detected;
NOAA NS&T = National Oceanic and Atmospheric Administration National Status and Trends

1991–1997, where the mean arsenic concentration in all foods was 0.036 mg/kg dry weight and arsenic was not detectable in about 88% of the foods and was detected at trace levels in another 7.8% of foods. The foods with the highest mean arsenic levels were haddock, canned tuna, fish sticks, shrimp, and fish sandwiches, with arsenic concentrations ranging from 5.33 to 0.568 mg/kg dry weight (Capar and Cunningham 2000). Nriagu and Lin (1995) analyzed 26 brands of wild rice sold in the United States and found arsenic levels ranging from 0.006 to 0.142 μg/g dry weight. Arsenic concentrations ranging from 0.05 to 0.4 μg/g are typically reported for rice from North America, Europe, and Taiwan (Meharg and Rahman 2003).

During a comprehensive total diet study extending from 1985 to 1988, foods were collected in six Canadian cities and processed into 112 composite food samples (Dabeka et al. 1993). The mean, median, and range of total arsenic in all samples were 0.0732, 0.0051, and <0.0001–4.840 μg/g, respectively. Food groups containing the highest mean arsenic levels were fish (1.662 μg/g), meat and poultry (0.0243 μg/g), bakery goods and cereals (0.0245 μg/g), and fats and oils (0.0190 μg/g). Of the individual samples, marine fish had the highest arsenic levels, with a mean of 3.048 μg/g for the cooked composites and 2.466 μg/g for the raw samples. Canned fish (1.201 μg/g) and shellfish (2.041 μg/g) also contained high means. Cooked poultry, raw mushrooms, and chocolate bars contained 0.100, 0.084, and 0.105 μg/g, respectively.

National monitoring data from the Food Safety and Inspection Service National Residue Program (NRP) (1994–2000) found that the mean total arsenic concentration in livers of young chickens ranged from 0.33 to 0.43 μg/g, with an overall mean of 0.39 μg/g (Lasky et al. 2004). The mean arsenic concentrations in liver for mature chickens, turkeys, hogs, and all other species over the same time period ranged from 0.10 to 0.16 μg/g. Lasky et al. (2004) used the NRP arsenic data in livers of young chickens to estimate the concentrations of arsenic in muscle tissue, the most commonly consumed part of the chicken. Assuming that 65% of the arsenic in poultry and meat is inorganic, at a mean level of chicken consumption of 60 g/person/day, people may ingest an estimated 1.38–5.24 μg/day of inorganic arsenic from chicken.

A Danish study (Pedersen et al. 1994) reports the arsenic levels in beverages as the mean (range) in μg/L as follows: red wine, 9 (<2–25); white wine, 11 (<2–33); fortified wine, 5 (<2–11); beer, 7 (4–11); soft drinks, 3 (<2–8); miscellaneous juices, 8 (3–13); instant coffee, 4 (0.7–7); and instant cocoa, 5.6 (1.6–12.8).

In a study of dietary arsenic exposure in the Indigenous Peoples of the western Northwest Territories, Canada, fish contained the highest arsenic concentrations in foods consumed by the Dene and Métis populations with the highest concentration, 1.960 μg/g, found in smoked/dried cisco (fish). Other foods derived from land mammals, birds, and plants contained lower arsenic concentrations. A mean arsenic intake of <1.0 μg/kg/day was reported for this population (Berti et al. 1998).

The general consensus in the literature is that about 85–>90% of the arsenic in the edible parts of marine fish and shellfish is organic arsenic (e.g., arsenobetaine, arsenochloline, dimethylarsinic acid) and that approximately 10% is inorganic arsenic (EPA 2003b). However, the inorganic arsenic content in seafood may be highly variable. For example, a study in the Netherlands reported that inorganic arsenic comprised 0.1–41% of the total arsenic in seafood (Vaessen and van Ooik 1989). Buchet et al. (1994) found that, on the average, 3% of the total arsenic in mussels was inorganic in form. Some commercially available seaweeds, especially brown algae varieties, may have high percentages of the total arsenic present as inorganic arsenic (>50%) (Almela et al. 2002; Laparra et al. 2003). Arsenic concentrations ranging from 17 to 88 mg/kg dry weight were found in commercially available seaweeds (van Netten et al. 2000). Other arsenic compounds that may be found in seafood are arsenic-containing ribose derivatives called arsenosugars. Arsenosugars are the common organoarsenicals found in marine algae; they are also found in mussels, oysters, and clams (Le et al. 2004). Less information about the forms of arsenic in freshwater fish is known at this time (EPA 2003b).

Schoof et al. (1999a) reported on the analysis of 40 commodities anticipated to account for 90% of dietary inorganic arsenic intake. In this study, the amount of inorganic arsenic was measured in these foods. Consistent with earlier studies, total arsenic concentrations were highest in the seafood sampled (ranging from 160 ng/g in freshwater fish to 2,360 ng/g in marine fish). In contrast, average inorganic arsenic in seafood ranged from <1 to 2 ng/g. The highest inorganic arsenic concentrations were found in raw rice (74 ng/g), followed by flour (11 ng/g), grape juice (9 ng/g), and cooked spinach (6 ng/g).

Tobacco contains an average arsenic concentration of 1.5 ppm, or about 1.5 μg per cigarette (EPA 1998j). Before arsenical pesticides were banned, tobacco contained up to 52 mg As/kg, whereas after the ban, maximum arsenic levels were reduced to 3 μg/g (Kraus et al. 2000). An international literature survey reports arsenic yields of 0–1.4 μg/cigarette for mainstream (inhaled) cigarette smoke (Smith et al. 1997). The wide range of arsenic yields for flue-cured cigarettes suggests that the field history, soil, and fertilizer conditions under which the tobacco is grown will affect the arsenic concentration (Smith et al. 1997).

Arsenic emission factors of 0.015–0.023 μg/cigarette (mean 0.018±0.003 μg/cigarette) have been measured for sidestream smoke from a burning cigarette (Landsberger and Wu 1995).

A median arsenic concentration of 2.1 μg/g and a deposition rate of 0.008 μg/m^2/day was reported in house dust in homes evaluated as part of the German Environmental Survey in 1990–1992. A mean arsenic concentration of 7.3 μg/g was reported in house dust from 48 residences in Ottawa, Canada (Butte and Heinzow 2002). These arsenic concentrations are expected to be representative of background levels. In general high arsenic concentrations were found in household dust collected from homes in areas with known arsenic contamination. Mean arsenic concentrations of 12.6 (2.6–57) and 10.8 (1.0–49) μg/g were reported in house dust collected from the entryway and child play areas, respectively, from homes in a community in Washington State with a history of lead arsenate use (Wolz et al. 2003). Arsenic was detected in all 135 indoor floor dust samples collected as part of the NHEXAS from Arizona mining communities, ranging from 0.3–50.6 μg/g, (O'Rourke et al. 1999). A geometric mean arsenic concentration of 10.8 μg/g (range 1.0–172 μg/g) was reported in house dust from 96 homes in Middleport, New York, with historical pesticide manufacture, collected during the summer and fall of 2003 (Tsuji et al. 2005).

Arsenic has also been detected in several homeopathic medicines at concentrations up to 650 μg/g (Kerr and Saryan 1986). Some Asian proprietary medicines that are manufactured in China, Hong Kong, and other Asian countries have been reported to contain levels of inorganic arsenic ranging from 25 to 107,000 μg/g (Chan 1994). Fifty medicinally important leafy samples that were analyzed for elemental concentrations contained arsenic at levels ranging from 0.12 to 7.36 μg/g, with a mean of 2.38±1.2 μg/g (Reddy and Reddy 1997). Arsenic concentrations ranged from 0.005 to 3.77 μg/g in 95 dietary supplements purchased from retail stores in the Washington, DC area in 1999 (Dolan et al. 2003). Commercially available samples of Valarian, St. John's Wort, Passion Flower, and Echinacea were purchased in the United States and analyzed for various contaminants; arsenic concentrations were 0.0016–0.0085, 0.0065–0.017.8, 0.0024–0.0124, and 0.0021–0.0102 μg/g, respectively, in these samples (Huggett et al. 2001). Concentrations of heavy metals including the metalloid arsenic were evaluated in 54 samples of Asian remedies that were purchased in stores in Vietnam and Hong Kong that would be easily accessible to travelers, as well as in health food and Asian groceries in Florida, New York, and New Jersey. Four remedies were found to contain daily doses exceeding 0.1 mg. Two of these contained what would have been a potentially significant arsenic dose, with daily doses of 16 and 7.4 mg of arsenic (Garvey et al. 2001).

The possible presence of toxic compounds in waste materials has raised concerns about the fate of these compounds either during the composting process or when the composted product is applied to soils. Three waste compost products generated at the Connecticut Agricultural Experiment Station had arsenic levels of 12.8, 9.8, and 13 μg/g dry weight, respectively (Eitzer et al. 1997). The arsenic levels in municipal solid waste composts from 10 facilities across the United States ranged from 0.9 to 15.6 μg/g dry weight with a mean of 6.7 μg/g (He et al. 1995). These are lower than the EPA 503 regulatory limit for arsenic of 41 μg/g for agricultural use of sewage sludge (EPA 1993b). Concentrations of arsenic in U.S. sewage sludges, which are sometimes spread on soil, were <1 μg/g. Arsenic is a common impurity in minerals used in fertilizers. A comprehensive Italian study found that the arsenic content in a number of mineral and synthetic fertilizers ranged from 2.2 to 322 mg/kg with a sample of triple superphosphate having the highest level (Senesi et al. 1999). Arsenic naturally occurs in coal and crude oil at levels of 0.34–130 and 0.0024–1.63 ppm, respectively, which would account for its presence in flue gas, fly ash, and bottom ash from power plants (Pacyna 1987).

Background arsenic levels in living organisms are usually <1 μg/g wet weight (Eisler 1994). Levels are higher in areas with mining and smelting activity or where arsenical pesticides were used. Eisler (1994) has an extensive listing of arsenic levels in terrestrial and aquatic flora and fauna from literature sources to about 1990. The U.S. Fish and Wildlife Service's National Contaminant Biomonitoring Program have analyzed contaminants in fish at 116 stations (rivers and the Great Lakes) across the United States. The geometric mean concentration of arsenic for the five collection periods starting in 1976 were (period, concentration wet weight basis): 1976–1977, 0.199 μg/g; 1978–1979, 0.129 μg/g; 1980–1981, 0.119 μg/g; 1984, 0.106 μg/g; and 1986, 0.083 μg/g (Schmitt et al. 1999). In 1986, the maximum and 85th percentile arsenic levels were 1.53 and 0.24 μg/g, respectively. The highest concentrations of arsenic for all five collection periods were in bloaters from Lake Michigan at Sheboygan, Wisconsin. Arsenic levels declined by 50% at this site between 1976–1997 and 1984. The major source of arsenic into Lake Michigan was a facility at Marinette, Wisconsin, which manufactured arsenic herbicides. Table 6-4 contains arsenic levels in aquatic organisms from more recent studies. The Coeur d'Alene river basin in northern Idaho has been contaminated with heavy metals from mining and smelting operations since 1885 (Farag et al. 1998). A 1994 study determined the metal content of sediment, biofilm, and invertebrates at 13 sites in the basin, 10 with historic mining activity, and 3 reference sites. The mean arsenic levels in benthic macroinvertebrates at the mining sites ranged from 2.2 to 97.0 μg/g dry weight, compared to 2.1–2.4 μg/g dry weight at the reference sites. A study of aquatic organism in Swan Lake, a highly polluted sub-bay of Galveston Bay, Texas showed that arsenic concentrations were in the order snail>oyster>crab>shrimp>fish (Park and Presley 1997). In contrast to metals like silver, cadmium,

copper, and zinc, arsenic concentrations in oysters and mussels were less than in the sediment from which they were collected. No significant correlation was found between levels of arsenic in clams in the Indian River Lagoon in Florida with those found in sediment or water samples (Trocine and Trefry 1996). Small animals living at mining sites ingest more arsenic in their diet and have higher arsenic levels in their bodies than those living on uncontaminated sites (Erry et al. 1999). Seasonal variations in both arsenic intake and dietary composition may affect the amount of arsenic taken up by the body and transferred to predator animals. Tissue arsenic content of wood mice and bank voles living on both arsenic-contaminated mining sites and uncontaminated sites were greater in autumn than spring. The lower tissue arsenic levels in spring of rodents living on contaminated sites suggest that there is no progressive accumulation of arsenic in overwintering animals.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure to arsenic may include exposure to the more toxic inorganic forms of arsenic, organic forms of arsenic, or both. While many studies do not indicate the forms of arsenic to which people are exposed, this information may often be inferred from the source of exposure (e.g., fish generally contain arsenic as arsenobetaine). Yost et al. (1998) reported that the estimated daily dietary intake of inorganic arsenic for various age groups ranged from 8.3 to 14 μg/day and from 4.8 to 12.7 μg/day in the United States and Canada, respectively, with 21–40% of the total dietary arsenic occurring in inorganic forms.

Drinking water may also be a significant source of arsenic exposure in areas where arsenic is naturally present in groundwater. While estimates of arsenic intake for typical adults drinking 2 L of water per day average about 5 μg/day (EPA 1982c), intake can be much higher (10–100 μg/day) in geographical areas with high levels of arsenic in soil or groundwater (see Figure 6-2). It is assumed that nearly all arsenic in drinking water is inorganic (EPA 2001).

In the United States, food intake of arsenic has been estimated to range from 2 μg/day in infants to 92 μg/day in 60–65-year-old men (see Table 6-5) (Tao and Bolger 1999). The average intake of inorganic arsenic are estimated to range from 1.34 μg/day in infants to 12.54 μg/day in 60–65-year-old men. Tao and Bolger (1999) assumed that 10% of the total arsenic in seafood was inorganic and that 100% of the arsenic in all other foods was inorganic. The greatest dietary contribution to total arsenic was seafood (76–96%) for all age groups, except infants. For infants, seafood and rice products contributed 42 and 31%, respectively. Adult dietary arsenic intakes reported for other countries range

Table 6-5. Mean Daily Dietary Intake of Arsenic for Selected U.S. Population Groups

Mean daily intake (µg/kg body weight/day)	Date of study		
	1984–1986[a]	1986–1991[b]	1991–1997[c]
Provisional tolerable daily intake (PTDI)[d]	2.1	2.1	2.1
6–11 months	0.82	0.5	0.31
2 years	1.22	0.81	1.80
14–16 years, female	0.54	0.36	0.41
14–16 years, male	0.60	0.39	0.24
25–30 years, female	0.66	0.44	0.44
25–30 years, male	0.76	0.51	0.72
60–65 years, female	0.71	0.46	1.08
60–65 years, male	0.74	0.48	1.14

[a]Gunderson 1995a
[b]Gunderson 1995b
[c]Tao and Bolger 1999
[d]No agreement has been reached on a maximum acceptable intake for total arsenic; the FAO/WHO has assigned a PTDI for inorganic arsenic of 2.1 µg/kg body weight for adults. Data from FDA studies. FDA does not recommend daily intake levels for Arsenic.

from 11.7 to 280 μg/day (Tao and Bolger 1999). Schoof et al. (1999b) estimated that intake of inorganic arsenic in the U.S. diet ranges from 1 to 20 μg/day, with a mean of 3.2 μg/day. In contrast, these estimates of inorganic arsenic intakes are based on measured inorganic arsenic concentrations from a market basket survey.

The FDA conducted earlier Total Diet Studies in 1984–1986 and 1986–1991. For the sampling period of June 1984 to April 1986, the total daily intake of arsenic from foods was 58.1 μg for a 25–30-year-old male with seafood contributing 87% of the total (Gunderson 1995a). For the sampling period from July 1986 to April 1991, the total daily intake of arsenic from foods was lower, 38.6 μg for a 25–30-year-old male. Seafood again was the major source of arsenic, contributing 88% of the total (Gunderson 1995b). Results of the two Total Diet Studies for selected population groups are shown in Table 6-5. The Total Diet Study for the sampling period from September 1991 to December 1996, shows that arsenic, at ≥0.03 μg/g, was found in 55 (21%) of the 261–264 foods/mixed dishes analyzed. The highest concentrations again were found in seafood, followed by rice/rice cereal, mushrooms, and poultry. The estimated total daily intake of arsenic from foods was 56.6 μg for a 25–30-year-old male. Seafood was the major contributor, accounting for 88–96% of the estimated total arsenic intake of adults.

Average daily dietary exposures to arsenic were estimated for approximately 120,000 U.S. adults by combining data on annual diet, as measured by a food frequency questionnaire, with residue data for table-ready foods that were collected for the annual FDA Total Diet Study. Dietary exposures to arsenic were highly variable, with a mean of 50.6 μg/day (range, 1.01–1,081 μg/day) for females and 58.5 μg/day (range, 0.21–1,276 μg/day) for males (MacIntosh et al. 1997). Inorganic arsenic intake in 969 men and women was assessed by a semi-quantitative food frequency questionnaire in combination with a database for total arsenic content in foods and by toenail concentrations of arsenic. The mean estimated average daily consumption of inorganic arsenic was 10.22 μg/day with a range of 0.93–104.89 μg/day. An assumption of 1.5% of the total arsenic in fish and 20% of the total arsenic in shellfish was inorganic arsenic was used in this assessment (MacIntosh et al. 1997).

During a comprehensive total diet study extending from 1985 to 1988, the estimated daily dietary ingestion of total arsenic by the average Canadian was 38.1 μg and varied from 14.9 μg for the 1–4 year-old-age group to 59.2 μg for 20–39-year-old males (Dabeka et al. 1993). Daily intakes of arsenic from food by women in the Shiga Prefecture, Japan, were investigated by the duplicate portion method and by the market basket method. In 1991 and 1992, the daily intakes determined by the duplicate portion

method were 206 and 210 µg, respectively. Those determined by the market basket method were 160 and 280 µg, respectively (Tsuda et al. 1995b).

Arsenic concentrations in human breast milk have been reported to range from 4 to <10 µg/L in pooled human milk samples from Scotland and Finland to 200 µg/L in samples from Antofagasta, Chile, where there is a high natural environmental concentration of arsenic (Broomhall and Kovar 1986). The arsenic concentration in the breast milk of 35 women in Ismir, Turkey, a volcanic area with high thermal activity ranged from 3.24 to 5.41 µg/L, with a median of 4.22 µg/L (Ulman et al. 1998). Sternowsky et al. (2002) analyzed breast milk from 36 women from three different regions in Germany. These regions included the city of Hamburg, a rural area, Soltau, Lower Saxony, and Munster, the potentially contaminated area. Arsenic was not detected (<0.3 µg/L) in 154 of 187 samples, with the highest concentration, 2.8 µg/L, found in a sample from the rural area. The geometric means from the three areas were comparable.

The mean arsenic levels in three groups of cows in the region that grazed on land impacted by lava and thermal activity were 4.71, 4.46, and 4.93 µg/L, compared to 5.25 µg/L for cows kept in sheds and fed commercial pellet feed and municipal water (Ulman et al. 1998). Mean arsenic concentrations in cow's milk ranging from 18.6 to 17.1 µg/L and from 16.7 to 18.0 µg/L were reported for cow's grazing in nonindustrial and an industrial regions, respectively, in Turkey (Erdogan et al. 2004).

A Danish study found that carrots grown in soil containing 30 µg/g of arsenic, which is somewhat above the 20 µg/g limit for total arsenic set by Denmark for growing produce, contained 0.014 µg/g fresh weight of arsenic, all in the form of inorganic As(III) and As(V) (Helgesen and Larsen 1998). An adult consuming 376 grams of vegetables a day (90^{th} percentile) represented solely by carrots would consume 5.3 µg of arsenic a day. The study concluded that the estimated intake of arsenic from produce grown in soil meeting regulatory limits was low compared with other food sources and water.

If vegetables are grown in planters made of wood treated with CCA, arsenic may leach out of the wood and be taken up by the vegetables. In a study by Rahman et al. (2004), arsenic was found to diffuse into the soil from the CCA-treated wood, with the highest concentrations found at 0–2 cm from the CCA-treated wood and a steady decline in concentration with increased distance from the wood. Crops grown within 0–2 cm of the CCA-treated wood contained higher concentrations of arsenic than those grown at 1.5 m from the treated wood. However, the concentrations are below U.S. FDA tolerance limits that have been set for arsenic in select food items. In addition, food grown in this manner is unlikely to constitute a significant part of a person’s diet.

In 2003, U.S. manufacturers of arsenical wood preservatives began a voluntary transition from CCA to other wood preservatives in wood products for certain residential uses, such as play structures, picnic tables, decks, fencing, and boardwalks. This phase out was completed on December 31, 2003; wood treated prior to this date could still be used and structures made with CCA-treated wood would not be affected. CCA-treated wood products continue to be used in industrial applications (EPA 2003a). EPA's Consumer Awareness Program (CAP) for CCA is a voluntary program established by the manufacturers of CCA products to inform consumers about the proper handling, use, and disposal of CCA-treated wood. Additional information about this program can be found from EPA (2007a).

The arsenic content in the human body is 3–4 mg and tends to increase with age. Arsenic concentrations in most tissues of the human body are <0.3 to 147 μg/g dry weight, excluding hair, nails, and teeth. Mammals tend to accumulate arsenic in keratin-rich tissues such as hair and nails. The normal concentrations of arsenic range from about 0.08 to 0.25 μg/g in hair, and 0.34 μg/g in nails. The normal concentration of arsenic in urine can range from 5 to 40 μg per day (total) (Mandal and Suzuki 2002). Table 6-6 contains arsenic levels in various human tissues.

A German study investigated the transfer of arsenic from the environment to humans in the northern Palatine region, a former mining area characterized by high soil levels of arsenic (<2–605 μg/g) in residential areas compared to a region in southern lower Saxony with nonelevated levels of arsenic in soil (Gebel et al. 1998a). None of the residents were occupationally exposed to arsenic and the arsenic levels in drinking water were generally below 0.015 mg/L. The mean levels of arsenic in urine and hair were lower in the reference area than in the former mining area (see Table 6-6), although within the mining area, there was a slight increase in arsenic levels in hair and arsenic excreted in urine with increasing arsenic content in soil. Children in the Palatine region did not have higher contents of arsenic in their hair or urine. The most significant factor contributing to elevated levels of arsenic in hair and urine was seafood consumption. In the combined population of people living in mining areas containing high levels of arsenic in soil and other areas, the level of arsenic in urine was positively associated with the extent of seafood consumption. However, the study also showed that seafood consumption does not lead to an extreme increase in excretion of arsenic in the urine. There are apparently other, unidentified factors affecting the urine levels. Only arsenic in urine, not in hair, was significantly correlated with age. The level of arsenic in urine was very slightly, but significantly correlated with the consumption of home-grown produce. Tobacco smoking had no correlation with the arsenic content of either hair or urine (Gebel et al. 1998a).

Table 6-6. Levels of Arsenic in Human Tissue and Urine—Recent Studies

Site population	Sample	Concentration		Units	Reference
		Mean[a]	Range		
Fort Valley, Georgia, Pesticide manufacturing facility (Superfund site)					
40 workers (samples collected at end of work week)	Urine, random	11.6	<1–57	µg/L	Hewitt et al. 1995
	Urine, 24-hour	11.0	<1–54	µg/L	
	Hair	0.78	<0.01–6.3	µg/g	
	Fingernails	0.79	<0.01–6.1	µg/g	
Hermosa, Sonora, Mexico					
Children, ages 7–11, exposed to arsenic in water (mean concentration [mean dose]):	Urine, 24-hour				Wyatt et al. 1998a, 1998b
9 µg/L [0.481 µg/kg/day]		10.26	4.05–19.68	µg/day	
15 µg/L [0.867 µg/kg/day]		10.54	2.82–20.44	µg/day	
30 µg/L [1.92 µg/kg/day]		25.18	5.44–93.28	µg/day	
Glasgow, Scotland					
Adults, normal (n=1,250)	Hair	0.650	0.20–8.17	µg/g	Raie 1996
Adults, postmortem (n=9)	Liver	0.048 [0.024]	0.011–0.152	µg/g	
Infants, postmortem (n=9)	Liver	0.0099 [0.007]	0.0034–0.019	µg/g	
Adults, postmortem (n=8)	Lung	0.044 [0.022]	0.0121–0.125	µg/g	
Infants, postmortem (n=9)	Lung	0.007 [0.0055]	0.0011–0.015	µg/g	
Adults, postmortem (n=9)	Spleen	0.015 [0.008]	0.001–0.063	µg/g	
Infants, postmortem (n=8)	Spleen	0.0049 [0.0045]	0.0011–0.0088	µg/g	
Palatinate Region, Germany (high As)[b]					
Residents (n=199)	Urine, 24-hour	3.96 [3.21]	<0.1–18.32	µg/g	Gebel et al. 1998a
Residents (n=211)	Hair	0.028 [0.016]	<0.005–0.154	µg/g	
Saxony, Germany (low As—reference)[b]					
Residents (n=75)	Urine, 24-hour	7.58 [6.20]	0.29–23.78	µg/g	Gebel et al. 1998a
Residents (n=74)	Hair	0.069 [0.053]	0.013–0.682	µg/g	
Ismir, Turkey, (volcanic area with high thermal activity)					
Nonoccupationally exposed women (n=35)	Breast milk	4.23 [4.26]	3.24–5.41	µg/L	Ulman et al. 1998
Erlangen-Nurenberg Germany 1/92–12/93					
Nonoccupationally exposed people (n=50)	Lung	5.5	<1–13.0	ng/g ww	Kraus et al. 2000
		28.4	<1–73.6	ng/g dw	

Table 6-6. Levels of Arsenic in Human Tissue and Urine—Recent Studies

Site population	Sample	Concentration		Units	Reference
		Mean[a]	Range		
Tarragona (Catalonia, Spain) 1997–1999					
Nonoccupationally exposed people (n=78)	Lung	<0.05		µg/g ww	Garcia et al. 2001
	Bone	<0.05			
	Kidney	<0.05			
	Liver	<0.05			
	Lung	<0.05			
West Bengal, India					
Residents consuming arsenic-contaminated water (n=47)	Fingernail	7.32	2.14–40.25	µg/g	Mandal et al. 2003
	Hair	4.46	0.70–16.17		
Residents consuming nonarsenic-contaminated water (n=15)	Fingernail	0.19	0.11–0.30		
	Hair	0.07	0.03–0.12		
Middleport, NY, USA					
Children <7 years (n=77)	Urine	15.1[c]	2.1–59.6	µg/L	Tsuji et al. 2005
Children <13 years (n=142)	Urine	15.7[c]	2.1–59.9		
Children ≥7 years and adults (n=362)	Urine	15.8[c]	3.9–773		
All participants	Urine	15.7[c]	2.1–773		

[a]Medians, if reported, are in brackets.
[b]The reference group (Saxony) had significantly higher levels of arsenic in urine and hair. However, data from both groups correspond to normal range reference data.
[c]Geometric mean, total arsenic

dw = dry weight; ww = wet weight

A study was performed to look at the arsenic levels, as well as the arsenic species present, in hair and nail samples from individuals in an arsenic-affected area in West Bengal, India. Mean arsenic concentrations in hair and fingernails of the chronically arsenic exposed population were 4.46 and 7.32 μg/g, respectively and were 0.07 and 0.19 μg/g in a control population. Fingernail samples were found to contain mostly inorganic arsenic (>80%) as a mixture of As(III) and As(V), as well as DMA(III) and DMA(V). Hair samples also mostly contained inorganic arsenic (>90%), as well as MMA(V) and DMA(V) (Mandal et al. 2003).

Arsenic in soil in communities surrounding former smelters is a public health concern, especially for infants and children who may consume significant quantities of soil. Since lead arsenate was used in apple and other fruit orchards, often at very high application rates, and this compound would be expected to accumulate and persist in surface soil, there are concerns to human health when these when old orchards are converted into subdivisions or when they are used to grow food crops or forage. However, arsenic in soil may be imbedded in minerals or occur as insoluble compounds such as sulfides and therefore, not be taken up by the body from the gastrointestinal tract. In addition, oxidation of mineral surfaces may result in armoring the primary mineral grain by a secondary reaction product. Arsenic-bearing solids are often encapsulated in insoluble matrices such as silica, further diminishing arsenic availability (Davis et al. 1992).

Sarkar and Datta (2004) examined the bioavailability of arsenic from two soils with different arsenic retention capacities. In this study, Immokalee (Florida) and Orelia (Texas) soils were incubated after spiking with sodium arsenate for 4 months. The Immokalee soil is a sandy spodosol with low Fe/Al, Ca/Mg, and P contents and is likely to have minimal arsenic retention capacity. The Orelia soil is a sandy clay that is expected to have strong arsenic retention capacity. Arsenic speciation and bioavailability were studied immediately after spiking and after 4 months of incubation. Approximately 85% of the total arsenic (soluble and exchangeable fractions) was considered bioavailable and phytoavailable immediately after pesticide application for the Immokalee soil; after 4 months of incubation, this decreased to approximately 46%. Immediately after pesticide application, the amounts of arsenic extracted in the soluble/exchangeable and Fe/Al-bound fractions were similar that of the Immokalee soil. After 4 months, the soluble arsenic decreased to approximately 45% and the Fe/Al-bound arsenic increased to about 40%. Experiments looking at the bioavailability of arsenic from these two soils indicated that the potentially irreversible adsorption of arsenic by the Orelia soil rendered a significant portion of the total arsenic unavailable for absorption by the human gastrointestinal system. Initially after pesticide application,

100% of the arsenic was bioavailable; after 4 months, the bioavailable fraction was found to decrease to 88 and 69% in the Immokalee and Orelia soils, respectively (Sarkar and Datta 2004).

Hamel et al. (1998) used synthetic gastric juice to estimate the bioaccessible fraction of metals in the stomach with varying liquid to solid ratios. They found that the bioaccessibility may vary in different soils and with varying liquid to solid ratios. Bioaccessibility was defined as the amount of metal that is soluble in synthetic gastric juice and therefore, potentially available for uptake across the intestinal lumen, while bioavailability was defined as the amount that was actually taken across the cell membranes. Arsenic bioaccessibility for National Institute of Standards and Technology (NIST) Montana Soil SRM 2710, with a certified arsenic concentration of 626 μg/g, was fairly consistent across the liquid-to-solid ratios and ranged from 41.8±18 to 56±21%. The extractability of a hazardous waste contaminated soil from Jersey City, New Jersey, was different than that observed for the Montana NIST soil. For the Jersey City soil, which had an arsenic concentration of 1,120 μg/g, there was an increase in the bioaccessible arsenic as the liquid-to-solid ratio increased. Bioaccessible arsenic ranged from 4.5±0.8 (at a liquid-to-solid ratio of 100:1) to 25±9% (at a ratio of 5,000:1). Similarly, smelter impacted soils from Anaconda, Montana contain metal-arsenic oxides and phosphates whose bioaccessibility is limited by solubility restraints for residence times typical of the gastrointestinal tract (Davis et al. 1992, 1996).

Inhalation of arsenic from ambient air is usually a minor exposure route for the general population. For example, the dose to a person who breathes 20 m^3/day of air containing 20–30 ng/m^3 (see Section 6.4.1) would be about 0.4–0.6 μg/day. However, smokers may be exposed to arsenic by inhalation of mainstream smoke. Assuming that 20% of the arsenic in cigarettes is present in smoke, an individual smoking two packs of cigarettes per day would inhale about 12 μg of arsenic (EPA 1984a). However, a German study of the arsenic levels in lung tissue of 50 unexposed deceased people (see Table 6-6) found no significant difference in lung arsenic concentrations of smokers versus nonsmokers, nor were there any significant age- or sex-related differences (Kraus et al. 2000). Before arsenical pesticides were banned, tobacco contained up to 52 μg As/g, whereas after the ban, maximum arsenic levels were reduced to 3 μg/g.

Occupational exposure to arsenic may be significant in several industries, mainly nonferrous smelting, arsenic production, wood preservation, glass manufacturing, and arsenical pesticide production and application. Since arsenic compounds are used as a desiccant for cotton, workers involved in harvesting and ginning cotton may be exposed to arsenic. Occupational exposure would be via inhalation and dermal contact. Should any arsenic be retained in the cotton, workers handling the fabric and the general

public would be exposed. The electronics industry is expanding the use of gallium arsenide in the production of electro-optical devices and integrated circuits, and workers in the industry where gallium arsenide is used may be exposed to hazardous substances such as arsenic, arsine, and various acids (Sheehy and Jones 1993). Occupational exposure to arsenic is generally assessed by measuring urinary excretion of arsenic. Past exposure is commonly assessed by arsenic levels in hair. Different types of occupational exposures may result in different uptakes of arsenic because of the bioavailability of the form of arsenic to which workers are exposed. For example, maintenance workers at a Slovak coal-fired power plant exposed to 8-hour TWA arsenic air concentrations of 48.3 μg/m^3 (range, 0.17–375.2) had urinary total arsenic levels of 16.9 μg As/g creatinine (range, 2.6–50.8), suggesting that bioavailability of arsenic from airborne coal fly ash is about one-third that from in copper smelters and similar settings (Yager et al. 1997). Approximately 90% of the arsenic-containing particulates were ≥3.5 μm. Apostoli et al. (1999) monitored 51 glass workers exposed to arsenic trioxide by measuring dust in the breathing zone. The mean concentration of arsenic in air was 82.9 μg/m^3 (1.5–312 μg/m^3); exposure was higher for workers involved in handling the particulate matter. The occupation exposures to principal contaminants, including arsenic, at five coal-fired power plants were evaluated during June–August 2002. Eight air samples were collected per similar exposure group at four of the five facilities; inorganic arsenic concentrations in all samples were below the limit of detection (0.37–0.72 μg/m^3), as well as being below the OSHA permissible exposure limit (PEL) of 10 μg/m^3 (Bird et al. 2004).

NIOSH researchers conducted a study of arsenic exposures and control systems for gallium arsenide operations at three microelectronics facilities during 1986–1987 (Sheehy and Jones 1993). Results at one plant showed that in all processes evaluated but one, the average arsenic exposures were at or above the OSHA action level of 5 μg/m^3, with a maximum exposure of 8.2 μg/m^3. While cleaning the Liquid Encapsulated Czochralski (LEC) pullers, the average potential arsenic exposure of the cleaning operators was 100 times the OSHA PEL of 10 μg/m^3. Area arsenic samples collected at the plant in break-rooms and offices, 20–60 feet from the process rooms, had average arsenic concentrations of 1.4 μg/m^3. At the other two plants, personal exposures to arsenic were well controlled for all processes evaluated.

A study has been conducted to examine the relationship between total arsenic levels in hair of employees in a semiconductor fabrication facility and job responsibility, a surrogate variable for arsenic exposure (de Peyster and Silvers 1995). Airborne arsenic was found in areas where equipment was cleaned but not in administrative areas. The highest airborne arsenic level found in the study, 15 μg/m^3, was collected from the breathing zone of a maintenance employee who was cleaning a source housing over a period of 2 hours in an area with local exhaust ventilation. A concentration of 2 μg/m^3 was found during the

remainder of the cleaning period (~53 minutes). Workers in maintenance who were regularly assigned to cleaning equipment, and therefore presumed to have the highest exposure potential, had a mean hair arsenic level of 0.042 μg/g. This was higher than the mean of 0.033 μg/g observed in administrative controls, but the difference was not significant. Maintenance workers who only occasionally cleaned and maintained arsenic-contaminated equipment had a mean hair arsenic level of 0.034 μg/g, which was comparable to the controls. The highest group mean hair arsenic level of 0.044 μg/g, surprisingly, was found in supervisors and engineers who were presumed to have the lowest exposure potential of all workers in the process areas. However, the highest concentrations of hair arsenic in engineers, 0.076 and 0.106 μg/g, were observed in two heavy smokers who smoked 1–2 packs of cigarettes per day. A 2-way analysis of variance indicated that smoking appeared to be a significant contributing factor whereas occupational exposure was not.

Hwang and Chen (2000) evaluated arsenic exposure in 21 maintenance engineers (exposed group) and 10 computer programmers (control group) at 3 semiconductor manufacturing facilities. Samples of air, wipe, and urine, as well as used cleaning cloths and gloves were collected to determine arsenic exposure. Arsenic was undetectable in 46 of the 93 air samples, and most samples were generally below the recommended occupational exposure limit (10 $\mu g/m^3$) in work areas during ion implanter maintenance. Arsine was detectable in 22 of the 45 area air samples and in 15 of the 35 personal air samples; however, all concentrations were well below the occupational exposure limit of 50 ppb (160 $\mu g/m^3$). Mean arsine concentrations ranged from not detected to 4.0 ppb (15 $\mu g/m^3$) in area air samples, and the mean arsine concentration of personal air for maintenance engineers was 4.3 ppb (14 $\mu g/m^3$). Arsenic concentrations in wipe samples, used cleaning cloths, and gloves, varied from not detected to 146 $\mu g/cm^2$. During ion implanter maintenance, urinary arsenic levels were found to increase (1.0–7.8 μg/g creatinine) in the maintenance engineers, from a mean baseline concentration of 3.6 μg/g creatinine. The average urinary arsenic level for the computer programmers was 3.8 μg/g creatinine (Hwang and Chen 2000). Mean arsenic concentrations in blood of 103 workers in the optoelectronic industry and 67 controls were 8.58 and 7.85 μg/L, respectively (Liao et al. 2004).

Concentrations of various metals, including arsenic, were measured in autopsy tissues (liver, lung, kidney, brain, and bone) collected from 78 nonoccupationally exposed subjects from Tarragona County, Spain between 1997 and 1999. In general, arsenic concentrations were under the analytical detection limit (0.05 μg/g wet weight) in all tissues (Garcia et al. 2001).

CCA preservatives are commonly used for treating timber used in constructions in marine and other humid environments or in contact with the ground. Exposure to CCA compounds may occur through dermal contact and inhalation of dust while working with the treated timber. Nygren et al. (1992) investigated the occupational exposure to airborne dust, chromium, copper, and arsenic in six joinery shops in Sweden where impregnated wood was used for most of their production. The mean airborne concentration of arsenic around various types of joinery machines ranged from 0.54 to 3.1 μg/m^3. No increased concentrations of arsenic were found in the workers' urine. A study was carried out in Denmark to evaluate arsenic exposure in taxidermists, workers impregnating wood with CCA solutions, fence builders, construction workers, and workers impregnating electric pylons with arsenic solution (Jensen and Olsen 1995). Airborne arsenic exposure was documented in 19 of 27 individuals working with products containing arsenic. The maximum exposure concentration was 17.3 μg/m^3, found for a single worker who was filling an impregnation container with CCA paste. Median exposures for indoor workers producing garden fences and weekend cottages were 3.7 and 0.9 μg/m^3, respectively. The maximum urine concentration reported in the study was 294.5 nanomoles arsenic per millimole creatinine (195 μg As/g creatinine) and was from the injector impregnating electric pylons. The median concentration in workers on electric pylons was 80 nanomoles arsenic per millimole creatinine (53 μg As/g creatinine), which was 6 times the concentration in reference individuals. Urine arsenic levels in workers producing garden fences and in taxidermists were 2.9 and 1.8 times the reference level, respectively.

The NIOSH National Occupational Exposure Survey (NOES) conducted in 1981–1983 estimated that about 55,000 workers were potentially exposed to arsenic (NOES 1990). The NOES was based on field surveys of 4,490 facilities that included virtually all workplace environments, except mining and agriculture, where eight or more persons are employed. The principal exposure pathway is probably inhalation of arsenic adsorbed to particulates, but ingestion and possibly dermal exposure may also be common. Since arsenic is no longer produced in the United States (see Section 5.1) and many arsenical pesticide uses have been banned (see Chapter 8), it is likely that the number of workers occupationally exposed to arsenic has decreased markedly in more recent years.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

As with adults, most children are exposed to arsenic largely through their diet. Since the greatest dietary intake of arsenic is from fish and seafood, infants and young children for whom a substantial part of their food is milk, would not be exposed to arsenic from dietary sources as much as older children. Even when mothers consumer large amounts of seafood, there does not appear to be any major transfer of arsenobetaine, the major form of arsenic in seafood, from seafood to milk (Grandjean et al. 1995). Arsenic concentrations were very low in human milk sampled from 88 mothers in the Faroe Islands, where the seafood diet includes pilot whale meat and blubber. The total arsenic concentrations ranged from 0.1 to 4.4 μg/kg, with a median of 1.6 μg/kg (Grandjean et al. 1995). The arsenic concentration in the breast milk of 35 women in Ismir, Turkey, a volcanic area with high thermal activity ranged from 3.24 to 5.41 μg/L, with a median of 4.22 μg/L (Ulman et al. 1998). The mean arsenic levels in three groups of cows in the region that grazed on land impacted by lava and thermal activity were 4.71, 4.46, and 4.93 μg/L, compared to 5.25 μg/L for cows kept in sheds and fed commercial pellet feed and municipal water. The arsenic levels in the urine of pregnant women and the cord blood of their infants were 0.625±0.027 and 0.825±0.079 μg/L, respectively. The authors concluded that there was no harmful exposure to arsenic in volcanic areas with high arsenic levels from suckling infants or feeding them local cow's milk, nor was there harm to the newborns from their mother's diet. Sternowsky et al. (2002) analyzed breast milk from 36 women from three different regions in Germany. These regions included the city of Hamburg, a rural area, Soltau, Lower Saxony, and Munster, the potentially contaminated area. Arsenic was not detected (<0.3 μg/L) in 154 of 187 samples, with the highest concentration, 2.8 μg/L, found in a sample from the rural area. The geometric mean arsenic concentrations from the three areas were comparable. Calculated oral intakes of arsenic were between 0.12 and 0.37 μg/day for an infant at 3 months of age and weighing 6 kg.

According to the FDA study of 1986–1991, the mean daily intakes of arsenic are 0.5 and 0.81 μg/kg body weight per day for a 6–11-month-old infant and 2-year-old child, respectively (Gunderson 1995b). This

can be compared to a mean daily intake of 0.51 μg/kg-body weight per day for a 25–30-year-old male (see Table 6-5). A Total Diet Study, from September 1991 to December 1996, estimated that the average inorganic arsenic intake for children of various age/sex groups were (age-sex group, total arsenic intake in μg/day, inorganic arsenic intake in μg/day): 6–11 months, 2.15, 1.35; 2 years, 23.4, 4.41; 6 years, 30.3, 4.64; 10 years, 13.3, 4.21; and 14–16 years (females), 21.8, 5.15; 14–16 years (males), 15.4, 4.51 (Tao and Bolger 1999). The greatest dietary contribution (76–96%) of total arsenic intake for all age groups other than infants was seafood. For infants, 41 and 34% of the estimated total arsenic intakes are from seafood and rice/rice cereals, respectively (Tao and Bolger 1999). Only for toddlers does the intake approach the World Health Organization's (WHO) provisional tolerable daily intake (PTDI) for inorganic arsenic (see Table 6-5). A 1985–1988 Canadian total diet study estimated that 1–4-year-olds ingested 14.9 μg of total arsenic per day compared with 38.1 μg by the average Canadian and 59.2 μg for 20–39-year-old males (Dabeka et al. 1993). Yost et al. (2004) estimated the mean dietary intake for inorganic arsenic for children (1–6 years of age) to be 3.2 μg/day, with a range of 1.6–6.2 μg/day for the 10^{th} and 95^{th} percentiles, respectively. Inorganic arsenic intake was predominantly contributed by grain and grain products, fruits and fruit juices, rice and rice products, and milk (Yost et al. 2004). Total arsenic and arsenobentaine concentrations were measured in 16 baby food samples obtained from manufactures in Spain; total arsenic concentrations ranged from 2.042 to 0.270 μg/g in plaice with vegetables and sole with white sauce, respectively. Arsenobetaine, which is the arsenical commonly found in fish, accounted for essentially 100% of the arsenic present in the samples (Vinas et al. 2003).

Arsenic exposure from drinking water may be elevated especially in groundwater from areas where arsenic occurs naturally in soil such as the western and north central sections of the United States (see Table 6-3 and Figure 6-2).

Arsenic exposure in communities near mining and smelting facilities or where arsenic had formerly been applied to agricultural land are a public health concern, especially for infants and children. Since arsenic remains in the surface soil indefinitely and long past land uses may be forgotten, people may not realize that they are living in areas where high levels of arsenic may occur in soil. Contaminated soils pose a particular hazard to children because of both hand-to-mouth behavior and intentional ingestion of soil (pica) that contains metals and other contaminants (Hamel et al. 1998). In these communities, arsenic may contaminate carpeting or may have been tracked in from outside. Children may be exposed to this arsenic while crawling around or playing on contaminated carpeting. Exposure may also result from dermal contact with the soil, or by inhaling the dust and then swallowing it after mucociliary transport up

out of the lungs. Because much of the arsenic in soil is embedded in or adsorbed to soil particles or insoluble, it may not be in a form accessible for uptake by the body.

Hwang et al. (1997b) studied the arsenic exposure of children in Anaconda, Montana, in the vicinity of a former copper smelter from the summer of 1992 through the summer of 1993. Environmental samples and first morning voided urine samples from 414 children <72 months old were collected. Attention was focused on that fraction of the environmental source that was thought to be of the greatest risk to the child (i.e., arsenic in small particles [<250 μm]) that could most readily adhere to hands and toys and could be inadvertently ingested. Average arsenic levels in different types of soil ranged from 121 to 236 μg/g. Several studies have reported mean soil ingestion values for children ranging from 9 to 1,834 μg /day. Assuming that high arsenic exposure areas have average arsenic levels in soil from 60 to 150 μg/g, the resulting daily arsenic intake from soil could range from 1 to 275 μg/day per child. The geometric mean of speciated urinary arsenic (combined As(III), As(V), MMA and DMA) was 8.6±1.7 μg/L (n=289) in the Hwang study. A nationwide survey on arsenic exposure in the vicinity of smelter sites revealed that children without excess arsenic exposure had average total urinary arsenic levels ranging from 5 to 10 μg/L (Hwang et al. 1997a). Compared to these values, the mean total urinary arsenic values found in the Hwang study were markedly higher, but they were still well below the WHO-recommended maximum excretion level for total arsenic of 100 μg/L as an action level for intervention. The investigators hypothesized that the relatively low urinary arsenic levels found in the study were probably a reflection of the low bioavailability of some forms of arsenic in contaminated soil. Hwang et al. (1997a) stated that arsenic intake through skin contact is insignificant and may be neglected in the assessment of childhood arsenic exposure. They recommend that parents or guardians pay more attention to their children's activity, especially hand-to-mouth behavior, even though the environmental contaminants might be elevated only slightly. Children in the northern Palatine region of German study, a former mining area characterized by high levels of arsenic (<2–605 μg/g) in residential areas did not show higher arsenic levels in their hair or urine than children from a reference area of Germany (Gebel et al. 1998a).

While CCA registrants voluntarily canceled the production of CCA-treated wood for residential use in 2003, there is a potential for exposure to arsenic from existing structures (Zartarian et al. 2006). Based on a review of existing studies, Hemond and Solo-Gabriele (2004) estimated that children with contact with CCA-treated wood may be subjected to doses in the range of tens of micrograms of arsenic per day. The most important route of exposure appeared to be by hand-to-mouth activities after contact with the CCA-treated wood. Kwon et al. (2004) compared the amounts of water-soluble arsenic on hands of children in

contact with CCA-treated wood structures or sand in playgrounds. The mean amount of water-soluble arsenic on children's hands from playgrounds without CCA-treated wood was 0.095 μg (range 0.011–0.41 μg). A mean amount of water-soluble arsenic on children's hands from playgrounds with CCA-treated wood was 0.5 μg (range 0.0078–3.5 μg) (Kwon et al. 2004). Additional data from the study by Kwon et al. (2004) showed that total arsenic collected in hand-washing water (insoluble arsenic on the filter combined with the water-soluble arsenic in the filtrate) was 0.934 and 0.265 μg for the CCA playgrounds and the non-CCA playgrounds, respectively (Wang et al. 2005). Two wood surface swab samples collected from 217 play structures constructed from CCA-treated wood in the City of Toronto, Canada were sampled and analyzed for inorganic arsenic (Ursitti et al. 2004). Dislodgeable arsenic concentrations were found to vary widely from nondetectable (0.08–0.25 μg/100 cm^2) to 521 μg/100 cm^2 (mean = 41.6 μg/100 cm^2), and were found to not be a useful predictor of soil arsenic levels (Ursitti et al. 2004).

Shalat et al. (2006) evaluated postexposure hand rinses and urine for total arsenic for 11 children (13–71 months) in homes in Miami-Dade County, Florida, with and without CCA-treated playgrounds. Seven playgrounds were included in this study, and five of these contained either CCA-treated or partially CCA-treated wood. In addition, samples of wood, soil (5–8 cm from the base of the playground structure), mulch (when present), and synthetic wipes were analyzed for total arsenic. Wood and soil arsenic concentration were <2.0 and <3 mg/kg for the non-CCA-treated playgrounds, respectively. Mean arsenic concentrations of 2,380 mg/kg (range 1,440–3,270 mg/kg) and 19 mg/kg (4.0–42 mg/kg) were reported for wood and soil, respectively, in the playgrounds with CCA-treated wood. An arsenic concentration in mulch at one playground without CCA-treated wood was 0.4 mg/kg, and arsenic concentrations were 0.6 and 69 mg/kg in mulch at two of the playgrounds with CCA-treated wood. The amount of arsenic removed by synthetic wipes from the non-CCA-treated wood was <0.5 μg, while the mean amount of arsenic removed from the CCA-treated wood was 117 μg (range 1.0–313 μg). The amount of arsenic in hand rinses from children who played at the playgrounds with non-CCA-treated wood and at the playgrounds with CCA-treated wood were <0.2 and 0.6 μg (range <0.2–1.9 μg), respectively. The mean urinary total arsenic concentration was 0.0136 μg/L (range 0.0072–0.0231 μg/L) for all children. No association between assess to CCA-treated playgrounds and urinary arsenic levels was found (Shalat et al. 2006).

The potential exposure children may receive from playing in play structures constructed from CCA-treated wood is generally smaller than that they would receive from food and water. For comparison, Yost et al. (2004) estimated the mean dietary intake for inorganic arsenic for children (1–6 years of age)

to be 3.2 μg/day, with a range of 1.6–6.2 μg/day for the 10th and 95th percentiles, respectively. In a Total Diet Study, from September 1991 to December 1996, estimated average total intakes for children aged 6–11 months, 2 years, 6 years, and 10 years were 2.15, 23.4, 30.3, and 13.3 μg/day, respectively. Average inorganic arsenic intakes for the same age groups were estimated as 1.35, 4.41, 4.64, and 4.21 μg/day, respectively, based on data for total arsenic in foods and the assumption that 10% of the total arsenic in seafood was inorganic and that 100% of the arsenic in all other foods was inorganic (Tao and Bolger 1999). Hand washing after play would reduce the potential exposure to children to arsenic after playing on play structures constructed with CCA-treated wood, since most of the arsenic on the children's hands was removed with water (Kwon et al. 2004).

Concentrations of several toxic metals, including the metalloid arsenic, were measured in the placentas of 200 women in two urban cities in Ukraine, Kyiv and Dniprodzerzhinsk. Arsenic was detected in only 5% of the samples with concentrations ranging from <0.156 to 0.378 μg/g. In a study in Bulgaria, placental arsenic concentrations of 7 and 23 μg/g were reported in a control and smelter area, respectively. A placental arsenic concentration of 34 μg/g was reported in a region of Argentina with high concentrations of arsenic in drinking water (Zadorozhnaja et al. 2000).

Parents can inadvertently carry hazardous materials home from work on their clothes, skin, hair, and tools, and in their vehicles (DHHS 1995). Falk et al. (1981b) reported a case of hepatic angiosarcoma in a child that could be associated with arsenic contamination of a parent's clothing, the water supply, and the environment. The father worked in a copper mine and smelter area where his clothing was contaminated with dust containing arsenic. His daughter, who exhibited a high degree of pica, ate soil from the yard, and licked soil off her father's shoes. In a study of arsenic levels in homes in Hawaii, Klemmer et al. (1975) found higher levels in homes of employees of firms that used arsenic for pesticides or wood preservation, compared to homes where residents' work did not involve arsenic. The concentration of arsenic in dust from the homes of workers exposed to arsenic ranged from 5.2 to 1,080 μg/g, compared to concentrations of 1.1–31 μg/g in dust from control homes.

While the harmful effects of many components of tobacco smoke are well known, those due to heavy metals in the smoke have not been sufficiently emphasized. The adverse health effects of these toxic metals on the fetus through maternal smoking are of special concern (Chiba and Masironi 1992). The concentration of arsenic in tobacco is relatively low, usually below detectable limits (<1 μg/g). Although the concentrations of inorganic and organic arsenic in the urine of adults do not appear to be influenced by smoking, a positive association was found between urinary arsenic levels in children and parental

smoking habits. As detailed in a WHO report, the mean arsenic level in the urine of children of nonsmoking parents was 4.2 μg/g creatinine, in children with one smoking parent, it was 5.5 μg/g, and in children with both parents smoking, it was 13 μg/g (Chiba and Masironi 1992). Tsuji et al. (2005) reported geometric mean concentrations of total arsenic of 15.1 and 15.7 μg/L in children <7 and <13 years old, respectively, from households in Middleport, New York, where historical pesticide manufacture was associated with arsenic in soil. Geometric mean concentrations of inorganic arsenic, MMA, and DMA were 0.81, 0.54, and 2.5 μg/L, respectively, in children <7 years old and 0.83, 0.55, and 3.0 μg/L, respectively, in children <13 years old (Tsuji et al. 2005).

The use of Chinese herbal medicines (CHM) appears to be common among Chinese women. Both CHM and Chinese proprietary medicines (CPM) are used for treatment of minor ailments in babies and children. Herbal medicines are available in capsule or tablet form in drug stores, supermarkets, and by mail. The CPM "Sin Lak Pill," "Lu Shen Wan," and other anti-asthma preparations have been found to contain inorganic arsenic levels ranging from 25 to 107,000 μg/g, and cases of acute arsenic poisoning have been found in children and adults using these CPM (Chan 1994). Babies and children are particularly at risk because they may be given higher doses of these preparations per kg of body weight than adults would normally consume. They may also lack the hepatic enzymes responsible for drug biotransformation and detoxification (Chan 1994). Concentrations of heavy metals, including arsenic, were evaluated in 54 samples of Asian remedies that were purchased in stores in Vietnam and Hong Kong that would be easily accessible to travelers, as well as in health food and Asian groceries in Florida, New York, and New Jersey. One remedy that was recommended to treat children's fever would expose a 15 kg child to approximately 5.0 mg of arsenic per day (Garvey et al. 2001). A folk remedy, purchased in California, for the treatment of chicken pox, flu-like symptoms, and nasal congestion, which had been given to two children in Wisconsin, was found to contain 36% arsenic acid. One-half teaspoon of this powder (about 500 mg of arsenic) was dissolved in hot water and taken 2–3 times per day (Werner et al. 2001).

Various metallic pigments and colors in the form of salts or lakes are used in toy production. Therefore, children may be exposed to toxic metals while playing with toys, especially when they lick, suck, or swallow a toy or a piece of a toy. Toys produced in European Union Markets must conform to restrictions concerning the bioavailability of toxic metals, including arsenic. The maximum limit for bioavailability of arsenic from the accessible parts of a toy is set to 0.1 μg/day. This corresponds to an arsenic migration limit of 25 μg/g for all toy material, including modeling clay and paints (Rastogi and Pritzl 1996). A study was carried out to determine whether crayons, water colors, and water-based paints

conform with the migration limits for toxic metals (Rastogi and Pritzl 1996). For the analysis, 94 samples representing 48 products were obtained from China, Taiwan, Japan, the United States, and European countries. Fifty-two samples showed migration of arsenic, ranging from 0.01 to 3.75 μg/g.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to arsenic (see Section 6.5), there are several groups within the general population that have potentially high exposures (higher than background levels) to arsenic. These populations include individuals living in proximity to sites where arsenic was produced, used (e.g., as a pesticide), or disposed, and individuals living near one of the 1,684 NPL hazardous waste sites where arsenic has been found at elevated levels in some environmental media (HazDat 2006). It also includes point sources such as smelters, coal-fired power plants, and municipal incinerators. People living in areas of volcanic activity may be exposed to higher levels of arsenic since high levels are more likely to be present in the environment. Other populations at risk of potentially high levels of exposure include those whose water supply contains high levels of arsenic and those consuming large amounts of seafood or seaweed. However, as pointed out previously (see Section 6.4.4), arsenic in fish and shellfish, is largely in the form of the less harmful organic arsenical, arsenobetaine; however, some commercially available seaweeds, especially brown algae varieties, may have high percentages of the total arsenic present as inorganic arsenic (>50%) (Almela et al. 2002; Laparra et al. 2003). While elevated urinary arsenic excretion levels have been associated with the consumption of fish and seafood, in a study of 32 sport fish consumers from Lakes Erie, Huron, and Michigan, only 6 (19%) had detectable urine arsenic concentrations, >4 μg/L, and 5 of these consumed fish from Lake Huron (Anderson et al. 1998). Exposure of high levels of arsenic in drinking water is more apt to be absorbed by the body and be harmful than exposure to arsenic in seafood. For example, a group of 36 people in Zimapán, Mexico who consumed water from an aquifer with 1.0 mg As/L had hair arsenic levels of 2.6–14.1 μg/g (10 μg/g average), compared with 2.4–13.9 μg/g (6.19 μg/g average) for a reference population that consumed bottled water with <0.014 mg/L arsenic (Armienta et al. 1997).

A study was conducted to determine if significant arsenic exposure was occurring at a Superfund site in Fort Valley, Georgia (Hewitt et al. 1995). Random urine, 24-hour urine, hair, and fingernail samples were collected at the end of the workweek from 40 employees at an active pesticide manufacturing facility where arsenical pesticides had been produced for over 50 years prior to the mid-1970s. Measurement of arsenic in the urine is considered to be the best method for monitoring recent exposure in industrial populations. Hair and fingernail analyses may provide an indication of exposures that occurred

up to several months prior to testing, but both can adsorb and strongly retain arsenic from external sources. Since arsenic is rapidly cleared from the blood (half-life of 3–4 hours), blood arsenic levels are not considered suitable for monitoring populations for chronic low-level arsenic exposure. Results of the Hewitt study are summarized in Table 6-6. Urinary arsenic levels for all workers were well within the commonly accepted normal range of <100 μg/L.

As noted above, workers in a number of industries may have high exposures to arsenic, especially if proper safety procedures are not followed. For members of the general population, above-average exposure to arsenic from drinking water is possible in areas of high natural arsenic levels in groundwater or elevated arsenic levels in drinking water due to industrial discharges, pesticide applications, or leaching from hazardous waste facilities. Individuals living in the vicinity of large smelters and other industrial emitters of arsenic may be exposed to above-average arsenic levels both in the air, and as a result of atmospheric deposition, in water and soil and subsequent uptake into crops.

People sawing or drilling arsenic-treated wood without protective masks or burning this wood may be exposed to elevated levels of arsenic in air.

Recreational and subsistence fishers who consume appreciably higher amounts of locally caught fish from contaminated bodies of water may be exposed to higher levels of arsenic associated with dietary intake. Arsenic contamination has triggered the issuance of several human health advisories (EPA 1998g). As of December 1997, arsenic was identified as the causative pollutant in a restricted consumption advisory for the general population for all fish in a 7-mile area including Devil's Swamp Lake and Bayou Baton Rouge in Louisiana. A public health advisory has been issued for consumption of fish and shellfish from the Duwamish River, Seattle, Washington due to arsenic and other chemicals (WSDOE 2005).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of arsenic.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The chemical and physical properties of the arsenic species of chief toxicological and environmental concern are sufficiently well characterized to allow estimation of the environmental fates of these compounds. However, more information regarding the K_{ow} and K_{oc} values of the organic arsenicals would help predict the fate of these compounds in the environment.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2004, became available in May of 2006. This database is updated yearly and should provide a list of industrial production facilities and emissions.

While arsenic has not been produced in the United States since 1985, the United States is the largest consumer of arsenic and substantial quantities of arsenic are imported, primarily as arsenic trioxide (USGS 2006a). The agricultural use of inorganic arsenic pesticides have been discontinued in the United States. However, some organic arsenicals still may be used in agriculture. Current production and use data for individual arsenical pesticides and other arsenic compounds would help to estimate human exposure to the various arsenic species. Because arsenical pesticides are so persistent, a more complete picture of past use of these products would enable us to predict what areas may contain high levels of arsenic in soil.

Comprehensive estimates on emissions of arsenic date to the early 1980s (Nriagu and Pacyna 1988). The industrial picture has changed considerably since then and emission controls are being mandated more and more. For example, emission factors for Canadian smelters calculated in 1993 were grossly lower than those estimated in 1983 (Skeaff and Dubreuil 1997). There is a need for accurate and up-to-date measurements of atmospheric arsenic releases from both natural and anthropogenic sources to better assess human exposure to arsenic and guide environmental protection measures.

Environmental Fate. The interconversion of the various arsenic species and transport among the environmental media is complex and not all aspects are well-studied. Additional quantitative data on the rates of oxidation, reduction, and biotransformation reactions of arsenic compounds, and how these depend on environmental conditions would be useful in evaluating and predicting the fate and transport of arsenic at hazardous waste sites and other areas.

Bioavailability from Environmental Media. Toxicokinetic and toxicity studies establish that bioaccessible (e.g., soluble, not strongly adsorbed to soil or embedded in minerals) arsenic is highly absorbed following inhalation and oral exposure (see Sections 3.4.1.2 and 3.4.1.1). Some work has been done on the effect of environmental matrix (soil, food) on accessibility and absorption of arsenic (Davis et al. 1992, 1996; Hamel et al. 1998; Roberts et al. 2002, 2007), but additional data would be valuable. Limited data suggests that dermal absorption of arsenic is very low (see Section 3.4.1.3) (Lowney et al. 2005), further data would be useful to establish whether arsenic uptake occurs from contact with contaminated soil or water, since humans may be exposed by these routes near hazardous waste sites.

Food Chain Bioaccumulation. Bioconcentration factors have been measured for several freshwater and marine species. While some species (mainly marine algae and shellfish) tend to bioconcentrate arsenic (EPA 1980a; Roper et al. 1996), it is not biomagnified through the food chain (Eisler 1994; EPA 1979, 1982b, 1983e, 2003b; Williams et al. 2006).

Carrots growing on land containing somewhat more than the permissible of arsenic in crop land did not contain levels of arsenic that were harmful (Helgesen and Larsen 1998). However, further research on the uptake of arsenic by a variety of plants in a wide range of arsenic polluted sites (e.g., mining area, orchards previously treated with lead arsenate) would be valuable in assessing human exposure near such sites through the consumption of vegetables from home gardens.

Exposure Levels in Environmental Media. Additional reliable monitoring data for the levels of arsenic in contaminated media at hazardous waste sites are needed or need to be made available, so that the information obtained on levels of arsenic in the environment can be used in combination with the known body burden of arsenic to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Extensive monitoring data are available for total arsenic in all environmental media. Additional monitoring studies, specifically those that include identification of arsenic species, would allow more precise estimation of current exposure levels and possible human health risks.

Exposure Levels in Humans. Arsenic has been detected in human tissues, including blood, urine, hair, nails, and internal organs. Data are available for populations exposed in the workplace and for the general population (de Peyster and Silvers 1995; Jensen and Olsen 1995; Nygren et al. 1992), and some studies have been published on exposures near waste sites (Hwang et al. 1997a; Tsuji et al. 2005). Additional biomonitoring studies of residents near waste sites that contain arsenic would be helpful in evaluating the likely human health risks from these sites.

While some data are available on the speciation of arsenic in food, additional data on the particular species of arsenic, rather than just the total arsenic concentration, present in foods, especially seafood, are needed to better estimate the potential hazards to human health by the consumption of these foods (Ryan et al. 2001).

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Contaminated soils pose a particular hazard to children because of pica and hand-to-mouth activities. Some studies have been performed on exposure and body burden (Hwang et al. 1997a), but additional studies, including investigations of unique pathways for exposures of children and the amount of soil a child ingests, would provide valuable data. Small amounts of arsenic were found to be transferred to hands of children playing on play structures constructed from CCA-treated wood (Hemond and Solo-Gabriele 2004; Kwon et al. 2004; Shalat et al. 2006; Ursitti et al. 2004; Wang et al. 2005). Based on a review of existing studies, Hemond and Solo-Gabriele (2004) estimated that children with contact with CCA-treated wood may be subjected to doses in the range of tens of micrograms of arsenic per day and suggested that exposure by this route warrants further study. The PTDI assigned by the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) applies to adults. Studies are needed to assess whether children are different in their weight adjusted intake of arsenic. No childhood-specific means for reducing exposure were identified.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children’s Susceptibility.

Exposure Registries. No exposure registries for arsenic were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2006) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-7.

The U.S. Geological Survey, along with other federal and state agencies, industry, and academia, is conducting the National Geochemical Survey (NGS) in order to produce a body of geochemical data for the United States based primarily on stream sediments that have been analyzed using a consistent set of analytical methods. The goal of the NGS is to analyze at least one stream sediment sample in every 289 km^2 area by a single analytical method across the entire United States (USGS 2007b).

EPA is conducting a 4-year (2000–2003) national screening-level study of contaminants in freshwater fish, referred to as the National Fish Tissue Study (EPA 2004c). This study will allow the EPA to develop national estimates of the mean concentrations of 268 chemicals in tissues of fish from lakes and reservoirs of the coterminous United States. EPA analysis of the data from this study was scheduled to begin in January 2005, with the final report scheduled to be released in 2006. Interim raw data have been released each year, and are available from EPA. Fish samples have been analyzed for total inorganic arsenic (As(III) and As(V) combined), arsenic(III), arsenic(V), MMA(V), and DMA(V). Analysis for total arsenic was not performed as part of this study.

The American Water Works Association Research Foundation (AWWARF) supports research on arsenic in drinking water.

Table 6-7. Ongoing Studies on the Environmental Fate and Exposure of Humans to Arsenic

Investigator	Affiliation	Research description	Sponsor
Basta, NT	Ohio State University, School of Natural Resources, Columbus, Ohio	Heavy metal and trace element biogeochemistry in soils; chemical speciation, bioavailability, and toxicity	USDA
Blum, CB	Columbia University Health Sciences, New York, New York	Bioavailability lead and arsenic in soil to humans	NIEHS
Hamilton, JW	Dartmouth College, Hanover, New Hampshire	Toxic metals—biological and environmental implications	NIEHS
Hoppin, J	Not specified	Monitoring of arsenic and other compounds in the blood and urine of a cohort of pregnant women in Norway	NIEHS
Kpomblekou, AK; Ankumah, RO	Tuskegee University, Agriculture and Home Economics, Tuskegee, Alabama	Biochemical processes in soils treated with trace-element-enriched broiler litter; to determine total arsenic and other metal concentrations and the distribution of their chemical forms in soils under long-term broiler litter treatments	USDA
Loeppert, RH	Texas A&M University, Soil and Crop Sciences, College Station, Texas	Inorganic chemical processes influencing soil and water quality	USDA
Peryea, FJ	Wenatchee Tree Fruit Research & Extension Center Washington State University, Pullman, Washington	Quantification of biogeochemical processes in lead arsenate-contaminated orchard soils and development of soil and plant management practices to minimize the toxicity risks that these soils impose on agricultural crops and to human and environmental health	USDA
Miller, DM; DeLaune, P; Miller, WP	University of Arkansas, Crop, Soil and Environmental Sciences, Fayetteville, Arkansas	Arsenic levels in soils of northwest Arkansas	USDA
van Geen, A	Columbia University, Lamont-Doherty Earth Observatory, Palisades, New York	Studies on arsenic in groundwater in Bangladesh	NSF

Table 6-7. Ongoing Studies on the Environmental Fate and Exposure of Humans to Arsenic

Investigator	Affiliation	Research description	Sponsor
Walker, MJ et al.	University of Nevada, Natural Resources and Environmental Sciences, Reno, Nevada	Arsenic in Churchill County, Nevada domestic water supplies	USDA
Zheng, Y	Columbia University Health Sciences, New York, New York	Arsenic mobilization in Bangladesh groundwater	NIEHS

NIEHS = National Institute of Environmental Health Sciences; NSF = National Science Foundation; USDA = U.S. Department of Agriculture

Source: FEDRIP 2006

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring arsenic, its metabolites, and other biomarkers of exposure and effect to arsenic. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Atomic absorption spectrophotometry (AAS) is the most common analytical procedure for measuring arsenic in biological materials (Curatola et al. 1978; Foà et al. 1984; Johnson and Farmer 1989; Mushak et al. 1977; Norin and Vahter 1981; Sotera et al. 1988). In AAS analysis, the sample is heated in a flame or in a graphite furnace until the element atomizes. The ground-state atomic vapor absorbs mono-chromatic radiation from a source and a photoelectric detector measures the intensity of transmitted radiation (APHA 1989b). Inductively-coupled plasma atomic emission spectrometry (ICP-AES) and ICP-mass spectrometry (ICP-MS) are increasingly common techniques for the analysis of arsenic; both methods can generally provide lower detection limits than absorbance detection methods.

Samples may be prepared for AAS in a variety of ways. Most often, the gaseous hydride procedure is employed (Curatola et al. 1978; Foà et al. 1984; Johnson and Farmer 1989; Norin and Vahter 1981). In this procedure, arsenic in the sample is reduced to arsine (AsH_3), a gas that is then trapped and introduced into the flame. This approach measures total inorganic arsenic, but may not detect all organic forms unless preceded by a digestion step. Digestion or wet-ashing with nitric, sulfuric, and/or perchloric acids degrades the organic arsenic species to inorganic arsenic so that recovery of total arsenic from biological materials can be achieved (Maher 1989; Mushak et al. 1977; Versieck et al. 1983). In microwave assisted digestion, harsh oxidation conditions are used in conjunction with microwave heating (Benramdane et al. 1999b). For accurate results, it is important to check the completeness of the oxidation; however, this is seldom done (WHO 1981).

The arsenic concentration in biological fluids and tissues may also be determined by neutron activation analysis (NAA) (Landsberger and Simsons 1987; Versieck et al. 1983). In this approach, the sample is irradiated with a source of neutrons that converts a portion of the arsenic atoms to radioactive isotopes, which can be quantified after separation from radioisotopes of other chemicals. Neutron activation has limited use because of the limited number of nuclear reactors in the United States providing this service and the need to dispose of radioactive waste. X-ray fluorescence is also capable of measuring arsenic in biological materials (Bloch and Shapiro 1986; Clyne et al. 1989; Nielson and Sanders 1983) and environmental samples (see Section 7.2). This method has the advantage that no sample digestion or separation steps are required. Hydride generation combined with atomic fluorescence spectroscopy (HG-AFS) is a relatively new technique that provides freedom from interference offered by hydride generation with sensitivity better than to 20 parts per trillion and linearity up to 10 ppm (PSA 2000).

Speciation of arsenic (i.e., analysis of organic arsenic compounds or different inorganic species, rather than total arsenic) is usually accomplished by employing separation procedures prior to introduction of the sample material into a detection system. Various types of chromatography or chelation-extraction techniques are most commonly used in combination with AAS, ICP-AES, or ICP-MS detection methods (Dix et al. 1987; Foà et al. 1984; Johnson and Farmer 1989; Mushak et al. 1977; Norin et al. 1987; Thomas and Sniatecki 1995). In one method, high performance liquid chromatography (HPLC) is combined with HG-AFS to quantify As(III), dimethylarsinic acid (DMA), momomethyl arsonic acid (MMA), and As(V) (PSA 2000). Another approach involves selective reduction of arsenate and arsenite (permitting quantification of individual inorganic arsenic species), and selective distillation of methyl arsines to quantify MMA and DMA (Andreae 1977; Braman et al. 1977; Crecelius 1978). Most methods for measuring arsenic in biological samples are unable to measure arsenobetaine with any accuracy because it does not form a hydride and it gives a different response from inorganic arsenic in electrothermal AAS. Ebdon et al. (1999) successfully employed HPLC coupled with ICP-MS to determine arsenic speciation in blood plasma, which was entirely arsenobetaine. Øygard et al. (1999) developed a simple method to determine inorganic arsenic in biological samples. Their method, which involves initially distilling inorganic arsenic from the sample as $AsCl_3$ using HCl, avoids separating and quantifying all of the different arsenic species, which is both costly and time-consuming.

Table 7-1 summarizes a variety of methods for measuring total arsenic and individual arsenic species in biological materials. None of these methods have been standardized by EPA or other federal agencies.

Table 7-1. Analytical Methods for Determining Arsenic in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Methods for total arsenic:					
Blood	Digestion with nitric acid and hydrogen peroxide; dry ash with magnesium oxide/magnesium nitrate; reduction with sodium borohydride	HGAAS	0.5 µg/L	95–102	Foà et al. 1984
Blood, hair	Wet ash with nitric/perchloric acids; reduction with sodium borohydride	HGAAS	0.1 µg/L[a]	95–105	Valentine et al. 1979
Serum	Irradiation; digestion with nitric/ perchloric/sulfuric acids; extraction with toluene	NAA	0.088 ng/mL[a]	94–98	Versieck et al. 1983
Urine	Irradiate epithermally	NAA	40–100 ng/g	93–109	Landsberger and Simsons 1987
Urine	Digestion with nitric and perchloric acid; reduction with tin chloride; generation arsine by addition of zinc; reaction with SDDC	Colorimetric photometry	0.5 µg/sample	90–110	Pinto et al. 1976
Urine	Pretreatment with L-cysteine; reduction with potassium iodide/ ascorbic acid	Flow injection HGAAS	0.1 µg/L	95–100	Guo et al. 1997
Urine	Drying sample; irradiation with x-rays	XRF	0.2 µg/L[a]	92–108	Clyne et al. 1989
Hair	Wet ashing with nitric/sulfuric acids and hydrogen peroxide; reduction to arsine with sodium borohydride	HGAAS	0.06 µg/g	93	Curatola et al. 1978
Soft tissue	Digestion with nitric/sulfuric acids; complexation with DDDC in potassium iodide; extraction with chloroform	GFAAS	0.2 ppm	79.8	Mushak et al. 1977
Nails	Wet ashing with nitric/sulfuric acids and hydrogen peroxide; reduction to arsine with sodium borohydride	HGAAS	1.5 µg/g	No data	Agahian et al. 1990
Methods for arsenic speciation:					
Urine	Separation of As^{+3}, As^{+5}, MMA, and DMA on anion/cation exchange resin column; reduction to respective arsines with sodium borohydride	IEC/HGAAS	0.5 µg/L	93–106	Johnson and Farmer 1989
Urine	Reduction of As^{+3}, As^{+5}, MMA, and DMA to arsines with sodium borohydride	HGAAS	0.08 µg/L	97–104	Norin and Vahter 1981

Table 7-1. Analytical Methods for Determining Arsenic in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Reduction of As^{+3}, As^{+5}, MMA, and DMA to arsines; collection in cold trap; selective distillation by slow warming	Atomic emission (direct-current plasma)	≤1 ng for all four species	No data	Braman et al. 1977
Urine	Extraction with chloroform/ methanol; column separation with chloroform/methanol; elution on cation exchange column with ammonium hydroxide	HGAAS/TLC/ HRMS	0.34 mg/ sample[a]	No data	Tam et al. 1982
Blood/ tissue	Acidification with hydrochloric acid; complexation with TGM; extraction into cyclohexane; separation on capillary column	GLC/ECD	0.1 mg/mL	No data	Dix et al. 1987
Blood plasma	Separation by HPLC	HPLC/ICP-MS	2.5 ng As/mL	~100	Ebdon et al. 1999
Urine	Separation by anion exchange chromatography; detection by direct coupling of column to ICP-MS	IEC/ICP-MS	<0.45 µg/L for all species	No data	Inoue et al. 1994
Marine biota	Extraction with methanol-water; removal of fats by liquid-liquid extraction or solid-phase cartridge	HPLC/ICP-MS	6–25 ng/mL	94.6 (fish muscle CRM)	Sniatecki 1994
Marine biota	Separation by anion exchange coupled with HPLC; on-line microwave oxidation	HPLC/ HGAAS	0.3–0.9 ng	95–110 (recovery of spike in fish tissue)	López-Gonzálvez et al. 1994
Biological samples—Inorganic arsenic	Distill inorganic arsenic as $AsCl_3$ using HCl after prereduction of As(V) with KI/HCl	Flow-injection HGAAS	0.045 mg/kg (dry matter)	No data	Øygard et al. 1999

[a]Lowest reported concentration

CRM = certified reference material; DDDC = diethylammonium diethyldithiocarbamate; DMA = dimethylarsinate; ECD = electron capture detector; GFAAS = graphite furnace atomic absorption spectrometry; GLC = gas-liquid chromatography; HGAAS = hydride generation atomic absorption spectrometry; HRMS = high resolution mass spectrometry; ICP-MS = inductively-coupled plasma mass spectrometry; IEC = ion exchange chromatography; HPLC = high-performance liquid chromatography; MMA = monomethylarsonate; NAA = neutron activation analysis; SDDC = silver diethyldithiocarbamate; TGM = thioglycolic acid methylester; TLC = thin layer chromatography; XRF = x-ray fluorescence

Detection limits in blood and urine are about 0.1–1 ppb for most techniques; limits for hair and tissues are usually somewhat higher.

7.2 ENVIRONMENTAL SAMPLES

Arsenic in environmental samples is also measured most often by AAS techniques, with samples prepared by digestion with nitric, sulfuric, and/or perchloric acids (Dabeka and Lacroix 1987; EPA 1983b, 1994a, 1994b; Hershey et al. 1988). Other methods employed include a spectrophotometric technique in which a soluble red complex of arsine and silver diethyldithiocarbamate (SDDC) is formed (APHA 1977; EPA 1983c, 1983d), ICP-AES (EPA 2000c; NIOSH 2003), graphite furnace AAS (EPA 1983b, 1994b; NIOSH 1994b), ICP-MS (EPA 1991, 1994a, 1998j), and x-ray fluorescence (Khan et al. 1989; Nielson and Sanders 1983).

HPLC is currently the most common technique for separation of the species of arsenic found in seafood (Benramdane et al. 1999b; Guerin et al. 1999; Kumaresan and Riyazuddin 2001). An advantage of HPLC over other separation methods (e.g., gas chromatography [GC]) is that the arsenic species do not need to be derivatized prior to separation, avoiding concerns over complete conversion to the derivative for detection.

Since arsenic in air is usually associated with particulate matter, standard methods involve collection of air samples on glass fiber or membrane filters, acid extraction of the filters, arsine generation, and analysis by SDDC spectrophotometry or AAS (APHA 1977; NIOSH 1984).

Methods standardized by the EPA for measuring total arsenic in water and waste water, solid wastes, soil, and sediments include: ICP-MS (EPA 1998j, 1994a, 1991), ICP-AES (EPA 1996d), graphite furnace AAS (EPA 1994b), quartz furnace hydride generation AAS (EPA 1996h), and an electrochemical method using anodic stripping voltammetry (ASV) (EPA 1996e). A modification using cryogenic GC to EPA Method 1632 (HG/AAS) allows the technique to be adopted for the species As(III), As(V), MMA, and DMA to the 0.003 ppb level (EPA 1998l). Similar methods are recommended by APHA for water using AAS/hydride generation (APHA 1989c), AAS/graphite furnace technique (APHA 1989b), ICP (APHA 1989d), or SDDC spectrophotometry (APHA 1989a). The AAS/hydride generation method is generally resistant to matrix and chemical interferences (APHA 1989a). Techniques to compensate for these interferences have been described by EPA (1982b).

Analysis for arsenic in foods is also most frequently accomplished by AAS techniques (Arenas et al. 1988; Dabeka and Lacroix 1987; Hershey et al. 1988; Tam and Lacroix 1982). Hydride generation is the sample preparation method most often employed (Arenas et al. 1988; Hershey et al. 1988), but interferences must be evaluated and minimized.

Speciation of inorganic arsenic in environmental samples is usually accomplished by chromatographic separation, chelation-extraction or elution of As(III), and then reduction of As(V) with subsequent similar treatment (Butler 1988; López-Gonzálvez et al. 1994; Mok et al. 1988; Rabano et al. 1989).

Methods are also available for quantifying organic arsenicals in environmental media, including arsenobetaine in fish (Beauchemin et al. 1988; Cannon et al. 1983) and other organic forms of arsenic in water, soil, and foods using hyphenated methods of separation and detection (HPLC/ICP-MS, HPLC/HGAAS, IC/ICP-MS) (Andreae 1977; Braman et al. 1977; Comber and Howard 1989; Crecelius 1978; Heitkemper et al. 1994; López-Gonzálvez et al. 1994; Odanaka et al. 1983; Teräsahde et al. 1996).

Methods have been developed for extraction of arsenic species from solid seafood samples that included treatment of the sample with mixtures of organic solvents (alcohols or chloroform) and water to extract the arsenic compounds that are soluble in water or polar organic solvents. These extracts can be subsequently analyzed by HPLC. Enzymatic digestion using trypsin has also been used to extract arsenic compounds from seafood samples (Benramdane et al. 1999b). These extraction techniques are used in place of digestion when speciated data are needed.

A summary of selected methods for analysis of total arsenic and individual inorganic and organic arsenic species in environmental samples is presented in Table 7-2.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of arsenic.

Table 7-2. Analytical Methods for Determining Arsenic in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Methods for total arsenic:					
Air (particulates)	Collection on cellulose ester membrane filter; digestion with nitric acid, sulfuric acid, and perchloric acid	NIOSH Method 7900; HGAAS	0.02 µg/sample	No data	NIOSH 1994a
Air (particulate arsenic and arsenic trioxide vapor)	Collection on Na_2CO_3-impregnated cellulose ester membrane filter and H_2O_2	NIOSH Method 7901; GFAAS	0.06 µg/sample	No data	NIOSH 1994b
Air	Collection on cellulose ester membrane filter; digestion with nitric acid, sulfuric acid, and perchloric acid	NIOSH Method 7300; ICP-AES	0.140 µg/filter	No data	NIOSH 2003
Water/waste water/solid wastes	Acid digestion	EPA Method 6010C; ICP-AES	35 µg/L	86	EPA 2000c
Water/waste water/solid wastes	Digestion with nitric and hydrochloric acids	EPA Method 200.7; ICP-AES	8 µg/L	106	EPA 1994c
Water/soil/ solid waste	Digestion with nitric acid and hydrogen peroxide	EPA Methods 206.2 and 7060A; GFAAS with $Ni(NO_3)_2$ modifier	1 µg/L	85–106	EPA 1983b, 1994b
Water/waste water/solid waste	Digestion with nitric acid	EPA Methods 200.8, 6020 and 6020A ICP-MS	0.4 µg/L	97–114	EPA 1991, 1994a, 1998j
Water/soil/ solid waste	Digestion with nitric/sulfuric acid; reduction to As^{+3} with tin chloride; reduction to arsine with zinc in acid solution	EPA Method 206.3	2 µg/L	85–94	EPA 1983c
Water	Reduction to arsine in acid solution; reaction with SDDC	EPA Method 206.4; SDDC colorimetric spectrophoto-metry at 510 nm	10 µg/L	100	EPA 1983d
Water	Digestion with 6M HCl; reduction to arsine with sodium borohydride; cold trap and desorption into quartz furnace	EPA Method 1632; HGAAS	2 ng/L	No data	EPA 1998l

Table 7-2. Analytical Methods for Determining Arsenic in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Digestion with nitric acid; dry ashing with magnesium oxide; reduction with ascorbic acid; precipitation with APDC in presence of nickel carrier	GFAAS	10 ng	86–107	Dabeka and Lacroix 1987
Food	Digestion with nitric/sulfuric/ perchloric acids; reduction to trivalent arsenic with potassium iodide; reduction to arsine with sodium borohydride	HGAAS	0.1 µg/g	98–110	Hershey et al. 1988
Soil, rock, coal	Preparation of pellet	XRF (backscatter)	4 mg/kg	SRM recoveries: 110±4 in soil; 100±1in rock; 97±18 in coal	Nielson and Sanders 1983
Methods for species of arsenic:					
Air (particulate organo-arsenals)	Collection on PTFE filter	NIOSH Method 5022; ion chromatography/HGAAS	0.2 µg As/sample	No data	NIOSH 1994c
Air (arsine)	Collection on coconut shell charcoal; digestion with nitric acid	NIOSH Method 6001; GFAAS	0.004 µg/sample	No data	NIOSH 1994d
Air particulates (As^{+3} and As^{+5} only)	Collection on PFTE filter in high volume dichotomous virtual impactor; desorption with ethanolic hydrochloric acid; selective reduction of As^{+3} to arsine with zinc in acid and reduction of As^{+5} to arsine with sodium tetrahydrodiborate	HGAAS	1 ng/m^3	95±7 (As^{+3}); 100±8 (As^{+5}) on spiked materials	Rabano et al. 1989
Water	Selective elution of As^{+3} with orthophosphoric acid; elution and conversion of As^{+5} to As^{+3} with sulfur dioxide	IEC/amperometric detector (detects As^{+3} only)	0.9 µg/L	95% of converted As^{+5} recovered	Butler 1988
Water/soil	Selective complexation of As^{+5} with ammonium molybdate; extraction with isoamyl alcohol to separate from As^{+3}	Colorimetric spectrometry at 712 nm	No data	No data	Brown and Button 1979

Table 7-2. Analytical Methods for Determining Arsenic in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Selective extraction of As^{+3} with APDC into chloroform; back extraction with nitric acid; reduction of As^{+5} to As^{+3} with thiosulfate and extract	NAA	0.01 ppb	No data	Braman et al. 1977
Food (arseno-betaine in fish)	Extraction of arsenobetaine with methanol/chloroform; digestion with nitric acid/ magnesium nitrate for remainder of As species	HPLC/ICP-MS	0.3 ng as arsenobetaine	101±4 recovery of arseno-betaine	Beauchemin et al. 1988
Water/waste water/soil (inorganic species)	Acidification or digestion with hydrochloric acid	EPA Method 7063; ASV	0.1 µg/L	96–102	EPA 1996e
Water (As(III), As(V), MMA, and DMA)	Cryogenic GC, Digestion with 6M HCl; reduction to arsine with sodium boro-hydride; cold trap and desorption into quartz furnace	EPA Method 1632 appendix; HGAAS	3 ng/L	No data	EPA 1998l
Water	Reduction to arsines; cold trap and selectively warm to separate arsine species	AAS	2 ng/L	91–109	Andreae 1977
Water	Reduction of MMA, DMA and inorganic As (control pH to select As^{+3} or As^{+5}) to arsines with sodium tetra-hydroborate; cold trap and selectively warm to separate arsine species	HGAAS	0.019–0.061 ng	No data	Comber and Howard 1989
Water/soil	Extraction with sodium bicarbonate; reduction of inorganic arsenic, MMA and DMA to hydrides with sodium borohydride; cold trap arsines in n-heptane	HG-HCT/GC-MID	0.2–0.4 µg/L	97–102	Odanaka et al. 1983

AAS = atomic absorption spectrophotometry; APDC = ammonium pyrrolidine dithiocarbamate; ASV = anodic stripping voltammetry; DMA = dimethylarsinate; EPA = Environmental Protection Agency; GC-MID = gas chromatography-multiple ion detection; GFAAS = graphite furnace atomic absorption spectrometry; HGAAS=hydride generation-atomic absorption spectroscopy; HG-HCT = hydride generation-heptane cold trap; HPLC = high performance liquid chromatography; ICP-AES = inductively coupled plasma-atomic emission spectrometry; ICP-MS = inductively coupled plasma-mass spectrometry; IEC = ion exchange chromatography; MMA = monomethylarsonate; NAA = neutron activation analysis; NIOSH = National Institute of Occupational Safety and Health; PTFE = polytetrafluoroethylene; SDDC = silver diethyldithiocarbamate; SRM = standard reference material; XRF = x-ray fluorescence

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. The most common biomarker for arsenic exposure is analysis of total arsenic in urine (Hughes 2006). Existing methods are sufficiently sensitive to measure background levels of arsenic in various tissues and biological fluids for average persons, and to detect increases as a result of above-average exposure (Agahian et al. 1990; Clyne et al. 1989; Curatola et al. 1978; Foà et al. 1984; Gebel et al. 1998b; Landsberger and Simsons 1987; Mushak et al. 1977; Pinto et al. 1976; Valentine et al. 1979; Versieck et al. 1983). The precision and accuracy of these methods are documented. Methods are also available that can distinguish nontoxic forms of arsenic (arsenobetaine) from inorganic and organic derivatives that are of health concern (Braman et al. 1977; Dix et al. 1987; Johnson and Farmer 1989; Norin and Vahter 1981; Tam et al. 1982). Further efforts to improve accuracy, reduce interferences, and detect multiple species using a single analysis would be valuable. Arsenic is believed to act by inhibition of numerous cellular and molecular processes. However, these effects are not specific to arsenic, and most can only be measured in tissue extracts.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Arsenic is ubiquitous in the environment. It is found in air, water, soil, sediments, and food in several inorganic and organic forms. Analytical methods exist for the analysis of arsenic species in all of these environmental media, and these methods have the sensitivity to measure background levels and to detect elevated concentrations due to emissions from sources such as smelters, chemical plants, or hazardous waste sites (APHA 1977, 1989c; EPA 1982b, 1983b, 1983c, 1983d, 1991, 1994b, 1994c, 1996f, 1996h, 1998j, 2000c; NIOSH 1994a, 1994b, 2003). However, further research to reduce chemical and matrix interferences may improve the speed and accuracy of the analyses.

Le et al. (2004) pointed out that there is a need for the development of certified reference materials (CRMs) for speciation analysis. A shortcoming of many CRMs is that they are only certified for the total concentration of arsenic, and only limited information is available on the identity and concentrations of specific arsenic species in some CRMs.

Continued improvement of the methods for determination of the particular species of arsenic, rather than just the total arsenic concentration, present in foods, especially seafood, is needed since different arsenic species poses different hazards to individuals consuming these foods.

7.3.2 Ongoing Studies

The information in Table 7-3 was found as a result of a search of the Federal Research in Progress database (FEDRIP 2006).

Table 7-3. Ongoing Studies on Analytical Methods for Arsenic in Environmental and Biological Samples

Investigator	Affiliation	Research description	Sponsor
Styblo, M	University of North Carolina Chapel Hill, Chapel Hill, North Carolina	Optimized hydride generation system for arsenic analysis	Fogarty International Center
Dietze, WT	Tracedetect, Inc., Seattle, Washington	A continuous monitor for arsenic in drinking water	NIEHS
Dasgupta, PK	Texas Tech University, Department of Chemistry, Lubbock, Texas	A green fieldable analyzer for arsenic	NSF

NIEHS = National Institute of Environmental Health Sciences; NSF = National Science Foundation

Source: FEDRIP 2006

8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines pertaining to arsenic and its metabolites in air, water, and other media are summarized in Table 8-1.

ATSDR has not derived inhalation MRLs or an intermediate-duration oral MRL for inorganic arsenic, or any MRLs for organic arsenic, due to lack of suitable data.

ATSDR has derived an acute-duration oral MRL for inorganic arsenic of 0.005 mg As/kg/day based on a LOAEL of 0.05 mg As/kg/day for gastrointestinal effects and facial edema in Japanese people who ingested arsenic-contaminated soy sauce for 2–3 weeks (Mizuta et al. 1956). An uncertainty factor of 10 (10 for use of a LOAEL and 1 for human variability) was applied.

ATSDR has derived a chronic-duration oral MRL of 0.0003 mg/kg/day for inorganic arsenic based on a NOAEL of 0.0008 mg As/kg/day for dermal effects in a Taiwanese farming population exposed to arsenic in well water (Tseng 1977; Tseng et al. 1968). An uncertainty factor of 3 (for human variability) was applied.

EPA (IRIS 2007) has derived a chronic oral reference dose (RfD) of 0.0003 mg As/kg/day for inorganic arsenic, based on a NOAEL of 0.0008 mg As/kg/day for dermal effects and possible vascular complications in a Taiwanese farming population exposed to arsenic in well water (Tseng 1977; Tseng et al. 1968). An uncertainty factor of 3 (to account for the lack of reproductive data and uncertainty in whether the NOAEL accounts for all sensitive individuals) was applied. No reference concentration (RfC) for chronic inhalation exposures to arsenic was reported. EPA is currently revising the assessment for inorganic arsenic.

The Department of Health and Human Services (DHHS) has determined that inorganic arsenic is known to be a human carcinogen (NTP 2005). The EPA has determined that inorganic arsenic is a human carcinogen and has assigned it the cancer classification, Group A (IRIS 2007). EPA's quantitative estimates of carcinogenic risk from oral exposures include a cancer slope factor of 1.5 mg/kg/day and a drinking water unit risk of $5x10^{-5}$ µg/L. The inhalation unit risk for cancer is 0.0043 µg/m^3 (IRIS 2007).

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification for arsenic and arsenic compounds	Group 1[a]	IARC 2004
WHO	Air quality guidelines	$1.5x10^{-3}$ unit risk[b]	WHO 2000
	Drinking water quality guidelines for arsenic	0.01 mg/L[c]	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (TWA) for arsenic and inorganic compounds	0.01 mg/m^3	ACGIH 2004
EPA	Hazardous air pollutant (arsenic and inorganic compounds, including arsine)	Yes	EPA 2004b 42 USC 7412
NIOSH	REL (15-minute ceiling limit) for arsenic and inorganic compounds[d]	0.002 mg/m^3	NIOSH 2005a
	IDLH for arsenic and inorganic compounds[d]	5 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry for arsenic organic compounds	0.5 mg/m^3	OSHA 2005d 29 CFR 1910.1000
	PEL (8-hour TWA) for general industry for arsenic inorganic compounds	10 $\mu g/m^3$	OSHA 2005c 29 CFR 1910.1018
	PEL (8-hour TWA) for construction industry for arsenic organic compounds	0.5 mg/m^3	OSHA 2005b 29 CFR 1926.55
	PEL (8-hour TWA) for shipyard industry for arsenic organic compounds	0.5 mg/m^3	OSHA 2005a 29 CFR 1915.1000
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2005d 40 CFR 116.4
	Arsenic pentoxide, arsenic trioxide, calcium arsenate, and sodium arsenite		
	Drinking water standards and health advisories for arsenic		EPA 2004a
	DWEL	0.01 mg/L	
	National primary drinking water standards for arsenic		EPA 2002a
	MCLG	Zero	
	MCL	0.01 mg/L[e]	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2005e 40 CFR 117.3
	Arsenic pentoxide, arsenic trioxide, calcium arsenate, sodium arsenite	1 pound	

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Water quality criteria for human health consumption of arsenic:		EPA 2002b
	Water + Organism	0.018 µg/L[f]	
	Organism only	0.14 µg/L[f]	
c. Food			
EPA	Tolerances for residues		
	Dimethylarsinic acid		EPA 2005i 40 CFR 180.311
	Cotton (undelinted seed)	2.8 ppm	
	Methanearsonic acid		EPA 2005j 40 CFR 180.289
	Cotton (undelinted seed)	0.7 ppm	
	Cotton, hulls	0.9 ppm	
	Fruit, citrus	0.35 ppm	
FDA	Bottled drinking water	0.01 mg/L	FDA 2005 21 CFR 165.110
USDA	Nonsynthetic substances prohibited for use in organic crop production	Arsenic	USDA 2004 7 CFR 205.602
d. Other			
ACGIH	Carcinogenicity classification for arsenic and arsenic compounds	A1[g]	ACGIH 2004
	Biological exposure indices for inorganic arsenic plus methylated metabolites in urine at the end of the workweek	35 µg As/L	
EPA	Carcinogenicity classification	Group A[i]	IRIS 2007
	Oral slope factor	1.5 per mg/kg/day	
	Inhalation unit risk	4.3×10^{-3} per µg/m^3	
	RfC	No data	
	RfD	3×10^{-4} mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2005f 40 CFR 302.4
	Reportable quantity		
	Arsenic	Not applicable[j]	
	Arsenic acid, arsenic pentoxide, arsenic trioxide, calcium arsenate, dimethylarsinic acid, and sodium arsenite	1 pound	
	Effective date of toxic chemical release reporting for arsenic	01/01/87	EPA 2005h 40 CFR 372.65

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Superfund, emergency planning, and community right-to-know		
	Extremely hazardous substances		EPA 2005g 40 CFR 355, Appendix A
	Reportable quantity		
	Arsenic pentoxide, calcium arsenate, and sodium arsenite	1 pound	
	Threshold planning quantities		
	Arsenic pentoxide	100/10,000 pounds	
	Calcium arsenate and sodium arsenite	500/10,000 pounds	
NTP	Carcinogenicity classification	Known human carcinogen	NTP 2005

[a]Group 1: carcinogenic to humans
[b]Cancer risk estimates for lifetime exposure to a concentration of 1 µg/m3.
[c]Provisional guideline value: as there is evidence of a hazard, but the available information on health effects is limited.
[d]NIOSH potential occupational carcinogen
[e]MCL will become effective on 01/23/06.
[f]This criterion is based on carcinogenicity of 10^{-6} risk.
[g]A1: confirmed human carcinogen
[h]A3: confirmed animal carcinogen with unknown relevance to humans
[i]Group A: known human carcinogen
[j]Indicates that no reportable quantity is being assigned to the generic or broad class.

ACGIH = American Conference of Governmental Industrial Hygienists; CERCLA = Comprehensive Environmetnal Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NAS/NRC = National Academy of Sciences/National Research Council; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; USDA = United States Department of Agriculture; WHO = World Health Organization

EPA is currently revising the assessment for inorganic arsenic. The International Agency for Research on Cancer (IARC) cites sufficient evidence of a relationship between exposure to arsenic and human cancer. IARC classification of arsenic is Group 1 (IARC 2004). The American Conference of Governmental Industrial Hygienists (ACGIH) classifies arsenic (elemental and inorganic compound) as a confirmed human carcinogen, cancer category A1 (ACGIH 2004).

ATSDR has derived an intermediate-duration oral MRL of 0.1 mg MMA/kg/day for MMA based on a $BMDL_{10}$ of 12.38 mg MMA/kg/day for diarrhea observed in rats exposed to MMA in the diet for 13 weeks (Arnold et al. 2003) and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.01 mg MMA/kg/day for MMA based on a $BMDL_{10}$ of 1.09 mg MMA/kg/day for increased incidence of progressive nephropathy in male mice exposed to MMA in the diet for 2 years (Arnold et al. 2003) and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.02 mg DMA/kg/day for DMA based on a $BMDL_{10}$ of 1.80 mg DMA/kg/day for increased vacuolization of the urothelium in the urinary bladder of female mice exposed to DMA in the diet for 2 years (Arnold et al. 2006) and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

EPA has not derived RfD values for organic arsenicals (IRIS 2007).

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Inorganic Arsenic
CAS Number: 7440-38-2
Date: August 2007
Profile Status: Post-Public Comment, Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 29
Species: Human

Minimal Risk Level: 0.005 [X] mg/kg/day [ ] ppm

Reference: Mizuta N, Mizuta M, Ito F, et al. 1956. An outbreak of acute arsenic poisoning caused by arsenic-contaminated soy-sauce (shōyu): A clinical report of 220 cases. Bull Yamaguchi Med Sch 4(2-3):131-149.

Experimental design: Mizuta et al. (1956) summarized findings from 220 poisoning cases associated with an episode of arsenic contamination of soy sauce in Japan. The soy sauce was contaminated with approximately 0.1 mg As/mL, probably as calcium arsenate. Arsenic intake in the cases was estimated by the researchers to be 3 mg/day (0.05 mg/kg/day, assuming 55 kg average body weight for this Asian population). Duration of exposure was 2–3 weeks in most cases. Clinical symptoms were recorded. Seventy patients were examined opthalmologically. Laboratory tests were performed on some patients and included hematology, urinalysis, fecal exam, occult blood in gastric and duodenal juice, biochemical examination of blood, liver function tests, electrocardiograph, and liver biopsy.

Effects noted in study and corresponding doses: The primary symptoms were edema of the face, and gastrointestinal and upper respiratory symptoms initially, followed in some patients by skin lesions and neuropathy. Other effects included mild anemia and leukopenia, mild degenerative liver lesions and hepatic dysfunction, abnormal electrocardiogram, and ocular lesions. For derivation of the acute oral MRL, facial edema and gastrointestinal symptoms (nausea, vomiting, diarrhea), which were characteristic of the initial poisoning and then subsided, were considered to be the critical effects.

Dose and end point used for MRL derivation: 0.05 mg As/kg/day

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[X] 1 [ ] 3 [ ] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The MRL is supported by the case of a man and wife in upstate New York who experienced gastrointestinal symptoms (nausea, diarrhea, abdominal cramps) starting almost immediately after beginning intermittent consumption of arsenic-tainted drinking water at an estimated dose of 0.05 mg As/kg/day (Franzblau and Lilis 1989). Gastrointestinal symptoms have been widely reported in other acute arsenic poisoning reports as well, although in some cases, the doses were higher and effects were severe, and in other cases, dose information was not available. The UF of 1 for intrahuman variability reflects the fact that the database includes persons of various ethnicities and age groups, including infants.

Agency Contact (Chemical Manager): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Inorganic Arsenic
CAS Number: 7440-38-2
Date: August 2007
Profile Status: Post-Public Comment, Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 134
Species: Human

Minimal Risk Level: 0.0003 [X] mg/kg/day [ ] ppm

References: Tseng, WP, Chu HM, How SW, et al. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst 40:453-463.

Tseng, WP. 1977. Effects and dose-response relationships of cancer and Blackfoot disease with arsenic. Environ Health Perspect 19:109-119.

Experimental design: Tseng et al. (1968) and Tseng (1977) investigated the incidence of Blackfoot disease and dermal lesions (hyperkeratosis and hyperpigmentation) in a large number of poor farmers (both male and female) exposed to high levels of arsenic in well water in Taiwan. A control group consisting of 17,000 people was identified. The authors stated that the incidence of dermal lesions increased with dose, but individual doses were not provided. However, incidence data were provided based on stratification of the exposed population into low (<300 μg/L), medium (300–600 μg/L), or high (>600 μg/L) exposure levels. Doses were calculated from group mean arsenic concentrations in well water, assuming the intake parameters described by Abernathy et al. (1989). Accordingly, the control, low-, medium-, and high-exposure levels correspond to doses of 0.0008, 0.014, 0.038, and 0.065 mg As/kg/day, respectively. The NOAEL identified by Tseng (1977) (0.0008 mg As/kg/day) was limited by the fact that the majority of the population was <20 years of age and the incidence of skin lesions increased as a function of age, and because the estimates of water intake and dietary arsenic intake are highly uncertain. Schoof et al. (1998) estimated that dietary intakes of arsenic from rice and yams may have been 15–211 μg/day (mean 61 μg/day), based on arsenic analyses of foods collected in Taiwan in 1993–1995. Use of the 50 μg/day estimate would result in an approximate doubling of the NOAEL (0.0016 mg/kg/day).

Effects noted in study and corresponding doses: A clear dose-response relationship was observed for characteristic skin lesions:

0.0008 mg As/kg/day	= control group (NOAEL)
0.014 mg As/kg/day	= hyperpigmentation and keratosis of the skin (less serious LOAEL)
0.038–0.065 mg As/kg/day	= increased incidence of dermal lesions

Dose and end point used for MRL derivation: 0.0008 mg As/kg/day

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)

[ ] 1 [x] 3 [ ] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? The arithmetic mean concentration of arsenic in well water for the control group (0.009 mg/L) was converted to a NOAEL of 0.0008 mg As/kg/day as described below:

$$\left[\left(\frac{0.009mg}{L}\times\frac{4.5L}{day}\right)+\frac{0.002mg}{day}\right]\div 55kg = 0.0008mgAs/kg/day$$

This NOAEL conversion assumed a water intake of 4.5 L/day and a body weight of 55 kg, and includes an estimation of arsenic intake of 0.002 mg As/kg/day from food. These assumptions are detailed in Abernathy et al. (1989). This approach to deriving a chronic oral MRL is identical to EPA's approach to deriving a chronic oral RfD.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The MRL is supported by a number of well conducted epidemiological studies that identify reliable NOAELs and LOAELs for dermal effects. EPA (1981b) identified a NOAEL of 0.006–0.007 mg As/kg/day for dermal lesions in several small populations in Utah. Harrington et al. (1978) identified a NOAEL of 0.003 mg As/kg/day for dermal effects in a small population in Alaska. Guha Mazumder et al. (1988) identified a NOAEL of 0.009 mg As/kg/day and a LOAEL of 0.006 mg As/kg/day for pigmentation changes and hyperkeratosis in a small population in India. Haque et al. (2003) identified a LOAEL of 0.0043 mg As/kg/day for hyperpigmentation and hyperkeratosis in a case-control study in India. Cebrían et al. (1983) identified a NOAEL of 0.0004 mg As/kg/day and a LOAEL of 0.022 mg As/kg/day in two regions in Mexico. Borgoño and Greiber (1972) and Zaldívar (1974) identified a LOAEL of 0.02 mg As/kg/day for abnormal skin pigmentation in patients in Chile, and Borgoño et al. (1980) identified a LOAEL of 0.01 mg As/kg/day for the same effect in school children in Chile. Valentine et al. (1985) reported a NOAEL of 0.02 mg As/kg/day for dermal effects in several small populations in California. Collectively, these studies indicate that the threshold dose for hyperpigmentation and hyperkeratosis is approximately 0.002 mg As/kg/day.

Agency Contacts (Chemical Managers): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Monomethylarsonic acid (MMA)
CAS Number: 124-58-3
Date: August 2007
Profile Status: Post-Public Comment, Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 12
Species: Rat

Minimal Risk Level: 0.1 [X] mg MMA/kg/day [ ] ppm

References: Arnold LL, Eldan M, van Gemert M, et al. 2003. Chronic studies evaluating the carcinogenicity of monomethylarsonic acid in rats and mice. Toxicology 190:197-219.

Crown S, Nyska A, Waner T. 1990. Methanearsonic acid: Combined chronic feeding and oncogenicity study in the rat. Conducted by Life Science Research Israel Ltd., Ness Ziona Israel. Submitted to EPA Office of Pesticide Programs (MRID 41669001).

Experimental design: Groups of 60 male and 60 female Fischer 344 rats were exposed to 0, 50, 400, or 1,300 ppm MMA in the diet for 104 weeks. Using the average doses for weeks 1–50 reported in an unpublished version of this study (Crown et al. 1990), doses of 0, 3.5, 30.2, and 106.9 mg MMA/kg/day and 0, 4.2, 35.9, and 123.3 mg MMA/kg/day were calculated for males and females, respectively. Body weights, food consumption, and water intake were monitored regularly. Blood was taken at 3, 6, and 12 months for clinical chemistry measurements, and urine samples were collected at the same interval.

Effects noted in study and corresponding doses: Mortality was increased in high-dose males and females during the first 52 weeks of the study. Body weights were decreased in the mid- and high-dose groups of both sexes; however, at 51 weeks, only the body weight for the high-dose males was <10% of the control weight (14.5%). Food and water consumption was increased in the mid- and high-dose groups. Diarrhea was observed in 100% of the high-dose males and females and in 16.7 and 40% of the mid-dose males and females during the first 52 weeks of exposure. Diarrhea first occurred after 3 weeks of exposure to the high dose and 4 weeks of exposure to the mid-dose group; the severity of the diarrhea was dose-related. The gastrointestinal system was the primary target in animals dying early; numerous macroscopic and histological alterations were observed.

Dose and end point used for MRL derivation: Benchmark dose analysis of the dose-response data (Table A-1) for diarrhea in male and female rats exposed to MMA in the diet for 1–52 weeks (incidence data reported in Crown et al. 1990) was conducted. All available dichotomous models in EPA's Benchmark Dose Software (version 1.4.1) were fit to the data. Predicted doses associated with a 10% extra risk were calculated. As assessed by the chi-square goodness-of-fit statistic, all models, with the exception of the quantal linear model for male incidence data and the quantal linear model for female incidence data, provided an adequate fit (X^2 p>0.1) (Table A-2). Comparing across models, a better fit is generally indicated by a lower Akaike's Information Criteria (AIC). As assessed by AIC, the gamma model for the males (Figure A-1) and the 2-degree polynomial multi-stage model for the females (Figure A-2) provide the best fit to the data. The predicted BMD_{10} and $BMDL_{10}$ are 28.25 mg MMA/kg/day and 22.99 mg MMA/kg/day for the male rat incidence data and 16.17 mg MMA/kg/day, and 12.38 mg MMA/kg/day for the female rat incidence data.

Table A-1. Incidences of Diarrhea in Rats Exposed to MMA in the Diet for 1–52 Weeks

Dietary concentration (ppm)	Dose (mg MMA/kg/day)	Incidence
Male rats		
0	0	2/60
50	3.5	0/60
400	30.2	10/60
1,300	106.9	60/60
Female rats		
0	0	0/60
50	4.2	0/60
400	35.9	24/60
1,300	123.3	60/60

Sources: Arnold et al. 2003; Crown et al. 1990

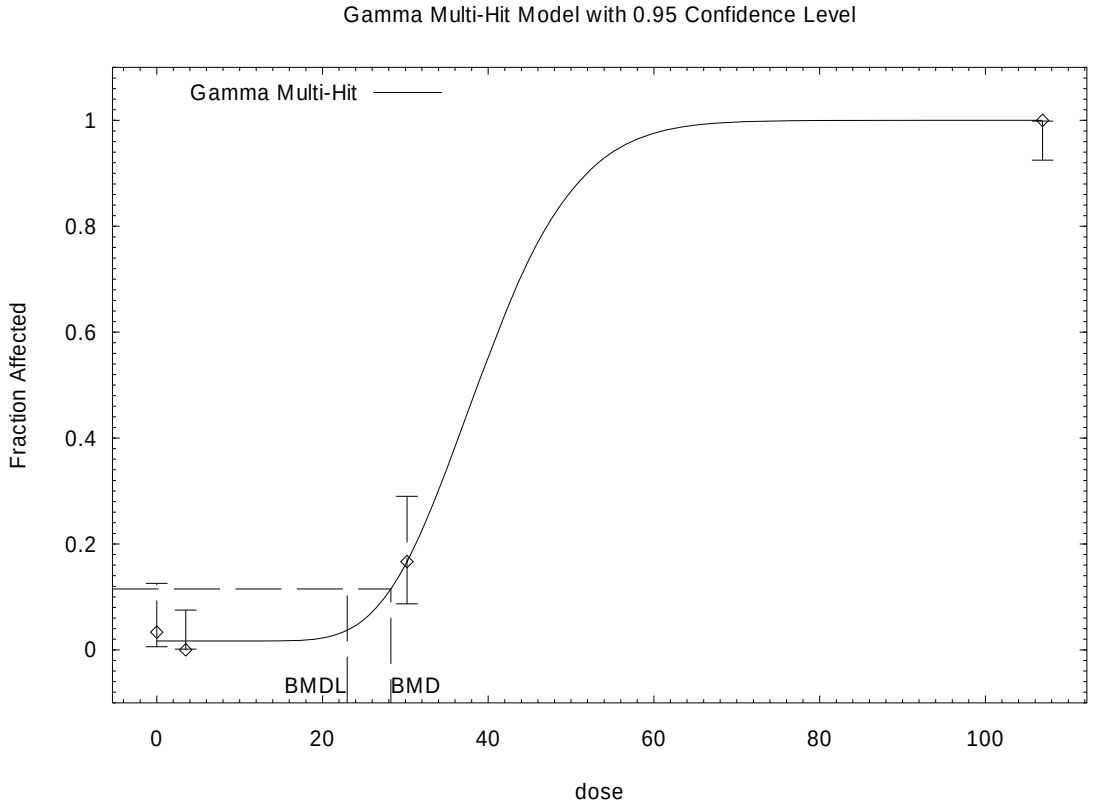
Table A-2. Modeling Predictions for the Incidence of Diarrhea in Rats Exposed to MMA in the Diet for 1–52 Weeks

Model	BMD_{10} (mg MMA/kg/day)	$BMDL_{10}$ (mg MMA/kg/day)	x^2 *p*-value	AIC
Male rats				
Gamma[a]	**28.25**	**22.99**	**0.36**	**78.41**
Logistic	24.60	20.19	0.16	79.59
Log-logistic[b]	29.32	24.73	0.15	80.41
Multi-stage[c]	25.74	19.90	0.35	78.51
Probit	23.11	18.67	0.11	80.02
Log-probit[b]	28.79	24.47	0.15	80.41
Quantal linear	6.317	5.079	0.00	123.06
Weibull[a]	27.99	20.66	0.15	80.41
Female rats				
Gamma[a]	26.81	15.18	1.00	84.76
Logistic	32.85	21.49	1.00	84.76
Log-logistic[b]	31.97	20.16	1.00	84.76
Multi-stage[c]	**16.17**	**12.38**	**0.90**	**83.88**
Probit	29.89	19.11	1.00	84.76
Log-probit[b]	28.95	18.87	1.00	84.76
Quantal linear	5.33	4.33	0.00	106.52
Weibull[a]	27.83	13.58	1.00	84.76

Sources: Arnold et al. 2003; Crown et al. 1990

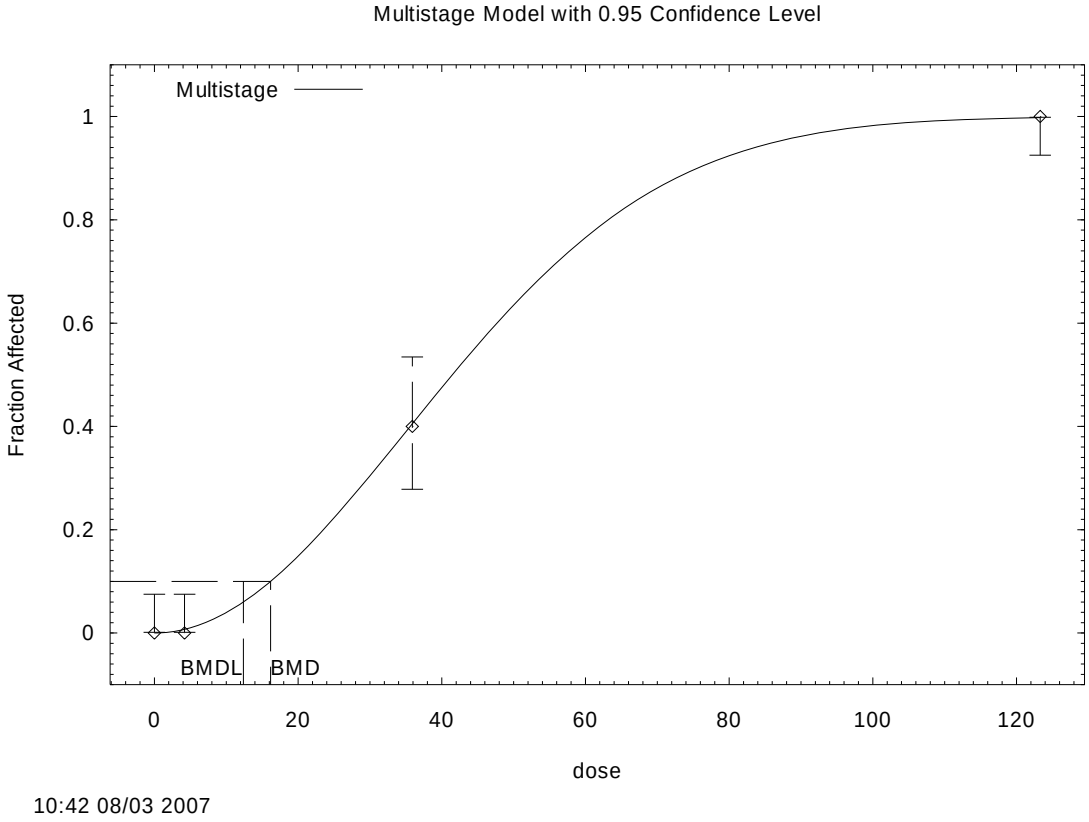
[a]Restrict power ≥1.
[b]Slope restricted to >1.
[c]Restrict betas ≥0; lowest degree polynomial with an adequate fit is reported; degree of polynomial=3.
[d]Restrict betas ≥0; lowest degree polynomial with an adequate fit is reported; degree of polynomial=2.

Figure A-1. Predicted and Observed Incidence of Diarrhea in Male Rats Exposed to MMA in the Diet for 1–52 Weeks*



*BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of mg MMA/kg/day.

Figure A-2. Predicted and Observed Incidence of Diarrhea in Female Rats Exposed to MMA in the Diet for 52 Weeks*



*BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of mg MMA/kg/day.

The $BMDL_{10}$ of 12.38 mg MMA/kg/day for female rats was selected as the point of departure for deriving the intermediate-duration oral MRL because it was lower than the $BMDL_{10}$ (22.99 mg MMA/kg/day) calculated using the male incidence data.

[ ] NOAEL [ ] LOAEL [X] BMDL

Uncertainty factors used in MRL derivation: 100

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses calculated using the average of the achieved doses for weeks 1–50 reported in Crown et al. (1990): 0, 3.5, 30.2, and 106.9 mg MMA/kg/day for males and 0, 4.2, 35.9, and 123.3 mg MMA/kg/day for females.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Increases in the incidence of diarrhea has also been observed in dogs administered via capsule 2 mg MMA/kg/day for 52 weeks (Waner and Nyska 1988); the increased incidence of diarrhea started during weeks 25–28. At 35 mg MMA/kg/day, vomiting was also observed in the dogs. Diarrhea has also been observed in rats and mice exposed to MMA for 2 years (Arnold et al. 2003); the LOAELs are 25.7 and 67.1 mg MMA/kg/day, respectively.

Agency Contacts (Chemical Managers): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Monomethylarsonic acid (MMA)
CAS Number: 124-58-3
Date: August 2007
Profile Status: Post-Public Comment, Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 21
Species: Mouse

Minimal Risk Level: 0.01 [X] mg MMA/kg/day [ ] ppm

References: Arnold LL, Eldan M, van Gemert M, et al. 2003. Chronic studies evaluating the carcinogenicity of monomethylarsonic acid in rats and mice. Toxicology 190:197-219.

Gur E, Piraic H, Waner T. 1991. Methanearsonic acid: Combined oncogenicity study in the mouse. Conducted by Life Science Research Israel Ltd., Ness Ziona Israel. Submitted to EPA Office of Pesticide Programs (MRID 42173201).

Experimental design: Groups of 52 male and 52 female $B6C3F_1$ mice were exposed to 0, 10, 50, 200, or 400 ppm of MMA in the diet for 104 weeks. The reported MMA doses were 0, 1.2, 6.0, 24.9, and 67.1 mg MMA/kg/day (males) and 0, 1.4, 7.0, 31.2, and 101 mg MMA/kg/day (females). Body weights, food consumption, and water intake were monitored regularly. Blood was taken at 3, 6, 12, 18, and 24 months for white cell counts. At sacrifice, complete necropsies were performed, including histological examination of at least 13 organs.

Effects noted in study and corresponding doses: No treatment-related increases in mortality were observed. Significant decreases in body weights were observed in males and females exposed to 32.2 or 48.5 mg As/kg/day, respectively; at week 104, the males weighed 17% less than controls and females weighed 23% less. Food consumption was increased in females exposed to 101 mg MMA/kg/day, and water consumption was increased in 67.1 mg MMA/kg/day males and 31.2 and 101 mg MMA/kg/day females. Loose and mucoid feces were noted in mice exposed to 67.1/101 mg MMA/kg/day. No changes were seen in white cell counts of either sex. Small decreases in the weights of heart, spleen, kidney, and liver were seen in some animals, but the decreases were not statistically significant. Squamous metaplasia of the cecum, colon, and rectum was observed at 67.1/101 mg MMA/kg/day. The incidences of metaplasia in the cecum, colon, and rectum were 29/49, 14/49, and 39/49 in males and 38/52, 17/52, and 42/52 in females; metaplasia was not observed in other groups of male or female mice. An increased incidence of progressive glomerulonephropathy (incidence of 25/52, 27/52, 38/52, 39/52, and 46/52 in the 0, 1.2, 6.0, 24.9, and 67.1 mg MMA/kg/day) was observed in males; the incidence was significantly higher (Fisher Exact Test) than controls at ≥6.0 mg MMA/kg/day. Significant increases in the incidence of nephrocalcinosis was observed in the males at 24.9 and 67.1 mg MMA/kg/day (Fisher Exact Test) (incidence of 25/52, 30/52, 30/52, 45/522 45/51 and 0/52, 1/52, 1/52, 2/52, and 5/52 in males and females, respectively). The investigators noted that the kidney lesions were consistent with the normal spectrum of spontaneous renal lesions and there was no difference in character or severity of the lesions between groups. A reduction in the incidence of cortical focal hyperplasia in the adrenal gland of male mice exposed to 67.1 mg MMA/kg/day was possibly related to MMA exposure; the toxicological significance of this effect is not known.

Dose and end point used for MRL derivation: Benchmark dose analysis of the dose-response data (Table A-3) for progressive glomerulonephropathy in male mice exposed to MMA in the diet for 2 years

(incidence data reported in Gur et al. 1991) was conducted. All available dichotomous models in EPA's Benchmark Dose Software (version 1.4.1) were fit to the data. Predicted doses associated with a 10% extra risk were calculated. As assessed by the chi-square goodness-of-fit statistic, all models, with the exception of the log-probit model, provided an adequate fit (X^2 p>0.1) (Table A-4). Comparing across models, a better fit is generally indicated by a lower Akaike's Information Criteria (AIC). As assessed by AIC, the log-logistic model (Figure A-3) provided the best fit to the data. The predicted BMD_{10} and $BMDL_{10}$ for the incidence data are 2.09 and 1.09 mg MMA/kg/day.

Table A-3. Incidence of Progressive Glomerulonephropathy in Male Mice Exposed to MMA in the Diet for 2 Years

Dietary Concentration (ppm)	Dose (mg MMA/kg/day)	Incidence
0	0	25/52
10	1.2	27/52
50	6.0	38/52
200	24.9	39/52
400	67.1	46/52

Sources: Arnold et al. 2003; Gur et al. 1991

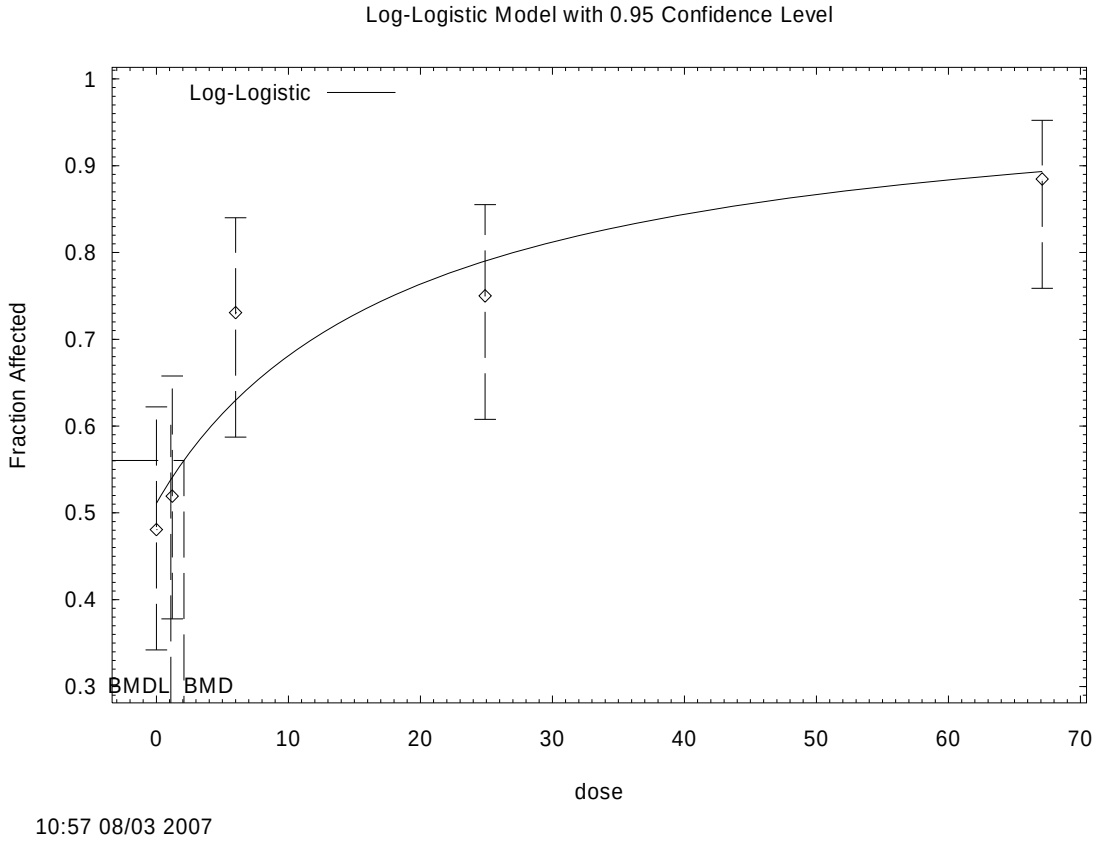
Table A-4. Modeling Predictions for the Incidence of Progressive Glomerulonephropathy in Male Mice Exposed to MMA in the Diet for 2 Years

Model	BMD_{10} (mg MMA/kg/day)	$BMDL_{10}$ (mg MMA/kg/day)	x^2 p-value	AIC
Gamma[a]	4.60	3.15	0.18	309.33
Logistic	6.09	4.45	0.13	310.15
Log-logistic[b]	**2.09**	**1.09**	**0.38**	**307.47**
Multi-stage[c]	4.60	3.15	0.18	309.33
Probit	6.62	5.00	0.11	310.43
Log-probit[b]	8.54	5.50	0.08	311.11
Quantal linear	4.60	3.15	0.18	309.33
Weibull[a]	4.60	3.15	0.18	309.33

Sources: Arnold et al. 2003; Gur et al. 1991

[a]Restrict power ≥1.
[b]Slope restricted to >1.
[c]Restrict betas ≥0; lowest degree polynomial with an adequate fit is reported; degree of polynomial=1.

Figure A-3. Predicted and Observed Incidence of Progressive Glomerulonephropathy in Male Mice Exposed to MMA*



*BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of mg MMA/kg/day.

The $BMDL_{10}$ of 1.09 mg MMA/kg/day for male mice was selected as the point of departure for deriving the chronic-duration oral MRL.

[ ] NOAEL [ ] LOAEL [X] BMDL

Uncertainty factors used in MRL derivation: 100

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses calculated using the average of the achieved doses reported in Gur et al. (1991): 0, 1.2, 6.0, 24.9, and 67.1 mg MMA/kg/day for males and 0, 1.4, 7.0, 31.2, and 101 mg MMA/kg/day for females.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: An exacerbation of chronic progressive nephropathy (an increase in the severity of the nephropathy) has also been observed in rats exposed to ≥33.9 mg MMA/kg/day for 2 years (Arnold et al. 2003).

Agency Contacts (Chemical Managers): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Dimethylarsinic acid (DMA)
CAS Number: 75-60-5
Date: August 2007
Profile Status: Post-Public Comment, Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 35
Species: Mouse

Minimal Risk Level: 0.02 [X] mg DMA/kg/day [ ] ppm

References: Arnold LL, Eldan M, Nyska A, et al. 2006. Dimethylarsinic acid: Results of chronic toxicity/oncogenicity studies in F344 rats and B6C3F$_1$ mice. Toxicology 223:82-100.

Gur E, Nyska A, Pirak M, et al. 1989b. Cacodylic acid: Oncogenicity study in the mouse. Conducted by Life Science Research Israel Ltd., Ness Ziona Israel. Submitted to EPA Office of Pesticide Programs (MRID 41914601).

Experimental design: Groups of 56 male and 56 female B6C3F$_1$ mice were exposed to 0, 8, 40, 200, or 500 ppm DMA in the diet for 2 years. The investigators reported the dietary doses were equivalent to approximately 0, 1.3, 7.8, 37, and 94 mg DMA/kg/day. The following parameters were used to assess toxicity: clinical observations, body weight, food consumption, water consumption, differential leukocyte levels measured at 12, 18, and 24 months in mice in the control and 94 mg DMA/kg/day groups, organ weights (brain, kidneys, liver, and testes), and histopathological examination of major tissues and organs.

Effects noted in study and corresponding doses: No deaths were observed. Decreases in body weight gain were observed in the male mice exposed to 94 mg DMA/kg/day; the difference was <10% and was not considered adverse. An increase in water consumption was observed in males exposed to 94 mg DMA/kg/day during weeks 60–96. No treatment-related clinical signs were observed. In the female mice exposed to 94 mg DMA/kg/day, a statistically significant decrease in lymphocytes and increase in monocytes were observed at 24 months. Treatment related nonneoplastic alterations were observed in the urinary bladder and kidneys. In the urinary bladder, increases in the vacuolization of the superficial cells of the urothelium were observed in males exposed to 37 or 94 mg DMA/kg/day (0/44, 1/50, 0/50, 36/45, 48/48) and in females exposed to 7.8, 37, or 94 mg DMA/kg/day (1/45, 1/48, 26/43, 47/47, 43/43); incidence data reported in Gur et al. (1989b). An increased incidence of progressive glomerulonephropathy was observed in males at 37 mg DMA/kg/day (16/44, 22/50, 17/50, 34/45, 30/50) and an increased incidence of nephrocalcinosis was also observed in male mice at 94 mg DMA/kg/day (30/44, 25/50, 27/50, 29/50, 45/50). Neoplastic alterations were limited to an increased incidence of fibrosarcoma of the skin in females exposed to 94 mg DMA/kg/day; the incidence was 3/56, 0/55, 1/56, 1/56, and 6/56 in the 0, 1.3, 7.8, 37, and 94 mg DMA/kg/day groups, respectively; however it was concluded that this lesion was not related to DMA exposure.

Dose and end point used for MRL derivation: Benchmark dose analysis of the dose-response data (Table A-5) for vacuolization of the urothelium in the urinary bladder in female mice exposed to DMA in the diet for 2 years (incidence data reported in Gur et al. 1989b) was conducted. All available dichotomous models in EPA's Benchmark Dose Software (version 1.4.1) were fit to the data. Predicted doses associated with a 10% extra risk were calculated. As assessed by the chi-square goodness-of-fit statistic, all models, with the exception of the quantal linear model, provided an adequate fit (X^2 p>0.1) (Table A-6). Comparing across models, a better fit is generally indicated by a lower AIC. The AIC

values were similar for the logistic, multi-stage, and probit models; of these three models, the multi-stage had the lowest BMD_{10} and was selected for the analysis (see Figure A-4). The predicted BMD_{10} and $BMDL_{10}$ for the incidence data are 2.68 and 1.80 mg DMA/kg/day.

Table A-5. Incidence of Vacuolization of Urotheium in Urinary Bladder of Female Mice Exposed to DMA in the Diet for 2 Years

Dietary concentration (ppm)	Dose (mg DMA/kg/day)	Incidence
0	0	1/45
8	1.3	1/48
40	7.8	26/43
200	37	47/47
500	94	43/43

Sources: Arnold et al. 2006; Gur et al. 1989b

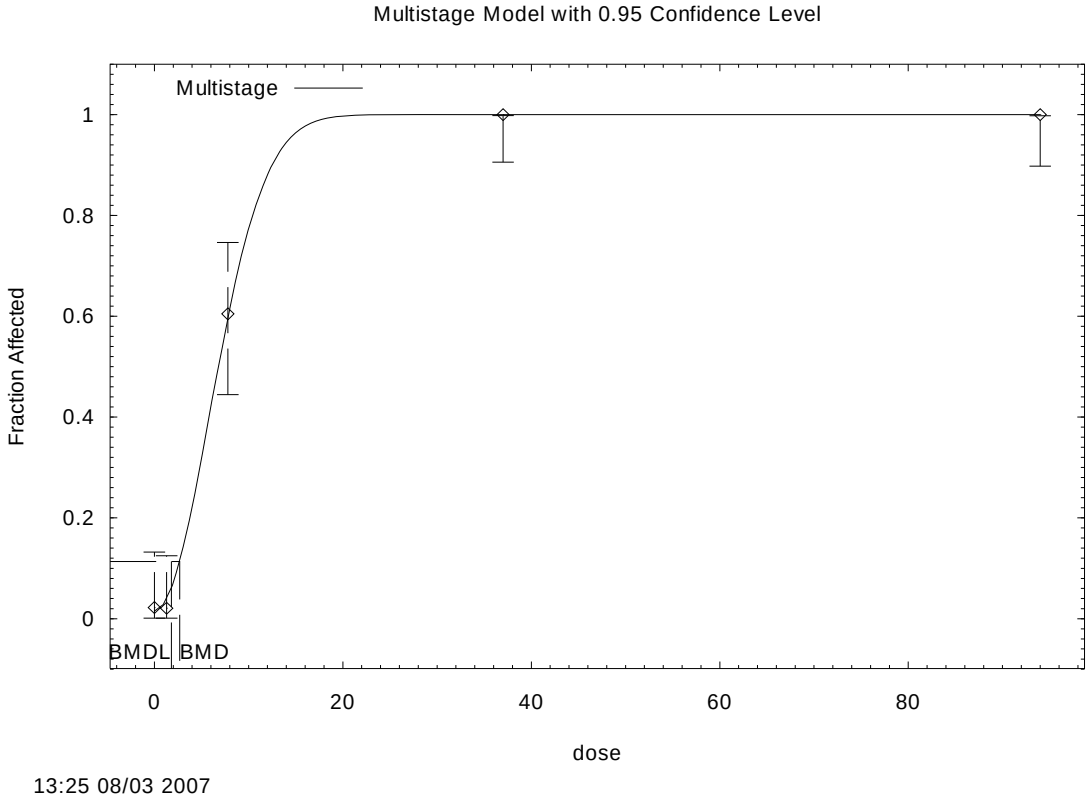
Table A-6. Modeling Predictions for the Incidence of Vacuolization in of Urothelium in Urinary Bladder of Female Mice Exposed to DMA in the Diet for 2 Years

Model	BMD_{10} (mg DMA/kg/day)	$BMDL_{10}$ (mg DMA/kg/day)	x^2 *p*-value	AIC
Gamma[a]	5.01	1.85	1.00	83.03
Logistic	3.66	2.78	0.95	81.37
Log-logistic[b]	6.23	2.34	1.00	83.03
Multi-stage[c]	**2.68**	**1.80**	**0.90**	**81.69**
Probit	3.20	2.46	0.89	81.60
Log-probit[b]	5.03	2.00	1.00	83.03
Quantal linear	0.98	0.76	0.07	91.75
Weibull[a]	4.77	1.88	1.00	83.03

Sources: Arnold et al. 2006; Gur et al. 1989b

[a]Restrict power ≥1.
[b]Slope restricted to >1.
[c]Restrict betas ≥0; lowest degree polynomial with an adequate fit is reported; degree of polynomial=2.

Figure A-4. Predicted and Observed Incidence of Vacuolization of Urothelium in Urinary Bladder of Female Mice*



Source: Arnold et al. 2006

*BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of mg DMA/kg/day.

The $BMDL_{10}$ of 1.80 mg DMA/kg/day for female mice was selected as the point of departure for deriving the chronic-duration oral MRL.

[ ] NOAEL [ ] LOAEL [X] BMDL

Uncertainty factors used in MRL derivation: 100

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses reported in Gur et al. (1989b): 0, 1.3, 7.8, 37, and 94 mg DMA/kg/day.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: One other study has investigated the chronic toxicity of DMA in species other than rats. In this study, administration of 16 mg DMA/kg/day via a capsule for 52 weeks resulted in increases in the incidence of diarrhea; no histological alterations were observed (Zomber et al. 1989).

Agency Contacts (Chemical Managers): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

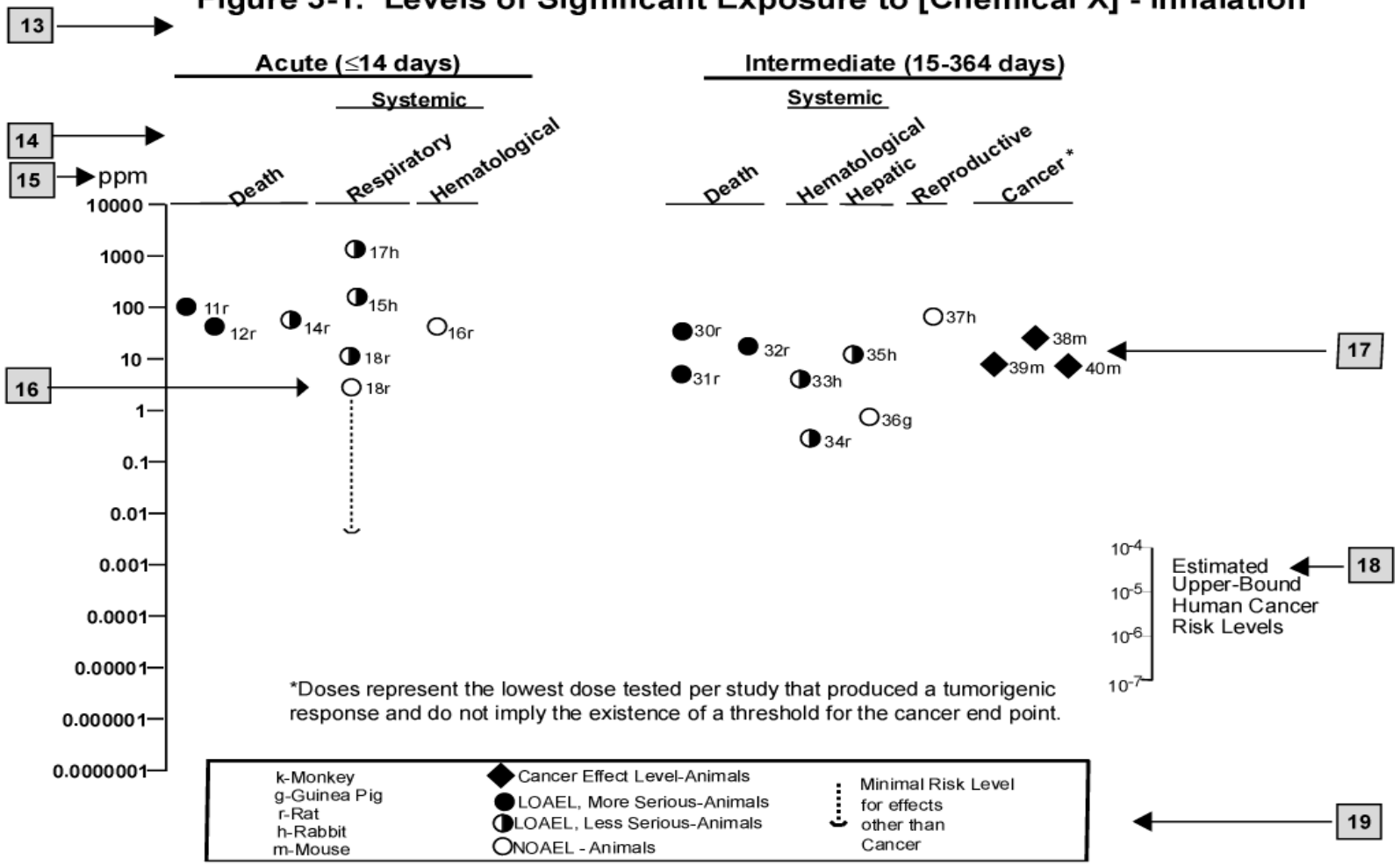
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX

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TOXICOLOGICAL PROFILE FOR BARIUM AND BARIUM COMPOUNDS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

August 2007

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Barium and Barium Compounds, Draft for Public Comment was released in September 2005. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-32
Atlanta, Georgia 30333

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

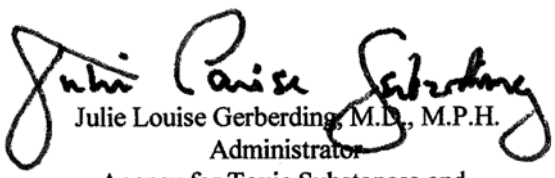
(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Howard Frumkin, M.D., Dr. P.H.
Director
National Center for Environmental Health/
Agency for Toxic Substances and
Disease Registry



Julie Louise Gerberding, M.D., M.P.H.
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Agency for Toxic Substances and
Disease Registry

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014); and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for barium and barium. The panel consisted of the following members:

1. Michael Dourson, Ph.D., DABT, Toxicological Excellence for Risk Assessment, Cincinnati, Ohio;

2. Ernest Foulkes, Ph.D., University of Cincinnati, Cincinnati, Ohio; and

3. Richard Leggett, Ph.D., Private Consultant, Knoxville, Tennessee.

These experts collectively have knowledge of barium and barium compound's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about barium and barium compounds and the effects of exposure to these chemicals.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Barium and barium compounds have been found in at least 798 of the 1,684 current or former NPL sites; however, the total number of NPL sites evaluated for these substances is not known. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to barium and barium compounds, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS BARIUM?

Barium is a silvery-white metal that takes on a silver-yellow color when exposed to air. Barium occurs in nature in many different forms called compounds. These compounds are solids, existing as powders or crystals, and they do not burn well. Two forms of barium, barium sulfate and barium carbonate, are often found in nature as underground ore deposits. Barium is sometimes found naturally in drinking water and food. Because certain barium compounds (barium sulfate and barium carbonate) do not mix well with water, the amount of barium usually found in drinking water is small. Other barium compounds, such as barium chloride, barium nitrate, and barium hydroxide, are manufactured from barium sulfate. Barium compounds such

as barium acetate, barium chloride, barium hydroxide, barium nitrate, and barium sulfide dissolve more easily in water than barium sulfate and barium carbonate, but because they are not commonly found in nature, they do not typically end up in drinking water unless the water is contaminated by barium compounds that are released from waste sites.

Barium and barium compounds are used for many important purposes. Barium sulfate ore is mined and used in several industries. It is used mostly by the oil and gas industries to make drilling muds. Drilling muds make it easier to drill through rock by keeping the drill bit lubricated. Barium sulfate is also used to make paints, bricks, tiles, glass, rubber, and other barium compounds. Some barium compounds, such as barium carbonate, barium chloride, and barium hydroxide, are used to make ceramics, insect and rat poisons, and additives for oils and fuels; in the treatment of boiler water; in the production of barium greases; as a component in sealants, paper manufacturing, and sugar refining; in animal and vegetable oil refining; and in the protection of objects made of limestone from deterioration. Barium sulfate is sometimes used by doctors to perform medical tests and take x-ray photographs of the stomach and intestines.

More information on the chemical and physical properties and use of barium is found in Chapters 4 and 5.

1.2 WHAT HAPPENS TO BARIUM WHEN IT ENTERS THE ENVIRONMENT?

The length of time that barium will last in air, land, water, or sediments following release of barium into these media depends on the form of barium released. Barium compounds that do not dissolve well in water, such as barium sulfate and barium carbonate, can persist for a long time in the environment. Barium compounds, such as barium chloride, barium nitrate, or barium hydroxide, that dissolve easily in water usually do not last in these forms for a long time in the environment. The barium in these compounds that is dissolved in water quickly combines with sulfate or carbonate that are naturally found in water and become the longer lasting forms (barium sulfate and barium carbonate). Barium sulfate and barium carbonate are the barium compounds most commonly found in the soil and water. If barium sulfate and barium carbonate

are released onto land, they will combine with particles of soil. More information on the environmental fate of barium is found in Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO BARIUM?

Background levels of barium in the environment are very low. The air that most people breathe contains about 0.0015 parts of barium per billion parts of air (ppb). The air around factories that release barium compounds into the air has about 0.33 ppb or less of barium. Most surface water and public water supplies contain on average 0.030 parts of barium per million parts of water (ppm) or less, but can average as high as 0.30 ppm in some regions of the United States. In some areas that have underground water wells, drinking water may contain more barium than the 2 ppm limit set by EPA. The highest amount measured from these water wells has been 10 ppm. The amount of barium found in soil ranges from about 15 to 3,500 ppm. Some foods, such as Brazil nuts, seaweed, fish, and certain plants, may contain high amounts of barium. The amount of barium found in food and water usually is not high enough to be a health concern. However, information is still being collected to determine if long-term exposure to low levels of barium causes any health problems.

People with the greatest known risk of exposure to high levels of barium are those working in industries that make or use barium compounds. Most of these exposed persons breathe air that contains barium sulfate or barium carbonate. Sometimes they are exposed to one of the more harmful barium compounds (for example, barium chloride or barium hydroxide) by breathing the dust from these compounds or by getting them on their skin. Barium carbonate can be harmful if accidentally eaten because it will dissolve in the acids within the stomach unlike barium sulfate, which will not dissolve in the stomach. Many hazardous waste sites contain barium compounds, and these sites may be a source of exposure for people living and working near them. Exposure near hazardous waste sites may occur by breathing dust, eating soil or plants, or drinking water that is polluted with barium. People near these sites may also get soil or water that contains barium on their skin. More information on how you might be exposed to barium is found in Chapter 6.

1.4 HOW CAN BARIUM ENTER AND LEAVE MY BODY?

Barium enters your body when you breathe air, eat food, or drink water containing barium. It may also enter your body to a small extent when you have direct skin contact with barium compounds. The amount of barium that enters the bloodstream after you breathe, eat, or drink it depends on the barium compound. Some barium compounds that are soluble, such as barium chloride, can enter bloodstream more easily than insoluble barium compounds such as barium sulfate. Some barium compounds (for example, barium chloride) can enter your body through your skin, but this is very rare and usually occurs in industrial accidents at factories where they make or use barium compounds. Barium at hazardous waste sites may enter your body if you breathe dust, eat soil or plants, or drink water polluted with barium from this area.

Barium that enters your body by breathing, eating, or drinking is removed mainly in feces and urine. Most of the barium that enters your body is removed within 1–2 weeks. Most of the small amount of barium that stays in your body goes into the bones and teeth. More information on how barium enters and leaves your body is found in Chapter 3.

1.5 HOW CAN BARIUM AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

The health effects associated with exposure to different barium compounds depend on how well the specific barium compound dissolves in water or in the stomach. For example, barium sulfate

does not easily dissolve in water and causes few harmful health effects. Doctors sometimes give barium sulfate orally or by placing it directly in the rectum of patients for purposes of making x-rays of the stomach or intestines. The use of this particular barium compound in this type of medical test is not harmful to people. Barium compounds such as barium acetate, barium chloride, barium hydroxide, barium nitrate, and barium sulfide that dissolve in water can cause harmful health effects. Barium carbonate does not dissolve in water, but does dissolve in the stomach; it can also cause harmful health effects.

Eating or drinking very large amounts of barium compounds that dissolve in water or in the stomach can cause changes in heart rhythm or paralysis in humans. Some people who did not seek medical treatment soon after eating or drinking a very large amount of barium have died. Some people who eat or drink somewhat smaller amounts of barium for a short period may experience vomiting, abdominal cramps, diarrhea, difficulties in breathing, increased or decreased blood pressure, numbness around the face, and muscle weakness. One study showed that people who drank water containing as much as 10 ppm of barium for 4 weeks did not have increased blood pressure or abnormal heart rhythms. The health effects of barium have been studied more often in experimental animals than in humans. Rats that ate or drank barium over short periods had swelling and irritation of the intestines, changes in organ weights, decreased body weight, and increased numbers of deaths. Rats and mice that drank barium over long periods had damage to the kidneys, decreases in body weight, and decreased survival. We have no information about the ability of barium to affect reproduction in humans; a study in experimental animals did not find reproductive effects.

Some studies of humans and experimental animals exposed to barium in the air have reported damage to the lungs, but other studies have not found these effects. We have no reliable information about the health effects in humans or experimental animals that are exposed to barium by direct skin contact.

Barium has not been shown to cause cancer in humans or in experimental animals drinking barium in water. The Department of Health and Human Services and the International Agency for Research on Cancer have not classified barium as to its carcinogenicity. The EPA has

determined that barium is not likely to be carcinogenic to humans following ingestion and that there is insufficient information to determine whether it will be carcinogenic to humans following inhalation exposure.

More information on the health effects of barium can be found in Chapter 3.

1.6 HOW CAN BARIUM AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

We do not know whether children will be more or less sensitive than adults to barium toxicity. A study in rats that swallowed barium found a decrease in newborn body weight; we do not know if a similar effect would be seen in humans.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO BARIUM?

If your doctor finds that you have been exposed to substantial amounts of barium, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

The greatest potential source of barium exposure is through food and drinking water. However, the amount of barium in foods and drinking water are typically too low to be of concern.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO BARIUM?

There is no routine medical test to determine whether you have been exposed to barium. Doctors can measure barium in body tissues and fluids, such as bones, blood, urine, and feces, using very complex instruments. These tests cannot be used to predict the extent of the exposure or potential health effects. This is normally done only for cases of severe barium poisoning and for medical research.

More information on testing for barium exposure is found in Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for barium include the following:

The EPA has determined that drinking water should not contain more than 2.0 milligrams (mg) barium per liter (L) of water (2.0 mg/L).

OSHA has a legally enforceable occupational exposure limit of 0.5 mg of soluble barium compounds per cubic meter (m^3) of air averaged over an 8-hour work day. The OSHA 8-hour exposure limit for barium sulfate dust in air is 15 mg/m^3 for total dust. NIOSH considers

exposure to barium chloride levels of 50 mg/m^3 and higher as immediately dangerous to life or health.

More information on government regulations can be found in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BARIUM IN THE UNITED STATES

Barium is an alkaline earth metal, principally found as barite (barium sulfate) and witherite (barium carbonate) ores. Barium and barium compounds have a variety of uses including as getters in electronic tubes (barium alloys), rodenticide (barium carbonate), colorant in paints (barium carbonate and barium sulfate), and x-ray contrast medium (barium sulfate). Barium naturally occurs in food and groundwater. Barium concentrations in drinking water in the United States typically average 30 μg/L, but can average as high as 302 μg/L. However, individuals residing in certain regions of Kentucky, northern Illinois, New Mexico, and Pennsylvania who rely on groundwater for their source of drinking water may be exposed to barium concentrations as high as 10 times the maximum contaminant level (MCL) in drinking water of 2.0 mg/L. Low levels of barium are also found in ambient air; levels are typically less than 0.05 μg barium/m^3.

There is little quantitative information regarding the extent of barium absorption following inhalation, oral, or dermal exposure. Available evidence indicates that barium is absorbed to some extent following inhalation, oral, and dermal exposure; however, in some cases, absorption is expected to be limited. For example, there is some evidence that gastrointestinal absorption of barium in humans is <5–30% of the administered dose. The general population can be exposed to barium via inhalation, oral, or dermal exposure; under most circumstances, oral exposure would be the predominant route of exposure.

2.2 SUMMARY OF HEALTH EFFECTS

An important factor affecting the development of adverse health effects in humans is the solubility of the barium compound to which the individual is exposed. Soluble barium compounds would generally be expected to be of greater health concern than insoluble barium compounds because of their greater potential for absorption. The various barium compounds have different solubilities in water and body fluids and therefore serve as variable sources of the Ba^{2+} ion. The Ba^{2+} ion and the soluble compounds of barium (notably chloride, nitrate, hydroxide) are toxic to humans. Although barium carbonate is relatively insoluble in water, it is toxic to humans because it is soluble in the gastrointestinal tract. The insoluble compounds of barium (notably sulfate) are inefficient sources of Ba^{2+} ion and are therefore generally nontoxic to humans. The insoluble, nontoxic nature of barium sulfate has made it practical to use this particular barium compound in medical applications as a contrast media for x-ray examination of

the gastrointestinal tract. Barium provides an opaque contrasting medium when ingested or given by enema prior to x-ray examination. Under these routine medical situations, barium sulfate is generally safe. However, barium sulfate or other insoluble barium compounds may potentially be toxic when it is introduced into the gastrointestinal tract under conditions where there is colon cancer or perforations of the gastrointestinal tract and barium is able to enter the blood stream.

There are a number of reports of serious health effects in individuals intentionally or accidentally exposed to barium carbonate or chloride. The predominant effect is hypokalemia, which can result in ventricular tachycardia, hypertension and/or hypotension, muscle weakness, and paralysis. Barium is a competitive potassium channel antagonist that blocks the passive efflux of intracellular potassium, resulting in a shift of potassium from extracellular to intracellular compartments. The net result of this shift is a significant decrease in the potassium concentration in the blood plasma. Although the case reports did not provide information on doses, it is likely that the doses were high. In addition to the effects associated with hypokalemia, gastrointestinal effects such as vomiting, abdominal cramps, and watery diarrhea are typically reported shortly after ingestion. Similar effects have been reported in cases of individuals exposed to very high concentrations of airborne barium; the effects include electrocardiogram (ECG) abnormalities, muscle weakness and paralysis, hypokalemia, and abdominal cramps, nausea, and vomiting.

Several investigators have examined whether exposure to much lower doses of barium would adversely affect the cardiovascular system. A population-based study found significant increases in the risk of death from cardiovascular disease among residents 65 years of age and older living in communities with high levels of barium in the drinking water. However, these data cannot be used to establish a causal relationship because the study did not control for other cardiovascular risk factors or the use of water softeners, which would decrease barium levels and increase sodium levels. Two other studies did not find alterations in blood pressure and cardiac rhythm. In general, animal studies designed to assess cardiovascular function have not found significant alterations in blood pressure or ECG readings following low-dose oral exposure. One study did find significant increases in blood pressure in rats exposed to 0.80 mg barium/kg/day. However, the use of a low mineral diet with less than adequate levels of calcium may have influenced the study results.

The available animal data provide strong evidence that the most sensitive adverse effect of barium is renal toxicity. There are some reports of renal effects in case reports of individuals ingesting high doses of barium. Nephropathy has been observed in rats and mice following long-term oral exposure to barium.

In both species, there is a steep dose-response curve for the incidence of nephropathy. For example, nephropathy was not observed in mice exposed to 205 mg barium/kg/day for an intermediate duration; at 450 mg barium/kg/day, 95% of the animals exhibited mild to moderate nephropathy. Data in mice also suggest that the severity and sensitivity to renal lesions is related to duration of exposure. As noted previously, a 205 mg barium/kg/day dose is a no effect level in mice exposed to barium chloride for 90 days; a 2-year exposure to 200 mg barium/kg/day resulted in moderate to marked nephropathy.

The potential for barium to induce reproductive and developmental effects has not been well investigated. Decreases in the number of sperm and sperm quality and a shortened estrous cycle and morphological alterations in the ovaries were observed in rats exposed to 2.2 mg barium/m^3 and higher in air for an intermediate duration. Interpretation of these data is limited by the poor reporting of the study design and results, in particular, whether the incidence was significantly different from controls. In general, oral exposure studies have not found morphological alterations in reproductive tissues of rats or mice exposed to 180 or 450 mg barium/kg/day, respectively, as barium chloride in drinking water for an intermediate duration. Additionally, no significant alterations in reproductive performance was observed in rats or mice exposed to 200 mg barium/kg/day as barium chloride in drinking water. Decreased pup birth weight and a nonsignificant decrease in litter size have been observed in the offspring of rats exposed to 180/200 mg barium/kg/day as barium chloride in drinking water prior to mating.

Several studies have examined the carcinogenic potential of barium following oral exposure and did not find significant increases in the tumor incidence. No studies have adequately assessed the carcinogenicity of barium following inhalation exposure. The Department of Health and Human Services (DHHS) and the International Agency for Research on Cancer (IARC) have not assessed the carcinogenicity of barium. The EPA has concluded that barium is not classifiable as to human carcinogenicity, Group D. However, under EPA's revised guidelines for carcinogen risk assessment, barium is considered not likely to be carcinogenic to humans following oral exposure and its carcinogenic potential cannot be determined following inhalation exposure.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for barium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive

health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for barium because studies evaluating the effects of barium in humans and animals following acute, intermediate, and chronic inhalation exposure were inadequate for establishing the exposure concentrations associated with adverse health effects. Five reports of occupational exposure to barium have been identified. In one study (Doig 1976), a benign pneumoconiosis was observed in several workers exposed to barium sulfate; two other studies did not find barium-related alterations in the respiratory tract of workers exposed to barium sulfate (Seaton et al. 1986) or barium carbonate (Essing et al. 1976). Other effects reported in the occupational exposure studies were an increase in blood pressure (Essing et al. 1976), gastrointestinal distress, muscle weakness and paralysis, absence of deep tendon reflex, and decreased serum potassium levels in a worker exposed to barium carbonate powder (Shankle and Keane 1988). A fifth study did not find alterations in plasma potassium levels in welders using barium-containing electrodes (Zschiesche et al. 1992). Interpretation of these studies is limited by the small number of subjects, possible lack of a control group, and/or the lack of quantitative exposure information.

Three animal studies evaluating the toxicity of inhaled barium have also been identified. Two of the studies reported adverse respiratory tract effects including lung lesions (perivascular and peribronchial sclerosis and focal thickening of the intraalveolar septa) in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust 4 hours/day, 6 days/week for 4 months (Tarasenko et al. 1977) and bronchoconstriction in guinea pigs exposed to 0.06 mg barium/m^3/minute as barium chloride for an unspecified amount of time

(Hicks et al. 1986). The third study (Cullen et al. 2000) did not find histological alterations in the lungs of rats exposed to 44.1 mg barium/m^3 as barium sulfate for 7 hours/day, 5 days/week for 119 days. Increases in blood pressure were observed in the Tarasenko et al. (1977) and Hicks et al. (1986) studies. Tarasenko et al. (1977) also reported hematological, reproductive, and developmental effects in rats exposed to barium carbonate dust. None of these studies provide a suitable basis for an inhalation MRL. The Tarasenko et al. (1977) studies are limited by poor reporting of the study design and results, lack of incidence data, and lack of statistical analysis for many of the end points. The Hicks et al. (1986) study did not report the frequency or length of exposure, the number of animals used was not clearly reported, and it does not appear that control animals were used. Although the Cullen et al. (2000) study was well reported and designed, it only examined the respiratory tract and did not identify an adverse effect level. Oral exposure studies identify the kidney as the most sensitive target of toxicity; this end point was not evaluated in the Cullen et al. (2000) study.

Oral MRLs

There are numerous case reports of individuals intentionally or accidentally ingesting unreported but presumably high doses of barium (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Silva 2003; Talwar and Sharma 1979; Wetherill et al. 1981). The consistently observed effects included abdominal distress (vomiting, abdominal cramping, and watery diarrhea), numbness around the face, muscle weakness, paralysis, and ventricular tachycardia.

Information on the acute oral toxicity of barium is limited to two studies in rats conducted by Borzelleca et al. (1988). A nonsignificant increase in mortality (3/20 females compared to 0/20 in controls) was found in rats receiving gavage doses of 198 mg barium/kg/day as barium chloride in water for 10 days. In the other study conducted by this group, 15/20 animals died after a single dose of 198 mg barium/kg/day as barium chloride in water. In the 10-day study, significant decreases in relative kidney weight (kidney:brain ratio) were observed in female rats administered 66–138 mg barium/kg/day and decreases in blood urea nitrogen (BUN) levels were observed in female rats dosed with 66–198 mg barium/kg/day and male rats dosed with 198 mg barium/kg/day. The magnitude of change in BUN levels was small (less than 15%) and was not dose-related; the decrease in BUN was not considered to be biologically significant. Additionally, BUN levels are typically increased in response to kidney damage. Significant decreases in absolute ovary weight and relative ovary weight (ovary:brain ratio) were observed at 198 mg barium/kg/day in the 10-day study. The biological significance of this change in organ weight is

questionable; no gross alterations in the ovaries were observed in this study and no histological alterations were observed in rats or mice exposed to barium chloride for acute, intermediate, or chronic durations to barium doses as high as 180 mg barium/kg/day in rats (NTP 1994) and 495 mg barium/kg/day in mice (NTP 1994).

The data are considered inadequate for derivation of an acute-duration oral MRL for barium. The available animal studies (Borzelleca et al. 1988) have evaluated the toxicity of barium chloride in repeated dose studies; however, neither study identified a non-lethal biologically significant adverse effect level. Longer-term studies identify the kidney as the most sensitive target; however, it is not known if the kidney would also be the most sensitive target following acute-duration exposure. Data in mice suggest that the severity and sensitivity to renal lesions are related to duration of exposure. The intermediate-duration mouse study identified a NOAEL of 205 mg barium/kg/day; however; a 2-year exposure to 200 mg barium/kg/day resulted in moderate to marked nephropathy (NTP 1994). Derivation of an MRL using the highest identified no-observed-adverse-effect level (NOAEL) is not recommended at this time because critical targets of toxicity and dose-response relationships have not been established for this exposure category. The exposure levels are poorly characterized in the available reports of human poisonings, acute-duration animal studies have failed to identify the critical target of barium toxicity, and it is possible that the critical target (kidneys) following long-term exposure may not be a sensitive target following short-term exposure.

- An MRL of 0.2 mg barium/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to barium.

Information on the oral toxicity of barium in humans following intermediate-duration oral exposure is limited to an experimental study in which men were exposed to 0.1 or 0.2 mg barium/kg/day as barium chloride in drinking water for 4 weeks (Wones et al. 1990). No significant alterations in blood pressure or ECG readings, relative to initial baseline measurements, were found.

A number of animal studies have evaluated barium toxicity following intermediate-duration oral exposure. Several of these studies focused on the cardiovascular system or assessed cardiovascular function. Perry et al. (1983, 1985, 1989) reported significant increases in blood pressure in rats administered 8.6 or 11 mg barium/kg/day as barium chloride in drinking water for 1 or 4 months, respectively. NTP (1994) and McCauley et al. (1985) did not find significant alterations in blood pressure or ECG readings in rats exposed to 150 or 180 mg barium/kg/day in drinking water for 13 or 16 weeks, respectively. The reason for the differences between the results from the Perry et al. (1983, 1985, 1989)

studies and the NTP (1994) and McCauley et al. (1985) studies is not known. It is possible that the low-mineral diet used in the Perry et al. (1983, 1985, 1989) studies influenced the results. The calcium content of the rye-based diet was 3.8 mg/kg, which is lower than the concentration recommended for maintenance, growth, and reproduction of laboratory rats (NRC 1995b).

The results of the McCauley et al. (1985) and NTP (1994) studies suggest that the kidney is the most sensitive target of toxicity in rats and mice. In the McCauley et al. (1985) study, glomerular alterations consisting of fused podocytes and thickening of the capillary basement membrane were found in uninephrectomized Sprague Dawley rats, Dahl salt-sensitive rats, and Dahl salt-resistant rats exposed to 150 mg barium/kg/day in drinking water for 16 weeks. In the NTP (1994) 13-week rat study, significant increases in absolute and relative kidney weights were observed in female rats exposed to 115 or 180 mg barium/kg/day and in males exposed to 200 mg barium/kg/day. At 200 and 180 mg barium/kg/day, minimal to mild dilatation of the proximal convoluted tubules of the outer medulla and renal cortex was observed in the males and females, respectively; an increase in mortality (30%) was also observed in the males exposed to 200 mg barium/kg/day. In mice, mild to moderate nephropathy (characterized as tubule dilatation, regeneration, and atrophy) was observed in 100% of the males exposed to 450 mg barium/kg/day and 90% of the females exposed to 495 mg barium/kg/day; no renal lesions were observed at the next lowest dose level (205 and 200 mg barium/kg/day in males and females, respectively). Other effects observed at the 450/495 mg barium/kg/day dose level included weight loss, spleen and thymus atrophy, and increased mortality (60% of the males and 70% of females died after 5 weeks of exposure).

Other end points that have been examined in rats and mice include neurotoxicity, reproductive toxicity, and developmental toxicity. In male and female rats, slight decreases in undifferentiated motor activity were observed at 10 mg barium/kg/day and higher. However, the difference between motor activity in the barium-exposed rats and the controls was less than 20% and was not considered to be biologically significant. At 180 mg barium/kg/day, the difference was 30% in the female rats, which was considered to be adverse. No significant alterations were found on the remaining neurobehavioral tests (grip strength, tail flick latency, startle response, and hindlimb foot splay). In mice, a significant decrease in forelimb grip strength was observed in females exposed to 495 mg barium/kg/day; this may have been due to debilitation. No other alterations in neurobehavioral performance were found. No effects on reproductive tissues or reproductive performance were observed in rats or mice exposed to approximately 200 mg barium/kg/day (Dietz et al. 1992; NTP 1994). Pre-mating exposure of male and female rats to 180/200 mg barium/kg/day resulted in decreased pup birth weight and a nonsignificant decrease in litter size; the NOAEL for these effects was 110/115 mg barium/kg/day (Dietz et al. 1992). No developmental

effects were observed in mice exposed to 200 mg barium/kg/day (Dietz et al. 1992). Another study (Tarasenko et al. 1977) also reported developmental effects (increased offspring mortality during the first 2 months and disturbances in liver function) in an unspecified animal species; however, the lack of information on experimental methods, exposure conditions, and results limits the usefulness of this study for evaluating the potential of aluminum to induce developmental toxicity.

Based on these data, the kidney appears to be the most sensitive target following intermediate-duration oral exposure to barium. Three studies identified adverse effect levels for kidney effects: (1) a lowest-observed-adverse-effect level (LOAEL) of 150 mg barium/kg/day was identified in uninephrectomized and salt-sensitive and salt resistant rats (McCauley et al. 1985), (2) a LOAEL of 115 mg barium/kg/day was identified for increased kidney weight in rats; the NOAEL was 65 mg barium/kg/day (NTP 1994), and (3) a LOAEL of 450 mg barium/kg/day for nephropathy in mice; the NOAEL was 205 mg barium/kg/day (NTP 1994). The NTP (1994) 13-week rat study, which identified the lowest LOAEL for a kidney effect, was selected as the basis of the intermediate-duration oral MRL; the change in kidney weight was considered an early indicator of potentially more serious effects in the kidney.

In this study (NTP 1994), groups of 10 male and 10 female F344/N rats were administered 0, 125, 500, 1,000, 2,000, or 4,000 ppm barium chloride dihydrate (0, 10, 30, 65, 110, and 200 mg barium/kg/day for males and 0, 10, 35, 65, 115, and 180 mg barium/kg/day for females) in drinking water for 90 days. Exposure-related deaths were observed during the last week of the study in 30% of the males and 10% of the females exposed to 200/180 mg barium/kg/day. Significant decreases in final body weights were observed in the 200 mg barium/kg/day males (13% lower than controls) and 180 mg barium/kg/day females (8% lower than controls); significant decreases in water consumption (approximately 30% lower than controls) were also observed at this dose level. Significant increases in absolute and relative kidney weights were observed in females exposed to 115 or 180 mg barium/kg/day and increases in relative kidney weights were also observed in males at 200 mg barium/kg/day; an increase in relative kidney weight was also observed in the females exposed to 65 mg barium/kg/day; The magnitude of the increases in relative kidney weights were 7, 14, and 19% in the females exposed to 65, 115, and 180 mg barium/kg/day and 12% in males exposed to 200 mg barium/kg/day. Minimal to mild, focal to multifocal dilatation of the proximal renal cortex was observed in three male and three female rats in the 200/180 mg barium/kg/day group. The small increase in relative kidney weight (7%) observed in the female rats exposed to 65 mg barium/kg/day was not considered biologically significant because it is not supported by an increase in histological alterations in the kidney at 65 or 115 mg barium/kg/day or in rats exposed

to 75 mg barium/kg/day for 2 years (NTP 1994). Thus, this study identifies a NOAEL of 65 mg barium/kg/day and a LOAEL of 115 mg barium/kg/day.

A NOAEL/LOAEL approach was used to derive the MRL because none of the available benchmark dose models provided an adequate fit to the absolute or relative kidney weight data. Thus, the intermediate-duration oral MRL of 0.2 mg barium/kg/day was calculated by dividing the NOAEL of 65 mg barium/kg/day by an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability) and a modifying factor of 3. The modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

- An MRL of 0.2 mg barium/kg/day has been derived for chronic-duration oral exposure (>365 days) to barium.

Several human and animal studies have examined the toxicity of barium following chronic-duration exposure. Two community-based studies have evaluated the possible association between elevated levels of barium in drinking water and increased risk of cardiovascular disease. No significant alterations in blood pressure measurements or increases in the prevalence of hypertension, heart disease, or stroke were found among residents of two communities with elevated (0.2 mg barium/kg/day) or low (0.003 mg barium/kg/day) levels of barium in drinking water (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981). In the second study, significantly higher mortality rates, particularly among individuals 65 years of age and older, for cardiovascular disease and heart disease (arteriosclerosis) were found in a community with elevated barium drinking water levels (0.06–0.3 mg barium/kg/day) as compared to a community with low barium levels (0.006 mg barium/kg/day) (Brenniman and Levy 1985; Brenniman et

al. 1979a, 1981). A common limitation of both studies is the lack of information on tap water consumption, actual barium intakes, and duration of exposure. Additionally, the second study did not control for a number of potential confounding variables, particularly the use of water softeners, which would have resulted in a decrease in barium levels in the drinking water and an increase in sodium levels.

Significant increases in blood pressure were observed in rats exposed to 0.8 mg barium/kg/day as barium chloride in drinking water for 16 months (Perry et al. 1983, 1985, 1989); the NOAEL for this effect was 0.17 mg barium/kg/day. At higher doses (7.2 mg barium/kg/day), depressed rates of cardiac contraction, reduced cardiac electrical conductivity, and decreased cardiac ATP levels were observed. As noted in the discussion of the intermediate-duration oral MRL, interpretation of the results of this study is limited due to the low mineral diet, which may have supplied inadequate levels of calcium. No adverse effects were observed in rats exposed to 60 mg barium/kg/day as barium chloride in drinking water for 2 years (NTP 1994), 15 mg barium/kg/day to an unspecified barium compound in drinking water for 68 weeks (McCauley et al. 1985), or 0.7 mg barium/kg/day as barium acetate in drinking water for a lifetime (Schroeder and Mitchener 1975a). In mice exposed to barium chloride in drinking water for 2 years, marked renal nephropathy was observed at 160 mg barium/kg/day; the increased incidence of nephropathy in the next lowest dose group (75 mg barium/kg/day) was not statistically significant. Other adverse effects observed at 160 mg barium/kg/day included weight loss and increased mortality (NTP 1994).

As with intermediate-duration exposure, the animal data provide suggestive evidence that the kidney is the most sensitive target of toxicity. A serious LOAEL of 160 mg barium/kg/day was identified for nephropathy in mice (NTP 1994); the NOAEL identified in this study is 75 mg/kg/day. Although no kidney lesions were observed in rats exposed to doses as high as 60 mg barium/kg/day (NTP 1994), the doses utilized in the study may not have been high enough to cause kidney damage. Biologically significant kidney alterations were observed at 115 mg barium/kg/day and higher in rats exposed for an intermediate duration (NTP 1994). The chronic-duration mouse study (NTP 1994) was selected as the basis of the chronic-duration MRL for barium.

In this study (NTP 1994), groups of 60 male and 60 female B6C3F1 mice were exposed to 0, 500, 1,250, or 2,500 ppm barium chloride dehydrate (0, 30, 75, and 160 mg barium/kg/day for males and 0, 40, 90, and 200 mg barium/kg/day for females) in drinking water for 2 years. Increased mortality attributed to renal lesions was observed in the 160/200 mg/kg/day group. Decreased body weights (<7%) were observed in the barium-exposed mice. The investigators noted that a moderate to marked weight loss was

observed in animals dying early. No significant alterations in hematology or clinical chemistry parameters were observed. A significant increase in the incidence of nephropathy was observed in male and female mice exposed to 160/200 mg/kg/day. The nephropathy was characterized by extensive regeneration of cortical and medullary tubule epithelium, tubule dilatation, hyaline cast formation, multifocal interstitial fibrosis, and glomerulosclerosis in some kidneys. The average severity of the nephropathy was 3.6 (moderate to marked) for both the males and females in the 160/200 mg/kg/day group.

A benchmark analysis of the incidence data for nephropathy in mice was conducted; details of this analysis are presented in Appendix A. A benchmark dose (BMD) of 80.06 mg barium/kg/day, which corresponds to a 5% increase in the incidence of nephropathy was calculated; the 95% lower confidence limit on the BMD (BMDL) was 61.13 mg barium/kg/day. The $BMDL_{05}$ was selected as the point of departure for deriving the chronic-duration oral MRL. The dose corresponding to a predicted 5% incidence was selected over the typically 10% incidence as a precaution due to the severity of the observed effects (moderate to marked severity nephropathy), which resulted in marked weight loss and increased mortality. Thus, the chronic-duration oral MRL of 0.2 mg barium/kg/day is based on the $BMDL_{05}$ of 61 mg barium/kg/day in male mice and an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability) and a modifying factor of 3. The modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

2. RELEVANCE TO PUBLIC HEALTH

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of barium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

When evaluating the health effects of barium compounds, it is important to keep in mind that different barium compounds have different solubilities in water and body fluids and therefore serve as variable sources of the Ba^{2+} ion. The Ba^{2+} ion and the soluble compounds of barium (notably chloride, nitrate, and hydroxide) are generally highly toxic to humans and experimental animals. The insoluble barium compounds (notably sulfate) are inefficient sources of the Ba^{2+} ion and therefore are generally nontoxic. Although barium carbonate is insoluble in water, barium ions would be released from ingested barium carbonate in the acid milieu of the stomach. Throughout the following section (3.2), the health effects by route of exposure of both soluble and insoluble barium compounds are discussed.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a

considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Studies evaluating the effects of barium following acute, intermediate, and chronic inhalation exposure are limited to several case reports of humans exposed occupationally (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988), an experimental exposure to barium in welding fumes (Zschiesche et al. 1992), and three experimental studies with animals (Cullen et al. 2000; Hicks et al. 1986; Tarasenko et al. 1977). These case reports and animal studies are not adequate for firmly establishing the health effects of barium by inhalation because of a number of significant study limitations. The case reports are generally inadequate because data were available for a limited number of exposed subjects and because exposure conditions (duration, frequency, dose) were not well characterized (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988). One of the animal studies was limited in that apparently no control animals were used, an inhalation chamber providing a controlled dose and environment was not used, and there was a lack of information regarding

the vehicle used, purity of the test material, duration and frequency of exposure, and number of animals tested (Hicks et al. 1986). The second animal study consisted of several experiments, but was generally limited in that the authors provided few details regarding experimental methods, exposure conditions, and test results, and no information as to the number of animals tested, purity of the test material, or statistical methods used; furthermore, in some experiments, it was not clear whether or not control animals were used (Tarasenko et al. 1977). The third study examined a limited number of end points (Cullen et al. 2000). In view of the major limitations associated with the available case reports and studies, results from these reports should be regarded as providing only preliminary and/or suggestive evidence that acute, intermediate, and chronic inhalation exposure to barium may potentially be associated with adverse health effects. Findings from the various case reports and animal studies are briefly described below.

3.2.1.1 Death

No studies were located regarding death in humans or animals after inhalation exposure to barium.

3.2.1.2 Systemic Effects

No studies were located regarding endocrine, dermal, or ocular effects in humans or animals after inhalation exposure to barium.

Respiratory Effects. Two reports of workers exposed chronically to dust from barium sulfate demonstrated that this exposure had a minor effect on the lungs. In one study, a benign pneumoconiosis was observed in several factory workers (Doig 1976). In a second study in which workers were exposed by mining barium sulfate, silicosis was observed but was attributed to inhalation of quartz (Seaton et al. 1986). In contrast, a study of workers chronically exposed to barium carbonate dust reported no respiratory symptoms attributable to barium exposure (Essing et al. 1976). X-ray analysis of the lungs also showed no abnormalities attributable to barium dust.

Studies regarding respiratory effects in animals following inhalation exposure to barium are limited to three reports (Cullen et al. 2000; Hicks et al. 1986; Tarasenko et al. 1977). Pulmonary lesions (perivascular and peribronchial sclerosis and focal thickening of the interalveolar septa) were observed in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust 4 hours/day, 6 days/week for 4 months (Tarasenko et al. 1977). Bronchoconstriction was reportedly noted in guinea pigs following inhalation for an unspecified period of time to 0.06 mg barium/m^3/minute as aerosolized barium chloride solution

(Hicks et al. 1986). In contrast to these finding, no adverse histological alterations were observed in the lungs of rats exposed to 44.1 mg barium/m^3 as barium sulfate for 119 days (Cullen et al. 2000).

Cardiovascular Effects. Three of 12 workers chronically exposed to barium carbonate dust had elevated blood pressure and 2 workers had ECG abnormalities (Essing et al. 1976). However, it is unknown whether this represented an increased incidence because no comparison with a control population was performed. Increased blood pressure and cardiac irregularities were reportedly observed in guinea pigs exposed by inhalation for an unspecified period of time to 0.06 mg barium/m^3/minute as aerosolized barium chloride solution (Hicks et al. 1986). Tarasenko et al. (1977) reported a 32% increase in arterial pressure and alterations in ECG readings suggestive of disturbances in heart conductivity following proserine administration in rats exposed to 3.6 mg barium/m^3 as barium carbonate; no ECG alterations were observed prior to proserine administration.

Gastrointestinal Effects. Abdominal cramps, nausea, and vomiting were experienced by a 22-year-old factory worker accidentally exposed by acute inhalation to a large but unspecified amount of barium carbonate powder (Shankle and Keane 1988). No animal studies were located regarding gastrointestinal effects in animals after inhalation exposure to barium.

Hematological Effects. Altered hematological parameters were observed in rats following inhalation for an intermediate exposure period to 3.6 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). Reported changes included decreased blood hemoglobin and thrombocyte count.

Musculoskeletal Effects. After accidental exposure to a large amount of barium carbonate powder by acute inhalation, a 22-year-old factory worker developed progressive muscle weakness and paralysis of the extremities and neck (Shankle and Keane 1988); this is likely due to the low serum potassium level rather than a direct effect on muscle tissue. X-ray analysis of the bones and skeletal muscles of the pelvis and thighs of workers chronically exposed to barium carbonate dust revealed no apparent build up of insoluble barium in these tissues (Essing et al. 1976). No studies were located regarding musculoskeletal effects in animals after inhalation exposure to barium.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to barium. Impaired detoxifying function of the liver was noted in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). No other details were reported.

Renal Effects. Renal failure occurred in a 22-year-old worker accidentally exposed by acute inhalation to barium carbonate powder (Shankle and Keane 1988). No studies were located regarding renal effects in animals after inhalation exposure to barium.

Body Weight Effects. A 21% decrease in body weight gain was observed in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust for 4 months (Tarasenko et al. 1977).

Metabolic Effects. Decreases in plasma potassium concentrations were observed in two groups of welders using barium-containing electrodes; the barium levels in the work environment were 4.4 and 0.3 mg/m^3 (Zschiesche et al. 1992). However, this was not observed in a third group of welders exposed to 2.0 mg barium/m^3. A low serum potassium level was also observed in a worker accidentally exposed to barium carbonate powder (Shankle and Keane 1988). Additionally, the plasma potassium concentrations were not statistically different from levels measured prior to barium exposure. Tarasenko et al. (1977) reported a decrease in urinary calcium levels and increased blood phosphorus levels in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust for an intermediate duration (Tarasenko et al. 1977). This study also reported a decrease in blood glucose levels in barium-exposed rats.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to barium.

3.2.1.4 Neurological Effects

Absence of deep tendon reflexes was observed in a 22-year-old man accidentally exposed by acute inhalation to barium carbonate powder (Shankle and Keane 1988); as noted previously, this is probably due to the barium-induced low potassium levels. No studies were located regarding neurological effects in animals after inhalation exposure to barium.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to barium. Only one limited report was available regarding reproductive effects in animals following intermediate inhalation exposure to barium carbonate (Tarasenko et al. 1977). Disturbances in spermatogenesis, including decreased number of sperm, decreased percentage of motile sperm, and decreased osmotic

resistance of sperm, were reportedly observed in male rats exposed by inhalation for one cycle of spermatogenesis to 15.8 mg barium/m^3 as barium carbonate dust. The testicles of these treated rats reportedly had an increase in the number of ducts with desquamated epithelium and a reduced number of ducts with 12^{th}-stage meiosis. The condition of the testicles of treated rats returned to normal 30 days after cessation of barium carbonate treatment (Tarasenko et al. 1977). Similar observations were noted in a second experiment in which male rats were exposed by inhalation for an intermediate period to 3.6 mg barium/m^3 as barium carbonate dust. In a third experiment by the same authors, female rats exposed by inhalation for an intermediate period to 2.2 or 9.4 mg barium/m^3 as barium carbonate dust reportedly developed a shortened estrous cycle and alterations in the morphological structure of the ovaries.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to barium. Only one limited report was available regarding developmental effects in animals after intermediate inhalation exposure to barium (Tarasenko et al. 1977). Reduced survival, underdevelopment, lowered weight gain, and various hematologic alterations (erythropenia, leukocytosis, eosinophilia, neutrophilia) were reported in the offspring of female rats exposed by inhalation for an intermediate period to 2.2 or 9.4 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). No other significant details regarding this developmental study were reported.

3.2.1.7 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to barium.

3.2.2 Oral Exposure

The majority of studies evaluating the health effects of barium are oral exposure studies. The available oral studies include numerous case reports of humans exposed orally to barium through accidental or intentional ingestion, several epidemiological and statistical investigations of humans exposed to drinking water containing barium, and various experimental animal studies involving acute, intermediate, or chronic exposure to barium either by gavage or by drinking water. Findings from the various oral studies are summarized below.

3.2.2.1 Death

Death has been reported in a number of case reports of accidental or intentional ingestion of barium salts. The cause of death was attributed to cardiac arrest, severe gastrointestinal hemorrhage, or unknown causes (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Jourdan et al. 2001; McNally 1925; Ogen et al. 1967; Talwar and Sharma 1979). Doses in these cases were not known.

In addition to case reports of death in humans, several studies have examined mortality rates in residents living in communities with elevated barium levels in the drinking water (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). Two studies found no statistical correlations between barium concentrations in drinking water and total mortality and/or cardiovascular mortality rates in exposed populations (Elwood et al. 1974; Schroeder and Kraemer 1974). Interpretation of the study results are limited by the lack of information on exposure conditions (dose, duration, frequency) and the number of people exposed. Results of a third study indicated that relative to communities with little or no barium in drinking water, communities with elevated concentrations of barium in their drinking water had significantly higher mortality rates for all causes, heart disease, arteriosclerosis, and all cardiovascular disease (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981). This epidemiological study had a number of confounding variables, including possible use in the study population of home water softeners that would remove barium from the drinking water, inclusion of communities that had significant changes in population, lack of a way to control for length of time an individual lived in a community, and widely varying concentrations of other contaminants (calcium, sodium, magnesium) in the drinking water.

The LD_{50} values for barium chloride in rats range from 132 to 277 mg barium/kg (Borzelleca et al. 1988; Tardiff et al. 1980). Significant increases in mortality were observed in rats and mice exposed to 200 or 450 mg barium/kg/day as barium chloride in drinking water for 90 days (NTP 1994). Survival was not affected at 110 or 205 mg barium/kg/day in the rats or mice, respectively. No changes in mortality were observed in rats chronically exposed to doses as high as 60 mg barium/kg/day as barium chloride in the drinking water (NTP 1994). An increase in mortality, attributable to nephropathy, was observed in mice chronically exposed to 160 mg barium/kg/day as barium chloride in drinking water (NTP 1994); the number of deaths was similar to controls in mice exposed to 75 mg barium/kg/day. In male mice exposed to 0.95 mg barium/kg/day as barium acetate in drinking water, a significant decrease in longevity (defined as average lifespan of the last five surviving animals) was observed; however, no significant differences in mean lifespan were observed (Schroeder and Mitchener 1975b). Similarly, lifespan was not

significantly altered in female mice exposed to 0.95 mg barium/kg/day (Schroeder and Mitchener 1975b) or male or female rats exposed to 0.7 mg barium/kg/day as barium acetate in drinking water (Schroeder and Mitchener 1975a).

LD_{50} values and reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Limited data are available regarding respiratory effects in animals following oral barium exposure. Fluid in the trachea was observed in rats receiving a single gavage dose of 198 mg barium/kg as barium chloride (Borzelleca et al. 1988). However, this effect was not observed when rats were dosed with 198 mg barium/kg/day as barium chloride for 10 days (Borzelleca et al. 1988). No significant alterations in lung weights, gross lesions, or histopathological alterations were observed in the respiratory tracts of rats and mice exposed to doses as high as 110 or 70 mg barium/kg/day, 180 or 450 mg barium/kg/day, or 60 and 160 mg barium/kg/day for intermediate or chronic durations, respectively (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980) or lifetime exposure to 0.7 or 0.95 mg barium/kg/day, respectively, as barium acetate via drinking water (Schroeder and Mitchener 1975a).

Cardiovascular Effects. As demonstrated in numerous case reports, acute exposure to presumably high doses of barium carbonate, barium sulfate, or barium chloride can result in serious effects on heart rhythm. Barium adversely affects cardiac automaticity resulting in ventricular tachycardia and other disruptions of rhythm (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Silva 2003; Talwar and Sharma 1979; Wetherill et al. 1981). Hypotension has also been reported in some cases (Koch et al. 2003; Talwar and Sharma 1979). The likely cause of these effects was barium-induced hypokalemia.

Several human studies have investigated a possible association between exposure to low levels of barium and alterations in blood pressure and cardiac rhythms. In a small-scale (11 subjects) study of individuals exposed to 0.1 or 0.2 mg barium/kg/day as barium chloride in drinking water for 4 weeks, no significant alterations in blood pressure or ECG readings were found (Wones et al. 1990). There was no significant

Table 3-1 Levels of Significant Exposure to Barium - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (GW)				198 (death in 15/20 rats)	Borzelleca et al. 1988 Barium chloride	
2	Rat (Sprague-Dawley)	once (GW)				269 F (LD50 in females)	Borzelleca et al. 1988 Barium chloride	
3	Rat (NS)	once (GW)				132 (LD50 adult) 220 (LD50 weanling)	Tardiff et al. 1980 Barium chloride	
Systemic								
4	Rat (Sprague-Dawley)	10 d 1 x/d (GW)	Resp	198			Borzelleca et al. 1988 Barium chloride	
			Cardio	198				
			Gastro	198				
			Hemato	198				
			Hepatic	198				
			Renal	198				
			Ocular	198				
			Bd Wt	198				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
5	Rat (Sprague-Dawley)	once (GW)	Resp	66	198 (fluid in trachea)		Borzelleca et al. 1988 Barium chloride	
			Cardio	198				
			Gastro	66	198 (inflammation of small and large intestine)			
			Hemato	198				
			Hepatic	66	198 (decreased liver/brain weight ratio; darkened liver)			
			Renal	66	198 (increased kidney/body weight ratio)			
			Ocular	66	198 (ocular discharge)			
			Bd Wt	66	198 (decreased body weight)			
			Other	198				
Immuno/ Lymphoret								
6	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		198			Borzelleca et al. 1988 Barium chloride	Evaluated weight and occurrence of gross lesions in thymus.
Neurological								
7	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		198			Borzelleca et al. 1988 Barium chloride	

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
8	Rat (Sprague-Dawley)	once (GW)		198			Borzelleca et al. 1988 Barium chloride	Evaluated testes and ovary weights.
9	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		138 F	198 F (decreased ovary weight and ovaries/brain ratio)		Borzelleca et al. 1988 Barium chloride	Evaluated testes and ovary weights.
INTERMEDIATE EXPOSURE								
Death								
10	Rat (Fischer- 344)	90 d (W)				200 M (30% mortality)	NTP 1994 Barium chloride	
11	Mouse (B6C3F1)	90 d (W)				450 M (60% mortality)	NTP 1994 Barium chloride	
Systemic								
12	Human (NS)	4 wk 7 d/wk (W)	Cardio	0.2 M			Wones et al. 1990 Barium chloride	
13	Rat (Dahl)	16 wk (W)	Cardio	150			McCauley et al. 1985 NR	Study used salt resistant and salt sensitive rat strains.
			Renal	15	150 (fused podocytes and thickening of the capillary basement membrane in glomeruli)			

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Rat (Sprague-Dawley)	16 wk (W)	Cardio	150			McCauley et al. 1985 NR	Study used uninephrecomized rats.
			Renal	15	150 (fused podocytes and thickening of the capillary basement membrane in glomeruli)			
15	Rat (Sprague-Dawley)	36 wk (W)	Resp	37.5 M			McCauley et al. 1985 NR	
			Cardio	37.5 M				
			Gastro	37.5 M				
			Musc/skel	37.5 M				
			Hepatic	37.5 M				
			Renal	37.5 M				
			Ocular	37.5 M				
			Bd Wt	37.5 M				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Rat (Sprague-Dawley)	46 wk (W)	Resp	37.5 F			McCauley et al. 1985 NR	
			Cardio	37.5 F				
			Gastro	37.5 F				
			Musc/skel	37.5 F				
			Hepatic	37.5 F				
			Renal	37.5 F				
			Ocular	37.5 F				
			Bd Wt	37.5 F				
17	Rat (Fischer- 344)	15 d (W)	Resp	110			NTP 1994 Barium chloride	
			Cardio	110				
			Gastro	110				
			Hemato	110				
			Hepatic	110				
			Renal	110				
			Bd Wt	110				
			Metab	110				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Rat (Fischer- 344)	90 d (W)	Resp	180 F			NTP 1994 Barium chloride	
			Cardio	180 F				
			Gastro	180 F				
			Hemato	180 F				
			Musc/skel	180 F				
			Hepatic	180 F				
			Renal	65[b] F	180 F (dilatation of proximal renal cortex)			
					115 F (increased kidney weight)			
			Ocular	180 F				
			Bd Wt	110 M	200 M (13% lower final body weight)			
			Metab	180 F				
19	Rat (Long- Evans)	1 mo 7 d/wk (W)	Cardio	1 F	8.6 F (increased blood pressure)		Perry et al. 1983, 1985, 1989 Barium chloride	Animals were fed a low mineral diet.
20	Rat (Long- Evans)	4 mo 7 d/wk (W)	Cardio	1.2 F	11 F (increased blood pressure)		Perry et al. 1983, 1985, 1989 Barium chloride	Animals were fed a low mineral diet.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Rat Charles-River	13 wk 7 d/wk (W)	Resp	35			Tardiff et al. 1980 Barium chloride	
			Cardio	35				
			Hemato	35				
			Musc/skel	35				
			Hepatic	35				
			Renal	35				
			Bd Wt	35				
22	Mouse (B6C3F1)	90 d (W)	Resp	450 M			NTP 1994 Barium chloride	
			Cardio	450 M				
			Gastro	450 M				
			Hemato	450 M				
			Musc/skel	450 M				
			Hepatic	450 M				
			Renal	205 M		450 M (nephropathy)		
			Ocular	450 M				
			Bd Wt	205 M		450 M (30% lower final body weight)		
			Metab	450 M				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
23	Mouse (B6C3F1)	15 d (W)	Resp	70 M			NTP 1994 Barium chloride	
			Cardio	70 M				
			Gastro	70 M				
			Hemato	70 M				
			Hepatic	70 M				
			Renal	70 M				
			Bd Wt	70 M				
			Metab	70 M				
Immuno/ Lymphoret								
24	Rat (Sprague-Dawley)	36 wk (W)		37.5 M			McCauley et al. 1985 NR	Histological examination of thymus and lymph nodes.
25	Rat (Sprague-Dawley)	46 wk (W)		37.5 F			McCauley et al. 1985 NR	Histological examination of thymus and lymph nodes.
26	Rat (Fischer- 344)	90 d (W)		180 F			NTP 1994 Barium chloride	Histological examination of spleen and thymus.
27	Mouse (B6C3F1)	90 d (W)		205 M	450 M (thymic and splenic atrophy)		NTP 1994 Barium chloride	Histological examination of spleen and thymus.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
28	Rat (Sprague-Dawley)	36 wk (W)		37.5 M			McCauley et al. 1985 NR	Histological examination of brain.
29	Rat (Sprague-Dawley)	46 wk (W)		37.5 F			McCauley et al. 1985 NR	Histological examination of brain.
30	Rat (Fischer- 344)	90 d (W)		115 F	180 F (decreased spontaneous motor activity)		NTP 1994 Barium chloride	
31	Rat (Fischer- 344)	15 d (W)		110			NTP 1994 Barium chloride	
32	Rat Charles-River	13 wk 7 d/wk (W)		35			Tardiff et al. 1980 Barium chloride	Histological examination of brain.
33	Mouse (B6C3F1)	90 d (W)		200 F	495 F (decreased forelimb grip strength)		NTP 1994 Barium chloride	
34	Mouse (B6C3F1)	15 d (W)		70 M			NTP 1994 Barium chloride	
Reproductive								
35	Rat (Fischer- 344)	M: 60 d F: 30 d (W)		200 M 180[c] F			Dietz et al. 1992 Barium chloride	

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Rat (Sprague-Dawley)	36 wk (W)		37.5 M			McCauley et al. 1985 NR	Histological examination of reproductive tissues.
37	Rat (Sprague-Dawley)	46 wk (W)		37.5 F			McCauley et al. 1985 NR	Histological examination of reproductive tissues.
38	Rat (Fischer- 344)	90 d (W)		200 M 180[c] F			NTP 1994 Barium chloride	Histological examination of reproductive tissues.
39	Rat (Fischer- 344)	15 d (W)		110			NTP 1994 Barium chloride	
40	Mouse (B6C3F1)	M: 60 d F: 30 d (W)		205 M 200[c] F			Dietz et al. 1992 Barium chloride	
41	Mouse (B6C3F1)	90 d (W)		450[c] M 495 F			NTP 1994 Barium chloride	Histological examination of reproductive tisses.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
42	Mouse (B6C3F1)	15 d (W)		70[c] M 85 F			NTP 1994 Barium chloride	
Developmental								
43	Rat (Fischer- 344)	M: 60 d F: 30 d (W)		115 F	180 F (decreased pup body weight and nonsignificant decrease in litter size)		Dietz et al. 1992 Barium chloride	
44	Mouse (B6C3F1)	M: 60 d F: 30 d (W)		200 F			Dietz et al. 1992 Barium chloride	
CHRONIC EXPOSURE								
Death								
45	Mouse (B6C3F1)	2 yr (W)				160 M (increased mortality)	NTP 1994 Barium chloride	
Systemic								
46	Rat (Sprague-Dawley)	68 wk (W)	Resp	15 M			McCauley et al. 1985 NR	
			Cardio	15 M				
			Gastro	15 M				
			Musc/skel	15 M				
			Hepatic	15 M				
			Renal	15 M				
			Ocular	15 M				
			Bd Wt	15 M				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
47	Rat (Fischer- 344)	2 yr (W)	Resp	60 M			NTP 1994 Barium chloride	
			Cardio	60 M				
			Gastro	60 M				
			Hemato	60 M				
			Musc/skel	60 M				
			Hepatic	60 M				
			Renal	60 M				
			Ocular	60 M				
			Bd Wt	60 M				
			Metab	60 M				
48	Rat (Long- Evans)	16 mo 7 d/wk (W)	Cardio	0.17 F	0.8 F (increased blood pressure)		Perry et al. 1983, 1985, 1989 Barium chloride	Animals were fed a low mineral diet.
					7.2 F (depressed rates of cardiac contraction and electrical conductivity)			

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
49	Mouse (B6C3F1)	2 yr (W)	Resp	160 M			NTP 1994 Barium chloride	
			Cardio	160 M				
			Gastro	160 M				
			Hemato	160 M				
			Musc/skel	160 M				
			Hepatic	160 M				
			Renal	75 M[d]		160 M (marked nephropathy)		
			Ocular	160 M				
			Bd Wt	75 M		160 M (weight loss)		
Immuno/ Lymphoret								
50	Rat (Sprague-Dawley)	68 wk (W)		15 M			McCauley et al. 1985 NR	Histological examination of thymus and lymph nodes.
51	Rat (Fischer- 344)	2 yr (W)		60 M			NTP 1994 Barium chloride	Histological examination of spleen and thymus.
52	Mouse (B6C3F1)	2 yr (W)		75 M	160 M (lymphoid depletion in the spleen and decreased relative and absolute spleen weight)		NTP 1994 Barium chloride	Histological examination of thymus and spleen.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
53	Rat (Sprague-Dawley)	68 wk (W)		15 M			McCauley et al. 1985 NR	Histological examination of brain.
54	Rat (Fischer- 344)	2 yr (W)		60 M			NTP 1994 Barium chloride	Histological examination of brain.
55	Mouse (B6C3F1)	2 yr (W)		160 M			NTP 1994 Barium chloride	Histological examination of brain.
Reproductive								
56	Rat (Sprague-Dawley)	68 wk (W)		15 M			McCauley et al. 1985 NR	Histological examination of reproductive tissues.
57	Rat (Fischer- 344)	2 yr (W)		60[c] M 75 F			NTP 1994 Barium chloride	Histological examination of reproductive tissues.
58	Mouse (B6C3F1)	2 yr (W)		160[c] M 200 F			NTP 1994 Barium chloride	Histological examination of reproductive tissues.

a The number corresponds to entries in Figure 3-1.

b Used to derive an intermediate duration oral minimal risk level (MRL) of 0.2 mg barium/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) and modifying factor of 3 to account for database deficiencies.

c Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

d The chronic-duration oral MRL of 0.2 mg barium/kg/day was calculated using benchmark dose analysis. The BMDL5 of 61 mg barium/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability) and modifying factor of 3 to account for database deficiencies.

Cardio = cardiovascular; d = day; F = female; Gastro = gastrointestinal; (GW) = gavage in water; Hemato = hematological; LD50 = lethal dose, 50% kill; M = male; mo = month; Musc/skel = musculoskeletal; NS = not specified; NR = not reported; Resp = respiratory; (W) = drinking water; wk = week; x = time(s); yr = year

Figure 3-1 Levels of Significant Exposure to Barium - Oral

Acute (≤14 days)

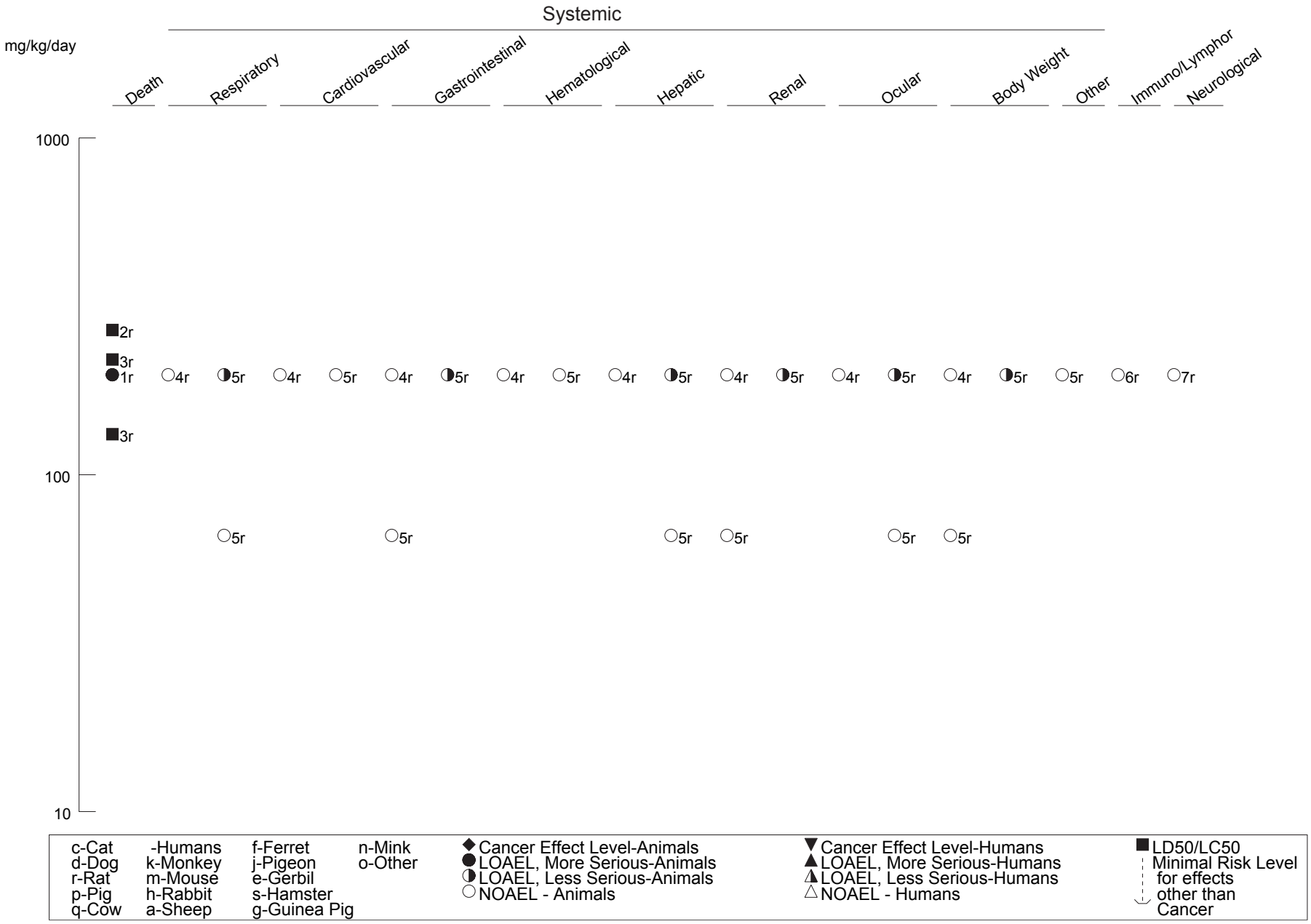


Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Acute (≤14 days)

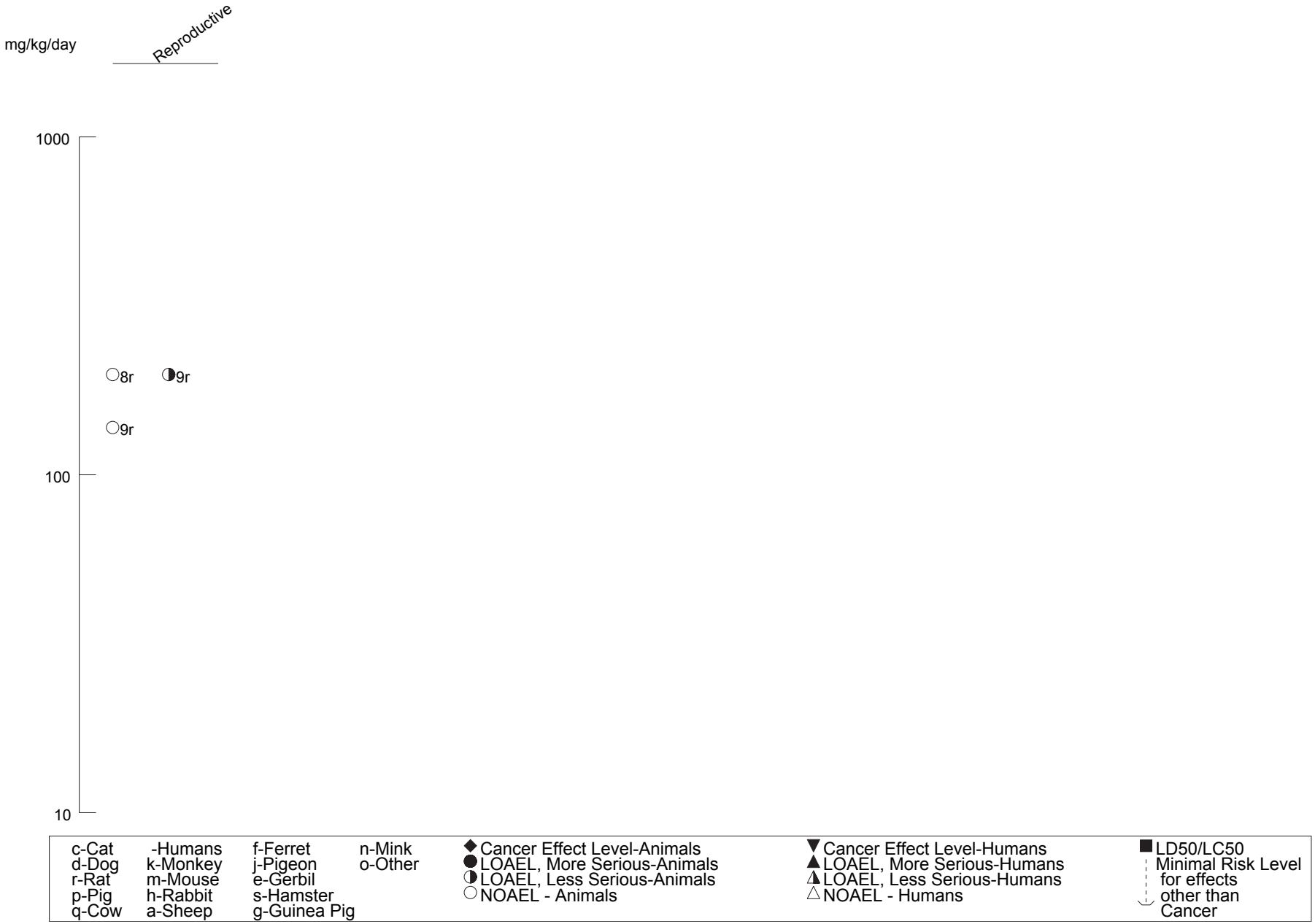


Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Intermediate (15-364 days)

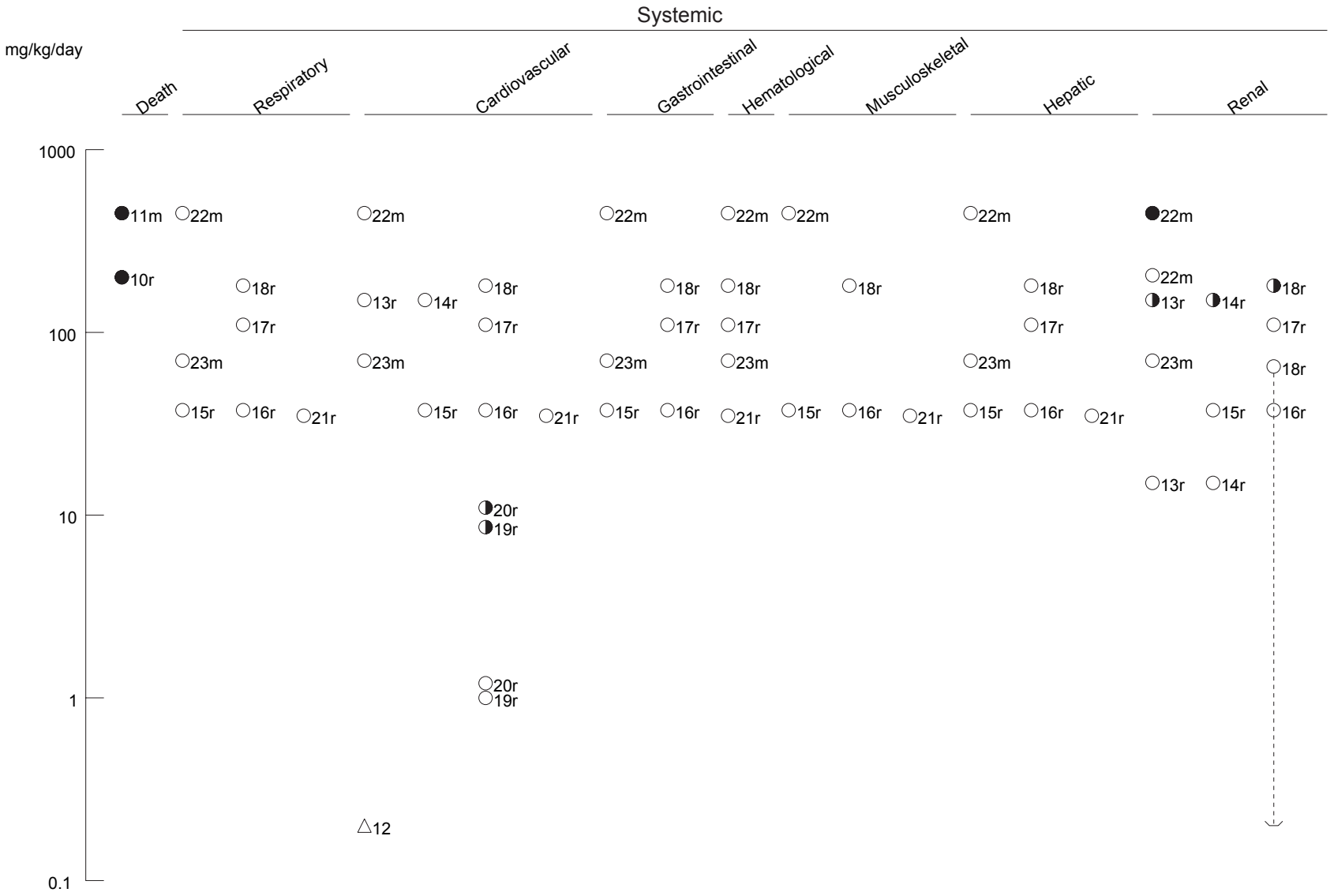


Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Intermediate (15-364 days)

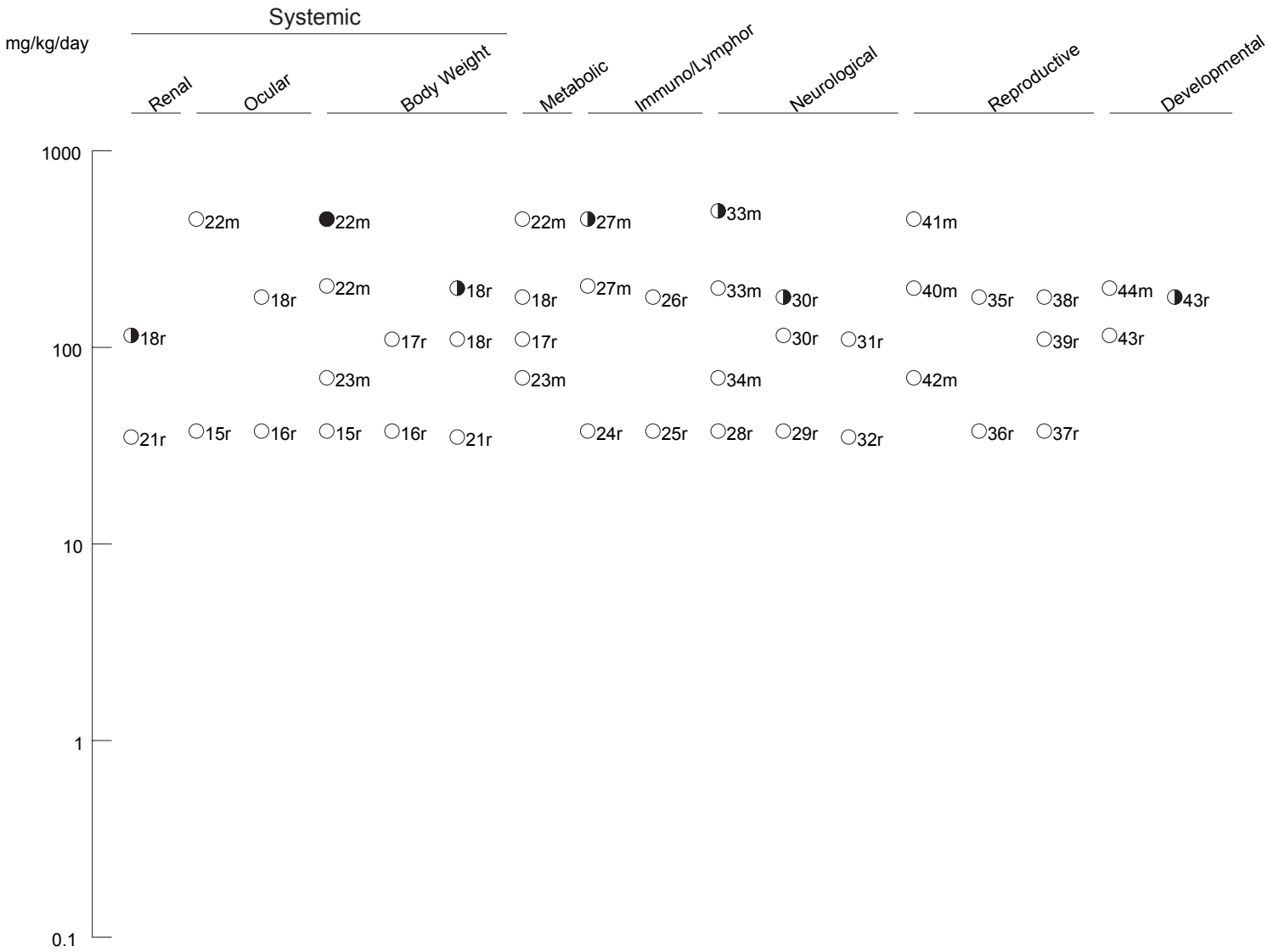
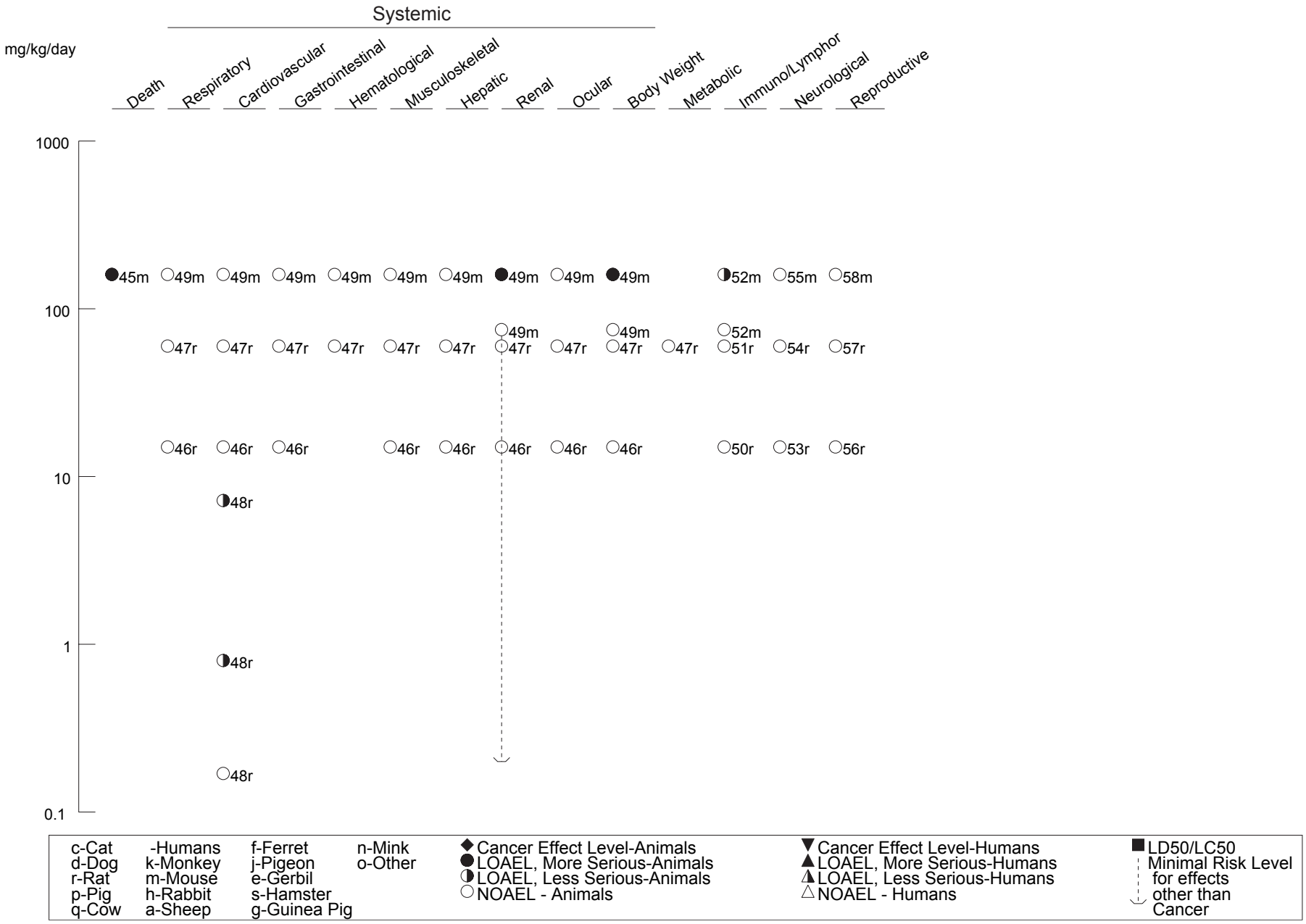


Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Chronic (≥365 days)



alteration in blood pressure measurements or alterations in hypertension, heart disease, or stroke among residents of two communities with elevated (0.2 mg barium/kg/day) or low (0.003 mg barium/kg/day) levels of barium in drinking water (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981). Interpretation of this study is limited by the lack of information on tap water consumption, and the fact that blood pressure was measured 3 times in a single 20-minute period and not repeatedly over a longer period, and the incidence of hypertension, stroke, and heart disease was taken from subject-completed questionnaires and not confirmed by testing or examination of medical records. Brenniman and associates (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981) also conducted a mortality study of residents living in communities with elevated or low barium levels in drinking water. Significantly higher mortality rates for cardiovascular disease and heart disease (arteriosclerosis) were found in the elevated barium communities (0.06–0.3 mg barium/kg/day) than in the low barium communities (0.006 mg barium/kg/day). The largest difference between the groups was in individuals 65 years of age and older. These results should be interpreted cautiously because the study did not control for a number of potential confounding variables such as the use of water softeners, which would reduce the amount of barium and increase sodium levels, duration of exposure, or actual barium intakes.

Several animal studies have examined potential cardiovascular end points following acute-, intermediate-, or chronic-duration exposures. No histological alterations have been observed in the hearts of rats and mice exposed to barium chloride, barium acetate, or an unspecified barium compound for intermediate or chronic durations (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a; Tardiff et al. 1980). Significant increases in systolic blood pressure were observed in rats exposed to 8.6 or 11 mg barium/kg/day for 1 or 4 months, respectively; no effect levels were 1.0 and 1.2 mg barium/kg/day (Perry et al. 1983, 1985, 1989). When the duration of exposure was longer (8–16 months), the LOAEL for increased blood pressure was 0.80 mg barium/kg/day and the NOAEL was 0.17 mg barium/kg/day (Perry et al. 1983, 1985, 1989). Depressed rates of cardiac contraction and cardiac conductivity and decreased cardiac ATP levels were observed in another group of rats exposed to 7.2 mg barium/kg/day. In contrast to the findings in the Perry study (1983, 1985, 1989), no significant alterations in blood pressure were observed in rats exposed to up to 150 mg barium/kg/day in drinking water for 16 weeks (McCauley et al. 1985); it should be noted that the McCauley et al. (1985) studies were conducted in uninephrectomized rats or Dahl salt-sensitive and salt-resistant rats. NTP (1994) also found no significant alterations in blood pressure, heart rate, or ECG readings in rats exposed to 180 mg barium/kg/day for 45 or 90 days. The low metal diet used in the Perry et al. (1983, 1985, 1989) study may have influenced the study outcome.

Gastrointestinal Effects. All cases of acute oral barium poisoning in adults exhibit gastrointestinal disturbances as the initial symptoms. These include gastric pain, vomiting, and diarrhea (Das and Singh 1970; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Silva 2003; Talwar and Sharma 1979; Wetherill et al. 1981). In one case, severe gastrointestinal hemorrhage occurred in an adult male victim (Diengott et al. 1964).

Although gastrointestinal effects have been observed in some animal studies, most studies have not found effects. Inflammation of the intestines was noted in rats receiving a single gavage dose of 198 mg barium/kg as barium chloride (Borzelleca et al. 1988); but not in rats administered 10 doses of 198 mg barium/kg/day (Borzelleca et al. 1988). Stomach rupture, bowel obstruction, and gastrointestinal hemorrhage have been observed in rats dosed with barium sulfate; however, those adverse effects were most likely due to the massive doses of barium sulfate used in the study (25–40% of body weight) and not necessarily to barium toxicity (Boyd and Abel 1966). A 15-day exposure of male and female rats and mice to 110 or 70 mg barium/kg/day as barium chloride in drinking water, respectively, did not result in histological alterations in the gastrointestinal tract (NTP 1994). No gross or microscopic lesions of the esophagus, stomach, pancreas, small intestines, or colon were noted in several intermediate and chronic experiments in which male and female rats were exposed to doses as high as 180 mg barium/kg/day as an unspecified barium compound or barium chloride in drinking water (McCauley et al. 1985; NTP 1994) or male and female mice exposed to doses as high as 450 mg barium/kg/day as barium chloride (NTP 1994).

Hematological Effects. Results of animal studies indicate that acute, intermediate, and chronic oral exposure to barium is not associated with any adverse hematological effects. No alterations were found in rats administered 198 mg barium/kg/day as barium chloride for 10 days (Borzelleca et al. 1988) or in rats or mice exposed to 110 or 70 mg/kg/day, respectively, as barium chloride in drinking water for 15 days (NTP 1994). Intermediate and chronic oral exposure of rats to barium acetate and barium chloride in drinking water has not been associated with any significant or treatment-related changes in a variety of hematological parameters (NTP 1994; Tardiff et al. 1980). Elemental barium doses in these intermediate and chronic drinking water studies ranged from 15 to 450 mg/kg/day.

Musculoskeletal Effects. The predominant musculoskeletal effect observed in cases of barium toxicity in humans is progressive muscle weakness, often leading to partial or total paralysis (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). In severe cases, the paralysis affects

the respiratory system (Das and Singh 1970; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). The likely cause of the muscle weakness was the barium-induced hypokalemia rather than a direct effect on muscles.

Very limited animal data are available regarding the musculoskeletal effects of barium following oral exposure. No gross and microscopic lesions were observed in skeletal system of several intermediate and chronic experiments in which rats were exposed to an unspecified barium compound or barium chloride in drinking water at doses as high as 180 mg barium/kg/day for intermediate duration and as high as 60 mg barium/kg/day for chronic duration (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980); similarly, no effects were observed in mice exposed to 450 or 160 mg barium/kg/day as barium chloride in drinking water for intermediate or chronic durations, respectively (NTP 1994).

Hepatic Effects. In one case study involving accidental acute ingestion of barium carbonate in an adult female, some degeneration of the liver was noted post-mortem (McNally 1925). Adverse hepatic effects in animals following oral barium exposure have been minor or have not been observed. Decreased liver/brain weight ratio and darkened liver were observed in rats administered a single gavage dose of 198 mg barium/kg as barium chloride; however, these changes were not associated with any microscopic hepatic lesions or alterations in serum enzymes (e.g., serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], alkaline phosphatase). No histological or liver weight alterations were observed in rats dosed with 198 mg barium/kg/day as barium chloride for 1 or 10 days (Borzelleca et al. 1988) or in rats and mice exposed to 110 or 70 mg barium/kg/day, respectively, as barium chloride in drinking water for 15 days (NTP 1994). Intermediate and chronic studies involving oral exposure of rats or mice to barium in drinking water did not find significant alterations in liver weight or liver histopathology following exposure to doses as high as 180 mg barium/kg/day for rats and 450 mg barium/kg/day for mice (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a, 1975b; Tardiff et al. 1980).

Renal Effects. Toxic effects on the kidneys have been observed in several adult cases of acute barium poisoning. Effects include hemoglobin in the urine (Gould et al. 1973) (which may be indicative of kidney damage), renal insufficiency (Lewi and Bar-Khayim 1964; Phelan et al. 1984), degeneration of the kidneys (McNally 1925), and acute renal failure (Wetherill et al. 1981).

Studies in animals suggest that the kidney is a critical target of barium toxicity. An increase in relative kidney weight (kidney/brain weight ratio) was observed in male and female rats receiving a single gavage

dose of 198 mg barium/kg/day as barium chloride in water (Borzelleca et al. 1988). Increases in relative kidney weight (kidney to brain weight ratio) were also observed in female rats receiving gavage doses of 66, 96, or 138 mg barium/kg/day as barium chloride in water for 10 days, but not at 198 mg barium/kg/day (Borzelleca et al. 1988). Significant reductions in blood urea nitrogen (BUN) were also observed in females exposed to 66–198 mg barium/kg/day and in males exposed to 198 mg barium/kg/day. The changes in BUN levels were not considered to be biologically significant because BUN levels are typically increased in response to kidney damage, the magnitude of change was slight (less than 15%), and there were no differences between the barium-exposed groups. The changes in relative kidney weights or BUN levels were not associated with gross or microscopic renal lesions. Studies of rats and mice did not find significant alterations in kidney weights or the incidence of renal lesions following a 15-day exposure to 110 or 70 mg barium/kg/day, respectively, as barium chloride in drinking water (NTP 1994).

Exposure of rats to doses as high as 65 mg barium/kg/day for an intermediate duration did not result in any alterations in kidney weight or the occurrence of histopathological lesions (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980). At 115 mg barium/kg/day, significant increases in absolute and relative kidney weights were observed in female rats (NTP 1994). Electron microscopy detected glomerular lesions consisting of fused podocyte processes and thickening of the capillary basement membrane in rats exposed to 150 mg barium/kg/day (McCauley et al. 1985). At slightly higher doses (180 mg barium/kg/day), minimal to mild dilatation of the proximal convoluted tubules of the outer medulla and renal cortex was observed in male and female rats (NTP 1994). In mice, nephropathy characterized by mild to moderate tubule dilatation, regeneration, and atrophy was observed in males and females exposed to 450 mg barium/kg/day as barium chloride, but not to 205 mg barium/kg/day (NTP 1994).

Three chronic-duration studies assessed the renal toxicity of barium. No adverse effects were observed in rats exposed via drinking water to 15 mg barium/kg/day of an unspecified barium compound for 68 weeks (McCauley et al. 1985), 60 mg barium/kg/day as barium chloride for 2 years (NTP 1994), or lifetime exposure to 0.7 mg barium/kg/day as barium acetate (Schroeder and Mitchener 1975a). In mice, exposure to 160–200 mg barium/kg/day resulted in moderate to marked nephropathy, characterized by extensive regeneration of cortical and medullary tubule epithelium, tubule dilatation, hyaline cast formation, interstitial fibrosis, and glomerulosclerosis (NTP 1994); at the next lowest dose tested (75 mg barium/kg/day), the incidence of nephropathy did not differ from controls. No kidney lesions were observed in mice following lifetime exposure to 0.95 mg barium/kg/day as barium acetate (Schroeder and Mitchener 1975b).

Dermal Effects. No studies were located regarding dermal effects in humans or animals after oral exposure to barium.

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to barium. In studies with Sprague-Dawley rats, ocular discharge following administration of a single gavage dose of 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988); this was not reported in rats dosed for 10 days (Borzelleca et al. 1988). A nonsignificant increase in retinal dystrophy was observed in rats following intermediate and chronic oral exposure to 12–37.5 mg barium/kg/day as an unspecified barium compound (McCauley et al. 1985). Although the retinal dystrophy was statistically insignificant, a dose-related trend was observed if different duration exposure groups were combined (McCauley et al. 1985). Both ocular discharge and retinal dystrophy are commonly observed in Sprague-Dawley rats; consequently, the ocular lesions noted in these animal studies cannot necessarily be attributed to oral barium exposure. Ocular lesions were not observed in F344 rats or B6C3F1 mice exposed to barium chloride in drinking water for 90 days or 2 years to doses as high as 180 mg barium/kg/day in rats and 450 mg barium/kg/day in mice (NTP 1994).

Body Weight Effects. Body weight has been monitored in a number of acute, intermediate, and chronic studies in which rats and mice were exposed orally to barium compounds (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a, 1975b; Tardiff et al. 1980). In general, body weight effects have only been observed at lethal doses. A decrease in body weight was observed in rats receiving a single gavage dose of 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988), in rats exposed to 200 mg barium/kg/day as barium chloride in drinking water for an intermediate duration (NTP 1994), and in mice exposed to 450 or 160 mg barium/kg/day as barium chloride in drinking water for intermediate and chronic durations, respectively (NTP 1994).

Metabolic Effects. Hypokalemia is a common finding in cases of severe barium poisoning (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). In a group of cases examined by Deng et al. (1991), serum potassium levels ranged from 0.8 to 2.7 mEq/L; normal values range from 3.5 to 5 mEq/L. Alterations in serum potassium levels have not been reported in rats exposed to 110 or 180 mg barium/kg/day as barium chloride in drinking water for 15 or 90 days,, respectively (NTP 1994).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to barium. Several animal studies have examined potential lymphoreticular effects, particularly damage to the thymus, spleen, and lymph nodes. Acute gavage exposure of rats to doses as high as 198 mg barium/kg/day as barium chloride for 1 or 10 days was not associated with any changes in thymus weight or any gross lesions of the thymus (Borzelleca et al. 1988). Intermediate and chronic oral exposure of rats to nominal concentrations of barium in drinking water of 37.5 and 15 mg/kg/day, respectively, of an unspecified barium compound was not associated with lesions of the lymph nodes or thymus upon gross and histopathologic examination (McCauley et al. 1985). No histopathological alterations were observed in the spleen or thymus of rats exposed to 180 or 60 mg barium/kg/day for an intermediate or chronic duration, respectively (NTP 1994). In mice, thymic and splenic atrophy were observed at 450 mg barium/kg/day after intermediate exposure and lymphoid depletion in the spleen and decreased spleen weight were observed at 160 mg barium/kg/day after chronic exposure (NTP 1994). These effects were probably secondary to the severe nephropathy and weight loss observed at these doses.

No studies have assessed the potential of barium to impair immune function.

The highest NOAEL values for lymphoreticular effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.4 Neurological Effects

Numbness and tingling around the mouth and neck were sometimes among the first symptoms of barium toxicity in humans (Lewi and Bar-Khayim 1964; Morton 1945). Occasionally, these neurological symptoms extended to the extremities (Das and Singh 1970; Lewi and Bar-Khayim 1964). Partial and complete paralysis occurred in severe cases, often accompanied by an absence of deep tendon reflexes (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). Post-mortem examination in one case of poisoning by ingestion of barium sulfide revealed brain congestion and edema (McNally 1925).

Animal studies have not found significant alterations in brain weight or histopathology following acute gavage exposure of rats for 1 or 10 days to doses as high as 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988), intermediate oral exposure of rats to doses as high as 115 mg barium/kg/day in drinking water (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980), intermediate-duration exposure of

mice to doses less than 450 mg barium/kg/day as barium chloride in drinking water (NTP 1994), or chronic exposure of rats and mice to doses greater than 60 or 160 mg barium/kg/day as barium chloride in drinking water, respectively (NTP 1994). Neurobehavioral performance (spontaneous motor activity, grip strength, tail flick latency, startle response, hindlimb foot splay) was evaluated in rats and mice exposed to barium chloride for 15 or 90 days (NTP 1994). No alterations were observed in rats or mice following a 15-day exposure to 110 or 70 mg barium/kg/day. Slight decreases in motor activity were observed in rats exposed to 10–115 mg barium/kg/day for 90 days; these changes were not considered to be biologically significant. However, in female rats exposed to 180 mg barium/kg/day, spontaneous motor activity was 30% lower than controls; this difference was considered to be biologically significant. In mice, the only alteration noted was a decrease in forelimb grip strength in females exposed to 495 mg barium/kg/day for 90 days; the investigators noted that this may have been due to debilitation. The highest NOAEL values and reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to barium. However, limited data are available from acute, intermediate, and chronic animal studies in which certain reproductive organs were weighed and examined grossly and microscopically following oral barium exposure. Gavage exposure of rats to doses of 198 mg barium/kg/day as barium chloride for 10 days resulted in decreased ovary weight and decreased ovary/brain weight ratio (Borzelleca et al. 1988); no alterations were observed after a single gavage dose with 198 mg barium/kg/day (Borzelleca et al. 1988). Neither study found changes in testicular weight, and no gross lesions of the ovaries or testes were observed at this dose. No histological alterations were observed in the reproductive tissues of male and female rats and mice exposed to 110 mg barium/kg/day (rats) or 70/85 mg barium/kg/day (mice) as barium chloride in drinking water (NTP 1994). Intermediate and chronic oral exposure of rats to barium in drinking water at doses of 200 mg barium/kg/day and lower was not associated with any gross or histopathologic lesions of the uterus, ovaries, or testes (Dietz et al. 1992; McCauley et al. 1985; NTP 1994). Similarly, no histopathological alterations were observed in reproductive tissues of mice exposed to 495 mg barium/kg/day and lower for an intermediate duration (NTP 1994) or 160 mg barium/kg/day or lower for a chronic duration (NTP 1994). Additionally, no alterations in epididymal sperm counts, sperm motility, or sperm morphology were observed in rats or mice exposed to 200 or 205 mg barium/kg/day, respectively, as barium chloride in drinking water for 60 days (Dietz et al. 1992).

There are limited data on the potential of barium to impair reproductive function. No significant alterations in pregnancy rate or gestation length were observed in rats or mice exposed to approximately 200 mg barium/kg/day as barium chloride in drinking water (Dietz et al. 1992); the males were exposed for 60 days prior to mating and the females were exposed for 30 days.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

Studies regarding developmental effects of barium following oral exposure are limited to one human study (Morton et al. 1976) and three animal studies (Dietz et al. 1992; Tarasenko et al. 1977). A statistically significant negative correlation was found between barium concentrations in drinking water and human congenital malformation rates of the central nervous system in South Wales (Morton et al. 1976). A negative correlation implies that as the barium concentration in drinking water increased, the rate of central nervous system malformations decreased. This statistical study is of limited value in identifying a NOAEL for developmental effects because exposure conditions (duration and frequency of exposure, dose, number of subjects exposed) were not characterized.

Developmental effects were reported in a study in which an unspecified animal species was orally administered a dose of barium carbonate that was equal to 1/16 of the LD_{50} for 24 days prior to conception and pregnancy (Tarasenko et al. 1977). Reported effects in offspring included increased mortality during the first 2 months, increased leukocyte count, disturbances in liver function, and increased urinary excretion of hippuric acid. This study is inadequate for evaluating developmental effects of oral barium exposure because of major study limitations. These limitations include a general lack of information provided by the authors regarding experimental methods, exposure conditions, and test results, and no information as to the species and number of animals tested, the purity of the test material, the statistical methods used, and whether or not controls were used.

In studies by Dietz et al. (1992), male rats and mice were exposed to barium chloride in drinking water for 60 days and mated to females exposed to barium chloride for 30 days. In the rats, exposure to 180/200 mg barium/kg/day resulted in significant decreases in pup birth weights. Decreases in the live litter size at postnatal days 0 and 5 were also observed in the 180/200 mg barium/kg/day group, but the difference was not statistically significant; litter sizes were 9.0 and 9.3 pups in controls on days 0 and 5,

and 7.2 and 7.1 pups on days 0 and 5 in the 200 mg barium/kg/day group. No adverse developmental effects were observed in the mice (highest dose tested was 200 mg barium/kg/day).

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

No studies were located regarding cancer in humans after oral exposure to barium. Several animal studies evaluated the induction of tumors following chronic oral exposure to barium (NTP 1994; Schroeder and Mitchener 1975a, 1975b). In studies by Schroeder and Mitchener (1975a, 1975b), rats and mice were exposed to 0.7 and 0.95 mg barium/kg/day, respectively, as barium acetate in drinking water for lifetime. No differences in the incidence of tumors were noted between treated animals and vehicle controls in either study. These studies are inadequate for evaluating the carcinogenic potential of barium because insufficient numbers of animals were used for a carcinogenicity study, it was not determined whether or not a maximum tolerated dose was achieved, a complete histological examination was not performed, the purity of the test material was not specified, and only one exposure dose was used in each study. Studies conducted by the NTP (1994) are considered adequate for carcinogenicity assessment. In rats exposed to doses as high as 60–75 mg barium/kg/day as barium chloride in drinking water, significant negative trends for mononuclear cell leukemia, adrenal medulla pheochromocytoma, and mammary gland neoplasms were found. No significant increases in malignant tumors were observed. Similarly, no increases in malignant tumor incidences were observed in mice chronically exposed to doses up to 160–200 mg barium/kg/day as barium chloride in drinking water.

3.2.3 Dermal Exposure

Limited information is available regarding the health effects of barium following dermal exposure. Barium salts would be expected to have a local effect on skin surfaces and would not likely be absorbed systematically to any great extent. Available studies include a case report of an individual exposed dermally to molten barium chloride (Stewart and Hummel 1984), a skin irritation study evaluating barium carbonate in experimental animals (Tarasenko et al. 1977), and a skin-painting study in which mice were exposed dermally to a barium hydroxide extract of tobacco leaf (Van Duuren et al. 1968). No reliable information was available from any of these dermal studies to identify study NOAELs or LOAELs for barium. In the case report (Stewart and Hummel 1984), the dermal burns that developed in the individual

exposed to molten barium chloride may potentially have contributed to some of the reported health effects, which are described briefly in Section 3.2.3.2 (Systemic Effects).

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to barium.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals after dermal exposure to barium.

Cardiovascular Effects. An abnormal electrocardiogram was observed in a 62-year-old man burned by molten barium chloride (Stewart and Hummel 1984). No studies were located regarding cardiovascular effects in animals after dermal exposure to barium.

Gastrointestinal Effects. A 62-year-old man experienced vomiting after he was accidentally burned by molten barium chloride (Stewart and Hummel 1984). No studies were located regarding gastrointestinal effects in animals after dermal exposure to barium.

Dermal Effects. Molten barium chloride induced burns on the skin of a 62-year-old man who was accidentally exposed through an explosion. The dermal burns, however, were very probably due to the molten nature of the material and not necessarily to barium chloride (Stewart and Hummel 1984).

The dermal effects of barium carbonate were examined in a study with rats and rabbits (Tarasenko et al. 1977). When barium carbonate in lanolin was applied to the skin, ulcers developed. These dermal lesions reportedly disappeared within a month when dermal treatment was discontinued. Although these findings suggest that barium carbonate may be a dermal irritant, these particular investigations are inadequate for establishing the dermal effects of barium because of a number of significant study limitations. The authors provided few details regarding experimental methods and results, and no information as to the concentration of barium carbonate used, the number of animals used, and whether or not controls were used.

Ocular Effects. Information on the ocular toxicity of barium is limited to a study conducted by Tarasenko et al. (1977) in rats and rabbits. When barium carbonate powder was introduced into the

conjunctival sac, purulent discharge, conjunctivitis, and slight opacity of the cornea developed. As noted in the Dermal Effects section, interpretation of these results is limited by the poor reporting of study methods and results, lack of information on barium carbonate concentration, and whether controls were used.

Metabolic Effects. A 62-year-old victim accidentally exposed to molten barium chloride had a depressed plasma potassium level when admitted to the hospital (Stewart and Hummel 1984).

No studies were located regarding the following health effects in humans or animals after dermal exposure to barium:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding cancer in humans after dermal exposure to barium. Dysplasia of the cervical epithelium was reportedly induced in a woman who had a barium chloride solution applied to her cervix (Ayre 1966). The use of dimethyl sulfoxide in combination with the barium chloride solution reportedly enhanced the ability of barium chloride to induce dysplasia. Dysplasia can be regarded as a potential precancerous lesion. The significance of the observations reported in this study are difficult to assess, since only one subject was exposed and because there have been no reports of similar findings in other human or animal studies. Also, the vehicle used was not specified in this study.

No studies were located regarding cancer in animals after dermal exposure to barium. However, results of one skin-painting study with mice suggest that barium hydroxide extract derived from tobacco leaf may act as a tumor-promoting agent (Van Duuren et al. 1968); the purity of the barium hydroxide extract was not reported. In this study, mice were treated dermally for an unspecified period of time with either barium hydroxide extract alone, 7,12-dimethylbenz(a)anthracene (DMBA) alone (an initiating agent), or a combination of DMBA and barium hydroxide extract. After 1 year, none of the mice treated with barium hydroxide extract developed skin tumors. However, 3 out of 20 mice treated with DMBA alone and 7 out of 20 mice treated with a combination of both barium hydroxide extract and DMBA developed skin

papillomas and carcinomas. These results provide limited, but suggestive evidence that barium hydroxide extract of tobacco leaf acted as a tumor-promoting agent. However, it can not be determined whether or not this apparent positive tumorigenic response was due to barium hydroxide or some other component of the barium hydroxide tobacco leaf extract.

3.3 GENOTOXICITY

In vivo studies of barium genotoxicity are limited to a study in *Drosophila melanogaster*. In this study, positive results were found in the somatic mutation and recombination test when high levels of barium nitrate were used; the results were inconclusive at low barium nitrate levels (Yesilada 2001). *In vitro* studies were limited and summarized in Table 3-2. No significant alterations in gene mutation frequency were observed in *Salmonella typhimurium* (Monaco et al. 1990, 1991; NTP 1994) or *Escherichia coli* (Rossman et al. 1991). Similarly, barium chloride or barium nitrate did not result in deoxyribonucleic acid (DNA) damage in *Bacillus subtilis* (Kanematsu et al. 1980; Nishioka 1975). Tests of the fidelity of DNA synthesis using an avian myeloblastosis virus (AMV) DNA polymerase system showed that neither barium acetate nor barium chloride affect the accuracy of DNA replication (Sirover and Loeb 1976a, 1976b). However, studies with a DNA polymerase I system from *Micrococcus luteus*, demonstrated that concentrations of barium ion ≤0.1 mM stimulated DNA polymerase activity while concentrations greater than this inhibited polymerase activity (Korman et al. 1978). The significance of the inhibitory and stimulatory effects has not been determined. Results from an experiment designed to test the effect of barium chloride on sporulation frequency, recombination frequency, and meiotic failures in *Saccharomyces cerevisiae* demonstrated a definite inhibition of sporulation. Effects on recombination frequency and meiotic failures were ambiguous. Barium chloride may have caused a marginal increase in recombination frequency and information of diploid clones (Sora et al. 1986), but the data are inconclusive. In mammalian test systems, barium chloride did not increase the frequency of sister chromatid exchange or chromosome aberrations in Chinese hamster cells (NTP 1994). However, an increase in gene mutations was observed at the TK locus of L5178Y mouse lymphoma cells in the presence of metabolic activation, but not without metabolic activation (NTP 1994).

Table 3-2. Genotoxicity of Barium and Barium Compounds *In Vitro*

Species (test system)	End point	Results	Reference	Compound
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation frequency (with or without S9 activation)	–	Monaco et al. 1990, 1991; NTP 1994	Barium chloride
Escherichia coli WP2s(λ)	Gene mutation frequency	–	Rossman et al. 1991	Barium chloride
Bacillus subtilis	DNA damage (rec assay)	–	Kanematsu et al. 1980; Nishioka 1975	Barium chloride, barium nitrate
Eukaryotic organisms:				
Fungi				
Saccharomyces cerevesiae	Meiosis	–	Sora et al. 1986	Barium chloride
Avian myeloblastosis virus DNA polymerase	DNA synthesis	–	Sirover and Loeb 1976a, 1976b	Barium chloride, barium acetate
Mammalian cells:				
CHO cells	Sister chromatid exchange (with or without S9 activation)	–	NTP 1994	Barium chloride
CHO cells	Chromosome aberration (with or without S9 activation)	–	NTP 1994	Barium chloride
Mouse lymphoma cells	Gene mutation at TK locus With S9 activation Without S9 activation	 + –	NTP 1994	Barium chloride

– = negative result; + = positive result; CHO = Chinese hamster ovary

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding absorption of barium in humans following inhalation exposure. Several animal studies have investigated the absorption of barium chloride or barium sulfate following inhalation, intratracheal injection, or nasal deposition. The results of these studies suggest that the rate and extent of absorption of barium from the respiratory tract depend on the exposure level, how much barium reaches the alveolar spaces, the clearance rate from the upper respiratory tract, and the solubility of the particular form of barium that was administered. Approximately 50–75% of inhaled barium chloride or barium sulfate is absorbed from the respiratory tract (Cuddihy and Griffith 1972; Morrow et al. 1968); approximately 65% of the barium chloride deposited in the nose is absorbed (Cuddihy and Ozog 1973b). Most of the barium absorption occurs within the first 24 hours (Cuddihy and Griffith 1972; Cuddihy et al. 1974). Barium chloride appears to be more rapidly absorbed than barium sulfate (Cuddihy et al. 1974), although the differences in particle size (AMADs of 2.3 and 1.0 µm for barium chloride and barium sulfate, respectively) may have influenced the absorption rate. In contrast to the rapid absorption of barium following inhalation or nasal deposition, most of the barium sulfate that is injected directly into the trachea of rats can be taken up into the epithelium membranes and remains in these membranes for at least a few weeks (Gore and Patrick 1982; Takahashi and Patrick 1987), suggesting that clearance in the upper respiratory tract is more efficient than in the trachea. Following intratracheal injection, the clearance of barium sulfate from the lungs was independent of lung burden over the range of 23.3–2,330 µg (Cember et al. 1961); this is consistent with the lack of evidence of lung overload following intermediate-duration inhalation exposure to 37.5 or 75 mg/m^3 barium sulfate (MMAD 4.3 µm, σg 1.7) (Cullen et al. 2000). Species differences in the retention of intratracheally administered radiolabelled (^{133}Ba) barium sulfate have been found. The percentages of ^{133}Ba retained in the trachea 1 week after administration were 0.41, 0.145, 0.044, and 0.043% in rats, rabbits, dogs, and monkeys, respectively (Takahashi and Patrick 1987; Takahashi et al. 1993).

3.4.1.2 Oral Exposure

The absorption of barium from the gastrointestinal tract is compound dependent. Barium sulfate is extremely insoluble and very little, if any, ingested barium sulfate is absorbed. Acid-soluble barium compounds, such as barium chloride and barium carbonate, are absorbed through the gastrointestinal

tract, although the amount of barium absorbed is highly variable. Older human studies estimated that barium was poorly absorbed; approximately 1–15% of the ingested dose was estimated to be absorbed (Harrision et al. 1956; LeRoy et al. 1966; Schroeder et al. 1972; Tipton et al. 1969). A re-examination of the methods used in these studies found a number of flaws; Leggett (1992) estimated that barium absorption in these studies was approximately 3–60%. Studies in adult rats and dogs estimated fractional absorption at 7% (Cuddihy and Griffith 1972; Taylor et al. 1962). Several unpublished animal studies discussed by Leggett (1992) found absorption rates of 1–50%. Experiments in rats have shown that younger animals (22 days old or less) absorb about 10 times more barium chloride from the gastrointestinal tract (63–84%) than do older animals (about 7%) (Taylor et al. 1962). Absorption was higher in fasted adult rats (20%) as compared to fed rats (7%). The International Commission for Radiation Protection (ICRP) estimates that the gastrointestinal absorption of barium is 20% in adults, 30% for children aged 1–15 years, and 60% in infants (ICRP 1993).

3.4.1.3 Dermal Exposure

No studies were located regarding absorption of barium in humans after dermal exposure. One animal study showed that barium applied to the skin of piglets was found in the various layers of the skin (Shvydko et al. 1971). Barium is not expected to cross the intact skin because of the high polarity of the forms in which it is most commonly encountered.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Shortly after dogs were exposed to radiolabelled (^{140}Ba) barium chloride, elevated activity was found in the upper respiratory tract, stomach, and small intestine (30% of initial burden), lungs and tracheobronchial tissue (6%), and various internal organs (64%) (Cuddihy and Griffith 1972). One day post-exposure, 44% of the label was detected in the skeleton, 1% in blood, and 4% in muscle; 26% of the dose was excreted.

3.4.2.2 Oral Exposure

In humans, barium is predominantly found in bone; approximately 90% of the barium in the body was detected in the bone (Schroeder et al. 1972). Approximately 1–2% of the total body burden was found in muscle, adipose, skin, and connective tissue. This information is supported by a number of studies

(Bauer et al. 1957; Losee et al. 1974; Miller et al. 1985; Sowden 1958; Sowden and Stitch 1957; Sowden and Pirie 1958). Significant increases in the levels of barium in bone were found in rats administered barium chloride in the diet or barium as a component of Brazil nuts for 29 days (Stoewsand et al. 1988); this study did not examine other tissues. A study by McCauley and Washington (1983) in which rats were exposed to barium chloride and barium carbonate in drinking water found the following non-skeletal distribution (skeletal tissue was not examined in the study) 24 hours after ingestion: heart > eye > skeletal muscle > kidney > blood > liver.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of barium in humans or animals after dermal exposure.

3.4.2.4 Other Routes of Exposure

Human injection studies support the findings of the inhalation and oral exposure studies. Barium is rapidly cleared from the blood and distributed to bone (Bauer et al. 1957; Harrison et al. 1966, 1967; Newton et al. 1991). A long-term study of barium retention in humans injected with ^{133}Ba found that after the first couple of years, bone turnover was the most significant contributor to barium losses from the skeleton (Newton et al. 2001).

3.4.3 Metabolism

Barium is not metabolized in the body, but it may be transported or incorporated into complexes or tissues.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies have been located regarding excretion of barium following inhalation exposure in humans. Studies in animals demonstrate that the fecal excretion of barium exceeds urinary excretion (Cember et al. 1961; Cuddihy and Griffith 1972; Cuddihy et al. 1974). In dogs, 30% of the total barium excretion was accounted for by urine (Morrow et al. 1964).

3.4.4.2 Oral Exposure

A study of two humans ingesting a normal diet found that fecal excretion of barium was 2–3 times higher than urinary excretion over a 30-day period (Tipton et al. 1966). A 29-day rat study also demonstrated that the feces was the primary route of excretion following exposure to barium chloride in the diet or barium from brazil nuts (Stoewsand et al. 1988).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of barium in humans or animals after dermal exposure.

3.4.4.4 Other Routes of Exposure

Several human studies have examined the excretion of barium following parenteral administration. These studies confirm the findings of the inhalation or oral exposure studies that barium is primarily excreted in the feces. In a study, one subject receiving an intravenous injection of ^{133}Ba, 84% of the radiolabelled barium was excreted within the first 6 days, primarily in the feces (75% of total dose) (Harrison et al. 1967; Newton et al. 1977). The ratio of fecal to urinary barium excretion in six subjects injected with ^{133}Ba ranged from 6 to 15 for the first 2 weeks (Newton et al. 1991).

A study in rats (Edel et al. 1991) found that biliary excretion did not significantly contribute to the total amount of barium excreted in the feces, suggesting that other physiological routes were responsible for fecal barium. A study of rabbits administered an intravenous injection of radiolabelled barium also found that barium was primarily excreted in the feces. After the first day, fecal excretion was approximately twice as high as urinary excretion. The barium was primarily excreted in the first 5 days after exposure; after 9 days, approximately 50% of the dose was excreted (Liniecki 1971).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based

pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste

sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-2 shows a conceptualized representation of a PBPK model.

If PBPK models for barium exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No information on available PBPK models for barium has been identified.

3.5 MECHANISMS OF ACTION

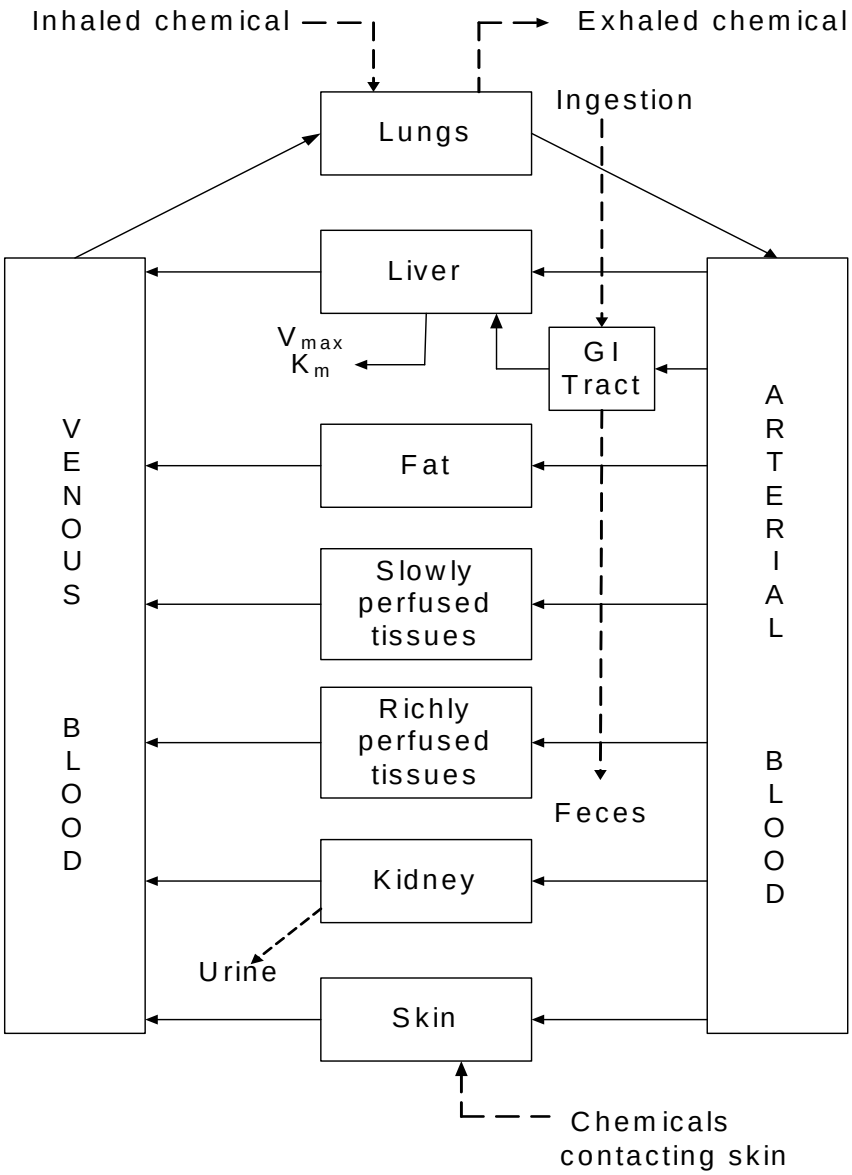
3.5.1 Pharmacokinetic Mechanisms

No studies were located for animals or humans that describe observed mechanisms for barium absorption across the skin, lung, or gut or barium distribution, metabolism, or excretion.

3.5.2 Mechanisms of Toxicity

The mechanism of barium toxicity has not been fully elucidated. Presumably, high-dose exposure to barium consistently results in a number of effects including ventricular tachycardia, hypertension and/or hypotension, and muscle weakness and paralysis (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Talwar and Sharma 1979; Wetherill et al. 1981). There is strong evidence that many of these effects result from increases in intracellular potassium levels. Barium is a competitive potassium channel antagonist that blocks the passive efflux of intracellular potassium, resulting in a shift of potassium from extracellular to intracellular compartments (Roza and Berman 1971). The intracellular translocation of potassium results in a decreased resting membrane potential, making the muscle fibers electrically unexcitable and causing paralysis (Koch et al. 2003). Hypokalemia (serum potassium levels below 3.5 mEq/L) has been reported in a number of individuals exposed to high doses of barium (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). Intravenous infusion of potassium often relieves many of the symptoms of barium toxicity (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988). However, there is also evidence that some of these effects may be due to barium-induced neuromuscular blockade and membrane depolarization (Phelan et al. 1984; Thomas et al. 1998). Two investigators (Phelan et al. 1984; Thomas et al. 1998) have shown an apparent direct relationship

Figure 3-2. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

between serum barium levels and the degree of paralysis or muscle weakness in two individuals orally exposed to barium.

3.5.3 Animal-to-Human Extrapolations

Most of the available data in humans comes from case reports involving acute oral exposure to presumably high doses of barium; the primary effects noted were gastrointestinal distress and effects associated with hypokalemia (e.g., ventricular tachycardia, hypo or hypertension, paralysis). Only one human exposure study (Wones et al. 1990) provided reliable information on exposure level; this study did not find any significant alterations in blood pressure in subjects exposed to relatively low doses of barium. The available data in laboratory animals suggest that toxicity of ingested barium is similar across species. Studies conducted by the NTP (1994) in rats and mice found similar targets of toxicity; although some differences in sensitivity were found between the species. Following intermediate-duration exposure, renal effects were observed at lower doses in rats (115 mg barium/kg/day) than in mice (450 mg barium/kg/day). However, NTP (1994) concluded that rats and mice were equally sensitive to the barium-induced renal effects because adverse effect levels when estimated on a per unit surface area basis were similar for the two species. In the absence of contrary data, it is assumed that humans and animals would have similar targets of toxicity and equal sensitivity.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active

chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in human and/or animals after exposure to barium; additionally, *in vitro* studies were not located.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage

may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There is limited information on age-related differences in the toxicity of barium in humans or animals. Deng et al. (1991) and Lewi and Bar-Khayim (1964) reported cases from two food poisoning incidents that involved exposure of adults and children. Both reports noted that children did not seem to be affected by the barium carbonate exposure; however, these data should be interpreted cautiously because neither involved examination of exposed children and no information is available on barium carbonate intake. There are limited data on the developmental toxicity of barium in laboratory animals. The body weights of the offspring of rats exposed to barium chloride prior to mating were significantly lower than

control pup body weights. A decrease in litter size was also observed, although the difference was not statistically significant (Dietz et al. 1992). No developmental effects were observed in the offspring of mice exposed to barium chloride prior to mating (Dietz et al. 1992). Reduced survival and decreased body weight were observed in the offspring of rats exposed to barium carbonate dust (Tarasenko et al. 1977); however, poor reporting of the study methods and results limits the interpretation of the Tarasenko et al. (1977) study.

There are some data suggesting possible age-related differences in toxicokinetic properties of barium. A higher rate (about 10 times higher) of absorption was found in younger rats compared to older rats (Taylor et al. 1962). A study of cadmium and mercury also found higher permeability in the jejunum of immature rats as compared to mature animals (Foulkes and Bergman 1993). An unpublished study by Della Rosa summarized by ICRP (1993) found higher barium retention in dogs aged 43 (2.3% retained) or 150 (2.0%) days, compared to dogs aged 250 days (0.8%) or adult dogs (0.4–0.6%). Information on biomarkers, interactions, and methods for reducing toxic effects of barium (discussed in Sections 3.8, 3.10, and 3.11) comes from studies in adults and mature animals; no child-specific information was identified. In the absence of data to the contrary, it is assumed that this information will also be applicable to children.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental

conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to barium are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by barium are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

At present, there are no well-established biomarkers of exposure and effect for barium. Data suggesting possible biomarkers are presented below.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Barium

Barium can be measured in bone, blood, urine, and feces. It has been shown to be sequestered in bone and teeth and excreted in feces and urine. Background levels of barium in bone are approximately 2 µg/g wet weight (ICRP 1974; Schroeder et al. 1972). Background levels of barium in blood, urine, and feces will vary with daily intake of barium. However, the following levels have been reported: bone, 2 ppm (ICRP 1974; Schroeder et al. 1972); feces, 690–1,215 µg/day (ICRP 1974; Schroeder et al. 1972; Tipton et al. 1969); and urine, 17–50 µg/day (ICRP 1974; Schroeder et al. 1972; Tipton et al. 1969). In the United States, the geometric mean concentration of barium in the urine is approximately 1.5 µg/L (CDC 2005). There are no data correlating bone, blood, urine, or feces levels of barium with specific exposure levels. For more detailed information on the toxicokinetics of barium, see Section 3.4.

3.8.2 Biomarkers Used to Characterize Effects Caused by Barium

Reports of individuals exposed to high levels of barium suggest that cardiovascular, nervous, and gastrointestinal systems are targets of barium toxicity (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). The likely cause of most of these effects is barium induced hypokalemia. Gastrointestinal disturbances are usually the first symptoms of acute barium exposure. Hypokalemia, hypertension, and abnormalities in heart rhythm frequently occur shortly afterwards. General muscle weakness is a frequent symptom, sometimes followed by paralysis. Nerve conduction is often affected, resulting in numbness and tingling of the mouth, neck and extremities. Loss of deep tendon reflexes may also occur. Not all symptoms appear in every case of acute barium poisoning. Although the observation of hypokalemia and gastrointestinal upset may be indicative of exposure to high doses of barium, other toxicants and disease states can produce these effects.

Animal studies also suggest that the kidney is a target of barium toxicity; the observed nephropathy is not specific to barium and would not be a sensitive biomarker of effect.

3.9 INTERACTIONS WITH OTHER CHEMICALS

There are no data regarding the interaction between barium and various chemicals potentially found at hazardous waste sites. However, there are data that suggest that barium may interact with other cations and certain prescription drugs. Drug interactions are of relevance because individuals exposed to barium by living or working near hazardous waste sites contaminated with this substance may also be taking prescription drugs.

The cations potassium, calcium, and magnesium also interact with barium. Barium exposure, for example, may cause a buildup of potassium inside the cell resulting in extracellular hypokalemia, which is believed to mediate barium-induced paralysis. In fact, potassium is a powerful antagonist of the cardiotoxic and paralyzing effects of barium in animals (Foster et al. 1977; Jaklinski et al. 1967; Roza and Berman 1971; Schott and McArdle 1974) and is used as an antidote in cases of acute barium poisoning. Calcium and magnesium suppress uptake of barium by pancreatic islets *in vitro*. Conversely, barium, in low concentrations, stimulates calcium uptake in these cells. Although the data are insufficient to

determine the significance of these findings to human health effects, displacement of calcium may be the mechanism by which barium stimulates insulin release (Berggren et al. 1983).

Among the drugs that are known to interact with barium, the barbiturates sodium pentobarbital and phenobarbital, were found to have an increased depressive effect on the hearts of rats exposed to barium (Kopp et al. 1985; Perry et al. 1983, 1989). This hypersensitivity of the cardiovascular system to anesthesia was not observed in similarly treated animals that were anesthetized with xylazine plus ketamine. Results of the study indicated that the hypersensitivity was specific to the barbiturates and not a generalized effect of anesthesia (Kopp et al. 1985).

Other medically prescribed drugs interact with barium. Experiments with mice indicated that atropine significantly antagonized antinociception and death induced by intracerebroventricular injection of barium chloride (Segreti et al. 1979; Welch et al. 1983). These same studies also found that naloxone, a narcotic antagonist, inhibited the lethal toxicity of barium (Segreti et al. 1979; Welch et al. 1983). Propranolol had no effect on barium-induced paralysis in rats (Schott and McArdle 1974). Verapamil rapidly abolished cardiac dysrhythmias in rabbits injected with barium chloride (Mattila et al. 1986). In the same study, pretreatment with the tricyclic antidepressant, doxepin, was found to offer some protection against barium-induced dysrhythmias (Mattila et al. 1986). Ouabain, which is an inhibitor of Na^+-K^+ ATPase, while not widely prescribed, has been shown to rapidly reverse the paralyzing effects of barium. It has been hypothesized that ouabain works by reducing barium-induced hypokalemia by allowing some intracellular potassium to escape. However, this hypothesis has not yet been proved or disproved because of the complexity of the mechanism involved (Schott and McArdle 1974).

Other substances can affect barium pharmacokinetics. One study showed that sodium alginate could reduce retention of orally administered barium, possibly by inhibiting absorption in the gut (Sutton et al. 1972). This could be useful in treating cases of acute barium ingestion. Lysine and lactose increase absorption of barium and could increase the toxic effects of oral exposure (Lengemann 1959).

A human study involving one adult female was performed by applying barium chloride, alone and in combination, with dimethyl sulfoxide to the cervical epithelium. Dimethyl sulfoxide significantly enhanced the ability of barium chloride to induce dysplasia with unusual cell formation in the cervical epithelium (Ayre 1966). The significance of this is difficult to determine since there was only one subject, there were no controls, and few details of the experiment were provided.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to barium than will most persons exposed to the same level of barium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of barium, or compromised function of organs affected by barium. Populations who are at greater risk due to their unusually high exposure to barium are discussed in Section 6.7, Populations with Potentially High Exposures.

The limited data available suggest that certain subgroups of the population may be more susceptible to barium exposure than the general population. These include people with cardiovascular problems or lung disease, those taking certain prescription drugs, children, pregnant women, and smokers.

Animal studies suggest that the kidney may be a sensitive target of barium toxicity; thus, individuals with impaired renal function may have a higher risk of developing barium-induced kidney damage. There is suggestive evidence that barium may affect blood pressure. Therefore, humans with hypertension could be at increased risk from either chronic, intermediate, or acute barium exposure. Barbiturates have been shown to have an enhanced depressant effect on the heart in barium-exposed animals (Kopp et al. 1985; Perry et al. 1983, 1989). Individuals on this type of medication may experience an increased risk of heart problems on exposure to barium.

Since exposure to high doses of barium has been repeatedly demonstrated to significantly decrease serum potassium in both humans and animals (Foster et al. 1977; Gould et al. 1973; Phelan et al. 1984; Roza and Berman 1971), individuals taking diuretics may have a more severe hypokalemic reaction to barium toxicity.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to barium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to barium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for

medical advice. The following texts provide specific information about treatment following exposures to barium:

Dreisbach RH, Robertson WO, eds. 1987. Handbook of poisoning: Prevention, diagnosis and treatment. 12th ed. Norwalk, CT: Appleton & Lange, 119-120.

Haddad LM, Winchester JF, eds. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: WB Saunders Company, 1129.

3.11.1 Reducing Peak Absorption Following Exposure

The general population is typically exposed to barium through consumption of food and drinking water; workers may also be exposed to barium via inhalation or dermal contact. General recommendations for reducing absorption of barium following exposure have included removing the exposed individual from the contaminated area and removing contaminated clothing, followed by washing with mild soap and water. If the eyes and skin were exposed, they are flushed with water. Lavage or emesis has also been suggested; however, high concentrations of barium cause nausea and emesis should not be induced in cases where substantial vomiting has already occurred (Haddad and Winchester 1990). Furthermore, there is a risk of aspiration of vomitus during emesis. Administration of soluble sulfates orally will also limit absorption of barium by causing precipitation of an insoluble form of barium (barium sulfate) (Dreisbach and Robertson 1987; Haddad and Winchester 1990). However, intravenous administration of sulfate salts should be avoided because barium precipitate in the kidneys will cause renal failure (Dreisbach and Robertson 1987; Koch et al. 2003).

3.11.2 Reducing Body Burden

Barium is primarily distributed to the bone and teeth; it is not known if the barium distributed to these tissues would result in toxicity. A method for reducing the levels of barium in bone and teeth has not been identified. Removal of barium from the bloodstream may be facilitated by infusing with saline and inducing saline diuresis (Dreisbach and Robertson 1987). As described in several case reports of barium poisoning (Bahlmann et al. 2005; Koch et al. 2003; Thomas et al. 1998; Wells and Wood 2001), hemodialysis resulted in significant decreases in the levels of barium in the blood and improved clinical signs.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Hypokalemia is commonly seen in cases of acute barium toxicity and may be responsible for some of the symptoms of barium poisoning (Proctor et al. 1988). Plasma potassium should be monitored and hypokalemia may be relieved by intravenous infusion of potassium (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988).

3.12 ADEQUACY OF THE DATABASE

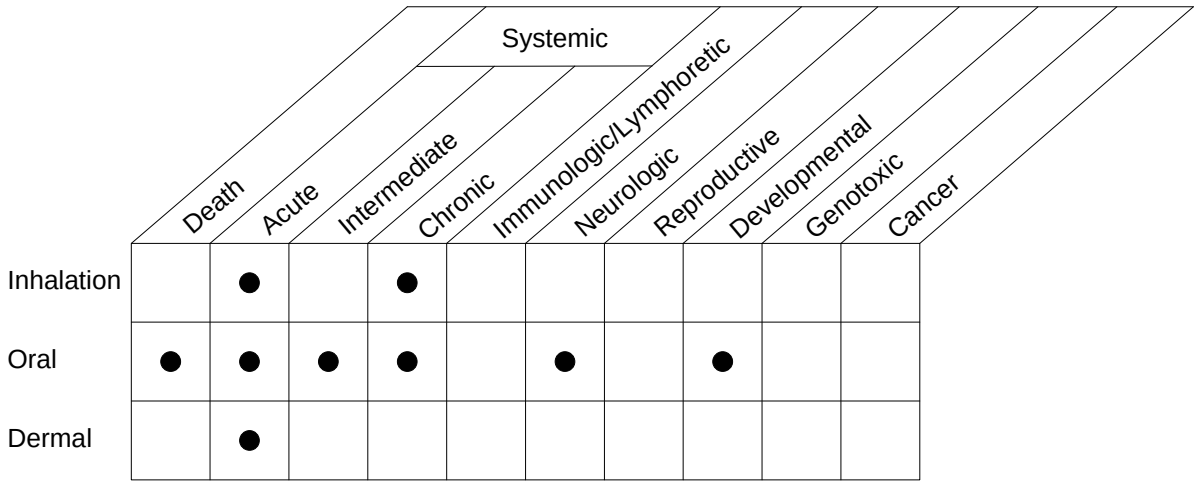
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of barium and compounds is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of barium and compounds.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

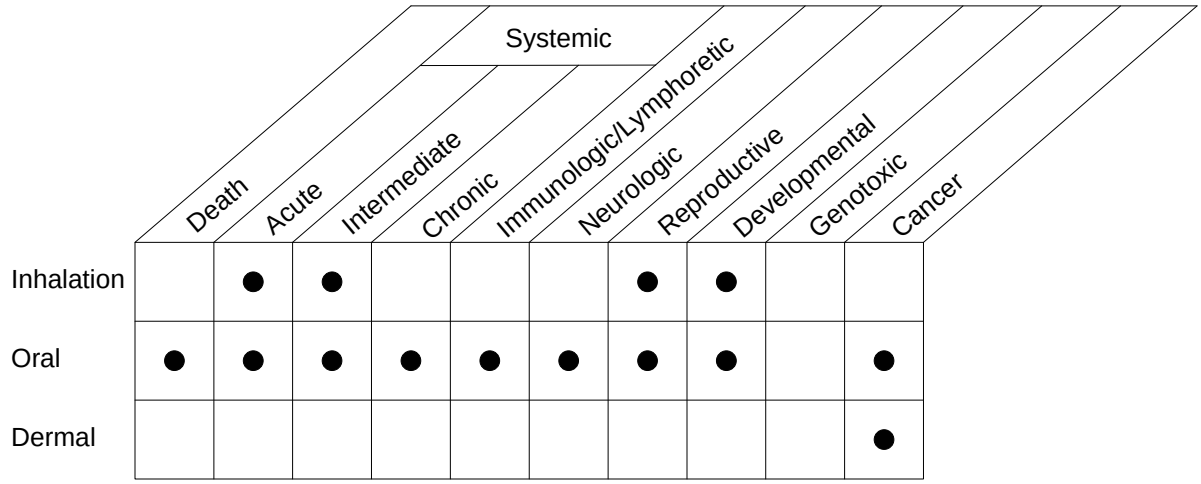
3.12.1 Existing Information on Health Effects of Barium and Barium Compounds

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to barium and barium compounds are summarized in Figure 3-3. The purpose of this figure is to illustrate the existing information concerning the health effects of barium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-3. Existing Information on Health Effects of Barium and Barium Compounds



Human



Animal

● Existing Studies

There is little information regarding health effects in humans following inhalation, oral, or dermal exposure to barium and barium compounds (Figure 3-3). Inhalation studies are limited to several case reports of individuals exposed acutely or chronically through occupational exposure (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988). A number of case reports of acute oral exposure to high doses of barium have been identified (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). Additionally, there is information from a single intermediate-duration experimental study (Wones et al. 1990) and several human epidemiological studies or statistical studies examining mortality and morbidity rates in communities having exposure to barium through drinking water supplies (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). Dermal studies are limited to one case report of an exposed individual (Stewart and Hummel 1984).

The majority of studies conducted on animals have been oral exposure studies (Figure 3-3). Available inhalation studies with experimental animals (Hicks et al. 1986; Tarasenko et al. 1977) can only suggest information on the health effects of barium because these studies have a number of limitations and deficiencies; a third inhalation study (Cullen et al. 2000) is limited to the examination of the respiratory tract. The available oral studies have examined a number of end points, although most studies focused on various systemic effects for acute (Borzelleca et al. 1988; Boyd and Abel 1966; Tardiff et al. 1980), intermediate (Dietz et al. 1992; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Tarasenko et al. 1977; Tardiff et al. 1980), and chronic exposure (Kopp et al. 1985; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a, 1975b). Dermal studies with experimental animals are limited to one skin irritation study (Tarasenko et al. 1977) and one study evaluating the tumor-promoting activity of barium (Van Duuren et al. 1968).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are limited data on the acute toxicity of barium following inhalation, oral, or dermal exposure. Data on the toxicity of inhaled barium are limited to a human experimental study in which welders were exposed to fumes from barium-containing electrodes (Zschiesche et al. 1992), a case of a worker exposed to a large amount barium carbonate dust (Shankle and Keane 1988), and a study in which guinea pigs were exposed to a single concentration of barium chloride for unspecific amount of time (Hicks et al. 1986). Although none of these studies are suitable for derivation of an MRL, the Hicks et al. (1986) study does identify two potential end points (increased

blood pressure and bronchoconstriction). Additional inhalation studies are needed to fully evaluate the toxicity of barium and establish concentration-response relationships.

Most of the available information on the acute toxicity of barium comes from human case reports involving oral exposure to soluble barium compounds and oral toxicity studies in animals. There are a number of case reports of individuals accidentally or intentionally ingesting large doses of barium (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). In general, dose levels were not reported; based on the severity of the observed effects, it is likely that the doses were very high. The observed effects included effects associated with hypokalemia (cardiac arrest, ventricular tachycardia, muscle weakness, and paralysis), gastrointestinal distress (vomiting, gastric pain, and diarrhea), and kidney damage (hemoglobin in the urine, renal insufficiency, degeneration, and acute renal failure). Several studies in experimental animals have examined the acute oral toxicity of barium chloride (Borzelleca et al. 1988; Tardiff et al. 1980). These studies have determined LD_{50} values and evaluated potential systemic, neurological, and reproductive end points. These studies have not consistently identified targets of toxicity or adverse effect levels. The available data were considered inadequate for derivation of an acute oral MRL. Human data consistently identify the gastrointestinal tract as a target of barium toxicity; most case reports of individuals ingesting soluble barium compounds report vomiting, diarrhea, and/or abdominal pain as one of the early signs of toxicity. However, none of the animal studies have adequately investigated this end point; rodents are not a good model for examining gastrointestinal irritation. Animal studies are needed to identify the critical targets of barium toxicity and establish dose-response relationships; these studies should include a more appropriate animal model for investigating potential gastrointestinal effects.

Two studies have examined the dermal toxicity of barium. One is a case report on an individual burned with molten barium chloride (Stewart and Hummel 1984); extrapolation of the results of this study to environmental exposure scenarios is complicated by the thermal burns. Tarasenko et al. (1977) examined the dermal and ocular toxicity of barium carbonate in several animal species. Poor reporting of the experimental design and results limits the interpretation of the study. Additional dermal toxicity studies are needed for several barium compounds to confirm the Tarasenko et al. (1977) study findings that barium is a local irritant and to establish the existence of remote toxicity.

Intermediate-Duration Exposure. No human studies have examined the toxicity of barium in humans following intermediate-duration inhalation exposure. Two animal studies have been identified

(Cullen et al. 2000; Tarasenko et al. 1977). The Tarasenko et al. (1977) study examined systemic, reproductive, and developmental end points. However, interpretation of the results is limited by poor reporting of the study design and results. The Cullen et al. (2000) study only examined the respiratory tract. As these studies were considered inadequate for development of an inhalation MRL, additional studies examining a variety of end points are needed to identify the critical targets of barium toxicity and to establish concentration-response relationships.

One human experimental study examined the cardiovascular toxicity of barium (Wones et al. 1990) following oral exposure; no adverse effects were found. Several animal studies also examined the oral systemic toxicity (McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Tardiff et al. 1980), neurotoxicity (NTP 1994), reproductive toxicity (Dietz et al. 1992), and developmental toxicity (Dietz et al. 1992; Tarasenko et al. 1977) of barium. The results of these studies suggest that the kidney is the most sensitive target of toxicity following intermediate-duration oral exposure. An intermediate-duration oral MRL based on kidney effects in rats exposed to barium chloride for 13 weeks (NTP 1994) has been derived.

Information on the oral toxicity of barium following intermediate-duration exposure comes from a human experimental study examining cardiovascular toxicity (Wones et al. 1990) and several animal studies examining systemic toxicity (McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Tardiff et al. 1980), neurotoxicity (NTP 1994), reproductive toxicity (Dietz et al. 1992; NTP 1994), and developmental toxicity (Dietz et al. 1992). The human study did not find significant alterations in blood pressure or ECG readings in adults exposed to fairly low doses (Wones et al. 1990). Effects observed in the animal studies include increased blood pressure (Perry et al. 1983, 1985, 1989), kidney damage (glomerular alterations consisting of fused podocytes and thickening of the capillary basement membrane and mild to moderate nephropathy) (McCauley et al. 1985; NTP 1994), and developmental toxicity (decreased pup birth weight) (Dietz et al. 1992). The increase in blood pressure was observed at the lowest adverse effect level; however, two other studies (McCauley et al. 1985; NTP 1994) did not find significant alterations in blood pressure or ECG readings in rats exposed to higher doses of barium. The low-mineral diet used in the Perry et al. (1983, 1985, 1989) studies may have influenced the results. The calcium content of the rye-based diet was 3.8 mg/kg, which is lower than the concentration recommended for maintenance, growth, and reproduction of laboratory rats (NRC 1995). Additional studies are needed to support this hypothesis. The results of the McCauley et al. (1985) and NTP (1994) studies suggest that the kidney is the most sensitive target of toxicity in rats and mice following intermediate-duration oral

exposure; an intermediate-duration oral MRL was derived based on kidney effects observed in rats exposed to barium chloride for 13 weeks (NTP 1994).

No studies have examined the toxicity in humans or animals following intermediate-duration dermal exposure. Studies are needed to assess the potential toxicity of various barium compounds and to establish whether dermal exposure would result in remote toxicity.

Chronic-Duration Exposure and Cancer. The toxicity of barium following chronic-duration inhalation exposure is limited to three occupational exposure studies (Doig 1976; Essing et al. 1976; Seaton et al. 1986). These studies focused on potential respiratory tract effects and are limited by co-exposure to other compounds, small number of tested workers, and/or lack of a comparison group. Well-designed studies examining a number of potential end points are needed to identify the critical targets of barium toxicity and establish concentration-response relationships. These studies would be useful for deriving a chronic-duration inhalation MRL for barium.

Three groups of investigators have examined the effect of living in a community with elevated barium levels in the drinking water and the risk of mortality and cardiovascular effects (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). These studies are limited by a number of factors including the lack of information on barium ingestion levels and the possible use of water softeners, which may have removed barium from the drinking water and increased the sodium content of the water. Several studies in rats and mice have examined the chronic toxicity of barium (NTP 1994; Perry et al. 1989; Schroeder and Mitchener 1975a, 1975b). The Perry et al. (1989) study found significant increases in systolic blood pressure in rats fed a relatively low concentration of barium in the diet; however, the contribution of the low mineral basal diet to the observed effect is not known. Several rat studies did not find adverse effects at the highest doses tested (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a). Marked renal nephropathy was observed in mice (NTP 1994); this study and effect were the basis of the chronic-duration MRL for barium. The available toxicokinetic data suggest that barium accumulates in bone; it is not known if this accumulation would result in adverse effects. Studies designed to test the possible association between high levels of barium in bone and adverse bone effects would be useful.

Data on the dermal toxicity of barium are limited to a skin tumor promotion study using barium hydroxide extract from tobacco plants (Van Duuren et al. 1968); the study did not examine noncancerous

end points. Additional dermal exposure studies are needed to evaluate whether various barium compounds are irritants and can cause remote-site toxicity.

No studies assessing the carcinogenicity of barium following chronic inhalation exposure were identified. The carcinogenicity of ingested barium has been assessed in several long-term oral exposure studies in rats and mice (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a, 1975b). These studies did not find significant increases in the incidence of neoplastic lesions in either species. Although a study by Van Duuren et al. (1968) provided evidence suggesting that barium hydroxide extract derived from tobacco leaf may act as a tumor-promoting agent when applied with a tumor initiating agent, there are no studies to assess barium's potential to be a complete carcinogen following dermal exposure. Based on the results of the oral study, it can be predicted that inhalation or dermal exposure to barium would not result in remote site carcinogenicity; however, it is not known if long-term exposure would result in respiratory tract cancer following inhalation exposure or skin cancer following dermal exposure. Inhalation and dermal exposure cancer studies are needed to address these questions.

Genotoxicity. The genotoxicity of barium has not been well characterized. One study used an *in vivo* assay to assess genotoxic potential (Yesilada 2001); increases in somatic mutations were observed in *D. melanogaster* following exposure to high levels of barium nitrate. The available data utilizing *in vitro* assays have not found significant alterations in gene mutation frequency or DNA damage in non-mammalian systems (Kanematsu et al. 1980; Monaco et al. 1990, 1991; Nishioka 1975; NTP 1994; Rossman et al. 1991; Sirover and Loeb 1976a, 1976b). In mammalian test systems, barium did not have clastogenic effects (NTP 1994), but did increase the frequency of gene mutation (NTP 1994). The available data are inadequate to thoroughly assess the genotoxic potential of barium; additionally studies, particularly *in vivo* assays, are needed.

Reproductive Toxicity. The reproductive effects of barium have not been thoroughly studied. There are no studies regarding reproductive effects in humans following barium exposure. Several animal studies have examined potential end points of reproductive toxicity. In the only inhalation exposure study (Tarasenko et al. 1977), a number of adverse effects were reported, including disturbances in spermatogenesis, shortened estrus cycle, and histological damage to the testes and ovaries. However, limited reporting of the study design and results and the lack of incidence data and statistical analysis limit the interpretation of the study results. Although a 10-day gavage study found significant decreases in relative and absolute ovary weights (Borzelleca et al. 1988), other oral exposure studies have not found alterations in organ weights or histological alterations in reproductive tissues following acute-,

intermediate-, or chronic-duration exposure (McCauley et al. 1985; NTP 1994). Additionally, no alterations in sperm morphology, motility, or counts were observed in rats or mice exposed to barium in drinking water for 60 days (Dietz et al. 1992). Only one oral study evaluated reproductive function (Dietz et al. 1992) and found no alterations in pregnancy rate or gestation length in rats or mice. A two-generation study would be useful for further evaluating the potential reproductive toxicity of barium. No dermal exposure studies examining reproductive end points were identified; based on available toxicokinetic data. Additional studies are needed to further assess if reproductive toxicity is an end point of concern for barium.

Developmental Toxicity. The developmental effects of barium have not been studied extensively in either humans or animals. One limited statistical study evaluated the degree of correlation between barium concentrations in drinking water and human congenital malformation rates of the central nervous system (Morton et al. 1976). Results of the study indicated there was a negative statistical correlation between these parameters, implying that a lower risk of congenital abnormalities was found in populations with higher barium levels. Two animal studies evaluated the potential developmental toxicity of barium. Reduced survival, underdevelopment, lowered body weight, decreased lability of the peripheral nervous system, and various blood disorders were reportedly noted in the offspring of rats following inhalation to barium for an intermediate exposure period (Tarasenko et al. 1977). The investigators also noted increased mortality and systemic toxicity in the offspring of rats orally exposed to barium during conception and pregnancy. As noted previously, interpretation of the results from the Tarasenko et al. (1977) studies are limited because the studies were poorly reported and no incidence data or statistical analysis were reported. In a mating study involving oral exposure to barium chloride prior to mating (Dietz et al. 1992), decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in rats; no adverse effects were observed in mice. It is not known if the decrease in body weight observed in the rat offspring was secondary to maternal toxicity or was a direct effect on the fetus. Additional developmental toxicity studies, particularly studies involving oral exposure during gestation and lactation, would be useful to confirm the results of the Tarasenko et al. (1977) and Dietz et al. (1992) studies. Developmental toxicity studies via dermal exposure are also needed because this end point has not been evaluated for this route of exposure.

Immunotoxicity. The effect of barium on the immune system has not been well studied. No studies were available regarding immunological effects in humans or animals following inhalation, oral, or dermal exposure to barium. Several oral exposure studies in animals examining lymphoreticular end points such as thymus and lymph node histopathology have not reported adverse effects at nonlethal

doses (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994). Screening studies are needed to evaluate the potential immunotoxicity of barium following inhalation, oral, or dermal exposure.

Neurotoxicity. Exposure to high oral doses of barium is associated with numbness and tingling around the mouth and neck (Lewi and Bar-Khayim 1964; Morton 1945); higher doses can result in partial or complete paralysis (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). Absence of a deep tendon reflex has been reported in an individual exposed to airborne barium carbonate powder (Shankle and Keane 1988). Oral exposure of rats and mice to barium has not been associated with changes in brain weight or gross or microscopic lesions of the brain (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994; Tardiff et al. 1980). NTP (1994) evaluated neurobehavioral performance in rats and mice exposed to barium chloride in drinking water for acute or intermediate durations. Decreases in spontaneous motor activity were observed in rats exposed for an intermediate duration. Decreased grip strength was also observed in mice; however, this was likely due to debilitation rather than neurotoxicity. The human data demonstrate that at presumably high doses, barium affects action potentials of muscles and nerve cells by increasing cellular potassium levels. However, oral studies are needed to establish a dose-response relationship for these neurological effects. No data were available regarding neurological effects in animals following inhalation exposure or humans and/or animals following dermal exposure. Additional studies would be useful to further evaluate the neurotoxic potential of barium.

Epidemiological and Human Dosimetry Studies. A limited number of epidemiological and human dosimetry studies evaluating the health effects of barium are available (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974; Wones et al. 1990). These studies have primarily focused on the potential of barium to adversely affect cardiovascular function by altering blood pressure or increasing the risk of death due to cardiovascular disease; consistent results have not been found. However, all of the available human studies on barium have limitations and/or confounding variables that make it difficult to draw firm conclusions regarding the health effects of barium (see Sections 3.2.2.1 and 3.2.2.2 for discussions on the specific limitations associated with available epidemiological and human dosimetry studies). Several human studies have also examined the potential toxicity of inhaled barium to the respiratory tract or cardiovascular system (Doig 1976; Essing et al. 1976; Seaton et al. 1986). As with the oral studies, limitations in the study reporting or confounding variables preclude using the studies to establish causal relationships. In addition to these epidemiological or experimental studies, there are numerous case reports of individuals ingesting large doses of barium (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995;

Gould et al. 1973; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981) or exposed to airborne barium carbonate (Shankle and Keane 1988). In general, these studies reported serious health effects such as death, ventricular tachycardia, and paralysis. Animal studies provide evidence that the kidney is a sensitive target of toxicity; there is also some evidence that the cardiovascular and neurological systems and the developing organisms are targets of barium toxicity (Dietz et al. 1992; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989). Additional epidemiological and/or human dosimetry studies would be useful to determine the effects of low doses of barium on these end points. Studies of workers exposed to airborne barium would also be useful for establishing the toxicity of barium to the respiratory tract.

Biomarkers of Exposure and Effect.

Exposure. There are no established biomarkers of exposure for barium. Analytical methods exist for measuring barium in blood, urine, feces, and biological tissues (Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987); however, there are no data correlating levels of barium in these tissues and fluids with exposure. Studies associating barium levels in biological media (such as blood or urine) with exposure concentrations or doses would be useful for establishing biomarkers of exposure.

Effect. Symptoms of barium toxicity, such as hypokalemia, gastrointestinal upset, hyper- or hypotension, ventricular tachycardia, and numbness and tingling around the mouth and neck (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981) are well documented. However, there are no quantitative studies correlating these effects with dose and these effects are not specific to barium toxicity. For purposes of facilitating medical surveillance, studies to determine useful biomarkers of effect for barium, particularly effects associated with low doses of barium, would be useful.

Absorption, Distribution, Metabolism, and Excretion. The database on absorption, distribution, metabolism, and excretion of barium is limited. Existing studies indicate that barium is absorbed from the respiratory tract (Cuddihy and Griffith 1972; Cuddihy and Ozog 1973b; Morrow et al. 1968) and gastrointestinal tract (Cuddihy and Griffith 1972; Harrison et al. 1956; Leggett 1992; LeRoy et al. 1966; Schroeder et al. 1972; Taylor et al. 1962;Tipton et al. 1969), primarily deposited in the bones and teeth (Bauer et al. 1957; Cuddihy and Griffith 1972; Losee et al. 1974; Miller et al. 1985; Sowden 1958;

Sowden and Pirie 1958; Sowden and Stitch 1957), and excreted mostly in feces and urine (Cuddihy and Griffith 1972; Tipton et al. 1966). Deposition in bones and teeth and excretion in feces and urine appear to be independent of the route of exposure. Essentially no data exist on absorption, distribution, or excretion following dermal exposure; however, this route is not considered to be a significant source of exposure to barium. No significant data exist on the metabolism of barium compounds in the body. Additional studies evaluating the binding and/or complexing of barium and barium compounds with biological macromolecules or organic molecules in the body would be useful. Studies quantifying the extent of absorption following inhalation, oral, and dermal exposure also would be useful because of limited absorption data. A wide variety of individual differences in absorption efficiencies have been detected in the available human studies; studies examining factors influencing barium absorption would be useful.

Comparative Toxicokinetics. Based on available data, there do not appear to be significant differences in the toxicokinetics of barium between species (Chou and Chin 1943; Cuddihy and Griffith 1972; McCauley and Washington 1983), although there is some indication that a larger percentage of absorbed barium is excreted in the feces of humans compared to that of experimental animals. However, there are not enough similar studies on different species to determine this with certainty. Studies on different species would increase confidence in the reliability of the existing database.

Methods for Reducing Toxic Effects. Methods have been reported for limiting oral and dermal absorption of barium compounds (Bronstein and Currance 1988; Dreisbach and Robertson 1987; Haddad and Winchester 1990) and for counteracting the hypokalemia that is produced by barium in acute high-level exposure situations (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988). Contradictions exist in the literature regarding the efficacy or desirability of administering emetics (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Additional studies clarifying this issue would be helpful. Also, studies directed at finding a more efficient way to remove barium from the body would be useful. It is unclear whether mechanisms other than hypokalemia contribute to the toxic effects produced in acute high-level exposure situations. Additional information on the mechanisms responsible for the toxic effects of barium could aid in the development of effective treatments. Magnesium has been reported to antagonize the neuromuscular effects (Dreisbach and Robertson 1987). Additional studies examining the efficacy of administering soluble magnesium salts to antagonize the effects of barium would also be helpful. No information was located on treatment strategies for long-term low-level exposures. Research on procedures for mitigating such chronic exposure situations would be helpful.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There is very little information on the toxicity of barium in children. Two reports of food poisonings with barium carbonate (Deng et al. 1991; Lewi and Bar-Khayim 1964) provide some suggestive information that children may not be as sensitive as adults to barium carbonate toxicity; however, the lack of detailed examination of the exposed children and lack of exposure information limits the interpretation of these data. No human or animal toxicity studies have been designed to assess possible differences in the toxicity of barium. There is some information suggesting that infants and young children may have a higher barium absorption rate than adults (ICRP 1993; Taylor et al. 1962). Other potential toxicokinetic differences have not been thoroughly investigated. Additional studies are needed to evaluate potential age-specific differences in toxicity and toxicokinetics.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing studies were reported in the FEDRIP (2006) database.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Barium is an alkaline earth metal with an atomic number of 56 and is classified in Group IIA of the periodic table of elements. Its outer shell of electrons has a $6s^2$ configuration. Because barium is highly reactive, it exists in the environment in the +2 oxidation state, which is its only oxidation state.

Barium forms useful alloys with aluminum and magnesium, which are used as getters in electronic tubes to remove residual gases (Genter 2001). Barium is also used as a deoxidizer for steel and other metals (Boffito 2002).

Barium reacts with several other elements to form commercially-important compounds. Of these, eight barium compounds are covered in this chapter: barium acetate, barium carbonate, barium chloride, barium cyanide, barium, hydroxide, barium oxide, barium sulfate, and barium sulfide. Their chemical formulas, structures, synonyms, and identification numbers, in addition to those for barium metal, are listed in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Metallic barium is a silvery-white soft metal, but takes on a silver-yellow color when exposed to air (Boffito 2002; Genter 2001). Like other alkaline earth metals, barium decomposes in water, evolving hydrogen gas. Barium oxidizes readily in moist air. In powdered form, barium reacts violently with air. Because of its high reactivity, barium does not exist as the metal in the environment; it exists in a combined state with other elements.

The barium compounds, barium acetate, barium chloride, barium cyanide, barium hydroxide, and barium oxide, are quite soluble in water. Barium carbonate and sulfate are poorly soluble in water. Barium oxide reacts rapidly with carbon dioxide in water to form barium hydroxide and barium carbonate (Dibello et al. 2003). Barium sulfide slowly decomposes in water, forming barium hydroxide and barium hydrosulfide. Barium sulfide is also known to undergo slow oxidation in solution to form elemental sulfur and various oxidized sulfur species including the sulfite, thiosulfate, polythionates, and sulfate. The water solubility of barium compounds increases with decreasing pH (IPCS 1991).

Table 4-1. Chemical Identity of Barium and Barium Compounds[a]

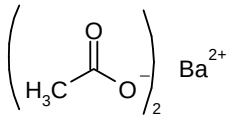
Characteristic	Barium	Barium acetate	Barium carbonate
Synonyms	No data	Acetic acid, barium salt; barium diacetate	Carbonic acid, barium salt; barium monocarbonate; Pigment White 10; BW-C3; BW-P
Trade names	No data	No data	No data
Chemical formula	Ba	$Ba(C_2H_3O_2)_2$	$BaCO_3$
Chemical structure	Ba		$[Ba^{2+}]$ $[CO_3^{2-}]$
Identification numbers:			
CAS registry	7440-39-3	543-80-6	513-77-9
NIOSH RTECS	CQ8370000[b]	AF4550000[b]	CQ8600000[b]
EPA hazardous waste	D005	No data	D005
DOT/UN/NA/IMCO shipping	UN1440/IMO 4.3	No data	UN 1564/IMO 6.1
HSDB	4481	No data	950
EINECS	231-149-1	208-849-0	208-167-3
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Barium and Barium Compounds[a]

Characteristic	Barium chloride	Barium cyanide	Barium hydroxide
Synonyms	Barium dichloride; NCI-C61074; SBa 0108E	Barium dicyanide	Barium dihydroxide; barium hydroxide lime; caustic baryta
Trade names	No data	No data	No data
Chemical formula	$BaCl_2$	$Ba(CN)_2$	$Ba(OH)_2$
Chemical structure	$[Ba^{2+}]\ [Cl^-]_2$	$[Ba^{2+}]\ [CN^-]_2$	$[Ba^{2+}]\ [OH^-]_2$
Identification numbers:			
CAS registry	10361-37-2	542-62-1	17194-00-2
NIOSH RTECS	CQ8750000[b]	CQ8785000[b]	CQ9200000[b]
EPA hazardous waste	D005	PO13/D003/D005	D005
DOT/UN/NA/IMCO shipping	UN 1564/IMO 6.1	UN 1565/IMO 6.1	UN 1564/IMO 6.1
HSDB	2633	403	1605
EINECS	233-788-1	208-822-3	241-234-5
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Barium and Barium Compounds[a]

Characteristic	Barium oxide	Barium sulfate	Barium sulfide
Synonyms	Barium monoxide; barium protoxide; baryta; calcined baryta	Artificial heavy spar; artificial barite; baridol; barytes; blanc fixe; C.I. Pigment White 21; Citobaryum; Enamel White; E-Z-Paque; Solbar; precipitated barium sulphate; sulfuric acid, barium salt[f]	Barium suphide
Trade names	No data	No data	No data
Chemical formula	BaO	$BaSO_4$	BaS
Chemical structure	$[Ba^{2+}]$ $[O^{2-}]$	$[Ba^{2+}]$ $[SO_4^{2-}]$	$[Ba^{2+}]$ $[S^{2-}]$
Identification numbers:			
CAS registry	1304-28-5	7727-43-7	21109-95-5
NIOSH RTECS	CQ9800000[b]	CR0600000[b]	CR0660000[b]
EPA hazardous waste	No data	D005	No data
DOT/UN/NA/IMCO shipping	UN1884	UN1564/IMO6.1	UN1564/IMDG6.1[c]
EINECS	215-127-9	231-784-4	244-214-4
HSDB	No data	5041	No data
NCI	No data	No data	No data

[a]All information obtained from HSDB 2007 and ChemIDplus 2007 except where noted
[b]RTECS 2007
[c]Kresse et al. 2007

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Commercial chemical Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances

4. CHEMICAL AND PHYSICAL INFORMATION

Information regarding the physical and chemical properties of barium and barium compounds is located in Table 4-2.

Table 4-2. Physical and Chemical Properties of Barium and Barium Compounds[a]

Property	Barium	Barium acetate	Barium carbonate
Molecular weight	137.327	255.416 (anhydrous) 273.431 (monohydrate)	197.336
Physical description	Silvery-yellow metal; cubic	White powder (anhydrous); white crystals (monohydrate)	White orthorhombic crystals
Melting point	727 °C	Decomposes at 110 °C (monohydrate)	1,555 °C
Boling point	1,897 °C	No data	No data
Density	3.62 g/cm^3	2.47 g/cm^3 (anhydrous); 2.19 g/cm^3 (monohydrate)	4.2865 g/cm^3
Specific gravity	No data	2.02 (below 24.7 °C)[b]	No data
Odor	No data	No data	Odorless[c]
Odor threshold	No data	No data	No data
Solubility:			
Water	Reacts with water	79.2 g/100 g water at 25 °C	0.0014 g/100 g water at 20 °C; soluble in dilute HCl, HNO_3, and acetic acid[d]; soluble in NH_4Cl and NH_4NO_3 solutions[d]
Organic solvents	Slightly soluble in ethanol	Slightly soluble in ethanol (monohydrate)	Insoluble in alcohol[e]
Partition coefficients	No data	No data	No data
Vapor pressure	6.65x10^{-4} mmHg (at 630 °C)[f]; 0.998 mmHg (at 1,050 °C)[f]	No data	Essentially zero[g]
Henry's law coefficients	No data	No data	No data
Autoignition temperature	No data	No data	Nonflammable[c]
Flashpoint	No data	No data	Nonflammable[c]
Flammability limits	Explosion hazard if exposed to moist air[d]	No data	Nonflammable[c]
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Barium and Barium Compounds[a]

Property	Barium chloride	Barium cyanide	Barium hydroxide
Molecular weight	208.232 (anhydrous); 244.263 (dihydrate)[e]	189.361	171.342 (anhydrous); 189.357 (monohydrate); 315.464 (octahydrate)
Physical description	White hygroscopic orthorhombic crystals (anhydrous); white monoclinic crystals (dihydrate)	White crystalline powder	White powder (anhydrous, monohydrate); white monoclinic crystals (octahydrate)
Melting point	962 °C (anhydrous); decomposes at approximately 120 °C (dihydrate)	No data	408 °C (anhydrous); decomposes at 78 °C (octahydrate)
Boling point	1,560 °C (anhydrous)	No data	No data
Density	3.9 g/cm^3 (anhydrous); 3.097 g/cm^3 (dihydrate)	No data	3.743 g/cm^3 (monohydrate); 2.18 g/cm^3 (octahydrate)
Specific gravity	No data	No data	4.495 (anhydrous)[h]
Odor	Odorless[g]	No data	No data
Odor threshold	No data	No data	No data
Solubility:			
Water	37.0 g/100 g water at 25 °C	800 g/L (at 14 °C)[e]	4.91 g/100 g water at 25 °C
Organic solvents	Insoluble in ethanol (dehydrate)	180 g/L (in 70% alcohol at 14 °C)[e]	Soluble in methanol[d]
Partition coefficients	No data	No data	No data
Vapor pressure	Essentially zero[g]	No data	0 mm Hg at 15 °C (monohydrate)[i]; 11.4 mm Hg at 15 °C (water vapor pressure of octahydrate)[i]
Henry's law coefficients	No data	No data	No data
Autoignition temperature	No data	Nonflammable[c]	No data
Flashpoint	No data	Nonflammable[c]	No data
Flammability limits	No data	Nonflammable[c]	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	Explosive >216 °C[j]

Table 4-2. Physical and Chemical Properties of Barium and Barium Compounds[a]

Property	Barium oxide	Barium sulfate	Barium sulfide
Molecular weight	153.326	233.391	169.393
Physical description	White-yellow powder; cubic and hexagonal crystals	White orthorhombic crystals	Colorless cubic crystals or gray powder
Melting point	1,972 °C	1,580 °C	2,229 °C
Boling point	No data	No data	No data
Density	5.72 g/cm^3 (cubic)	4.49 g/cm^3	4.3 g/cm^3
Specific gravity	5.32 (hexagonal)[b]	4.50[b]	No data
Odor	Odorless[g]	Odorless[d]	Sulfurous
Odor threshold	No data	No data	No data
Solubility:			
Water	1.5 g/100 g water at 20 °C	00.00031 g/100 g water at 20 °C	8.94 g/100 g water at 25 °C
Organic solvents	Soluble in ethanol; insoluble in acetone	Insoluble in ethanol	No data
Partition coefficients	No data	No data	No data
Vapor pressure	Essentially zero[g]	No data	No data
Henry's law coefficients	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	Produces heat on contact with water or steam[k]	Noncombustible[k]	Flammable by spontaneous chemical reactions[k]
Conversion factors	No data	No data	No data
Explosive limits	Contact with CO_2 may cause explosion[k]	Heating with aluminum may cause violent explosions[k]	Air, moisture, or acid fumes may cause it to ignite[k]

[a]All information obtained from Lide 2005 except where noted
[b]Dibello et al. 2003
[c]DOT 2005
[d]Budavari et al. 2001
[e]Weast 1989
[f]Boffito 2002
[g]NIOSH/OSHA 1978
[h]Perry and Chilton 1973
[i]Preisman and Davis 1948
[j]HSDB 2007
[k]Lewis 2000

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Barium is a dense alkaline earth metal that occurs naturally in ore deposits and makes up 0.05% of the Earth's crust (Genter 2001). Barium and its compounds may be found in nature or produced industrially for various uses. The largest natural source of barium is barite ore, which is composed largely of barium sulfate and is found in beds or masses in limestone, dolomite, shales, and other sedimentary formations (Miner 1969b). The major impurities in crude barite ore are iron(III) oxide, aluminum oxide, silica, and strontium sulfate (WHO 2001). Crude barite is turned into crushed barite which not only has its own industrial uses but also serves, in turn, as the source for the production of other barium compounds. Crushed barite is first converted to barium sulfide by high-temperature, solid-phase reduction with a carbonaceous reducing agent. Barium sulfide is the starting point for the chemical manufacture of most other barium compounds (Dibello et al. 2003). One such useful compound is lithophone consisting of 28% zinc sulfide (ZnS) and 72% barium sulfate ($BaSO_4$), which is used as a white pigment in paints. Barium sulfate is produced from high-grade (75–98%) ore in association with granite and shale, crushed, and then beneficiated by washing, jigging, heavy-media separation, tabling, floatation, or magnetic separation (Stokinger 1981; USGS 2004). Barium carbonate ($BaCO_3$) occurs in nature as witherite; however, it has little economic significance due to its rareness, impurities, and almost fully depleted deposits (Kresse et al. 2007).

In 2005, the major producer of barite in the United States was from mines in Nevada. Significantly smaller amounts were produced from a single mine in Georgia. Total U.S. production for 2004 was 532,000 metric tons, a figure that represented 7.3% of world production. This production figure is 14% higher than for 2003. In 2004, 24 grinding plants within the United States produced 2,440,000 metric tons of ground or crushed (processed) barite ore. Fourteen facilities, 6 in Louisiana and 8 in Texas, produced American Petroleum Institute (API)-grade barite in 2004. These stand-alone grinding plants received barite from China and India for grinding to API specifications for the oil and gas drilling markets. Of the total production of ground and crushed barite ore in 2004, 94% (2,300,000 metric tons) was used in well drilling operations. Louisiana and Texas were the major U.S. consumers of processed barite ore (1,803,000 metric tons); much of this consumption was driven by exploration for natural gas. The demand for barite in the United States is expected to increase, while the level of drilling activity in North America remains high due to a strong demand in the United States for natural gas. The remaining 6% (142,000 metric tons) was used as filler and extenders and in the manufacture of glass and barium chemicals, such as barium sulfide (USGS 2004, 2006). A list of production and processing facilities for

barium and barium compounds in the United States along with the production or processing volume for each are provided in Tables 5-1 and 5-2 (TRI04 2006). A listing of specific manufactures of barite and barium compounds is given in Table 5-3.

5.2 IMPORT/EXPORT

For the year 2004, U.S. imports of crude barite ore totaled 1,960,000 metric tons, which was a 17% increase from levels reported in 2003. Estimates for 2005 predict a 17% increase in imports to 2,350,000 metric tons. Export volumes were at 70,000 metric tons, a 37% increase from 2003 levels. Estimates indicate a 22% increase in exports to 90,000 metric tons in 2005. Import of barium chloride, barium nitrate, and barium carbonate amounted to 130, 4,300, and 10,200 metric tons in 2004, respectively. Imports of barium oxide, hydroxide, and peroxides were reported to be 3,540 metric tons (USGS 2004, 2006).

5.3 USE

Barium and its compounds are used in oil and gas drilling muds, automotive paints, stabilizers for plastics, case hardening steels, bricks, tiles, lubricating oils, and jet fuel as well as in various types of pesticides (Bodek et al. 1988; Venugopal and Luckey 1978; WHO 2001). The largest use of mined barite, which accounts for 94% of the total output, is oil and gas well drilling (USGS 2006). The rest of barite ore (or crude barium sulfate) is utilized frequently as a colorant in paint, as a flux to reduce melting temperature in the manufacture of glass, and as a filler in plastics, rubber, and brake linings as well as in the production of other barium compounds (Dibello et al. 2003). Such barium compounds as the carbonate, chloride, and hydroxide are important in the brick, ceramic, photographic, and chemical manufacturing industries (Bodek et al. 1988).

Industrial uses of barium and its compounds are wide and varied. Barium metal and its alloys, for example, are often used as "getters" to remove gases from vacuum tubes due to their ability to absorb gases (Stokinger 1981). One of barium carbonate's major uses is as a rodenticide (Meister 2004; Worthing 1987); however, it also plays an important role in the brick, tile, ceramics, oil drilling, and chemical manufacturing industries (Dibello et al. 2003; ILO 1983). Barium sulfate, in the chemically treated, *blanc fixe* form, is used in high-quality paints as well as in glass- and papermaking (ILO 1983; Kresse et al. 2007). Barium sulfate is also added to concrete to increase the radiation shielding of this material. The chloride is used for chlorine and sodium hydroxide manufacture, as a flux for aluminum alloys, in pigment and textile dye manufacture, and in the treatment of boiler water (Dibello et al. 2003).

Table 5-1. Facilities that Produce, Process, or Use Barium

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	8	0	999,999	1, 5, 12, 13, 14
AL	23	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13, 14
AR	10	0	49,999,999	1, 3, 5, 7, 8, 11, 12
AZ	8	0	9,999,999	1, 5, 7, 10, 13
CA	34	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	8	100	99,999	2, 6, 7, 8, 12, 14
CT	3	100	999,999	1, 2, 4, 6, 7, 8, 9, 12
DE	4	100,000	999,999	2, 3, 9, 13, 14
FL	2	0	999,999	1, 5, 8
GA	13	0	49,999,999	1, 2, 3, 4, 6, 7, 8, 14
IA	12	0	999,999	1, 2, 5, 7, 10, 11, 12
ID	7	10,000	999,999	1, 3, 5, 12, 13
IL	22	100	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	19	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12
KS	13	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
KY	14	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9
LA	6	0	99,999	1, 5, 6, 8, 12
MA	6	1,000	99,999	1, 3, 7, 8, 11
MD	7	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 11, 12
ME	4	100	99,999	1, 5, 8, 13
MI	36	0	999,999	1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	21	100	999,999	1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
MO	11	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 13, 14
MS	10	100	999,999	2, 3, 7, 8, 11
MT	3	10,000	99,999	1, 5, 8, 9, 12
NC	18	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
ND	1	100,000	999,999	1, 5, 9, 12
NE	14	100	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
NJ	17	0	999,999	2, 3, 6, 7, 8, 10, 11
NM	6	0	49,999,999	6, 7, 8, 9, 11, 12, 14
NV	6	100	9,999,999	1, 5, 6, 7, 10, 13
NY	20	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13
OH	54	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	19	0	999,999	1, 2, 3, 5, 7, 8, 11, 12, 13
OR	9	0	999,999	1, 2, 3, 5, 6, 7, 12, 13
PA	27	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
PR	2	10,000	999,999	12
RI	3	10,000	99,999	2, 3, 4, 6, 7
SC	21	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 11, 12
SD	2	100,000	999,999	1, 5, 12, 14

Table 5-1. Facilities that Produce, Process, or Use Barium

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TN	19	100	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	46	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	9	1,000	999,999	1, 2, 3, 5, 7, 8, 11, 12
VA	15	0	999,999	1, 2, 5, 6, 7, 8, 10, 12
VT	1	1,000	9,999	11
WA	3	0	999,999	2, 5, 7, 8, 12, 13, 14
WI	13	0	999,999	1, 3, 5, 6, 7, 8, 10, 11, 12, 14
WV	10	0	999,999	2, 3, 7, 8, 10, 12
WY	2	0	999	1, 2, 13

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI04 2006 (Data are from 2004)

Table 5-2. Facilities that Produce, Process, or Use Barium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	4	0	9,999,999	1, 5, 12, 14
AL	58	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	47	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	41	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	89	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	41	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
CT	25	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
DE	17	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
FL	51	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	79	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	2	1,000	99,999	1, 5, 10
IA	42	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	14	0	9,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 13, 14
IL	136	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	109	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	48	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
KY	80	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	56	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
MA	42	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MD	52	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
ME	25	0	99,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 13
MI	125	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	46	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	68	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MS	39	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	14	100	9,999,999	1, 3, 4, 5, 6, 7, 9, 12, 13, 14
NC	77	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	18	0	9,999,999	1, 5, 8, 9, 12, 13, 14
NE	32	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
NH	10	0	99,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12
NJ	103	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	21	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
NV	19	0	499,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13
NY	121	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	169	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	43	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	27	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
PA	153	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Barium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PR	3	10,000	999,999	1, 2, 4, 5, 6
RI	12	100	99,999	2, 3, 4, 6, 7, 8, 11
SC	50	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	7	1,000	999,999	1, 5, 7, 8, 9, 12, 13
TN	71	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	114	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	41	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	44	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
VT	6	1,000	99,999	1, 5, 7, 8, 11
WA	26	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	54	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	34	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WY	23	0	9,999,999	1, 3, 4, 5, 9, 12, 13, 14

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI04 2006 (Data are from 2004)

Table 5-3. Current U.S. Manufacturers of Barium Metal and Selected Barium Compounds[a]

Company	Location
Barite (barium sulfate, natural):	
CIMBAR Performance Minerals	Cadet, Missouri
	Cartersville, Georgia
	Chatsworth, Georgia
Elementis Pigments, Inc.	East St. Louis, Illinois
Huber Engineered Materials Division	Quincy, Illinois
M-I, SWACO	Amelia, Louisiana
	Battle Mountain, Nevada
	Galveston, Texas
	Westlake, Louisiana
New Riverdale Ochre Company, Inc.	Cartersville, Georgia
Unimin Corporation	Plant location not specified
Barium sulfate (synthetic):	
Barium and Chemicals, Inc.	Steubenville, Ohio
CIMBAR Performance Minerals	Cartersville, Georgia
GFS Chemicals, Inc.	Columbus, Ohio
Johnson Matthey, Inc. Alfa Aesar	Ward Hill, Massachusetts
Mineral and Pigment Solutions, Inc.	South Plainfield, New Jersey
Barium acetate:	
Barium and Chemicals, Inc.	Steubenville, Ohio
Barium carbonate:	
Barium and Chemicals, Inc.	Steubenville, Ohio
CERAC, Inc.	Milwaukee, Wisconsin
Chemical Products Corporation	Cartersville, Georgia
Johnson Matthey, Inc. Alfa Aesar	Ward Hill, Massachusetts
Mallinckrodt Inc. Pharmaceuticals Group	St. Louis, Missouri
Osram Sylvania Inc.	Towanda, Pennsylvania
Barium chloride:	
Barium and Chemicals, Inc.	Steubenville, Ohio
Chemical Products Corporation	Cartersville, Georgia
GFS Chemical, Inc.	Columbus, Ohio
Johnson Matthey, Inc. Alfa Aesar	Ward Hill, Massachusetts
Mallinckrodt Inc. Pharmaceuticals Group	St. Louis, Missouri
Osram Sylvania Inc.	Towanda, Pennsylvania
Barium hydroxide:	
Barium and Chemicals, Inc.[b,c,d]	Steubenville, Ohio
Johnson Matthey, Inc. Alfa Aesar[b,c]	Ward Hill, Massachusetts
Mallinckrodt, Inc. Pharmaceuticals Group[e]	St. Louis, Missouri
Barium oxide:	
Barium and Chemicals, Inc.	Steubenville, Ohio

Table 5-3. Current U.S. Manufacturers of Barium Metal and Selected Barium Compounds[a]

Company	Location
Barium sulfide:	
Barium and Chemicals, Inc.	Steubenville, Ohio
Chemical Products Corporation	Cartersville, Georgia
Johnson Matthey, Inc. Alfa Aesar	Ward Hill, Massachusetts

[a]Derived from SRI 2006 unless otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed.
[b]Barium hydroxide, anhydrous [$Ba(OH)_2$]
[c]Barium hydroxide octahydrate [$Ba(OH)_2 \cdot 8H_2O$]
[d]Barium hydroxide monohydrate [$Ba(OH)_2 \cdot H_2O$]
[e]Barium hydroxide, hydration not specified

Barium oxide is used to dry gases and solvents, strengthen ceramics, and as a component in some specialty cements. Barium hydroxide plays a role in glass manufacturing, synthetic rubber vulcanization, in the production of barium greases and plasticizers, as a component in sealants, pigment dispersion, paper manufacturing, sugar refining, in animal and vegetable oil refining, and in the protection of objects made of limestone from deterioration. Barium acetate is used in printing fabrics, in lubricating grease, and as a catalyst for organic reactions. Finally, the main function of barium sulfide is to act as a starting point for the production of a number of other barium compounds (Dibello et al. 2003; ILO 1983). This compound is also used in the production of thin-film electroluminescent phosphors and the vulcanization of carbon black-filled neoprene rubbers.

Barium and its compounds have several important medical uses as well. Barium chloride was formerly used in treating complete heart block, because periods of marked bradycardia and asystole were prevented through its use. This use was abandoned, however, mainly due to barium chloride's toxicity (Hayes 1982). Characterized by extreme insolubility, chemically pure barium sulfate is non toxic to humans. It is frequently utilized as a benign, radiopaque aid to x-ray diagnosis in colorectal and some upper gastrointestinal examinations, because it is normally not absorbed by the body after oral intake (de Zwart et al. 2001; Doull et al. 1980; ILO 1983; Lin 1996; Newman 1998; Pijl et al. 2002; Rae 1977).

5.4 DISPOSAL

In case of a spill, it is suggested that persons not wearing protective equipment be restricted from the area. Furthermore, ventilation should be provided in the room and the spilled material collected in as safe a manner as possible. Persons in charge of vessels or facilities are required to notify the National Response Center (NRC) immediately, when there is a release of this designated hazardous substance, in an amount equal to or greater than its reportable quantity of 1,000 pounds or 454 kg (HSDB 2007). Barium compounds (particularly soluble ones) should be placed in sealed containers and reclaimed or disposed of in a secured sanitary landfill (IPCS 1991; NIOSH/OSHA 1978). It is also suggested that all federal, state, and local regulations concerning barium disposal should be followed (HSDB 2007). No other guidelines or regulations concerning disposal of barium and its compounds were found.

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

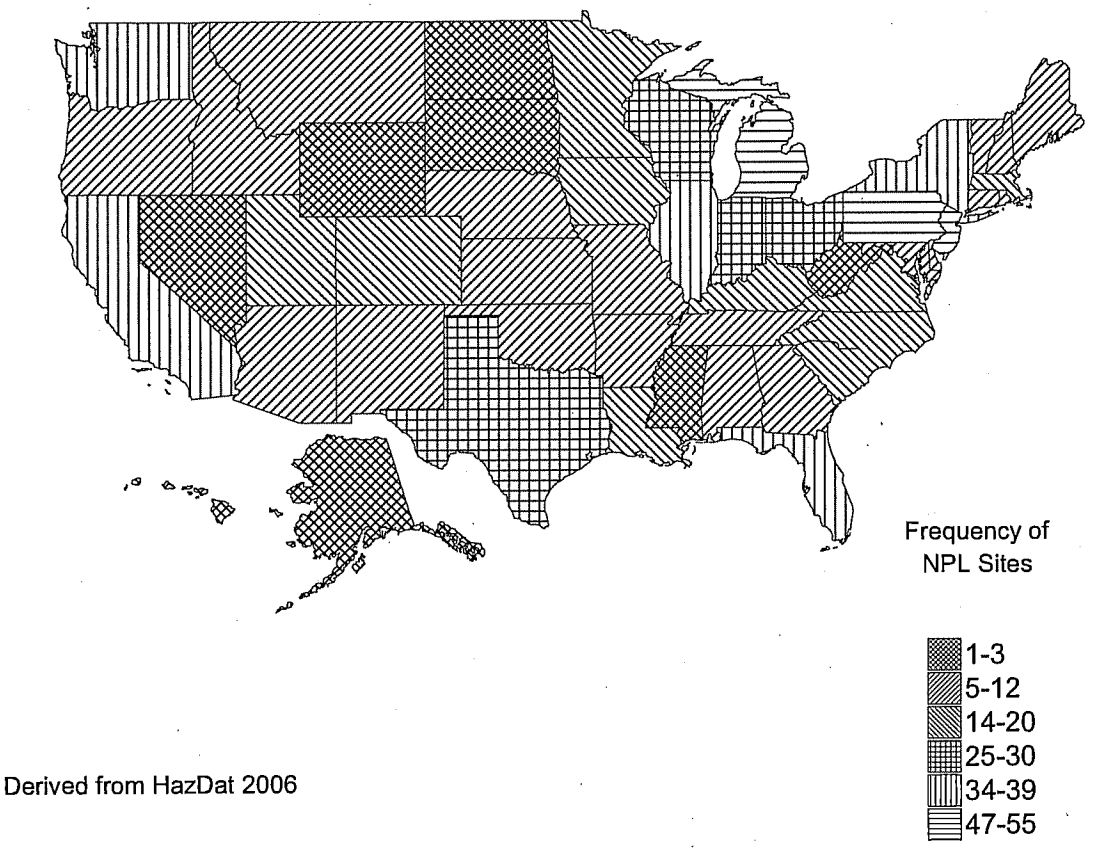
Barium has been identified in at least 798 of the 1,684 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2006). However, the number of sites evaluated for barium is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 794 are located within the United States, 1 is in the Territory of Guam, and 3 are located in the Commonwealth of Puerto Rico (the Territory of Guam and the Commonwealth of Puerto Rico are not shown).

Barium is a naturally occurring component of minerals that are found in small but widely distributed amounts in the earth's crust, especially in igneous rocks, sandstone, shale, and coal (Kunesh 1978; Miner 1969a). Barium enters the environment naturally through the weathering of rocks and minerals. Anthropogenic releases are primarily associated with industrial processes. Barium is present in the atmosphere, urban and rural surface water, soils, and many foods.

Under natural conditions, barium is stable in the +2 valence state and is found primarily in the form of inorganic complexes. Conditions such as pH, Eh (oxidation-reduction potential), cation exchange capacity, and the presence of sulfate, carbonate, and metal oxides (e.g., oxides of aluminum, manganese, silicon, and titanium) will affect the partitioning of barium and its compounds in the environment. The major features of the biogeochemical cycle of barium include wet and dry deposition to land and surface water, leaching from geological formations to groundwater, adsorption to soil and sediment particulates, and biomagnification in terrestrial and aquatic food chains.

The general population is exposed to barium through consumption of drinking water and foods, usually at low levels. Workers in barium mining or processing industries and individuals who reside near such industries might be exposed to relatively high levels, primarily through the inhalation of fugitive dust containing barium compounds. The most recent occupational exposure estimates indicate that about 10,000 people were potentially exposed to barium and about 474,000 to barium compounds in workplace environments in the United States in 1980 (NIOSH 1989a).

Figure 6-1. Frequency of NPL Sites with Barium Contamination



6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005d). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005d).

Barium is a highly reactive metal that occurs naturally only in a combined state. The element is released to environmental media by both natural processes and anthropogenic sources.

According to the SARA Section 313 Toxics Release Inventory (TRI), an estimated total of 230 million pounds (105,000 metric tons) of barium and barium compounds were released to the environment from manufacturing and processing facilities in the United States in 2004 (TRI04 2006) (see Tables 6-1 and 6-2). Most of these barium releases were to land. The TRI data must be viewed with caution since only certain types of facilities were required to report. This is not an exhaustive list.

6.2.1 Air

Estimated combined releases of 2.51 million pounds (1,140 metric tons) of barium (0.35 million pounds) and barium compounds (2.16 million pounds) to the atmosphere from 1,107 domestic manufacturing and processing facilities in 2004, accounted for about 1.09% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases are summarized in Tables 6-1 and 6-2.

Barium is released primarily to the atmosphere as a result of industrial emissions during the mining, refining, and production of barium and barium chemicals, fossil fuel combustion (Miner 1969a), and

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Barium[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	3	24,620	0	0	306,812	0	146,620	184,812	331,432
AL	5	6,963	504	0	39,889	4,748	7,459	44,645	52,104
AZ	2	1,062	0	0	1,950,946	0	1,823,807	128,201	1,952,008
CA	2	1,911	0	0	797,507	78	799,418	78	799,496
CO	1	0	0	No data	0	0	No data	0	0
CT	1	4	4	0	0	3,515	4	3,519	3,523
DE	1	20	64	0	0	0	84	0	84
GA	4	81	0	0	3,757	0	81	3,757	3,837
IA	4	36,228	0	0	163	0	36,228	163	36,391
ID	1	14	0	0	130,611	0	130,625	0	130,625
IL	3	9,428	61	0	45,553	0	9,489	45,553	55,042
IN	2	10	255	0	18,074	16,900	10	35,229	35,239
KS	2	7,501	0	0	161,964	526,878	169,465	526,878	696,343
KY	2	75,258	0	0	0	0	75,258	0	75,258
MI	5	230	666	0	44,245	271,175	896	315,420	316,316
MN	2	114,719	0	0	694	0	114,719	694	115,413
MO	1	0	0	0	0	81	0	81	81
NC	3	11	0	0	1,559	0	11	1,559	1,570
NE	6	23,979	3,320	0	37,786	362,667	65,080	362,672	427,752
NJ	2	89	0	0	30	272	89	302	391
NM	1	0	0	0	0	0	0	0	0
NV	2	1,243	0	0	817,749	0	818,992	0	818,992
NY	5	35,001	137	0	3,073	15,991	35,140	19,062	54,202
OH	14	866	372	16,649	287,615	6,472	220,822	91,152	311,974
OK	1	1,906	5	0	250	0	1,906	255	2,161
OR	1	0	0	0	230,293	1	230,293	1	230,294
PA	4	756	0	0	344,131	51,746	322,501	74,132	396,633
SC	2	253	0	0	0	72	253	72	325
SD	1	500	0	0	39,480	0	39,980	0	39,980
TN	1	0	0	No data	0	0	No data	0	0
TX	9	7,392	4,029	0	71,083	7	81,473	1,038	82,511
UT	2	10	0	0	31,035	0	31,010	35	31,045
VA	2	0	1,900	0	111,900	0	95,900	17,900	113,800
WI	1	0	0	0	257,400	0	0	257,400	257,400

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Barium[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WV	2	4,214	10	0	77,821	201	82,045	202	82,246
Total	100	354,269	11,327	16,649	5,811,421	1,260,803	5,339,658	2,114,811	7,454,470

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Barium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	16,122	0	0	16,122	0	32,244	0	32,244
AL	34	69,621	94,049	3,900	11,966,847	67,278	12,062,542	139,153	12,201,695
AR	16	28,134	107,680	0	2,906,741	44,565	3,038,693	48,427	3,087,120
AZ	10	11,779	0	0	3,951,882	61	3,962,437	1,285	3,963,722
CA	14	8,998	514	0	56,003	3,624	20,826	48,313	69,139
CO	18	14,440	2,232	0	8,687,234	7,500	5,019,424	3,691,982	8,711,406
CT	4	505	5	0	66,963	22,315	540	89,248	89,788
DE	3	17,256	9,034	0	480,594	121,025	486,290	141,619	627,909
FL	22	49,588	9,750	0	2,232,733	216,852	2,134,494	374,429	2,508,924
GA	29	61,732	112,867	0	8,660,091	19,737	8,798,097	56,330	8,854,427
HI	1	45	0	0	29,331	0	45	29,331	29,376
IA	24	142,028	3,709	0	4,358,835	229,865	3,293,915	1,440,522	4,734,437
ID	6	8,334	11,400	0	137,167	83	98,901	58,083	156,984
IL	56	218,005	114,459	0	13,593,791	370,276	6,061,909	8,234,621	14,296,530
IN	45	72,823	31,471	0	8,274,849	82,196	7,095,068	1,366,271	8,461,340
KS	12	78,277	938	0	4,774,271	250	4,853,486	250	4,853,736
KY	38	49,663	76,268	0	7,134,938	211,117	5,405,100	2,066,886	7,471,986
LA	17	70,200	40,931	1,367	4,315,727	8,307	4,411,344	25,188	4,436,532
MA	14	2,275	1,283	0	257,892	21,982	20,043	263,389	283,432
MD	18	9,340	1,880	59	468,562	697,038	90,155	1,086,724	1,176,879
ME	6	1,301	4,100	0	81,692	0	71,193	15,900	87,093
MI	32	55,968	125,134	56	10,513,385	24,961	7,965,087	2,754,417	10,719,504
MN	22	48,772	22,540	0	8,233,091	71,522	7,430,251	945,673	8,375,924
MO	30	231,257	11,722	0	10,226,716	731	10,356,850	113,576	10,470,426
MS	16	5,973	14,703	0	1,626,877	528	1,627,878	20,203	1,648,081
MT	6	111,530	781	0	8,892,216	175,814	8,951,015	229,325	9,180,340
NC	31	30,632	68,807	0	3,082,682	171,007	2,921,804	431,324	3,353,127
ND	9	39,926	24,052	0	13,826,846	6,786	7,126,843	6,770,767	13,897,610
NE	11	37,560	52	0	3,982,921	6,350	3,739,570	287,313	4,026,883
NH	5	1,532	0	0	26,500	1,583	9,632	19,983	29,615
NJ	20	7,826	9,949	0	96,325	297,053	7,832	403,321	411,153
NM	6	13,400	250	0	5,210,450	750	5,204,409	20,441	5,224,850
NV	4	25,974	0	0	1,432,649	37	1,458,623	37	1,458,660
NY	24	18,085	136,769	0	1,454,199	311,766	790,432	1,130,387	1,920,819
OH	94	43,103	82,835	319	8,642,836	424,109	5,383,148	3,810,054	9,193,202
OK	12	25,481	11,600	0	2,005,538	19	1,737,944	304,694	2,042,638
OR	5	12,393	2,120	0	115,146	0	100,513	29,146	129,659

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Barium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
PA	72	50,576	40,857	250	3,948,212	422,230	1,469,982	2,992,143	4,462,125
PR	1	1,542	0	0	91	0	1,633	0	1,633
RI	3	5	23	0	1,072	477	28	1,549	1,577
SC	36	27,220	51,763	0	1,313,342	678,479	1,263,992	806,812	2,070,803
SD	2	1,057	36	0	731,856	0	681,949	51,000	732,949
TN	24	64,154	106,884	0	4,653,790	334	4,240,684	584,478	4,825,162
TX	48	158,316	67,044	0	16,122,300	3,011,576	16,164,215	3,195,022	19,359,236
UT	9	5,422	100	0	3,661,314	3,902	3,510,292	160,446	3,670,738
VA	28	25,919	26,448	0	2,006,961	189,025	1,704,517	543,836	2,248,353
VT	1	250	5	0	0	28,667	250	28,672	28,922
WA	11	1,318	3,118	0	2,274,705	42	2,119,156	160,027	2,279,183
WI	30	37,077	20,145	0	890,567	1,023,144	342,849	1,628,084	1,970,933
WV	20	75,248	18,436	0	5,243,526	78,000	4,479,752	935,458	5,415,210
WY	7	68,528	3,229	0	7,343,092	0	6,751,399	663,450	7,414,849
Total	1,007	2,156,511	1,471,972	5,951	210,011,467	9,052,963	174,499,278	48,199,586	222,698,864

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

entrainment of soil and rock dust into the air (Schroeder 1970). In addition, coal ash, containing widely variable amounts of barium, is also a source of airborne barium particulates (Miner 1969a; Schroeder 1970). In 1969, an estimated 18% of the total U.S. barium emissions to the atmosphere resulted from the processing of barite ore, and more than 28% of the total was estimated to be from the production of barium chemicals. The manufacture of various end products (e.g., drilling well muds, and glass, paint, and rubber products) and the combustion of coal were estimated to account for an additional 23 and 26% of the total barium emissions for 1969, respectively (Davis 1972).

Estimates of barium releases from individual industrial processes are available for particulate emissions from the drying and calcining of barium compounds and for fugitive dust emissions during the processing of barite ore. Soluble barium compounds (unspecified) are emitted as particulates from barium chemical dryers and calciners to the atmosphere during the processing of barium carbonate, barium chloride, and barium hydroxide (Reznik and Toy 1978). Uncontrolled particulate emissions of soluble barium compounds from chemical dryers and calciners during barium processing operations may range from 0.04 to 10 g/kg of final product. Controlled particulate emissions are less than 0.25 g/kg of final product. Based on an uncontrolled emission factor of 5 g/kg and a controlled emission factor of 0.25 g/kg, total particulate emissions from the drying and calcining of barium carbonate, barium chloride, and barium hydroxide are estimated to be 160 metric tons (352,800 pounds) per year (Reznik and Toy 1978).

Fugitive dust emissions occur during processing (grinding and mixing) of barite ore and may also occur during the loading of bulk product of various barium compounds into railroad hopper cars (Reznik and Toy 1978). Based on an emission factor of 1 g/kg, total emissions of fugitive dust from the domestic barium chemicals industry during the grinding of barite ore have been estimated to be approximately 90 metric tons (198,450 pounds) per year (Reznik and Toy 1978). Other particulate emissions from the industrial production of barium compounds include an estimated 820 metric tons (1.8 million pounds) per year from uncontrolled kilns during the processing of barite ore and 8 metric tons (17,640 pounds) per year from black ash (i.e., barium sulfide) rotary kilns during the production of barium hydroxide (Reznik and Toy 1978). Electric utilities that burn bituminous coal emit a small fraction of the barium contained in coal into the air. For example, it is estimated that 830 pounds/year of barium are released to air from a 650 megawatt (MW) plant, in comparison to 270,000 pounds/year released as ash to land-based waste sites (Rubin 1999).

The use of barium in the form of organometallic compounds as a smoke suppressant in diesel fuels results in the release of solids to the atmosphere (Miner 1969a; Ng and Patterson 1982; Schroeder 1970). The

maximum concentration of soluble barium in exhaust gases containing barium-based smoke suppressants released from test diesel engines and operating diesel vehicles is estimated to be 12,000 μg/m^3, when the barium concentration in the diesel fuel is 0.075% by weight and 25% of the exhausted barium (at a sampling point 10 feet from the engine and upstream from the muffler) is soluble (Golothan 1967). Thus, 1 L of this exhaust gas contains an estimated 12 μg soluble barium or 48 μg total barium (Schroeder 1970). However, recent legislation requiring the use of low-sulfur fuel in diesel engines has eliminated the need for barium as a sulfur-scavenging additive and, therefore, has greatly reduced the emissions of barium from diesel engine exhaust (Schauer et al. 1999; Winkler 2002).

6.2.2 Water

Estimated combined releases of 1.48 million pounds (674 metric tons) of barium (0.01 million pounds) and barium compounds (1.47 million pounds) to surface water from 1,107 domestic manufacturing and processing facilities in 2004, accounted for about 0.64% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006).

The primary source of naturally occurring barium in drinking water results from the leaching and eroding of sedimentary rocks into groundwater (Kojola et al. 1978). Although barium occurs naturally in most surface water bodies (i.e., approximately 99% of those examined) (DOI 1970), releases of barium to surface waters from natural sources are much lower than those to groundwater (Kojola et al. 1978).

About 80% of the barium produced is used as barite to make high-density oil and gas well drilling muds, and during offshore drilling operations there are periodic discharges of drilling wastes in the form of cuttings and muds into the ocean (Ng and Patterson 1982). For example, in the Santa Barbara Channel region, about 10% of the muds used are lost into the ocean (Ng and Patterson 1982). Operations involving three drilling platforms in the Santa Maria Basin off the coast of central California released approximately $1.8x10^6$ kg of barium to the ocean in discharged muds, cuttings, and waste water from 1986 to 1994 (Phillips et al. 1998). The use of barium in offshore drilling operations may increase barium pollution, especially in coastal sediments (Ng and Patterson 1982).

6.2.3 Soil

Estimated combined releases of 216 million pounds (98,095 metric tons) of barium (5.81 million pounds) and barium compounds (210 million pounds) to soils from 1,107 domestic manufacturing and processing facilities in 2004, accounted for about 93.7% of the estimated total environmental releases from facilities

required to report to the TRI (TRI04 2006). An additional combined total of 0.023 million pounds (10 metric tons) from barium (0.017 million pounds) and barium compounds (0.006 million pounds), constituting about 0.01% of the total environmental emissions, were released via underground injection (TRI04 2006). These releases are summarized in Tables 6-1 and 6-2.

The process of drilling for crude oil and natural gas generates waste drilling fluids or muds, which are often disposed of by land farming. Most of these fluids are water based and contain barite and other metal salts. Thus, barium may be introduced into soils as the result of land farming these slurried reserve pit wastes (Bates 1988).

The use of barium fluorosilicate and carbonate as insecticides (Beliles 1979; Meister 2004) might also contribute to the presence of barium in agricultural soils.

Barium has been detected with a positive geometric mean concentration of 100.5 ppm in soil samples from approximately 52% of the hazardous waste sites that have had samples analyzed by the CLP (CLPSD 1989). Note that these data from the CLPSD represent frequency of occurrence and concentration data for NPL sites only.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Most barium released to the environment from industrial sources is in forms that do not become widely dispersed (Ng and Patterson 1982). In the atmosphere, barium is likely to be present in particulate form (EPA 1984). Although chemical reactions may cause changes in speciation of barium in air, the main mechanisms for the removal of barium compounds from the atmosphere are likely to be wet and dry deposition (EPA 1984).

In aquatic media, barium is likely to precipitate out of solution as an insoluble salt (i.e., as $BaSO_4$ or $BaCO_3$). Waterborne barium may also adsorb to suspended particulate matter through the formation of ion pairs with natural anions such as bicarbonate or sulfate in the matter (Bodek et al. 1988; EPA 1984; Giusti et al. 1993; Lagas et al. 1984; Tanizaki et al. 1992). Precipitation of barium sulfate salts is accelerated when rivers enter the ocean because of the high sulfate content (905 mg/L) in the ocean (Bowen 1966; WHO 2001). It is estimated that only 0.006% of the total barium input into oceans from freshwater sources remains in solution (Chow et al. 1978; WHO 2001). Sedimentation of suspended

solids removes a large portion of the barium content from surface waters (Benes et al. 1983). There is evidence to suggest that the precipitation of barium from the surface of fresh and marine waters occurs, in part, as the result of the barite crystal formation in microorganisms (González-Muñoz et al. 2003). Barium in sediments is found largely in the form of barium sulfate (barite). Coarse silt sediment in a turbulent environment will often grind and cleave the barium sulfate from the sediment particles leaving a buildup of dense barites (Merefield 1987). Estimated soil:water distribution coefficients (Kd) (i.e., the ratio of the quantity of barium sorbed per gram of sorbent to the concentration of barium remaining in solution at equilibrium) range from 200 to 2,800 for sediments and sandy loam soils (DOE 1984; Rai et al. 1984).

The uptake of barium by fish and marine organisms is also an important removal mechanism (Bowen 1966; Schroeder 1970). Barium levels in sea water range from 2 to 63 µg/L with a mean concentration of about 13 µg/L (Bowen 1979). Barium was found to bioconcentrate in marine plants by a factor of 400–4,000 times the level present in the water (Bowen 1966). Bioconcentration factors in marine animals, plankton, and brown algae of 100, 120, and 260, respectively, have been reported (Schroeder 1970). In freshwater, a bioconcentration factor of 129 was estimated in fish where the barium in water was 0.07 mg/L (Hope et al. 1996).

Barium added to soils (e.g., from the land farming of waste drilling muds) may either be taken up by vegetation or transported through soil with precipitation (Bates 1988). Relative to the amount of barium found in soils, little is typically bioconcentrated by plants (Schroeder 1970). For example, a bioconcentration factor of 0.4 has been estimated for plants in a Virginia floodplain with a barium soil concentration of 104.2 mg/kg (Hope et al. 1996). However, there are some plants, such as legumes, forage plants, Brazil nuts, and mushrooms that accumulate barium (Aruguete et al. 1998; IPCS 1991; WHO 2001). Bioconcentration factors from 2 to 20 have been reported for tomatoes and soybeans (WHO 2001).

Barium is not very mobile in most soil systems, due to the formation of water-insoluble salts and an inability of the barium ion to form soluble complexes with fulvic and humic acids (WHO 2001). The rate of transportation of barium in soil is dependent on the characteristics of the soil material. Soil properties that influence the transportation of barium to groundwater are cation exchange capacity, calcium carbonate ($CaCO_3$) content and pH. In soil with a high cation exchange capacity (e.g., fine textured mineral soils or soils with high organic matter content), barium mobility will be limited by adsorption (Bates 1988; Kabata-Pendias and Pendias 1984). High $CaCO_3$ content limits mobility by precipitation of

the element as $BaCO_3$ (Lagas et al. 1984). Barium will also precipitate as barium sulfate in the presence of sulfate ions (Bodek et al. 1988; Lagas et al. 1984). Barium is more mobile and is more likely to be leached from soils in the presence of chloride due to the high solubility of barium chloride as compared to other chemical forms of barium (Bates 1988; Lagas et al. 1984). Barium may become more mobile in soils under acid conditions as barium in water-insoluble salts, such as barium sulfate and carbonate, becomes more soluble (WHO 2001). Barium complexes with fatty acids (e.g., in acidic landfill leachate) will be much more mobile in the soil due to the lower charge of these complexes and subsequent reduction in adsorption capacity (Lagas et al. 1984).

Barium mobility in soil is reduced by the precipitation of barium carbonate and sulfate. Humic and fulvic acid have not been found to increase the mobility of barium (EPA 1984).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Elemental barium undergoes oxidation in air and is oxidized readily in moist air (Boffito 2002; EPA 1983; Kresse et al. 2007; Kunesh 1978). The residence time of barium in the atmosphere may be several days, depending on the size of the particulate formed, the chemical nature of the particulate, and environmental factors such as rainfall (EPA 1984; WHO 2001).

6.3.2.2 Water

Under natural conditions, barium will form compounds in the +2 oxidation state. Barium does not hydrolyze appreciably except in highly alkaline environments (i.e., at pH levels ≥10) (Bodek et al. 1988).

Appreciable levels of barium sulfate occur because natural water often contains high sulfate concentrations, especially ocean water. Since the solubility of barium sulfate is low, only trace amounts of barium dissolve in surface water (Bodek et al. 1988; NAS 1977). At pH levels of 9.3 or below, barium sulfate may limit barium concentrations in natural waters (Bodek et al. 1988). The solubility of barium sulfate increases considerably in the presence of chloride (Cl^-) and other anions (e.g., NO_3^- and CO_3^{-2}), and at pH levels of 9.3 or below, the barium ion (Ba^{2+}) is the dominant species (Bodek et al. 1988; NAS 1977). The Ba^{2+} ion is stable under the pH-Eh range of natural systems. However, natural and treated waters usually contain sufficient sulfate so that a barium ion concentration of more than 1,000–

1,500 μg/L cannot be maintained in solution (EPA 1983; Hem 1959; Lagas et al. 1984; McCabe et al. 1970).

As pH levels increase above 9.3 and in the presence of carbonate, barium carbonate becomes the dominant species (Bodek et al. 1988; Singer 1974). Barium carbonate also exhibits fast precipitation kinetics and very low solubility and in alkaline environments limits the soluble barium concentration (Faust and Aly 1981; Hem 1959; Rai et al. 1984; Singer 1974). Barium forms salts of low solubility with arsenate, chromate, fluoride, oxalate, and phosphate ions (Bodek et al. 1988; EPA 1983; Kunesh 1978). The chloride, hydroxide, and nitrate of barium are water-soluble (Bodek et al. 1988; EPA 1983; Kirkpatrick 1978) and are frequently detected in aqueous environments (Rai et al. 1984).

Barium also forms complexes with natural organics in water (e.g., fatty acids in acidic landfill leachates) to a limited extent (Lagas et al. 1984; Morel 1983; Rai et al. 1984).

6.3.2.3 Sediment and Soil

Barium reacts with metal oxides and hydroxides in soil and is subsequently adsorbed onto soil particulates (Hem 1959; Rai et al. 1984). Adsorption onto metal oxides in soils and sediments probably acts as a control over the concentration of barium in natural waters (Bodek et al. 1988). Under typical environmental conditions, barium displaces other adsorbed alkaline earth metals from MnO_2, SiO_2, and TiO_2 (Rai et al. 1984). However, barium is displaced from Al_2O_3 by other alkaline earth metals (Rai et al. 1984). The ionic radius of the barium 2+ ion, its typical oxidation state, makes isomorphous substitution possible only with strontium, and generally not with the other members of the alkaline earth elements (Kirkpatrick 1978). Among the other elements that occur with barium in nature, substitution is common only with potassium but not with the smaller ions of sodium, iron, manganese, aluminum, and silicon (Kirkpatrick 1978).

Barium is also adsorbed onto soil and subsoil through electrostatic interactions (Bodek et al. 1988; Singer 1974). The cation exchange capacity of the sorbent largely controls the retention of barium in soils (Bodek et al. 1988). Barium is strongly adsorbed by clay minerals (Kabata-Pendias and Pendias 1984; Lagas et al. 1984).

Barium can also form salts with acetate, nitrate, chloride, and hydroxide ions in soil. The mobility of barium in soils increases upon formation of these water soluble salts (Bodek et al. 1988). In general, the solubility of barium compounds increases with decreasing pH.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to barium depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of barium in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on barium levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring barium in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

The concentration of barium in ambient air is estimated to be <0.05 $\mu g/m^3$ (IPCS 1991). Airborne barium likely exists as the carbonate or sulfate salts and is carried on particulate matter that results as a consequence of natural processes (e.g., suspension of soil dust) or anthropogenic activities (e.g., combustion process, mining and calcining of barium ores) (WHO 2001). However, there is no apparent correlation between the degree of industrialization and barium concentrations in ambient air (Winkler 2002). Particulate matter from diesel exhaust was once a source of barium in ambient air. However, barium emissions from diesel engines has been greatly diminished to near zero emissions with the current use of low-sulfur diesel fuels, which do not require the addition of barium as a sulfur-scavenging agent (Hildemann et al. 1991; Schauer et al. 1999; Shahin et al. 2000; Winkler 2002).

Tabor and Warren (1958) report urban and suburban air concentrations of barium ranging from <0.005 to 1.5 $\mu g/m^3$. In another study of barium concentrations in ambient air, values ranged from 0.0015 to 0.95 mg/m^3 (EPA 1984). No distinct pattern related to industrialization appeared in the results reported on 754 samples from 18 cities and four suburban areas in the United States. For example, in Houston, Texas and its suburbs, 76% of the samples contained barium at levels ranging from 0.005 to 1.5 $\mu g/m^3$, whereas in Fort Worth, Texas, 66% of the samples had values <0.005 $\mu g/m^3$ (Tabor and Warren 1958).

Another compilation of atmospheric data shows barium concentrations in urban atmospheres of North America ranging from $2x10^{-4}$ to $2.8x10^{-2}$ $\mu g/m^3$ with a mean concentration of $1.2x10^{-2}$ $\mu g/m^3$ (Bowen

1979). In contrast, barium levels in samples from the South Pole and northern Norway were $1.6x10^{-5}$ and $7.3x19^{-4}$ μg/m^3, respectively (Bowen 1979). Mean barium concentrations in background air collected between April and October 2002 on the campus of the University of Birmingham, United Kingdom, were 0.32 and 1.4 ng/m^3 in the <0.5 and 3.0–7.2 μm particular matter fractions, respectively (Birmili et al. 2006).

Maximum ground-level barium concentrations (as soluble compounds) associated with uncontrolled atmospheric particulate emissions from chemical dryers and calciners at barium-processing plants have been estimated (using dispersion modeling) to range from 1.3 to 330 μg/m^3 over a 24-hour averaging time at locations along facility boundaries (i.e., away from the source of emission) (Reznik and Toy 1978).

Barium has been measured in dust samples taken from 49 residences in Ottawa, Canada. Mean and median concentrations of 405.56 and 222.22 mg barium/kg dust, respectively, were measured within a sub-fraction of the dust samples where the particulate sizes ranged from 100 to 250 μm (Butte and Heinzow 2002; Rasmussen et al. 2001).

Barium has been measured in rain and snow collected near Claremont, New Hampshire in 1996–1997 (Feng et al. 2000). Barium concentrations in rain ranged from 0.22 to 0.84 μg/L with a mean concentration of 0.39 μg/L. In snow, barium concentrations ranged from 0.64 to 7.44 μg/L with a mean concentration of 1.5 μg/L.

Barium has been detected in air samples collected at 24 of the 798 hazardous waste sites where barium has been detected in some environmental medium (HazDat 2006). The HazDat information includes data from both NPL and other Superfund sites. Concentrations of barium in air ranged from 0.015 to 327,000,000 μg/m^3 in 16 onsite (HazDat 2006). In comparison, concentrations of barium in air ranged from 0.0135 to 561,000,000 μg/m^3 in 12 offsite samples (HazDat 2006).

6.4.2 Water

Barium has been found in almost all raw surface waters and public drinking water supplies sampled (i.e., approximately 99%) (Kopp 1969) at concentrations ranging from ≤5 to 15,000 μg/L with mean concentrations generally on the order of 10–60 μg/L (Barnett et al. 1969; Bowen 1979; DOI 1970; Durfor and Becker 1964; Durum and Haffty 1961; Elinder and Zenz 1994; EPA 2005c; Kopp 1969; Longerich et al. 1991; McCabe et al. 1970; Neal et al. 1996; Saleh and Wilson 1999; Tuovinen et al. 1980). Barium

concentrations are lowest (mean value of 15 μg/L) in the drainage basins of the western Great Lakes and highest (mean value of 90 μg/L) in the southwestern drainage basins of the lower Mississippi Valley (EPA 2005c). Barium concentrations in the shallow aquifer below Denver, Colorado, have been reported to range from 18 to 594 μg/L with a median value of 104 μg/L (Bruce and McMahon 1996). Barium concentrations in most drinking water supplies are <200 μg/L with a mean concentration of 28.6 μg/L (EPA 2005c). In California, mean and median values of 302 and 160 μg/L, respectively, were measured for barium concentrations in drinking water supplies (Storm 1994).

Barium concentrations in groundwater supplies have been known to exceed EPA's maximum contaminant level (MCL) of 2.0 mg/L (2,000 μg/L) (EPA 2002a); this may be due to leaching and erosion of barium from sedimentary rocks (Calabrese 1977; Kojola et al. 1978). For example, community water supplies from deep rock and drift wells in northeastern Illinois have been found to have barium concentrations ranging from 1,100 to 10,000 μg/L (Calabrese 1977). Many communities in Kentucky, Pennsylvania, and New Mexico have drinking water where the barium content is up to ten times higher than the MCL (EPA 2005c). Water samples taken from groundwater wells in Texas that are within 750 m of brine injection, dry, or plugged gas/oil wells contain barium ranging in concentration from 1.2 to 2,300 μg/L (Hudak and Wachal 2001).

A mean concentration of 167 μg/L for barium was measured in influent streams of a public waste water treatment plant in Melbourne, Australia (Wilkie et al. 1996). The amount of barium in the influent streams could not be accounted for based on the mean concentrations of barium in domestic water supplies (20 μg/L) or domestic sewage (38 μg/L). Instead, it is likely that the barium unaccounted for in the influent stream is the result of barium carried in effluents from industries that are discharged into the catchment area of the treatment plant.

Barium has also been found in sea water at concentrations ranging from 2 to 63 μg/L with a mean concentration of 13 μg/L (Bowen 1979).

Barium has been detected in surface water and groundwater samples collected at 257 and 561 of the 798 hazardous waste sites, respectively, where barium has been detected in some environmental medium (HazDat 2006). The HazDat information includes data from both NPL and other Superfund sites. Maximum concentrations of barium in surface water (lakes, streams, ponds, etc.) ranged from 0.33 to 18,100,000 μg/L in 77 onsite samples (HazDat 2006). In comparison, maximum concentrations of barium in surface water (lakes, streams, ponds, etc.) ranged from 10 to 73,8000 μg/L in 112 offsite

samples (HazDat 2006). The maximum concentrations of barium in groundwater ranged from 0.064 to 2,100,000 µg/L in 442 onsite samples (HazDat 2006). In comparison, maximum concentrations of barium in groundwater ranged from 0.05 to 803,000 µg/L in 260 offsite samples (HazDat 2006).

6.4.3 Sediment and Soil

Barium is relatively abundant in the earth's crust and is found in most soils at concentrations (Table 6-3) ranging from about 15 to 3,500 ppm (dry weight) and mean values ranging between 265 and 835 ppm, depending on soil type (EPA 1995a; Kabata-Pendias and Pendias 1984; Lide 2005; Zenz et al. 1994). The barium content in cultivated and uncultivated soil samples collected during a number of field studies ranged from 15 to 1,000 ppm (mean concentration of 300 ppm) for B horizon soils (subsurface soils) in the eastern United States and from 70 to 5,000 ppm (mean concentration of 560 ppm) for B horizon soils in the western United States (Bowen 1979; Schroeder 1970; Shacklette and Boerngen 1984). Barium content ranged from 150 to 1,500 ppm for surface horizon soils collected in Colorado (mean concentration of 550 ppm) (Connor and Shacklette 1975). Soil samples (0–6 inch depth) taken from three New England cities, Boston, Providence and Springfield, were reported to have mean barium concentrations of 53.95, 45.29 and 45.17 mg/kg, respectively, and upper 95% interval values of 66.25, 59.43, and 51.03 mg/kg, respectively (Bradley et al. 1994). Soil samples were obtained from areas that were not influenced by industrial activity, such as along roads and sidewalks, parks and open lots, and may account for why the mean values for barium concentration were well below a mean value of 420 mg/kg for the United States.

Geometric mean concentrations of barium in sediments taken from 16 sampling sites along the southern shore of Lake Ontario and southeastern shore of Lake Erie ranged from 6.0 to 143.6 µg/g (dry weight) (Lowe and Day 2002). Thirteen of the 16 sites had mean barium concentrations that exceeded EPA's guidelines (20–60 µg barium/g dry weight) for defining moderately polluted harbor sediments for this metal. However, these concentrations are lower than the mean barium concentration of 482.1 µg/g in sediments collected from Lake Pontchartrain near New Orleans, Louisiana (USGS 2002c). The barium content in total suspended solids collected from the Mississippi River before it enters Lake Pontchartrain was 599 µg/g.

Barium concentrations in sediments near offshore drilling platforms are typically higher than unaffected sediments. Surficial and suspended sediments collected within 500 m of a drilling platform in the Santa Maria Basin offshore of central California contained barium at concentrations of 923 and 736 mg/kg dry

Table 6-3. Concentrations of Barium in Surface Soils of the United States[a,b]

Soil	Concentration[c]	
	Mean	Range
Sandy and lithosols on sandstone	400	20–1,500
Light loamy soils	555	70–1,000
Loess and soils on silt deposits	675	200–1,500
Clay and clay loamy soils	535	150–1,500
Alluvial soils	660	200–1,500
Soils over granite and gneisses	785	300–1,500
Soils over volcanic rocks	770	500–1,500
Soils over limestones and calcareous rocks	520	150–1,500
Soils on glacial till and drift	765	300–1,500
Light desert soils	835	300–2,000
Silty prairie soils	765	200–1,500
Chernozems and dark prairie soils	595	100–1,000
Organic light soils	265	10–700
Forest soils	505	150–2,000
Various soils	560	70–3,000
Mean concentration in Earth's crust[d]	500	—
Mean concentration in Earth's crust[e]	425	—

[a]Data obtained from Kabata-Pendias and Pendias (1984) unless indicated otherwise
[b]Data are for whole soil profiles
[c]Concentrations expressed as ppm dry weight
[d]Zenz et al. 1994
[e]Lide 2000

Source: Adapted from EPA 1995a

weight, respectively (Phillips et al. 1998). These values were higher (although not statistically significant) than the values of 869 and 687 mg/kg dry weight measured in surficial and suspended sediments, respectively, collected at a distance of 1,000 meters from the platform and are similar to the predrilling concentrations of barium in these sediments. In other California coastal sediments, for example the Southern California Bight, barium concentrations range from 145 to 1,259 ppm with an average of 720 ppm (Chow et al. 1978). Median barium concentration ranges in sediments from the lake system in Chiapas, Mexico were 54.4–121.2 and 50.3–155.3 μg/g dry weight in three lakes during the dry (June 2002) and rainy (September 2000) seasons, respectively (Pascual-Barrera et al. 2004). This lake system is an area of petroleum extraction and processing. Barium concentrations ranging from 180 to 2,800 μg/g dry weight (mean 729 μg/g dry weight) were reported in surface sediments (<63 μm fraction) collected in April 2002 from eight stations in Izmit Bay, Turkey (Pekey 2006).

Barium has been detected in soil and sediment samples collected at 369 and 260 of the 798 hazardous waste sites, respectively, where barium has been detected in some environmental medium (HazDat 2006). The HazDat information includes data from both NPL and other Superfund sites. Maximum concentrations of barium in soil (topsoil, <3 inches depth) ranged from 1.59 to 13,000 ppm in 84 onsite samples (HazDat 2006). In comparison, maximum concentrations of barium in soil (topsoil, <3 inches depth) ranged from 3 to 54,700 ppm in 28 offsite samples (HazDat 2006). Maximum concentrations of barium in sediment (lakes, streams, ponds, etc.) ranged from 13.1 to 17,600 ppm in 36 onsite samples (HazDat 2006). In comparison, maximum concentrations of barium in sediment (lakes, streams, ponds, etc.) ranged from 0.156 to 26,400 ppm in 92 offsite samples (HazDat 2006).

6.4.4 Other Environmental Media

Barium occurs in many foods at generally low levels (Table 6-4). In the Canadian Total Diet Study, the concentrations of barium were found to be less than 4 ppm (4,000 ng/g) in a variety of foods (Health Canada 2005). However, Brazil nuts have notably high concentrations of barium (3,000–4,000 ppm) (Beliles 1979). Some plants bioconcentrate barium from the soil (Beliles 1979; Reeves 1979; Schroeder 1970). The barium content in corn samples from Georgia, Missouri, and Wisconsin collected during a number of field studies ranged from 5 to 150 ppm with mean concentrations ranging from 15 to 54 ppm (Connor and Shacklette 1975). The barium content in other cultivated plants (e.g., lima beans, cabbage, soybeans, and tomatoes) from Georgia, Missouri, and Wisconsin ranged from 7 to 1,500 ppm with mean concentrations in various plants ranging between 38 and 450 ppm. The highest levels occurred in

Table 6-4. Concentrations of Barium in Food Obtained from the Canadian Total Diet Study Between 1993 and 1999

Food Categories	Concentration (ng/g)	
	Average[a]	Range[b]
Milk	71.22	67.96–73.24
Dairy produce (ice cream, yogurt, cheese, cream)	332.37	70.61–962.93[c]
Meats (beef, pork veal, lamb, organ meats)	131.82	12.06–237.57
Eggs	456.69	456.69
Poultry (chicken, turkey)	52.53	52.53
Fish (marine, fresh water, canned) and shellfish	137.28	36.17–481.34
Soups (meat, cream, tomato, dehydrated)	130.01	119.66–154.53
Breads, cereals, pasta, rice, pastries (cake, pies)	891.16	45.86–3,840.40[d]
Vegetables	425.69	47.99–2,282.23[e]
Fruits	570.33	57.62–3,750.03[f]
Oils, fats, butter	32.45	20.67–53.08
Candy, syrups, jams, gelatin, puddings, honey, sugar	300.60	4.86–903.07[g]
Peanut butter and peanuts	2,919.11	2,919.11
Beverages (beer, wine, coffee, tea, soft drinks, tap water)	70.94	13.05–151.82
Baby foods and formula	196.46	46.98–481.85
Frozen entrees	457.76	393.57–594.11
Processed foods (pizza, burgers, French fries, hot dog, etc.)	516.96	278.43–864.58

[a]Values represent the average barium concentration in the foods covered under the individual food categories.
[b]Values represent the range of average concentrations of the food items covered under the individual food categories.
[c]The highest barium concentrations were found in unprocessed cheeses (962.93 ng/g).
[d]The highest barium concentrations were found in wheat and bran cereals (3,840.40 ng/g), whole wheat bread (1,494.06 ng/g), muffins (1,434.30 ng/g), and cookies (1,029.13 ng/g).
[e]The highest barium concentrations were found in beets (2,282.23 ng/g) and carrots (1,309.25 ng/g).
[f]The highest barium concentrations were found in raspberries (3,750.03 ng/g) and strawberries (1,176.48 ng/g).
[g]The highest barium concentrations were found in chocolate candy bars (903.07 ng/g).

Source: Health Canada (2005)

cabbage from Georgia and soybeans from Missouri and the lowest levels occurring in Georgia tomatoes (Connor and Shacklette 1975).

Grippo et al. (2006) measured various metal concentrations in dietary supplements purchased from random local vendors in the Little Rock, Arkansas area between 2002 and 2003. Barium concentrations in botanicals were 0.0200 and 15.4 ng/g in samples of milk thistle and kava kava, respectively. Barium concentrations in ephedra-containing supplements were 0.0400 and 93.3 ng/g in Virgin Earth and Xenadrine RFA-1, respectively. The authors noted that all metals measured in this study were detected at concentrations below toxic levels or physiological limits for daily intake, where such limits have been identified (Grippo et al. 2006).

The Wyoming Game and Fish Department collected game fish during the 2000–2001 season to survey the state's fisheries for metal contamination. Ninety-six fish composites (fillets) were collected, representing 11 species, from 28 lakes and reservoirs across Wyoming. In this study, barium concentrations were at or below the method detection limit of 0.05 mg/kg (Dailey et al. 2005). Mean barium concentrations ranging from 0.057 to 0.255 mg/kg wet weight were reported in muscle tissue of five species of sturgeons collected from the Caspian Sea (Pourang et al. 2005).

Barium is also found in anaerobic sewage sludge at concentrations ranging from 100 to 9,000 ppm (mean concentration of 800 ppm) and in aerobic sewage sludge at concentrations ranging from 100 to 300 ppm (mean concentration of 200 ppm) (Sommers 1977).

Barium concentrations in leachates from municipal landfills range from 0.11 to 9,220 μg/L (EPA 1990, 1991; Roy 1994).

Barium concentrations in fertilizers and soil amendments range from <0.2 to 669 μg/g mean (Raven and Loeppert 1997). The highest levels are in tilemsi phosphate rock (669 μg/g), austenite (408 μg/g), milorganite (165 μg/g), manure (153 μg/g), and compost (131 μg/g). There is some concern that continued use of fertilizers and soil amendments, which contain high amounts of barium and other metals, may result in an accumulation of barium in agricultural soils. The accumulation of barium in soils that is due to the continued use of fertilizers and soil amendments and the potential for increased content of barium in agricultural products and potential harm to the environment have not yet been assessed (Raven and Loeppert 1997).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The primary routes of exposure of humans to barium are consumption of food and water and inhalation of ambient air (ICRP 1974; Reeves 1979; WHO 2001). Based on compliance monitoring data from the Federal Reporting Data System (FRDS), of the approximately 214 million people in the United States who are connected to a public water supply, it is estimated that about 150,000 people are exposed to barium concentrations greater than EPA's MCL of 2.0 mg/L (2,000 μg/L) (EPA 2002a). However, since 94% of all samples collected from public water supplies of the 100 largest cities in the United States had barium concentrations <100 μg/L (Durfor and Becker 1964), it is likely that most of the people connected to a public water supply receive drinking water with barium concentrations below the MCL. In a survey of drinking water from residences in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin) taken from the National Human Exposure Assessment Survey (NHEXAS) in 1995, an average barium concentration of 30 μg/L was obtained, with a 90^{th} percentile value of 77 μg/L (Thomas et al. 1999). Assuming an average adult drinking water consumption rate of 2 L/day and that barium is present at concentrations of 30 μg/L, the average adult daily intake of barium through the consumption of drinking water would be 60 μg/day (0.86 μg/kg/day for a 70-kg adult). However, the International Commission for Radiation Protection (ICRP) estimates that the gastrointestinal absorption of barium is <5% (ICRP 1973).

The International Commission on Radiological Protection (ICRP 1974) has estimated that intake of barium through inhalation ranges from 0.09 to 26 μg/day. Based on reported urban air concentrations for barium (<0.005–1.5 $\mu g/m^3$) (Tabor and Warren 1958) and assuming an average adult ventilation rate of 20 m^3/day (EPA 1989), the calculated daily respiratory intake of barium ranges from <0.1 to 30 μg, which is comparable to the ICRP estimated intake range above. Based on the 8-hour time-weighted average threshold limit value (TLV) in workplace air of 500 $\mu g/m^3$ (ACGIH 2004), and assuming an 8-hour inhalation of 10 m^3 of air, a daily barium workplace intake of 5,000 μg can be calculated. NAS (1977) estimated that 75% of inhaled barium could be absorbed into the bloodstream if soluble barium salts were involved.

Since average ground level concentrations of an emission vary with the distance from the emission point, the population around a source site will be exposed to differing emission levels. Using an average population density of 27 persons/km^2 (based on actual population data from areas surrounding barium production and processing plants), it has been estimated that approximately 0–886 persons within an area of up to 32.8 km^2 around a source site could be exposed to soluble barium compound concentrations of

>1.67 μg/m^3 in ambient air (Reznik and Toy 1978). Assuming that the average adult daily ventilation rate is 20 m^3 (EPA 1989), breathing these ambient air barium concentrations would result in daily respiratory intakes of >32 μg. No other correlations have been established between barium concentrations in air and geographical areas or land-use types.

The day-to-day intake of barium is likely to vary with the quantity and types of food ingested since the barium content in foods varies widely (Schroeder 1970). Based on consumption of food and beverages in long-term balance studies of four individuals, daily barium intake was estimated to range from 650 to 1,770 μg/day, or from 9.30 to 25.3 μg/kg body weight/day based on an adult weight of 70 kg (Tipton et al. 1966, 1969). Assuming an estimated average barium intake of 60 μg/day from drinking water that is based on the barium concentrations in drinking water obtained in the NHEXAS EPA Region V study (Thomas et al. 1999) and a consumption of 2 L of water per day, the barium intake from the consumption of non-drinking water dietary sources alone would range from 590 to 1,710 μg/day. Thus, food is typically the primary source of barium exposure for the general population. Gastrointestinal absorption of barium from food was reported to be approximately 6% (ranging from 1 to 15%) (ICRP 1974). However, reevaluation of this ICRP data and the data from other studies (Harrison et al. 1956; LeRoy et al. 1966); Tipton et al. 1969, Schroeder et al. 1972) using the methods of re-estimating barium absorption, which are based on current information of systemic kinetics of barium (Leggett 1992), suggest that gastrointestinal absorption of barium may be higher, generally ranging between 7 and 30% and could be as high as 95% in some individuals.

In the Canadian Total Diet Study (TDS) of 1993–1999, the average barium intake in individuals surveyed was found to be highest in young children (Health Canada 2005). The average barium intake ranged from 20.760 to 25.251 μg/kg body weight/day for children ages 0–4 years old (Table 6-5). For individuals older than 4 years, the average barium intake decreased for both males and females with increasing age to values of 9.704 (20–39 years) and 7.839 (>65 years) μg/kg body weight/day in males and 8.418 (20–39 years) and 7.546 (>65 years) μg/kg body weight) in females. The average daily barium intakes from the Canadian TDS for males and females of all ages (8.817 μg/kg body weight/day) is in reasonable agreement with the low end of the daily intake range for barium of 9.30 μg/kg body weight/day determined by Tipton et al. (1966, 1969).

Mean daily balances (excluding loss via hair and sweat) determined from long-term balance studies of four adult subjects ranged from a negative balance of 800 μg to a positive balance of 890 μg (Tipton et al. 1966, 1969). Based on data from these studies, Schroeder (1970) estimated that human daily intake

Table 6-5. Average Dietary Intake of Barium in Different Age/Sex Groups from the Canadian Total Diet Study (1993–1999)

Sex	Age	Intake[a]
Male and female	0–1 months	20.760
Male and female	2–3 months	23.350
Male and female	4–6 months	21.414
Male and female	7–9 months	21.213
Male and female	10–12 months	22.823
Male and female	1–4 years	25.251
Male and female	5–11 years	18.741
Male	12–19 years	11.759
Male	20–39 years	9.704
Male	40–64 years	8.976
Male	≥65 years	7.839
Female	12–19 years	9.280
Female	20–39 years	8.418
Female	40–64 years	7.855
Female	≥65 years	7.546
Male and female	All ages	8.817

[a]micrograms barium per kilogram body weight per day

Source: Health Canada (2005)

from food (1,160 μg), water (80 μg), and air (10 μg) would be approximately 1,250 μg, and that loss from urine (180 μg), feces (1,010 μg) and other sources (e.g., sweat and hair) (85 μg) would be 1,275 μg. Using these latter estimates of barium intake and loss, a negative barium balance of 25 μg would occur. According to ICRP, the average daily intake of barium from food and fluids (750 μg) and ambient air (0.09–26 μg) ranges from 750 to 776 μg. In addition, ICRP (1974) estimated that approximately 825 μg of barium is lost daily through the urine (50 μg), feces (690 μg), sweat (10 μg), and hair (75 μg). These intake and loss estimates indicate a negative daily balance of up to 75 μg. However, these negative daily balance values of 25 and 75 μg are not significant. Also, it is not expected that a negative daily balance would maintain a total body content of barium for a 70-kg adult of 22,000 μg, a value that was estimated from a study of barium content in major human organs and tissues (ICRP 1974; Schroeder et al. 1972). Ninety-three percent of this barium was found in bone and connective tissue. The remaining 7% of barium exists largely in fat, skin, and lungs.

Barium content in the human population has been determined in urine and major organs and tissues in more current studies. Barium concentrations in urine for the United States population aged 6 years and older were measured in the Third National Health and Nutrition Examination Survey (NHANES). The geometric mean (95% confidence interval) for the creatinine-adjusted levels of barium in urines for all ages was 1.44 (1.31–1.58) μg per gram of creatinine (CDC 2005). Within age groups, the geometric means for the barium concentration in urine decreased as a function of age, from 2.20 μg per gram of creatinine (6–11 years) to 1.45 μg per gram of creatinine (12–19 years) and 1.37 μg per gram of creatinine (20 years and older). The geometric mean concentration of barium in females (1.59 μg per gram of creatinine) was slightly higher than in males (1.30 μg per gram of creatinine). As a function of ethnicity, non-Hispanic whites had the highest geometric mean barium concentrations (1.62 μg per gram of creatinine) followed by Mexican Americans (1.18 μg per gram of creatinine) and non-Hispanic African Americans (0.891 μg per gram of creatinine). A median urinary concentration of 1,146 ng/L (range 295–5,250 ng/L) was reported in urine of 50 healthy individuals, aged 20–68 years, in central Italy (Alimonti et al. 2005).

Occupational exposure to barium primarily occurs in workers and miners who inhale barium sulfate (or the ore, barite) and barium carbonate dust during the mining of barite and the manufacturing and processing (e.g., mixing, grinding, and loading) of barium compounds (Beliles 1979; Reznik and Toy 1978; Schroeder 1970). Inhalation exposure to barium is also known to occur for industrial welders, especially those using barium-containing stick electrodes and self-shielded flux core wires, and those

working in ceramic factories (Ramakrishna et al. 1996; Roig-Navarro et al. 1997; WHO 2001; Zschiesche et al. 1992).

Data from a workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, estimated the number of workers potentially exposed to various chemicals in the workplace in 1980 (NIOSH 1989a), including a separate tally of female workers. The data for barium and barium compounds included in the survey are summarized in Table 6-6. The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. This is a survey that provides only estimates of the number of workers potentially exposed to chemicals in the workplace.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

The main exposures of children to barium are expected to occur mainly from the diet or by dermal contact with barium-containing dust, with minor exposures through barium in air. Data on the daily intake of barium in the total diet of children in the United States were not located in the available literature. However, the average daily intake of barium in children has been determined in a Canadian Total Diet Study (1993–1999), showing that children ages 0–48 months have the highest barium intake through their diet in comparison to older children (>4 years) and adults (Health Canada 2005). The average barium intake in young male and female children increased from 20.760 for infants (0–1 month) to 25.251 μg/kg body weight/day for children ages 1–4 years (Table 6-5). For older children (>4 years), there is a continual decrease in the average daily barium intake, with values of 18.741 μg/kg body weight/day for

Table 6-6. Number of Workers Potentially Exposed to Barium and Barium Compounds

Chemical	Number of plants	Total workers (female workers)
Barium	815	10,308 (3,598)
Barium carbonate	4,494	61,019 (6,889)
Barium chloride	4,293	57,767 (15,249)
Barium hydroxide	1,423	35,351 (12,208)
Barium oxide (BaO_2)	46	511 (325)
Barium nitrate	353	9,625 (2,699)
Barium sulfate	20,089	305,887 (83,800)
Barium sulfide	7	7 (0)
Chromic acid (H_2CrO_4), barium salt (1:1)	20	3,546 (1,984)

Source: NIOSH 1989a

individuals aged 5–11 years and then down to 11.759 μg/kg body weight/day for males and 9.280 μg/kg body weight/day for females aged 12–19 years. It is expected that the data obtained from the Canadian Total Diet Study will reasonably approximate the daily barium intake for children living in the United States. It is estimated that for children in the United States, the barium intake through drinking water will range between 36 and 60 μg/day. This estimate is based on an average concentration of 30 μg barium/L in drinking water within the United States (Thomas et al. 1999) and the consumption of 1.2–2.0 L water/day. A factor to be taken into account is that fractional intestinal absorption of metals in young children, as in young mammals, may be higher than in adults (Foulkes and Bergman 1993). Dermal contact with barium in household dust is not expected to result in uptake of barium through the skin. Oral intake of barium through hand-to-mouth exposures to barium-containing dust is likely to occur. However, it is not known how much barium is taken in through this route of exposure. There is also the potential of oral intake of barium through the licking or ingestion of crayons or water colors, but it is not known how much barium is ingested or how much is bioavailable (Rastogi and Pritzl 1996).

Dietary intake of barium in 3-month-old infants has been given by Biego et al. (1998) for exclusive consumption of various types of milk. The average barium intake from the consumption of breast milk only was determined to be 4 μg/day. Barium intake increases with exclusive consumption of bottled milk (39 μg/day), evaporated milk (42 μg/day), formula (44 μg/day), and dried milk (59 μg/day). The highest average intake of barium occurred with exclusive consumption of soya milk (91 μg/day). These intakes are based on an average daily intake of milk of 700 mL.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The general population is commonly exposed to barium primarily through ingestion of drinking water and consumption of food and beverages. However, certain populations face greater than average exposures to this element due to environmental sources, such as drinking water (EPA 1987). High levels of barium have been reported in groundwater from deep rock and drift wells in several communities in northeastern Illinois (Brenniman et al. 1981; Calabrese 1977) where barium is a naturally occurring geochemical pollutant found almost exclusively in the Cambrian-Ordovician Aquifer (Gilkeson et al. 1978). Other populations that might receive increased exposure to barium are consumers of crops grown on soils that have been used for the land farming of waste oil-well drilling muds (Bates 1988). Individuals who work at or live near barium mining, manufacturing, or processing plants might inhale higher ambient air concentrations or increased amounts of fugitive dust containing barium particulates. Populations living in the vicinity of the NPL sites known to be contaminated with barium may also be exposed to higher than

background levels of the compound through contact with contaminated waste site media or barium in offsite air or water. Barium has been measured in air, surface water, and groundwater collected offsite of some NPL sites (HazDat 2006). No information was found regarding the sizes of these populations or their intake levels of barium.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of barium is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of barium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of metallic barium and its inorganic compounds have been well characterized (Boffito 2002; CHRIS Manual 2005; Dibello et al. 2003; DOT 2004; Genter 2001; HSDB 2007; Kresse et al. 2007; Lewis 1997; Lide 2005; NIOSH/OSHA 1978; NIOSH 1999; Budavari et al. 2001; OHM/TADS 1989; Parmeggiani 1983; Perry and Chilton 1973; RTECS 2007; Lewis 2000; Stokinger 1981; Weast 1989). Physical and chemical properties of organic compounds of barium have not been comprehensively examined probably due to the limited extent of formation of these compounds. However, further study of the properties of these compounds would help in understanding their role in the environmental fate and transport of barium, particularly at hazardous waste sites where high levels of organic contaminants might be present.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this

information for 2004, became available in May of 2006. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Because barium compounds occur naturally and are widely used in oil well drilling muds, in steel, rubber and plastic products, glass and ceramics, chemical, and pyrotechnics industries, in insecticides, and as a smoke suppressant in diesel fuels (Bodek et al. 1988; Dibello et al. 2003; ILO 1983; Kirkpatrick 1985; Meister 2004; Stokinger 1981; Venugopal and Luckey 1978; WHO 2001; Worthing 1987), the potential for human exposure to these compounds, such as through ingestion of food and water or inhalation of ambient air, is substantial. Recent data on production volumes and import and export of barite and some barium compounds (e.g., barium chloride, barium carbonate, barium hydroxide, and barium oxide) are available (USGS 2006). In addition, only limited information on disposal of barium compounds was available (HSDB 2007; IPCS 1991; NIOSH/OSHA 1978). Additional information on production, import, export, and disposal would be useful in assessing the potential for the release of, and exposure to, barium compounds.

Environmental Fate. The partitioning of barium in environmental media is influenced by the specific form of the compound and such site-specific conditions as pH and cation exchange capacity (Bates 1988; Bodek et al. 1988; Bowen 1966; Giusti et al. 1993; Kabata-Pendias and Pendias 1984; Lagas et al. 1984; Tanizaki et al. 1992). Upon release to the environment, barium is most likely to partition to soils and sediments (Chow et al. 1978; DOE 1984; Rai et al. 1984; WHO 2001). Barium is transported in the atmosphere, surface waters, soil runoff, and groundwater. In surface waters and soils, barium may ionize and form various salts depending on the pH and the availability of anions (Bates 1988; Bodek et al. 1988; Bowen 1966; Kabata-Pendias and Pendias 1984; Lagas et al. 1984; WHO 2001). Additional information on the transport and transformation of barium in the atmosphere would be useful in developing a more complete understanding of the environmental fate of barium compounds.

Bioavailability from Environmental Media. Barium is absorbed following ingestion (Chou and Chin 1943; Cuddihy and Griffith 1972; McCauley and Washington 1983; Taylor et al. 1962) and inhalation (Cuddihy and Ozog 1973b). The bioavailability of barium from air, water, and food has been examined rather extensively in animals (Chou and Chin 1943; Cuddihy and Griffith 1972; McCauley and Washington 1983; Taylor et al. 1962) and humans (Tipton et al. 1969). However, bioavailability from soil has not been studied. Since soil is an important repository for barium, information on barium absorption from ingested soil would be useful in developing an understanding of the potential for exposure following ingestion of contaminated soils, particularly at hazardous waste sites.

Food Chain Bioaccumulation. There is information that barium bioconcentrates in certain plants and aquatic organisms (Aruguete et al. 1998; Bowen 1966; Hope et al. 1996; IPCS 1991; Schroeder 1970; WHO 2001). However, the extent to which plants bioconcentrate barium from soil or to which uptake occurs in terrestrial animals is not well characterized. Further studies on the bioconcentration of barium by plants and terrestrial animals and on the biomagnification of barium in terrestrial and aquatic food chains would be useful to better characterize the environmental fate of barium and define the importance of food chain accumulation as a source of human exposure.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of barium in contaminated media at hazardous waste sites are needed so that the information obtained on levels of barium in the environment can be used in combination with the known body burden of barium to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. The need for additional information on the relationship between barium exposure and levels of barium achieved *in vivo* is essential if such concentrations are to be used as biomonitors of exposure.

Barium has been detected in the atmosphere (Bowen 1979; EPA 1984; Hildemann et al. 1991; IPCS 1991; Schauer et al. 1999; Shahin et al. 2000; WHO 2001; Winkler 2002), surface water (Barnett et al. 1969; Bowen 1979; DOI 1970; Durfor and Becker 1964; Durum and Haffty 1961; Elinder and Zenz 1994; EPA 2005c; Kopp 1969; Longerich et al. 1991; McCabe et al. 1970; Neal et al. 1996; Saleh and Wilson 1999; Tuovinen et al. 1980), groundwater (Bruce and McMahon 1996; Calabrese 1977; Hudak and Wachal 2001; Kojola et al. 1978), soils (Bowen 1979; Bradley et al. 1994; EPA 1995a; Kabata-Pendias and Pendias 1984; Lide 2005; Schroeder 1970; Shacklette and Boerngen 1984; Zenz et al. 1994), and foodstuffs (Beliles 1979; Connor and Shacklette 1975; Health Canada 2005; Schroeder 1970). There are reliable data to characterize the potential for human exposure via intake of drinking water (Durfor and Becker 1964; Hadjimarkos 1967; Thomas et al. 1999), and foods (Health Canada 2005; Tipton et al. 1966, 1969). Recent data on barium levels in plants and ambient air, soils, and groundwater, particularly from hazardous waste sites, would be useful in helping to develop a more complete understanding of the potential for human exposure.

Exposure Levels in Humans. Barium can be detected in blood, urine, feces, and biological tissues (CDC 2001, 2003; Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987). However, there are no data correlating barium levels in tissues and fluids with exposure levels. Recent biomonitoring data exist for the U.S. general population (CDC 2005), although there are limited monitoring data for occupational

exposure and for populations living near hazardous waste sites. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Data on the exposure of children in the United States to barium are very limited. It is expected that the largest exposure to barium will be through the diet. Therefore, market basket surveys or total diet studies similar to those conducted by the U.S. Food and Drug Administration would be useful for providing data on typical levels of exposure via dietary intake for children in the United States. Data are available for barium intake in Canadian children obtained from a 1993–1999 total diet study (Health Canada 2005) and in a separate study (Biego et al. 1998) in infants (3 months old) from the exclusive consumption of breast milk and other types of milk.

Exposure Registries. No exposure registries for barium were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

Three ongoing studies concerning the fate/transport of barium and measurement of barium in environmental media were identified in the Federal Research in Progress database (FEDRIP 2005). These studies are summarized in Table 6-7. No other pertinent ongoing studies were identified.

Table 6-7. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Barium and Barium Compounds

Investigator	Affiliation	Research description	Sponsor
Batiza, R	Oregon State University	The proposed research will attempt to quantify the cold seep barite contribution to the marine sediment record by first quantifying the cold seep barite (an important carrier of barium) contribution to barium and radon fluxes within the San Clemente basin and then, secondly, quantify the effects of this source on the chemical signature of barite in the basin sediments.	NSF
Naehr, TM; MacDonald, IR	Texas A&M University Corpus Christi	Acquisition of a basic powder x-ray difractometer system for qualitative and quantitative phase analysis in studies of (1) geologic materials to enhance research into the formation of diagenetic barite and silicate minerals in sediments from the Peruvian Continental Margin, (2) the authigenic seafloor deposits at sites of active submarine fluid expulsion in the Gulf of Mexico region to elucidate the geo-chemical environment at these sites, and (3) barium and other metals in soil and sediment samples.	NSF
Odom, JW	Auburn University	Develop analytical techniques for total and plant-available forms of barium and other metals in soils and for total analysis of these metals in plant material; determine the normal occurrence of both total and extractable forms of these elements in selected soil profiles; and ascertain the availability of soil test calibration data and soil test procedures for these elements.	Hatch

NSF = National Science Foundation

Source: FEDRIP 2005

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring barium, its metabolites, and other biomarkers of exposure and effect to barium. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Inductively coupled plasma-atomic emission spectrometry (ICP-AES) has been used for measuring low levels of barium in the blood, urine, and bones of humans and animals (Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987) (see Table 7-1). In general, biological samples are nebulized and the resulting aerosol is transported to the plasma torch. Atomic-line emission spectra are produced by the inductively coupled plasma for specific element and the intensities of the lines (bands) are monitored by a photomultiplier tube. A line emission at 455.50 nm was observed for barium (Mauras and Allain 1979; Oppenheimer et al. 1984). Detection limits of 0.25 μg barium/L of urine, 0.6 μg barium/L of blood, and 0.0005 μg of barium per gram of bone were achieved (Mauras and Allain 1979; Shiraishi et al. 1987). Advantages of ICP-AES technique include moderate costs, fairly rapid analysis time, and high sensitivity (Mauras and Allain 1979; Oppenheimer et al. 1984). The presence of spectral interferences is a disadvantage of ICP-AES technique. These interferences are caused when a sample contains elements or compounds that have analytical emission lines (bands) that overlap the line chosen for the analyte. Boric acid or sodium borate (at a concentration of >100 mg boron/L of sample) was reported to interfere with the line emission spectra of barium at 455.50 nm (Mauras and Allain 1979).

Neutron activation analysis (NAA) technique has also been used for determining low levels of barium in human blood (Olehy et al. 1966). This technique is based on the interaction of the nuclei of individual barium atoms with neutron irradiation, resulting in the emission of x-rays (photons). Detection limits of 7 μg barium/L of erythrocyte and 66 μg barium/L of plasma were obtained (Olehy et al. 1966). The advantages of the NAA technique include minimal sample preparation and the fact that destruction of the

Table 7-1. Analytical Methods for Determining Barium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine and blood	Dilute sample with demineralized water, introduce into the plasma and analyze	ICP-AES	0.25 µg/L (urine); 0.6 µg/L (blood)	3–7% coefficient of variation	Mauras and Allain 1979
Urine	Dilute sample with demineralized water, introduce into the plasma and analyze	ICP-AES	0.2 µg/L	No data	Schramel 1988
Erythrocyte and plasma	Ash sample, digest with acid and irradiate	NAA	7 µg/L (erythrocyte); 66 µg/L (plasma)	28.5% RSD (erythrocyte) 7.6% RSD (plasma)	Olehy et al. 1966
Biological tissues	Digest sample in acid; precipitate as the sulfate and analyze	Gravimetry	No data	No data	Borchardt et al. 1961
Visceral materials (intestine, stomach, liver, spleen, and kidney)	Ash sample and analyze	AES	No data	86.8–130.5%	Baisane et al. 1979
Fetus bones	Ash sample and digest with acid	ICP-AES	0.0005 µg/g	0.5% RSD	Shiraishi et al. 1987

AES = atomic emission spectroscopy; ICP-AES = inductively coupled plasma-atomic emission spectrometry; NAA = neutron activation analysis; RSD = relative standard deviation

sample is not needed to conduct the analysis. Disadvantages of this technique include its high costs and a nuclear reactor may not be readily available to many laboratories.

Gravimetric and spectrometric techniques have also been described for quantifying barium in tissues. Borchardt et al. (1961) measured barium in tissues gravimetrically following digestion of 15–20 grams of sample in a 2:1 (by volume) mixture of sulfuric and nitric acids. The barium in the samples was precipitated out as the sulfate, dried, and weighed. No limits of detection were given. Recovery of barium from acid-digested tissues can be impaired when organic ions react with barium and interfere with the formation of the barium sulfate precipitate. However, Borchardt et al. (1961) reported that no such interferences were observed in their assay and that complete recovery of barium from the sample was obtained. In another method, Baisane et al. (1979) used atomic emission spectroscopy to measure barium in visceral material. The method required ashing of tissue samples by heating with a burner or a muffle furnace and then fusing the ash with graphite and lithium carbonate. The barium in the fused ash was quantified by using an electric arc as an excitation source and monitoring the barium emission at 2,335 Å. Limits of detection were not given, but recoveries ranged from 86.8 to 130.5%.

7.2 ENVIRONMENTAL SAMPLES

Atomic absorption spectroscopy (AAS) is the most prevalent analytical technique for measuring low levels of barium in air, water, waste water, geological materials (calcium carbonate), unused lubricating oil, and diagnostic meals containing barium sulfate (see Table 7-2).

Samples may be prepared for AAS in a variety of ways (EPA 1974, 1994a, 1994b, 1996; Hui-Ming and Yao-Han 1984; Johnson et al. 1983; Murata and Noguchi 1974; Pierce and Brown 1977; Renshaw 1973; Sharp and Knevel 1971; Sugiyama et al. 1984). Acid digestion with nitric acid is the most common method of preparation. Sample dilution with nitric acid or other agents to solubilize barium from the matrix can also be employed. If the concentration of barium in the dissolved sample is very low, preconcentration techniques such as chelation or extraction may be employed.

Flame atomic absorption spectroscopy (FAAS) (Methods 208.1 and 7080) and graphite furnace atomic absorption spectroscopy (GFAAS) (Methods 208.2 and 7081) are the techniques recommended by the Office of Solid Waste and Emergency Response of EPA for determining ppb (µg/L) levels of barium in water and waste water (EPA 1974, 1979, 1992, 1994a, 1994b). Parts-per-trillion (sub µg/L) levels of barium in seawater and freshwater have been detected by GFAAS (Epstein and Zander 1979; Roe and Froelich

Table 7-2. Analytical Methods for Determining Barium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect sample on cellulose membrane and extract with hot acid; evaporate extract to dryness and dissolve residue in acid	FAAS	2 µg per sample	102%	NIOSH 1994 (Method 7056)
Air	Collect sample on cellulose or PVC membrane; extract with hot acid and evaporate at 150 °C to near dryness; dissolve residue in acid	ICP-AES	0.005 µg per sample	97.7–102.4%	NIOSH 2003 (Method 7300)
Water	Reflux with addition of HNO_3 and HCl; filter	ICP-MS	0.8 µg/L	95%	EPA 1994a (Method 200.8)
	Reflux with addition of HNO_3 and HCl; filter	ICP-AES	1 µg/L	92%	EPA 1994b (Method 200.7)
	Acidify with HNO_3; filter	FAAS	100 µg/L	94%	EPA 1974 (Method 208.1)
	Reflux with addition of HNO_3 and HCl	FAAS	33.5–132 µg/L (working range)	104.5–106.9% (33.5 µg/L)	ASTM 2000 (Method D4382)
	Acidify sample and pass through ion-exchange resin	FAAS	3 µg/L	11.6% RSD	Pierce and Brown 1977
	Pass sample through ion-exchange resin	FAES	µg/L levels	No data	Johnson et al. 1983
	Extract sample with buffered HFA solution	FAAS	5 µg/L	No data	Edelbeck and West 1970
	No data	GFAAS	7 µg/L	90–110%	Fagioli et al. 1988
	Inject sample directly into graphite furnace	GFAAS	0.6 µg/L (seawater); 0.2 µg/L (freshwater)	13% RSD	Roe and Froelich 1984
Seawater and brackish water	Acidify and inject	DCAP-AES	10–20 mg/L (working range)	108.8% (10 mg/L)	ASTM 1999 (Method D3986)
Water and waste water	Digest sample and evaporate to dryness; dissolve residue in acid	FAAS, GFAAS	100 µg/L (FAAS); 2 µg/L (GFAAS)	94–113% (FAAS); 96–102% (GFAAS)	EPA 1974, 1979, 1992, 1994 (Methods 208.1, 208.2, 7080, and 7081)
Industrial waste water	Digest sample; mix with cation-exchange resin; dry and analyze	XFS	290 µg/L (in 500 mL samples)	5.1% RSD	Murata and Noguchi 1974

Table 7-2. Analytical Methods for Determining Barium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Unused lubricating oil	Dissolve sample in 2-methyl-propan-2-ol:toluene (3:2); add potassium naphthenate solution	FAAS	No data	No data	Holding and Rowson 1975
Rocks and minerals (calcium carbonate)	Precipitate barium from sample; dissolve in ammoniacal solution of EDTA	FAAS	Low µg/g levels	118%	Bano 1973
Soil	Digest sample in HNO_3 and H_2O_2, filter, dilute with acid	GFAAS	0.2 µg/g dry weight	96%	EPA 1978, 1996 (Methods 3050B and 208.2)
Sediment, soil, rocks	Digest sample in a mixture of HCl, HNO_3, and $HClO_4$ by heating to dryness; resuspend residue in HNO_3 and H_2O_2 and heat; cool and dilute in 1% HNO_3	ICP-MS	0.15 ppm	96–102%	USGS 2002a (Method T20)
Sediment, rocks, plants	Digest sample in a mixture of HF, HNO_3, and $HClO_4$ by heating to dryness; resuspend residue in $HClO_4$ and heat to dryness; resuspend in aqua regia, dilute with 1% HNO_3, and reheat	ICP-AES	0.3 ppm	95–106%	USGS 2002b (Methods E011 and T01)
Food, beverage	Homogenize sample; microwave digestion of sample in HNO_3; centrifuge	ICP-AES	0.03 mg/kg (food) 0.004 mg/kg (beverage)	86–94% (food) 86–92% (beverage)	EPA 1995b
Diagnostic meals containing barium sulfate	Add sample to EDTA solution and warm	FAAS	No data	98.6–102.5%	Sharp and Knevel 1971
Compound formulation ($Ba^{14}CO^3$)	Prepare solution of sample in EDTA and count	Scintillation spectrometry	No data	No data	Larsen 1973

$Ba^{14}CO_3$ = radiolabeled barium carbonate; DCAP-AES = direct-current argon plasma-atomic emission spectroscopy; EDTA = ethylenediamine tetraacetic acid; FAAS = flame atomic absorption spectroscopy; FAES = flame atomic emission spectroscopy; GFAAS = graphite furnace atomic absorption spectroscopy; HCl = hydrochloric acid; $HClO_4$ = perchloric acid; HF = hydrofluoric acid; HFA = hexafluoroacetylacetone; HNO_3 = nitric acid; H_2O_2 = hydrogen peroxide; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry; PVC = polyvinyl chloride; RSD = relative standard deviation; XFS = x-ray fluorescence spectroscopy

1984). The advantages that GFAAS and FAAS techniques offer are that they are sensitive techniques, use relatively simple and inexpensive instrumentation, and have high accuracy and precision. In addition, GFAAS technique requires a small amount of sample and is more sensitive than FAAS methodology for determining barium in aqueous media (Edelbeck and West 1970; Oppenheimer et al. 1984).

FAAS (Method 7056) is the technique recommended by NIOSH for detecting soluble barium compounds in air (NIOSH 1994). AAS has also been employed for detecting barium in air at 20 ppb (Miner 1969a).

Other analytical techniques that have been employed for measuring barium and its compounds in environmental media include x-ray fluorescence spectroscopy (XFS), neutron activation analysis (NAA), direct current argon plasma-atomic emission spectroscopy (DCAP-AES), inductively coupled plasma-mass spectrometry (ICP-MS), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), scintillation spectroscopy, and spectrography (Boothe and James 1985; Landis and Coons 1954; Larsen 1973; Murata and Noguchi 1974; Oppenheimer et al. 1984). XFS and NAA methods are less sensitive than other available analytical methods for measuring barium in environmental media. Scintillation spectroscopy and spectrography are less commonly used to measure barium in the environment relative to other analytical methods. ICP-MS and ICP-AES offer low detection sensitivities that are typically at the ppb level and are becoming more routinely used for analysis of samples with complex mixtures of metals and metal complexes. For example, ICP-AES (Method 7300) is a technique recommended by NIOSH for analyzing soluble barium compounds in air with a limit of detection of 0.005 μg per sample (approximately 0.005 $\mu g/m^3$), which is 400 times less than the detection limit for another NIOSH method (7056) that uses FAAS as the technique to quantify barium in air (NIOSH 1994, 2003). ICP-AES (Methods E011 and T01) and ICP-MS (Method T20) are recommended by the U.S. Geological Survey (USGS) for measuring the barium content in sediments and rocks (USGS 2002a, 2002b). ICP-AES is also used to quantify barium and other trace metals in food and beverages with minimum detection limits of 0.004–0.3 mg/kg (ppm) and recoveries of 86–94% (EPA 1995b). ICP-MS is a useful technique for isotopic analysis of barium to determine sources of environmental emissions of barium compounds.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of barium is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research

designed to determine the health effects (and techniques for developing methods to determine such health effects) of barium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Several methods are available for measuring biomarkers of exposure. ICP-AES is the analytical method used for measuring barium in blood, urine and bone of humans and animals at ppt (sub μg/L) levels (Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987). NAA technique has also been employed for measuring barium in blood of humans and animals at ppb (μg/L) levels (Olehy et al. 1966). These techniques are sensitive for measuring background levels of barium in the population. However, information is needed on whether data collected using these techniques can be used to correlate the levels of barium in biological tissues and fluids with exposure levels.

Effect. At present, no biomarkers of effect are available for barium. There are no data to indicate whether a biomarker, if available, would be preferred over chemical analysis for monitoring effects from long- and short-term exposure to barium.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. GFAAS and FAAS are the most widely used analytical techniques for measuring barium and its compounds in air (NIOSH 1987), water (ASTM 2000; Edelbeck and West 1970; EPA 1974, 1994a, 1994b; Fagioli et al. 1988; Johnson et al. 1983; Pierce and Brown 1977; Roe and Froelich 1984), seawater and brackish water (ASTM 1999), waste water (EPA 1974, 1979, 1992, 1994b), rocks and minerals (Bano 1973), unused lubricating oil (Holding and Rowson 1975), soil (EPA 1978, 1996), and diagnostic meals (Sharp and Knevel 1971). The media of most concern for potential human exposure to barium is water. GFAAS and FAAS techniques are sensitive for measuring background levels of barium in aqueous media (Epstein and Zander 1979; Roe and Froelich 1984). However, it is not known whether

these techniques are sensitive for measuring levels of barium at which health effects might begin to occur. FAAS and GFAAS are the methods (Methods 208.1, 208.2, 7080, and 7081) recommended by EPA for detecting ppb levels of barium in water and waste water (EPA 1974, 1979, 1992, 1994c). GFAAS has also been employed to detect ppt levels of barium in aqueous media (Epstein and Zander 1979; Roe and Froelich 1984). ICP-MS and ICP-AES quantitative methods are increasing in use for routine analysis of barium at ppb levels and are capable of ppt levels of detection when ion chromatographic and other prepurification methods are used in sample preparation and analysis. Therefore, analytical methods are available that are sufficiently specific and sensitive to measure barium in the environment, and no data needs have been identified at this time.

7.3.2 Ongoing Studies

No ongoing studies regarding techniques for measuring and determining barium in biological and environmental samples were located.

8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines regarding barium and barium compounds in air, water, and other media are summarized in Table 8-1.

ATSDR has derived an intermediate-duration oral MRL of 0.2 mg barium/kg/day for barium. This MRL is based on a NOAEL of 65 mg barium/kg/day and a LOAEL of 115 mg barium/kg/day for increased kidney weight in female rats (NTP 1994) and an uncertainty factor of 100 (10 to account for animal to human extrapolation, and 10 for human variability) and modifying factor of 3 to account for the lack of an adequate developmental toxicity study

ATSDR has derived a chronic-duration oral MRL of 0.2 mg barium/kg/day for barium. The MRL is based on a $BMDL_{05}$ of 61 mg barium/kg/day for nephropathy in male mice (NTP 1994) and an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability) and modifying factor of 3 to account for the lack of an adequate developmental toxicity study.

EPA (IRIS 2006) has derived an oral reference dose (RfD) for barium of 0.2 mg/kg/day, based on a $BMDL_{05}$ of 63 mg/kg/day for nephropathy in male mice (NTP 1994) and an uncertainty factor of 300 (10 to account for animal to human extrapolation, 10 for human variability, and 3 for database deficiencies, particularly the lack of a two-generation reproductive toxicity study and an adequate investigation of developmental toxicity). EPA (IRIS 2006) has not recommended an inhalation reference concentration (RfC) for barium at this time.

Using their 1986 guidelines, EPA has determined that barium is not classifiable as a human carcinogen and has assigned it the cancer classification, Group D (IRIS 2006). Using their recent guidelines, EPA determined that barium is considered not likely to be carcinogenic to humans following oral exposure and its carcinogenic potential cannot be determined following inhalation exposure (IRIS 2006).

Table 8-1. Regulations and Guidelines Applicable to Barium and Barium Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2004
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	0.7 mg/L	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (TWA)		ACGIH 2004
	Barium and soluble compounds (as Ba)	0.5 mg/m^3	
	Barium sulfate	10 mg/m^3	
NIOSH	REL (TWA)		NIOSH 2005a, 2005b
	Barium chloride[a]	0.5 mg/m^3	
	Barium sulfate	10 mg/m^3 (total) 5.0 mg/m^3 (respiratory)	
	IDLH		
	Barium chloride	50 mg/m^3	
	Barium sulfate	No data	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2005c 29 CFR 1910.1000
	Barium, soluble compounds (as Ba)	0.5 mg/m^3	
	Barium sulfate	15 mg/m^3 (total dust) 5.0 mg/m^3 (respirable fraction)	
	PEL (8-hour TWA) for construction industry		OSHA 2005b 29 CFR 1926.55
	Barium, soluble compounds (as Ba)	0.5 mg/m^3	
	PEL (8-hour TWA) for shipyard industry		OSHA 2005a 29 CFR 1915.1000
	Barium, soluble compounds (as Ba)	0.5 mg/m^3	
	Barium sulfate	15 mg/m^3 (total dust) 5.0 mg/m^3 (respirable fraction)	
b. Water			
EPA	Drinking water standards and health advisories		EPA 2004
	1-day health advisory for a 10-kg child	0.7 mg/L	
	10-day health advisory for a 10-kg child	0.7 mg/L	

Table 8-1. Regulations and Guidelines Applicable to Barium and Barium Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	National primary drinking water standards		EPA 2002a
	MCLG	2.0 mg/L	
	MCL	2.0 mg/L	
	Reportable quantities of hazardous substances (barium cyanide) designated pursuant to Section 311 of the Clean Water Act	10 pounds	EPA 2005b 40 CFR 117.3
	Water quality criteria for human health consumption of:		EPA 2002b
	Water + organism	1.0 mg/L	
	Organism only	No data	
c. Food			
FDA	Bottled drinking water	2.0 mg/L	FDA 2004 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification	A4[b]	ACGIH 2004
EPA	Carcinogenicity classification	Group D[c]	IRIS 2006
	RfC	Not recommended at this time	
	RfD	0.2 mg/kg/day	
NTP	Carcinogenicity classification	No data	NTP 2005

[a]The REL also applies to other soluble barium compounds (as Ba) except barium sulfate.
[b]A4: not classifiable as a human carcinogen
[c]Group D: not classifiable as to human carcinogenicity

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

10. GLOSSARY

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar

ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Barium, Soluble Salts
CAS Numbers:
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] ppm

Reference: NTP. 1994. Toxicology and carcinogenesis studies of barium chloride dihydrate (CAS No. 10326-27-9) in F344/N rats and B6C3F1 mice (drinking water studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program. NTP TR 432.

Experimental design: Groups of 10 male and 10 female F344/N rats were administered 0, 125, 500, 1,000, 2,000, or 4,000 ppm barium chloride dihydrate in drinking water for 90 days. Using measured body weights and water consumption, the investigators estimated the daily barium doses to be 0, 10, 30, 65, 110, and 200 mg barium/kg/day for males and 0, 10, 35, 65, 115, and 180 mg barium/kg/day for females. Neurobehavioral tests (spontaneous motor activity, grip strength, tail flick latency, startle response, hindlimb foot splay) were performed prior to exposure and after 45 and 90 days of exposure. Cardiovascular testing (heart rate, blood pressure, and electrocardiogram) was conducted prior to exposure and after 45 and 91 days of exposure. Organ weights (adrenal gland, brain, heart, liver, kidney, lung, testis, thymus), blood analysis for hematological and clinical chemistry (barium, sodium, potassium, calcium, and phosphorus levels) alterations, and histological examination of major tissues and organs (only in the 200/180 mg/kg/day group) were conducted at termination; kidney, liver, spleen, and thymus of male and female rats in the 110/115 mg/kg/day groups and adrenal gland, heart, and salivary gland of female rats in the 115 mg/kg/day group were also examined microscopically.

Effect noted in study and corresponding doses: Exposure-related deaths were observed during the last week in 30% of the males and 10% of the females exposed to 200/180 mg barium/kg/day. Significant decreases in final body weights were also observed in the 200 mg barium/kg/day males (13% lower than controls) and 180 mg barium/kg/day females (8% lower than controls); significant decreases in water consumption (approximately 30% lower than controls) were also observed at this dose level. Marginal, but statistically significant, decreases in undifferentiated motor activity was observed in all groups of rats exposed to barium for 90 days, except females exposed to 115 mg barium/kg/day; no other alterations in neurobehavioral performance were observed. No significant alterations in heart rate, blood pressure, or EKG readings were observed. Significant increases in serum phosphorus levels were observed in males in the 110 and 200 mg barium/kg/day groups and females in the 35, 65, 115, and 180 mg barium/kg/day groups; however, the investigators noted that these increases were probably an artifact from hemolysis of collected blood samples. Significant increases in absolute and relative kidney weights were observed in females exposed to 115 or 180 mg barium/kg/day and increases in relative kidney weights were also observed in males at 200 mg barium/kg/day. An increase in relative kidney weight was also observed in the females exposed to 65 mg barium/kg/day. The magnitude of the increases in relative kidney weights were 7, 14, and 19% in the females exposed to 65, 115, and 180 mg barium/kg/day and 12% in males exposed to 200 mg barium/kg/day. ;Minimal to mild, focal to multifocal dilatation of the proximal convoluted tubules of the outer medulla and renal cortex was observed in three male and three female rats in the 200/180 mg barium/kg/day group. The small increase in relative kidney weight (7%) observed in

the female rats exposed to 65 mg barium/kg/day was not considered biologically significant because it is not supported by an increase in histological alterations in the kidney at 65 or 115 mg barium/kg/day or in rats exposed to 75 mg barium/kg/day for 2 years (NTP 1994).

Dose and end point used for MRL derivation: The MRL is based on a NOAEL of 65 mg barium/kg/day for increased absolute and relative kidney weight. The increased kidney weight was considered an early indicator of potentially more serious effects in the kidney. A NOAEL/LOAEL approach was used to derive the MRL because none of the available benchmark dose models provided an adequate fit to the absolute or relative kidney weight data.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation: 100

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifying Factor used in MRL derivation: 3

[X] 3 for database deficiences

A modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Doses were calculated by the investigators using measured drinking water consumption and body weight data.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: There are limited data on the toxicity of barium in humans following repeated doses. Wones et al. (1990) found no significant alterations in blood pressure or ECG readings, relative to initial baseline measurements in men experimentally exposed to up to 0.2 mg barium/kg/day as barium chloride in drinking water for 4 week (Wones et al. 1990). These findings are supported by several animal studies that did not find significant

alterations in blood pressure or ECG readings in rats exposed to 150–180 mg barium/kg/day in drinking water for 13 or 16 weeks, respectively (McCauley et al. 1985; NTP 1994). A study by Perry et al. (1983, 1985, 1989) found significant increases in blood pressure in rats administered 8.6 or 11 mg barium/kg/day as barium chloride in drinking water for 1 or 4 months, respectively. The reason for the differences between the results from the Perry et al. (1983, 1985, 1989) study and the NTP (1994) and McCauley et al. (1985) studies is not known. It is possible that the diet used in the Perry et al. (1983, 1985, 1989) study influenced the results. In this study, the rats were fed a low-mineral diet; the calcium content of the rye-based diet was 3.8 mg/kg, which is lower than the concentration recommended for maintenance, growth, and reproduction of laboratory rats (NRC 1995b).

The results of studies by McCauley et al. (1985) and NTP (1994) suggest that the kidney is the most sensitive target of toxicity in rats and mice. In the McCauley et al. (1985) study, glomerular alterations consisting of fused podocytes and thickening of the capillary basement membrane were found in rats exposed to 150 mg barium/kg/day in drinking water for 16 weeks. This lesion was found in uninephrectomized Sprague Dawley rats, Dahl salt-sensitive rats, and Dahl salt-resistant rats. In the NTP (1994) rat study, significant increases in absolute and relative kidney weights were observed in female rats exposed to 115 or 180 mg barium/kg/day and in males exposed to 200 mg barium/kg/day. A statistically significant increase in relative kidney weight was also observed in the females exposed to 65 mg barium/kg/day; however, the increase was small (7%) and was not considered biologically significant. At 200 and 180 mg barium/kg/day, minimal to mild dilatation of the proximal renal cortex was observed in the males and females, respectively; an increase in mortality (30%) was also observed in the males exposed to 200 mg barium/kg/day. In mice, mild to moderate nephropathy (characterized as tubule dilatation, regeneration, and atrophy) was observed in 100% of the males exposed to 450 mg barium/kg/day and 90% of the females exposed to 495 mg barium/kg/day; no renal lesions were observed at the next lowest dose level (205 and 200 mg barium/kg/day in males and females, respectively). Other effects observed at the 450/495 mg barium/kg/day dose level included weight loss, spleen and thymus atrophy, and increased mortality (60% of the males and 70% of females died after 5 weeks of exposure).

Other end points that have been examined in rats and mice include neurotoxicity, reproductive toxicity, and developmental toxicity. In male and female rats, slight decreases in undifferentiated motor activity were observed at 10 mg barium/kg/day and higher. However, with the exception of female rats exposed to 200 mg barium/kg/day, the difference between motor activity in the barium-exposed rats and the controls was less than 20%; this was not considered to be biologically significant. At 200 mg barium/kg/day, the difference was 30%, which was considered to be adverse. No significant alterations were found in performance on the remaining neurobehavioral tests (grip strength, tail flick latency, startle response, and hindlimb foot splay). In mice, a significant decrease in forelimb grip strength was observed in females exposed to 495 mg barium/kg/day; this may have been due to debilitation. No other alterations in neurobehavioral performance were found. No effects on reproductive tissues or reproductive performance were observed in rats or mice exposed to approximately 200 mg barium/kg/day (Dietz et al. 1992; NTP 1994). Pre-mating exposure to 180/200 mg barium/kg/day resulted in decreased litter size and body weight in rat offspring; the NOAEL for these effects was 110/115 mg barium/kg/day (Dietz et al. 1992). No developmental effects were observed in mice exposed to 200 mg barium/kg/day (Dietz et al. 1992).

Agency Contacts (Chemical Managers): Cassandra Smith and Yee-Wan Stevens

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Barium, Soluble Salts
CAS Numbers:
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 49
Species: Mouse

Minimal Risk Level: 0.2 [X] mg barium/kg/day [ ] ppm

Reference: NTP. 1994. Toxicology and carcinogenesis studies of barium chloride dihydrate (CAS No. 10326-27-9) in F344/N rats and B6C3F1 mice (drinking water studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC. NTP TR 432.

Experimental design: Groups of 60 male and 60 female B6C3F1 mice were administered 0, 500, 1,250, or 2,500 ppm barium chloride dehydrate in drinking water for 2 years. Using measured body weights and water consumption, the investigators estimated the daily barium doses to be 0, 30, 75, and 160 mg barium/kg/day for males and 0, 40, 90, and 200 mg barium/kg/day for females. Organ weights, blood analysis for hematological and clinical chemistry (barium, sodium, potassium, calcium, and phosphorus levels, and alanine aminotransferase, creatine kinase, lactate dehydrogenase, and gamma-glutamyltransferase activities) alterations (measured after 15 months), and histological examination of major tissues and organs were conducted at termination.

Effect noted in study and corresponding doses: Increased mortality attributed to renal lesions was observed in the 160/200 mg/kg/day group. Decreased body weights (<7%) were observed in the barium-exposed mice. The investigators noted that a moderate to marked weight loss was observed in animals dying early. No significant alterations in hematology or clinical chemistry parameters were observed. A significant increase in the incidence of nephropathy was observed in male and female mice exposed to 160/200 mg/kg/day. The nephropathy was characterized by extensive regeneration of cortical and medullary tubule epithelium, tubule dilatation, hyaline cast formation, multifocal interstitial fibrosis, and glomerulosclerosis in some kidneys. The incidence of nephropathy was 1/50, 0/50, 2/48, and 19/50 in the males and 0/50, 2/53, 1/50, and 37/50 in the females, respectively. The average severity of the nephropathy was 3.6 (moderate to marked) for both the males and females in the 160/200 mg/kg/day group. An increased incidence of lymphoid depletion in the spleen and decreased relative and absolute spleen were also observed in the 160/200 mg/kg/day group; however, this was attributed to debilitation associated with nephropathy rather than a direct effect on the spleen. No significant increases in the incidences of neoplasms were observed.

Dose and end point used for MRL derivation: Benchmark dose analysis of the dose-response data (Table A-1) for nephropathy in male and female mice exposed to barium chloride in drinking water for 2 years (NTP 1994) was conducted. EPA's Benchmark Dose Software (version 1.3.2) was used to fit nine mathematical models to the incidence data. Model fit was judged by the p-values associated with the chi-square goodness-of-fit statistic generated by the models and visual inspection of the plot of observed and predicted values. As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data for the incidence of nephropathy in male and female mice (x^2 p-value $\geq$0.1). As assessed by lowest Akaike Information Criterion (AIC), the logistic model for the male mouse

data and the gamma model for the female mouse data provide the greatest fit. The results of the benchmark dose analysis are presented in Table A-2.

Table A-1. Incidence of Nephropathy in Male and Female Mice Exposed to Barium Chloride in Drinking Water for 2 Years (NTP 1994)

Water concentration (ppm)	Dose (mg barium/kg/day)	Incidence
Males		
0	0	1/50
500	30	0/50
1,250	75	2/48
2,500	160	19/50
Females		
0	0	0/50
500	40	2/53
1,250	90	1/50
2,500	200	37/50

Table A-2. Predictions from Models for Doses Associated with 10 and 5% Extra Risk for the Incidence of Nephropathy in Male and Female Mice Exposed to Barium in Drinking Water for 2 Years (NTP 1994)

Model	BMD_{10} mg/kg/day	$BMDL_{10}$ mg/kg/day	BMD_5 mg/kg/day	$BMDL_5$ mg/kg/day	x^2 p-value	AIC
Male mice						
Logistic	**103.96**	**87.26**	**80.06**	**61.13**	**0.28**	**99.34**
Probit	96.13	80.07	71.96	54.66	0.13	100.11
Log-probit[a]	99.73	77.90	83.39	59.54	0.31	100.25
Gamma[b]	102.31	80.06	84.94	59.65	0.31	100.28
Log-logistic[a]	104.44	80.50	86.43	59.69	0.31	100.32
Weibull[b]	106.59	81.79	87.63	59.54	0.31	100.35
Quantal quadratic	82.83	69.51	57.80	48.5	0.14	101.89
Multi-stage[c]	82.83	69.14	57.80	44.97	0.14	101.89
Quantal linear	NA	NA	NA	NA	0.0032	111.94
Female mice						
Gamma[b]	125.59	101.49	113.96	87.66	0.34	90.89
Log-probit[a]	134.85	100.63	125.10	88.39	0.17	92.84
Log-logistic[a]	147.43	101.75	137.35	87.01	0.17	92.84
Weibull[b]	153.60	102.66	142.51	84.95	0.17	92.84
Logistic	NA	NA	NA	NA	0.08	92.35

Table A-2. Predictions from Models for Doses Associated with 10 and 5% Extra Risk for the Incidence of Nephropathy in Male and Female Mice Exposed to Barium in Drinking Water for 2 Years (NTP 1994)

Model	BMD_{10} mg/kg/day	$BMDL_{10}$ mg/kg/day	BMD_5 mg/kg/day	$BMDL_5$ mg/kg/day	x^2 p-value	AIC
Probit	NA	NA	NA	NA	0.03	94.03
Quantal quadratic	NA	NA	NA	NA	0.01	102.21
Multi-stage[c]	NA	NA	NA	NA	0.01	102.21
Quantal linear	NA	NA	NA	NA	0.00	126.61

[a]slope restricted to >1
[b]restrict power ≥1
[c]restrict betas ≥0

degree of polynomial = 2; NA = not applicable

The $BMDL_{05}$ for male mice was selected as the point of departure for deriving the chronic-duration oral MRL. Data from the male mice were used because they identify a lower BMDL than the female data. The predicted 5% incidence approach was selected over the other two approaches as a precaution due to the severity of the observed effects (moderate to marked severity nephropathy), which resulted in marked weight loss and increased mortality.

[ ] NOAEL [ ] LOAEL [X] BMDL

Uncertainty Factors used in MRL derivation: 300

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifying Factor used in MRL derivation: 3

[X] 3 for database deficiences

A modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose

the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Doses were calculated by the investigators using measured drinking water consumption and body weight data.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Several studies have examined the toxicity of barium following chronic-duration exposure. Significant increases in blood pressure were observed in rats exposed to 0.8 mg barium/kg/day as barium chloride in drinking water for 16 months (Perry et al. 1983, 1985, 1989); the NOAEL for this effect was 0.17 mg barium/kg/day. At higher doses (7.2 mg barium/kg/day), depressed rates of cardiac contraction, reduced cardiac electrical conductivity, and decreased cardiac ATP levels were observed. As noted in the discussion of the intermediate-duration oral MRL, interpretation of the results of this study is limited due to the low mineral diet which may have supplied inadequate levels of calcium.

No adverse effects were observed in rats exposed to 60 mg barium/kg/day as barium chloride in drinking water for 2 years (NTP 1994), 15 mg barium/kg/day to an unspecified barium compound in drinking water for 68 weeks (McCauley et al. 1985), or 0.7 mg barium/kg/day as barium acetate in drinking water for a lifetime (Schroeder and Mitchener 1975a). In mice exposed to barium chloride in drinking water for 2 years, marked renal nephropathy was observed at 160 mg barium/kg/day; the increased incidence of nephropathy in the next lowest dose group (75 mg barium/kg/day) was not statistically significant. Other adverse effects observed at 160 mg barium/kg/day included weight loss and increased mortality.

The animal data provide suggestive evidence that the kidney is the most sensitive target of toxicity. A serious LOAEL of 160 mg barium/kg/day was identified for nephropathy in mice (NTP 1994); the NOAEL identified in this study is 75 mg/kg/day. Although no kidney lesions were observed in rats exposed to doses as high as 60 mg barium/kg/day (NTP 1994), the doses utilized in the study may not have been high enough to cause kidney damage. Biologically significant kidney alterations were observed at 115 mg barium/kg/day and higher in rats exposed for an intermediate duration (NTP 1994).

Agency Contacts (Chemical Managers): Cassandra Smith and Yee-Wan Stevens

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

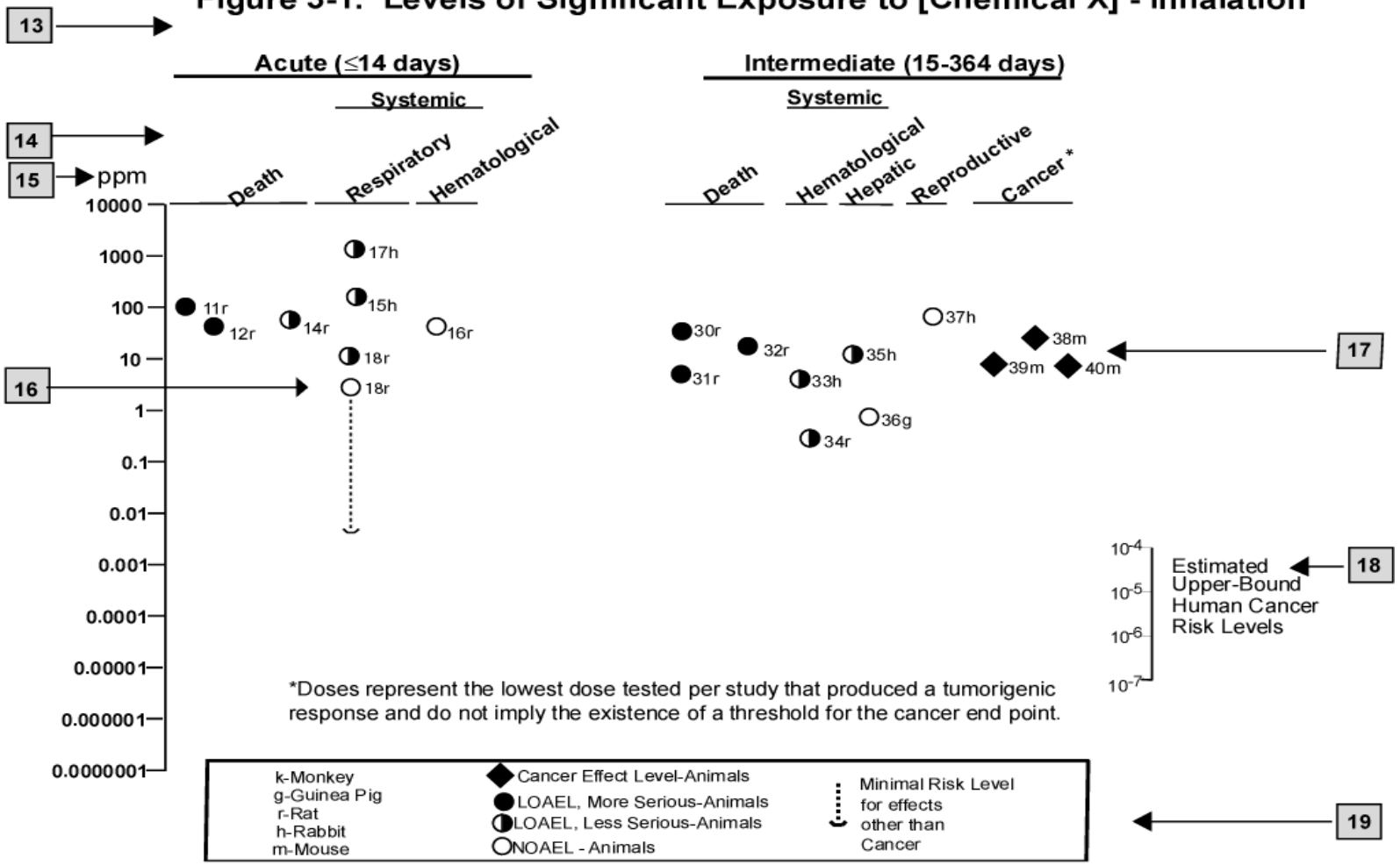
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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DRAFT
TOXICOLOGICAL PROFILE FOR
CADMIUM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2008

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UPDATE STATEMENT

A Toxicological Profile for Cadmium was released in 1999. This present edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mail Stop F-32
Atlanta, Georgia 30333

Background Information

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99 499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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Agency for Toxic Substances and
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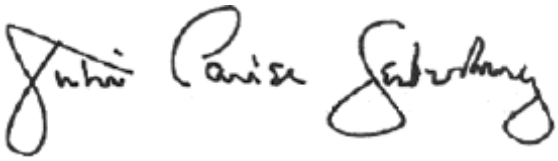

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QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for cadmium. The panel consisted of the following members:

1. Maryka H. Bhattacharyya, Ph.D., Senior Biochemist, Biosciences Division (BIO), Argonne National Laboratory, Lemont, Illinois 60439,

2. Masayuki Ikeda, Ph.D., M.D., Professor, Kyoto Industrial Health Association, Kyoto, Japan 604-8472, and

3. Zahir A Shaikh, Ph.D., Professor of Pharmacology and Toxicology, Director of the Center for Molecular Toxicology, University of Rhode Island, Kingston, Rhode Island 02881.

These experts collectively have knowledge of cadmium's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about cadmium and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Cadmium has been found in at least 1,014 of the 1,669 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which cadmium is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to cadmium or cadmium compounds, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS CADMIUM?

Description	Metal found in the earth's crust, associated with zinc, lead, and copper ores. Pure cadmium is a soft, silver-white metal. Cadmium chloride and cadmium sulfate are soluble in water.
Uses • **Manufacturing** • **Consumer products**	Most cadmium used in the United States is extracted as a byproduct during the production of other metals such as zinc, lead, or copper. Cadmium is also recovered from used batteries. Cadmium is used for the following: • batteries (83%) • pigments (8%) • coatings and platings (7%) • stabilizers for plastics (1.2%) • nonferrous alloys, photovoltaic devices, and other uses (0.8%)

For more information on the properties and uses of cadmium, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO CADMIUM WHEN IT ENTERS THE ENVIRONMENT?

Sources	Cadmium is emitted to soil, water, and air by non-ferrous metal mining and refining, manufacture and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal. Cadmium can accumulate in aquatic organisms and agricultural crops.
Fate • **Air** • **Soil** • **Water**	 Cadmium (as oxide, chloride, and sulfate) will exist in air as particles or vapors (from high temperature processes). It can be transported long distances in the atmosphere, where it will deposit (wet or dry) onto soils and water surfaces. Cadmium and its compounds may travel through soil, but its mobility depends on several factors such as pH and amount of organic matter, which will vary depending on the local environment. Generally, cadmium binds strongly to organic matter where it will be immobile in soil and be taken up by plant life, eventually, entering the food supply. Cadmium exists as the hydrated ion or as ionic complexes with other inorganic or organic substances. Soluble forms migrate in water. Insoluble forms of cadmium are immobile and will deposit and absorb to sediments.

1.3 HOW MIGHT I BE EXPOSED TO CADMIUM?

Food and smoking—primary sources of exposure	In the United States, for nonsmokers the primary source of cadmium exposure is from the food supply. People who regularly consume shellfish and organ meats will have higher exposures. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. Tobacco leaves accumulate high levels of cadmium from the soil. The national geometric mean blood cadmium level for adults is 0.47 µg/L. A geometric mean blood cadmium level of 1.58 µg/L for New York City smokers has been reported. The amount of cadmium absorbed from smoking one pack of cigarettes per day is about 1–3 µg/day. Direct measurement of cadmium levels in body tissues confirms that smoking roughly doubles cadmium body burden in comparison to not smoking.
Air	Except for people living near cadmium-emitting industries, inhalation of cadmium is not expected to be a major concern.
Water	EPA has mandated that water suppliers control cadmium concentrations in drinking water to <5 µg/L. Therefore, exposure to cadmium through public drinking water sources is not a major concern. Elevated cadmium levels in water sources in the vicinity of cadmium-emitting industries (historical and current) have been reported. Aquatic organisms will accumulate cadmium, possibly entering the food supply. People who fish in local waters as a means of food should be cautious and abide by any advisories.
Occupational exposure	Highest risk of exposure from processes involving heating cadmium-containing materials such as smelting and electroplating. Risk will vary depending on the workplace. Major route of exposure is through inhalation of dust and fumes or incidental ingestion from contaminated hands, food, or cigarettes. Exposure can be controlled through personal protective equipment, good industrial hygiene practices, and control and reduction of cadmium emissions.

In Chapter 6, you can find more information on how you might be exposed to cadmium.

1.4 HOW CAN CADMIUM ENTER AND LEAVE MY BODY?

Enter your body **• Inhalation**	About 25–60% of the cadmium you breathe will enter your body through your lungs.
• Ingestion	A small amount of the cadmium in food and water (about 5–10%) will enter your body through the digestive tract. If you do not have enough iron or other nutrients in your diet, you are likely to take up more cadmium from your food than usual.
• Dermal contact	Virtually no cadmium enters your body through your skin.
Leave your body	Most of the cadmium that enters your body goes to your kidney and liver and can remain there for many years. A small portion of the cadmium that enters your body leaves slowly in urine and feces. Your body can change most cadmium to a form that is not harmful, but too much cadmium can overload the ability of your liver and kidney to change the cadmium to a harmless form.

More information on how cadmium enters and leaves the body is found in Chapter 3.

1.5 HOW CAN CADMIUM AFFECT MY HEALTH?

Workers **• Inhalation**	Breathing air with very high levels of cadmium can severely damage the lungs and may cause death. In the United States, where proper industrial hygiene is generally practiced, inhaling very high levels of cadmium at work is expected to be rare and accidental. Breathing air with lower levels of cadmium over long periods of time (for years) results in a build-up of cadmium in the kidney, and if sufficiently high, may result in kidney disease.
Laboratory animals **• Inhalation**	Damage to the lungs and nasal cavity have been observed in animals exposed to cadmium.
Humans **• Oral**	Eating food or drinking water with very high cadmium levels severely irritates the stomach, leading to vomiting and diarrhea, and sometimes death. Eating lower levels of cadmium over a long period of time can lead to a build-up of cadmium in the kidneys. If the levels reach a high enough level, the cadmium in the kidney will cause kidney damage. Exposure to lower levels of cadmium for a long time can also cause bones to become fragile and break easily.
Laboratory animals **• Oral**	Kidney and bone effects have also been observed in laboratory animals ingesting cadmium. Anemia, liver disease, and nerve or brain damage have been observed in animals eating or drinking cadmium. We have no good information on people to indicate what levels people would need to eat or drink cadmium to result in these diseases, or if they would occur at all.
Cancer	Lung cancer has been found in some studies of workers exposed to cadmium in the air and studies of rats that breathed in cadmium. The U.S. Department of Health and Human Services (DHHS) has determined that cadmium and cadmium compounds are known human carcinogens. The International Agency for Research on Cancer (IARC) has determined that cadmium is carcinogenic to humans. The EPA has determined that cadmium is a probable human carcinogen.

More information on how cadmium can affect your health is found in Chapters 2 and 3.

1.6 HOW CAN CADMIUM AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in children	The health effects seen in children from exposure to toxic levels of cadmium are expected to be similar to the effects seen in adults (kidney, lung, and intestinal damage depending on the route of exposure). Harmful effects on child development or behavior have not generally been seen in populations exposed to cadmium, but more research is needed. A few studies in animals indicate that younger animals absorb more cadmium than adults. Animal studies also indicate that the young are more susceptible than adults to a loss of bone and decreased bone strength from exposure to cadmium. Cadmium is found in breast milk and a small amount will enter the infant's body through breastfeeding. The amount of cadmium that can pass to the infant depends on how much exposure the mother may have had.
Birth defects	We do not know whether cadmium can cause birth defects in people. Studies in animals exposed to high enough levels of cadmium during pregnancy have resulted in harmful effects in the young. The nervous system appears to be the most sensitive target. Young animals exposed to cadmium before birth have shown effects on behavior and learning. There is also some information from animal studies that high enough exposures to cadmium before birth can reduce body weights and affect the skeleton in the developing young.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CADMIUM?

Do not smoke tobacco products	Cadmium accumulates in tobacco leaves. The national geometric mean blood cadmium level for adults is 0.47 µg/L. Mean blood cadmium levels for smokers have been reported as high as 1.58 µg/L.
Good occupational hygiene	Occupational exposure can be controlled through personal protective equipment, good industrial hygiene practices, and control and reduction of cadmium emissions. Children can be exposed to cadmium through parents who work in cadmium-emitting industries. Therefore, good hygiene practices such as bathing and changing clothes before returning home may help reduce the cadmium transported from the job to the home.
Avoid cadmium contaminated areas and food	Check and obey local fishing advisories before consuming fish or shellfish from local waterways. Avoid hazardous waste sites.
Proper disposal of cadmium-containing products	Dispose of nickel-cadmium batteries properly. Many states have laws in effect that ban the disposal of batteries as municipal waste. Recycle old batteries whenever possible. Contact your local waste and recycling authority on how to properly dispose of paints and coatings.
Handle properly	Do not allow children to play with batteries. If mishandled, batteries could rupture. Children may also swallow small nickel-cadmium batteries.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CADMIUM?

Detecting exposure	Cadmium can be measured in blood, urine, hair, or nails. Urinary cadmium has been shown to accurately reflect the amount of cadmium in the body.
Measuring exposure	The amount of cadmium in your blood shows your recent exposure to cadmium. The amount of cadmium in your urine shows both your recent and your past exposure. Cadmium levels in hair or nails are not as useful as an indication of when or how much cadmium you may have taken in, partly because cadmium from outside of your body may attach to the hair or nails. Tests are also available to measure the amount of cadmium inside your liver and kidneys.

More information on how cadmium can be measured in exposed humans is presented in Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for cadmium include the following:

Drinking water	The EPA has determined that exposure to cadmium in drinking water at a concentration of 0.04 mg/L for up to 10 days is not expected to cause any adverse effects in a child. The EPA has determined that lifetime exposure to 0.005 mg/L cadmium in drinking water is not expected to cause any adverse effects.
Consumer products	The FDA has determined that cadmium levels in bottled water should not exceed 0.005 mg/L.
Workplace air	OSHA set a legal limit of 5 µg/m^3 cadmium averaged over an 8-hour work day.

More information on governmental rules regarding cadmium can be found in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CADMIUM IN THE UNITED STATES

Cadmium occurs in the earth's crust at a concentration of 0.1–0.5 ppm and is commonly associated with zinc, lead, and copper ores. It is also a natural constituent of ocean water with average levels between <5 and 110 ng/L, with higher levels reported near coastal areas and in marine phosphates and phosphorites. The cadmium concentration of natural surface water and groundwater is usually <1 μg/L. Surface soil concentrations will depend on several factors such as its mobility, natural geochemistry, and magnitude of contamination from sources such as fertilizers and atmospheric deposition. Natural emissions of cadmium to the environment can result from volcanic eruptions, forest fires, generation of sea salt aerosols, or other natural phenomena.

In the environment, cadmium exists in only one oxidation state (+2) and does not undergo oxidation-reduction reactions. In surface water and groundwater, cadmium can exist as the hydrated ion or as ionic complexes with other inorganic or organic substances. Soluble forms of cadmium can migrate in water. Insoluble forms of cadmium will settle and adsorb to sediments. Cadmium's fate in soil depends on several factors such as pH of the soil and the availability of organic matter. Generally, cadmium will bind strongly to organic matter and this will, for the most part, immobilize it. However, cadmium's behavior in soil will vary depending on the environmental conditions. It is not likely that cadmium will undergo significant transformation in the atmosphere. It will exist in particulate form and sometimes vapor form (emitted from high temperature processes) where it will undergo atmospheric transport and eventually deposit onto soils and surface waters.

Non-ferrous metal mining and refining, manufacture and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal are the main anthropogenic sources of cadmium in the environment. Except for those who live near cadmium-emitting industries, inhalation of cadmium in the ambient air may occur, but is not a major source of exposure. Water sources near cadmium-emitting industries, both with historic and current operations, have shown a marked elevation of cadmium in water sediments and aquatic organisms. Concentrations of cadmium in these polluted waters have ranged from <1.0 to 77 μg/L. For the U.S. population, cadmium exposure through the drinking water supply is of minor concern. Cadmium from polluted soil and water can accumulate in plants and organisms, thus entering the food supply.

In the United States, the largest source of cadmium exposure for nonsmoking adults and children is through dietary intake. The estimated daily intakes of cadmium in nonsmoking adult males and females living in the United States are 0.35 and 0.30 μg Cd/kg/day, respectively. Females generally absorb greater amounts of cadmium in the gastrointestinal tract. In general, leafy vegetables such as lettuce and spinach and staples such as potatoes and grains contain relatively high values of cadmium. Peanuts, soybeans, and sunflower seeds have naturally high levels of cadmium. People who regularly consume shellfish and organ meats (liver and kidney) have increased cadmium exposure.

Mean values of cadmium in the blood and urine of the U.S. population were reported in the National Health and Nutrition Examination Survey (NHANES) 1999–2002. Blood cadmium reflects both recent and cumulative exposures and urinary cadmium reflects cadmium exposure and the concentration of cadmium in the kidneys. The 20 years or older age group had geometric mean levels of blood and urine cadmium that were slightly higher than the younger age groups (0.468 and 0.273–0.281 μg/L in blood and urine, respectively). Females (0.421 μg/L, blood; 0.187–0.219 μg/L urine) had slightly higher blood and urine cadmium levels than males (0.403 μg/L, blood; 0.199–0.201 μg/L, urine).

Smoking greatly increases exposure to cadmium, as tobacco leaves naturally accumulate high amounts of cadmium. It has been estimated that tobacco smokers are exposed to 1.7 μg cadmium per cigarette, and about 10% is inhaled when smoked. A geometric mean blood cadmium level for a heavy smoker has been reported as high as 1.58 μg/L, compared to the estimated national mean of 0.47 μg/L for all adults. Nonsmokers may also be exposed to cadmium in cigarettes via second-hand smoke.

2.2 SUMMARY OF HEALTH EFFECTS

Since the early 1950s, when the hazards of occupational cadmium exposure were recognized, a large amount of information has been generated concerning the toxic effects of cadmium exposure in humans and laboratory animals. Toxicological properties of cadmium are similar for the several different salts and oxides of cadmium that have been investigated, although differences in absorption and distribution lead to different effect levels. For inhalation exposure, particle size and solubility in biological fluids (in contrast to solubility in water) appear to be the more important determinants of the toxicokinetics. For oral exposure, most experimental studies have used soluble cadmium, which exists as the Cd^{+2} ion regardless of the initial salt. Absorption appears to be similar for cadmium ion and cadmium complexed with proteins in food, except for a few specific types of foods such as Bluff oysters and seal meat. Also, poorly soluble cadmium pigments may be absorbed to a lesser extent than soluble cadmium ion. For the

general population, dietary exposure to cadmium is the most likely route of exposure. There is an extensive database on the toxicity of cadmium in environmentally exposed populations and in cadmium workers; however, most of these studies were focused on the presumed sensitive targets. These sensitive targets of cadmium toxicity are the kidney and bone following oral exposure and kidney and lung following inhalation exposure. Studies in animals support the identification of these sensitive targets and provide some suggestive evidence that the developing organisms may also be a sensitive target. There is also evidence to suggest that cadmium is a human carcinogen. Other effects that have been observed in humans and/or animals include reproductive toxicity, hepatic effects, hematological effects, and immunological effects.

The earliest indication of kidney damage in humans is an increased excretion of low molecular weight proteins, particularly β2-microglobulin, human complex forming glycoprotein (pHC) (also referred to as α1-microglobulin), and retinol binding protein; increased urinary levels of intracellular enzymes such as N-acetyl-β-glucosaminidase (NAG); and increased excretion of calcium and metallothione. Numerous studies of cadmium workers and populations living in areas with low, moderate, or high cadmium pollution have found significant associations between urinary cadmium levels and biomarker levels or significant increases in the prevalence of abnormal biomarker levels. At higher exposure levels, decreases in glomerular filtration rate, increased risk of renal replacement therapy (dialysis or kidney transplantation), and significant increases in the risk of deaths from renal disease have been observed. The sensitivity of the kidney to cadmium is related to its distribution in the body and *de novo* synthesis of metallothionein in the kidney. In the blood, cadmium is bound to metallothionein and is readily filtered at the glomerulus and reabsorbed in the proximal tubule. Within the tubular cells, the metallothionein is degraded in lysosomes and free cadmium is released; the synthesis of endogenous metallothionein by the tubular cells is then stimulated. However, when the total cadmium content in the renal cortex reaches between 50 and 300 μg/g wet weight, the amount of cadmium not bound to metallothionein becomes sufficiently high to cause tubular damage. Free cadmium ions may inactivate metal-dependent enzymes, activate calmodulin, and/or damage cell membranes through activation of oxygen species. Because the toxicity of cadmium is dependent on its concentration in the kidney, adverse effects in humans are typically not observed after shorter durations.

Acute inhalation exposure to cadmium at concentrations above about 5 mg/m^3 may cause destruction of lung epithelial cells, resulting in pulmonary edema, tracheobronchitis, and pneumonitis in both humans and animals. A single, high-level cadmium exposure can result in long-term impairment of lung function. At the cellular level, catalase, superoxide dismutase, non-protein sulfhydryl, glucose-6-phosphate

dehydrogenase, and glutathione peroxidase are decreased in response to cadmium lung insults. The respiratory response to cadmium is similar to the response seen with other agents that produce oxidative damage. There typically is an alveolar pneumocyte type 2 cell hyperplasia in response to type 1 cell damage and necrosis. Longer-term inhalation exposure at lower levels also leads to decreased lung function and emphysema in cadmium workers. Some tolerance to cadmium-induced lung irritation develops in exposed humans and animals, and respiratory function may recover after cessation of cadmium exposure. Another effect of long-term inhalation cadmium exposure is damage to the olfactory function and nasal epithelium. Lung damage has also been seen in a few studies of oral cadmium exposure in rats, but the lung effects are likely to be related to liver or kidney damage and subsequent changes in cellular metabolism.

Prolonged inhalation or ingestion exposure of humans to cadmium at levels causing renal dysfunction can lead to painful and debilitating bone disease in individuals with risk factors such as poor nutrition; the occurrence of these bone effects in elderly Japanese women exposed to high levels of cadmium in rice and water was referred to as Itai-Itai disease. Decreases in bone mineral density, increases in the risk of fractures, and increases in the risk of osteoporosis have also been observed in populations living in cadmium polluted areas or in cadmium nonpolluted areas. Similar effects have also been observed in young rats orally exposed to cadmium. Animal data strongly suggest that cadmium exposure results in increases in bone turnover and decreases in mineralization during the period of rapid bone growth. Although animal studies suggest that these effects are due to direct damage to the bone, it is likely that renal damage resulting in the loss of calcium and phosphate and alteration in renal metabolism of vitamin D would compound these effects.

There are few human data on developmental effects from exposure to cadmium. Some studies indicate that maternal cadmium exposure may cause decreased birth weight in humans, but most of these studies are of limited use because of weaknesses in the study design and lack of control for confounding factors. A number of other studies did not find a significant relationship between maternal cadmium levels and newborn body weight. In animals, cadmium has been shown to be a developmental toxin by the inhalation, oral, and parenteral routes. Decreased fetal weight, skeletal malformations, and delayed ossification are produced by relatively high maternal doses (1–20 mg/kg/day) due to placental toxicity, interference with fetal metabolism, and damage to the maternal liver. Neurodevelopmental effects have been observed at lower doses. Impaired performance on neurobehavioral tests were observed in the offspring of rats exposed to 0.02 mg/m^3 or ≥0.04 mg/kg/day.

The results of occupational exposure studies examining the possible association between cadmium exposure and an increased risk of lung cancer are inconsistent, with some studies finding significant increases in lung cancer deaths and other studies not finding increases. Interpretation of the results of many of the studies is complicated by inadequate controls for confounding factors such as co-exposure with other metal carcinogens and smoking, small number of lung cancer deaths, and the lack of significant relationships between cadmium exposure and duration. For prostate cancer, initial studies in European workers indicated an elevation in prostate cancer, but subsequent investigations found either no increases in prostate cancer or increases that were not statistically significant. Strong evidence from animal studies exists that cadmium inhalation can cause lung cancer, but only in rats. Most oral studies in laboratory animals have not found significant increases in cancer incidence. The Department of Health and Human Services concluded that there were sufficient human and animal data to conclude that cadmium is a known human carcinogen; likewise, IARC classified cadmium as carcinogenic to humans (Group 1). The EPA has classified cadmium as a probable human carcinogen by inhalation (Group B1), based on its assessment of limited evidence of an increase in lung cancer in humans and sufficient evidence of lung cancer in rats.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for cadmium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990d), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

The database on the toxicity of cadmium in humans and animals following inhalation or oral exposure is extensive. Target organs are similar among species and, in general, toxicokinetic properties after oral and inhalation exposures are similar. Most of the human data involve chronic inhalation exposure of workers or chronic dietary exposure of the general population or populations living in cadmium-polluted areas. Several approaches for characterizing cadmium exposure have been used in these studies. Occupational exposure studies have used current air concentrations or have estimated cumulative exposure based on historical and current monitoring data. Some epidemiology studies have estimated cumulative intake based on the levels of cadmium in rice, in populations where rice has been the dominant source of oral exposure to cadmium. However, most studies (particularly oral studies) have used urinary cadmium levels as a biomarker of exposure. As discussed in greater detail in Section 3.8.1, urinary cadmium levels correlate with cadmium body burden and cadmium concentration in kidney (a critical target organ for chronic exposure). The relationship between renal and urinary cadmium appears to be nearly linear at chronic intakes and kidney burdens that do not produce nephrotoxicity (i.e., elimination half-time is independent of dose). However, at high kidney cadmium burdens, associated with renal damage (>50 μg Cd/g cortex), the elimination half-time increases with increasing severity of renal damage. Linearity in the dose-urinary excretion relationship also does not appear to apply following an acute high exposure to cadmium. The Nordberg-Kjellström model (described in detail in Section 3.4.5.3) is a multicompartment pharmacokinetic model that can be used to estimate cadmium intakes (inhalation and oral exposure) associated with a given urinary cadmium level and/or kidney cadmium burden. The model has been extensively evaluated for predicting dose-kidney-urinary cadmium relationships within the linear range of the dose-urinary cadmium relationship.

Inhalation MRLs

Acute-duration Inhalation MRL

- An MRL of $3x10^{-5}$ mg Cd/m^3 (0.03 μg Cd/m^3) has been derived for acute-duration inhalation exposure (<14 days) to cadmium.

The acute toxicity of airborne cadmium, particularly cadmium oxide fumes, was first recognized in the early 1920s and there have been numerous case reports of cadmium workers dying after brief exposures to presumably high concentrations of cadmium fumes (European Chemicals Bureau 2007). The initial symptoms, similar to those observed in metal fume fever, are usually mild but rapidly progress to severe pulmonary edema and chemical pneumonitis. Persistent respiratory effects (often lasting years after the

exposure) have been reported in workers surviving these initial effects. There are limited monitoring data for these human reports; however, Elinder (1986b) estimated that an 8-hour exposure to 1–5 mg/m^3 would be immediately dangerous.

Animal studies support the findings in humans that acute exposure to cadmium results in lung damage. Single exposures to approximately 1–10 mg Cd/m^3 as cadmium chloride or cadmium oxide resulted in interstitial pneumonitis, diffuse alveolitis with hemorrhage, focal interstitial thickening, and edema (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart 1986; Henderson et al. 1979; Palmer et al. 1986). Repeated exposure to 6.1 mg Cd/m^3 1 hour/day for 5, 10, or 15 days resulted in emphysema in rats (Snider et al. 1973). Lower concentrations of 0.4–0.5 mg Cd/m^3 as cadmium oxide for 2–3 hours (Buckley and Bassett 1987b; Grose et al. 1987) or 0.17 mg Cd/m^3 as cadmium chloride 6 hours/day for 10 days (Klimisch 1993) resulted in mild hypercellularity and increases in lung weight. Alveolar histiocytic infiltration and focal inflammation and minimal fibrosis in alveolar septa were observed in rats exposed to 0.088 mg Cd/m^3 as cadmium oxide 6.2 hours/day, 5 days/week for 2 weeks (NTP 1995); in similarly exposed mice, histiocytic infiltration was observed at 0.088 mg Cd/m^3 (NTP 1995). At similar concentrations (0.19 or 0.88 mg Cd/m^3as cadmium chloride), decreases in humoral immune response were observed in mice exposed for 1–2 hours (Graham et al. 1978; Krzystyniak et al. 1987). Other effects that have been reported in animals acutely exposed to cadmium include erosion of the stomach, decreased body weight gain, and tremors in rats exposed to 132 mg Cd/m^3 as cadmium carbonate for 2 hours (Rusch et al. 1986) and weight loss and reduced activity in rats exposed to 112 mg Cd/m^3 as cadmium oxide for 2 hours (Rusch et al. 1986).

The NTP (1995) study was selected as the basis of an acute duration inhalation MRL. In this study, groups of five male and five female F344 rats were exposed to 0, 0.1, 0.3, 1, 3, or 10 mg cadmium oxide/m^3 (0, 0.088, 0.26, 0.88, 2.6, or 8.8 mg Cd/m^3) 6.2 hours/day, 5 days/week for 2 weeks. The mean median aerodynamic diameter (MMAD) of the cadmium oxide particles was 1.5 μm with a geometric standard deviation of 1.6–1.8. The animals were observed twice daily and weighed on days 1, 8, and at termination. Other parameters used to assess toxicity included organ weights (heart, kidney, liver, lungs, spleen, testis, and thymus) and histopathological examination (gross lesions, heart, kidney, liver, lungs, tracheobronchial lymph nodes, and nasal cavity and turbinates). All rats in the 8.8 mg Cd/m^3 group died by day 6; no other deaths occurred. A slight decrease in terminal body weights was observed at 2.6 mg Cd/m^3; however, the body weights were within 10% of control weights. Significant increases in relative and absolute lung weights were observed at 0.26 (males only), 0.88, and 2.6 mg Cd/m^3. Histological alterations were limited to the respiratory tract and consisted of alveolar histiocytic infiltrate and focal

inflammation and minimal fibrosis in alveolar septa at ≥0.088 mg Cd/m^3, necrosis of the epithelium lining alveolar ducts at ≥0.26 mg Cd/m^3, tracheobronchiolar lymph node inflammation at ≥0.88 mg Cd/m^3, degeneration of the nasal olfactory epithelium at 0.88 mg Cd/m^3, and inflammation and metaplasia of the nasal respiratory epithelium at 2.6 mg Cd/m^3.

The lowest-observed-adverse-effect level (LOAEL) of 0.088 mg Cd/m^3 was selected as the point of departure for derivation of the MRL; benchmark dose analysis was considered; however, the data were not suitable for benchmark dose analysis because the data do not provide sufficient information about the shape of the dose-response relationship below the 100% response level. The $LOAEL_{HEC}$ was calculated using the equations below.

$$LOAEL_{HEC} = LOAEL_{ADJ} \times RDDR$$

The duration-adjusted LOAEL ($LOAEL_{ADJ}$) was calculated as follows:

$$LOAEL_{ADJ} = 0.088 \text{ mg Cd/m}^3 \times 6.2 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days}$$
$$LOAEL_{ADJ} = 0.016 \text{ mg Cd/m}^3$$

The regional deposited dose ratio (RDDR) for the pulmonary region of 0.617 was calculated with EPA's RDDR calculator (EPA 1994a) using the final body weight of 0.194 kg for the male rats exposed to 0.088 mg Cd/m^3, the reported MMAD of 1.5 μm and the midpoint of the reported range of geometric standard deviations (1.7).

$$LOAEL_{HEC} = 0.016 \text{ mg Cd/m}^3 \times 0.617$$
$$LOAEL_{HEC} = 0.01 \text{ mg Cd/m}^3$$

The $LOAEL_{HEC}$ was divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability) resulting in an acute-duration inhalation MRL of 3×10^{-5} mg Cd/m^3 (0.03 μg Cd/m^3).

Intermediate-duration Inhalation MRL

There are no studies examining the intermediate-duration toxicity of inhaled cadmium in humans; however, numerous animal studies have identified several targets of cadmium toxicity. Increases in the number of bronchioalveolar macrophages, alveolar histiocytic infiltration, degeneration or metaplasia in

the larynx, and proliferations have been observed in rats and mice exposed to 0.022 mg Cd/m^3 as cadmium oxide or cadmium chloride (Glaser et al. 1986; NTP 1995; Prigge 1978a). At higher concentrations (>0.88 mg Cd/m^3), marked inflammation and fibrosis was observed in lungs of rats (Kutzman et al. 1986; NTP 1995). In general, these studies did not identify no-observed-adverse-effect levels (NOAELs) for lung effects. The NTP (1995) study also found significant increases in the incidence of inflammation of the nasal respiratory epithelium in rats exposed to 0.22 mg Cd/m^3 and degeneration of the nasal olfactory epithelium in mice exposed to 0.088 mg Cd/m^3. The NTP (1995) study did not find any histological alterations in non-respiratory tract tissues, alterations in urinalysis parameters, or changes in blood pressure (rats only) in rats or mice. Prigge (1978a, 1978b) reported increases in hemoglobin and hematocrit levels in rats continuously exposed to ≥0.052 mg Cd/m^3; however, this effect was not observed in the NTP (1995) studies. Reproductive effects (increased duration of estrous cycle and decreased spermatid counts) have also been observed at higher concentrations (0.88–1 mg Cd/m^3) (Baranski and Sitarek 1987; NTP 1995).

The studies by Baranski (1984, 1985) provide suggestive evidence that the developing organism is also a sensitive target of cadmium toxicity. Significant alterations in performance on neurobehavioral tests were observed in the offspring of rats exposed to 0.02 mg Cd/m^3 as cadmium oxide 5 hours/day, 5 days/week for 5 months prior to mating, during a 3-week mating period, and during gestation days 1–20. No other studies examined neurodevelopmental end points following inhalation exposure. However, the identification of neurodevelopmental effects as a sensitive target of cadmium toxicity is supported by several intermediate-duration animal studies finding neurodevelopmental effects including alterations in motor activity and delays in the development of sensory motor coordination reflexes (Ali et al. 1986; Baranski 1985; Desi et al. 1998; Nagymajtenyi et al. 1997). Other developmental effects observed in the inhalation studies included decreases in fetal body weight in the fetuses of rats exposed to 1.7 or 0.581 mg Cd/m^3 (NTP 1995; Prigge 1978b) and mice exposed to 0.4 mg Cd/m^3 (NTP 1995).

Based on the available animal data, the LOAEL of 0.022 mg Cd/m^3 for lung and larynx effects in mice (NTP 1995) and the LOAEL of 0.02 mg Cd/m^3 for neurodevelopmental effects (Baranski 1984, 1985) were evaluated as possible points of departure for the intermediate-duration inhalation MRL for cadmium. The LOAEL of 0.022 mg Cd/m^3 identified in the NTP (1995) mouse study was considered as the point of departure for the MRL because the NTP study provided more study details and information on particle size distribution. Because an MRL based on this LOAEL ($LOAEL_{HEC}$ of 1 μg Cd/m^3) would be lower than the chronic-duration inhalation MRL based on human data, an intermediate-duration inhalation MRL was not derived.

Chronic-duration Inhalation MRL

- An MRL of 0.01 μg Cd/m^3 has been derived for chronic-duration inhalation exposure (≥1 year) to cadmium.

Numerous studies examining the toxicity of cadmium in workers have identified the respiratory tract and the kidney as sensitive targets of toxicity. A variety of respiratory tract effects have been observed in cadmium workers including respiratory symptoms (e.g., dyspnea, coughing, wheezing), emphysema, and impaired lung function. However, many of these studies did not control for smoking, and thus, the role of cadmium in the induction of these effects is difficult to determine. Impaired lung function was reported in several studies that controlled for smoking (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976); other studies have not found significant alterations (Edling et al. 1986). The observed alterations included an increase in residual volume in workers exposed to air concentrations of cadmium fumes ranging from 0.008 (in 1990) to 1.53 mg/m^3 (in 1975) (mean urinary cadmium level in the workers was 4.3 μg/L) (Cortona et al. 1992); alterations in several lung function parameters (e.g., forced expiratory volume, transfer factor, transfer coefficient) in workers exposed to 0.034–0.156 mg/m^3 (Davison et al. 1988); and decreased force vital capacity in workers exposed to >0.2 mg/m^3 (Smith et al. 1976). Additionally, Chan et al. (1988) found significant improvements in several parameters of lung function of workers following reduction or cessation of cadmium exposure.

The renal toxicity of cadmium in workers chronically exposed to high levels of cadmium is well established. Observed effects include tubular proteinuria (increased excretion of low molecular weight proteins), decreased resorption of other solutes (increased excretion of enzymes such as NAG, amino acids, glucose, calcium, inorganic phosphate), evidence of increased glomerular permeability (increased excretion of albumin), increased kidney stone formation, and decreased glomerular filtration rate (GFR). The earliest sign of cadmium-induced kidney damage is an increase in urinary levels of low molecular weight proteins (particularly, β2-microglobulin, retinol binding protein, and pHC) in cadmium workers, as compared to levels found in a reference group of workers or the general population (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985a; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Shaikh et al. 1987; Toffoletto et al. 1992; Verschoor et al. 1987). Although increases in the excretion of low molecular weight proteins are not diagnostic of renal damage (Bernard et al. 1997; Järup et al. 1998b), tubular proteinuria is considered an adverse effect because it is an early change in a sequence of events which ultimately may result in compromised renal function (Bernard et al. 1997). Most investigators consider a 10% cadmium-

associated increase in the prevalence of abnormal levels of renal biomarkers (urinary β2-microglobulin, retinol binding protein, pHC) to be indicative of cadmium-induced renal disease in the population. However, there is less consensus on the low molecular protein level regarded as elevated or abnormal (cut-off point).

Several biomarkers of tubular damage have been used in occupational exposure studies; these include β2-microglobulin, retinol binding protein, NAG, and pHC. Of these biomarkers, which differ in their sensitivities to detect tubular damage, β2-microglobulin is the most widely used in occupational exposure studies. In healthy humans, urinary β2-microglobulin levels are <300 μg/24 hours (approximately 300 μg/g creatinine). Four studies have estimated the prevalence of abnormal urinary β2-microglobulin levels among cadmium workers using cut-off levels of 187–380 μg/g creatinine (Chen et al. 2006a; Elinder et al. 1985a; Jakubowski et al. 1987; Järup and Elinder 1994). The prevalence of abnormal urinary β2-microglobin levels was 10% among workers with urinary cadmium levels of 1.5 (≥60 years of age) or 5 (<60 years of age) μg/g creatinine (β2-microglobulin cut-off level of 220 μg/g creatinine) (Järup and Elinder 1994), 25% among workers with urinary cadmium levels of 2–5 μg/g creatinine (cut-off level of 300 μg/g creatinine) (Elinder et al. 1985a), 40% among workers with urinary cadmium levels of 5–10 μg/g creatinine (cut-off level of 187 μg/g creatinine) (Chen et al. 2006a), and 10% among workers with urinary cadmium levels of 10–15 μg/g creatinine (cut-off level of 380 μg/g creatinine (Jakubowski et al. 1987). A 10% prevalence of abnormal β2-microglobulin levels (cut-off level of 300 μg/g creatinine) was also observed in workers with a cumulative blood cadmium level of 300 μg-years/L (30 years of 10 μg/L) (Jakubowski et al. 1992) or blood cadmium level of 5.6 μg/L (cumulative exposure of 691 μg-years/m^3) (Järup et al. 1988).

Most of the studies reporting respiratory effects expressed cadmium exposure as air concentrations; however, these air concentrations may not be indicative of cadmium exposure over time. For example, in the Cortona et al. (1992) study, cadmium levels of 0.030 mg/m^3 were measured in 1990 in one foundry; in 1976, the cadmium levels in this foundry were 1.53 mg/m^3. Cortona et al. (1992) also reported cadmium body burden data; the mean urinary cadmium level in the workers was 4.3 μg/L (roughly equivalent to 4 μg/g creatinine). Renal effects have been observed at similar cadmium burdens. Most studies have reported renal effects in workers with urinary cadmium levels of ≥5 μg/g creatinine; Järup and Elinder (1994) found an increased prevalence of low molecular weight proteinuria in workers ≥60 years of age with mean urinary cadmium of 1.5 μg/g creatinine. The air concentration that would result in this urinary cadmium level would be considered a LOAEL. However, cadmium in the workplace air was not the only source of cadmium. The workers were also exposed to other sources of cadmium (e.g., cadmium in the

diet); both sources contributed to the renal cadmium burden. Thus, in order to calculate a chronic-duration inhalation MRL from the LOAEL identified in the Järup and Elinder (1994) study, the workers' other sources of cadmium need to be taken into consideration; this information was not reported in the study.

An alternative approach would be to use environmental exposure studies to establish a point of departure for the urinary cadmium-renal response relationship and pharmacokinetic models (ICRP 1994; Kjellström and Nordberg 1978) to predict cadmium air concentrations. As described in greater detail in the chronic oral MRL section, a meta-analysis of available environmental exposure studies was conducted to estimate an internal dose (urinary cadmium expressed as μg/g creatinine) corresponding to a 10% excess risk of low molecular weight proteinuria (urinary cadmium dose, UCD_{10}). For the inhalation MRL, the meta-analysis also included dose-response data from three occupational exposure studies (Chen et al. 2006a, 2006b; Järup and Elinder 1994; Roels et al. 1993). Analysis of the environmental exposure studies resulted in an estimation of a urinary cadmium level that would result in a 10% increase in the prevalence of β2-microglobulin proteinuria (1.34 μg/g creatinine); the 95% lower confidence limit on this value was 0.5 μg/g creatinine. The UCD_{10} values from the occupational exposure studies were 7.50 μg/g creatinine for the European cohorts (Järup and Elinder 1994; Roels et al. 1993) and 4.58 μg/g creatinine for the Chinese cohort (Chen et al. 2006a, 2006b). Because the dose-response analysis using the European environmental exposure studies provided the lowest UCD_{10}, it was selected for derivation of the chronic-duration inhalation MRL; the 95% lower confidence limit on this value ($UCDL_{10}$) of 0.5 μg/g creatinine was used as the point of departure for the MRL.

Deposition and clearance of inhaled cadmium oxide and cadmium sulfide particles were modeled using the ICRP Human Respiratory Tract Model (ICRP 1994). The ICRP model simulates deposition, retention, and absorption of inhaled cadmium particles of specific aerodynamic diameters, when specific parameters for cadmium clearance are used in the model (ICRP 1980). Cadmium-specific parameters represent categories of solubility and dissolution kinetics in the respiratory tract (e.g., slow, S; moderate, M; or fast, F). Cadmium compounds are classified as follows: oxides and hydroxides, S; sulfides, halides and nitrates, M; all other, including chloride salts, F.

Inhalation exposures ($\mu g/m^3$) to cadmium oxide or cadmium sulfide aerosols having particle diameters of 1, 5, or 10 μg (AMAD) were simulated using the ICRP model. Predicted mass transfers of cadmium from the respiratory tract to the gastrointestinal tract (i.e., mucocilliary transport) and to blood (i.e., absorption) were used as inputs to the gastrointestinal and blood compartments of the Nordberg-Kjellström

pharmacokinetic model (Kjellström and Nordberg 1978) to simulate the kidney and urinary cadmium levels that correspond to a given inhalation exposure.

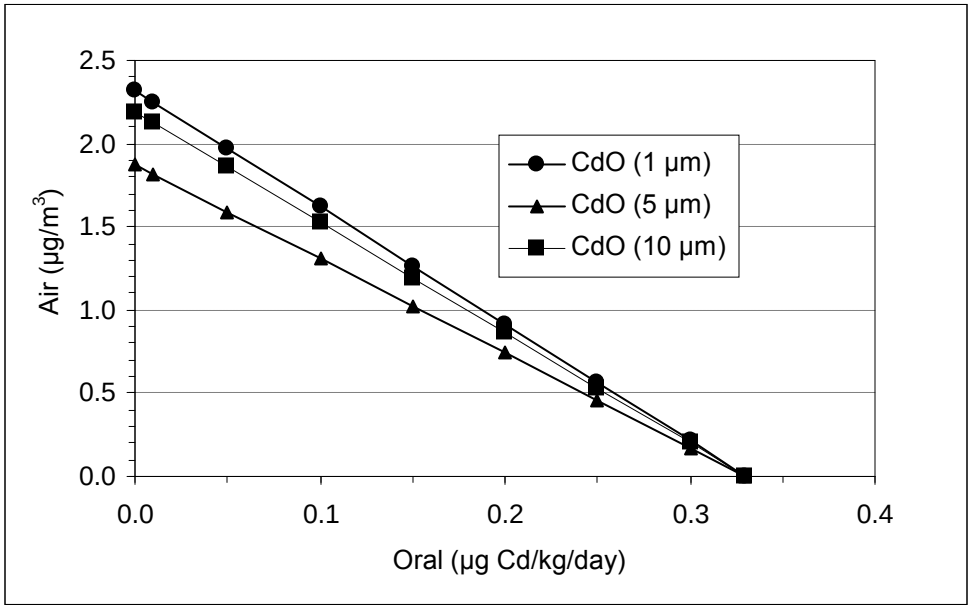
As illustrated in Figure 2-1, an airborne cadmium concentration of 1.8–2.4 μg/m^3 as cadmium oxide or 1.2–1.4 μg/m^3 as cadmium sulfide would result in a urinary cadmium level of 0.5 μg/g creatinine, assuming that there was no dietary source of cadmium. This assumption is not accurate because the diet is a significant contributor to the cadmium body burden. Thus, inhalation exposures were combined with ingestion intakes to estimate an internal dose in terms of urinary cadmium. The age-weighted average intakes of cadmium in non smoking males and females in the United States are 0.35 and 0.30 μg Cd/kg/day, respectively (0.32 μg/kg/day for males and females combined) (estimated from data in Choudhury et al. 2001). Based on the relationship predicted between chronic inhalation exposures to cadmium sulfide (activity median aerodynamic diameter [AMAD]=1 μm) and oral intakes that yield the same urinary cadmium level (Figure 2-1), exposure to an airborne cadmium concentration of 0.1 μg/m^3 and a dietary intake of 0.3 μg/kg/day would result in a urinary cadmium level of 0.5 μg/g creatinine. Dividing this cadmium air concentration (0.1 μg Cd/m^3) by an uncertainty factor of 3 for human variability and a modifying factor of 3 results in chronic-duration inhalation MRL of 0.01 μg Cd/m^3. The uncertainty factor of 3 for human variability was used to account for the possible increased sensitivity of diabetics (Åkesson et al. 2005; Buchet et al. 1990) and the modifying factor of 3 was used to account for the lack of adequate human data, which could be used to compare the relative sensitivities of the respiratory tract and kidneys. Although based on exposure to cadmium sulfide, the MRL would be protective of exposure to cadmium oxide; the pharmacokinetic models predict that exposure to 0.1 μg/m^3 as cadmium oxide (AMAD=1 μm) in combination with a dietary intake of 0.3 μg/kg/day would result in a urinary cadmium level of 0.4 μg/g creatinine.

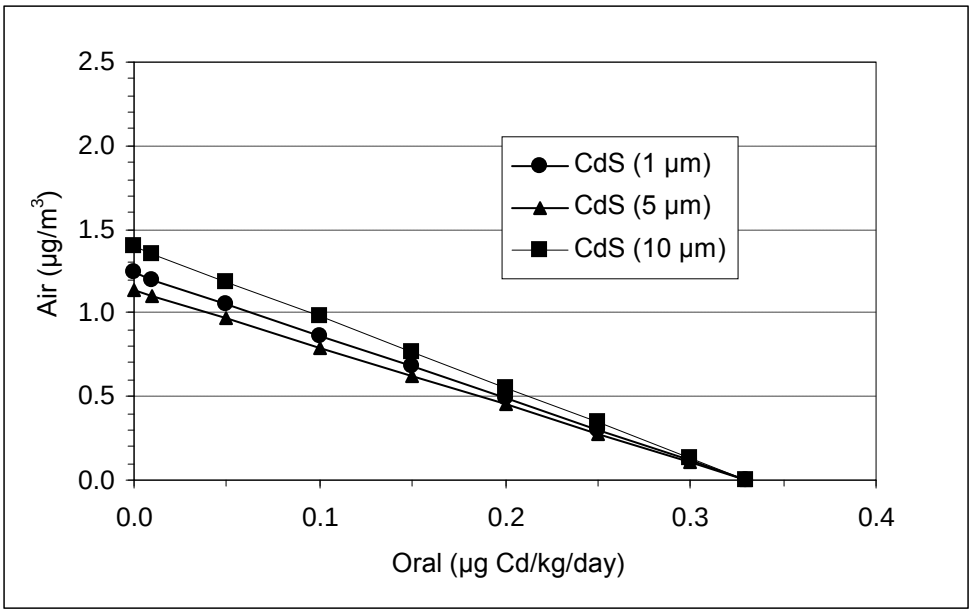
Oral MRLs

Acute-duration Oral MRL

There are no reliable studies on the acute toxicity of cadmium in humans; animal studies have identified several targets of toxicity. High exposures (>10 mg Cd/kg/day) to cadmium chloride administered via gavage or drinking water resulted in increases in hematological (increased hemoglobin, hematocrit, and erythrocytes, anemia), liver (focal necrosis and degeneration), kidney (focal necrosis of tubular epithelium), intestine (necrosis, hemorrhage, ulcers), stomach (gastritis, necrosis), neurological (decreased motor activity), and testicular (atrophy and necrosis, loss of spermatogenic elements) effects

Figure 2-1. Combined Chronic Oral Cadmium Intakes (µg/kg/day) and Inhalation Cadmium Exposures (µg/m^3) that Achieve a Urinary Cadmium Excretion of 0.5 µg/g Creatinine at Age 55 Years Predicted by the Cadmium Pharmacokinetic Model and the International Commission on Radiological Protection (ICRP) Human Respiratory Tract Model*





*The upper panel shows simulations of inhalation exposures to cadmium oxide (AMAD=1, 5, or 10 µm); the lower panel shows simulations of inhalation cadmium sulfide aerosols.

and decreases in body weight in rats and mice (Andersen et al. 1988; Basinger et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989; Dixon et al. 1976; Kotsonis and Klaassen 1977; Machemer and Lorke 1981; Sakata et al. 1988; Shimizu and Morita 1990). The NOAELs for these effects ranged from 1.12 to 65.6 mg Cd/kg/day.

Developmental effects have been observed at lower cadmium doses. Delayed ossification of the sternum and ribs was observed in the offspring of rats administered 2 mg Cd/kg/day via gavage on gestation days 7–16; at 40 mg Cd/kg/day, fused lower limbs, decreased number of live fetuses, and increased resorptions were observed (Baranski 1985). A significant increase in malformations was observed in the offspring of rats administered 18.39 mg Cd/kg/day on gestation days 6–15 (Machemer and Lorke 1981); no developmental effects were observed in the offspring of rats administered 12.5 mg Cd/kg/day via drinking water on gestation days 6–15 (Machemer and Lorke 1981).

Although the Baranski (1985) study identified the lowest LOAEL (2 mg Cd/kg/day) following acute-duration exposure, this study was not considered suitable for derivation of an MRL. The investigators noted that "a retarded process of ossification of the sternum and ribs was observed after exposure to cadmium at any of the doses used." However, the data were not shown and the statistical significance of the finding was not reported. Additionally, an intermediate-duration study conducted earlier by this investigator (Baranski et al. 1983) did not find delays in ossification in the offspring of rats administered up to 4 mg Cd/kg/day for 5 weeks prior to mating, during the 3-week mating period, and throughout gestation.

Intermediate-duration Oral MRL

- An MRL of 0.5 µg Cd/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to cadmium.

There are limited data on the toxicity of cadmium in humans following intermediate-duration exposure. Numerous animal studies have examined the systemic, immunological, neurological, reproductive, and developmental toxicity of cadmium. The most sensitive systemic effect following intermediate-duration oral exposure to cadmium appears to be damage to growing bone. Exposure to 0.2 mg Cd/kg/day as cadmium chloride in drinking water for 3–12 months resulted in decreases in bone mineral density, impaired mechanical strength of the lumbar spine, tibia, and femur bones, increased bone turnover, and increased incidence of deformed or fractured lumbar spine bone in young female rats (3 weeks of age at study initiation) (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c);

similar findings were observed in young male rats exposed to 0.5 mg Cd/kg/day for up to 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b). Decreases in bone strength were also observed in young rats exposed to 0.8 mg Cd/kg/day as cadmium chloride in drinking water for 4 weeks (Ogoshi et al. 1989); however, no skeletal effects were observed in adult or elderly female rats exposed to doses >20 mg Cd/kg/day for 4 weeks (Ogoshi et al. 1989). Decreases in bone calcium were observed in mice undergoing repeated pregnancy/lactation periods (Bhattacharyya et al. 1988b) or ovariectomized mice (Bhaattacharyya et al. 1988c); these changes were not observed in groups not under physiological stress.

Renal effects have been observed at higher doses than the skeletal effects. Vesiculation of the proximal tubules was observed in rats exposed to 1.18 mg Cd/kg/day as cadmium chloride in drinking water for 40 weeks (Gatta et al. 1989). At approximately 3–8 mg Cd/kg/day, proteinuria, tubular necrosis, and decreased renal clearance were observed in rats (Cha 1987; Itokawa et al. 1974; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Prigge 1978a). Liver necrosis and anemia (Cha 1987; Groten et al. 1990; Kawamura et al. 1978) were observed at similar cadmium doses.

Immunological effects have been observed in studies of monkeys, rats, and mice. The observed effects include increases in cell-mediated immune response in monkeys exposed to 5 mg Cd/kg/day as cadmium chloride in the diet for 10 weeks (Chopra et al. 1984), decreased humoral immune response in mice exposed to 2.8 mg Cd/kg/day as cadmium chloride in drinking water for 3 weeks (Blakley 1985), and greater susceptibility to lymphocytic leukemia virus in mice exposed to 1.9 mg Cd/kg/day as cadmium chloride in drinking water for 280 days (Blakley 1986).

Neurological effects observed in rats include decreases in motor activity at 3.1 or 9 mg Cd/kg/day (Kotsonis and Klaassen 1978; Nation et al. 1990) and increased passive avoidance at 5 mg Cd/kg/day (Nation et al. 1984). Reproductive effects (necrosis and atrophy of seminiferous tubules, decreased sperm count and motility) were observed in rats exposed to 8–12 mg Cd/kg/day (Cha 1987; Saxena et al. 1989).

A number of developmental effects have been observed in the offspring of rats exposed to cadmium during gestation and lactation. Decreases in glomerular filtration rates and increases in urinary fractional excretion of phosphate, magnesium, potassium, sodium, and calcium were observed in 60-day-old offspring of rats administered via gavage 0.5 mg Cd/kg/day on gestation days 1–21 (Jacquillet et al. 2007). Neurodevelopmental alterations have also been observed at the low maternal doses. Delays in the development of sensory motor coordination reflexes and increased motor activity were observed at 0.706 mg Cd/kg/day (gestation days 1–21) (Ali et al. 1986), decreased motor activity at 0.04 mg

Cd/kg/day (5–8 weeks of pre-gestation exposure, gestation days 1–21) (Baranski et al. 1983), decreased ambulation and rearing activity and altered ECG at 14 mg Cd/kg/day (gestation days 5–15, lactation days 2–28, postnatal days 1–56) (Desi et al. 1998) or 7 mg Cd/kg/day (F_2 and F_3 generations) (Nagymajtenyi et al. 1997) have been observed. Decreases in pup body weight were observed at ≥5 mg Cd/kg/day (Baranski 1987; Gupta et al. 1993; Kostial et al. 1993; Pond and Walker 1975) and decreases in fetal body weight or birth weight were observed at ≥2.4 mg Cd/kg/day (Petering et al. 1979; Sorell and Graziano 1990; Webster 1978; Sutou et al. 1980). Another commonly reported developmental effect was alterations in hematocrit levels or anemia in the offspring of animals exposed to ≥1.5 mg Cd/kg/day (Baranski 1987; Kelman et al. 1978; Webster 1978). Increases in the occurrence of malformations or anomalies is limited to a study by Sutou et al. (1980), which reported a significant delay in ossification in rats exposed to 10 mg Cd/kg/day.

The animal studies identify several sensitive targets of toxicity following intermediate-duration exposure to cadmium; these include skeletal mineralization in young female rats exposed for at least 3 months to 0.2 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c), decreased glomerular filtration in young rats exposed during gestation to maternal doses of 0.5 mg Cd/kg/day (Jacquillet et al. 2007), and neurodevelopmental effects following gestational exposure to 0.04 mg Cd/kg/day (Baranski et al. 1983). Although the Baranski et al. (1983) study reported the lowest LOAEL, it was not selected as the principal study for derivation of an intermediate-duration MRL. For locomotor activity, a significant decrease in activity was observed in female offspring exposed to 0.04, 0.4, and 4 mg Cd/kg/day, as compared to controls; however, no significant differences were found between the cadmium groups despite the 100-fold difference in doses. Locomotor activity was also decreased in males exposed to 0.4 or 4 mg Cd/kg/day. For the rotorod test, a significant decrease in the length of time the rat stayed on the rotorod was observed in males exposed to 0.04 and 0.4 mg Cd/kg/day, but not to 4 mg Cd/kg/day and in females exposed to 0.4 and 4 mg Cd/kg/day; no differences between the cadmium groups were observed in the males and females. The results were not well described and the investigators did not explain the lack of dose-response of the effects or the discrepancy between genders.

The skeletal effects observed in young rats exposed to cadmium during the period of rapid skeletal growth and mineralization was selected as the critical effect. The Brzóska and associate study (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2005a, 2005c) was selected as the principal study. In this study, groups of 40 3-week-old female Wistar rats were exposed to 0, 1, 5, or 50 mg Cd/L as cadmium chloride in drinking water for 12 months. The investigators noted that cadmium intakes were 0.059–0.219, 0.236–1.005, and 2.247–9.649 mg Cd/kg/day in the 1, 5, and 50 mg/L groups, respectively. Using

cadmium intake data presented in a figure, cadmium intakes of 0.2, 0.5, and 4 mg Cd/kg/day were estimated. Bone mineral density, bone mineral concentration, and mineralization area of the lumbar spine, femur, and total skeleton (bone mineral density only) were assessed after 3, 6, 9, or 12 months of exposure. The mechanical properties of the femur and tibia were evaluated after 12 months of exposure. Markers for bone resorption (urinary and serum levels of C-terminal cross-linking telopeptide of type I collagen [CTX]) and bone formation (serum osteocalcin, total alkaline phosphatase, and cortical bone and trabecular bone alkaline phosphatase), and serum and urinary levels of calcium were also measured at 3, 6, 9, and 12 months.

No significant alterations in body weight gain or food and water consumption were observed. Significant decreases in total skeletal bone mineral density was observed at ≥0.2 mg Cd/kg/day; the decrease was significant after 3 months in the 4 mg Cd/kg/day group, after 6 months in the 0.5 mg Cd/kg/day group, and after 9 months in the 0.2 mg Cd/kg/day group. Significant decreases in whole tibia and diaphysis bone mineral density were observed at ≥0.2 mg Cd/kg/day after 12 months of exposure. At 0.2 mg Cd/kg/day, bone mineral density was decreased at the proximal and distal ends of the femur after 6 months of exposure; diaphysis bone mineral density was not affected. At 0.5 mg Cd/kg/day, bone mineral density was decreased at the femur proximal and distal ends after 3 months of exposure and diaphysis bone mineral density after 6 months of exposure. At 4 mg Cd/kg/day decreases in femoral proximal, distal, and diaphysis bone mineral density were decreased after 3 months of exposure. Similarly, bone mineral density was significantly decreased in the lumbar spine in the 0.2 and 0.5 mg Cd/kg/day groups beginning at 6 months and at 3 months in the 4 mg Cd/kg/day group. Significant decreases in the mineralization area were observed in the femur and lumbar spine of rats exposed to 4 mg Cd/kg/day; lumbar spine bone mineral area was also affected at 0.5 mg Cd/kg/day. Significant decreases in tibia weight and length were observed at 4 mg Cd/kg/day. In tests of the mechanical properties of the tibia diaphysis, significant alterations in ultimate load, yield load, and displacement at load were observed at ≥0.2 mg Cd/kg/day; work to fracture was also significantly altered at 4 mg Cd/kg/day. In the mechanical properties compression tests of the tibia, significant alterations were observed in ultimate load, ultimate load, and stiffness at 0.2 mg Cd/kg/day; displacement at yield and work to fracture at ≥0.5 mg Cd/kg/day; and displacement at ultimate at 4 mg Cd/kg/day. Multiple regression analysis showed that the the cadmium-induced weakness in bone mechanical properties of the tibia was primarily due to its effects on bone composition, particularly the non-organic components, organic components, and the ratio of ash weight to organic weight. The mechanical properties of the femur were strongly influenced by the bone mineral density (at the whole bone and diaphysis). A significant decrease in femur length was observed at 6 months of exposure to ≥0.2 mg Cd/kg/day; however, decreases in length

were not observed at other time points in the 0.2 or 0.5 mg Cd/kg/day groups. Femur weight was significantly decreased at 4 mg Cd/kg/day. In tests of mechanical properties of the femur (neck and distal portions), decreases in yield load, ultimate load, displacement at ultimate, work to fracture (neck only), and stiffness (distal only) were observed at ≥0.2 mg Cd/kg/day. For the femoral diaphysis, significant alterations were observed for yield load, displacement at yield, and stiffness at ≥0.2 mg Cd/kg/day. Significant decreases in osteocalcin concentrations were observed in all cadmium groups during the first 6 months of exposure, but not during the last 6 months. Decreases in total alkaline phosphatase levels at 4 mg Cd/kg/day, trabecular bone alkaline phosphatase at 0.2 mg Cd/kg/day, and cortical bone alkaline phosphatase at 4 mg Cd/kg/day were observed. CTX was decreased at ≥0.2 mg Cd/kg/day. Total urinary calcium and fractional excretion of calcium were increased at ≥0.2 mg Cd/kg/day.

At the lowest dose tested, 0.2 mg Cd/kg/day, a number of skeletal alterations were observed including decreases in bone mineral density in the lumbar spine, femur, and tibia, alterations in the mechanical properties of the femur and tibia, decreases in osteocalcin levels, decreases in trabecular bone alkaline phosphatase, and decreases in CTX. Of these skeletal end points, the decrease in bone mineral density was selected as the critical effect because Brzóska et al. (2005a, 2005c) demonstrated that the bone mineral density was a stronger predictor of femur and tibia strength and the risk of fractures. As discussed in greater detail in Appendix A, available continuous models in the EPA Benchmark Dose Software (version 1.4.1c) were fit to data for changes in bone mineral density of the femur and lumbar spine in female rats resulting from exposure to cadmium in the drinking water for 6, 9, or 12 months (Brzóska and Moniuszko-Jakoniuk 2005d). The benchmark dose (BMD) and the 95% lower confidence limit (BMDL) is an estimate of the doses associated with a change of 1 standard deviation from the control. The $BMDL_{sd1}$ derived from the best fitting models for each dataset ranged from 0.05 to 0.17 mg Cd/kg/day. The $BMDL_{sd1}$ of 0.05 mg Cd/kg/day estimated from the 9-month lumbar spine data set was selected as the point of departure for the MRL. In young female rats, the process of intense bone formation occurs during the first 7 months of life (the first 6 months of exposure in this study); thereafter, the increase in bone mineral density slows. In the lumbar spine of the control group, the changes in bone mineral density at 3–6 months, 6–9 months, and 9–12 months were 15, 4, and 1%, respectively. Thus, the 9-month data may best reflect the effect of cadmium on bone mineral density during the period of rapid skeletal growth. The lumbar spine data was selected over the femur data set because trabecular bone, which is abundant in the spine, appears to be more susceptible to cadmium toxicity than cortical bone. The $BMDL_{sd1}$ was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an intermediate-duration oral MRL of 0.5 μg Cd/kg/day.

Chronic-duration Oral MRL

- An MRL of 0.1 μg/kg/day has been derived for chronic-duration oral exposure (≥1 year) to cadmium.

The database examining the chronic toxicity of cadmium following oral exposure is extensive. Although there are some chronic studies in animals, the majority of the studies in the chronic database examine the relationship between urinary cadmium levels (or cumulative cadmium intake) and adverse health effects in the general population or in populations living in cadmium polluted areas. A variety of health effects have been observed including increased blood pressure, skeletal defects (osteoporosis, increased bone fractures, decreased bone mineral density), kidney dysfunction, and alterations in reproductive hormone levels. These environmental exposure studies strongly support the identification of bone and kidney as the most sensitive targets of chronic cadmium toxicity.

Bone effects, particularly osteomalacia and/or osteoporosis and increased bone fractures, were first reported in Japanese women living in areas with heavy cadmium contamination. Chronic cadmium exposure has been shown to play a role in this disorder, referred to as Itai-Itai disease; however, other factors such as multiple pregnancies, poor nutrition (low calories, calcium, protein, vitamin D, and iron intakes), and low zinc levels in food also play important roles in the etiology. Although a conclusive role of cadmium in Itai-Itai has not been established, several other studies have found bone defects. Observed bone effects include increased risk of bone fractures in post-menopausal women with urinary cadmium levels of >1 μg/day (approximately >0.7 μg Cd/g creatinine; Staessen et al. 1999), individuals (>50 years of age) with urinary cadmium levels of >2 μg/g creatinine (Alfvén et al. 2004), and men and women (>40 years of age) with urinary cadmium levels of 9.20 and 12.86 μg/g creatinine, respectively (Wang et al. 2003); increased risk of osteoporosis in men (>60 years of age) with urinary cadmium levels of ≥1.5 μg/g creatinine (Alfvén et al. 2000), in males and females with urinary cadmium levels of ≥10 μg/g creatinine (Jin et al. 2004b), and in males and females (>40 years of age) with urinary cadmium levels of 9.20 and 12.86 μg/g creatinine, respectively (Wang et al. 2003); and decreased bone mineral density in women with urinary cadmium levels of >0.6 μg/g creatinine (Schutte et al. 2008) and post-menopausal women with urinary cadmium levels of >20 μg/g creatinine (Nordberg et al. 2002).

Evidence of renal dysfunction in environmentally exposed populations include increases in deaths from renal dysfunction in residents living in cadmium polluted areas of Japan (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 1995, 2004a, 2006), increases in renal replacement therapy which is indicative of severe renal dysfunction (Hellström et al.

2001), and increases in the excretion of biomarkers of renal dysfunction in association with increased cadmium intake, increased renal cadmium concentrations, increased blood cadmium levels, and/or increased urinary cadmium concentrations (Buchet et al. 1990; Cai et al. 1990, 1992, 1998, 2001; Hayano et al. 1996; Horiguchi et al. 2004; Ishizaki et al. 1989; Izuno et al. 2000; Järup et al. 2000; Jin et al. 2002, 2004a, 2004c; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002a; Monzawa et al. 1998; Nakadaira and Nishi 2003; Nakashima et al. 1997; Nogawa et al. 1989; Noonan et al. 2002; Nordberg et al. 1997; Olsson et al. 2002; Oo et al. 2000; Osawa et al. 2001; Roels et al. 1981b; Suwazono et al. 2006; Teeyakasem et al. 2007; Trzcinka-Ochocka et al. 2004; Uno et al. 2005; Yamanaka et al. 1998; Wu et al. 2001). The urinary excretion of several biomarkers have been shown to increase due to cadmium-related alterations in kidney function; these biomarkers include low molecular weight proteins (e.g., β2-microglobulin, pHC, retinol binding protein), intracellular tubular enzymes (e.g., NAG), amino acids, high molecular weight proteins (e.g., albumin), metallothionein, and electrolytes (e.g., potassium, sodium, calcium). Although the more severe renal effects have been observed in populations living in highly contaminated areas (e.g., decreased glomerular filtration rate), alterations in the above biomarkers have been observed in areas not considered to be cadmium polluted. Alterations in these biomarker levels appear to be the most sensitive indicator of cadmium toxicity. Many of the studies examining biomarkers have reported significant correlations between urinary cadmium levels and biomarker levels. However, these correlations do not provide insight into exposure levels associated with renal dysfunction. In this MRL analysis, attention was given to dose-response studies examining the derived quantitative relationships between cadmium exposure and the prevalence of abnormal biomarker levels. As discussed in the inhalation MRL section, a 10% increase in the prevalence of abnormal biomarker levels (particularly β2-microglobulin, pHC, or retinol binding protein) in association with increasing cadmium exposure is generally considered to be indicative of cadmium-associated renal dysfunction in populations. However, when examining the prevalence of abnormal levels, careful consideration should be given to the response criterion (cut-off level) used in the study. A wide range of cut-off levels have been used in the environmental exposure studies. For β2-microglobulin, the most commonly used biomarker, the cut-off values ranged from 283 to 1,129 μg/g creatinine. A summary of environmental studies finding significant dose-response associations between urinary cadmium (or cumulative cadmium intake) and the prevalence of abnormal levels of urinary biomarkers of renal dysfunction is presented in Table 2-1. The adverse effect levels range from urinary cadmium levels of 1 μg/g creatinine (Järup et al. 2000) to 9.51 μg/g creatinine (Jin et al. 2004a).

Table 2-1. Summary of Human Studies Finding Dose-Response Relationships Between Biomarkers of Renal Dysfunction and Cadmium Exposure

Population	Effect biomarker	Response criterion	Adverse effect level (urinary cadmium)	Reference
General population (Japan)	Total prt β2M NAG	157.4 µg/g creat. (M) 158.5 µg/g creat. (F) 507 µg/g creat. (M) 400 µg/g creat. (F) 8.2 µg/g creat. (M) 8.5 µg/g creat. (F)	2.4 µg/g creat.[a]	Suwazono et al. 2006
General population (Belgium)	β2M RBP NAG amino acid calcium	283 µg/24 hours 338 µg/24 hours 3-6 IU/24 hours 357 mg α-N/24 hours 4-9 mmol/24 hours	1.92 µg/g creat.[b]	Buchet et al. 1990
Residents in cadmium-polluted area (China)	β2M	355 µg/g creat. (M <45 years) >2,500 µg/g creat. (M ≥45 years) 500 µg/g creat. (F)	4–7.99 µg/g creat.[c]	Cai et al. 1998
Residents in cadmium-polluted area (China)	β2M RBP albumin	300 µg/g creat. 300 µg/g creat. 15 mg/g creat.	≥5 µg/g creat.	Jin et al. 2002
Residents in cadmium-polluted area (China)	β2M NAG albumin	800 µg/g creat. 15 U/g creat. 20 mg/g creat.	9.51 µg/g creat.	Jin et al. 2004a
Residents in cadmium-polluted area (China)	β2M	800 µg/g creat.	2–4 µg/g creat.[c]	Nordberg et al. 1997
Residents in cadmium-polluted area (Japan)	β2M	1,000 µg/g creat.	6.9 µg/g creat.	Cai et al. 2001
Residents in cadmium-polluted area (Japan)	β2M	1,000 µg/g creat. (M,F)	Cadmium intake: 150 µg/day	Nogawa et al. 1989; Kido and Nogawa 1993
Residents in cadmium-polluted area (Japan)	β2M	1,129 µg/g creat. (M) 1,059 µg/g creat. (F)	4–4.9 µg/g creat.[c]	Ishizaki et al. 1989; Hayano et al. 1996

Table 2-1. Summary of Human Studies Finding Dose-Response Relationships Between Biomarkers of Renal Dysfunction and Cadmium Exposure

Population	Effect biomarker	Response criterion	Adverse effect level (urinary cadmium)	Reference
Residents in cadmium-polluted area (Thailand)	β2M	400 µg/g creat.	6–10 µg/g creat.	Teeyakasem et al. 2007
Residents in cadmium-polluted area (includes occupationally exposed subjects (Sweden)	pHC	7.1 mg/g creat. (M) 5.3 mg/g creat. (F)	1 µg/g creat.[d]	Järup et al. 2000

[a]Mean urinary cadmium level
[b]>10% prevalence of abnormal β2-microglobulin, retinal binding protein, amino acid, and calcium values at 3.05, 2.87, 2.74, 4.29, or 1.92 µg/24 hours, respectively.
[c]Urinary cadmium level associated with an approximate doubling of prevalence of abnormal β2-microglobulin levels
[d]The European Chemicals Bureau (2007) recalculated this value (using raw data from Järup et al. 2000) to account for differences in age of the reference population and study population; based on these recalculations, a doubling of the probability of abnormal pHC values would occur at 2.62 µg/g creatinine for the total population and a 0.5 µg/g creatinine for the environmentally exposed population.

AAP = alanine aminopeptidase; β2M = β2-microglobulin; creat. = creatinine; F = female; M = male; NAG = N-acetyl-β-glucosaminidase; pHC = human complex-forming glycoprotein, also referred to as α1M; RBP = retinol binding protein

The adverse effect levels for renal effects were similar to those observed for skeletal effects. Because the renal effects database is stronger, it was used for derivation of a chronic-duration oral MRL for cadmium. Several approaches were considered for derivation of the MRL: (1) NOAEL/LOAEL approach using a single environmental exposure study finding an increased prevalence of abnormal renal effect biomarker levels, (2) selection of a point of departure from a published benchmark dose analysis, or (3) selection of a point of departure based on an analysis of the dose-response functions from a number of environmental exposure studies.

In the first approach, all studies in which individual internal doses for subjects were estimated based on urinary cadmium were considered. The Järup et al. (2000) study is selected as the principal study because it identified the lowest adverse effect level (Table 2-1). In this study, 1,021 individuals living near a nickel-cadmium battery factory (n=799) or employed at the factory (n=222) were examined. The mean urinary cadmium concentrations were 0.81 μg/g creatinine in men and 0.65 μg/g creatinine in women. A significant association was found between urinary cadmium concentrations and urinary pHC levels, after adjustment for age; the association remained statistically significant after removal of the cadmium workers from the analysis. The investigators estimated that a urinary cadmium level of 1 μg/g creatinine would be associated with a 10% increase in the prevalence of abnormal pHC levels above background prevalence (approximately a 10% added risk). However, the European Chemicals Bureau (2007) recalculated the probability of HC proteinuria because the reference population and the study population were not matched for age (40 versus 53 years, respectively). They estimated that the probability of HC proteinuria (13%) would be twice as high as the reference population at a urinary cadmium concentration of 0.5 μg/g creatinine.

The second approach involves the evaluation of five published benchmark dose analyses. The benchmark doses and the lower 95% confidence interval of the benchmark dose (BMDL) for low molecular weight proteinuria are presented in Table 2-2 (benchmark doses and BMDLs for all effect parameters are presented in Table 3-8 in the toxicological profile). The BMDL values corresponding to a 10% increase in the prevalence of low molecular weight proteinuria above background (excess risk) ranged from 0.7 μg/g creatinine (Uno et al. 2005) to 9.9 μg/g creatinine (Kobayashi et al. 2006). Both studies examined populations living in non-cadmium polluted areas of Japan and used β2-microglobulin as the effect biomarker. The large difference in cut-off values (233 versus 784 μg/g creatinine) likely contributed to the order of magnitude difference in BMDLs. The $BMDL_{10}$ of 0.7 μg/g creatinine is supported by the Suwazono et al. (2006) benchmark dose analysis, which found a similar $BMDL_{10}$ (0.81 μg/g creatinine) using pHC as the effect biomarker. The Uno et al. (2005) study examined 410 men

Table 2-2. Selected Benchmark Dose Estimations of Urinary Cadmium Levels Associated with Increases in the Prevalence of Low Molecular Weight Proteinuria

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
General population (Sweden)	pHC	6.8 mg/g creat. (95% cut-off)[a]		0.63 (F)	0.49 (F)	1.05 (F)	0.81 (F)	Suwazono et al. 2006
Residents in cadmium-polluted and non-polluted areas (Japan)	β2M	507 µg/g creat. (M) 400 µg/g creat. (F) (84% cut-off)[b]	Quantal linear model	1.5 (M) 1.4 (F)	1.2 (M) 1.1 (F)	3.1 (M) 2.9 (F)	2.5 (M) 2.3 (F)	Shimizu et al. 2006
		994 µg/g creat. (M) 784 µg/g creat. (F) (95% cut-off)[c]		2.3 (M) 1.7 (F)	1.8 (M) 1.4 (F)	4.7 (M) 3.5 (F)	3.7 (M) 2.9 (F)	
General population (Japan)	β2M	507 µg/g creat. (M) 400 µg/g creat. (F) (84% cut-off)[d]	Log-logistic model	2.9 (M) 3.8 (F)	2.4 (M) 3.3 (F)	5.0 (M) 6.6 (F)	4.0 (M) 5.5 (F)	Kobayashi et al. 2006
		994 µg/g creat. (M) 784 µg/g creat. (F) (95% cut-off)[e]		6.4 (M) 8.7 (F)	4.5 (M) 7.3 (F)	10.2 (M) 12.0 (F)	7.1 (M) 9.9 (F)	
General population (Japan)	β2M	233 µg/g creat. (M) 274 µg/g creat. (F) (84% cut-off)[f]	Quantal linear model	0.5 (M) 0.9 (F)	0.4 (M) 0.8 (F)	1.0 (M) 1.8 (F)	0.7 (M) 1.3 (F)	Uno et al. 2005
Residents in cadmium highly, or moderately polluted area (China)	β2M	800 µg/g creat. (95% cut-off)[g]	Quantal linear logistic regression model	5.86 (M) 9.98 (F)	4.74 (M) 8.47 (F)			Jin et al. 2004b
	RBP	0.300 mg/g creat. (95% cut-off)[g]		5.99 (M) 9.03 (F)	4.87 (M) 7.63 (F)			

[a]95th percentile of effect biomarkers on the "hypothetical" control distribution at a urinary cadmium level of zero.
[b]84% upper limit values from a group of 424 males and 1,611 females who did not smoke and lived in three different cadmium nonpolluted areas.
[c]95% upper limit values from a group of 424 males and 1,611 females who did not smoke and lived in three different cadmium nonpolluted areas.
[d]84% upper limit value of the target population of people who have not smoked.
[e]95% upper limit value of the target population of people who have not smoked.
[f]84% upper limit value of the target population.
[g]95% upper limit value from a control group 98 males and 155 females living in a cadmium nonpolluted area.

BMD = benchmark dose; BMDL = benchmark dose low; BMR = benchmark response; β2M = β2-microglobulin; creat. = creatinine; F = female; M = male; NAG = *N*-acetyl-β-D-glucosaminidase; NAG-B = *N*-acetyl-β-D-glucosaminidase's isoform B; RBP = retinol binding protein

and 418 women (aged 40–59 years) living in three areas of Japan without any known environmental cadmium pollution. Mean urinary cadmium concentrations were 1.3 and 1.6 μg/g creatinine in men and women, respectively. Cut-off levels for β2-microglobulin were 233 and 274 μg/g creatinine in males and females; these values represent the 84% upper limit values calculated from the target population assuming a log normal distribution.

The third approach involved a meta-analysis of selected environmental exposure dose-response studies. Studies were selected for inclusion in this analysis based on the following qualitative criteria: (1) the study measured urinary cadmium as indicator of internal dose; (2) the study measured reliable indicators of low molecular weight (LMW) proteinuria; (3) a dose-response relationship was reported in sufficient detail so that the dose-response function could be reproduced independently; (4) the study was of reasonable size to have provided statistical strength to the estimates of dose-response model parameters (i.e., most studies selected included several hundred to several thousand subjects); and (5) major co-variables that might affect the dose-response relationship (e.g., age, gender) were measured or constrained by design and included in the dose-response analysis. No attempt was made to weight selected studies for quality, statistical power, or statistical uncertainty in dose-response parameters. Studies using a cut-off value for β2-microglobulin of ≥1,000 μg/g creatinine were eliminated from the analysis based on the conclusions of Bernard et al. (1997) that urinary β2-microglobulin levels of 1,000–10,000 μg/g creatinine were indicative of irreversible tubular proteinuria, which may lead to an age-related decline in GFR. Additionally, an attempt was made to avoid using multiple analyses of the same study population.

The individual dose-response functions from each study were implemented to arrive at estimates of the internal dose (urinary cadmium expressed as μg/g creatinine) corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (urinary cadmium dose, UCD_{10}). Estimates were derived from the seven environmental exposure studies listed in Table 2-3. When available, male and female data were treated separately; thus, 11 dose-response relationships were analyzed. For studies that did not report the UCD_{10}, the value was estimated by iteration of the reported dose response relationship for varying values of urinary cadmium, until an excess risk of 10% was achieved:

$$ER = \frac{P(d) - P(0)}{1 - P(0)}$$

Table 2-3. Selected Studies of Dose-Response Relationship for Cadmium-Induced Low Molecular Weight Proteinuria

Reference	Population	Number	Effect biomarker	Response criterion	Dose-response model	UCD_{10} (µg/g creat.)
Buchet et al. 1990	General population (Belgium)	1,699 M 2,080 F	β2M	283 µg/24 hours	Logistic[a]	2.51 M 1.44 F
Suwazono et al. 2006	General population (Sweden)	790 F	pHC	3.6 U/g creat.	Logistic	0.81
Järup et al. 2000	Residents in cadmium polluted area (Sweden)	1,465 M,F	pHC	7.1 mg/g creat. M 5.3 mg/g creat. F	Logistic	0.6
Kobayashi et al. 2006	General population (Japan)	1,114 M 1,664 F	β2M	507 µg/g creat. M 400 µg/g creat. F	Log-logistic	5.0 M 6.6 F
Shimizu et al. 2006	Residents in cadmium polluted and non-polluted areas (Japan)	1,865 M 1,527 F	β2M	507 µg/g creat. M 400 µg/g creat. F	Log-logistic	5.1 M 4.2 F
Jin et al. 2004c	Residents in cadmium polluted or non-polluted area (China)	790 M,F	β2M	800 µg/g creat.	Logistic	9.5 M 15.4 F
Wu et al. 2001	Residents in cadmium polluted area (China)	247 M,F	β2M	800 µg/g creat. M 900 µg/g creat. F	Linear[b]	3.75

[a]Digitized from Figure 2 in Lauwerys et al. 1991
[b]Digitized from Figure 2 in Wu et al. 2001

β2M = β2-microglobulin; creat. = creatinine; F = female; M = male; pHC = human complex-forming glycoprotein (also referred to as α1-microglobulin); UCD_{10} = urinary cadmium level corresponding to a probability of 10% excess risk of low molecular weight proteinuria

where ER is the excess risk, P(d) is the probability of low molecular weight proteinuria associated with a given internal (i.e., urinary cadmium) dose, and P(0) is the background probability (i.e., the probability predicted by the dose-response model when urinary cadmium was zero). For studies that reported the dose-response relationship graphically, but did not report the actual dose-response function, a function was derived by least squares fitting based on data from a digitization of the graphic.

Aggregate UCD_{10} estimates and the estimates stratified by location (i.e., Europe, Japan, China) are presented in Figure 2-2. The lowest UCD_{10} (1.34 μg/g creatinine) was estimated from the European database and the 95% lower confidence limit on this UCD_{10} ($UCDL_{10}$) of 0.5 μg/g creatinine was considered as a potential point of departure for the MRL.

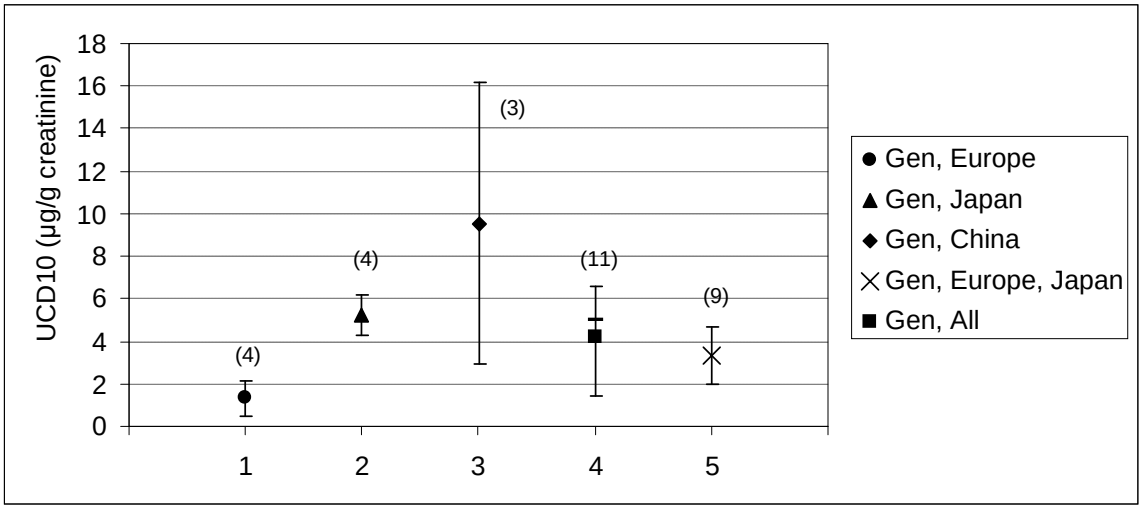
Points of departure selected using the three different approaches are similar: 0.5 μg/g creatinine from the Järup et al. (2000) study (using the European Chemicals Bureau 2007 recalculation), 0.7 μg/g creatinine from the Uno et al. (2005) benchmark dose analysis, and 0.5 μg/g creatinine from the dose-response analysis. The third approach (meta-analysis of environmental exposure studies) was selected for the derivation of the MRL because it uses the whole dose-response curves from several studies rather than data from a single study.

The $UCDL_{10}$ of 0.5 μg/g creatinine was transformed into estimates of chronic cadmium intake (expressed as μg Cd/kg/day) that would result in the $UCDL_{10}$ at age 55 (approximate age of peak cadmium concentration in the renal cortex associated with a constant chronic intake; Figure 2-3). The dose transformations were achieved by simulation using a modification of the Nordberg-Kjellström model (Kjellström and Nordberg 1978). The following modifications (Choudhury et al. 2001; Diamond et al. 2003) were made to the model: (1) the equations describing intercompartmental transfers of cadmium were implemented as differential equations in Advanced Computer Simulation Language (acslXtreme, version 2.4.0.9); (2) growth algorithms for males and females and corresponding organ weights (O'Flaherty 1993) were used to calculate age-specific cadmium concentrations from tissue cadmium masses; (3) the cadmium concentration in renal cortex (RC, μg/g) was calculated as follows:

$$RC = 1.5 \cdot \frac{K}{KW}$$

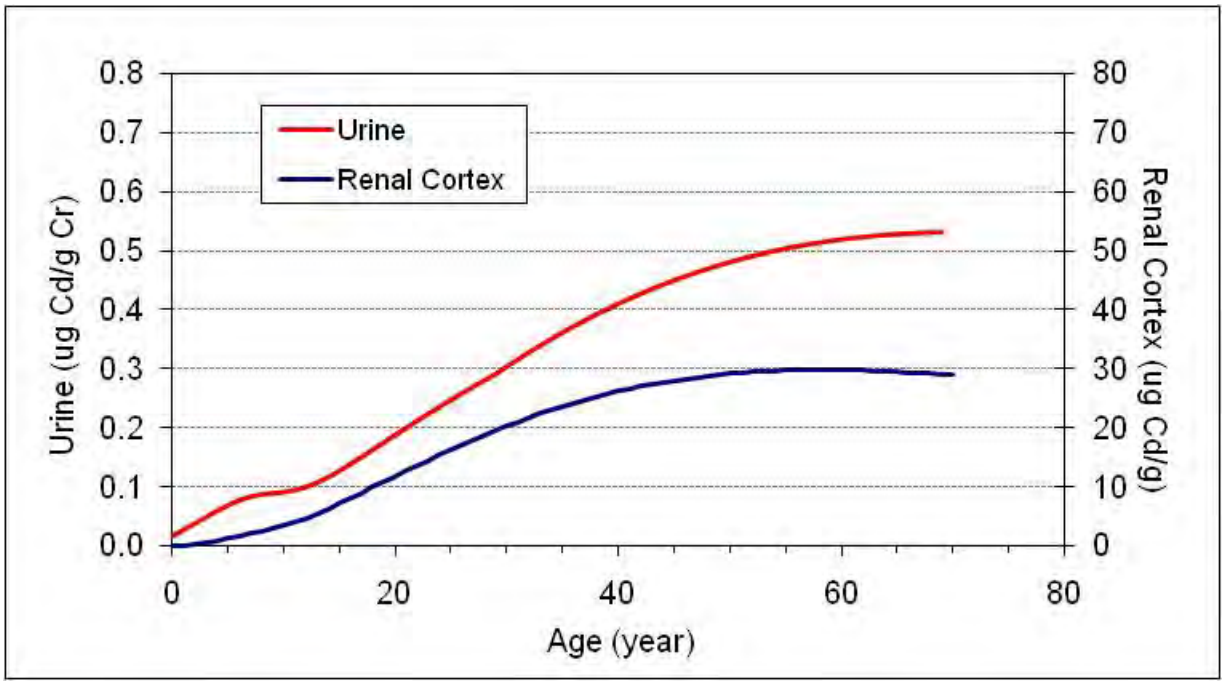
where K is the age-specific renal cadmium burden (μg) and KW is the age-specific kidney wet weight (g) (Friberg et al. 1974).

Figure 2-2. Estimates of the UCD_{10} from Environmental Exposure Dose-Response Studies*



*Estimates of urinary cadmium concentrations (µg/g creatinine) associated with a 10% excess risk of urinary β2-microglobulin (UCD_{10}) using data from European, Japanese, and Chinese studies. For the aggregate of studies (plot #4), the mean (-), median (▪), and 95% confidence intervals (CI) on the median are shown. All other plots show the mean and 95% CI on the mean. Numbers in parenthesis are the number of estimates of the UCD_{10}.

Figure 2-3. Urinary Cadmium (µg/g creatinine) and Renal Cortex Cadmium Concentration (µg/g wet tissue) Predicted by the Cadmium Pharmacokinetic Model*



*Shown is a simulation of peak renal cadmium concentration (at age 55) in females based on a chronic intake of 0.33 µg Cd/kg/day.

(4) the rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was calculated from the relationship between lean body mass (LBM) and Cr_{ur}; and (5) absorption of ingested cadmium was assumed to be 5% in males and 10% in females. The rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was estimated from the relationship between LBM (kg) and Cr_{ur}:

$$LBM = 27.2 \cdot Cr_{ur} + 8.58$$

where the constants 27.2 and 8.58 are the sample size-weighted arithmetic mean of estimates of these variables from eight studies reported in (Forbes and Bruining 1976). Lean body mass was estimated as follows (ICRP 1981):

$$LBM = BW \cdot 0.85, adult\ females$$
$$LBM = BW \cdot 0.88, adult males$$

where the central tendency for adult body weight for males and females were assumed to be 70 and 58 kg for adult European/American males and females, respectively.

Dose units expressed as cadmium intake (μg/kg/day), urinary cadmium excretion (μg/g creatinine), or kidney tissue cadmium (μg/g cortex) were interconverted by iterative pharmacokinetic model simulations of constant intakes for the life-time to age 55 years, the age at which renal cortex cadmium concentrations are predicted to reach their peak when the rate of intake (μg/kg/day) is constant.

The dietary cadmium intakes which would result in urinary cadmium levels of 1.34 and 0.5 μg/g creatinine (UCD_{10} and $UCDL_{10}$) are 0.97 and 0.33 μg/kg/day in females and 2.24 and 0.70 μg/kg/day in males. The dietary concentration associated with the $UCDL_{10}$ in females (0.33 μg/kg/day) was divided by an uncertainty factor of 3 for human variability resulting in a chronic-duration oral MRL of 0.1 μg/kg/day ($1x10^{-4}$ mg Cd/kg/day). The UCD is based on several large-scale environmental exposure studies that likely included sensitive subpopulations; however, there is concern that individuals with diabetes may be especially sensitive to the renal toxicity of cadmium (Åkesson et al. 2005; Buchet et al. 1990) and diabetics were excluded from a number of the human studies, and thus, an uncertainty factor of 3 was used.

The urinary cadmium point of departure used as the basis of the MRL (0.5 μg/g creatinine) is approximately 2-fold higher than the geometric mean urinary cadmium concentrations in the United

States, which is 0.261 µg/g creatinine for adults 20 years and older (CDC 2005). The MRL of 0.1 µg/kg/day is lower than the estimated age-weighted cadmium intake of 0.3 µg/kg/day (estimated from data in Choudhury et al. 2001). Because this intake is derived from the cadmium dietary exposure model which estimates food cadmium concentrations from national survey data and food consumption patterns, it should not be considered a precise value. A better comparison would be between the mean urinary cadmium concentration in adults living in the United States (0.261 µg/g creatinine) and the MRL expressed as a urinary cadmium concentration (0.2 µg/g creatinine).

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of cadmium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

The form of cadmium and the route of exposure can greatly affect the absorption and distribution of cadmium to various target sites, and therefore, the concentration at the target site and the severity of the observed effect. The mechanism of action, however, involves the cadmium cation's effect on the target site, and the cation is the same regardless of the anionic species. For inhaled cadmium compounds, the size of the cadmium particle (i.e., fume or aerosol) can also affect the absorption and distribution. The form of cadmium that is of most interest for health effects from inhalation exposure is cadmium oxide because that is the main form of airborne cadmium. For oral exposures, cadmium chloride is most often tested in animal studies because of its high water solubility and the resulting high concentrations of cadmium delivered to target sites. Studies on cadmium bound to metallothionein are also of interest because cadmium-metallothionein complexes may have different toxic profiles and are found in relatively high levels in organ meats (e.g., liver and kidney). Cadmium oxide and cadmium carbonate, which are relatively insoluble in water (but may dissolve at gastric pH), appear to be similar in absorption and toxicity to soluble cadmium. There are fewer studies available on other forms of cadmium including insoluble forms in water such as cadmium sulfide (a yellow pigment) and cadmium selenium sulfide (a red pigment), and a soluble form, cadmium sulfate, which is less soluble in a closed air system where there is a limited amount of dissolved carbon dioxide. Chapter 4 lists the chemical and physical properties of several cadmium compounds.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive,

developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of cadmium are indicated in Tables 3-1 and 3-6 and Figures 3-1 and 3-2. Because cancer effects could occur at lower exposure levels, Figure 3-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

The information in this section on health effects of inhalation exposure to cadmium in humans is derived from studies of workers exposed to cadmium fume or dusts in industries such as smelting, battery manufacturing, soldering, and pigment production. Adverse effects of human exposure to cadmium were first established among workers in a cadmium battery factory (Friberg 1950). Workers are exposed occupationally to cadmium primarily by inhalation of fumes or dust. Some gastrointestinal tract exposure may also occur when dust is removed from the lungs by mucociliary clearance and subsequently swallowed, or by ingestion of dust on hands, cigarettes, or food (Adamsson et al. 1979). In experiments with animals, some ingestion may also occur from inhalation exposures by mucociliary clearance or from animal grooming. The primary form of cadmium in occupational exposures is cadmium oxide. Experimental studies in laboratory animals have used cadmium oxide, cadmium chloride, and occasionally other forms of cadmium such as cadmium sulfide and cadmium sulfate. In general, the different forms of cadmium have similar toxicological effects by the inhalation route, although quantitative differences may exist from different absorption and distribution characteristics, particularly for the less soluble cadmium pigments such as cadmium sulfide and cadmium selenium sulfide (Buckley and Bassett 1987b; Klimisch 1993; Oldiges and Glaser 1986; Oldiges et al. 1989; Rusch et al. 1986).

Smokers inhale cadmium, but studies of cadmium exposure in the general population are considered in Section 3.2.2 because the primary route of exposure for the general population is through the diet. Also, the many other toxic compounds in cigarette smoke make it difficult to attribute specific adverse effects of smoking to the inhalation of cadmium.

3.2.1.1 Death

Numerous studies have shown that acute inhalation exposure to cadmium can cause death in humans and animals. In humans, several fatal inhalation exposures have occurred in occupational accidents. During the acute exposure, the general symptoms are relatively mild but, within a few days following exposure, severe pulmonary edema and chemical pneumonitis develop, leading to death due to respiratory failure (Beton et al. 1966; Lucas et al. 1980; Patwardhan and Finckh 1976; Seidal et al. 1993). The cadmium concentration in air was not measured in these cases of accidental death in humans. However, the lung concentrations of cadmium in the men who died from these accidental acute exposures were measured.

In micrograms of cadmium per gram wet weight (w/w) of lung tissue (μg/g), Patwardhan and Finckh (1976) reported 1.5 μg/g, Beton et al. (1966) reported 2.5 μg/g, Barrett et al. (1947) reported 3.5 μg/g, and Lucas et al. (1980) reported 4.7 μg/g. Based upon estimates of the percentage of inhaled cadmium fume that would be retained in the lungs, Barrett et al. (1947) calculated an exposure of 2,500 minutes x mg/m^3 in air would be fatal to humans. Beton et al. (1966) used a similar technique to estimate that an exposure to cadmium oxide in air of 8.63 mg/m^3 for 5 hours led to the fatal deaths of the five workers with cadmium lung burdens of 2.5 μg/g. The lower lung concentrations reported by Patwardhan and Finckh (1976) prompted Elinder (1986b) to estimate that an exposure of 1–5 mg/m^3 for 8 hours could be immediately dangerous. These estimates of air concentrations, however, are based on a number of uncertain assumptions concerning the duration of exposure and the retention of cadmium in the human lung being similar to that found in animal studies (Barrett et al. 1947; Elinder 1986b). No studies on deaths in humans from intermediate inhalation exposures were found. In a study on chronic exposures, Friberg (1950) attributes the deaths of 2 workers to exposure to cadmium dust in the air averaging 6.8 mg Cd/m^3 (range 3–15 mg/m^3). One worker was 57 years old at death (after 14 years of exposure to the dust) and the other was 60 years old at death (after 25 years of exposure to the dust). A detailed post-mortem evaluation for the 60-year-old worker showed the presence of emphysema and the occurrence of hyaline casts in renal tubules, as well as slight nephrotic changes. Pneumonia was the direct cause of death as an acute complication of chronic bronchitis and pulmonary emphysema. The exposure estimate of 6.8 mg Cd/m^3 is from only six samples taken in 1946. The conditions in earlier years were thought to be similar, but this exposure value is, at best, a very rough approximation of the actual exposures spanning 34 years.

Acute inhalation of cadmium oxide fumes has also led to death in rats, mice, rabbits, guinea pigs, dogs, and monkeys, with the mortality rate apparently being directly proportional to the product of the duration of exposure and the concentration of inhaled cadmium (Barrett et al. 1947). The most reliable LC_{50} (lethal concentration, 50% kill) (at 7 days) established by this study was 500 minute-mg cadmium oxide/m^3 for rats, equivalent to a 15-minute exposure to 30 mg Cd/m^3 (Barrett et al. 1947). Rusch et al. (1986) demonstrated high mortality rates in the Sprague-Dawley rat from a 2-hour exposure to cadmium fumes at 112 mg Cd/m^3 (25 of 32 died within 1 week). A 2-hour exposure to a different form of cadmium, cadmium carbonate, at 132 mg Cd/m^3 resulted in considerably lower mortality (3 of 22 died by day 30). No deaths resulted from a 2-hour exposure to cadmium sulfide at 99 mg Cd/m^3 or cadmium selenium sulfide (cadmium red pigment) at 97 mg Cd/m^3. Grose et al. (1987) reported 2 out of 36 rats died from a 2-hour, nose-only inhalation exposure to only 0.45 mg Cd/m^3 of cadmium oxide dusts, but the statistical significance of this low rate of mortality was not reported. A 3-day, 1-hour/day exposure to cadmium chloride aerosol at 61 mg Cd/m^3 resulted in the death of 17 of 18 rats exposed (Snider et al.

1973). In another study, no deaths were observed in rats from a cadmium yellow (cadmium sulfide) pigment exposure 6 hours/day for 10 days at 6.29 mg Cd/m^3 (Klimisch 1993). Thus, it appears that in acute exposures, the relatively more soluble cadmium chloride, cadmium oxide fume, and cadmium carbonate compounds are more toxic than the relatively less soluble cadmium sulfide compounds (Klimisch 1993; Rusch et al. 1986). Rusch et al. (1986) attribute this difference to higher lung absorption and retention times for the more soluble compounds, and greater mucociliary clearance for the less-soluble pigments. Glaser et al. (1986), however, demonstrated that toxicity does not strictly correlate with solubility, and that solubility of cadmium oxide in biological fluids may be greater than its solubility in water. In hamsters, Henderson et al. (1979) reported that a 30-minute exposure to 10.1 mg Cd/m^3 from cadmium chloride resulted in the death of 3 of 30 animals by day 6 postexposure. In rabbits, Friberg (1950) reported an LC_{50} (by day 14) from a 4-hour exposure to cadmium metal dusts at 28.4 mg Cd/m^3. Barrett et al. (1947) also reported LC_{50} values for cadmium oxide fume of 940 mg Cd/m^3 for a 14-minute exposure in the monkey, 46.7 mg/m^3 for a 15-minute exposure in the mouse, 204 mg Cd/m^3 for a 15-minute exposure in the guinea pig, and 230 mg Cd/m^3 for a 15-minute exposure in the dog. However, the authors report that these LC_{50} values are only approximations because of insufficiencies in the data or the small numbers of animals used.

At longer durations of exposure, lower concentrations cause lethality in rats. Cadmium oxide dust resulted in the deaths of 100% of the females at 1 mg Cd/m^3 for 5 hours/day, 5 days/week for 20 weeks, (Baranski and Sitarek 1987), and of 5 of 12 female rats at only 0.105 mg Cd/m^3 22 hours/day, 7 days/week for 63 days (Oldiges and Glaser 1986). Continuous inhalation exposure to cadmium oxide dust at 0.105 mg Cd/m^3 (i.e., 24 hours/day) for 63 days resulted in 5 of 12 deaths in female rats (Prigge 1978a). Five of 54 males died from a cadmium chloride exposure to 1.06 mg Cd/m^3 for 62 days, 5 days/week, 6 hours/day (Kutzman et al. 1986). Kutzman et al. (1986) determined that the concentration times hours of exposure to produce 50% mortality in rats was 390 mg-hour/m^3 (males) and 489 mg-hour/m^3 (females). Takenaka et al. (1983) reported that cadmium chloride at 0.0508 mg Cd/m^3 23 hours/day, 7 days/week for 18 months resulted in the death of 5 of 40 male rats.

Oldiges et al. (1989) evaluated the long-term effects in rats of inhaling cadmium as either cadmium chloride, cadmium sulfate, cadmium sulfide, or cadmium oxide. Rats were exposed to aerosols in nearly continuous exposures of 22 hours/day, 7 days/week for 18 months. An observation period of 12 months followed the exposure period. Oldiges et al. (1989) recorded mortality as exceeding 25% of the test animals during the exposure period or 75% of the test animals during the observation period. If either 25 or 75% mortality occurred, the exposure period or the observation period, respectively, was

terminated. The results showed that cadmium chloride at 0.030 mg Cd/m^3 was lethal to >75% of the male and female rats by 12 months of exposure; cadmium oxide dusts at 0.090 mg Cd/m^3 were lethal for >25% of the males by 7 months and 25% of the females by 11 months of exposure; cadmium oxide fume at the highest dose of 0.03 mg Cd/m^3 did not result in >25% mortality during exposure or 75% during the postexposure period; cadmium sulfate at 0.090 mg Cd/m^3 was lethal for >25% of the males during the exposure and for >75% of the females by 14 months following exposure; and cadmium sulfide at 0.090 mg Cd/m^3 was not lethal during the exposure period but was lethal to >75% of the males and females by 12 months postexposure. In these chronic studies, cadmium's lethal effects differed among the chemical forms in the following order from most to least toxic: cadmium chloride>cadmium sulfate ≈ cadmium oxide dust>cadmium sulfide, but lethality still occurred from all forms of cadmium. Oldiges and Glaser (1986) report that in their chronic studies and at the doses tested, cadmium toxicity appeared to be more related to the long-term lung retention of the bioavailable amounts of cadmium than to a simple function of solubility in water. Representative LOAEL and LC_{50} values for lethality in each species and duration category are recorded in Table 3-1 and are plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. In humans, inhalation exposure to high levels of cadmium oxide fumes or dust is intensely irritating to respiratory tissue, but symptoms can be delayed. During and immediately after (up to 2 hours) an acute exposure for 5 hours of 8.63 mg/m^3, Beton et al. (1966) reported that there were few symptoms of toxicity limited to coughing and slight irritation of the throat and mucosa. From 4 to 10 hours postexposure, influenza-like symptoms began to appear, including cough, tight chest, pain in chest on coughing, dyspnea, malaise, ache, chilling, sweating, shivering, and aching pain in back and limbs. From 8 hours to 7 days postexposure, more advanced stages of pulmonary response included severe dyspnea and wheezing, chest pain and precordial constriction, persistent cough, weakness and malaise, anorexia, nausea, diarrhea, nocturia, abdominal pain, hemoptysis, and prostration. Acute, high-level exposures can be fatal (see Section 3.2.1.1), and those who survive may have impaired lung function for years after a single acute exposure. A 34-year-old worker exposed to cadmium fume from soldering for 1 hour (dose not determined) had persistent impaired lung function when examined 4 years following the exposure (Barnhart and Rosenstock 1984). Initial symptoms were dyspnea, cough, myalgia, and fever. An initial chest X-ray revealed infiltrates. Townshend (1982) reports the case of a

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Human	5 hr (occup)				8.63 M (5 male workers died after a 5 hour exposure)	Beton et al. 1966 CdO fume	
2	Rat (NS)	10-15 min				30 (LC50 at 7 days)	Barrett et al. 1947 CdO fume	
3	Rat (Fischer- 344)	6.2 hr/d 5 d/wk 2 wk				8.8 (100% mortality by day 6)	NTP 1995 CdO	
4	Rat (Sprague-Dawley)	2 hr				112 (25/32 died within 1 week)	Rusch et al. 1986 CdO fume	
5	Rat (Sprague-Dawley)	3 d 1 hr/d				61 M (17/18 died within 3 days)	Snider et al. 1973 CdCl2	
6	Mouse (B6C3F1)	6.2 hr/d 5 d/wk 2 wk				8.8 (100% mortality by day 7)	NTP 1995 CdO	
7	Rabbit (NS)	4 hr				28.4 (LC50 at 14 days)	Friberg 1950 Cd metal dust	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
Systemic								
8	Rat (Long- Evans)	1 hr	Resp			5 M (pulmonary edema, enzyme changes associated with type 2 cell hyperplasia)	Boudreau et al. 1989 CdCl2	
9	Rat (Wistar)	3 hr	Resp		0.4 M (mild hypercellularity at the bronchoalveolar junction and in adjacent alveoli)	4.6 M (persistent focal interstitial thickening, increased collagen, general hypercellularity)	Buckley and Bassett 1987b CdO dust	
			Bd Wt	0.4 M	4.6 M (15% decreased body weight)			
10	Rat (Sprague-Dawley)	1 hr	Resp			6.5 M (severe pneumonitis)	Bus et al. 1978 CdCl2	
			Bd Wt		6.5 M (10.8% decreased body weight)			
11	Rat (Sprague-Dawley)	2 hr	Resp	0.45 M		4.5 M (moderate to severe pneumonitis, hemorrhage, edema)	Grose et al. 1987 CdCl2	
			Bd Wt			4.5 M (20% decreased body weight)		

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
12	Rat (Sprague-Dawley)	2 hr	Resp		0.45 M (significant increased absolute and relative lung weight)	4.5 M (severe pneumonitis, hyperplasia of type 2 cells and fibroblasts)	Grose et al. 1987 CdO dust	
			Bd Wt	0.45 M				
13	Rat (Lewis)	1-6 wk 5 d/wk 3 hr/d	Resp			1.6 M (interstitial pneumonitis)	Hart 1986 CdO dust	
14	Rat (Wistar)	10 d 6 hr/d	Bd Wt	0.17 M			Klimisch 1993 CdCl2	No histopathological examination.
15	Rat (Wistar)	10 d 6 hr/d	Bd Wt	6.29 M			Klimisch 1993 CdS	No histopathological examination.
16	Rat (Fischer- 344)	6.2 hr/d 5 d/wk 2 wk	Resp		0.88 F (degeneration of nasal olfactory epithelium)	8.8 (marked necrosis of alveolar ducts)	NTP 1995 CdO	
					0.088[b] (alveolar histiocytic infiltrate and focal inflammation in alveolar septa)			
			Hepatic	2.6				
			Renal	2.6				

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
17	Rat (Sprague-Dawley)	2 hr	Resp			6 M (alveolar type 1 cell damage and necrosis)	Palmer et al. 1986 CdCl2	
			Endocr	6 M				
			Bd Wt	6 M				
18	Rat (Sprague-Dawley)	2 hr	Gastro		132 (erosions of the stomach)		Rusch et al. 1986 CdCO3	
19	Rat (Sprague-Dawley)	5, 10, or 15 d 1 hr/d	Resp			6.1 M (emphysema)	Snider et al. 1973 CdCl2	
20	Rat (Sprague-Dawley)	3 d 1 hr/d	Resp			61 M (pulmonary hemorrhage)	Snider et al. 1973 CdCl2	
21	Mouse (B6C3F1)	6.2 hr/d 5 d/wk 2 wk	Resp		0.88 (fibrosis and inflammation around the alveolar ducts, necrosis of the alveolar duct epithelium)		NTP 1995 CdO	
					0.088 (histiocytic infiltrates)			
			Hepatic	2.6				
			Renal	2.6				

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
22	Hamster (Golden Syrian)	30 min	Resp		1.1 (moderate increase in PMN, 2-fold increase in acid phosphatase)	10.1 (severe pneumonitis)	Henderson et al. 1979 CdCl2	
23	Rabbit (New Zealand)	2 hr	Resp		4.5 M (mild, multifocal interstitial pneumonitis)		Grose et al. 1987 CdCl2	
24	Rabbit (New Zealand)	2 hr	Resp		0.45 M (increase in alveolar macrophages)	4.5 M (multifocal interstitial pneumonitis)	Grose et al. 1987 CdO dust	
			Bd Wt		0.45 M (unspecified decrease in body weight)			
Immuno/ Lymphoret								
25	Mouse (Swiss)	2 hr		0.11 F	0.19 F (decreased humoral immune response)		Graham et al. 1978 CdCl2	
26	Mouse (C57Bl/6)	60 min			0.88 F (reduction in spleen lymphocyte viability [35%], numbers, and humoral response (75%)]		Krzystyniak et al. 1987 CdCl2	
INTERMEDIATE EXPOSURE								
Death								
27	Rat (Wistar)	20 wk 5 d/wk 5 hr/d				1 F (13/13 died by week 20)	Baranski and Sitarek 1987 CdO dusts	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
28	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d				2.13 M (100% mortality by day 45)	Kutzman et al. 1986 CdCl2	
29	Rat (Wistar)	6 mo 40 hr/wk				0.09 (> 75% mortality by 11-12 months postexposure)	Oldiges et al. 1989 CdCl2	
30	Rat (Wistar)	6 mo 40 hr/wk				0.27 (> 75% mortality by 21-23 months postexposure)	Oldiges et al. 1989 CdS	
31	Rat (Wistar)	63d 24 hr/d				0.105 F (5/12 died)	Prigge 1978a CdO dust	
Systemic								
32	Rat (Wistar)	20 wk 5 d/wk 5 hr/d	Bd Wt	0.16 F		1 F (30-50% decreased body weight gain)	Baranski and Sitarek 1987 CdO dusts	
33	Rat (Wistar)	30 d 7 d/wk 22 hr/d	Resp		0.105 M (increased total bronchoalvelolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 CdCl2	No histopathology examination.
			Hemato		0.105 M (45% increase in WBC)			

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
34	Rat (Wistar)	30 d 7 d/wk 22 hr/d	Resp		0.098 M (increased total bronchoalvelolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 CdO dust	No histopathology examination.
			Hemato		0.098 M (45% increase in WBC)			
35	Rat (Wistar)	30 d 7 d/wk 22 hr/d	Resp		1.034 M (increased total bronchoalvelolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 CdS	No histopathological examination.
			Hemato	1.034 M				
			Bd Wt	1.034 M				
36	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d	Resp			1.06 M (marked fibrosis with significant increase in collagen)	Kutzman et al. 1986 CdCl2	
			Bd Wt	0.33	1.06 (14% decreased body weight)	2.13 (42-51% decreased body weight)		

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
37	Rat (Fischer- 344)	6.33 hr/d 5 d/wk 13 wk	Resp		0.022 F	(epithelial degeneration in the larynx)	0.88	(marked inflammation and moderate fibrosis in interstitium around alveolar ducts and terminal bronchioles)	NTP 1995 CdO	
					0.22	(Inflammation of nasal respiratory epithelium)				
			Cardio	0.88						
			Gastro	0.88						
			Hemato	0.88						
			Hepatic	0.88						
			Renal	0.88						
			Bd Wt	0.88						
38	Rat (Fischer 344)	4 wks 5 d/wk 6 hr/d	Resp	0.1 M					Oberdorster et al. 1994 CdCl2	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
39	Rat (Wistar)	63 or 90 d 24 hr/d	Resp		0.025 F (proliferations, histiocytic cell granulomas)		Prigge 1978a CdO dust	
			Hemato		0.052 F (increased hemoglobin and hematocrit)			
			Hepatic	0.105 F				
			Renal	0.105 F				
			Bd Wt		0.105 F (11% decrease in body weight)			
			Metab		0.105 F (decreased blood pH and pO2, increased pCO2)			
40	Rat (Wistar)	21 d Gd 1-21 24 hr/d	Resp		0.204 F (77% increased lung relative weight)		Prigge 1978b CdCl2	
			Hemato		0.204 F (8% increased hemoglobin, 5% increased hematocrit)			
			Hepatic	0.581 F				
			Renal	0.581 F				
			Bd Wt	0.394 F				

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
41	Rat (Wistar)	21 d Gd 1-21 24 hr/d	Resp		0.204 F (70% increased lung relative weight)		Prigge 1978b CdCl2	
			Hemato		0.581 F (increased hemoglobin [12%], hematocrit [12%], total biliurin [2-fold])			
			Hepatic	0.581 F				
			Renal	0.581 F				
			Bd Wt		0.394 F (12% decreased maternal weight gain)			
42	Mouse (B6C3F1)	6.33 hr/d 5 d/wk 13 wk	Resp		0.088 M (Degeneration of nasal olfactory epithelium)		NTP 1995 CdO	
					0.022 (alveolar histiocytic infiltrates and squamous metaplasia of the larynx)			
			Cardio	0.88				
			Gastro	0.88				
			Hepatic	0.88				
			Renal	0.88				
			Bd Wt	0.88				

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
43	Mouse (BALB/c)	4 wks 5 d/wk 6 hr/d	Resp		0.1 M (increased neutrophils, LDH and beta-glucuronidase; pulmonary inflammation)		Oberdorster et al. 1994 CdCl2	
44	Rabbit (NS)	9 mo 21 d/mo 3 hr/d	Resp			4 (chronic pneumonia, emphysema)	Friberg 1950 Cd metal dust	
			Hemato		4 (eosinophilia, lower hemoglobin)			
			Renal			4 (proteinuria)		
45	Rabbit (NS)	7 mo 23 d/mo 3 hr/d	Resp			5.6 (emphysema)	Friberg 1950 Cd metal dust	
			Renal			5.6 (proteinuria in 6/10 surviving to the end of exposure)		
46	Rabbit (NS)	4-6 wk 5 d/wk 6 hr/d	Resp			0.4 M (lung interstitial inflammation, type 2 cell hyperplasia)	Johansson et al. 1984 CdCl2	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
Reproductive								
47	Rat (Wistar)	5 hr/d 5 d/wk 5 mo premating, mating, Gd 1-20		0.16 F			Baranski 1984 CdO	
48	Rat (Wistar)	20 wk 5 d/wk 5 hr/d			1 F (increased duration of estrous cycle)		Baranski and Sitarek 1987 CdO dusts	
49	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d		1.06 M			Kutzman et al. 1986 CdCl2	
50	Rat (Fischer- 344)	6.33 hr/d 5 d/wk 13 wk		0.22 M 0.22 F	0.88 M (decreased spermatid counts 0.88 F (increased estrous cycle length)		NTP 1995 CdO	
Developmental								
51	Rat (Wistar)	5 hr/d 5 d/wk 5 mo premating, mating, Gd 1-20			0.02 F (altered performance on neurobehavioral tests)		Baranski 1984 CdO	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
52	Rat (Wistar)	4-5 mo 5 d/wk 5 hr/d			0.02 (altered performance on neurobehavioral tests)	0.16 (decreased pup viability)	Baranski 1985 CdO dusts	
53	Rat (Sprague-Dawley)	6.27 hr/d 7 d/wk Gd 4-19		0.4 F	1.7 F (decreased fetal body weight and reduced ossification)		NTP 1995 CdO	
54	Rat (Wistar)	21 d Gd 1-21 24 hr/d			0.581 (9% decreased fetal body weight, 12% increase in fetal alkaline phosphatase)		Prigge 1978b CdCl2	
55	Mouse (Swiss)	6.27 hr/d 7 d/wk Gd 4-17		0.04 F	0.4 F (decreased fetal body weight)		NTP 1995 CdO	
Cancer								
56	Rat (Wistar)	6 mo 40 hr/wk				0.09 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdCl2	
CHRONIC EXPOSURE								
Death								
57	Human	1-34 yr 5 d/wk 8 hr/d (occup)				6.8 M (2 fatalities from 14 years or 25 years of exposure to Cd dust)	Friberg 1950 Cd dust	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
58	Rat (Wistar)	413-455 d 7 d/wk 22 hr/d				0.095 M (6/20 died)	Oldiges and Glaser 1986 CdSO4	
59	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 M (>75% mortality by 12 months postexposure)	Oldiges et al. 1989 CdCl2	
60	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 (more than 25% died after 7 months [M] and 11 months [F] of exposure)	Oldiges et al. 1989 CdO dust	
61	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 (>75% mortality after 12 months postexposure)	Oldiges et al. 1989 CdS	
62	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 M (>25% mortality by 14 months of exposure) 0.09 F (>75% by 11 months postexposure)	Oldiges et al. 1989 CdSO4	
Systemic								
63	Human		Renal	0.0001[c] F			Buchet et al. 1990; Jarup et al. 2000; Suwazono et al. 2006 form not specified	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
64	Human	4-24 yr 5 d/wk 8 hr/d (occup)	Resp	0.025				Edling et al. 1986 CdO fume	
65	Human	30 yr 5 d/wk 8 hr/d (occup)	Renal	0.033		0.067	(pronounced proteinuria)	Elinder et al. 1985b CdO fume	
66	Human	30 yr 5 d/wk 8 hr/d (occup)	Renal	0.0153 M		0.0379 M	(100% incidence of proteinuria in the cohort exposed to this level for 21 years)	Falck et al. 1983 CdO fume	
67	Human	30 yr 5 d/wk 8 hr/d (occup)	Renal	0.017		0.023	(9.2% incidence of proteinuria)	Jarup et al. 1988 CdO dust	
68	Human	30 yr 5 d/wk 8 hr/d (occup)	Renal	0.0367 M				Mason et al. 1988 form not specified	
69	Human	30 yr 5 d/wk 8 hr/d (occup)	Renal	0.027				Thun et al. 1989 CdO dust or fume	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
70	Rat (Wistar)	18 mo 7 d/wk 23 hr/d	Resp			0.0134 M (adenomatous hyperplasia in the bronchoalveolar area)	Takenaka et al. 1983 CdCl2	
			Bd Wt	0.0508 M				
Cancer								
71	Human	6 mo - 43 yr 7 d/wk 8 hr/d (occup)				0.1 M (CEL: 50-111 lung cancer deaths per 1000 workers; 45 year exposure)	Stayner et al. 1992 CdO dust or fumes	
72	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdCl2	
73	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdO dust	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
74	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03	(CEL: lung bronchioalveolar adenomas, adenocarcinomas)	Oldiges et al. 1989 CdO fume	
75	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09	(CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdS	
76	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09	(CEL: lung bronchio-alveolar adenomas, adenocarcinomas, squamous cell carcinomas)	Oldiges et al. 1989 CdSO4	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m^3)	LOAEL			Reference Chemical Form	Comments
					Less Serious (mg/m^3)	Serious (mg/m^3)			
77	Rat (Wistar)	18 mo 7 d/wk 23 hr/d				0.0134 M	(CEL: lung epidermoid carcinomas, adenocarcinomas, and mucoepidermoid carcinomas)	Takenaka et al. 1983 CdCl2	

a The number corresponds to entries in Figure 3-1.

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.00003 mg Cd/m3 (0.03 ug Cd/m3); concentration was adjusted for intermittent exposure (6.2 hours/day, 5 days/week) and divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability).

c The chronic-duration inhalation MRL of 0.00001 mg Cd/m3 (0.01 ug Cd/m3) was calculated from the 95% lower confidence limit of the urinary cadmium level associated with a 10% increased risk of low molecular weight proteinuria (0.5 ug/g creatinine) estimated from a meta-analysis of select environmental exposure studies. An air concentration (together with an assumed dietary intake of 0.3 ug Cd/kg/day) which would result in this urinary cadmium concentration was estimated using the ICRP human respiratory tract model and a modification of the Nordberg-Kjellström pharmacokinetic model (see Appendix A for details on the meta-analysis and extrapolation to air concentration). This air concentration of 0.1 ug Cd/m3 was divided by an uncertainty factor of 3 for human variability and a modifying factor of 3.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Metab = metabolic; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; PMN = polymorphonuclear leukocyte; Resp = respiratory; WBC = white blood cells; wk = week(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to Cadmium - Inhalation

Acute (≤14 days)

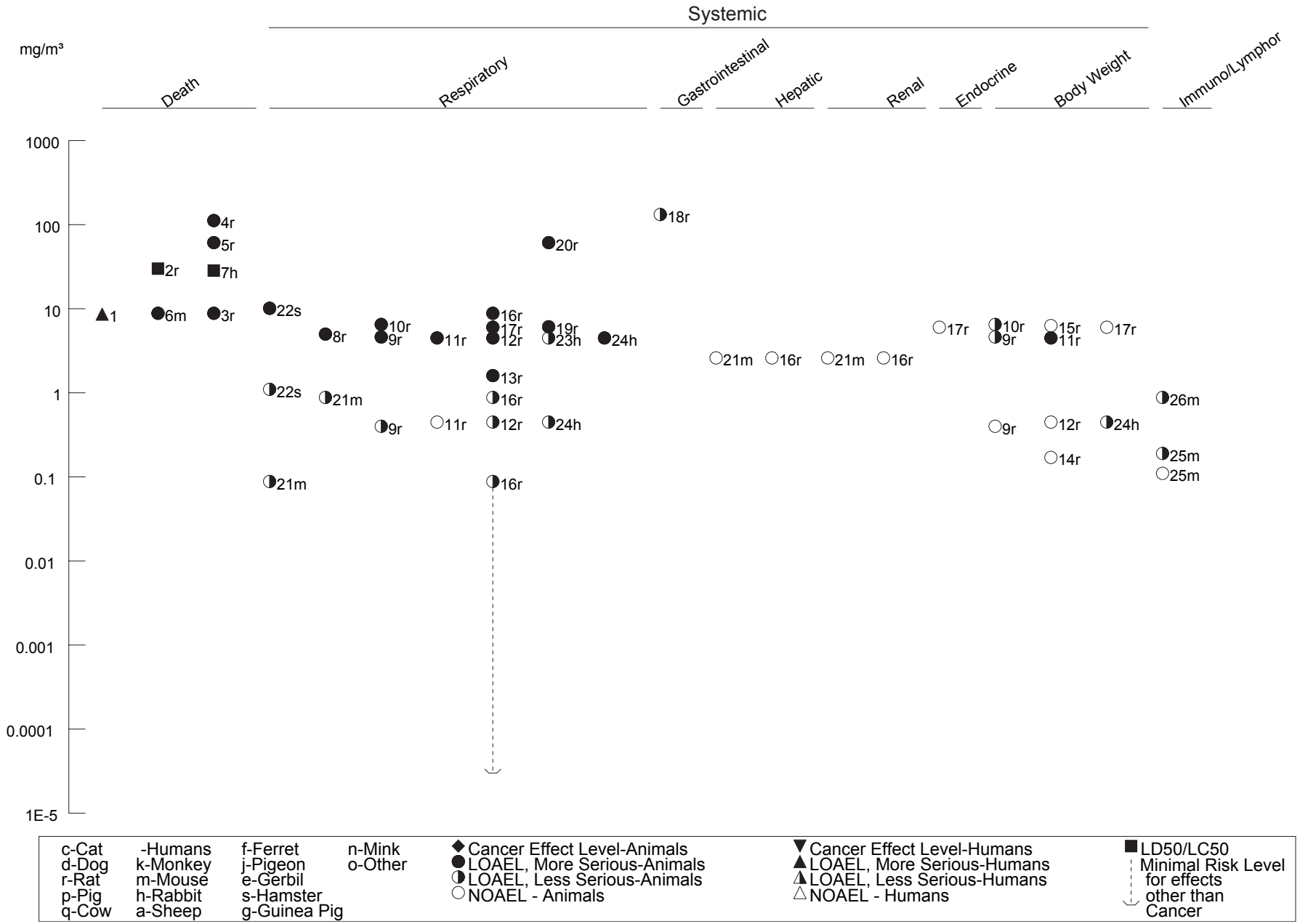


Figure 3-1 Levels of Significant Exposure to Cadmium - Inhalation *(Continued)*

Intermediate (15-364 days)

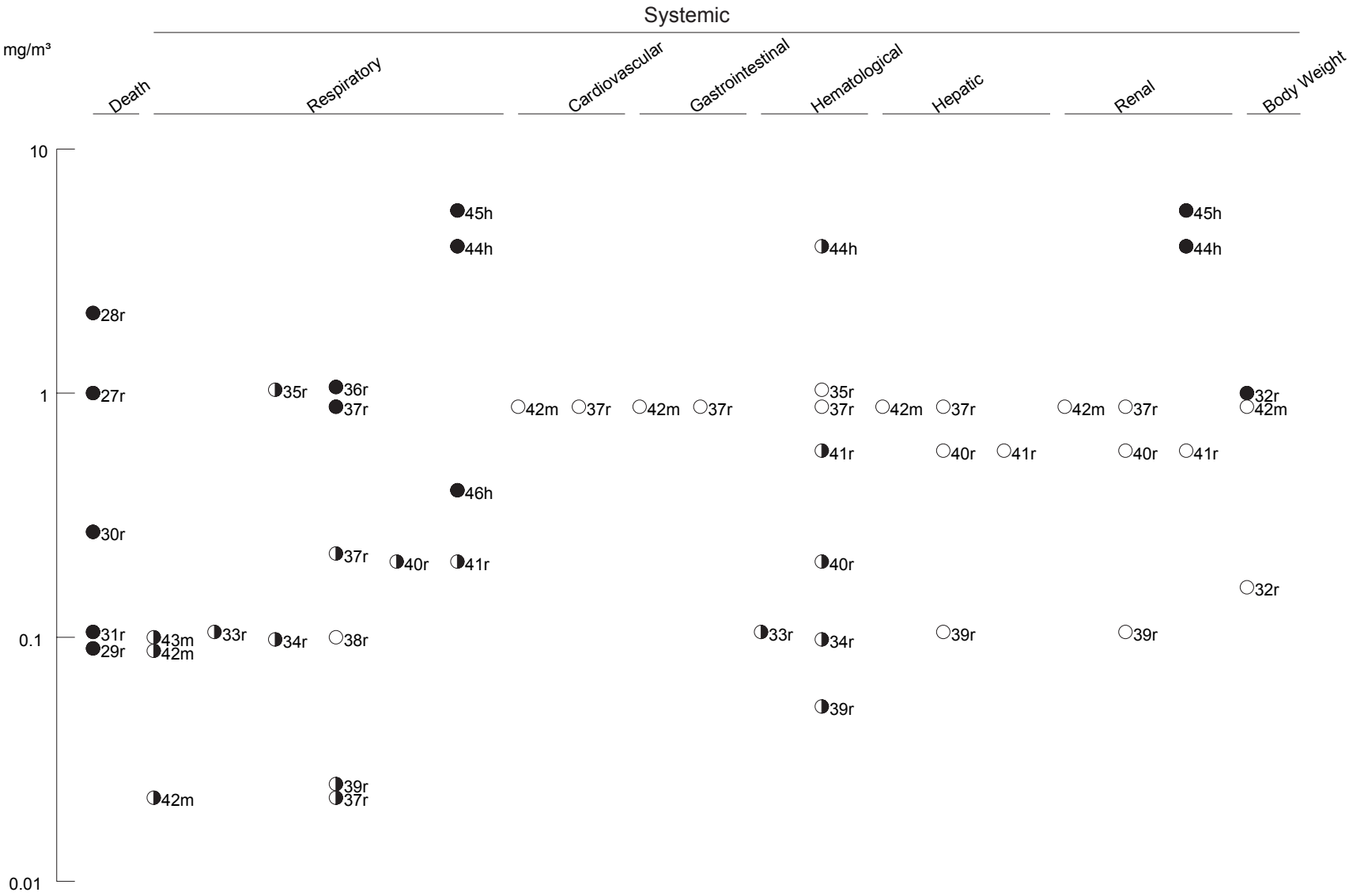
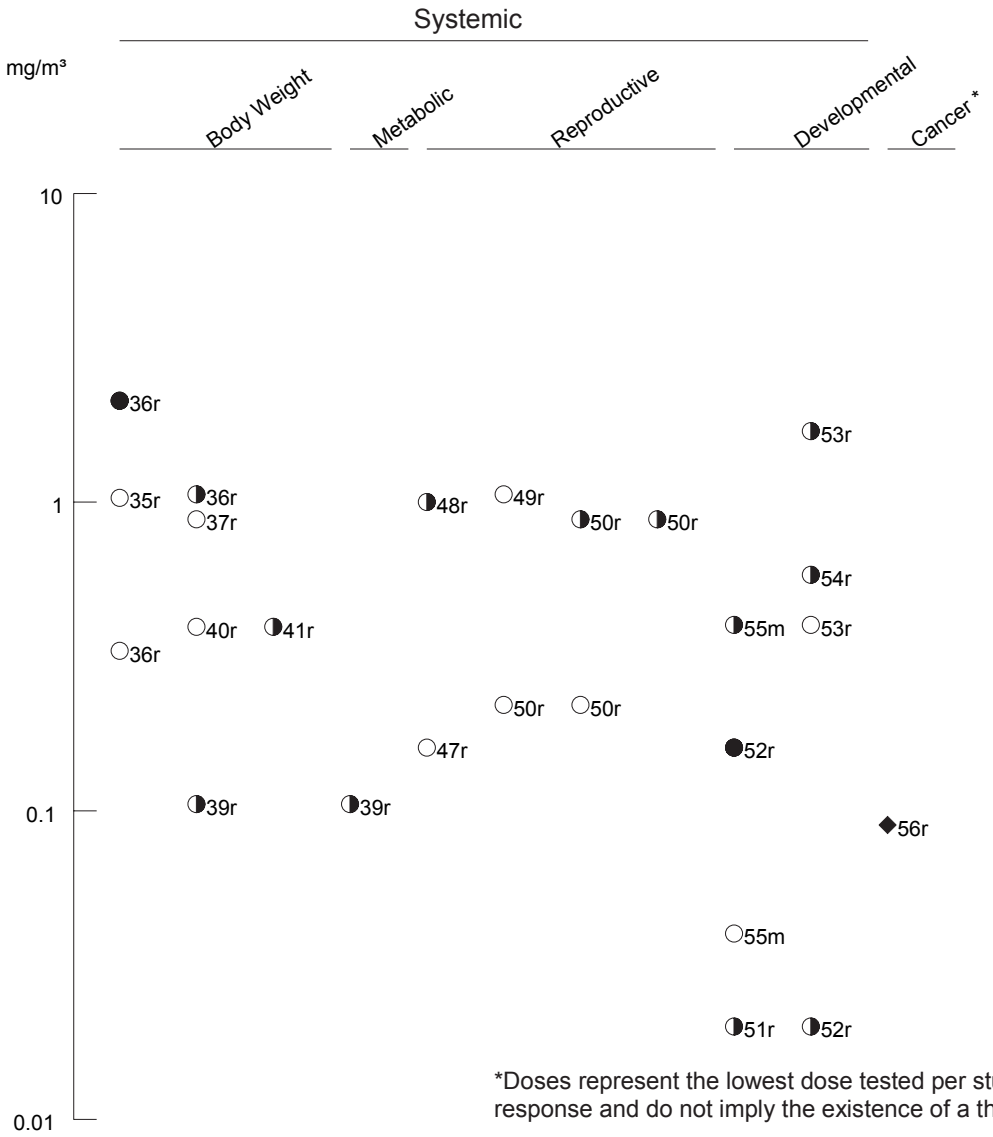


Figure 3-1 Levels of Significant Exposure to Cadmium - Inhalation *(Continued)*

Intermediate (15-364 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

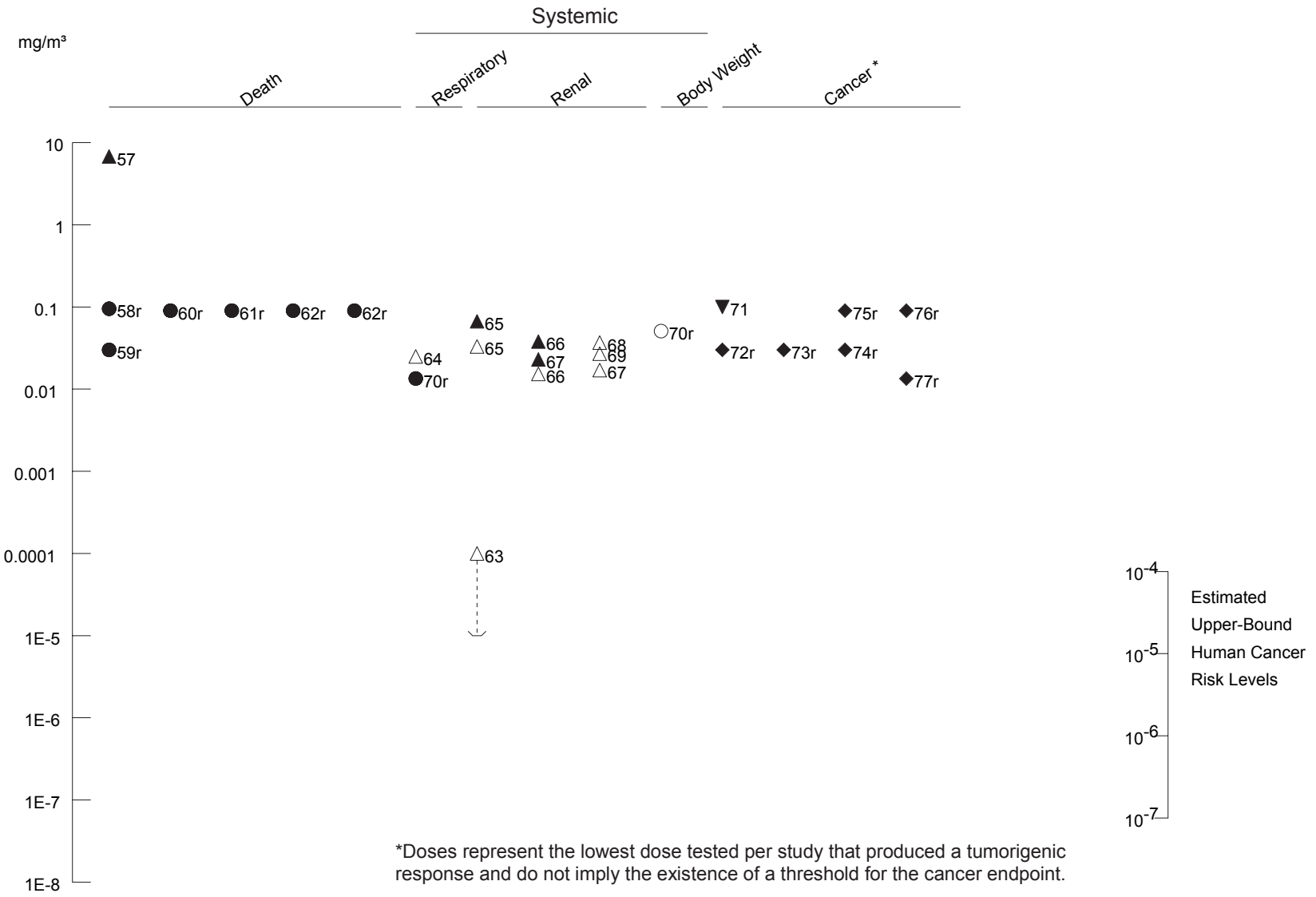
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◮ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-1 Levels of Significant Exposure to Cadmium - Inhalation *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	-Humans	f-Ferret	n-Mink
d-Dog	k-Monkey	j-Pigeon	o-Other
r-Rat	m-Mouse	e-Gerbil	
p-Pig	h-Rabbit	s-Hamster	
q-Cow	a-Sheep	g-Guinea Pig	

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

male welder who developed acute cadmium pneumonitis from a single exposure (dose not determined). Nine years after the exposure, this worker continued to show signs of progressive pulmonary fibrosis and had no improvement in respiratory function. Precise estimates of cadmium concentrations leading to acute respiratory effects in humans are not currently available.

The initial symptoms of respiratory distress observed in the higher acute exposures do not occur following lower-level, longer-term inhalation exposures (Friberg 1950). Longer-term occupational exposure to levels of cadmium below those causing lung inflammation, however, have been reported to cause emphysema and dyspnea in humans (Bonnell 1955; Friberg 1950; Lane and Campbell 1954; Smith et al. 1960). Kjellström et al. (1979) reported a significant increase in deaths due to respiratory diseases in cadmium-exposed battery factory workers exposed for >5 years.

A significant, dose-dependent excess in the ratio of observed to expected deaths from bronchitis (i.e., standardized mortality ratio [SMR]=434) but not emphysema was found among 6,995 men occupationally exposed to cadmium for an average of 11 years (Armstrong and Kazantzis 1983). The dose level was not determined.

The earlier occupational studies did not control for the health effects of cigarette smoking. There is some evidence that cadmium may accelerate the development of emphysema in smokers. Leduc et al. (1993) report a case history of a 59-year-old male worker who smoked a pack of cigarettes per day since age 16, but had no prior history of respiratory disease in 1975 until developing emphysema in 1979 after inhaling various concentrations of cadmium (range of 0.0164–1.192 mg/m^3, mean of 0.446 mg/m^3, about nine times the threshold value of 0.050 mg/m^3) for 4 years as a furnace operator. Very high levels of cadmium in air samples at the workplace and in the patient's blood, urine, and lung tissue confirmed massive exposures. Lung-function tests declined rapidly, with a faster than usual onset of emphysema compared to other smokers. The mean concentration of cadmium in a removed section of lung was 580 μg/g dry tissue, compared to 14 μg/g in three unexposed controls matched for age, sex, and smoking habit who had also undergone resection of a bronchial carcinoma. The authors state that this case supports the hypothesis for an etiological role of cadmium fume inhalation in the development of emphysema.

More recent studies that controlled for smoking report lung impairment in cadmium-exposed workers (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976). Cortona et al. (1992) measured respiratory function parameters in 69 smoking and nonsmoking male subjects (average age 45) who were exposed to concentrations of 0.008–1.53 mg/m^3 of cadmium fumes over a period of

several years in a factory that produced cadmium alloys (silver-cadmium-copper). Forced Expiratory Volume (FEV), Forced Vital Capacity (FVC), Residual Volume (RV), Transfer Factor by the carbon monoxide method (TLCO), and Transfer Coefficient (KCO) were measured in these exposed individuals. The study found that there were no significant differences in the FVC, FEV, TLCO, and KCO between the workers exposed to cadmium fumes and control (non-exposed) individuals. There was a significant increase in RV of >8% in exposed workers; this effect was notably greater in those with higher cumulative exposures to cadmium (>10%). It is uncertain how much of a factor on the increased RV was due to the tendency of smokers to develop an initial emphysematous alteration in lung tissue due to smoking.

Davison et al. (1988) evaluated lung function in 101 men who had manufactured copper-cadmium alloy in a plant in England for ≥1 years since 1926. The exposed men were compared to controls from the factory's other seven divisions matched for age and employment status. Smoking in exposed and control men was similar. Between 1951 and 1983, 933 measurements of airborne cadmium had been made, 697 with static samplers and 236 with personal samplers. The various sampling methods used before 1964 are no longer considered to be reliable, so estimates of air concentrations were made based on changes in production techniques, ventilation, levels of production, and discussions with occupational health physicians, industrial hygienist, the management, and the workers. Cadmium concentrations in air from 1926 to 1972 were determined to have declined from 0.6 to 0.156 mg/m^3. In 1973, concentrations were 0.085 mg/m^3; from 1974 to 1983, concentrations ranged from 0.034 to 0.058 mg/m^3. The lung function of 77 of the men occupationally exposed to cadmium was significantly impaired compared to the unexposed controls, with the greatest abnormalities in the highest-dose group. Forced expiratory volume in one second, ratio of forced expiratory volume to forced vital capacity, transfer factor, or transfer coefficient were significantly lower than expected and radiographic total lung capacity, residual volume, and the ratio of these two were significantly higher than expected. The greatest abnormalities were observed in workers with the highest cumulative exposure and the highest liver cadmium levels. Regression of the lung transfer coefficient versus cadmium exposure indicated a linear relationship with no apparent threshold.

Smith et al. (1976) studied the pulmonary function of 17 high-exposure workers, 12 low-exposure workers, and 17 controls. Cadmium air concentrations where high-exposure subjects worked were >0.2 mg/m^3. High-exposure subjects had worked at the plant a median of 26.4 years, with a maximum of 40.2 years, and low-exposure subjects had worked a median of 27.1 years, with a maximum of 34.8 years. Workers with high exposure to cadmium had significantly decreased the FVC compared to low-exposure

workers and controls. Chest X-rays indicated mild or moderate interstitial fibrosis in 29% of high exposure workers. A dose-response relationship was found between FVC and urinary cadmium, and with months of exposure to cadmium fume, but not cadmium sulfate aerosol. In an analysis of the smoking habits, there was no significant difference between the two cadmium-exposed groups with respect to the proportion of present or past cigarette smokers, the intensity or duration of cigarette smoking, or cigar or pipe smoking habits. The control subjects, however, had a significantly ($p<0.05$) "higher" exposure to cigarette smoke than the cadmium exposed workers with substantially greater numbers of pack-years, cigarettes smoked per day, and years smoked. A step-down and multiple regression analyses with a dependent variable of FVC (as percent of predicted), and the independent variables, age-height, cigarette pack-years, and urinary cadmium, resulted in no indication that an interaction between the independent variables led to the observed relationship between FVC and cadmium excretion.

Other studies, however, have not shown a cadmium-related increase in impaired respiratory function. Edling et al. (1986) studied Swedish workers occupationally exposed to cadmium oxide fume from cadmium-containing solders. Cadmium-containing solder had been used at the plant from 1955 to 1978. The results from the lung-function analysis showed no significant difference in symptoms or lung function between the cadmium-exposed and the reference group. The exposed and the reference groups were similar with respect to sex, age, and height. There was a higher percentage of smokers in the reference group (52%) than in the exposed group (42%), but the difference was not statistically significant. The authors could not explain why significant differences in effects were not seen in these workers since other studies have shown significant effects at comparable cadmium exposure levels. The authors suggest that a possible bias could have been introduced if people who had worked for >5 years in the plant had changed their occupation because of lung disease, so that only "healthy" workers remained. Significant effects may also have been found if the reference group included workers other than those who worked with solder, but the purpose of the study was to resolve the effects of cadmium exposure among workers with similar occupations. Evaluating the data from smokers and nonsmokers separately also showed no significant impairment in lung function between smoking exposed and smoking unexposed or nonsmoking exposed and nonsmoking unexposed. The lung impairment due to smoking was observed in that smokers in both the exposed and unexposed groups had a somewhat deteriorated closing volume and other lung function indicators in accordance with previous studies on the effects of smoking. These results support the hypothesis that the response to occupational dust exposure differs from the response to tobacco smoking.

Another possible reason for differing results is that lung injury caused by high-level cadmium exposure may be partially reversible (Bonnell 1955; Chan et al. 1988), with a return towards normal several years after exposures have been significantly reduced. Chan et al. (1988) studied a cohort of 36 female and 8 male workers at a Singapore cadmium battery factory exposed to cadmium oxide dust. Cadmium concentrations in air were 0.03–0.09 mg/m^3 (geometric means). Lung function was measured using spirometry, helium dilution, tidal sampling, X-ray, and respiratory symptoms. The recovery of lung function after reduction or cessation of occupational exposure to cadmium dusts was assessed. Total lung capacity increased following reduction of exposure and, following cessation of exposure, vital capacity, FEV, and prevalence of respiratory symptoms all improved. Blood and urine cadmium concentrations were considerably lower with the reduction or cessation of exposure and were consistent with a decrease in the cadmium air levels.

Additional respiratory symptoms less frequently reported in workers occupationally exposed to cadmium are chronic rhinitis and impairment or loss of the sense of smell (Adams et al. 1969; Bonnell 1955; Friberg 1950; Liu et al. 1985; Rose et al. 1992). The cause of these effects may be chronic irritation or necrosis of the nasal membranes, as they are generally found only in individuals with high-level exposure. An increased prevalence of abnormal parasinus radiographic findings in cadmium-exposed workers compared to other published reports on non-exposed populations was reported by Shaham et al. (1993).

Studies in animals confirm that inhalation exposure to cadmium can lead to respiratory injury. Single acute exposures in rats to 5–10 mg Cd/m^3 as cadmium oxide dust, cadmium oxide fume, or cadmium chloride for 1–5 hours resulted in moderate to severe, multifocal interstitial pneumonitis, diffuse alveolitis with hemorrhage, increased lung weight, inhibition of macrophages, focal interstitial thickening, edema, and necrosis of alveolar type 1 cells leading to type 2 cell hyperplasia and fibroblasts (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart et al. 1989a; NTP 1995; Palmer et al. 1986). Similar results (i.e., severe pneumonitis) were seen in hamsters exposed to cadmium chloride at 10 mg/m^3 for 30 minutes (Henderson et al. 1979) and in rabbits exposed to cadmium oxide dusts at 4.5 mg/m^3 for 2 hours (Grose et al. 1987). Exposures in rats to cadmium chloride at 6.1 mg Cd/m^3 1 hour/day for 5, 10, or 15 days resulted in emphysema; a 3-day exposure to 61 mg Cd/m^3 for 1 hour/day resulted in pulmonary hemorrhage (Snider et al. 1973). Repeated exposure to 0.088 mg Cd/m^3 as cadmium oxide for 2 weeks resulted in minimal to mild alveolar histiocytic (macrophage) infiltration in rats and mice, focal inflammation surrounding alveolar ducts and extending into the adjacent alveolar septa in rats, and hyperplasia in tracheobronchial lymph nodes in mice (NTP 1995). At higher concentrations, the severity of these lesions increased (the severity of the lung lesions was scored as

moderate at ≥0.88 mg Cd/m^3) and necrosis of the epithelial lining of the alveolar ducts was observed at ≥0.26 mg Cd/m^3 in rats and 0.88 mg Cd/m^3 in mice. The NTP (1995) study also found significant increases in the incidence of lesions in the nasal cavity; minimal-to-mild degeneration of the olfactory epithelium was observed in rats and mice exposed to 0.88 mg Cd/m^3 and hyperplasia and inflammation of respiratory epithelium were observed in rats at 2.6 mg Cd/m^3.

Persistent damage has been reported in an animal model following a single intratracheal exposure to 25, 100, or 400 µg cadmium chloride/kg body weight (Driscoll et al. 1992). Although most BALF biochemical (lactate dehydrogenase, total protein, and N-acetylglucosaminidase) and cellular (neutrophils and lymphocyte numbers) parameters returned to control levels 28 days after exposure, histopathological alterations including inflammation and fibrosis were still present 90 days post-exposure and the incidence and severity of the lesions were greater at 90 days compared to 28 days.

Intermediate-duration exposure to cadmium results in similar respiratory effects as seen in the acute exposures. Concentration-related increases in the severity and types of respiratory lesions have been observed. Because the intermediate-duration studies used different exposure protocols, intermittent exposure studies were duration-adjusted to continuous exposure (Table 3-2) to facilitate comparisons across these studies. The lowest adverse effect level for lung effects was 0.004 mg Cd/m^3 for alveolar epithelial hyperplasia in mice (NTP 1995). At 0.008–0.07 mg Cd/m^3, inflammation and minimal fibrosis were observed in rats, mice, and rabbits (Johansson et al. 1984; NTP 1995; Oberdörster et al. 1994) and marked inflammation and moderate fibrosis were observed in rats at 0.17 mg Cd/m^3 (NTP 1995). At ≥0.34 mg Cd/m^3, emphysema and chronic pneumonia were observed in rats and rabbits (Friberg 1950; Prigge 1978b). In addition to the widely reported effects in the lungs, NTP (1995) reported minimal lesions in the larynx of rats (epithelial degeneration) and mice (squamous metaplasia) exposed to 0.022 mg Cd/m^3 and minimal lesions in the nasal cavity in rats (inflammation of respiratory epithelium) and mice (degeneration of olfactory epithelium) exposed to 0.088 mg Cd/m^3. The toxicity of cadmium to the respiratory tract following intermediate-duration exposure is highlighted by the NTP (1995) rat and mouse studies. As summarized in Table 3-3, rats and mice were exposed to five concentrations (0.022, 0.044, 0.088, 0.22, and 0.88 mg Cd/m^3 as cadmium oxide) 6.33 hours/day, 5 days/week for 13 weeks. The earliest effects observed were alveolar histiocytic infiltrates, alveolar epithelial hyperplasia, and tracheal epithelial hyperplasia or squamous metaplasia; these lesions were all graded as minimal. With increasing concentrations, the severity of most lesions increased as did the type of lesion.

Table 3-2. Comparison of Lung Effects Across Intermediate-Duration Inhalation Studies

Species	Exposure frequency/duration	Adverse effect level (mg Cd/m^3)	Duration-adjusted adverse effect level (mg Cd/m^3)	Effect	Reference
Mouse	6.33 hours/day, 5 days/week, 13 weeks	0.022	0.004	Alveolar hyperplasia	NTP 1995
Rat	6.33 hours/day, 5 days/week, 13 weeks	0.044	0.008	Alveolar histiocytic infiltrates and hyperplasia	NTP 1995
Mouse	6.33 hours/day, 5 days/week, 13 weeks	0.044	0.008	Minimal fibrosis	NTP 1995
Mouse	6.33 hours/day, 5 days/week, 13 weeks	0.088	0.017	Moderate inflammation	NTP 1995
Rat	6.33 hours/day, 5 days/week, 13 weeks	0.22	0.017	Minimal fibrosis	NTP 1995
Mouse	6 hours/day, 5 days/week, 4 weeks	0.1	0.02	Inflammation	Oberdörster et al. 1994
Rat	24 hours/day, 7 days/week, 90 days	0.025	0.025	Proliferations	Prigge 1978a
Rat	6.33 hours/day, 5 days/week, 13 weeks	0.22	0.04	Inflammation	NTP 1995
Rat	6.33 hours/day, 5 days/week, 13 weeks	0.88	0.17	Marked inflammation and moderate fibrosis	NTP 1995
Mouse	6.33 hours/day, 5 days/week, 13 weeks	0.88	0.17	Moderate fibrosis	NTP 1995
Rat	6 hours/day, 5 days/week, 62 days	0.33	0.06	Fibrosis	Kutzman et al. 1986
Rabbit	6 hours/day, 5 days/week 4–6 weeks	0.4	0.07	Inflammation	Johansson et al. 1984
Rabbit	3 hours/day, 21 days/month, 9 months	4	0.34	Pneumonia/ emphysema	Friberg 1950
Rabbit	3 hours/day, 23 days/month, 7 months	5.6	0.53	Emphysema	Friberg 1950
Rat	24 hours/day, 7 days/week				Prigge 1978b

Table 3-3. Severity of Respiratory Effects in Rats and Mice Exposed to Cadmium Oxide for 13 Weeks[a]

	Concentration (mg Cd/m^3)					
	0	0.022	0.044	0.088	0.22	0.88
Male rats						
Lung						
Alveolar histiocytic infiltrate	—	—[b]	1.0[c]	2.0	3.0	3.0
Alveolar epithelial hyperplasia	—	—	1.0	1.0	2.0	2.1
Inflammation	—	—	—	—	2.6	4.0
Fibrosis	—	—	—	1.0	2.0	2.7
Mediastinal lymph node						
inflammation	—	—	—	1.3	3.2	3.3
Larynx						
Epithelial degeneration		1.0	1.0	1.0	1.0	1.0
Nose						
Olfactory epithelium degeneration	—	—	—		1.0	3.0
Olfactory epithelium respiratory metaplasia	—	—	—	—	—	1.3
Olfactory epithelium squamous metaplasia	—	—	—	—	—	1.9
Respiratory epithelium inflammation	—	—	—	—	1.0	2.6
Respiratory epithelium degeneration	—	—	—	—	—	1.5
Female rats						
Lung						
Alveolar histiocytic infiltrate	—	—	1.0	2.1	3.0	3.0
Alveolar epithelial hyperplasia	—	—	1.0	1.0	2.0	2.1
Inflammation	—	—	—		1.6	3.5
Fibrosis	—	—	—	1.0	2.0	2.1
Mediastinal lymph node						
inflammation	—	—	1.0	1.5	3.6	4.0
Larynx						
Epithelial degeneration	—	1.0	1.0	1.0	1.0	1.0
Nose						
Olfactory epithelium degeneration	—	—	—	—	1.0	2.8
Olfactory epithelium respiratory metaplasia	—	—	—	—	1.0	1.0
Olfactory epithelium squamous metaplasia	—	—	—	—	—	1.4
Respiratory epithelium inflammation	—	—	—	1.0	1.8	1.8
Male mice						
Lung						
Alveolar epithelial hyperplasia	—	1.0	1.0	1.8	1.7	2.0

Table 3-3. Severity of Respiratory Effects in Rats and Mice Exposed to Cadmium Oxide for 13 Weeks[a]

	Concentration (mg Cd/m^3)					
	0	0.022	0.044	0.088	0.22	0.88
Inflammation	—	—	—	3.0	2.2	2.7
Fibrosis	—	—	1.0	1.0	1.0	1.0
Tracheobronchial lymph node hyperplasia	—	—	1.0	2.3	2.4	2.7
Larynx						
Squamous metaplasia	—	1.0	1.0	1.0	1.0	1.1
Nose						
Olfactory epithelium degeneration	—	—	—	1.0	1.7	2.0
Olfactory epithelium respiratory metaplasia	—	—	—	—	1.0	1.5
Olfactory epithelium squamous metaplasia	—	—	—	—		1.0
Respiratory epithelium hyaline droplets	—	—	—	—	1.0	1.0
Female mice						
Lung						
Alveolar histiocytic infiltrate	—	1.0	1.0	2.0	2.0	3.0
Alveolar epithelial hyperplasia	—	—	—	1.4	2.0	2.0
Inflammation	—	—	—	2.3	2.1	2.9
Fibrosis	—	—	1.0	1.0	1.0	1.0
Tracheobronchial lymph node hyperplasia	—	—	1.0	1.5	2.0	2.4
Larynx						
Squamous metaplasia	—	1.0	1.0	1.0	1.0	1.0
Nose						
Olfactory epithelium degeneration	—	—	—	1.0	1.0	2.0
Olfactory epithelium respiratory metaplasia	—	—	—	—	—	1.0
Respiratory epithelium hyaline droplets	—	—	—	—	1.0	1.0

[a]Animals were exposed for 6.33 hours/day, 5 days/week.
[b]No lesions present or not significantly different from control group.
[c]Severity score: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Source: NTP 1995

There are fewer chronic-inhalation exposure studies that specifically reported systemic respiratory effects. Oldiges and Glaser (1986) report increased lung weights (amount unspecified) in rats from exposure to either cadmium sulfate at 0.092 mg Cd/m^3 or cadmium sulfide at 0.254 mg Cd/m^3 for 22 hours/day, 7 days/week for 413–455 days. Takenaka et al. (1983) observed adenomatous hyperplasia in the bronchoalveolar region in rats from exposure to cadmium chloride at 0.0134 mg Cd/m^3 for 23 hours/day, 7 days/week for 18 months.

The available data suggest that there may be species differences in the respiratory toxicity of cadmium. In a comparison of the pulmonary response to exposure to 0.1 mg Cd/m^3 as cadmium chloride 6 hours/day, 5 days/week for 4 weeks, Oberdörster et al. (1994) found that the inflammatory response in the lungs of mice was greater than that of rats exposed to the same cadmium concentration. However, the cadmium lung burden in mice was twice as high as the rat's lung burden. In the NTP (1995) study, adverse lung effects were observed at lower concentrations in mice compared to rats, but at the higher concentrations, the severity of the lung effects were greater in the rats. Although these data suggest species differences in the pulmonary toxicity of cadmium, more information is needed to evaluate if there are differences at given lung burdens.

Based on differences in the pharmacokinetic properties of various cadmium compounds, it is expected that differences in toxicity would be observed. As discussed in Oberdörster (1992), cadmium chloride and cadmium oxide elicited similar responses following a single intratracheal dose, whereas no response was observed for cadmium sulfide. However, Glaser et al. (1990) found similar responses following repeated exposures to various cadmium compounds.

Hart and colleagues (Hart 1986; Hart et al. 1989a, 2001) demonstrated that repeated low-concentration exposure to cadmium results in the development of adaptive survival response. In rats exposed to 1.6 mg Cd/m^3 as cadmium acetate 3 hours/day, 5 days/week, thickening of the alveolar septa and mononuclear cell and polymorphonuclear leukocyte aggregates were observed after 2 weeks of exposure (Hart 1986). However, the inflammatory response was decreased after 3 weeks of exposure and no significant histopathological alteration were observed in rats exposed for 4, 5, or 6 weeks. After 5 weeks of cadmium exposure, a single high concentration (8.4 mg Cd/m^3) resulted in less pulmonary damage compared to non-pretreated animals (Hart et al. 1989a). Multiple pulmonary resistance factors appear to contribute to this resistance/tolerance. These factors include increased levels of metallothionein, glutathione, and γ-glutamylcysteinesynthetase (Hart et al. 2001). However, as suggested by Hart et al. (2001), cadmium-adapted alveolar epithelial cells have a reduced ability to repair DNA damage and

apoptotic cell death is attenuated in these cells; thus, cadmium adapted animals may be more susceptible to tumor formation.

Cardiovascular Effects. Inhalation exposure to cadmium does not appear to have significant effects on the cardiovascular system. Most studies of workers occupationally exposed to cadmium have not found cadmium-related cardiovascular toxicity. In some studies, the mortality from cardiovascular disease was lower in the cadmium-exposed population. Armstrong and Kazantzis (1983) reported that a cohort of 6,995 British men occupationally exposed to cadmium for an average duration of 11 years had a significantly lower mortality from vascular disease.

Fifty-three male workers exposed to cadmium and lead and 52 male controls were examined for correlations in urine levels and blood pressure. The average duration of exposure was 12.5 years. Correlations between blood pressure and urinary cadmium in exposed workers were not significant after controlling for age or age and heart rate. Exposure to lead was a significant confounding factor (de Kort et al. 1987).

Friberg (1950) investigated the health of workers in a manufacturing plant that made cadmium-containing electrodes used in the production of batteries. Fifty-eight workers (30–50 years of age) were divided into two groups based on number of years at the plant. Workers were clinically examined for subjective symptoms and corresponding morphological or functional changes of the respiratory, cardiovascular, and excretory systems. The cardiovascular exam was largely unremarkable. Only a slight rise in blood pressure in a few cases was observed in Group 1. Electrocardiograms (EKG) were not significantly different from a matched control group in Group 1. Group 2 had neither increased blood pressure nor altered EKGs.

Kazantzis et al. (1988) studied mortality in a cohort of 6,958 cadmium-exposed male workers with average occupational exposures of 12 years. This was a follow-up study to the work of Armstrong and Kazantzis (1983). There was a significant deficit in deaths from cerebrovascular disease among men occupationally exposed to cadmium. There was no significant excess risk from hypertensive or renal disease.

Smith et al. (1980) studied 16 male high-exposure production workers and 11 male low-exposure office and supervisory workers for renal function. Average duration of exposure was 25 years. High-exposure workers were exposed to cadmium oxide concentrations of 0.23–45.2 mg/m^3 and cadmium sulfide

concentrations of 0.04–1.27 mg/m^3. No difference was found in hypertension between high- and low-exposure workers, adjusted for age and weight or cigarette smoking.

Sorahan and Waterhouse (1983) examined mortality rates in a cohort of 3,025 nickel-cadmium battery workers (2,559 males and 466 females). Cadmium levels in air ranged from 0.05 to 2.8 mg/m^3, primarily as cadmium oxide. Duration of exposure ranged from 1 to >6 years. No increase in mortality from diseases of the circulatory system (e.g., hypertension) was seen in cadmium-exposed workers.

Staessen and Lauwerys (1993), in a study known as the Cadmibel Study (a cross-sectional population study), evaluated 2,327 people from a random sample of the population of four Belgian districts chosen to provide a wide range of environmental exposure to cadmium. Participants completed a questionnaire regarding their medical history, current and past occupations, smoking habits, alcohol consumption, and intake of medications. Urine and blood samples were taken, and pulse rate, blood pressure, height, and weight were recorded. Exposure to cadmium was considered to be by both the oral and inhalation routes. Cadmium levels in blood and urine were significantly increased in the high-exposure areas compared to the low-exposure areas ($p<0.001$). Blood pressure was not correlated with the urine or blood cadmium levels. The prevalence of hypertension or other cardiovascular diseases was similar in all four districts, and was not correlated with urine or blood cadmium levels. A follow-up investigation of 692 participants of this study also showed no correlation with urine or blood calcium levels and the prevalence of hypertension after 5 years (Staessen et al. 2000). These results do not support a hypothesis that cadmium increases blood pressure, prevalence of hypertension, or other cardiovascular diseases.

One study found a statistically significant increase in blood pressure in exposed workers compared to controls (Thun et al. 1989), but mortality in this cohort was lower than expected (Thun et al. 1985).

There are limited data on the cardiotoxicity of cadmium in animals. No significant alterations in systolic blood pressure or histological alterations in the heart were observed in rats exposed to cadmium oxide concentrations as high as 0.88 mg Cd/m^3 for 13 weeks (NTP 1995).

Gastrointestinal Effects. In the cohort he studied, Friberg (1950) found no association between inhalation cadmium exposure in workers and symptoms of gastrointestinal toxicity. Symptoms that had been reported in case histories from the 1920s included pain or tenderness at the epigastrium associated with nausea and some constipation. No other human studies report any cadmium associated gastro-intestinal toxicity from inhalation exposure.

In the only animal study located, Rusch et al. (1986) observed erosion of the stomach in rats from exposure to cadmium carbonate at 132 mg Cd/m^3 for 2 hours. Postmortem evaluation was performed at 1, 3, 7, and 30 days postexposure. After the inhalation exposure in a whole-body chamber, rats were vacuumed to remove any cadmium carbonate dust adhering to the ventral and dorsal fur. The 132 mg Cd/m^3 dose is relatively high. Three of the 10 test animals died during the 2-hour exposure so the significance of the gastrointestinal effect in this study is unclear.

Hematological Effects. The evidence concerning hematological effects following inhalation exposure to cadmium is conflicting. Lowered hemoglobin concentrations and decreased packed cell volumes have been observed in some studies of workers occupationally exposed to cadmium (Bernard et al. 1979; Friberg 1950; Kagamimori et al. 1986), but not in others (Bonnell 1955; Chan et al. 1988; Davison et al. 1988). The changes that were found often were not statistically significant (Bernard et al. 1979; Friberg 1950), and examination of bone marrow of some workers with lowered hemoglobin revealed no detectable abnormalities (Friberg 1950).

Conflicting results on the hematologic effect of cadmium after inhalation exposure have also been obtained with animal studies. Rabbits exposed to cadmium oxide dust at 4 mg/m^3 for 3 hours/day, 21 days/month for 9 months developed eosinophilia and a slightly lower hemoglobin (Friberg 1950). In contrast, rats exposed to cadmium oxide dust at 0.052 mg Cd/m^3 for 24 hours/day for 90 days had increased hemoglobin and hematocrit that were attributed to decreased lung function (Prigge 1978a). Prigge (1978b) also reported increased hemoglobin and hematocrit in rats continuously exposed to cadmium chloride at 0.204 mg Cd/m^3 and higher for 21 days. Other studies report no Cd-related hematological effects. A nearly continuous 30-day exposure in rats to cadmium sulfide at 1.034 mg Cd/m^3 had no effect on red blood cell counts (Glaser et al. 1986). A nearly continuous 218-day exposure in rats to cadmium oxide dust or fume at 0.090 mg Cd/m^3 had no effect on a routine hematological evaluation (specific tests not reported) (Oldiges and Glaser 1986). A partial explanation for these conflicting results may be that Cd-induced anemia primarily results from impaired absorption of iron from the diet following gastrointestinal exposure to cadmium (see Section 3.2.2.2), and the amount of gastrointestinal exposure following cadmium inhalation is variable depending on the form and dose.

Musculoskeletal Effects. Case studies indicate that calcium deficiency, osteoporosis, or osteomalacia can develop in some workers after long-term occupational exposure to high levels of cadmium (Adams et al. 1969; Blainey et al. 1980; Bonnell 1955; Kazantzis 1979; Scott et al. 1980).

Effects on bone generally arise only after kidney damage has occurred and are likely to be secondary to resulting changes in calcium, phosphorus, and vitamin D metabolism (Blainey et al. 1980).

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to cadmium.

Hepatic Effects. Liver effects are not usually associated with inhalation exposure to cadmium. Friberg (1950) reported some nonspecific signs of liver disease in some workers from a group exposed to cadmium in the air for 20 years. Test results included increased serum gamma-globulin, and other indicators of abnormal serum globulins, including the flocculation test results of a positive Takata reaction and/or an elevated thymol values. These tests (the latter of which are not used today) were nonspecific indicators of cirrhosis or hepatitis. The significance of these test results with respect to cadmium exposure is questionable. Subsequent studies on workers exposed to cadmium in the air have not reported adverse liver effects (Adams et al. 1969; Bonnell 1955).

Liver effects have occasionally been found in animal studies. Cats examined within one day of inhalation exposure to an unspecified concentration of cadmium oxide fume had a variety of hepatic lesions, and liver changes from cell granulation at low doses to fatty infiltration at high doses (Prodan 1932). Increased serum alanine aminotransferase activity, indicative of liver damage, was seen in rats exposed for 30 days to 0.1 mg/m^3 cadmium, but activity had returned to normal 2 months after exposure (Glaser et al. 1986). Kutzman et al. (1986) reported an increased liver relative weight in rats from a cadmium chloride exposure at 1.06 mg Cd/m^3 for 6 hours/day, 5 days/week, for 62 days. Increased liver weight was not observed from a continuous cadmium chloride exposure at 0.029 mg Cd/m^3 for 255 days, from a continuous cadmium oxide exposure at 0.090 mg Cd/m^3 for 218 days, or from a continuous cadmium sulfate exposure at 0.095 mg Cd/m^3 for 413 days (Oldiges and Glaser 1986). Similar negative results were reported by Prigge (1978a, 1978b) for a 21-day exposure to cadmium chloride at 0.581 mg Cd/m^3, and for a 63-day exposure to cadmium oxide at 0.105 mg Cd/m^3 (a dose that was very toxic to the lungs). A continuous high-dose exposure to cadmium sulfide at 2.247 mg Cd/m^3 for 105 days did result in an unspecified increase in liver weight in surviving rats (Oldiges and Glaser 1986). Cadmium accumulates in the liver as well as the kidney, the main target organ for cadmium toxicity. The resistance of the liver to toxic effects from cadmium may be related to a higher capacity of the liver to produce metallothionein that would bind to cadmium and would lower the concentrations of free cadmium ions (see Section 3.4.3).

Renal Effects. There is very strong evidence that the kidney is the main target organ of cadmium toxicity following extended inhalation exposure. The sensitivity of the kidney to cadmium was recognized in an early investigation of workers exposed to cadmium oxide dust and cadmium fumes in a factory producing nickel-cadmium batteries (Friberg 1950). These workers suffered from a high incidence of abnormal renal function, indicated by proteinuria and a decrease in glomerular filtration rate. Many studies examining cadmium workers have reported various effects on the kidneys. Similar signs of renal damage have been observed in many other studies of workers occupationally exposed to cadmium (Adams et al. 1969; Bernard et al. 1979; Beton et al. 1966; Bonnell 1955; Bustueva et al. 1994; Chia et al. 1989; Elinder et al. 1985a, 1985b; Falck et al. 1983; Gompertz et al. 1983; Iwata et al. 1993; Jakubowski et al. 1987; Järup and Elinder 1993; Järup et al. 1988; Kjellström et al. 1977a; Liu et al. 1985; Mason et al. 1988; Piscator 1966; Roels et al. 1981b; Rose et al. 1992; Smith et al. 1980; Thun et al. 1989). Most of these studies did not report cadmium exposure levels; rather, urinary cadmium, blood cadmium, or cumulative exposures were used as biomarkers of exposure. Thus, these studies are not presented in the LSE table (Table 3-1). Selected occupational exposure studies are summarized in Table 3-4.

One of the first signs of kidney effects is tubular dysfunction characterized by an increased urinary excretion of low-molecular-weight proteins such as β2-microglobulin, human complex-forming glycoprotein (pHC) (also referred to as α1-microglobulin), and retinol binding protein or increased urinary levels of intracellular enzymes such as N-acetyl-β-glucosaminidase (NAG) (European Chemicals Bureau 2007; Järup et al. 1998b). Numerous occupational exposure studies have reported increases in urinary levels of these biomarkers (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985b; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Kawada et al. 1989; Roels et al. 1993; Shaikh et al. 1987; Thun et al. 1989; Toffoletto et al. 1992; Verschoor et al. 1987). At higher exposure levels, increased urinary levels of high-molecular-weight proteins such as albumin have been reported (Bernard et al. 1979, 1990; Chen et al. 2006a, 2006b; Elinder et al. 1985b; Mason et al. 1988; Roels et al. 1989, 1993; Thun et al. 1989), but there is some debate as to whether this represents glomerular damage (Bernard et al. 1979; Roels et al. 1989) or severe tubular damage (Elinder et al. 1985a; Mason et al. 1988; Piscator 1984).

Chronic exposure to very high cadmium levels can result in glomerular damage resulting in decreases in glomerular filtration rate (GFR) (Friberg 1950; Järup et al. 1995b; Roels et al. 1991). Järup et al. (1995b) found a dose-response relationship between blood cadmium levels and GFR in cadmium workers. At blood cadmium levels of 5.6 to <8.4 μg/L, 33.3% of the workers had decreased GFR (defined as <80% of referents); whereas all subjects with blood cadmium levels of ≥8.4 μg/L exhibited a decreased GFR.

Table 3-4. Summary of Occupational Exposure Studies Examining Renal Effects

Population	Effect	Adverse effect level	Reference
Zinc-cadmium smelter workers (n=87)	Age-related decline in maximal GFR was exacerbated in workers with cadmium-induced microproteinuria.	U-Cd: 11.1 µg/g creatinine	Roels et al. 1991
Workers using cadmium pigments in plastic production or using cadmium in welding (n=27)	Significant increase in urinary β2M and NAG levels.	U-Cd: 5 µg/g creatinine	Verschoor et al. 1987
Cadmium alloy workers (n=164)	Higher incidence of increased urinary β2M levels (>250 µg/L cut-off) when urinary cadmium levels exceeded 10 µg/g creatinine on one or more occasions, as compared to workers who never exceeded the 10 µg/g creatinine level.	U-Cd: 10 µg/g creatinine	Toffoletto et al. 1992
Cadmium smelter workers (n=53)	Significant increase in urinary protein and β2M levels.	U-Cd: 13.3 µg/g creatinine	Shaikh et al. 1987
Non-ferrous smelter workers (n=58)	Significant increase in urinary β2M, RBP protein, pHC, albumin, and transferrin levels.	U-Cd: >10 µg/g creatinine	Bernard et al. 1990
Workers exposed to cadmium pigment dust (n=58)	Significant correlation between urinary cadmium and NAG levels; significant correlation with β2M at one of the two time points.	U-Cd: 1.1–1.4 µg/g creatinine	Kawada et al. 1989
Zinc-cadmium smelter workers (n=50)	Significant association between urinary cadmium levels and urinary levels of NAG, albumin, and transferrin. At higher urinary cadmium levels (10 µg/g creatinine), there were significant associations with RBP and β2M.	U-Cd: 4 µg/g creatinine	Roels et al. 1993
Battery workers (n=561)	10% prevalence of abnormal β2M levels (220 µg/g creatinine cut-off).	U-Cd: 1.5 µg/g creatinine for ≥60 years of age U-Cd: 5 µg/g creatinine for <60 years of age	Järup and Elinder 1994
Alkaline battery factory workers (n=102)	10% prevalence of renal dysfunction (β2M >380 µg/g creatinine; RBP >130 µg/g creatinine).	U-Cd: 10–15 µg/g creatinine	Jakubowski et al. 1987
Workers at a factory using cadmium-containing solders (n=60)	25% prevalence of abnormal β2M levels (300 µg/g creatinine cut-off).	U-Cd: 2–5 µg/g creatinine	Elinder et al. 1985a

Table 3-4. Summary of Occupational Exposure Studies Examining Renal Effects

Population	Effect	Adverse effect level	Reference
Workers at nickel-cadmium battery factory (n=92)	Significant increase in pHC and NAG levels (after adjustment for age, gender, and race).	U-Cd: 5–10 µg/g creatinine	Chia et al. 1992
Cadmium smelter workers (n=85)	Significant increases in levels β2M and NAG levels and increased prevalence of abnormal levels of these biomarkers.	U-Cd: 5–10 µg/g creatinine	Chen et al. 2006a, 2006b
Alkaline battery factory workers (n=141)	10% prevalence of renal dysfunction (β2M >300 µg/L; RBP >300 µg/L).	B-Cd: 300 µg-years/L (30 years of 10 µg/L)	Jakubowski et al. 1992
Battery workers (n=440)	Approximately 10% prevalence of abnormal β2M levels (35 µg/mmol creatinine cut-off).	B-Cd: 5.6 µg/L Cumulative exposure: 691 µg-years/m^3	Järup et al. 1988
Cadmium recovery plant workers (n=45)	Significant association between cumulative exposure and urinary β2M, RBP, phosphate, and calcium and serum creatinine levels.	Cumulative exposure: 300 mg/m^3	Thun et al. 1989
Workers exposed to cadmium fumes (n=33)	Increased urinary β2M and protein levels (mean 6,375 µg/g creatinine and 246 mg/g creatinine, respectively) in 7 workers (mean in remaining 23 workers 53 µg/g creatinine and 34 mg/g creatinine).	Cumulative exposure: 1,137 µg/m^3/years	Falck et al. 1983

U-Cd = urinary cadmium, B-Cd = blood cadmium; GFR = glomerular filtration rate; pHC = human complex-forming glycoprotein (also referred to as α1-microglobulin); NAG = N-acetyl-β-glucosaminidase; β2M = β2-microglobulin; prt = protein; RBP = retinol binding protein

Another study did not find alterations in GFR in workers with urinary cadmium levels of approximately 11 μg/g creatinine; however, an exacerbation of the age-related decline in maximal GFR was observed (Roels et al. 1991). Other studies reported increases in serum creatinine levels, which are suggestive of impaired GFR (Roels et al. 1989; Thun et al. 1989).

Depressed tubular resorption of other solutes such as enzymes, amino acids, glucose, calcium, copper, and inorganic phosphate have been reported in workers with signs of tubular proteinuria (Elinder et al. 1985a, 1985b; Falck et al. 1983; Gompertz et al. 1983; Mason et al. 1988). An increased frequency of kidney stone formation has also been reported in cadmium workers (Elinder et al. 1985a; Falck et al. 1983; Järup and Elinder 1993; Kazantzis 1979; Scott et al. 1978; Thun et al. 1989; Trevisan and Gardin 2005). This effect is likely to be secondary to disruption of calcium metabolism due to kidney damage. Järup and Elinder (1993) calculated an incidence rate ratio (IRR) (after adjustment for age and calendar time) of 3.0 (95% CI 1.3–6.8) for the occurrence of kidney stones among workers with a cumulative exposure of ≥5000 $\mu g/m^3$ years; the IRR was not significantly elevated at lower cumulative exposure levels. Significant increases in kidney stone formation were observed in workers with increased urinary cadmium (median of 3.7 μg/g creatinine), blood cadmium (median of 7 μg/L), and urinary β2-microglobulin (median of 155 μg/g creatinine). The increased kidney stone formation may be secondary to the cadmium-induced kidney damage disruption of calcium metabolism.

Hellström et al. (2001) evaluated the association between occupational cadmium exposure and end stage renal disease among cadmium workers and residents living near a cadmium facility; renal replacement therapy was used as a surrogate for renal disease. The standardized rate ratios (SRRs) (95% CI) were 2.1 (0.6–5.3) and 2.5 (0.7–6.5) in male workers aged 20–79 or 40–79 years, respectively. Although the SRRs were not statistically significant, the ratios were significantly elevated in residents presumably exposed to lower cadmium levels (see Section 3.2.2.2 for more information on these results). Studies examining the cause of death among cadmium workers have not found significant increases in the standardized mortality ratios (SMRs) for nephritis or nephrosis (Armstrong and Kazantzis 1983; Järup et al. 1998a) or nonmalignant renal disease (Thun et al. 1985).

The data from studies of cadmium workers provide strong, clear evidence that the kidney is a sensitive target following chronic exposure, but the data do not clearly identify a threshold of toxicity. The earliest indication of an effect on the kidney is an increase in urinary levels of low molecular weight proteins particularly β2-microglobulin, retinol binding protein, and pHC. However, there is some question as to the adversity of these early indicators because increased excretion of low molecular weight proteins

precede the clinical manifestations (Bernard et al. 1997; Järup et al. 1998b). As noted by Bernard et al. (1997), the assessment of the health significance of changes affecting a biomarker involves localizing the changes in the sequence of events that ultimately results in compromised renal function and appreciating the probability that these changes may lead to a deterioration of renal function. Their guidelines for interpreting β2-microglobulin levels in cadmium workers are presented in Table 3-5.

Another aspect of interpreting alterations in renal biomarkers and assessing risk is the issue of the reversibility of cadmium-induced tubular dysfunction and impaired glomerular filtration rate. In workers exposed to high levels of cadmium, cessation of exposure does not generally result in a reversibility of kidney damage. Increases in urinary levels of β2-microglobulin, retinol binding protein, or total protein (Elinder et al. 1985b; Järup et al. 1993; Mason et al. 1999; Piscator 1984; Roels et al. 1989; Thun et al. 1989) or a decrease in glomerular filtration rate (Järup et al. 1993; Piscator 1984; Roels et al. 1989) have been observed in workers years after cadmium exposure cessation. However, in workers exposed to low levels of cadmium, cessation of exposure resulted in decreased or no change in urinary β2-microglobulin levels (McDiarmid et al. 1997; van Sittert et al. 1993). In studies by Roels et al. (1997) and Trzcinka-Ochocka et al. (2002), former cadmium workers were divided into groups based on historical cadmium levels and urinary β2-microglobulin or retinol binding protein levels. Both studies found that the reversibility of tubular dysfunction was dependent on the cadmium body burden and the severity of microproteinuria at the time cadmium exposure was reduced or ceased. In the Roels study, significant decreases in retinol binding protein levels and no change in β2-microglobulin levels were observed in workers whose urinary cadmium levels never exceeded 10 μg/g creatinine. Decreases in β2-microglobulin and retinol binding protein levels were also observed in workers whose β2-microglobulin levels were <300 μg/g creatinine or between 300 and 1,500 μg/g creatinine and urinary cadmium levels were >10 μg/g creatinine, but were never >20 μg/g creatinine. However, a progression of microproteinuria (increased urinary levels of β2-microglobulin and retinol binding protein levels) was observed in workers who had initial β2-microglobulin levels >1,500 μg/g creatinine and urinary cadmium levels >20 μg/g creatinine. In contrast, Trzcinka-Ochocka et al. (2002) found decreases in β2-microglobulin and retinol binding protein levels in groups of workers with initial β2-microglobulin and retinol binding protein levels of ≤300, >300, ≤1,500, or ≥1,500 μg/g creatinine; in all groups, the initial mean urinary cadmium levels were >20 μg/g creatinine. However, the risk of increased excretion of retinol binding protein was higher in the groups of workers with initial retinol binding protein levels of >300 μg/g creatinine. Logistic regression analysis demonstrated that the initial level of retinol binding protein was the most important determinant in reversibility of tubular proteinuria and that the influence of urinary cadmium level or length of time since exposure cessation was not statistically significant.

Table 3-5. Guidelines for Interpreting β2-microglobulin Levels

β2-Microglobulin level	Significance
<300 µg/g creatinine	Normal value.
300–1,000 µg/g creatinine	Incipient cadmium tubulopathy (possibility of reversibility after removal from exposure). No change in GFR.
1,000–10,000 µg/g creatinine	Irreversible tubular proteinuria which may lead to accelerated decline in the GFR with age. GFR normal or slightly altered.
>10,000 µg/g creatinine	Overt cadmium nephropathy usually associated with decreased GFR.

GFR = glomerular filtration rate

Source: Bernard et al. 1997

The available occupational exposure data suggest that tubular dysfunction generally develops only after cadmium reaches a threshold concentration in the renal cortex. However, a number of factors can influence urinary levels of β2-microglobulin or retinol binding protein and direct relationship between urinary levels of these proteins and a kidney cadmium concentration has not been established. Based on the findings of early occupational exposure studies, a number of investigators estimated that the "critical concentration" of cadmium in the renal cortex associated with increased incidence of renal dysfunction in an occupational setting was about 200 μg/g wet weight (Friberg et al. 1974; Kjellstr öm et al. 1977a; Roels et al. 1983); this corresponds to a urinary cadmium levels of 5–10 μg/g creatinine (European Chemicals Bureau 2007). Although 10 μg/g creatinine was initially established as a threshold urinary cadmium concentration, there is sufficient evidence to suggest that adverse effects occur at lower urinary cadmium levels (Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985b; Järup and Elinder 1994; Kawada et al. 1989; Roels et al. 1993; Verschoor et al. 1987).

Early animal studies confirmed that renal damage occurs following inhalation exposure to cadmium. Rabbits developed proteinuria after a 4-month inhalation exposure to cadmium metal dust at 4 mg/m^3 for 3 hours/day, 21 days/month; histologic lesions were found after an additional 3–4 months of exposure (Friberg 1950). Friberg (1950) noted that the degree of proteinuria was not especially pronounced. Most subsequent studies using inhalation exposure have not found proteinuria (Glaser et al. 1986; Kutzman et al. 1986; Prigge 1978a, 1978b), primarily because the levels of exposure and durations of follow-up (e.g., 1–5 mg/m^3 for intermediate exposures; 0.2–2 mg/m^3 for chronic exposures) that produce serious respiratory effects have not been sufficient to produce a critical concentration of cadmium in the kidney.

Dermal Effects. Dermal toxicity does not appear to be a significant effect of inhalation exposure to cadmium. Studies of workers occupationally exposed to cadmium have not reported dermal effects following acute or chronic exposure (Barnhart and Rosenstock 1984; Bonnell 1955; Friberg 1950). No study was located that specifically examined dermal toxicity in humans or animals following inhalation exposure to cadmium.

Ocular Effects. Ocular toxicity does not appear to be a significant effect of inhalation exposure to cadmium. Studies of workers occupationally exposed to cadmium have not reported ocular effects following acute or chronic exposure (Barnhart and Rosenstock 1984; Bonnell 1955; Friberg 1950). No study was located that specifically examined ocular toxicity in humans following inhalation exposure to cadmium.

Rats exposed to a single 2-hour inhalation exposure to about 100 mg Cd/m^3 as cadmium pigments had excessive lacrimation 4 hours after exposure (Rusch et al. 1986), but this was likely due to a direct irritation of the eyes rather than a systemic effect.

Body Weight Effects. No data were found regarding the effects of inhaled cadmium on human body weights.

In animals, cadmium has been shown to significantly reduce body weights. An acute exposure to cadmium oxide fumes at 112 mg Cd/m^3 for 2 hours (Rusch et al. 1986) and cadmium oxide dust at 4.6 mg Cd/m^3 for 3 hours (Buckley and Bassett 1987b) resulted in a significant reduction of body weight in male rats. Cadmium chloride at 6.5 mg Cd/m^3 for 1 hour or 4.5 mg Cd/m^3 for 2 hours produced significant reductions in male rat body weights (Bus et al. 1978; Grose et al. 1987). Cadmium carbonate at 132 mg Cd/m^3 for 2 hours slowed rat body weight gains (Rusch et al. 1986). NOAELs for acute cadmium chloride exposure have been reported at 0.45 mg Cd/m^3 for 2 hours (Grose et al. 1987); 0.17 mg Cd/m^3 for 6 hours/day for 10 days (Klimisch 1993); and 6 mg Cd/m^3 for 2 hours (Palmer et al. 1986). NOAELs for cadmium sulfide and cadmium selenium sulfide were much higher at 99 mg Cd/m^3 for 2 hours and 97 mg Cd/m^3 for 2 hours, respectively (Rusch et al. 1986). The effect of cadmium on body weight gain appears to compound-related, with cadmium chloride the most toxic and cadmium sulfide the least toxic. These compound-related differences are probably related to difference in absorption.

The body weight response also appears to be duration-related; lower NOAELs and LOAELs have been identified for intermediate-duration exposure. Levels of cadmium that significantly reduce rat body weights when administered for an intermediate exposure duration have been reported for cadmium chloride at around 1 mg Cd/m^3 for female and male rats (Baranski and Sitarek 1987; Kutzman et al. 1986), for cadmium chloride at around 0.394 mg Cd/m^3 for pregnant female rats (Prigge 1978a), and for cadmium dusts at 0.1 mg Cd/m^3 for female rats (Prigge 1978a). NOAELs have been reported for intermediate exposures to cadmium chloride at 0.394 mg Cd/m^3 for female nonpregnant rats (Prigge 1978a), 0.33 mg Cd/m^3 for rats (Kutzman et al. 1986), and 0.0508 mg Cd/m^3 for male rats (Takenaka et al. 1983). NOAELs have been reported for intermediate exposures to cadmium oxide dust at 0.16 mg Cd/m^3 for female rats (Baranski and Sitarek 1987) and 0.45 mg Cd/m^3 for male rabbits (Grose et al. 1987); and for cadmium sulfide at 1.034 mg Cd/m^3 for male rats (Glaser et al. 1986). A NOAEL for chronic exposure in rats to cadmium sulfate has been reported as 0.95 mg Cd/m^3 (Oldiges and Glaser 1986).

Other Systemic Effects. Yellow discoloration of the teeth has occasionally been reported in workers occupationally exposed to high levels of cadmium (Friberg 1950; Liu et al. 1985). No data were located to indicate that this was related to any functional impairment.

3.2.1.3 Immunological and Lymphoreticular Effects

There is limited evidence for immunological effects following inhalation exposure to cadmium. The blood of workers exposed to cadmium for 1–14 years had a slight but statistically significant decrease in the generation of reactive oxygen species by leukocytes compared to unexposed controls (Guillard and Lauwerys 1989). The toxicological significance of this effect is unclear.

Karakaya et al. (1994) measured blood and urine concentrations of cadmium, and serum IgG, IgM, and IgA in a group of 37 males employed in zinc/cadmium smelters and a small Cd-electroplating plant. Blood cadmium concentrations were significantly higher in exposed workers compared to controls in both the urine (2.39 versus 0.69 μg/100 mL, $p<0.001$) and the blood (5.55 versus 2.01 μg/g creatinine, $p<0.05$). No differences between the exposed and control serum concentrations of IgG, IgM, and IgA populations were observed. No changes in blood counts of white blood cells (lymphocyte, neutrophil, and eosinophil) were found between exposed and control populations, except for significantly increased monocyte counts. No other studies were located regarding immunological effects in humans following inhalation exposure to cadmium.

Acute inhalation exposure to cadmium chloride in mice at 0.190 mg Cd/m^3 for 2 hours can affect immune function, causing suppression of the primary humoral immune response (Graham et al. 1978). The NOAEL for immunological effects from the study by Graham et al. (1978) was 0.11 mg Cd/m^3. Krzystyniak et al. (1987) reported spleen lymphocyte cytotoxicity at 0.88 mg Cd/m^3 for 1 hour.

At intermediate-duration exposures, Kutzman et al. (1986) observed increased spleen relative weights and lymphoid hyperplasia from inhalation of cadmium chloride aerosols at 1.06 mg Cd/m^3 6 hours/day, 5 days/week for 62 days. Prigge (1978b) also observed increased relative spleen weights in pregnant females at 0.394 mg Cd/m^3 for an exposure of 24 hours/day for 21 days during gestation. Oldiges and Glaser (1986) observed enlarged thoracic lymph nodes in dead animals in a chronic-exposure study with cadmium sulfate at 0.092 mg Cd/m^3 for 22 hours/day, 7 days/week for 413–455 days; and in an intermediate study with cadmium oxide dust at 0.090 mg Cd/m^3 for 22 hours/day, 7 days/week for

218 days. However, other studies have found no effect on natural killer cell activity or viral induction of interferon in mice (Daniels et al. 1987). Evidence concerning the effect of inhalation exposure to cadmium on resistance to infection is conflicting, because the same exposure decreases resistance to bacterial infection while increasing resistance to viral infection (Bouley et al. 1982). The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Neurotoxicity is not generally associated with inhalation exposure to cadmium, although a few studies have specifically looked for neurological effects. Hart et al. (1989b) reported that in a group of 31 men occupationally exposed to cadmium in a refrigerator coil manufacturing plant (average exposure=14.5 years) there was a modest correlation between cadmium exposure and decreased performance on neuropsychologic tests for attention, psychomotor speed, and memory. The limited number of men studied makes it difficult to evaluate the significance of this effect.

Rose et al. (1992) studied the presence and severity of olfactory impairment in workers chronically exposed to cadmium fumes generated during a brazing operation. Detailed occupational history, medical history, and smoking history, and symptoms were collected for 55 workers. Body burden was estimated using urinary cadmium levels, and renal damage was assessed by urinary β2-microglobulin levels. Olfactory test scores from these workers were compared to a reference group of 16 male subjects that were selected according to the following criteria: (1) no history of taste or smell complaints, (2) no history of surgery to the upper respiratory tract, (3) no upper respiratory tract infection within 2 days of testing, and (4) no history of having been tested. The dose of the cadmium oxide fume received by the workers being evaluated in this study was not reported or estimated. For both the exposed workers and the reference group, 38% were smokers. A significant olfactory impairment was observed in the workers compared to the reference group ($p<0.003$). Thirteen percent of the workers were either moderately or severely hyposmic compared to none in the reference group, 44% of the workers were mildly hyposmic compared to 31% of the reference group, and only 44% of workers were normosmic. Although the odor-identification test findings for workers were similar to those of the reference group, butanol detection threshold scores were significantly lower in the worker population ($p<0.005$). The workers with both higher urinary cadmium levels and tubular proteinuria had the most significant olfactory dysfunction, with a selective defect in odor threshold. The results suggest that chronic occupational cadmium exposure sufficient to cause renal damage is also associated with impairment in olfactory

function. Some limitations of the study are that historical exposure to other confounders cannot be ruled out, the classification for nephrotoxicity is based on a single 24-hour urine β2-microglobulin level, and the smoking history of the reference group was unknown. No other human neurological studies from inhaled cadmium were found.

In rats, cadmium carbonate produced tremors from exposure to 132 mg Cd/m^3 for 2 hours, and cadmium fumes produced reduced activity at 112 mg Cd/m^3 for 2 hours (Rusch et al. 1986). Studies on continuous exposure to cadmium for 30 days have shown no neurological effects at 0.105 mg Cd/m^3 for cadmium chloride, 0.098 mg Cd/m^3 for cadmium dusts, or 1.034 mg Cd/m^3 for cadmium sulfide (Glaser et al. 1986). Cadmium chloride had no neurological effects at 0.33 mg Cd/m^3 for 5 days/week, 6 hours/day for a total of 62 daily exposures, but did significantly increase relative brain weight at 1.034 mg Cd/m^3 (Kutzman et al. 1986). No other studies were located regarding neurological effects in adult animals after inhalation exposure to cadmium. Neurological effects in offspring of rats exposed to cadmium by inhalation during gestation are discussed in Section 3.2.1.5. The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

Evidence is insufficient to determine an association between inhalation exposure to cadmium and reproductive effects.

Gennart et al. (1992) studied male reproductive effects of cadmium in 83 occupationally exposed blue-collar Belgian workers in two smelting operations. The workers were exposed to cadmium in dust and fumes. Information was recorded on age, residence, education, occupational and health history, actual and previous occupations, smoking habits, and coffee and alcohol consumption. Fertility parameters included dates of birth of wife and husband, date of marriage, and number of children born alive and their dates of birth. Blood and urine samples were also collected from each worker. Some cadmium workers had been excessively exposed; 25% of them already had signs of kidney dysfunction as evidenced by microproteinuria and/or a serum creatinine level >13 mg/L. No effects were observed on male fertility as evidenced by no significant influence of cadmium on the probability of a live birth. The limitation of this study, as described by the authors, included the fact that the wives were not interviewed and, therefore, factors that could have influenced their reproductive ability were not considered.

Men occupationally exposed to cadmium at levels causing renal damage had no change in testicular endocrine function, as measured by serum levels of testosterone, luteinizing hormone, and follicle-stimulating hormone (Mason 1990).

Noack-Fuller et al. (1993) measured concentrations of cadmium, lead, selenium, and zinc in whole semen and seminal fluid of 22 unexposed men (13 were smokers) to evaluate intra-individual variability and to examine the statistical association between element concentrations and semen characteristics and sperm motion parameters. None of the men had any known occupational exposure to cadmium. Concentrations of cadmium were similar in semen and seminal plasma (0.40±0.23 and 0.34±0.19 μg/L, respectively). Sperm motility ($p<0.02$), linear velocity ($p<0.001$), and curvilinear velocity (CV) ($p<0.002$) were significantly correlated with semen cadmium levels. Intra-individual coefficients of variation for sperm count (CV=46±4%) and sperm concentration (CV=37±6%) showed the highest variability. No positive correlation was found between cadmium concentration in semen and sperm density. The smokers had slightly elevated levels of cadmium. The concentrations of cadmium in semen of these volunteers were very low. Additional studies are needed (preferably with larger sample sizes) to evaluate the robustness of this association between cadmium (at the low levels detected) and sperm motion parameters. Saaranen et al. (1989) measured cadmium, selenium, and zinc in seminal fluid and serum in 64 men, half of whom were smokers. Smokers had significantly higher serum cadmium concentration than nonsmokers. Seminal fluid cadmium was also elevated in smokers, and was higher than serum cadmium in smokers consuming >20 cigarettes daily. Semen quality was measured for volume, sperm density, morphology, motility, and number of immature germ cells. No differences were found in semen quality or fertility between smokers and nonsmokers. There was no significant correlation between seminal fluid cadmium levels and semen quality or fertility.

Xu et al. (1993a) measured trace elements in blood and seminal plasma and their relationship to sperm quality in 221 Singapore men (age range 24–54; mean 34.8) who were undergoing initial screening for infertility. Men with significant past medical history and those who had been occupationally exposed were excluded. Parameters monitored included semen volume and sperm density, motility, morphology, and viability. Graphite furnace atomic absorption was used to determine cadmium concentration in blood and semen. No differences were observed in sperm quality (density, motility, morphology, volume, and viability) of the 221 men compared to a cohort of 38 fertility proven men (wives had recently conceived). Cadmium levels in blood did have a significant inverse relationship with sperm density ($r=-0.15$, $p<0.05$) in oligospermic men (sperm density <20 million/mL), but not in normospermic men. There was a significant reduction in sperm count in men with blood cadmium of >1.5 μg/L. Also, there was a weak

negative correlation between defective sperm and concentration of cadmium in semen ($r=-0.21$, $p<0.05$). The volume of semen was inversely proportional to the cadmium concentration in semen ($r=-0.29$, $p<0.05$). These findings suggest that cadmium may have an effect on the male reproductive system. Limitations of the study include lack of control for potential confounding factors such as the lower levels of zinc in seminal plasma, and the validity of using infertile men as the study group (i.e., again because of confounding factors that may be affecting both cadmium levels and sperm levels).

A postmortem study of men occupationally exposed to cadmium who died from emphysema found high levels of cadmium in their testes, but no histologic lesions other than those attributable to terminal illness (Smith et al. 1960)

Russian women occupationally exposed to cadmium concentrations up to 35 mg/m^3 had no irregularities in their menstrual cycles (Tsvetkova 1970). Fertility and other indices of reproductive function were not measured. No studies were located that showed reproductive effects in women following inhalation exposure to cadmium.

In rats, exposure to cadmium oxide dusts at 1 mg Cd/m^3 for 5 hours/day, 5 days/week for 20 weeks, increased the duration of the estrous cycle (Baranski and Sitarek 1987). Male and female rats exposed to cadmium concentrations of 1.06 mg/m^3 as cadmium chloride for 6 hours/day, 5 days/week for 62 days and subsequently mated with unexposed controls showed no loss in reproductive success measured by viable embryos and preimplantation losses, but males did have an increased relative testes weight (Kutzman et al. 1986). Similarly, no alterations in fertility in female rats exposed to 0.16 mg Cd/m^3 as cadmium oxide for 5 months prior to mating with unexposed males and during the mating and gestation periods (Baranski 1984). Tsvetkova (1970) studied rats exposed to cadmium sulfate aerosols at 2.8 mg Cd/m^3 before and during pregnancy. A lengthening of the estrous cycle was observed 2 months after the start of exposure in one-half of the exposed animals. By the fourth month, diestrus was 6.2 days in the exposed group compared to 1.2 days in controls. An increased in estrous cycle length was also observed in rats exposed to 0.88 mg Cd/m^3 as cadmium oxide for 13 weeks (NTP 1995); this study also reported a significant decrease in spermatid counts in males exposed to the same cadmium concentration. No other studies were found on reproductive effects in animals. The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

Russian women occupationally exposed to cadmium at concentrations ranging from 0.02 to 35 mg/m^3 had offspring with decreased birth weights compared to unexposed controls, but without congenital malformations (Tsvetkova 1970). No association was found between birth weights of offspring and length of maternal cadmium exposure. Moreover, no control was made for parity, maternal weight, gestational age, or other factors known to influence birth weight (Tsvetkova 1970). A nonsignificant decrease in birth weight was found in offspring of women with some occupational exposure to cadmium in France; however, no adverse effects were documented in these newborns (Huel et al. 1984). Huel et al. (1984) used hair samples to estimate exposure, and this method is limited without controls to distinguish between exogenous and endogenous sources. No other studies were located regarding developmental effects in humans after inhalation exposure to cadmium.

In utero exposure to cadmium results in significant decreases in pup viability, fetal body weight, pup body weight gain, delays in ossification, and impaired performance on neurobehavioral tests. Decreases in pup viability (percentage of pups born alive that survived until postnatal day 4) were observed in the offspring of rats exposed to 0.16 mg Cd/m^3 as cadmium oxide for 5 months prior to mating and during mating and gestation day 1–20 (Baranski 1984). Decreases in fetal body weight were observed in the offspring of rats exposed to ≥0.581 mg Cd/m^3 as cadmium chloride (Prigge 1978b) or cadmium oxide (NTP 1995) and mice exposed ≥0.4 mg Cd/m^3 as cadmium oxide (NTP 1995); maternal toxicity (decreased body weight gain and/or hypoactivity and dyspnea) were also observed at these exposure levels. Although Baranski (1984) did not find significant alterations in birth weight, a decrease in pup body weight gain was observed in the offspring of rats exposed to 0.16 mg Cd/m^3 as cadmium oxide. Delays in skeletal ossification have also been observed in the offspring of rats and mice exposed to 1.7 mg Cd/m^3 as cadmium oxide (NTP 1995); although Baranski (1985) also reported a delay in ossification in the offspring of rats, it is unclear whether the effect was observed at 0.02 mg Cd/m^3, 0.16 mg Cd/m^3, or both.

Baranski (1984, 1985) evaluated the potential of cadmium to induce neurobehavioral effects in the offspring of rats exposed to 0.02 or 0.16 mg Cd/m^3 as cadmium oxide for 5 months prior to mating, during mating and gestation day 1–20; the studies reported similar effects and it is unclear whether the papers are reporting the results from separate experiments. The neurobehavioral alterations included decreased exploratory motor activity and avoidance acquisition in 3 month old male and female offspring, respectively, exposed to 0.02 mg Cd/m^3. At 0.16 mg Cd/m^3, decreased avoidance acquisition in 3 month

old female offspring, exploratory motor activity in 3 month old male and female offspring, ambulations in open field test in 5 month old male offspring, and spontaneous mobility in male offspring and prolongation of latency in negative geotaxis test.

3.2.1.7 Cancer

The relationship between occupational exposure to cadmium and increased risk of cancer (particularly lung and prostate cancer) has been explored in a number of occupational exposure studies. The results of these studies are conflicting and the carcinogenicity of cadmium has not been unequivocally established. Overall, the results provide suggestive evidence of an increased risk of lung cancer in humans following prolonged inhalation exposure to cadmium. Initial studies indicated an elevation in prostate cancer among men occupationally exposed to cadmium (Kipling and Waterhouse 1967; Kjellström et al. 1979; Lemen et al. 1976), but subsequent investigations found either no increases in prostate cancer or increases that were not statistically significant (Elinder et al. 1985c; Kazantzis et al. 1988; Sorahan 1987; Sorahan and Esmen 2004; Thun et al. 1985). Based on an analysis of the mortality data from a 5-year update of the cohort from 17 plants in England and a review of the other epidemiological evidence, Kazantzis et al. (1992) concluded that cadmium does not appear to act as a prostatic carcinogen.

Significant increases in mortality from lung cancer have been reported in workers employed at a U.S. cadmium recovery facility (Stayner et al. 1992a; Thun et al. 1985), nickel-cadmium battery facilities in England (Sorahan 1987) and Sweden (Järup et al. 1998a), and in a cohort of workers at cadmium processing facilities and/or smelters (Ades and Kazantzis 1988; Kazantzis et al. 1988). However, no clear relationships between level and duration of cadmium exposure and lung cancer risk have been established and many of these studies did not account for confounding exposure to other carcinogenic metals (particularly arsenic and nickel) and cigarette smoking.

The possible association between occupational exposure to cadmium and lung cancer was investigated in several studies of a cohort of workers employed at a U.S. cadmium recovery facility. The cohort was initially examined by Lemen et al. (1976) who found a significant increase in deaths from malignant neoplasms of the respiratory tract among hourly workers employed for at least 2 years between 1940 and 1969. A re-examination of the cohort (deaths through 1978) also found statistically significant standardized mortality rates (SMRs) for malignant neoplasms in the respiratory tract (Thun et al. 1985). To adjust for possible arsenic exposure (between 1918 and 1925, the facility functioned as an arsenic smelter), workers were divided based on year of hire. Mortality from lung cancer was significantly

elevated in workers hired prior to 1926 and among workers hired after 1926 with 2 or more years of employment. Dividing the workers into three exposure groups based on estimated cumulative exposure resulted in a significant dose-related trend for lung cancer deaths; in the highest exposure group (cumulative exposures >8 years-mg/m^3), a 2- to 8-fold increase in the risk of lung cancer deaths was observed (Thun et al. 1985). A subsequent analysis of these data (workers followed through 1985) used comparisons of rates with the cohort rather than the U.S. population (Stayner et al. 1992a). Lung cancer mortality was significantly increased among non-Hispanic whites, among workers with the highest cumulative exposure (>2,291 days-mg/m^3), and among workers with the longest time since first exposure (>20 years). Lamm et al. (1992, 1994) used nearly the same data set for the U.S. cohort as Stayner et al. (1992a) in a nested case-control analysis that used the period of hire as a surrogate for arsenic exposure. Based on this analysis as a means to control for the confounding factor of arsenic exposure, Lamm et al. (1992, 1994) reported no residual association of lung cancer with cadmium. They also reported that cases were eight times more likely to have been cigarette smokers than were controls. Lamm et al. (1992, 1994) conclude that arsenic exposure and cigarette smoking were the major determinants of lung cancer risk, not cadmium exposure.

The reasons for these conflicting conclusions based on the same cohort data are unclear. Doll (1992) suggested some possible reasons including: (1) that the total number of cases was small (n=25) and that only 21 of these cases were included in both studies (i.e., each study included some cases that were not included in the other study); (2) that Stayner et al. (1992a) used national rather than regional mortality rates; (3) that the Lamm et al. (1992, 1994) control series was overmatched, although the matching by date of hire was necessary to control for arsenic exposure; and (4) that there are some concerns about the validity (i.e., biological relevance) of the dose-response-models used by Stayner et al. (1992a). In a response to Doll (1992), Stayner et al. (1993) reported that use of regional mortality rates would increase rather than decrease support for their conclusion, and that the nested case-control analysis of Lamm et al. (1992) used overmatched controls. Stayner et al. (1993) provided additional analyses including the use of the Armitage-Doll multistage model to support the conclusion of an increased risk of cancer from cadmium exposure. Sorahan and Lancashire (1994) subsequently raised concerns about inconsistencies and inaccuracies in the NIOSH job history data used in these studies on the U.S. cohort. Sorahan and Lancashire (1997) then conducted further analyses, based on detailed job histories extracted from time sheet records, to better resolve the potential confounding affects of arsenic. Poisson regression was used to investigate risks of mortality from lung cancer in relation to four concentrations of accumulative exposure to cadmium (<400, 400–999, 1,000–1,999, and >2,000 mg-days/m^3). After adjustment for age attained, year of hire, and Hispanic ethnicity; Sorahan and Lancashire (1997) report a significant positive

trend ($p<0.05$) between cumulative exposure to cadmium and risks of mortality from lung cancer. However, when the exposure to cadmium was evaluated with or without concurrent exposure to arsenic, a significant trend for lung cancer was only found for exposure to cadmium received in the presence of arsenic trioxide. Since there were only 21 deaths from lung cancer, Sorahan and Lancashire (1997) state that it is impossible to determine which of the following three hypotheses is the correct one: (1) cadmium oxide in the presence of arsenic trioxide is a human lung carcinogen, (2) cadmium oxide and arsenic trioxide are human lung carcinogens and cadmium sulphate and cadmium sulphide are not (i.e., cadmium sulphate and cadmium sulphide were the main cadmium compounds of exposure when arsenic was not present), or (3) arsenic trioxide is a human carcinogen and the three cadmium compounds are not carcinogenic.

The carcinogenicity of cadmium has also been examined in European alloy, battery, smelter, and process workers. A study of workers at two copper-cadmium alloy facilities in the United Kingdom found no significant increase in lung cancer mortality (Sorahan et al. 1995). Dividing the workers into groups based on cumulative cadmium exposure or time since first exposure did not result in significant increases in lung cancer deaths in the alloy workers. An initial study of workers at nickel-cadmium battery manufacturing facilities in the United Kingdom found a significant increase in cancer of the respiratory tract (Sorahan and Waterhouse 1983). A subsequent study (Sorahan 1987) found an increase in lung cancer deaths among workers with the highest exposure first employed between 1926 and 1946; no association was found in workers employed after 1946. Another study of nickel-cadmium battery workers in the United Kingdom did not find significant increases in lung cancer deaths (Sorahan and Esmen 2004), although a significant increase in pharyngeal cancer deaths was observed. A study of nickel cadmium battery workers in Sweden found an increase in lung cancer mortality, but the increase was not statistically significant (Elinder et al. 1985c). An update of this study, which includes additional workers, found a significant increase in lung cancer deaths (Järup et al. 1998a). However, there was no exposure-response relationship between cumulative exposure to cadmium (or nickel) and the risk of lung cancer. A significant increase in lung cancer mortality was observed in workers employed at a zinc-lead-cadmium smelter (Ades and Kazantzis 1988). However, no relationship between cumulative cadmium exposure and lung cancer deaths was found, suggesting that cadmium was not the causative agent. Another study of workers in 19 facilities in the United Kingdom that process cadmium did not find a statistically significant increase in lung cancer deaths (Armstrong and Kazantzis 1983). An update of this study found a significant increase in lung cancer deaths (Kazantzis et al. 1988). However, >60% of the lung cancer deaths were workers at the zinc-lead-cadmium smelter examined by Ades and Kazantzis (1988).

Studies in rats provide strong evidence of the lung carcinogenic potential of chronically inhaled cadmium. Oldiges et al. (1989) reported a clear dose response increase in lung tumors in male and female rats from an 18-month continuous exposure to either cadmium chloride, cadmium oxide dusts, cadmium oxide fume, cadmium sulfate, or cadmium sulfide. In the cadmium chloride study at 30 $\mu g/m^3$, the observation period in the males had to be shortened to 30 months (rather than 31) because of mortality in excess of 75%. No lung tumors were observed in control rats after 31 months of observation. A high incidence of nodules and tumors was seen in 30 $\mu g/m^3$ exposures to cadmium chloride in both males and females. Results showed lung nodules in 18 of 20 males and 15 of 18 females and primary lung tumors in 15 of 20 males and 13 of 18 females. Tumor incidence as bronchioalveolar adenomas, adenocarcinomas, squamous cell carcinomas, or combined epidermoid carcinoma and adenocarcinoma were 2, 12, 0, and 1 for males; and 4, 7, 0, and 2 for females, respectively. Increased lung tumors in males and females were also observed with chronic exposures to cadmium oxide dust or fume at 30 $\mu g/m^3$, to cadmium sulfate at 90 $\mu g/m^3$, and to cadmium sulfide at 90 $\mu g/m^3$ (Oldiges et al. 1989). Cadmium sulfate produced by photolysis of cadmium sulfide under the experimental conditions may have contributed to some of the response observed with cadmium sulfide (Konig et al. 1992).

Takenaka et al. (1983) also demonstrated cadmium carcinogenicity in male rats exposed to cadmium chloride aerosols at 0.0134, 0.0257, and 0.0508 mg Cd/m^3 for 18 months. The exposure produced a dose-related increase in lung epidermoid carcinomas, adenocarcinomas, and mucoepidermoid carcinomas starting at 20 months. No other type of tumor was observed to increase with increasing dose.

In a protocol similar to the studies by Oldiges et al. (1989), Heinrich et al. (1989) did not observe an increase in lung tumors in male or female Syrian golden hamsters from chronic inhalation exposure to either cadmium oxide dust or fumes, cadmium chloride, cadmium sulfate, or cadmium sulfide. In female mice, lung tumor incidence increased at all dose levels, but incidence in the controls was also high, and the cadmium-induced increases were not statistically significant. Lung tumors in the cadmium-treated mice also did not increase in a dose-responsive manner except for a weak increase from exposure to the cadmium oxide fumes (Heinrich et al. 1989).

The available data provide inconclusive evidence on the potential of cadmium to induce lung cancer in humans. The strongest evidence comes from early studies of workers at a U.S. cadmium recovery facility (Stayner et al. 1992a; Thun et al. 1985), but later examinations of this cohort did not find conclusive evidence (Lamm et al. 1992, 1994; Sorahan and Lancashire 1997). The inconsistent results may be due to

the small number of lung cancer cases and adjustments for possible early exposure to arsenic. Some studies of European cadmium workers have found significant increases in lung cancer (Ades and Kazantzis 1988; Järup et al. 1998a; Kazantzis et al. 1988; Sorahan 1987; Sorahan and Waterhouse 1983), but lung cancer deaths were not significantly associated with cumulative cadmium levels or duration of exposure and the investigators concluded that the effects may not have been related to cadmium exposure. Based on an early 1990s analysis of the available human and animal data, IARC (1993) classified cadmium as carcinogenic to humans (Group 1), based on sufficient evidence for carcinogenicity in both human and animal studies. Similarly, the DHHS (NTP 2005) classified cadmium and certain cadmium compounds as substances known to be human carcinogens. EPA classified cadmium as a probable human carcinogen by inhalation (Group B1), based on limited evidence of an increase in lung cancer in humans and sufficient evidence of lung cancer in rats (IRIS 2008). EPA estimated an inhalation unit risk (the risk corresponding to lifetime exposure to 1 $\mu g/m^3$) of $1.8x10^{-3}$ based on the Thun et al. (1985) study (IRIS 2008). A range of concentrations that correspond to upper bound lifetime excess risks of 10^{-4}–10^{-7} is shown in Figure 3-1.

3.2.2 Oral Exposure

Information on health effects of oral exposure to cadmium in humans is derived mainly from studies of residents living in cadmium-polluted areas. Cadmium exposure in these populations is often estimated by blood or urinary cadmium levels (see Section 3.8.1). Exposure in these cases occurs primarily through the diet, but smokers in these cohorts are also exposed to cadmium by inhalation. When evaluating oral exposure studies, smoking was treated as a confounding variable rather than an exposure route because of the large number of toxic compounds (in addition to cadmium) present in cigarette smoke, and because the primary concern is effects attributable to cadmium. Cadmium is more readily found in the free ionic form in water, while in food, the cadmium ion generally exists in a complex with a variety of ligands, including proteins such as metallothionein (Crews et al. 1989; Groten et al. 1990; Nordberg et al. 1986). Experimental studies in animals have generally used soluble salts of cadmium (such as cadmium chloride) for food, drinking water, and gavage exposures. The toxicological properties of the cadmium ion do not appear to depend on the counter ion, although absorption may be significantly affected by protein complexes (see Section 3.3.1.2).

3.2.2.1 Death

Intentional ingestion of cadmium has been used as a means of suicide, causing death due to massive fluid loss, edema, and widespread organ destruction (Buckler et al. 1986; Wisniewska-Knypl et al. 1971). The

doses ingested in two known fatal cases were estimated to be 25 mg Cd/kg from cadmium iodide (Wisniewska-Knypl et al. 1971) and 1,840 mg Cd/kg from cadmium chloride (Buckler et al. 1986). Time to death after cadmium iodide ingestion was 7 days (Wisniewska-Knypl et al. 1971) and 33 hours after ingestion of the cadmium chloride (Buckler et al. 1986).

In rats and mice, acute oral LD_{50} (lethal dose, 50% kill) values for cadmium range from about 100 to 300 mg/kg (Baer and Benson 1987; Basinger et al. 1988; Kostial et al. 1978; Kotsonis and Klaassen 1978; Shimizu and Morita 1990). The lowest dose causing death (2 of 20 animals) was 15.3 mg/kg in Sprague-Dawley rats (Borzelleca et al. 1989). Very young animals have lower LD_{50} values than adult animals (Kostial et al. 1978, 1989); this effect may be related to the greater fractional absorption of ingested cadmium in the immature organism (see Section 3.4.1.2). For example, the LD_{50} values in rats aged 2, 3, 6, 18, and 54 week are 47, 240, 216, 170, and 109 mg/kg, respectively (Kostial et al. 1978).

Deaths related to cadmium exposure have been reported in only two of the intermediate exposure studies found. In a study in Wistar rats exposed to cadmium chloride by gavage at 40 mg Cd/kg/day, 5 days/week for up to 14 weeks; 4 of 13 female Wistar rats died by 8 weeks (Baranski and Sitarek 1987). In mice, Blakley (1986) studied the effect of cadmium on chemical- and viral-induced tumor production. Female albino Swiss mice (8 weeks old, n=41) were administered cadmium chloride in the drinking water for 280 days at doses of 0, 5, 10, or 50 ppm. These mice have a high incidence of spontaneous lymphocytic leukemia of thymic origin. A significant 33% increase ($p=0.0228$, chi-square analysis) in deaths from virally induced leukemia was observed from exposure to 1.9 or 9.5 mg Cd/kg/day. The deaths were attributed to cadmium-impaired immunosurveillance mechanisms that control expression of the murine lymphocytic leukemia virus.

The LOAEL values from each reliable study for lethality in each species and duration category are recorded in Table 3-6 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-6 and plotted in Figure 3-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to cadmium.

Table 3-6 Levels of Significant Exposure to Cadmium - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (NS)	once (G)				29 (LD50 at 8 days; 2 weeks old)	Kostial et al. 1978 CdCl2	
						129 F (LD50 at 8 days; 6 weeks old)		
						104 F (LD50 at 8 days; 18 weeks old)		
2	Rat (Sprague-Dawley)	once (GW)				225 M (LD50 at 14 days)	Kotsonis and Klaassen 1977 CdCl2	
3	Rat (Sprague-Dawley)	2 wk (W)				42 M (7/9 died within 2 weeks)	Kotsonis and Klaassen 1978 CdCl2	
4	Rat (Sprague-Dawley)	once (GW)				327 M (LD50 at 24 hours; fed rats)	Shimizu and Morita 1990 CdCl2	
						107 M (LD50 at 24 hours; fasted rats)		
5	Mouse (Swiss-Webster)	once (GW)				95.5 M (LD50 at 96 hours)	Baer and Benson 1987 CdCl2	
6	Mouse (ICR)	once (GW)				112 M (5/10 died within 8 days)	Basinger et al. 1988 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
7	Rat (Wistar)	10 d Gd 7-16 once (GW)	Bd Wt	2 F	12 F (14% decreased maternal body weight)		Baranski 1985 CdCl2	
8	Rat (Sprague-Dawley)	10 d 1 x/d (GW)	Hemato	31.3 M 138 F	65.6 M (increased hemoglobin, hematocrit, erythrocytes)		Borzelleca et al. 1989 CdCl2	
			Hepatic	65.6 M		138 M (focal necrosis of hepatocytes)		
			Renal			15.3 (focal necrosis of tubular epithelium)		
			Bd Wt		15.3 M (18% decreased body weight)	31.3 M (23% decreased body weight)		
				31.3 F	65.6 F (18% decreased body weight)			
9	Rat (Sprague-Dawley)	10 d (W)	Hepatic	13.9			Borzelleca et al. 1989 CdCl2	
			Renal	13.9				
			Bd Wt	13.9				
				1.1 M	7.8 M (14% decreased body weight)	11.2 M (25% decreased body weight)		

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
10	Rat (Sprague-Dawley)	once (GW)	Cardio	150 M			Kotsonis and Klaassen 1977 CdCl2	
			Hemato	150 M				
			Hepatic	150 M				
			Renal		25 M (50% decrease in urine flow for first 2 days)			
			Bd Wt	100	150 M (initial 12% decreased body weight)			
11	Rat (Long- Evans)	Gd 6-15 (GW)	Gastro	6.13 F		61.32 F (intestinal necrosis, hemorrhage, ulcers)	Machemer and Lorke 1981 CdCl2	
			Bd Wt	1.84 F	6.13 F (27% decrease in body weight gain during treatment)	18.39 F (persistent 50% decrease in maternal body weight gain)		
12	Rat (Long- Evans)	Gd 6-15 (F)	Gastro	12.5 F			Machemer and Lorke 1981 CdCl2	
			Bd Wt	3.5 F	12.5 F (transient 19% decrease in maternal body weight gain during treatment)			
13	Rat (Wistar)	12 d (W)	Hemato		12 M (anemia)		Sakata et al. 1988 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Rat (Sprague-Dawley)	once (GW)	Hepatic		75 M (focal degeneration and necrosis of parenchymal cells)		Shimizu and Morita 1990 CdCl2	
15	Mouse (CBA/Bom)	once (GW)	Gastro	15.7 M	30.4 M (gastritis and enteritis)	88.8 M (severe gastric necrosis)	Andersen et al. 1988 CdCl2	
			Hepatic	15.7 M	30.4 M (fatty infiltration of liver cells, occasional hepatocellular necrosis)			
			Renal	59.6		88.8 M (tubular necrosis and casts)		
16	Mouse (ICR)	once (GW)	Gastro			112 M (glandular stomach epithelial necrosis)	Basinger et al. 1988 CdCl2	
			Hepatic			112 M (extensive hepatocellular coagulative necrosis)		
			Renal	112 M				
Immuno/ Lymphoret								
17	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		65.6 M 31.3 F	65.6 F (increased leukocyte counts)		Borzelleca et al. 1989 CdCl2	
Neurological								
18	Rat (Sprague-Dawley)	once (GW)		25 M	50 M (decreased motor activity)		Kotsonis and Klaassen 1977 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
19	Rat (Wistar)	once (GW)		50 M		100 M (testicular necrosis)	Bomhard et al. 1987 CdCl2	
20	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		138 F		65.6 M (testicular atrophy and loss of spermatogenic elements)	Borzelleca et al. 1989 CdCl2	
21	Rat (Sprague-Dawley)	once (GW)		25 M			Dixon et al. 1976 CdCl2	
22	Rat (Sprague-Dawley)	once (GW)		50 M		100 M (testicular necrosis; decreased spermatogenesis; decreased number females producing pups)	Kotsonis and Klaassen 1977 CdCl2	
23	Mouse (CBM/ Bom)	once (GW)		30.3 M		59.6 M (testicular necrosis)	Andersen et al. 1988 CdCl2	
Developmental								
24	Rat (Wistar)	10 d Gd 7-16 once (GW)			2 F (delayed ossification of the sternum and ribs)	40 (fused lower limbs, absent limbs, decreased number of live fetuses, increased number of resorptions)	Baranski 1985 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
25	Rat (Long- Evans)	1 x/d Gd 6-15 (GW)		6.13		18.39	(increased number of fetuses with malformations)	Machemer and Lorke 1981 CdCl2	
26	Rat (Long- Evans)	10 d Gd 6-15 (F)		12.5				Machemer and Lorke 1981 CdCl2	
INTERMEDIATE EXPOSURE									
Death									
27	Rat (Wistar)	14 wk 5 d/wk (GW)				40 F	(4/13 died by week 8; 7/13 by week 14)	Baranski and Sitarek 1987 CdCl2	
28	Mouse (Swiss)	280 d (W)				1.9 F	(24/41 died by 280 days)	Blakley 1986 CdCl2	
Systemic									
29	Monkey (Rhesus)	10 wk (F)	Bd Wt	5 M				Chopra et al. 1984 CdCl2	
30	Rat (Wistar)	14 wk 5 d/wk (GW)	Bd Wt	4 F		40 F	(29% decreased maternal body weight)	Baranski and Sitarek 1987 CdCl2	
31	Rat (Sprague-Dawley)	2-10 mo (W)	Renal			30 F	(B2-microglobulinuria)	Bernard et al. 1988a CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
32	Rat (Wistar)	daily 12 mo (W)	Musc/skel	0.2 M	0.5 M (increased lumbar spine deformities, decreased in lumbar spine mineralization, altered bone turnover parameters)		Brzoska and Moniuszko-Jakoniuk 2005a, 2005b CdCl2	
33	Rat (Wistar)	daily 12 mo (W)	Musc/skel		0.2[b] F (decreased bone mineralization, mechanical properties of tibia and femur, and altered bone turnover parameters)		Brzoska and Moniuszko-Jakoniuk 2005d; Brzoska et al. 2005a, 2005c CdCl2	
34	Rat (Wistar)	daily 12 mo (W)	Musc/skel		0.3 F (alterations in bone mineral content and density and mechanical properties of lumbar vertebral and femoral bones)		Brzoska et al. 2004b, 2005b CdCl2	
35	Rat (Sprague-Dawley)	4 or 7 mo (W)	Renal			15.2 F (albuminuria, transferrinuria, B2-microglobulinuria)	Cardenas et al. 1992a CdCl2	
36	Rat (Sprague-Dawley)	190 d (W)	Cardio		1.4 M (20% increase in diastolic blood pressure)		Carmignanti and Boscolo 1984 Cd acetate	
			Bd Wt	2.8 M				

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
37	Rat (Sprague-Dawley)	12 wk (W)	Hepatic		8.58 M (necrosis of central lobules)		Cha 1987 CdCl2	
			Renal		8.58 M (necrosis of proximal tubular epithelial cells and cloudy swelling)			
			Bd Wt		8.58 M (23% decreased in body weight gain; 9% total body weight decrease)			
38	Rat (Wistar)	170 d (W)	Bd Wt	56 F			Cifone et al. 1989a CdCl2	
39	Rat (Sprague-Dawley)	3 mo (W)	Hemato		2 (anemia)		Decker et al. 1958 CdCl2	
			Bd Wt		2 F (15% decreased body weight)	2 M (25% decreased body weight)		
40	Rat (Wistar)	4-60 wk (W)	Renal		1.18 (vesiculation of proximal tubules)		Gatta et al. 1989 CdCl2	
41	Rat	4 wk (F)	Hemato		2.5 M (anemia)		Groten et al. 1990 CdCl2	
			Renal	2.5 M				

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
42	Rat (Wistar)	120 d (W)	Hemato		3.6 M (anemia)		Itokawa et al. 1974 CdCl2	
			Renal		3.6 M (tubular necrosis and casts, glomerular adhesions)			
43	Rat (Sprague-Dawley)	7 wk (F)	Cardio			2.5 M (congested myocardium, separation of muscle fibers)	Jamall et al. 1989 CdCl2	
			Renal	2.5 M				
			Bd Wt	2.5 M				
44	Rat (Wistar)	90 d (W)	Hemato		8 F (anemia)		Kawamura et al. 1978 CdCl2	
			Musc/skel		8 F (osteomalacia changes)			
			Renal		8 F (decreased renal clearance)			
			Endocr	8 F				
			Bd Wt		8 F (12% decreased body weight)			
45	Rat (Sprague-Dawley)	22 d Gd 0-21 (W)	Hemato		1.5 F (slight anemia)		Kelman et al. 1978 form not specified	
			Musc/skel	3.8 F				

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
46	Rat (Sprague-Dawley)	24 wk (W)	Resp	8 M			Kotsonis and Klaassen 1978 CdCl2	
			Cardio	8 M				
			Gastro	8 M				
			Hemato	8 M				
			Musc/skel	8 M				
			Hepatic	8 M				
			Renal	1.2 M		3.1 M (proteinuria, slight focal tubular necrosis)		
			Endocr	8 M				
			Bd Wt	8 M				
47	Rat (Wistar)	3 mo (F)	Cardio	3			Loeser and Lorke 1977a CdCl2	
			Hemato	3				
			Hepatic	3				
			Renal	3				
			Endocr	3				
			Bd Wt	3				
48	Rat (Sprague-Dawley)	6-16 wk (W)	Resp			2.4 (lung fibrosis)	Miller et al. 1974b CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
49	Rat (Sprague-Dawley)	6 wk 5 d/wk 1 x/d (GW)	Hepatic	0.25 M			Muller et al. 1988 Cd acetate	
			Bd Wt	0.25 M				
50	Rat (NS)	4 wk (W)	Hemato		0.8 F (decreased hematocrit and hemoglobin)		Ogoshi et al. 1989 CdCl2	
			Musc/skel		0.8 F (decreased bone strength in young animals)			
			Bd Wt	0.8	1.6 F (10% decreased body weight gain)			
51	Rat (NS)	200 d (W)	Resp	0.6 M	1.2 M (reduced static compliance, lung lesions)		Petering et al. 1979 CdCl2	
52	Rat (Sprague-Dawley)	120 d (W)	Resp			3.62 M (emphysema)	Petering et al. 1979 CdCl2	
53	Rat (Sprague-Dawley)	111 d (90 d prior to Gd 1-21) (W)	Hemato	5.23 F			Petering et al. 1979 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
54	Rat (Sprague-Dawley)	Gd 1- Ld 1 (F)	Bd Wt			19.7 F (77-80% decreased maternal weight gain)	Pond and Walker 1975 CdCl2	
55	Rat (Wistar)	90 d (W)	Resp	16 F			Prigge 1978a CdCl2	
			Hemato		4 F (23% decreased serum iron)			
			Renal	4 F	8 F (35% increase in urine protein)			
			Bd Wt	8 F				
56	Rat (Wistar)	12, 26, 50, or 100 d (W)	Hemato			12 M (iron deficient anemia)	Sakata et al. 1988 CdCl2	
57	Rat (Sprague-Dawley)	7-12 mo (W)	Renal	13 F			Viau et al. 1984 CdCl2	
			Bd Wt	13 F				
58	Mouse (CF1)	252 d (F)	Musc/skel		0.65 F (decrease in femur calcium content in mice undergoing repeated pregnancy/lactation periods)		Bhattacharyya et al. 1988a, 1988b	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
59	Mouse (C57BL/6)	3-11 wk (W)	Bd Wt			12.5 M (63% decreased body weight gain)	Malave and de Ruffino 1984 CdCl2	
60	Mouse (B6C3F1)	16-46 wk (W)	Bd Wt			232 M (45% decreased body weight)	Waalkes et al. 1993 CdCl2	
61	Mouse (QS/CH)	Gd 1-19 (W)	Hemato	4.8 F	9.6 F (anemia)		Webster 1978 CdCl2	
			Bd Wt	4.8 F	9.6 F (14% decrease in maternal weight gain)			
62	Dog (Beagle)	3 mo (F)	Cardio	0.75			Loeser and Lorke 1977b CdCl2	
			Hemato	0.75				
			Hepatic	0.75				
			Renal	0.75				
			Bd Wt	0.75				
63	Rabbit (New Zealand)	9 mo (W)	Cardio		1.6 M (increased aortic resistance, reduced contractility)		Boscolo and Carmignani 1986 CdCl2	
			Renal	1.6 M				
			Bd Wt	1.6 M				

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
64	Rabbit (New Zealand and Belgian Giant)	200 d (W)	Hemato		14.9 M (anemia)		Stowe et al. 1972 CdCl2	
			Hepatic		14.9 M (focal hepatic fibrosis and biliary hyperplasia)			
			Renal			14.9 M (tubular necrosis, glomerular and interstitial fibrosis)		
			Endocr	14.9				
			Bd Wt		14.9 M (11% decrease in body weight)			
Immuno/ Lymphoret								
65	Monkey (Rhesus)	10 wk (F)			5 M (increased cell-mediated immune response)		Chopra et al. 1984 CdCl2	
66	Rat (Wistar)	170 d (W)			28 F (biphasic decrease then increase in natural killer cell activity)		Cifone et al. 1989a CdCl2	
67	Rat (Wistar)	3 mo (F)		3			Loeser and Lorke 1977a CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
68	Mouse (BDF1)	3 wk (W)		1.4 F	2.8 F (decreased humoral immune response)		Blakley 1985 CdCl2	
69	Mouse (Swiss)	280 d (W)			1.9 F (greater susceptibility to murine lymphocytic leukemia virus)		Blakley 1986 CdCl2	
70	Mouse (BDF1)	26 d (W)		12.5 F			Blakley 1988 CdCl2	
71	Mouse (Swiss-Webster)	30 d (W)		22 M			Bouley et al. 1984 Cd acetate	
72	Mouse (Swiss-Webster)	10 wk (W)		57 M			Exon et al. 1986 CdCl2, Cd acetate, or Cd sulfate	
73	Mouse (C57BL/6N)	12-16 wk (W)		19 F	57 F (reduced number of SRBC-activated, plaque-forming cells)		Krzystyniak et al. 1987 CdCl2	
74	Mouse (C57BL/6)	3-11 wk (W)			12.5 M (decreased suppressor cell activity)		Malave and de Ruffino 1984 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
75	Mouse (ICR)	10 wk (W)			0.75 M (induction of anti-nuclear autoantibodies)		Ohsawa et al. 1988 CdCl2	
Neurological								
76	Rat (Wistar)	14 wk 5 d/wk (GW)		4 F	40 F (aggressive behavior)		Baranski and Sitarek 1987 CdCl2	
77	Rat (Sprague-Dawley)	3-24 wk (W)		1.2 M	3.1 M (decreased motor activity)		Kotsonis and Klaassen 1978 CdCl2	
78	Rat (Sprague-Dawley)	55 d (F)		1 M	5 M (increased passive avoidance)		Nation et al. 1984 CdCl2	
79	Rat (Sprague-Dawley)	60 d (F)			9 M (decreased motor activity)		Nation et al. 1990 CdCl2	
Reproductive								
80	Rat (Wistar)	14 wk 5 d/wk (GW)		4 F	40 F (increased duration of estrus cycle)		Baranski and Sitarek 1987 CdCl2	
81	Rat (Wistar)	11 wk 5 d/wk (GW)		4 F			Baranski et al. 1983 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
82	Rat (Wistar)	10 wk 1 x/wk (GW)		5 M			Bomhard et al. 1987 CdCl2	Histopathology only.
83	Rat (Sprague-Dawley)	12 wk (W)			8.58 M (necrosis and atrophy of seminiferous tubule epithelium)		Cha 1987 CdCl2	
84	Rat	4 wk (F)		2.5 M			Groten et al. 1990 CdCl2	Histopathology only.
85	Rat (albino)	4 wk (W)		4.8 F			Kostial et al. 1993 CdCl2	
86	Rat (Sprague-Dawley)	24 wk (W)		8 M			Kotsonis and Klaassen 1978 CdCl2	
87	Rat (Wistar)	3 mo (F)		3			Loeser and Lorke 1977a CdCl2	Histopathology only.
88	Rat (NS)	120 d (W)			12.6 M (decreased sperm count and motility, seminiferous tubular damage)		Saxena et al. 1989 Cd acetate	
89	Rat (Long- Evans)	70-80 d (W)		4.64 M			Zenick et al. 1982 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
90	Dog (Beagle)	3 mo (F)		0.75			Loeser and Lorke 1977b CdCl2	
Developmental								
91	Rat (Wistar)	21 d Gd 1-21 (W)			0.706 (delayed development of sensory motor coordination reflexes; increased motor activity)		Ali et al. 1986 Cd acetate	
92	Rat (Wistar)	20 d Gd 1-20 (W)			9.6 (decreased fetal body weight [12%], body length [7%], and hematocrit [13%])		Baranski 1987 CdCl2	Decreased maternal water and food consumption.
93	Rat (Wistar)	11 wk 5 d/wk 1 x/d (GW)			0.04 (pup behavioral alterations)		Baranski et al. 1983 CdCl2	
94	Rat (Wistar)	11-94 d Gd 5-15 Ld 2-28 1 x/d ppd 1-56 5 d/wk 1 x/d (GW)			14 M (decreased horizontal ambulation and rearing activity; increased frequency of somatosensory, visual, and auditory electrocorticogram; prolonged latency and duration of evoked potentials)		Desi et al. 1998 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
95	Rat (Druckery)	Gd 0- Ld 21 (W)			5 (decreased pup brain and body weight at 7, 14, and 21 days)		Gupta et al 1993 Cd acetate	
96	Rat (Sprague-Dawley)	Gd 0-20 (W)			1.5 (12% decreased hematocrit)		Kelman et al. 1978 form not specified	
97	Rat (albino)	10 wk (W)			4.8 (12% decrease in pup body weight at weaning)		Kostial et al. 1993 CdCl2	
98	Rat (Wistar)	approx. 49 d 4 wk old through mating 7 d/wk 1 x/d (GO)			7 M (alterations in ambulation behavior; prolonged latency and duration of somatosensory evoked potentials)		Nagymajtenyi et al. 1997 CdCl2	
99	Rat (Sprague-Dawley)	60 d prior to Gd 1 or Gd 1-21 (W)			2.61 (decreased live birth weight)		Petering et al. 1979 CdCl2	
100	Rat (Sprague-Dawley)	Gd 1- Ld 1 (F)			19.7 (13-19% decreased pup birth weight)		Pond and Walker 1975 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
101	Rat (ITRC)	21 d Gd 0-20 (W)		21			Saxena et al. 1986 Cd acetate	
102	Rat (Sprague-Dawley)	15 d Gd 6-20 (W)		0.63	4.7 (8% decreased fetal body weight)		Sorell and Graziano 1990 CdCl2	
103	Rat (Sprague-Dawley)	9 wk 1 x/d (GW)		1	10 (delayed ossification, decreased body weight)		Sutou et al. 1980 form not specified	
104	Mouse (QS/CH)	19 d Gd 1-19 (W)			2.4 (decreased fetal body weight; severe anemia)		Webster 1978 CdCl2	
CHRONIC EXPOSURE								
Systemic								
105	Human		Renal	0.0003[c] F			Buchet et al. 1990; Jarup et al. 2000; Suwazono et al. 2006 form not specified	
106	Human	NS lifetime (F)	Renal	0.0021			Nogawa et al. 1989 form not specified	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
107	Human	>25 yr lifetime (environ)	Hemato	0.0078			Shiwen et al. 1990 Cd metal	
			Musc/skel	0.0078				
			Renal		0.0078 (increased excretion of low molecular weight proteins)			
108	Monkey (Rhesus)	9 yr (F)	Cardio	0.53 M	1.71 M (increased blood pressure during the first 1.5 years)		Akahori et al. 1994 CdCl2	
109	Rat (Sprague-Dawley)	18 mo (W)	Renal			13 F (loss of glomerular polyanion charge barrier, proteinuria)	Bernard et al. 1992 CdCl2	
110	Rat (Wistar)	72 wk (F)	Renal	3.5	17.5 (8 to 9-fold increase in LDH and GST starting at 13 weeks)		Bomhard et al. 1984 CdCl2	
111	Rat (Wistar)	daily 24 mo (W)	Musc/skel		0.08 F (decreases in bone mineral content and density of lumbar spine, altered bone turnover paramters, increases in deformed and fractured vertebral bodies)		Brzoska and Moniuszko-Jakoniuk 2004a, 2004b CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
112	Rat (Sprague-Dawley)	12 mo (W)	Hemato	0.79			Decker et al. 1958 CdCl2	
			Bd Wt	0.79				
113	Rat (Sprague-Dawley)	M: 92 wk F: 84 wk (W)	Cardio	4.01			Fingerle et al. 1982 CdCl2	
			Renal	0.8	1.51 (proximal tubule lesions)			
			Bd Wt	4.01				
114	Rat (Sprague-Dawley)	6, 12, or 18 mo (W)	Cardio	2.281 F			Mangler et al 1988 CdCl2	
			Hepatic	2.281 F				
			Renal		2.337 F (cloudy swelling of tubular cells)			
			Bd Wt	2.281 F				
115	Rat (Wistar)	31 mo (W)	Musc/skel			3.6 (muscle atrophy)	Sato et al. 1978 CdCl2	
			Bd Wt	3.6				
116	Rat (Wistar)	2 yr (W)	Renal	2.6 M			Shaikh et al. 1989 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
117	Rat (Wistar)	77 wk (F)	Bd Wt	3.5 M	7 M (10% decreased body weight)		Waalkes and Rehm 1992 CdCl2	
118	Mouse (CF1)	18 months (F)	Musc/skel	0.65 F	6.5 F (loss of bone calcium in ovariectomized mice)		Bhattacharyya et al. 1988c	
119	Mouse (CBA/H)	12 mo (W)	Hemato			57 (anemia and bone marrow hypoplasia)	Hays and Margaretten 1985 form not specified	
			Renal	57				
			Bd Wt			57 (21% decreased terminal body weight)		
Neurological								
120	Rat (Wistar)	31 mo (W)				3.6 (peripheral neuropathy)	Sato et al. 1978 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Cancer								
121	Rat (Wistar)	77 wk (F)				3.5 M (CEL: increased rates of prostatic adenomas)	Waalkes and Rehm 1992 CdCl2	

a The number corresponds to entries in Figure 3-2.

b The intermediate-duration oral MRL of 0.0005 mg Cd/kg/day (0.5 ug Cd/kg/day) was calculated using a benchmark dose analysis. The BMDL1std of 0.05 mg Cd/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability).

c The chronic-duration oral MRL of 0.0001 mg Cd/kg/day (0.1 ug Cd/kg/day) was calculated from the 95% lower confidence limit of the urinary cadmium level associated with a 10% increased risk of low molecular weight proteinuria (0.5 ug/g creatinine) estimated from a meta-analysis of select environmental exposure studies. An intake which would result in this urinary cadmium concentration was estimated using a modification of the Nordberg-Kjellström pharmacokinetic model (see Appendix A for details on the meta-analysis and extrapolation to dietary intake). This dose of 0.3 ug/kg/day was divided by an uncertainty factor of 3 for human variability.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; GST = glutathione-S-transferase; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LDH = Lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; ppd = post-parturition day; Resp = respiratory; SRBC = sheep red blood cells; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Cadmium - Oral

Acute (≤14 days)

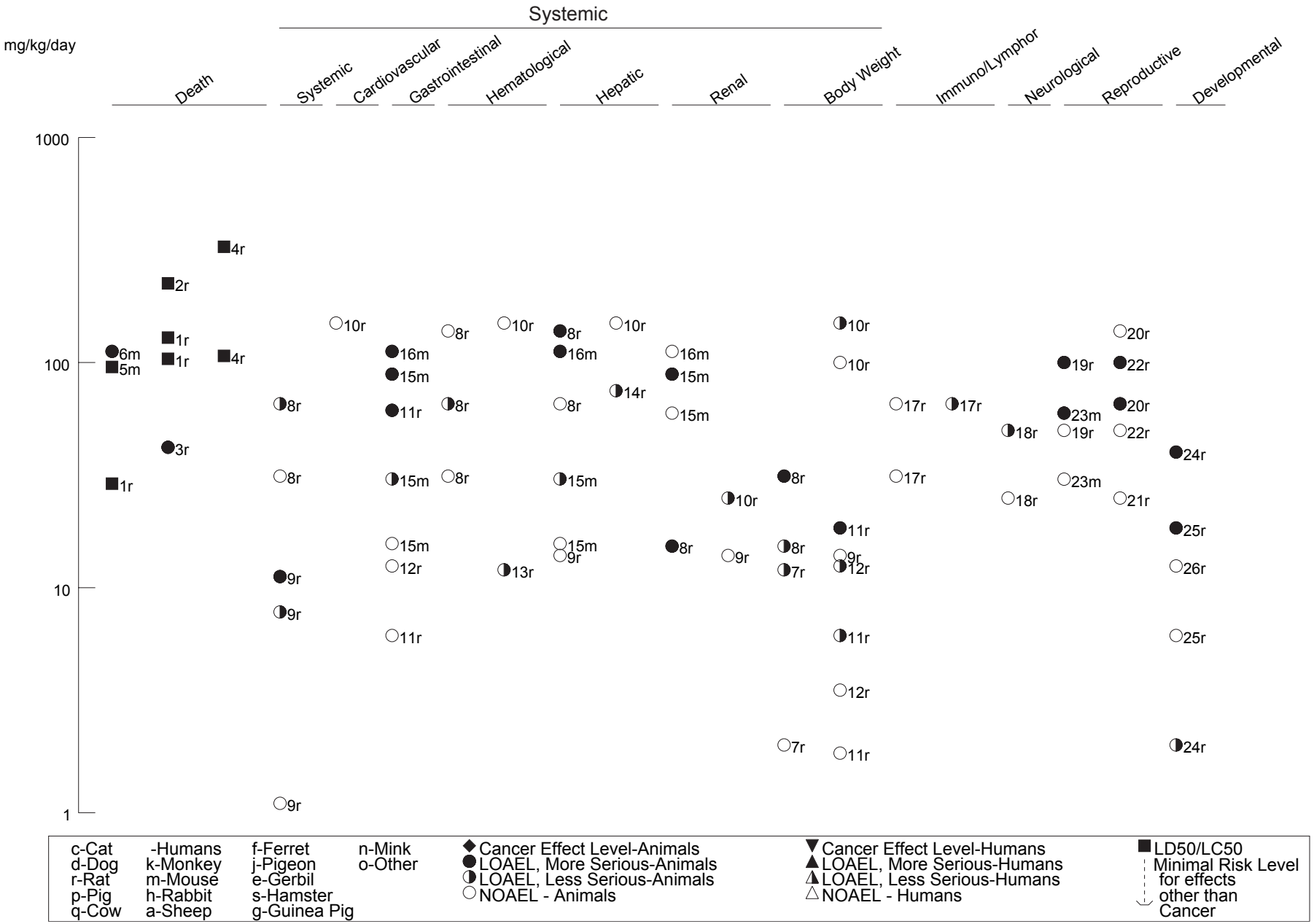


Figure 3-2 Levels of Significant Exposure to Cadmium - Oral *(Continued)*

Intermediate (15-364 days)

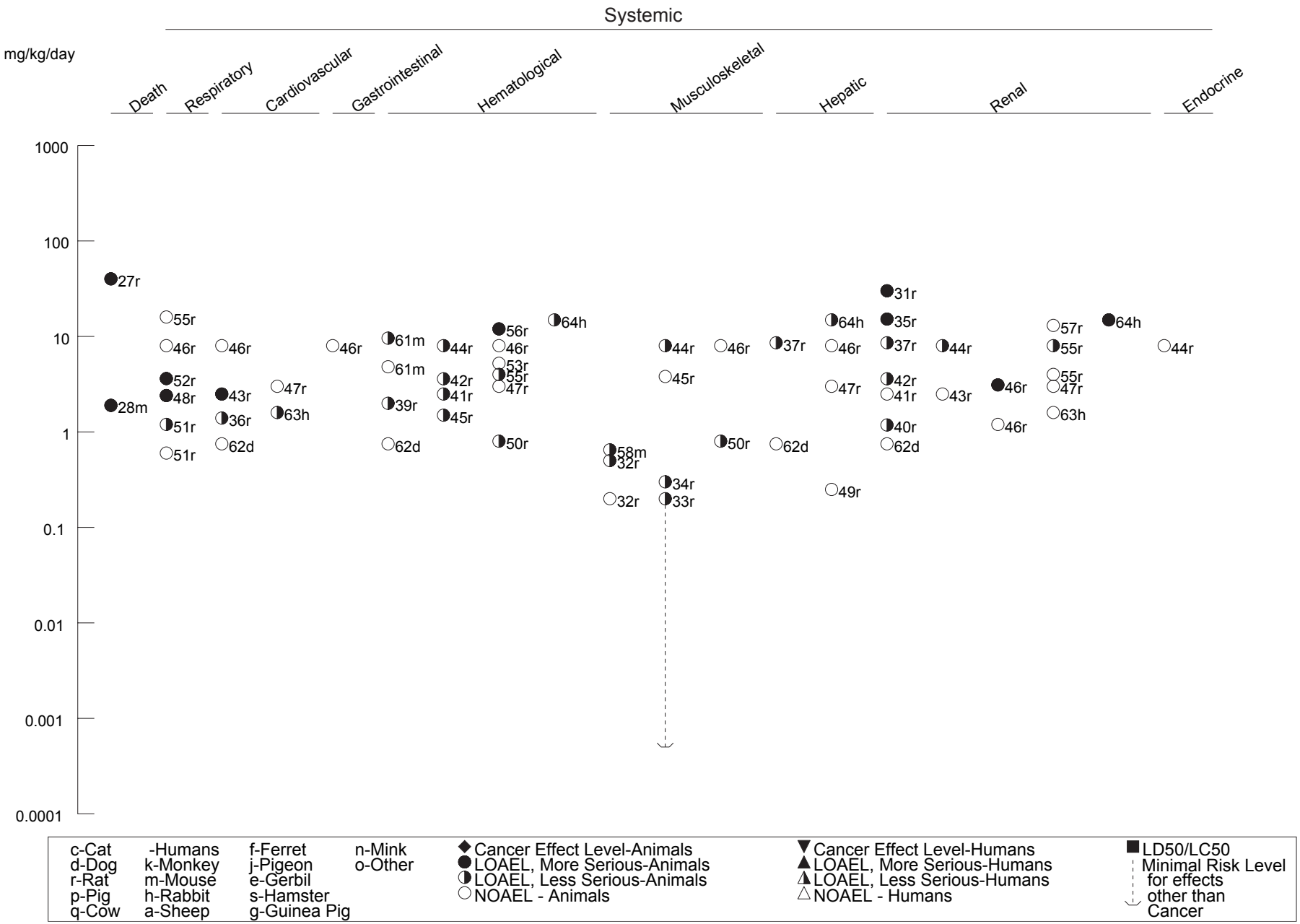


Figure 3-2 Levels of Significant Exposure to Cadmium - Oral *(Continued)*

Intermediate (15-364 days)

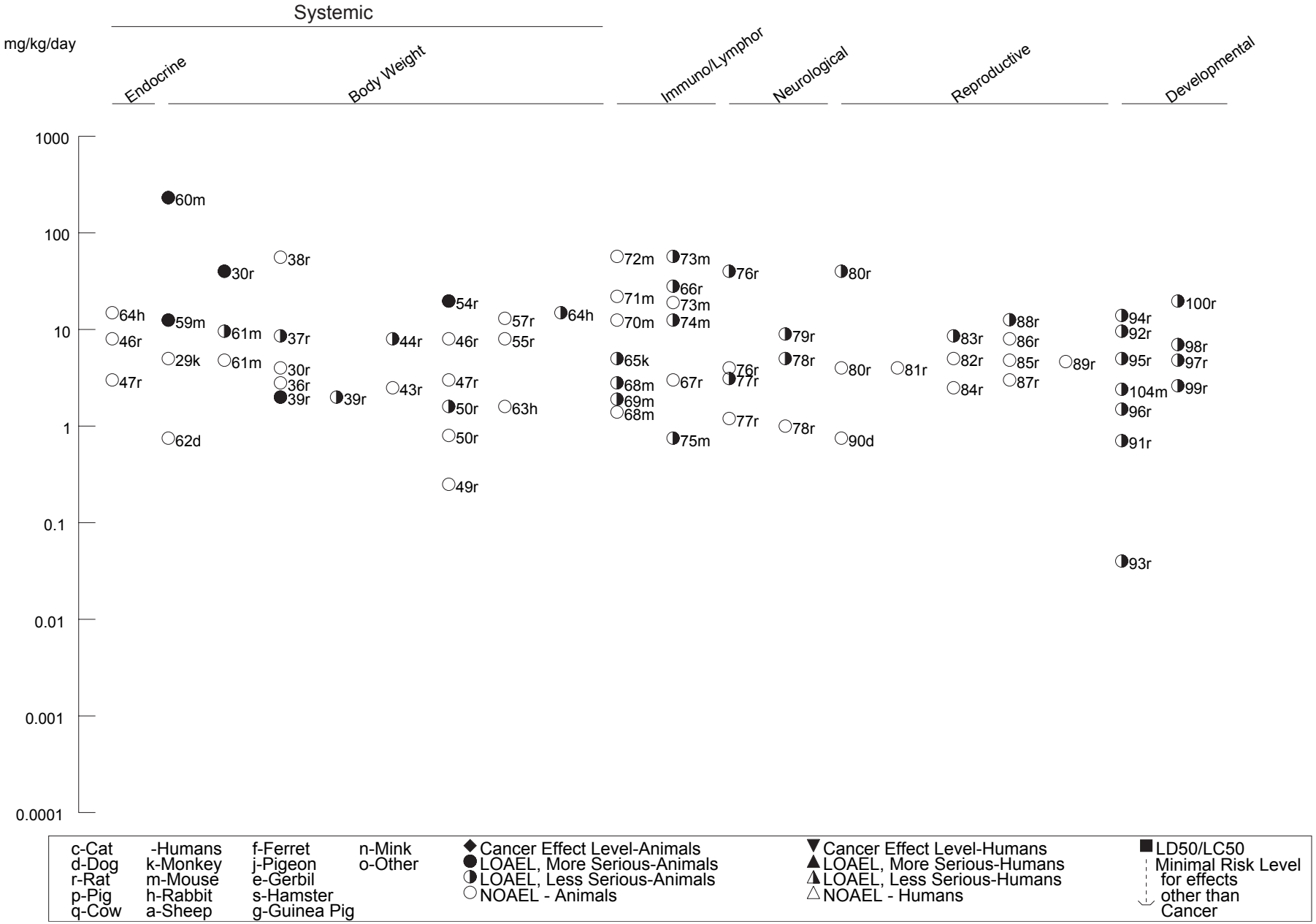


Figure 3-2 Levels of Significant Exposure to Cadmium - Oral *(Continued)*

Intermediate (15-364 days)

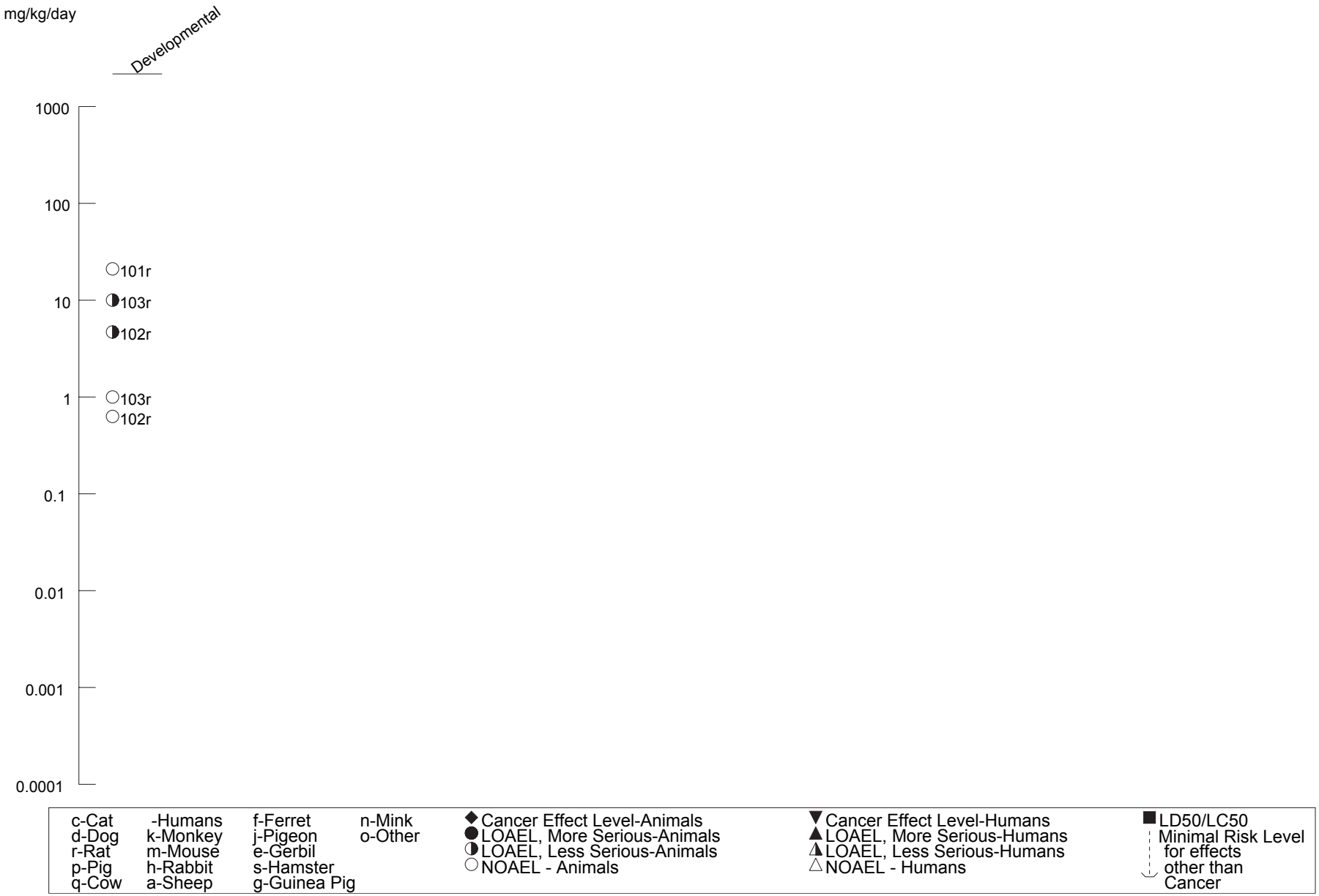
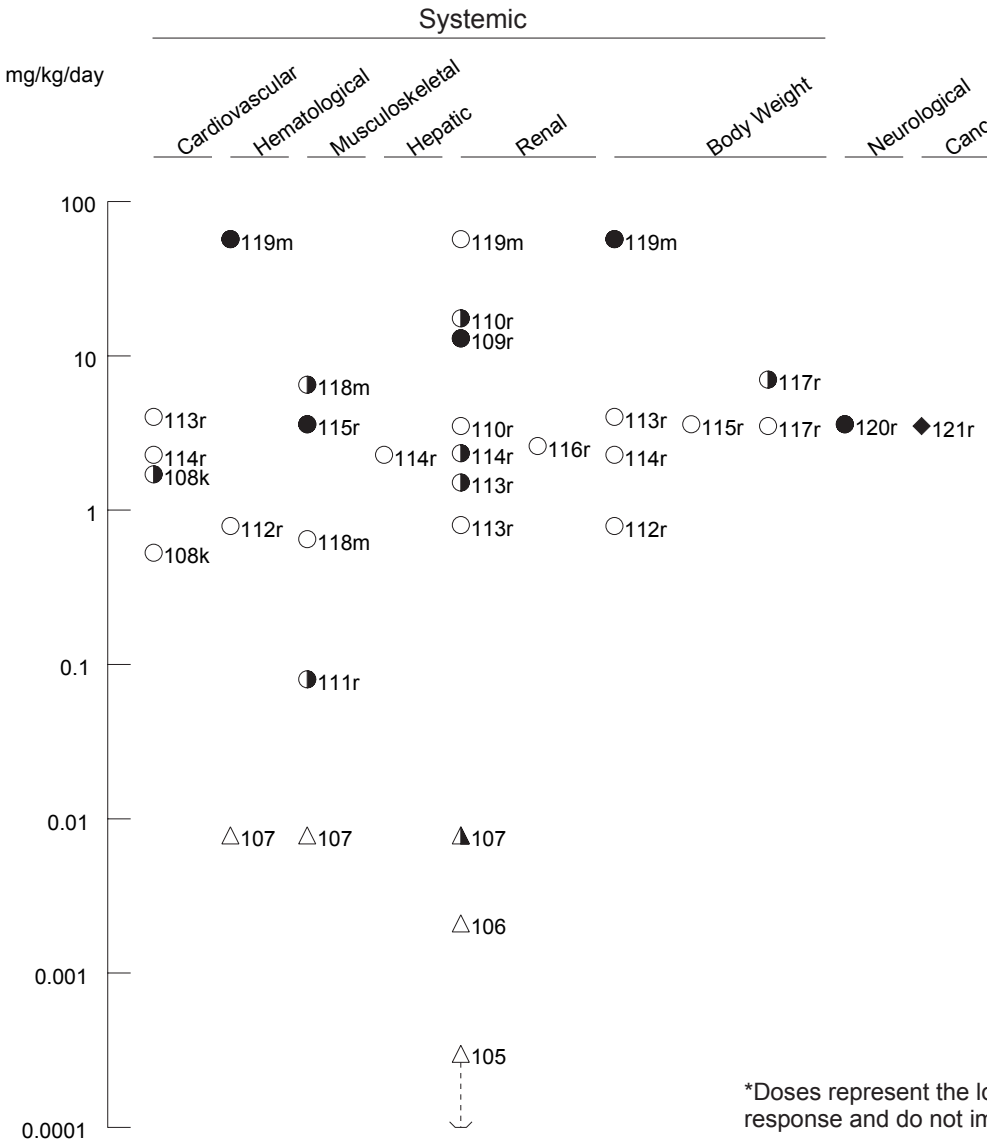


Figure 3-2 Levels of Significant Exposure to Cadmium - Oral *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◮ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

No respiratory effects were observed in Rhesus monkeys from 4 mg/kg/day of cadmium chloride in the food for 9 years (Masaoka et al. 1994). Intermediate-duration oral exposure caused fibrosis in lungs of rats exposed to 2.4 mg Cd/kg/day of cadmium chloride after 6 and 16 weeks (Miller et al. 1974b). Petering et al. (1979) observed a reduced static compliance and lung lesions (not specified) in male Sprague-Dawley rats exposed to 1.2 mg Cd/kg/day in water for 200 days. Zinc-deficient rats were more susceptible to lung lesions from exposure to cadmium chloride (Petering et al. 1979). Rats exposed to cadmium chloride at 3.62 mg Cd/kg/day in the drinking water for 120 days developed emphysema (Petering et al. 1979). No histopathologic lesions of the lung were found in male Sprague-Dawley rats after 24 weeks of exposure to cadmium in drinking water at a maximum dose of 8 mg/kg/day (Kotsonis and Klaassen 1978). Lung weight was unchanged in Wistar rats after 90 days of exposure in drinking water at 16 mg/kg/day (Prigge 1978a). Effects on the lung following oral exposure to cadmium may be secondary to systemic changes (Petering et al. 1979); however, the studies that found lung effects did not examine other systemic effects in the exposed rats (Miller et al. 1974b; Petering et al. 1979).

Cardiovascular Effects. Studies regarding cardiovascular effects in humans after oral exposure to cadmium have primarily investigated relationships between blood pressure and biomarkers of cadmium exposure such as cadmium levels in blood, urine, or other tissues. Smoking is an important confounding factor, because of the higher blood, urine, and tissue cadmium levels of smokers (see Section 3.4) and the known cardiovascular toxicity of cigarette smoking. Case-control and cohort epidemiologic studies that adequately control for smoking have typically found no association between body cadmium levels (primarily reflecting dietary exposure) and hypertension (Beevers et al. 1980; Cummins et al. 1980; Ewers et al. 1985; Lazebnik et al. 1989; Shiwen et al. 1990); however, some studies have found positive correlations (Geiger et al. 1989; Tulley and Lehmann 1982) or negative correlations (Kagamimori et al. 1986; Staessen et al. 1984). Similar conflicting findings have been reported in studies analyzing death rates from cardiovascular disease among populations with dietary cadmium exposure (Inskip et al. 1982; Shigematsu 1984). Disorders of the cardiac conduction system, lower blood pressure, and decreased frequency of cardiac ischemic changes were found among elderly women with past high dietary exposure to cadmium (Kagamimori et al. 1986). Rhythmic disturbances, including ventricular fibrillation, were seen in an individual who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

Several studies conducting cross-sectional analysis on data from the National Health and Nutrition Examination Surveys (NHANES), investigated associations between blood and urine cadmium levels and

cardiovascular effects (Everett and Frithsen 2008; Navas-Acien et al. 2005; Tellez-Plaza et al. 2008). Urinary cadmium levels were found to be strongly associated with peripheral arterial disease (PAD, defined as blood pressure ankle brachial index <0.0 in at least one leg) in analysis conducted on 728 participants (at least 40 years of age) in the NHANES 1999–2000 study (Navas-Acien et al. 2005). Individuals with PAD had a 36% higher mean urine cadmium level than individuals without PAD. This study also found that individuals with PAD had 49% higher urinary tungsten levels and urinary antimony levels exceeding 0.1 μg/L. Another study found a modest increase in systolic or diastolic blood pressure associated with increasing blood cadmium levels (geometric mean blood cadmium levels among all participants was 0.4 μg/L); no associations with blood pressure and urinary cadmium levels were found (Tellez-Plaza et al. 2008). The association between blood cadmium levels and blood pressure was stronger in participants who never smoked than in former smokers or current smokers. There were no associations between hypertension and cadmium levels in blood or urine. In the third study, analysis on 4,912 participants (45–79 years old) in the NHANES 1988–1994 survey found a significant association between urinary cadmium levels and myocardial infarction in women, but not men (Everett and Frithsen 2008). After adjusting for numerous risk factors including smoking, race, and family history, a significant increase in the risk of myocardial infarction was observed in women with urinary cadmium levels of ≥0.88 μg/g creatinine.

A single gavage dose of 150 mg/kg cadmium in male Sprague-Dawley rats had no effect on blood pressure (Kotsonis and Klaassen 1977). Oral exposure of rats, rabbits, and monkeys to cadmium over intermediate and chronic durations has been found to increase blood pressure in some studies (Akahori et al. 1994; Boscolo and Carmignani 1986; Carmignani and Boscolo 1984; Kopp et al. 1982; Perry et al. 1989; Tomera and Harakal 1988), but not in others (Fingerle et al. 1982; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a, 1977b; Mangler et al. 1988; Wills et al. 1981). In general, studies showing an effect on blood pressure have had control groups with lower blood pressure than studies showing no effect, and observed increases in blood pressure are generally small. At least in rats, the effect on blood pressure appears to be biphasic, reaching a maximum effect (an increase of 12–14 mm Hg in average systolic pressure) at intakes of 0.07 mg/kg/day, but decreasing to normal or even below normal at intakes 10–100 times higher (Kopp et al. 1982). Enlarged and arteriosclerotic hearts have been found in rats orally exposed to 0.35 mg Cd/kg/day for 3 years (Schroeder et al. 1965) or to 2.79 mg Cd/kg/day for 100 days (Wilson et al. 1941), but this effect is likely to be secondary to cadmium-induced anemia (Wilson et al. 1941). Histopathologic lesions of heart tissues (congestion, separation of muscle fibers) and decreased activity of antioxidant enzymes, but no increase in peroxidation, were found among rats given 2.5 mg/kg/day of cadmium in the diet for 7 weeks (Jamall et al. 1989).

Gastrointestinal Effects. Numerous human and animal studies indicate that oral exposure to cadmium in high concentrations causes severe irritation to the gastrointestinal epithelium (Andersen et al. 1988; Frant and Kleeman 1941). Common symptoms in humans following ingestion of food or beverages containing high concentrations of cadmium include nausea, vomiting, salivation, abdominal pain, cramps, and diarrhea (Baker and Hafner 1961; Buckler et al. 1986; Frant and Kleeman 1941; Nordberg et al. 1973; Shipman 1986; Wisniewska-Knypl et al. 1971). Although exact doses have not been measured, gastrointestinal symptoms have been caused in children by 16 mg/L cadmium in soft drinks (Nordberg et al. 1973) and 13 mg/L cadmium in popsicles (Frant and Kleeman 1941). Assuming an intake of 0.15 L (Nordberg et al. 1973) and a body weight of 35 kg, the emetic dose is 0.07 mg/kg. Although few studies have specifically examined gastrointestinal effects of longer-term cadmium exposure, no surveys of environmentally exposed populations have reported gastrointestinal symptoms (Morgan and Simms 1988; Roels et al. 1981a; Shigematsu 1984).

In rats and mice, histopathologic lesions (e.g., severe necrosis, hemorrhage, ulcers) in the gastrointestinal epithelium have been observed after high (>30 mg/kg/day) acute-duration oral cadmium exposure by gavage (Andersen et al. 1988; Basinger et al. 1988; Machemer and Lorke 1981), but not after lower levels (8 mg/kg/day in drinking water) for 24 weeks (Kotsonis and Klaassen 1978).

Hematological Effects. Oral cadmium exposure reduces gastrointestinal uptake of iron, which can result in anemia if dietary intake of iron is low. Anemia has been found in some instances among humans with chronic dietary exposure to cadmium (Kagamimori et al. 1986), but other studies have found no significant relationship between dietary cadmium exposure and anemia in humans (Roels et al. 1981a; Shiwen et al. 1990). Hypoproteinemia and hypoalbuminemia were reported in a male who ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

A number of studies have demonstrated that oral exposure to cadmium frequently produces anemia in laboratory animals, and that additional iron prevents anemia (Decker et al. 1958; Groten et al. 1990; Hays and Margaretten 1985; Itokawa et al. 1974; Kawamura et al. 1978; Kelman et al. 1978; Kozlowska et al. 1993; Ogoshi et al. 1989; Pleasants et al. 1992, 1993; Pond and Walker 1972; Sakata et al. 1988; Sorell and Graziano 1990; Stowe et al. 1972; Watanabe et al. 1986; Webster 1978; Wilson et al. 1941). Decreases in serum iron have also been reported (Prigge 1978a). Borzelleca et al. (1989) reported slight but statistically significant increases in hemoglobin, hematocrit, and erythrocytes in male rats at 65.6 mg/kg/day once a day for 10 days, but no change in females. Male Sprague-Dawley rats receiving a

single gavage dose of 150 mg/kg cadmium showed no signs of anemia 14 days later (Kotsonis and Klaassen 1977), but anemia was produced in male Wistar rats after 12 days of drinking-water exposure to 12 mg/kg/day (Sakata et al. 1988). Most intermediate-duration exposure studies in rats have shown evidence of anemia at doses of 2–14 mg/kg day (Decker et al. 1958; Groten et al. 1990; Itokawa et al. 1974; Kawamura et al. 1978; Pleasants et al. 1993; Pond and Walker 1972; Sakata et al. 1988; Wilson et al. 1941). However, some intermediate-duration studies have found no change in hemoglobin (Kotsonis and Klaassen 1978; Loeser and Lorke 1977a; Petering et al. 1979; Prigge 1978a) in rats treated at similar doses. Anemia has also been seen in intermediate-duration studies in mice (Webster 1978) and rabbits (Stowe et al. 1972), but not in dogs (Loeser and Lorke 1977b). The result in dogs may be due to the relatively low dose of cadmium (0.75 mg/kg/day) used in this study. Hematological effects following chronic-duration oral exposure to cadmium are less well characterized. In monkeys maintained on 4 mg/kg/day cadmium in food, pale feces, and clinical signs of anemia occurred after 90 weeks, but the anemia was associated with a decreased food intake rather than an increase in reticulocytes (Masaoka et al. 1994). Anemia was not present in rats exposed via drinking water for 12 months to the relatively low dose of 0.79 mg/kg/day (Decker et al. 1958). The number of erythroid progenitor cells in bone marrow is decreased in mice exposed to 57 mg/kg/day of cadmium in drinking water for 12 months (Hays and Margaretten 1985), but is increased in rats exposed to 12 mg/kg/day of cadmium in drinking water for up to 100 days (Sakata et al. 1988). Thus, the question remains open whether factors, in addition to reduced gastrointestinal absorption of iron, such as direct cytotoxicity to marrow or inhibition of heme synthesis may contribute to anemia.

Musculoskeletal Effects. Osteomalacia, osteoporosis, bone fractures, and decreased bone mineral density have been observed in several populations exposed to elevated levels of cadmium in the diet. Bone effects were first reported in residents in the Jinzu River Basin, a cadmium-contaminated area in Japan. The disease termed Itai-Itai or "ouch-ouch" disease most often affected women with several risk factors such as poor nutrition, multiparity, and post-menopausal status (Shigematsu 1984). The disease was characterized by multiple fractures of the long bones, osteomalacia, and osteoporosis in combination with proteinuria (Järup et al. 1998b; Nordberg et al. 1997). Other Japanese populations with dietary cadmium exposure have also been found to have elevated osteoporosis and osteomalacia in both men and women (Kido et al. 1989b). Kagamimori et al. (1986) evaluated elderly Japanese women with heavy cadmium exposure from ingesting polluted drinking water, rice, and fish during World Wars I and II; and continued low-grade cadmium exposure from agricultural produce. Of 56 cases of Itai-Itai disease, 26 were accompanied by osteomalacia and 26 were without osteomalacia. Another study found that the degree of loss of bone density is correlated with urinary excretion of β2-microglobulin, an index of renal

injury (see Section 3.5.2) (Kido et al. 1990a). The bone effects observed in Itai-Itai disease and in other studies of Japanese populations exposed to high levels of cadmium in rice are primarily due to kidney damage, which results from a progressive disturbance in renal metabolism of vitamin D to its biologically active form (Nogawa et al. 1987, 1990) and an increased urinary excretion of calcium (Buchet et al. 1990). These results suggest that bone changes may be secondary to disruption in kidney of vitamin D metabolism and resulting imbalances in calcium absorption and excretion. A recent study of women living in the Jinzu River basin found that bone turnover, particularly bone formation, was influenced by renal tubular function (Aoshima et al. 2003). However, it is possible that some bone effects are not mediated via the kidney.

Bone effects have also been observed in communities outside of Japan and in populations exposed to low levels of cadmium. In a study of Swedish women environmentally exposed to cadmium, a significant negative relationship between urinary cadmium levels and bone mineral density was observed (Åkesson et al. 2005); the mean urinary cadmium level of the population was 0.52 μg/L. In Swedish residents living in an area with known cadmium pollution from battery manufacturing facilities, significant associations were noted between blood cadmium levels and bone mineral density and between urinary cadmium levels and risk of fractures and osteoporosis. There were significant decreases in bone mineral density in environmentally exposed subjects older than 60 years of age with blood cadmium levels of ≥0.56 μg/L (Alfvén et al. 2002a). Increases in the risk of bone fractures were observed in subjects (approximately 10% of all subjects examined had environmental and occupational exposure to cadmium) older than 50 years of age with urinary cadmium levels >2 μg/g creatinine; no significant associations were found in subjects under 50 years of age (Alfvén et al. 2004). Another study of this population found significant increases in the risk of osteoporosis among men >60 years of age with urinary cadmium levels ≥5 μg/g creatinine; however, an increased risk of osteoporosis was not observed in women (Alfvén et al. 2000). A Belgian study in which residents living near zinc smelters found a 2-fold increase in cadmium exposure (as assessed via urinary cadmium levels) was associated with a decrease in proximal and distal forearm bone density of approximately 0.1 g/cm^2 among post-menopausal women (Staessen et al. 1999). For women with urinary cadmium levels >1 μg/day, the incidence of bone fracture was 13.5 per 1,000 person-years. Another study of a subset of the women living near a zinc smelters (Schutte et al. 2008) provides suggestive evidence that cadmium has a direct osteotoxic effect. Significant associations between urinary cadmium levels and the levels of two pyridinium crosslinks of collagen (urinary levels of hydroxylysylpyridinoline and lysylpyridinoline), proximal forearm bone mineral density, and serum parathyroid hormone levels were found. In almost all of the examined women, urinary levels of retinol binding protein were below the cut-off level of 338 μg/day, suggesting no cadmium-induced effect on

renal tubular function. Similar results have been observed in several studies of residents living in areas of China with moderate or high cadmium pollution levels (Jin et al. 2004b; Nordberg et al. 2002; Wang et al. 2003; Zhu et al. 2004). There were significant increases in the prevalence of low forearm bone mineral density in post-menopausal women with urinary cadmium levels >20 μg/g creatinine and in men, pre-menopausal women, and post-menopausal women with blood cadmium levels >20 μg/L (Nordberg et al. 2002). An increase in bone fractures was observed in males and females over the age of 40 years living in the area of high cadmium exposure (mean urinary cadmium levels in the area were 9.20 and 12.86 μg/g creatinine in the males and females, respectively) (Wang et al. 2003). A significant dose-response relationship between urinary cadmium levels and the prevalence of osteoporosis was observed (Jin et al. 2004b; Wang et al. 2003; Zhu et al. 2004); the Jin et al. (2004b) study found that 23 of the 31 subjects with osteoporosis also exhibited signs of renal dysfunction.

A number of animal studies confirm the findings of the epidemiology data suggesting that the bone is a sensitive target of cadmium toxicity. Decreases in bone mineralization and bone mineral density have been observed in female rats exposed to ≥0.2 mg Cd/kg/day in the lumbar spine, femur, and tibia (Brzóska et al. 2004b, 2005a, 2005b, 2005c) and in male rats exposed to 0.5 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b) for an intermediate duration and in female rats chronically exposed to 0.08 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2004a, 2004b). In the series of studies conducted by Brzóska and associates, the occurrence of osteopenia and osteoporosis was evaluated using data for bone mineral density of the cadmium-exposed rats, control rats, and healthy adult rats. Osteopenia was observed in male rats exposed to 0.5 mg Cd/kg/day for 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b) and in female rats exposed to 0.08 mg Cd/kg/day for 12 or 18 months (Brzóska and Moniuszko-Jakoniuk 2004a, 2004b); osteoporosis was observed in male rats exposed to 4 mg Cd/kg/day for 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b) and in female rats exposed to 0.08 mg Cd/kg/day for 24 months (Brzóska and Moniuszko-Jakoniuk 2004a, 2004b).

The decreases in bone mineralization resulted in altered mechanical properties (e.g., stiffness, load, displacement at load) of the vertebral body, femur, and tibia and increases in the number of animals with deformed or fractured lumbar spinal bone in female rats exposed to ≥0.2 mg Cd/kg/day for an intermediate duration (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005b, 2005a, 2005c; Ogoshi et al. 1989); increases in lumbar spine deformities were also observed in male rats exposed to 0.5 mg Cd/kg/day for 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b) and in female rats exposed to 0.08 mg Cd/kg/day for 24 months (Brzóska and Moniuszko-Jakoniuk 2004a, 2004b).

The studies by Brzóska and associates reported significant alterations in biochemical markers of bone turnover. During the first 6 months of a 1-year study, significant decreases in osteocalcin concentrations were observed in female rats exposed to ≥0.2 mg Cd/kg/day; no alterations were observed during the last 6 months of the study (Brzóska and Moniuszko-Jakoniuk 2005d). Observed changes in alkaline phosphatase levels included decreases in total serum levels in the 4 mg Cd/kg/day group after 6, 9, or 12 months of exposure, decreases in trabecular bone levels at ≥0.2 mg Cd/kg/day after 3, 6, or 9 months of exposure and at 0.5 mg Cd/kg/day at 12 months, decreases in cortical bone levels at 4 mg Cd/kg/day after 3 months of exposure, and increases in trabecular bone and cortical bone alkaline phosphatase at 4 mg Cd/kg/day after 12 months (Brzóska and Moniuszko-Jakoniuk 2005d). Serum C-terminal telopeptides of type I collagen concentration (CTX) was significantly decreased after 3 or 6 months of exposure or increased after 9 or 12 months in rats exposed to ≥0.2 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2005d). As noted by Brzóska and Moniuszko-Jakoniuk (2005d), these alterations in bone turnover markers indicate that cadmium exposure at the stage of intensive skeletal development leads to low bone turnover and induces high bone turnover due to enhanced resorption at the stage of consolidation of bone mass and at skeletal maturity.

Decreased calcium content of bone and increased urinary calcium excretion are common findings in intermediate- and chronic-duration studies in the 0.2–8 mg Cd/kg/day range (Brzóska and Moniuszko-Jakoniuk 2005d; Kawamura et al. 1978; Nogawa et al. 1981b; Pleasants et al. 1992; Watanabe et al. 1986). In contrast, Kotsonis and Klaassen (1978) reported no change in bone calcification after a 24-week exposure via drinking water at 8 mg/kg/day, and Kelman et al. (1978) reported no significant change in stable or radiolabeled calcium in any maternal rat tissues from a 3.8 mg/kg/day in drinking water for 22 days during gestation.

Gender, age, and nutritional state appear to influence cadmium toxicity on bone. In the series of experiments conducted by Brzóska and associates, alterations in bone mineral density and the mechanical strength of the lumbar spine and femur were observed in female rats exposed to ≥0.2 mg Cd/kg/day and in male rats at 0.5 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b, 2005d; Brzoska et al. 2005a, 2005c); no adverse bone effects were observed in males exposed to 0.2 mg Cd/kg/day. In the Ogoshi et al. (1989) study, decreases in the mechanical strength of the femur bone were observed in young rats (21 days of age) exposed to 0.8 mg Cd/kg/day for 4 weeks; however, no alterations in bone strength were observed in adult (24 weeks of age) or elderly (1.5 years of age) rats exposed to cadmium doses as high as 25.6 mg Cd/kg/day for 4 weeks. Adverse effects on bone are exacerbated by a calcium-

deficient diet (Itokawa et al. 1974; Kimura et al. 1974; Larsson and Piscator 1971; Wang and Bhattacharyya 1993; Wang et al. 1994), by ovariectomy (Bhattacharyya et al. 1988c), or by multiple rounds of gestation and lactation (Bhattacharyya et al. 1988b).

Hepatic Effects. Liver damage is not usually associated with oral cadmium exposure, except at very high levels of exposure. In humans, a fatal dose of cadmium can cause pronounced liver damage (Buckler et al. 1986; Wisniewska-Knypl et al. 1971). Nishino et al. (1988) reported increased serum concentrations of the urea-cycle amino acids among individuals exposed to cadmium in the diet, and that these levels reflected liver as well as kidney damage. No cadmium-related alterations in liver biomarkers including serum levels of alkaline phosphatase, alanine aminotransferase, asparate aminotransferase, lactate dehydrogenase, and γ-glutamyl transpeptidase were observed in women living in cadmium non-polluted areas in Japan (Ikeda et al. 1997, 2000). No other studies were located regarding hepatic effects in humans after oral exposure to cadmium.

Hepatic effects have been found in rats, mice, and rabbits after oral cadmium exposure. Acute exposure via gavage at doses of 30–138 mg/kg/day causes liver necrosis in most studies (Andersen et al. 1988; Basinger et al. 1988; Borzelleca et al. 1989; Shimizu and Morita 1990), although histopathologic evidence of liver damage was not seen in one study at a gavage dose of 150 mg/kg (Kotsonis and Klaassen 1977). Exposure of rats for 10 days to drinking water containing 13.9 mg Cd/kg/day was without effect on the liver (Borzelleca et al. 1989). Depletion of liver glutathione by fasting increases the liver necrosis following acute oral exposure to cadmium in rats (Shimizu and Morita 1990).

In a 10-week study, male Rhesus monkeys exposed to 4 mg/kg/day cadmium chloride via gavage, had a significant decrease in glutathione peroxidase in liver, kidney, heart, and lung in the following order: liver>kidney>heart>lung; a significant decrease in glutathione *S*-transferase (GST) activity towards 1-chloro-2,4-dinitrobenzene in all four organs in the following order: liver>lung>kidney>heart; and a significant increase in GST activity towards ethacrynic acid in all four organs in the following order: heart>lung>kidney>liver (Sidhu et al. 1993). Intermediate-duration exposure causes histopathologic changes in the liver (e.g., necrosis of central lobules, focal hepatic fibrosis, biliary hyperplasia) at doses of 1.6–15 mg/kg/day (Cha 1987; Gill et al. 1989b; Miller et al. 1974a; Schroeder et al. 1965; Stowe et al. 1972; Wilson et al. 1941), and metabolic alterations (e.g., decreased cytochrome c oxidase activity in mitochondria, increased ALT and AST activities) at doses of 0.05–10 mg/kg/day (Groten et al. 1990; Muller and Stacey 1988; Muller et al. 1988; Sporn et al. 1970; Steibert et al. 1984; Tewari et al. 1986b).

Decreased relative liver weight to body weight has also been reported in male rats fed 5.95 mg/kg/day for 6 weeks (Kozlowska et al. 1993).

Other intermediate and chronic duration studies have not found liver effects in animals following oral exposure. These studies include a daily gavage exposure of 14 mg/kg/day for 6 weeks in rats (Hopf et al. 1990), a 3-month exposure to cadmium in food at 3 mg/kg/day in rats (Loeser and Lorke 1977a), a 24-week exposure to cadmium in water at 8 mg/kg/day in rats (Kotsonis and Klaassen 1978), and a 3-month exposure in food at 0.75 mg/kg/day in dogs (Loeser and Lorke 1977b). Kopp et al. (1982) report no hepatic effects from a chronic exposure of 18 months to cadmium in water at 0.65 mg/kg/day in rats.

Renal Effects. Numerous studies indicate that the kidney is the primary target organ of cadmium toxicity following extended oral exposure, with effects similar to those seen following inhalation exposure (see Section 3.2.1.2). Most of the data involves chronic exposure to cadmium; two case reports involving acute exposure to large doses of cadmium also found kidney effects. In two fatal cases of oral cadmium poisoning, anuria was present in one individual who ingested 25 mg/kg cadmium as cadmium iodide. Damage to the kidneys was reported at autopsy, but was not further specified (Wisniewska-Knypl et al. 1971). The kidneys were reported as normal at autopsy in an individual who died 2 days after ingesting 1,840 mg/kg cadmium (Buckler et al. 1986).

Several studies have found associations between increased mortality and renal dysfunction in residents living in cadmium polluted areas. Significant increases in SMRs were found in residents living in cadmium polluted areas of Japan with elevated levels of biomarkers of renal dysfunction (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 1995, 2004a, 2006). Among the studies that examined cause of death, significant increases in deaths from renal diseases were found in the residents that were categorized as biomarker-positive (urinary levels of the renal biomarker was higher than the cut-off value); the cut-off values used were β2-microglobulin ≥1,000 μg/g creatinine (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Nakagawa et al. 1993; Nishijo et al. 2004a, 2006) or retinol binding protein ≥4 mg/L (Nishijo et al. 1995). Other studies have found that mortality increased in proportion to the renal biomarker level (β2-microglobulin, protein, or glucose) (Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 2004a, 2006). Increases in mortality from renal diseases have also been observed among populations living in cadmium polluted areas of Belgium (Lauwerys and De Wals 1981) and England (Inskip et al. 1982); however, statistical analysis was not reported in the Belgium study and the increase in renal disease was not statistically significant in the other study.

Elevated levels of several biomarkers of renal dysfunction and/or associations between cadmium burden and these biomarkers have been found in studies of populations living in cadmium non-polluted areas of Japan (Ezaki et al. 2003; Ikeda et al. 1999; Suwazono et al. 2000; Oo et al. 2000; Uno et al. 2005; Yamanaka et al. 1998), Belgium (Buchet et al. 1990; Roels et al. 1981a), and the United States (Noonan et al. 2002) and in populations living in cadmium polluted areas of China (Cai et al. 1990, 1992, 1998; Jin et al. 2002, 2004a, 2004c; Nordberg et al. 1997; Wu et al. 2001), Japan (Cai et al. 2001; Hayano et al. 1996; Ishizaki et al. 1989; Izuno et al. 2000; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002b; Monzawa et al. 1998; Nakadaira and Nishi 2003; Nakashima et al. 1997; Nogawa et al. 1989; Osawa et al. 2001; Watanabe et al. 2002), Thailand (Teeyakasem et al. 2007), Sweden (Järup et al. 2000; Olsson et al. 2002), and Poland (Trzcinka-Ochocka et al. 2004). Most of these studies did not estimate cadmium intake; rather, exposure was characterized based on the levels of cadmium in rice, blood, or urine. The oral route is assumed to be the primary route of exposure, although the inhalation route, particularly in smokers, may have contributed to the overall cadmium body burden. The epidemiology data are summarized in Table 3-7 and brief discussions of the better designed studies providing valuable dose-response data follows.

Buchet et al. (1990) examined 1,699 non-occupationally exposed males and females (aged 20–80 years) living in Belgium. Urinary cadmium levels significantly correlated with urinary β2-microglobulin, retinol binding protein, NAG, amino acid, and calcium levels; the partial r^2 values were 0.0036, 0.0210, 0.0684, 0.0160, and 0.0168, respectively. The probability that individuals would have abnormal values for the renal biomarkers (defined as >95th percentile for subjects without diabetes or urinary tract diseases and who did not regularly take analgesics) was estimated using logistic regression models with adjustments for age, gender, smoking, disease, and use of analgesics. It was estimated that >10% of β2-microglobulin, retinol binding protein, amino acid, and calcium values would be abnormal when 24-hour urinary cadmium levels were >3.05, 2.87, 2.74, 4.29, or 1.92 μg/24 hour, respectively.

Järup et al. (2000) examined 1,021 individuals living near a nickel-cadmium battery plant in Sweden for at least 5 years (n=799) or employed as battery workers (n=222). The mean urinary cadmium levels were 0.81 and 0.65 μg/g creatinine in males and females, respectively. Urinary cadmium levels were significantly associated with urinary human complex-forming glycoprotein (pHC; also referred to as α1-microglobulin) levels, after adjustment for age. The relationship remained statistically significant after removal of the cadmium workers from the analysis. The prevalence of abnormal pHC values (defined as exceeding the 95th percentile in a Swedish reference population; >7.1 and 5.3 mg/g creatinine

Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
General population (Japan) 10,753 females; 35–60 years old	1.26 µg/g creat.	β2M pHC	Significant correlation between urinary cadmium and effect biomarkers; however, no significant relationship was established when age was factored into analysis.	Ezaki et al. 2003
General population (Japan) 470 nonsmoking females	2.1 µg/g creat.	β2M pHC	Significant correlation between urinary cadmium (not corrected for creat.) and pHC and β2M.	Ikeda et al. 1999
General population (Japan) 1,105 males, 1,648 females; >50 years old	1.8 µg/g creat. (M) 2.4 µg/g creat. (F)	β2M Total protein NAG	Significant correlation between urinary cadmium and protein and β2M. Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Suwazono et al. 2000
General population (Japan) 568 males, 742 females; ≥50 years old	2.2–3.4 µg/L (M) 2.8–3.9 µg/L (F)	total protein NAG β2M	Significant correlation (with age adjustment) between urinary cadmium and effect biomarkers.	Oo et al. 2000
General population (Japan) 558 males, 743 females; ≥50 years old	1.3 µg/g creat. (M) 1.3 µg/g creat. (F)	β2M total protein NAG	Significant correlation between urinary cadmium and effect biomarkers (NAG was only significant in females). Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Yamanaka et al. 1998
General population (Japan) 410 males, 418 females; 40–59 years old	0.8 µg/g creat. (M) 1.8 µg/g creat. (F) (median levels)	β2M protein NAG	Significant associations between urinary cadmium and effect biomarkers (protein only significant in males). Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Uno et al. 2005
General population (Belgium) 175 females; mean age 81.1–82.3 years old	0.040–0.093 µg/hour	β2M protein amino acids albumin	Dose-response relationship between urinary cadmium and urinary protein and amino acids; significant relationship with β2M and albumin only in the two areas with highest urinary cadmium levels.	Roels et al. 1981a

Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
General population (Belgium) 1,699 males, females; 20–80 years old		β2M protein NAG amino acids calcium	Significant correlation between urinary cadmium and effect biomarkers. Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Buchet et al. 1990
General population (United States) 88 males, 71 females; 6–17 years old; 71 males, 80 females; ≥18 years old	0.07 µg/g creat. (M, child) 0.08 µg/g creat. (F, child) 0.24 µg/g creat. (M, adult) 0.23 µg/g creat. (F, adult)	β2M NAG AAP albumin	No significant associations (after correction for age, sex) between urinary cadmium and effect biomarkers in children. Significant association (after age and gender adjustment) between urinary cadmium and NAG and AAP in adults. Dose-response relationship between urinary cadmium and NAG and AAP.	Noonan et al. 2002
Residents in cadmium-polluted area (China) 433 males and females	11.27 µg/g creat.	β2M NAG	Significantly higher effect biomarkers levels.	Cai et al. 1990, 1992
Residents in cadmium-polluted area (China) 219 males and females		β2M	Significant dose-response relationship between urinary cadmium, blood cadmium, and cumulative Cd intake and β2M; prevalence of abnormal values.	Cai et al. 1998
Residents in cadmium-polluted area (China) 118 males, 170 females in high exposure group 80 males, 158 females in moderate exposure group	High: 11.18 µg/g creat. Mod.: 3.55 µg/g creat.	β2M RBP albumin	Significant correlation between urinary cadmium and effect biomarkers. Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Jin et al. 2002
Residents in cadmium-polluted area (China) 118 males, 170 females in high exposure group 80 males, 158 females in moderate exposure group		β2M NAG NAG-B RBP albumin	Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Jin et al. 2004c

Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
Residents in cadmium-polluted area (China) 66 males, 22 females	9.12 µg/g creat.	β2M NAG albumin	Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Jin et al. 2004a
Residents in cadmium-polluted area (China) 120 males, 127 females in high exposure group 125 males, 122 females in moderate exposure group	High: 9.40 µg/L (M) 12.13 µg/L (F) Mod.: 1.28 µg/L (M) 2.05 µg/L (F)	β2M albumin	Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Nordberg et al. 1997
Residents in cadmium-polluted area (China) 122 males, 125 females	6.1 µg/g creat. (M) 7.5 µg/g creat. (F)	β2M NAG calcium	Effect biomarkers significantly higher than controls. Dose-response relationship between urinary cadmium and effect biomarkers.	Wu et al. 2001
Residents in cadmium-polluted area (Japan) 127 males; mean age 72.1–73.6 years old	6.8–6.9 µg/g creat.	β2M	Higher prevalence of abnormal effect biomarkers compared to controls.	Cai et al. 2001
Residents in cadmium-polluted area (Japan) 1,178 females	3.16–4.08 µg/g creat.	β2M	No significant association between urinary cadmium and effect biomarkers.	Horiguchi et al. 2004
Residents in cadmium-polluted area (Japan) 82 males, 56 females		β2M	Significant association between cadmium intake and effect biomarkers in males only.	Izuno et al. 2000
Residents in cadmium-polluted area (Japan) 634 males, 411 females		Protein	Significant association between cadmium intake and increased prevalence of abnormal levels of urinary protein in males.	Kobayashi et al. 2002a; Watanabe et al. 2002
Residents in cadmium-polluted area (Japan) 1,419 males, 1,745 females	4.6 µg/g creat. (M) 7.2 µg/g creat. (F)	Potassium sodium	Significantly higher urinary potassium levels, compared to controls. Significant correlation between urinary potassium and urinary cadmium and β2M. Urinary sodium not significantly different than controls and not correlated with urinary cadmium.	Monzawa et al. 1998

Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
Residents in cadmium-polluted area (Japan) 44 males, 54 females	2.69 µg/g creat. (M) 4.68 µg/g creat. (F)	β2M pHC NAG protein inorganic phosphorus	Significant correlation between urinary cadmium and effect biomarkers (except β2M in males).	Nakadaira and Nishi 2003
Residents in cadmium-polluted area (Japan) 832 males, 871 females		β2M protein amino nitrogen	Significant correlation between cadmium concentration in rice and effect biomarkers. Dose-response relationship between cadmium levels in rice and prevalence of abnormal β2M (males) and protein (females) levels.	Nakashima et al. 1997
Residents in cadmium-polluted area (Japan) 826 males, 641 females		Protein	Dose response relationship between cadmium levels in rice and prevalence of abnormal effect biomarker levels.	Osawa et al. 2001
Residents in cadmium-polluted area (Japan) 878 males, 972 females		β2M	Dose response relationship between cadmium in rice and effect biomarkers.	Nogawa et al. 1989
Residents in cadmium-polluted area (Japan) 1,424 males, 1,754 females	4.56 µg/g creat. (M) 7.15 µg/g creat. (F)	β2M	β2M significantly higher than controls. Dose-response relationship between urinary cadmium and prevalence of abnormal β2M levels.	Ishizaki et al. 1989
Residents in cadmium-polluted area (Japan) 878 males, 972 females		β2M	Dose response relationship between cadmium in rice and prevalence of abnormal β2M levels.	Kido and Nogawa 1993
Residents in cadmium-polluted area (Japan) 1,403 males, 1,716 females; ≥50 years old	4.56 µg/g creat. (M) 7.15 µg/g creat. (F)	β2M	Dose response relationship between urinary cadmium and prevalence of abnormal β2M levels.	Hayano et al. 1996
Residents in cadmium-polluted area (Japan) 120 males, 280 females	1.78 µg/g creat. (M) 2.27 µg/g creat. (F)	NAG	Significant correlation between urinary cadmium and NAG.	Kawada et al. 1992

Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
Residents in cadmium-polluted area (Thailand) 58 males, 70 females	12 µg/g creat.	β2M pHC NAG protein albumin	Significant correlation between urinary cadmium and effect biomarkers. Dose-response relationship between urinary cadmium and prevalence of abnormal β2M levels.	Teeyakasem et al. 2007
Residents in cadmium-polluted area (includes occupationally exposed subjects (Sweden)	0.81 µg/g creat. (M) 0.66 µg/g creat. (F)	pHC	Linear relationship between urinary cadmium and pHC (relationship remained significant after removal of occupationally exposed subjects.	Järup et al. 2000
Residents in cadmium-polluted area (Sweden) 57 males, 48 females	0.26 µg/g creat.	β2M protein HC NAG albumin	Significant correlation between urinary and blood cadmium and effect biomarkers. β2M clearance was significantly explained by urinary cadmium levels.	Olsson et al. 2002
Residents in cadmium-polluted area (Poland) 44 males, 128 females only exposed as adults 72 males, 64 females exposed as children	0.97 µg/g creat. (childhood exposure) 2.23 µg/g creat. (adult exposure)	β2M RBP NAG NAG-A NAG-B albumin	In childhood exposure group, significant correlations between urinary cadmium and β2M, RBP, and albumin. In adult exposure group, significant correlations between urinary cadmium and all effect biomarkers.	Trzcinka-Ochocka et al. 2004

AAP = alanine aminopeptidase; β2M = β2-microglobulin; creat. = creatinine; F = female; M = male; Mod. = moderate; NAG = N-acetyl-β-glucosaminidase; pHC = human complex-forming glycoprotein, also referred to as α1M; RBP = retinol binding protein

for males and females, respectively) was estimated to increase by 10% at urinary cadmium levels of 1 μg/g creatinine. The European Chemicals Bureau (2007) recalculated the probability of HC proteinuria (using the raw data from Järup and associates) to account for the differences in age of the reference population (mean of 40 years) and study population (mean of 53 years). Based on these recalculations, the urinary cadmium level associated with a 10% increased probability of abnormal pHC values (20% total probability) was 2.62 μg/g creatinine for the total population. In the environmental exposed subgroup, a urinary cadmium level of 0.5 μg/g creatinine was associated with a 13% probability (doubling of the probability in reference population) of abnormal pHC values.

Noonan et al. (2002) examined residents in Pennsylvania living near a defunct zinc smelting facility (geometric mean urinary cadmium level of 0.14 μg/g creatinine) and a reference community located 10 miles from the facility (geometric mean urinary cadmium levels of 0.12 μg/g creatinine). The data from the two communities were pooled because there were no differences in urinary cadmium levels between them. β2-microglobulin, NAG, alanine aminopeptidase (AAP), and albumin levels were measured as biomarkers of renal dysfunction. The geometric mean urinary cadmium levels were 0.07 and 0.08 μg/g creatinine in 88 males and 71 females aged 6–17 years and 0.24 and 0.23 μg/g creatinine in 71 males and 80 females aged ≥18 years. No significant correlations between urinary cadmium levels and renal biomarkers were observed in the children, after adjustment for creatinine, age, and gender. In adults, significant correlations (after adjustment for creatinine, age, gender, smoking, and self-reported diabetes or thyroid disease) between urinary cadmium and NAG (partial correlation coefficient of 0.20, 95% CI of 0.05–0.36) and AAP (partial correlation coefficient of 0.21 and 95% CI of 0.05–0.36) were observed. Significant dose-effect relationships were also found for these two biomarkers. Urinary cadmium levels were not significantly associated with elevated levels of β2-microglobulin or albumin.

Nogawa et al. (1980) examined 878 males and 972 females aged ≥50 years living in the Kakehashi River basin in Japan; the Kakehashi River, cadmium polluted from an upstream mine, was used to irrigate rice fields. β2-Microglobulin measured in morning urine samples was used as a biomarker of renal dysfunction and cadmium intake was estimated from rice samples collected in 1974. Cadmium levels in rice were considered to be representative of cadmium intake because over 70% of the total cadmium intake has been shown to come from rice. Cadmium in the rice ranged from 0.10 to 0.69 μg/g. β2-Microglobulin levels were significantly higher in the study population compared to a reference population of 113 males and 161 females living in a nearby area. A significant dose-related association between total cadmium intake and prevalence of abnormal β2-microglobulin values (defined as β2-microglobulin levels of ≥1,000 μg/g creatinine) was found. The total cadmium intake, which resulted

in a prevalence of abnormal β2-microglobulin levels equal to the control group, was 1,678 mg in males (prevalence in controls was 6.0%) and 1,763 mg in females (prevalence in controls was 5.0%). A further analysis of the exposed subjects (Hochi et al. 1995) found that the prevalence of abnormal β2-microglobulin levels (using a cut-off level of 1,000 μg/g creatinine) exceeded the prevalence in the reference population when cadmium intake was ≥2 g and the subjects were divided into subgroups by age. The prevalence of abnormal β2-microglobulin levels at a given cadmium intake increased with age.

Yamanaka et al. (1998) examined 558 males and 743 females aged ≥50 years living in a cadmium non-polluted area in Japan. Urinary cadmium level was used as a biomarker of exposure and urinary β2-microglobulin, total protein, and NAG as biomarkers of renal dysfunction. The geometric mean urinary cadmium levels were 1.3 and 1.3 μg/g creatinine in males and females, respectively. Significant correlations (after adjustment for age) between urinary cadmium levels and total protein, β2-microglobulin, and NAG were found. Abnormal levels of renal biomarkers were defined as exceeding the 84% upper limit value calculated from a referent group of 2,778 non-exposed individuals; the cut-off values were 124.8 and 120.8 mg/g creatinine for total protein in males and females, 492 and 403 μg/g creatinine for β2-microglobulin, and 8.0 and 8.5 U/g creatinine for NAG. Dose-response relationships between urinary cadmium levels and prevalence of abnormal levels of β2-microglobulin, total protein, and NAG were found. The odds ratios (95% CI) were 6.589 (3.383–12.833), 3.065 (1.700–5.526), and 1.887 (1.090–3.268) for protein, β2-microglobulin, and NAG in males and 17.486 (7.520–40.660), 5.625 (3.032–10.435), and 2.313 (1.399–3.824) for protein, β2-microglobulin, and NAG in females.

Another study of residents living in a cadmium non-polluted area of Japan examined 346 males and 529 females from one area (area A) and 222 males and 413 females in another area (area B); all subjects were ≥50 years of age and were not occupationally exposed to heavy metals (Oo et al. 2000). The geometric mean urinary cadmium levels were 2.2 and 2.8 μg/L in males and females in area A and 3.4 and 3.9 μg/L in area B. Significant correlations (with adjustment for age) were found between urinary cadmium and urinary levels of protein, β2-microglobulin (not significant in males in area B) and NAG levels. A significant association between urinary cadmium levels and the prevalence (cut-off levels from same referent population as Yamanaka et al. 1998) of abnormal levels of urinary protein (cut-off level of 113.8 and 96.8 μg/L in males and females), β2-microglobulin (378 and 275 μg/L) (only significant in females in area A), and NAG (8.0 and 7.2 μg/L). The odds ratios (95% CI) for an increase in prevalence of abnormal renal biomarkers were 8.810 (3.401–22.819) and 11.282 (3.301–38.362) for protein in males in areas A and B, respectively, 8.234 (3.696–18.343) and 23.901 (8.897–64.210) for protein in females in areas A and B; 2.558 (1.246–5.248) for β2-microglobulin in females in area A; 47.944 (14.193–161.954)

and 9.940 (3.153–31.340) for NAG in males in areas A and B; and 72.945 (21.873–243.263) and 25.374 (9.452–68.117) for NAG in females in areas A and B.

In a re-examination of the populations studied by Yamanaka et al. (1998) and Oo et al. (2000), Suwazono et al. (2000) measured cadmium levels in blood and urine and urinary levels of total protein, β2-microglobulin, and NAG in 1,105 males and 1,648 females over the age of 50 years. The geometric mean concentrations of cadmium in urine were 1.8 and 2.4 μg/g creatinine in males and females, respectively, and blood cadmium levels were 2.0 and 1.8 ng/g in males and females. After adjustment for age, significant associations between urinary cadmium levels and urinary protein and β2-microglobulin in males and females were found. Additionally, blood cadmium levels were significantly associated with urinary protein and NAG levels in males and urinary protein, β2-microglobulin, and NAG levels in females. Cut-off levels (defined as the 84% upper limit values from 424 male and 1,611 female nonsmoking subjects) of 157.4 and 158.5 mg/g creatinine for protein in males and females, respectively, 507 and 400 μg/g creatinine for β2-microglobulin in males and females, respectively, and 8.2 and 8.5 μg/g creatinine for NAG in males and females, respectively, were used to evaluate the prevalence of abnormal levels of renal biomarkers. Logistic regression analysis demonstrated significant associations between urinary cadmium levels and increased prevalence of abnormal levels of total protein (odds ratio of 3.923, 95% CI of 2.2028–7.590) and β2-microglobulin (odds ratio of 2.259, 95% CI of 1.372–3.717) in males; in females, significant associations were found for total protein (odds ratio of 7.763; 95% CI of 4.231–14.243), β2-microglobulin (odds ratio of 2.259, 95% CI of 1.879–4.281), and NAG (odds ratio of 1.882, 95% CI of 1.311–2.702). For blood cadmium levels, the only significant association found was for an increased prevalence of abnormal total protein levels in females (odds ratio of 3.490, 95% CI of 1.661–7.331).

Jin et al. (2002) examined three populations living various distances from a nonferrous metal smelter. The geometric mean levels of urinary cadmium were 11.18 and 12.86 μg/g creatinine in males (n=294) and females (n=171) in the highly polluted area, 3.55 and 4.45 μg/g creatinine in males (n=243) and females (n=162) in the moderately polluted area, and 1.83 and 1.79 μg/g creatinine in males (n=253) and females (n=155) in the control area. Significant correlations were found between urinary (and blood) cadmium levels and renal biomarkers (β2-microglobulin, retinol binding protein, and albumin). Cut-off values for β2-microglobulin, retinol binding protein, and albumin of 300 μg/g creatinine, 300 μg/g creatinine, and 15 mg/g creatinine, respectively, were used to assess possible dose-response relationships (no additional information was provided); although 300 μg/g creatinine was reported as the cut-off values for β2-microglobulin, subsequent analysis of this data set (Jin et al. 2004c) reported a cut-off value of

800 μg/g creatinine. Significant dose-response relationships between urinary (and blood) cadmium and the prevalence of abnormal levels of renal markers of kidney dysfunction were found.

Unlike the studies discussed above, Hellström et al. (2001) used the incidence of renal replacement therapy (dialysis or kidney transplantation) as an indicator of renal dysfunction, in particular, end-stage renal disease. Residents of Kalmar County, Sweden were divided into four exposure groups: high exposure (workers at cadmium battery production facility), moderate (residents living within 2 km of the cadmium battery facility), low (residents living between 2 and 10 km of the facility), and no exposure (residents living at least 10 km from the facility); all subjects were 20–79 years of age. The Mentel-Haenszel rate ratio (MH-RR) for renal replacement therapy in the cadmium exposed group was 1.8 (95% CI 1.3–2.3); among the environmentally exposed group, the MH-RR was 1.7 (95% CI 1.3–2.3). The age SRRs were 1.9 (95% CI 1.3–2.5) and 1.9 (95% CI 1.2–2.6) for subjects in the moderate exposure group aged 20–79 years or 40–79 years, respectively. The trend for increasing MH-RR with increasing exposure was statistically significant. The age SRRs were not significantly elevated in the low exposure group. The investigators noted that the causes of end stage renal disease were similar in the cadmium exposed and unexposed groups. When only primary renal diseases (excludes renal failure secondary to diabetes or vascular or systemic diseases) were considered, the MH-RR was 1.7 (95% CI 1.1–2.6) for all cadmium exposed individuals and 2.1 (95% CI 1.4–3.2) for cadmium exposed individuals aged 40–79 years. Although urinary cadmium levels were not assessed in this study, other studies in this area found mean urinary cadmium levels of 1.0 and 0.46 μg/g creatinine in residents living within 0.5 and 0.5–1 km, respectively, of the battery facility (Järup et al. 1995a) and 0.38 and 0.55 μg/g creatinine in men and women, respectively, living in the contaminated area (Alfvén et al. 2000).

Although there is strong evidence to suggest a relationship between urinary cadmium excretion and excretion of renal biomarkers (particularly low molecular weight proteins such as β2-microglobulin, pHC, and retinol binding protein), there is less agreement about the significance of the early renal changes and the threshold urinary cadmium levels associated with renal damage. Several studies monitoring populations following a decrease in cadmium exposure have attempted to address the question of the reversibility of early renal changes. In Japan, cadmium-contaminated soil used in rice paddies was replaced resulting in decreasing urinary cadmium levels in residents consuming rice grown in these fields (Cai et al. 2001; Iwata et al. 1993; Kobayashi et al. 2008). Although, cadmium exposure decreased over the same time period, the levels of renal biomarkers increased (Cai et al. 2001; Iwata et al. 1993; Kido et al. 1988; Kobayashi et al. 2008) and the prevalence of abnormal values remained higher compared to the reference population (Cai et al. 2001). Although significant decreases in urinary cadmium levels were

observed over time, cadmium burdens still remained high; urinary cadmium levels at the later time periods were 6.03–9.6 μg/g creatinine (Cai et al. 2001; Iwata et al. 1993; Kido et al. 1988). Kobayashi et al. (2008) found significant correlations (after adjustment for age) between the amount of time since soil replacement and increases in urinary levels of retinol binding protein, total protein, and glucose (males only). In contrast, a follow-up study of a portion of the population examined by Buchet et al. (1990) found small, but statistically significant, decreases in urinary cadmium levels and urinary levels of β2-microglobulin, NAG, and retinol binding protein (Hotz et al. 1999). Urinary cadmium levels in this study (0.6–0.9 μg/g creatinine at baseline and 0.5–0.8 μg/g creatinine at follow-up) were much lower than levels in the Japanese studies. Although the data are inconclusive, there is some indication of reversibility of renal damage associated with exposure to low levels of cadmium following a substantial decrease in cadmium intake.

A number of investigators have examined different approaches to establishing a safe cadmium body burden (as assessed by urinary cadmium levels). Several benchmark dose analyses of data from populations living in cadmium non-polluted areas in Sweden (Suwazono et al. 2006) or Japan (Kobayashi et al. 2006; Uno et al. 2005) or cadmium polluted areas in Japan (Shimizu et al. 2006) or China (Jin et al. 2004c) have been conducted. The analyses used urinary cadmium levels as a biomarker of cadmium exposure and the prevalence of abnormal levels of β2-microglobulin, pHC, protein, NAG, retinol binding protein, albumin, or glomerular filtration rate as biomarkers of renal effects. As summarized in Table 3-8, the BMDs for urinary cadmium levels vary widely between the studies depending on the renal biomarker and the cut-off level used. For example, when NAG is used as the effect biomarker, the $BMD_{0.05}$ (dose associated with a 5% extra risk) values of 0.64, 12.0–10.8, and 6.36–7.74 μg/g creatinine were calculated by Suwazono et al. (2006), Kobayashi et al. (2006), and Jin et al. (2004c) when the 95% upper limit cut-off value of 3.6, 16.0–16.6, and 15.0 U/g creatinine, respectively, was used. The BMDL (95% confidence bound of the BMD) is typically considered a no adverse effect levels; the results of these benchmark doses analyses suggest that chronic exposure to cadmium resulting in urinary cadmium levels of 0.3–11.31 or 0.6–11.4 μg/g creatinine would be associated with a 5 or 10% additional risk of renal dysfunction.

Ikeda and associates used regression analysis to predict a threshold urinary cadmium level. Plotting urinary cadmium levels against β2-microglobulin levels taken from published data from populations living in cadmium polluted and non polluted areas of Japan resulted in a distribution shaped like the letter "J". The threshold level was defined as the point of flexion in the "J" shaped curve. In the first

Table 3-8. Benchmark Dose Estimations of Urinary Cadmium Levels

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
General population (Sweden) 790 females; 53–64 years old	NAG	3.6 U/g creat. (95% cut-off)[a]		0.64	0.50	1.08	0.83	Suwazono et al. 2006
	pHC	6.8 mg/g creat. (95% cut-off)[a]		0.63	0.49	1.05	0.81	
	Estimated GFR	78.5 mL/minute (95% cut-off)[a]		1.08	0.70	1.80	1.18	
Residents in cadmium-polluted (1,397 males, 1,706 females) and cadmium nonpolluted areas (Japan) (130 males, 159 females); ≥50 years old	β2M	507 µg/g creat. (M) 400 µg/g creat. (F) (84% cut-off)[b]	Quantal linear model	1.5 (M) 1.4 (F)	1.2 (M) 1.1 (F)	3.1 (M) 2.9 (F)	2.5 (M) 2.3 (F)	Shimizu et al. 2006
		507 µg/g creat. (M) 400 µg/g creat. (F) (84% cut-off)[b]	Log-logistic model	3.7 (M) 2.6 (F)	2.9 (M) 1.5 (F)	5.1 (M) 6.3 (F)	4.2 (M) 2.7 (F)	
		994 µg/g creat. (M) 784 µg/g creat. (F) (95% cut-off)[c]	Quantal linear model	2.3 (M) 1.7 (F)	1.8 (M) 1.4 (F)	4.7 (M) 3.5 (F)	3.7 (M) 2.9 (F)	
		994 µg/g creat. (M) 784 µg/g creat. (F) (95% cut-off)[c]	Log-logistic model	4.8 (M) 4.4 (F)	3.9 (M) 3.2 (F)	6.3 (M) 6.4 (F)	5.5 (M) 5.1 (F)	

Table 3-8. Benchmark Dose Estimations of Urinary Cadmium Levels

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
General population (Japan) 1,114 males, 1,664 females	Protein	157 mg/g creat. (M) 159 mg/g creat. (F) (84% cut-off)[d]	Log-logistic model	3.6 (M) 4.8 (F)	3.1 (M) 4.2 (F)	5.6 (M) 7.5 (F)	4.9 (M) 6.6 (F)	Kobayashi et al. 2006
		309 mg/g creat. (M) 311 mg/g creat. (F) (95% cut-off)[e]		10.6 (M) 8.7 (F)	6.8 (M) 7.3 (F)	15.3 (M) 12.0 (F)	9.6 (M) 9.9 (F)	
	β2M	507 µg/g creat. (M) 400 µg/g creat. (F) (84% cut-off)[d]		2.9 (M) 3.8 (F)	2.4 (M) 3.3 (F)	5.0 (M) 6.6 (F)	4.0 (M) 5.5 (F)	
		994 µg/g creat. (M) 784 µg/g creat. (F) (95% cut-off)[e]		6.4 (M) 8.7 (F)	4.5 (M) 7.3 (F)	10.2 (M) 12.0 (F)	7.1 (M) 9.9 (F)	
	NAG	8.2 U/g creat. (M) 8.5 U/g creat. (F) (84% cut-off)[d]		4.8 (M) 4.7 (F)	3.3 (M) 3.7 (F)	8.3 (M) 8.3 (F)	5.7 (M) 6.4 (F)	
		16.0 U/g creat. (M) 16.6 U/g creat. (F) (95% cut-off)[e]		12.0 (M) 10.8 (F)	7.7 (M) 8.5 (F)	16.4 (M) 14.8 (F)	10.3 (M) 11.4 (F)	
General population (Japan) 410 males, 418 females; 40–59 years old	Protein	70 mg/g creat. (M) 70 mg/g creat. (F) (84% cut-off)[f]	Quantal linear model	0.9 (M) 3.2 (F)	0.6 (M) 1.8 (F)	1.9 (M) 6.6 (F)	1.2 (M) 3.6 (F)	Uno et al. 2005
	β2M	233 µg/g creat. (M) 274 µg/g creat. (F) (84% cut-off)[f]		0.5 (M) 0.9 (F)	0.4 (M) 0.8 (F)	1.0 (M) 1.8 (F)	0.7 (M) 1.3 (F)	
	NAG	2.4 U/g creat. (M) 2.5 U/g creat. (F) (84% cut-off)[f]		0.3 (M) 0.8 (F)	0.3 (M) 0.6 (F)	0.7 (M) 1.6 (F)	0.6 (M) 1.2 (F)	

Table 3-8. Benchmark Dose Estimations of Urinary Cadmium Levels

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
Residents in cadmium highly polluted area (China) 123 males, 171 females Residents in cadmium moderately polluted area (China) 81 males, 162 females	NAG	15.0 U/g creat. (95% cut-off)[g]	Quantal linear logistic regression model	6.36 (M) 7.74 (F)	5.83 (M) 5.46 (F)			Jin et al. 2004c
	NAG-B	4.0 U/g creat. (95% cut-off)[g]		4.88 (M) 4.24 (F)	3.98 (M) 3.70 (F)			
	β2M	800 µg/g creat. (95% cut-off)[g]		5.86 (M) 9.98 (F)	4.74 (M) 8.47 (F)			
	RBP	0.300 mg/g creat. (95% cut-off)[g]		5.99 (M) 9.03 (F)	4.87 (M) 7.63 (F)			
	albumin	25.0 mg/g creat. (95% cut-off)[g]		16.72 (M) 14.42 (F)	11.18 (M) 11.31 (F)			

[a]95[th] percentile of effect biomarkers on the "hypothetical" control distribution at a urinary cadmium level of zero.
[b]84% upper limit values from a group of 424 males and 1,611 females who did not smoke and lived in three different cadmium nonpolluted areas.
[c]95% upper limit values from a group of 424 males and 1,611 females who did not smoke and lived in three different cadmium nonpolluted areas.
[d]84% upper limit value of the target population of people who have not smoked.
[e]95% upper limit value of the target population of people who have not smoked.
[f]84% upper limit value of the target population.
[g]95% upper limit value from a control group 98 males and 155 females living in a cadmium nonpolluted area.

BMD = benchmark dose; BMDL = lower 95% confidence limit on the benchmark dose; BMR = benchmark response; β2M = β2-microglobulin; creat. = creatinine; F = female; M = male; NAG = *N*-acetyl-β-D-glucosaminidase; NAG-B = *N*-acetyl-β-D-glucosaminidase's isoform B; RBP = retinol binding protein

investigation (Ikeda et al. 2003b), the point of flexion was estimated as the point of intersection between two regression lines: one with no elevation in β2-microgloublin from non-exposed populations and the other when β2-microglobulin was >400 or >1,000 μg/g creatinine using data from exposed populations. Although no specific data were given for the two populations, the investigators noted that the highest urinary cadmium levels in the non-exposed populations were 5.6 and 3.6 μg/g creatinine in females and males, respectively. The points of intersection of the regression lines were 11.0 and 11.7 μg/g creatinine in females using the >400 and 1,000 μg/g creatinine criteria, respectively, and 10.0 and 11.0 μg/g creatinine in males. The second investigation also used published data on Japanese populations living in polluted and non-polluted areas (Ikeda et al. 2005b). The urinary cadmium levels ranged from 0.2 to 7.8 μg/g creatinine and from 0.8 to 31.6 μg/g creatinine in the non-polluted and polluted areas, respectively, and the data for the two populations were combined. Plotting urinary cadmium levels against β2-microglobulin levels showed that there was a marked increase in β2-microglobulin levels (levels exceeded 1,000 μg/g creatinine) when urinary cadmium levels exceeded 4 μg/g creatinine. The urinary cadmium levels at the point of intersection of the regression line for urinary cadmium levels of ≤2 or ≤5 μg/g creatinine was 6.7 and 6.7 μg/g creatinine using ordinary scales and 3.7 and 3.7 μg/g creatinine using double logarithmic scales. These urinary cadmium levels corresponded to β2-micro-globluin levels of 139 and 267 μg/g creatinine with the ordinary scales and 118 and 118 μg/g creatinine using the double logarithmic scales. Using these regression equations and a critical β2-microglobulin level of 1,000 μg/g creatinine resulted in urinary cadmium levels of 7.6 (ordinary scales) or 8.1 (double logarithmic scales) μg/g creatinine. Based on this analysis, the investigators concluded that at urinary cadmium levels of >4 μg/g creatinine, there is a substantial increase in β2-microglobulin levels (Ikeda et al. 2005b).

A third approach used to identify a threshold level was a meta-analysis conducted by Gamo et al. (2006) using published data on environmentally exposed populations. Urinary cadmium was used as a biomarker of exposure and the prevalence of abnormal levels of β2-microglobulin as an indicator of renal dysfunction. The investigators estimated maximum permissible geometric mean urinary cadmium levels in age- and gender-specific populations that would not result in a significant increase in the prevalence of abnormal β2-microglobulin levels. They concluded that the geometric mean urinary cadmium level for a population in a small geographical area should not exceed 3 μg/g creatinine; in a nationwide population, the geometric mean should not exceed 2 μg/g creatinine.

Numerous studies in rats, mice, and rabbits confirm that oral exposure to cadmium causes kidney damage including proteinuria and tubular damage (Andersen et al. 1988; Bernard et al. 1980, 1988a, 1992;

Bomhard et al. 1984; Borzelleca et al. 1989; Cardenas et al. 1992a, 1992b; Cha 1987; Fingerle et al. 1982; Gatta et al. 1989; Gill et al. 1989b; Itokawa et al. 1974; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Kozlowska et al. 1993; Mangler et al. 1988; Masaoka et al. 1994; Pleasants et al. 1992, 1993; Prigge 1978a; Steibert et al. 1984; Stowe et al. 1972; Wilson et al. 1941). Histopathological findings include focal necrosis of proximal tubular epithelial cells and cloudy swelling in renal tubules (Cha 1987). Some studies have also shown no effect on renal function (Basinger et al. 1988; Borzelleca et al. 1989; Boscolo and Carmignani 1986; Groten et al. 1990; Jamall et al. 1989; Loeser and Lorke 1977a, 1977b).

In acute-duration gavage studies in rats, decreased urine flow (Kotsonis and Klaassen 1977) and histopathologic evidence of kidney damage have been reported (Borzelleca et al. 1989) at the very high doses of 150 and 138 mg/kg/day, respectively. No effect on renal function was reported in rats receiving 13.9 mg/kg/day for 10 days in drinking water (Borzelleca et al. 1989). Mice treated with a single gavage dose showed tubular necrosis at 88.8 mg/kg in one study (Andersen et al. 1988), but no effects on the kidney in another study at a dose of 112 mg/kg (Basinger et al. 1988). Proteinuria is a common finding in intermediate-duration oral exposure studies in rats (Bernard et al. 1988a; Cardenas et al. 1992a, 1992b; Kotsonis and Klaassen 1978; Prigge 1978a), as are histopathologic changes in the kidney (Gatta et al. 1989; Itokawa et al. 1974; Kotsonis and Klaassen 1978; Wilson et al. 1941). Renal clearance was decreased in one study (Kawamura et al. 1978). Both increases (Pleasants et al. 1992, 1993) and decreases (Kozlowska et al. 1993) in relative kidney weight have been reported. These effects occurred in rats at doses ranging from 2 to 30 mg/kg/day. No renal effects were seen in dogs receiving 0.75 mg/kg/day cadmium for 3 months (Loeser and Lorke 1977b), but interstitial renal fibrosis was observed in rabbits exposed to 14.9 mg/kg/day for 200 days (Stowe et al. 1972). Renal dysfunction has been reported in Rhesus monkeys exposed to 1.2 mg/kg/day for 9 years, but not at 0.4 mg/kg/day (Masaoka et al. 1994). Adverse renal effects are common in rats following chronic-duration oral exposure to cadmium. Proteinuria (Bernard et al. 1992; Bomhard et al. 1984) and histopathologic damage (Fingerle et al. 1982; Mangler et al. 1988) have been reported at doses ranging from 1.8 to 12.5 mg/kg/day cadmium.

The hypothesis that a critical concentration of approximately 200 μg/g in the renal cortex must be reached before proteinuria develops is generally supported by the animal data (Bhattacharyya et al. 1988c; Kotsonis and Klaassen 1978; Mangler et al. 1988; Shaikh et al. 1989; Viau et al. 1984).

Endocrine Effects. Using data from the NHANES 1988–1994, Schwartz et al. (2003) investigated possible associations between cadmium exposure (as measured by urinary cadmium levels) and the

prevalence of impaired fasting glucose and diabetes. Analysis on 8,722 participants of the survey (≥40 years old) showed a dose-related increase in both impaired fasting glucose and diabetes after adjusting for age, ethnicity, sex, and BMI. No other studies were located regarding endocrine effects in humans after oral exposure to cadmium.

Evidence for endocrine effects in animals after oral exposure to cadmium is limited to histopathologic examination of endocrine tissues. No adverse effects were seen in parathyroid glands from female Wistar rats exposed to 8 mg Cd/kg/day via drinking water for 90 days (Kawamura et al. 1978) or in adrenal gland from male Sprague-Dawley rats exposed to 8 mg/kg/day via drinking water for 24 weeks (Kotsonis and Klaassen 1978). Pituitary, adrenals, thyroid, and thymus were unaffected in Wistar rats exposed to 3 mg/kg/day cadmium via feed for 3 months (Loeser and Lorke 1977a). Wilson et al. (1941) reported pancreatic atrophy and pancreatitis in rats from cadmium at 2.79 mg/kg/day via feed for 100 days. In rabbits exposed to 14.9 mg Cd/kg body weight/day via drinking water for 200 days, the pancreas had moderate concentrations of cadmium, but no interstitial fibrosis or other pathologic alterations (Stowe et al. 1972).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to cadmium.

Coarse fur was reported in Long-Evans rats receiving 6.13 mg/kg/day cadmium during Gd 6–15 (Machemer and Lorke 1981). A ruffled hair coat was reported in Wistar rats receiving 40 mg/kg/day cadmium by gavage 5 days/week for 14 weeks (Baranski and Sitarek 1987). No other reports of dermal effects after oral exposure to cadmium were located.

Ocular Effects. No studies were located regarding ocular effects in humans or animals after oral exposure to cadmium.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to cadmium.

Decreased body weight and decreased rates of growth are common findings in studies where experimental animals are orally exposed to cadmium. Sprague-Dawley rats receiving a single gavage dose of 150 mg/kg cadmium exhibited a 12% decrease in body weight, but 100 mg/kg had no effect (Kotsonis and Klaassen 1977). Daily gavage doses of 15.3 mg/kg over a 10-day period caused a 79% decrease in

body weight gain in male Sprague-Dawley rats (Borzelleca et al. 1989). Significant reductions in maternal weight gain have also been reported (Baranski 1985; Machemer and Lorke 1981).

Body weight reductions are also seen in intermediate-duration studies. For example, in a 14-week exposure via drinking water in male Long-Evans rats, 2.9 mg/kg/day had no effect on body weight gain; however, 5.8 mg/kg/day caused a 6–23% decrease and 11.6 mg/kg/day caused a 47–58% decrease (Pleasants et al. 1992, 1993). In general, intermediate-duration doses in feed or drinking water of ≤3 mg/kg/day have either no effect or only a small effect (10–20% decrease) on body weight in rats (Carmignani and Boscolo 1984; Jamall et al. 1989; Loeser and Lorke 1977a; Muller et al. 1988; Ogoshi et al. 1989; Perry et al. 1989; Wilson et al. 1941). Higher doses (4–14 mg/kg/day) had no effect in some studies (Kostial et al. 1993; Kotsonis and Klaassen 1978; Prigge 1978a; Viau et al. 1984) and small effects in others (Cha 1987; Kawamura et al. 1978; Kozlowska et al. 1993). A 29% decrease in maternal weight gain was observed in rats exposed to a high dose of 40 mg/kg/day (Baranski and Sitarek 1987). In mice, a dose of 4.8 mg/kg/day had no effect on maternal weight gain, but a dose of 9.6 mg/kg/day caused a 14% decrease (Webster 1978). A high dose of 232 mg/kg/day in mice caused a 29% decrease in body weight (Waalkes et al. 1993). Beagle dogs were unaffected at 0.75 mg/kg/day (Loeser and Lorke 1977b), as were rabbits at up to 2.2 mg/kg/day (Boscolo and Carmignani 1986; Tomera and Harakal 1988). A small decrease (11%) was seen in rabbits exposed to 14.9 mg/kg/day for 200 days (Stowe et al. 1972).

A chronic-duration study in Rhesus monkeys reported decreased growth rates at 0.4 mg/kg/day, but no effect at 0.12 mg/kg/day (Masaoka et al. 1994). No effect on body weight was seen in rats at up to 4.4 mg/kg/day (Decker et al. 1958; Fingerle et al. 1982; Mangler et al. 1988), but a small effect was seen at 7 mg/kg/day (Waalkes and Rehm 1992). Decreased terminal body weight was observed in mice after 12 months of drinking-water exposure to a high dose of 57 mg/kg/day (Hays and Margaretten 1985).

Metabolic Effects. Hyperthermia and metabolic acidosis were reported in a human male who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

No studies were located regarding metabolic effects in animals after oral exposure to cadmium.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to cadmium.

Numerous studies in rats, mice, and monkeys have established the capability of cadmium to affect the immune system, but the clinical significance of the effects is not clear. In mice, intermediate-duration oral exposure to cadmium has been shown to increase resistance to viral infection (Exon et al. 1986), to be without effect on natural or acquired resistance to infection (Bouley et al. 1984), and to increase mortality from virally-induced leukemia (Blakley 1986; Malave and de Ruffino 1984). Oral cadmium exposure has also been found to suppress the humoral immune response of mouse splenic cells to sheep red blood cell antigen in 6-week-old mice (Blakley 1985), but not in 12-month-old mice (Blakley 1988). The author suggests that "natural" age-related immune system dysfunction masked any cadmium suppressive effect in the 12-month-old mice, and that immunotoxicological investigations in aged models appear to be a poor indicator of immune response in the general population. Oral cadmium exposure has also been found to increase the cell-mediated immune response of monkeys (Chopra et al. 1984), to induce anti-nuclear antibodies in mice (Ohsawa et al. 1988), to increase circulating leukocytes in female rats (Borzelleca et al. 1989), and to exhibit time-dependent inhibitory and stimulative effects (Cifone et al. 1989b) or no effect (Stacey et al. 1988a) on natural killer cell activity in rats. The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 3-6 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

A few studies have reported an association between environmental cadmium exposure and neuropsychological functioning. These studies used hair cadmium as an index of exposure (see Section 3.8.1 for a discussion of the limitations of using hair as an indicator of exposure). End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985), and disruptive behavior in Navy recruits (Struempler et al. 1985). The usefulness of the data from these studies is limited because of the potential confounding effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and an inadequate quantification of cadmium exposure.

Although cadmium-induced neurotoxicity has not been clearly demonstrated in human studies, it has been observed in animal studies. Both a single oral exposure (Kotsonis and Klaassen 1977) and intermediate-duration exposure of adult rats to cadmium resulted in significantly decreased motor activity (Kotsonis and Klaassen 1978; Nation et al. 1990). Intermediate-duration oral exposure to cadmium has also been reported to cause weakness and muscle atrophy (Sato et al. 1978), induce aggressive behavior (Baranski and Sitarek 1987), induce anxiety as manifested by increased passive avoidance behavior (Nation et al.

1984) and by increased ethanol consumption (Nation et al. 1989), and alter brain biogenic amine content and enzyme activities (Murthy et al. 1989). Doses associated with these effects range from 5 to 40 mg/kg/day cadmium. Degenerative changes in the choroid plexus have been reported in mice exposed to 1.4 mg/kg/day cadmium in drinking water for 22 weeks (Valois and Webster 1989). Peripheral neuropathy has been reported in rats after a 31-month exposure to cadmium in drinking water (Sato et al. 1978). Neurological effects in offspring of animals orally exposed to cadmium during gestation are discussed in Section 3.2.2.5. The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-6 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

Several studies have examined the possible association between increased cadmium exposure and male reproductive toxicity; however, most studies focused on sex steroid hormone levels and the results appear to be inconsistent. Akinloye et al. (2006) found significant associations between increasing blood cadmium levels and increasing levels of serum luteinizing hormone, follicle stimulating hormone, prolactin, and testosterone among infertile men (sperm counts <20 million/cm^3 or no spermatozoa in semen). A significant association between increased blood cadmium levels and increased serum testosterone was also found in a group of workers with slight to moderate lead exposure (Telišman et al. 2000); however, neither study controlled for smoking. A study by Jurasović et al. (2004) found significant associations between blood cadmium levels and increased serum estradiol, follicle stimulating hormone, and testosterone levels in infertile men after adjusting for age, smoking, alcohol consumption, and biomarkers of lead, copper, zinc, and selenium. In contrast, a study of Chinese men living in areas with high levels of cadmium in rice did not find significant correlations between urinary or blood cadmium levels and serum testosterone, follicle stimulating hormone, or luteininzing hormone levels after adjusting for BMI, age, smoking, and alcohol consumption (Zeng et al. 2004a). However, they did find that the prevalence of abnormally elevated serum testosterone levels (>95^{th} percentile for controls) increased with exposure to cadmium. Using NHANES III data, Menke et al. (2008) found significant associations between urinary cadmium levels and serum testosterone and estradiol levels, but the associations were no longer significant after adjusting from smoking status and serum cotinine levels. Differences in study populations (e.g., infertile men, background cadmium exposure, high cadmium dietary exposure) and confounding factors (e.g., smoking, lead exposure) limit the interpretation of these results.

Three studies examined the possible association between cadmium exposure and sperm quality. In infertile men, increasing serum cadmium levels were significantly associated with abnormal sperm morphology and decreased sperm counts, sperm motility, and sperm viability (Akinloye et al. 2006). Another study found significant associations between blood cadmium levels and abnormal sperm morphology and decreased sperm motility in workers with slight to moderate lead exposure (Telišman et al. 2000). As noted previously, neither study adjusted for smoking. No significant correlations between blood cadmium levels and sperm quality were observed in infertile men with or without adjustment for smoking (Jurasović et al. 2004). Among men exposed to high levels of environmental cadmium, blood cadmium levels were significantly higher in men with abnormal digital rectal examinations of the prostate and trend analysis showed a dose-response relationship between cadmium exposure and the prevalence of abnormal prostate specific antigen (Zeng et al. 2004b).

No studies were located regarding reproductive effects in women after oral exposure to cadmium,

A number of animal studies have shown adverse reproductive effects to male and female reproductive capacity from cadmium exposure. In male rats and mice, acute oral exposure to near-lethal (60–100 mg/kg) doses can cause testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989), and concomitant decreased fertility (Kotsonis and Klaassen 1978). Lower-dose acute exposures of 25–50 mg/kg did not result in reproductive toxicity in male animals (Andersen et al. 1988; Bomhard et al. 1987; Dixon et al. 1976).

The following intermediate-duration dosing regimens resulted in neither testicular histopathologic lesions nor a decrease in male reproductive success: 0.25 mg Cd/kg/day via gavage for 10 weeks (Bomhard et al. 1987); 5 mg/kg/day via water for 30–90 days (Dixon et al. 1976); 2.5 mg/kg/day via food for 4 weeks (Groten et al. 1990); 8 mg/kg/day via water for 24 weeks (Kotsonis and Klaassen 1978); 3 mg/kg/day via food for 12 weeks (Loeser and Lorke 1977a, 1977b); 2.9 mg/kg/day via water for 14 weeks (Pleasants et al. 1992); and 4.64 mg/kg/day via water for 70–80 days (Zenick et al. 1982). Some dosing regimens have resulted in adverse reproductive effects. Male rats exposed to 8.58 mg Cd/kg/day in water for 10 weeks developed necrosis and atrophy of seminiferous tubule epithelium (Cha 1987). Rats exposed to 5.8 mg/kg/day via water for 14 weeks (Pleasants et al. 1992) or 11.6 mg/kg/day via water for 14 weeks (Pleasants et al. 1993) developed increased testes weight. Rats exposed to 12.9 mg/kg/day in water for 120 days developed significantly increased relative testis weight, decreased sperm count and motility, decreased seminiferous tubular diameter, and seminiferous tubular damage (pyknotic nuclei, multinucleated giant cells, interstitial edema, and dilated blood vessels) (Saxena et al. 1989). In a

protocol designed to assess the effects of vitamins on cadmium toxicity, Pleasants et al. (1992, 1993) reported that vitamins A and D_3 reduced the amount of cadmium-related increase in testis weight. Bomhard et al. (1987) reported no histopathologic lesions (other than those found in control animals as part of aging) in testes of rats receiving 10 weekly doses of 5 mg Cd/kg and followed for up to 30 months.

Higher doses of cadmium were generally needed to elicit a reproductive toxic response in females compared to the males. Although a dose of 65.6 mg Cd/kg/day via gavage for 10 days was sufficient to produce testicular atrophy and loss of spermatogenic element in male rats, no effects were seen in female rats up to 138 mg/kg/day (Borzelleca et al. 1989). Decreased percentage of fertilized females and percentage of pregnancies were reported at 61.32 mg Cd/kg/day via gavage for 10 days during gestation (Gd 6–15) (Machemer and Lorke 1981). No effect was seen at doses up to 18.39 mg/kg/day (Machemer and Lorke 1981). Baranski (1987) also reported no treatment related effects on number or percentage of females pregnant with 28.8 mg Cd/kg/day via gavage for gestation days (Gds) 1–20. Baranski and Sitarek (1987), however, administered 40 mg/kg by gavage 5 days/week for 14 weeks to female rats and observed a significant increased duration (twice as long) of the estrus cycle starting at 7–8 weeks and persisting to 14 weeks of exposure and the termination of the experiment. This adverse effect was not seen at 4 mg/kg (Baranski et al. 1983; Baranski and Sitarek 1987).

Petering et al. (1979) exposed female rats to either 2.61 mg/kg/day via drinking water for 60 days prior to gestation or during gestation, or 5.23 mg/kg/day via drinking water for 111 days including 90 days prior gestation plus 21 days during gestation. These doses had no significant effects compared with controls for the number of pups stillborn. Pond and Walker (1975) also observed no effects in females from a cadmium exposure of 19.7 mg/kg/day via food for 21–25 days, including Gd 1 through lactation day (Ld) 1, on number of pups born. No effects from a cadmium exposure on number of pups born to females were observed for an exposure of 8.2 mg/kg/day via food for 15 days, including Gd 6–20 (Sorell and Graziano 1990).

A dose of 10 mg Cd/kg/day once a day via gavage for 9 weeks (6 weeks prior to gestation and 3 weeks of gestation) significantly decreased the number of copulating and pregnant females, and the number of implants and live fetuses (Sutou et al. 1980). No effect was seen at 1 mg/kg/day (Sutou et al. 1980).

Reproductive effects on both male and female rats orally exposed to 2.5 mg/kg/day via drinking water for 180 days may have resulted in the observed decrease in litter size and increased interval between litters. Both males and females were treated over two generations. Three of five pairs failed to breed in the

second generations (Schroeder and Mitchener 1971). No histopathologic lesions were found in testes or uteri of dogs given cadmium chloride at 0.75 mg/kg/day via food for 3 months (Loeser and Lorke 1977b).

Male rats were exposed to 0–14 mg Cd/kg/day via food for 77 weeks. The incidence of prostatic hyperplasias was increased above controls (1.8%) from the 3.5 mg Cd/kg/day dose. The overall incidence for prostatic lesions for all cadmium-treated groups was much lower in zinc-deficient rats, possibly because of a marked increase in prostatic atrophy that was associated with reduced zinc intake. Moreover, there was not a clear dose-response increase in prostatic proliferative lesions. Testicular tumors (exclusively benign interstitial tumors) increased significantly only at the highest-dose cadmium with diets adequate in zinc. Male Wistar rats exposed to cadmium in the drinking water at 0, 25, 50, 100, or 200 ppm developed tumors of the prostate (50 ppm), testes (200 ppm), and hematopoietic system (50 ppm), while dietary zinc deficiency has complex, apparently inhibitory effects on cadmium carcinogenesis by this route (Waalkes and Rehm 1992).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-6 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

There are very limited data on the developmental effects of cadmium in humans. Several studies have examined the possible relationship between maternal cadmium levels and newborn size. No significant association between maternal blood cadmium levels and newborn body weight were observed in women with mean blood cadmium levels of 0.7 μg/L (Mokhtar et al. 2002), 1.04 μg/L (Nishijo et al. 2004b), 1.4 μg/L (Galicia-García et al. 1997), or 1.72 μg/L (Zhang et al. 2004) or urinary cadmium levels of >2 nmol/mmol creatinine (Nishijo et al. 2002); the Nishijo et al. (2002, 2004b), and Zhang et al. (2004) studies used statistical adjustments for maternal age, maternal size, and/or gestation age. Two studies found an association between cord blood cadmium levels and decreasing birthweight (Galicia-García et al. 1997; Salpietro et al. 2002); however, the association was only statistically significant in the Salpietro et al. (2002) study. A significant association between newborn height and maternal blood cadmium levels was observed in women with a mean blood cadmium level of 9.29 nmol/L (Nishijo et al. 2004b); other studies have not found this association (Mokhtar et al. 2002; Nishijo et al. 2002; Zhang et al. 2004). Nishijo et al. (2002) found a significant negative correlation between maternal urinary cadmium levels and gestation length; Mokhtar et al. (2002) did not find a significant association between maternal blood cadmium levels and gestation length.

Urinary cadmium content was measured in women 3 days after giving birth and compared to smoking habits and birth weight of offspring. Among nonsmoking women, when cadmium content was expressed as μg/L, cadmium levels were higher in women with infants of below-normal birth weight. However, when cadmium content was expressed as μg/g creatinine, cadmium levels were lower in women with infants with below-normal birth weight. Cadmium levels in smoking women were lower in both μg/L and μg/g in women with infants with below-normal birth weight (Cresta et al. 1989).

A number of studies in rats and mice indicate that cadmium can be fetotoxic from oral exposures prior to and during gestation. This fetotoxicity is most often manifested as reduced fetal or pup weights (Ali et al. 1986; Baranski 1987; Gupta et al. 1993; Kelman et al. 1978; Kostial et al. 1993; Petering et al. 1979; Pond and Walker 1975; Sorell and Graziano 1990; Sutou et al. 1980; Webster 1978; Whelton et al. 1988), but malformations, primarily of the skeleton, have been found in some studies (Baranski 1985; Machemer and Lorke 1981; Schroeder and Mitchener 1971). Malformations or skeletal effects reported include sirenomelia (fused lower limbs), amelia (absence of one or more limbs), and delayed ossification of the sternum and ribs (Baranski 1985); dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis (Machemer and Lorke 1981); and sharp angulation of the distal third of the tail (Schroeder and Mitchener 1971). Dosing levels were in the 1–20 mg/kg/day range.

The most sensitive indicator of developmental toxicity of cadmium in animals appears to be neuro-behavioral development. Offspring of female rats orally exposed to cadmium at a dose of 0.04 mg/kg/day prior to and during gestation had reduced exploratory locomotor activity and rotorod performance at age 2 months (Baranski et al. 1983). Pups from dams exposed to 0.7 mg/kg/day during gestation had significant delays in cliff aversion and swimming behavior. Locomotor activity was significantly increased. In post-weaning measurements, locomotor activity was significantly decreased in treated groups at 60 days of age; conditioned avoidance behavior was also significantly decreased when tested at 60 and 90 days of age (Ali et al. 1986).

Nagymajtenyi et al. (1997) also reported behavioral and functional neurotoxicological changes caused by cadmium in a three-generational study in rats. Three consecutive generations of Wistar rats were orally treated by gavage with 3.5, 7.0, or 14.0 mg Cd/kg bw (as cadmium chloride diluted in distilled water) over the period of pregnancy, lactation, and 8 weeks after weaning. Behavioral (open field behavior) and electrophysiological (spontaneous and evoked cortical activity, etc.) parameters of male rats from each generation were investigated at the age of 12 weeks. The main behavioral outcomes were increased

vertical exploration activity (rearing) and increased exploration of an open-field center. The spontaneous and evoked electrophysiological variables showed dose- and generation-dependent changes (increased frequencies in the electrocorticogram, lengthened latency and duration of evoked potentials, etc.) signaling a change in neural functions. The results indicate that low-level, multigeneration exposure of rats to inorganic cadmium can affect nervous system function.

Desi et al. (1998) continued the above studies to further evaluate cadmium associated changes in behavior and neurological function in rats following different dosage regimens during pregnancy. Female Wistar rats were given 3.5, 7.0, or 14.0 mg Cd/kg body weight (cadmium chloride dissolved in distilled water) in three different treatment regimes: days 5–15 of pregnancy; days 5–15 of pregnancy + 4 weeks of lactation; and days 5–15 of pregnancy + 4 weeks of lactation followed by the same oral treatment of male rats of the F_1 generation for 8 weeks. The behavioral (open-field exploration) and electrophysiological (electrocorticogram, cortical-evoked potentials, conduction velocity and refractory periods of a peripheral nerve) parameters of F_1 male rats exposed by various treatments were investigated at the age of 12 weeks. The results indicate that cadmium altered the spontaneous and evoked electrophysiological functions (e.g., increased the frequency of the electrocorticogram, lengthened the latency and duration of evoked potentials, etc.) in a dose- and duration-dependent manner. Only combining treatment during the prenatal development and the 4-week suckling period resulted in a significant dose-dependent decrease of horizontal and vertical exploratory activity and a significantly lower exploration frequency of the open-field center. The results suggest that low-level pre- and postnatal inorganic cadmium exposure affects the electrophysiological and higher order functions of the nervous system.

A study by Gupta et al. (1993) examined the developmental profiles of DNA, RNA, proteins, DNA synthesis, thymidine kinase activity, and concentrations of zinc and cadmium in the brain of neonates from dams exposed to cadmium acetate at 5–6.3 mg/kg/day in drinking water during gestation, and 7–8 mg/kg/day during a 21-day lactation period. Pup brain and body weights were significantly decreased in the cadmium exposed pups on Ld 7–21. Cadmium brain accumulation was significantly increased in exposed pups on Ld 7 and remained at similar levels on Ld 14 and 21. DNA and thymidine kinase brain levels were significantly decreased in treated pups compared with controls on Ld 7, 14, and 21. The toxicological significance of changes in DNA incorporation and thymidine kinase activity are uncertain.

Xu et al. (1993b) determined lipid peroxide (LPO) concentrations in rat pups in various organs as an index of cadmium toxicity. Male and female Wistar mice were exposed to cadmium in drinking water at 0, 5.7, or 14.25 mg/kg/day for 2 months prior to mating. The pregnant females continued to be exposed

during gestation and lactation. Litter size and pup survival rates were unaffected by cadmium. Body weights were not statistically different between the exposed and control groups. In pups, brain weights (at 5.7 and 14.25 mg/kg/day) and liver, kidney, and heart weights (at 14.25 mg/kg/day) were significantly decreased. Although the relative organ weights were lower in the high-dose group, the difference from controls was not statistically significant. LPO concentrations in all organs were significantly increased in pups on Ld 7 at 14.25 mg/kg/day except in the kidney; concentrations in the liver, heart, and brain were 131.5, 156, and 237.4%, respectively, of the concentrations in controls.

In contrast to most of the study results, Saxena et al. (1986) reported no developmental effects from an exposure to 21 mg Cd/kg/day via drinking water during gestation (Gd 0–20). This study evaluated simultaneous exposure to lindane (20 mg lindane/kg via gavage on Gd 6–14) and cadmium acetate in drinking water at doses that individually did not cause maternal or developmental effects. Maternal toxicity (significantly decreased weight gain) and developmental toxicity were only observed in the cadmium plus lindane group. Fetal body weight was significantly decreased; intrauterine death and the rate of skeletal anomalies were significantly increased. Anomalies consisted of decreased ossification, wavy ribs, and scrambled sternebrae.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-6 and plotted in Figure 3-2.

3.2.2.7 Cancer

A few studies of cancer rates among humans orally exposed to cadmium have been performed. No significant increase in cancer rates was found among residents of a cadmium-polluted village in England (Inskip et al. 1982) or in prostate, kidney, or urinary tract cancer among residents of a cadmium-polluted area of Belgium (Lauwerys and De Wals 1981). The geographic distribution of elevated rates of prostate cancer incidence was shown to parallel the distribution of elevated cadmium concentrations in water, soil, or grain crops in Alberta, Canada (Bako et al. 1982). In none of these three studies were estimates made of cadmium exposures of populations as a whole or of individuals with cancer. A retrospective mortality study was done for three areas of Japan classified on the basis of rice cadmium content as highly polluted, slightly polluted, or non-polluted. No significant differences were found in mortality from cancer of all sites including prostate cancer (Shigematsu 1984).

One study examined cadmium, zinc, and copper in human kidney tumors and normal kidneys. Kidneys with renal cell carcinoma in cortex from 31 cases (20 men and 11 women) were compared to kidneys of patients who had died from causes other than a malignant disease from 17 controls (9 men and 8 women). No one in this study had been occupationally exposed. Smoking habits for patients were recorded. The level of cadmium in tumor tissue did not correlate with cadmium in cortex or medulla in the same kidney. No significant difference was found between cases and controls, although smoking cases had higher levels of cadmium. It was concluded that cadmium was not a risk factor for renal cell carcinoma (Hardell et al. 1994).

Inhabitants of cadmium-polluted areas of Japan with elevated urinary retinol binding protein excretion had a mortality rate from malignant neoplasms no different from expected (Nakagawa et al. 1987). Overall, there is little evidence of an association between oral exposure to cadmium and increased cancer rates in humans, but the statistical power of the available studies to detect an effect was not high.

In rats and mice, earlier studies on chronic oral exposure to cadmium have not reported an increased overall cancer incidence or the incidence of specific tumor types (Kanisawa and Schroeder 1969; Levy and Clack 1975; Levy et al. 1975; Löser 1980; Mangler et al. 1988; Schroeder et al. 1964, 1965). However, maximum daily doses tested were only 1 mg/kg/day in mice (Schroeder et al. 1964) and 3.5 mg/kg/day in rats (Löser 1980) and, in most of these studies, histopathologic examination was limited compared to contemporary standards. Löser (1980) did perform a relatively thorough histological examination. A few additional animal studies of noncancer effects of chronic-duration oral cadmium exposure have indicated that no dose-related increases in tumors were found at maximum doses of 4.01 mg/kg/day in rats (Fingerle et al. 1982) or 8 mg/kg/day in mice (Watanabe et al. 1986).

Waalkes and Rehm (1992) evaluated the effects of chronic dietary zinc deficiency on oral cadmium carcinogenesis in male Wistar rats. Rats were exposed to cadmium at 0, 25, 50, 100, or 200 ppm with adequate (60 ppm) zinc or deficient zinc (7 ppm) in the diet for 77 weeks. A complete necropsy was performed on all animals. Survival rate and food consumption were not affected in this study. The incidence of prostatic proliferative lesions, both hyperplasias and adenomas, was significantly increased above controls (1.9%) in both zinc adequate (22.7%) and zinc deficient (15.4%) only in rats fed 50 ppm cadmium; the incidence in the higher exposure groups (13 and 0% in the 100 ppm group and 11.5 and 4% in the 200 ppm group). The overall incidence for prostatic lesions for all cadmium-treated groups was much lower in zinc-deficient rats, possibly because of a marked increase in prostatic atrophy that was associated with reduced zinc intake. Moreover, there was not a clear dose-response increase in prostatic

proliferative lesions. Cadmium treatment resulted in an elevated leukemia incidence (large granular lymphocytes; maximum 4.8-fold over control) in both zinc-adequate and zinc-deficient groups. A significant increase in the incidence of leukemia in the zinc-adequate diet was seen at 50 and 100 ppm cadmium, but not at 200 ppm. Zinc deficiency reduced the potency of cadmium (i.e., higher doses needed for comparable incidence). There was a consistent increase in the incidence of leukemia with an increasing cadmium dose in the zinc-deficient group, but the increase was statistically significant only at 200 ppm. The highest incidence of leukemia observed from cadmium (28%), however, was seen in the 200 ppm zinc-deficient rats. Testicular tumors (exclusively benign interstitial tumors) increased significantly only at 200 ppm cadmium with diets adequate in zinc. A significant positive trend was noted for development of testicular neoplasia with increased cadmium dose. Thus, oral cadmium exposure, in this study, was associated with tumors of the prostate, testes, and hematopoietic system in rats, while dietary zinc deficiency has complex, apparently inhibitory, effects on cadmium carcinogenesis by this route.

A subsequent study by Waalkes et al. (1993) using male B6C3F_1 mice evaluated the effects of cadmium exposure on tumor incidence at various times after the initiation of the carcinogenic process. The possible role of metallothionein in the susceptibility of transformed cells to cadmium cytotoxicity was also evaluated. At 5 weeks of age, mice received an intraperitoneal injection of *N*-nitrosodiethylamine (NDEA) at 90 mg/kg. At 2, 4, 8, 16, or 32 weeks post-NDEA injection, mice received water containing 1,000 ppm cadmium *ad libitum* for up to 48 weeks of post-NDEA exposure. Cadmium exposure caused a marked "reduction" in liver tumor incidence in NDEA treated mice even when given as late as 32 weeks after the initial NDEA treatment. Cadmium alone eliminated the spontaneously occurring incidence of liver tumors (i.e., none out of 25 compared with 5 of 25 in the controls). Liver tumors produced by NDEA were typically basophilic adenomas. Cadmium resulted in a modest reduction in lung tumor incidence, statistically significant (28% reduction) only for the 16–48-week cadmium treated group pretreated with NDEA. Lung tumors were typically adenomas of alveolar cell origin. Cadmium alone eliminated spontaneously occurring lung tumors compared with the controls. Cadmium did significantly reduce the multiplicity of tumors induced by NDEA. NDEA alone typically induced seven tumors per lung, while NDEA plus cadmium treatment reduced the number of tumors to 2.5–3.5 (data taken from a graph) with some cases showing an 80% reduction in tumor numbers. Lung tumors found in the cadmium plus NDEA-treatment groups were also of a smaller overall size than those found in the NDEA-only treatment groups. Relatively little metallothionein was present in liver carcinomas, liver adenomas, and lung adenomas as indicated by immunohistochemistry. This finding was confirmed biochemically for the liver tumors. The authors concluded that cadmium can effectively “impair” tumor formation in

the lungs and liver of male B6C3F$_1$ mice, and appears to be able to selectively destroy existing preneoplastic and/or tumor cells (adenomas). The mechanism may involve a reduced activity and responsiveness of the metallothionein system in transformed liver cells.

A two-stage initiation/promotion experiment evaluated the promoting effects of cadmium chloride in the drinking water in rats. Cadmium exposure resulted in the following alterations in tumorigenic outcome: in the liver, hepatocellular carcinomas (initiated with diethyl nitrosamine) were decreased; in the stomach, tumors (initiated with N-methyl-*N*'-nitro-nitrosoguanidine plus NaCl at 10% in the diet) were not affected; in the kidney, tumors (initiated with *N*-ethyl-*N*-hydroxyethyl nitrosamine) showed increased dysplastic foci but no increase in renal cell tumors; in the pancreas, tumors (initiated with *N*-nitrosobis [2-oxopropyl] amine), had a nonsignificant increase in adenocarcinomas (female hamster study); and in the skin (initiated with 7,12-dimethyl benz(a)anthracene), there was no effect (female SENCAR mouse study) (Kurokawa et al. 1989).

Neither the human nor the animal studies provide sufficient evidence to determine whether or not cadmium is a carcinogen by the oral route.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to cadmium.

Some guinea pigs died 2 or 6 weeks after being exposed in a skin depot (3.1 cm^2) to 2 mL of 0.239 molar aqueous of cadmium chloride (0.14 mg/kg body weight) (Wahlberg 1965). However, it is difficult to attribute these deaths to cadmium exposure, due to the low dose compared to oral LD_{50} values and to the fact that no necropsy was done to determine whether the exposed guinea pigs might have died from pneumonia (which killed some control guinea pigs) (Wahlberg 1965).

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to cadmium.

Dermal Effects. Among eczema patients routinely patch-tested with 2% cadmium chloride, 25 out of 1,502 showed some reaction (Wahlberg 1977). Since no reaction was found at lower dilutions in reactive patients (Wahlberg 1977), the effect was likely direct irritation of the skin and is indicated as a LOAEL value in Table 3-9.

No studies were located regarding dermal effects in animals after dermal exposure to cadmium.

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to cadmium.

Rats exposed to high concentrations of cadmium pigments or cadmium oxide in air had excessive lacrimation four hours after exposure (Rusch et al. 1986), possibly due to a direct irritation effect on the eyes.

3.2.3.3 Immunological and Lymphoreticular Effects

Dermal exposure to cadmium does not appear to affect the immune system significantly. One report of workers with extensive exposure to cadmium dust reported an increase in complaints of eczema (Friberg 1950); however, no subsequent studies have confirmed any association. Routine patch tests among dermatitis and eczema patients using up to 2% cadmium chloride solutions have found skin irritation at 2%, but no evidence of allergic reactions at a dose of 1% among people without known prior cadmium exposure (Rudzki et al. 1988; Wahlberg 1977) or among workers occupationally exposed to cadmium (Rudzki et al. 1988). Individuals with yellow tattoos containing cadmium sulfide often experience swelling of the surrounding skin on exposure to ultra violet (UV) irradiation (Bjornberg 1963); however, this may be the result of dermal damage from the photoconductivity of cadmium sulfide rather than a direct immunological reaction.

Guinea pigs showed no contact sensitization following intradermal or topical exposure to cadmium chloride at concentrations up to 0.5% (Wahlberg and Boman 1979). The NOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 3-9.

Table 3-9 Levels of Significant Exposure to Cadmium - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
ACUTE EXPOSURE									
Systemic									
Human	once	Dermal	1 Percent (%)	2 Percent (%)	(skin irritation)			Wahlberg 1977 CdCl2	
Rat (Sprague-Dawley)	2 hr	Ocular		99 mg/m³	(excessive lacrimation)	112 mg/m³	(eyes closed from exposure)	Rusch et al. 1986 CdSeS	
				97 mg/m³	(excessive lacrimation)				
Immuno/ Lymphoret									
Human	once		1 Percent (%)					Rudzki et al. 1988 CdCl2	

hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

No studies were located regarding the following health effects in humans or animals after dermal exposure to cadmium:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

The genotoxic potential of cadmium has been studied in *in vivo* studies of cadmium workers, members of the general population, and rodents as summarized in Table 3-10. Although not always consistent, these results suggest that cadmium is a clastogenic agent, as judged by the induction of DNA damage, micronuclei, sister chromatid exchange (SCE), and chromosomal aberrations.

Palus et al. (2003) examined peripheral lymphocytes from workers occupationally exposed to cadmium and found statistically significant increases compared to the control population in micronuclei rates and sister chromatid exchanges as well as evidence of an increased incidence of leukocytes with DNA fragmentation. Examination of lymphocytes and leukocytes from workers occupationally exposed to cadmium and lead or to cadmium, lead, and zinc showed increased frequency of chromosomal aberrations compared to control groups (Bauchinger et al. 1976; Deknudt and Leonard 1975; Deknudt et al. 1973), but this effect was not observed in men exposed primarily to cadmium (Bui et al. 1975; O'Riordan et al. 1978). Human lymphocytes from individuals inhabiting cadmium-polluted areas of China have been found to have increased micronuclei rates and a higher frequency of chromosomal aberrations and severe aberration types, in comparison to control populations with either no known exposure to cadmium or low-level exposure (Fu et al. 1999; Tang et al. 1990). Bui et al. (1975) examined blood samples from four female Japanese patients with Itai-Itai disease and found no evidence to indicate that cadmium is capable of inducing chromosomal damage.

For the most part, cadmium exposure via inhalation (Valverde et al. 2000), oral (Devi et al. 2001; Kasuba et al. 2002), and parenteral (Fahmy and Aly 2000; Kasuba et al. 2002; Mukherjee et al. 1988a; Saplakoglu et al. 1997; Wronska-Nofer et al. 1999; Zhou et al. 2004b) routes has been shown to be associated with DNA damage and induction of micronuclei in rodent cells.

Table 3-10. Genotoxicity of Cadmium *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Inhalation exposure:			
Human lymphocytes	Chromosomal aberrations	+	Deknudt et al. 1973
Human lymphocytes	Chromosomal aberrations	–	Bui et al. 1975
Human lymphocytes	Chromosomal aberrations	+	Deknudt and Leonard 1975
Human lymphocytes	Chromosomal aberrations	+	Bauchinger et al. 1976
Human lymphocytes	Chromosomal aberrations	–	O'Riordan et al. 1978
Human lymphocytes	Chromosomal aberrations	+	Alessio et al. 1993
Mouse bone marrow	DNA damage	+	Valverde et al. 2000
Mouse brain cells	DNA damage	+	Valverde et al. 2000
Mouse testicular cells	DNA damage	+	Valverde et al. 2000
Mouse liver cells	DNA damage	+	Valverde et al. 2000
Mouse kidney cells	DNA damage	+	Valverde et al. 2000
Mouse lung cells	DNA damage	+	Valverde et al. 2000
Mouse nasal epithelial cells	DNA damage	+	Valverde et al. 2000
Human lymphocytes	DNA damage	+	Palus et al. 2003
Human lymphocytes	Micronuclei	+	Palus et al. 2003
Human lymphocytes	Sister chromatid exchanges	+	Palus et al. 2003
Oral exposure:			
Rat bone cells	Altered gene expression	+	Ohba et al. 2007
Mouse bone marrow	Chromosomal aberrations	–	Deknudt and Gerber 1979
Mouse bone marrow	Chromosomal aberrations	+	Mukherjee et al. 1988b
Rat bone marrow	Chromosomal aberrations	–	Desi et al. 2000
Human leukocytes	Chromosomal aberrations	+	Shiraishi and Yoshida 1972
Human lymphocytes	Chromosomal aberrations	–	Bui et al. 1975
Human lymphocytes	Chromosomal aberrations	+	Tang et al. 1990
Human lymphocytes	Chromosomal aberrations	+	Fu et al. 1999
Mouse leukocytes	DNA damage	+	Devi et al. 2001
Rat lymphocytes	DNA damage	+	Kasuba et al. 2002
Rat spermatogenesis	Dominant lethal mutations	–	Sutou et al. 1980
Rat spermatogenesis	Dominant lethal mutations	–	Zenick et al. 1982
Rat lymphocytes	Micronuclei	+	Kasuba et al. 2002
Human lymphocytes	Micronuclei	+	Fu et al. 1999
Intraperitoneal exposure:			
Mouse oocytes	Aneuploidy	–	Mailhes et al. 1988
Mouse spermatocytes	Chromosomal aberrations	+	Selypes et al. 1992
Mouse bone marrow	Chromosomal aberrations	+	Fahmy and Aly 2000
Mouse spermatocytes	Chromosomal aberrations	+	Fahmy and Aly 2000
Mouse bone marrow	Chromosomal aberrations	–	Bruce and Heddle 1979
Mouse bone marrow	Chromosomal aberrations	+	Mukherjee et al. 1988a

Table 3-10. Genotoxicity of Cadmium *In Vivo*

Species (test system)	End point	Results	Reference
Mouse spermatocytes	Chromosomal translocations	–	Gilliavod and Leonard 1975
Rat lung cells	DNA strand breaks	+	Saplakoglu et al. 1997
Rat kidney cells	DNA strand breaks	+	Saplakoglu et al. 1997
Rat liver cells	DNA strand breaks	–	Saplakoglu et al. 1997
Mouse spermatogenesis	Dominant lethal mutations	–	Epstein et al. 1972
Mouse spermatogenesis	Dominant lethal mutations	–	Gilliavod and Leonard 1975
Mouse oocytes	Dominant lethal mutations	–	Suter 1975
Rat lymphocytes hprt locus	Gene mutation	±	Jianhua et al. 2006
Mouse bone marrow	Micronuclei	±	Mukherjee et al. 1988a
Mouse bone marrow	Micronuclei	+	Wronska-Nofer et al. 1999
Mouse bone marrow	Micronuclei	+	Fahmy and Aly 2000
Mouse bone marrow	Sister chromatid exchanges	+	Mukherjee et al. 1988a
Mouse bone marrow	Sister chromatid exchanges	+	Fahmy and Aly 2000
Mouse spermatozoa	Sperm morphology	–	Bruce and Heddle 1979
Mouse spermatozoa	Sperm morphology	+	Mukherjee et al. 1988a
Syrian hamster embryo cells	Transformation	+	DiPaulo and Castro 1979
Subcutaneous exposure:			
Mouse testicular cells	Altered gene expression	+	Zhou et al. 2004b
Mouse blastocysts	Aneuploidy	+	Watanabe and Endo 1982
Syrian hamster oocytes	Aneuploidy	+	Watanabe et al. 1979
Mouse bone marrow	Chromosomal aberrations	+	Karmakar et al. 1998
Mouse testicular cells	DNA damage	–	Zhou et al. 2004b
Rat lymphocytes	DNA damage	+	Kasuba et al. 2002
Rat lymphocytes	Micronuclei	+	Kasuba et al. 2002
Mouse bone marrow	Sister chromatid exchanges	–	Nayak et al. 1989
Mouse fetal liver and lung cells	Sister chromatid exchanges	–	Nayak et al. 1989

– = negative result; + = positive result; ± = weakly positive result; DNA = deoxyribonucleic acid

Evidence of the potential for cadmium to induce SCE (Fahmy and Aly 2000; Mukherjee et al. 1988a; Nayak et al. 1989) and chromosomal aberrations (Bruce and Heddle 1979; Desi et al. 2000; DiPaulo and Castro 1979; Fahmy and Aly 2000; Karmakar et al. 1998; Mukherjee et al. 1988a; Tang et al. 1990; Watanabe et al. 1979) is mixed. Data regarding the aneugenic potential of cadmium are limited and also conflicting. Watanabe and Endo (1982) observed an increased incidence of mouse blastocysts with trisomies and triploidies from female mice treated subcutaneously with cadmium compared to control mice. Watanabe et al. (1979) reported that subcutaneous exposure to cadmium induced mutagenicity in hamster oocytes, and in particular, induced the production of diploid oocytes. However, Mailhes et al. (1988) did not observe an increased incidence of hyperploid oocytes in female mice treated with cadmium via intraperitoneal injection.

No evidence for germ cell mutations (the dominant lethal test) has been observed in male rats orally exposed to cadmium (Sutou et al. 1980; Zenick et al. 1982) or in mice exposed to cadmium via inhalation (Gilliavod and Leonard 1975; Suter 1975) or intraperitoneal exposure (Epstein et al. 1972). However, chromosomal aberrations in mouse spermatocytes and Syrian hamster oocytes (Fahmy and Aly 2000; Selypes et al. 1992; Watanabe et al. 1979) and altered gene expression in mouse testicular cells (Zhou et al. 2004b) have been observed following cadmium exposure.

Data based on *in vitro* examination of the genotoxic effects of cadmium in microorganisms, yeast, insects, and mammalian cells are summarized in Table 3-11. For the most part, *in vitro* data support the *in vivo* data suggesting that cadmium has the potential to induce DNA damage, micronuclei, chromosomal aberrations, and genetic mutations.

In vitro studies have shown that cadmium induces genetic mutations in hamster and mouse cells (Amacher and Paillet 1980; Filipic and Hei 2004; Honma et al. 1999; Jianhua et al. 2006; Oberly et al. 1982), transformation in rodent cells (Casto et al. 1979; Terracio and Nachtigal 1988), unscheduled DNA synthesis in rat cells (Denizeau and Marion 1989), DNA breaks in human cells (Depault et al. 2006; Lopez-Ortal et al. 1999; Mikhailova et al. 1997), DNA lesions in hamster cells (Jianhua et al. 2006), and inhibits DNA repair in human and hamster cells (Lutzen et al. 2004; Lynn et al. 1997). Misra et al. (1998) did not observe DNA damage in rat cells following treatment with cadmium, but DNA damage has been noted in human cells (Fatur et al. 2002; Rozgaj et al. 2002).

Table 3-11. Genotoxicity of Cadmium *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Bacillus subtilis	DNA repair	No data	±	Nishioka 1975
B. subtilis	DNA repair	No data	±	Kanematsu et al. 1980
Salmonella typhimurium (plate incorporation)	Gene mutation	–	–	Bruce and Heddle 1979
S. typhimurium (liquid suspension)	Gene mutation	–	–	Milvy and Kay 1978
S. typhimurium (liquid suspension)	Gene mutation	No data	±	Mandel and Ryser 1984
S. typhimurium (plate incorporation)	Gene mutation	–	+	Wong 1988
Eukaryotic organisms:				
Yeast:				
Saccharomyces cerevisiae	Gene mutation	No data	+	Putrament et al. 1977
S. cerevisiae	lntrachromosomal recombination	No data	+	Schiestl et al. 1989
Insects:				
Drosophila melanogaster	Dominant lethal mutations	No data	+	Vasudev and Krishnamurthy 1979
D. melanogaster	Nondisjunction	No data	–	Ramel and Magnusson 1979
D. melanogaster	Sex-linked recessive lethal mutations	No data	–	Inoue and Watanabe 1978
Mammalian cells:				
Mouse spleen cells	Chromosomal aberration	No data	+	Fahmy and Aly 2000
Chinese hamster ovary Hy cells	Chromosomal aberration	No data	+	Rohr and Bauchinger 1976
Chinese hamster ovary CHO cells	Chromosomal aberration	No data	+	Deaven and Campbell 1980
Chinese hamster ovary CHO cells	Chromosomal aberration	No data	+	Cai and Arenaz 1998
Human leukocytes	Chromosomal aberrations	No data	+	Shiraishi et al. 1972
Human blood lymphocytes	Chromosomal aberration	No data	–	Paton and Allison 1972
Human blood lymphocytes	Chromosomal aberration	No data	+	Shiraishi et al. 1972
Human blood lymphocytes	Chromosomal aberration	No data	–	Deknudt and Deminatti 1978

Table 3-11. Genotoxicity of Cadmium *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Human blood lymphocytes	Chromosomal aberration	No data	±	Gasiorek and Bauchinger 1981
Human blood lymphocytes	DNA breaks	No data	+	Depault et al. 2006
Human lymphoblastoid cells	DNA breaks	No data	+	Mikhailova et al. 1997
Human fetal hepatic WRL-68 cells	DNA breaks	No data	+	Lopez-Ortal et al. 1999
Chinese hamster ovary CHO-K1 cells	DNA damage	No data	–	Misra et al. 1998
Rat L6 myoblast cells	DNA damage	No data	–	Misra et al. 1998
Rat Clone 9 liver cells	DNA damage	No data	–	Misra et al. 1998
Rat TRI 1215 liver cells	DNA damage	No data	–	Misra et al. 1998
Human blood lymphocytes	DNA damage	No data	+	Rozgaj et al. 2002
Human hepatoma cells (HepG2)	DNA damage	No data	+	Fatur et al. 2002
V79 Chinese hamster lung cells	DNA lesions	No data	+	Jianhua et al. 2006
Chinese hamster ovary CHO-K1 cells	DNA repair	No data	+	Lynn et al. 1997
Human 293T-Tet-Off-hMLH1 cells	DNA repair	No data	+	Lutzen et al. 2004
V79 Chinese hamster lung cells hprt locus	Gene mutation	No data	+	Jianhua et al. 2006
A_L human-hamster hybrid CD59 gene	Gene mutation	No data	+	Filipic and Hei 2004
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	No data	±	Amacher and Paillet 1980
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	No data	+	Oberly et al. 1982
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	+	+	Honma et al. 1999
Human blood lymphocytes	Micronuclei	No data	+	Migliore et al. 1999
Human blood lymphocytes (G_0 phase)	Micronuclei	No data	–	Kasuba and Rozgaj 2002
Human blood lymphocytes (S phase)	Micronuclei	No data	+	Kasuba and Rozgaj 2002
Human diploid fibroblasts (MRC-5)	Micronuclei	No data	+	Seoane and Dulout 2001
Mouse spleen cells	Sister chromatid exchanges	No data	+	Fahmy and Aly 2000
Human blood lymphocytes	Sister chromatid exchanges	No data	–	Bassendowska-Karska and Zawadzka-Kos 1987
Human blood lymphocytes (G_0 phase)	Sister chromatid exchanges	No data	–	Saplakoglu and Iscan 1998

Table 3-11. Genotoxicity of Cadmium *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Human blood lymphocytes (S phase)	Sister chromatid exchanges	No data	+	Saplakoglu and Iscan 1998
Syrian hamster embryo cells	Transformation	No data	+	Casto et al. 1979
Rat ventral prostate cells	Transformation	No data	+	Terracio and Nachtigal 1988
Rat hepatocytes	Unscheduled DNA synthesis	No data	+	Denizeau and Marion 1989

— = negative result; + = positive result; ± = weakly positive; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NA = not applicable; RNA = ribonucleic acid

Chromosomal aberrations following cadmium exposure have been observed in Chinese hamster ovary cells (Cai and Arenaz 1998; Deaven and Campbell 1980; Rohr and Bauchinger 1976), but studies on human cells have shown mixed results (Deknudt and Deminatti 1978; Gasiorek and Bauchinger 1981; Paton and Allison 1972; Shiraishi et al. 1972). For the most part, *in vitro* studies have not shown cadmium to induce SCE in human cells (Bassendowska-Karska and Zawadzka-Kos 1987; Saplakoglu and Iscan 1998). However, a study by Fahmy and Aly (2000) did observe SCE in mouse spleen cells following cadmium treatment. Kasuba and Rozgaj (2002) and Saplakoglu and Iscan (1998) evaluated the ability of cadmium to induce micronuclei and SCE in human lymphocytes *in vitro* respectively, at two different stages of the cell cycle, G_0 and S phase. These studies observed that the genotoxicity of cadmium may vary depending on the stage of the cell cycle as both micronuclei and SCE were induced in cells in S phase, but not in cells in G_0 phase. These observations may in part explain some of the contradictory findings regarding cadmium genotoxicity in the literature.

Positive mutagenicity results have been found in some studies using bacterial cells (Kanematsu et al. 1980; Mandel and Ryser 1984; Nishioka 1975; Wong 1988), in studies using yeast (Putrament et al. 1977; Schiestl et al. 1989), and in a single study using *Drosophila melanogaster* (Vasudev and Krishnamurthy 1979). Other studies report negative mutagenicity results in bacterial cells (Bruce and Heddle 1979; Milvy and Kay 1978) and in *D. melanogaster* (Inoue and Watanabe 1978; Ramel and Mangusson 1979).

3.4 TOXICOKINETICS

Cadmium metal and cadmium salts are not well absorbed; approximately 25, 1–10, or <1% of the dose is absorbed following inhalation, oral, or dermal exposure. Several factors can influence inhalation and oral absorption efficiency; for example, cadmium in cigarette smoke has a higher absorption efficiency due to its small particle size and because cadmium is more efficiently absorbed from the gastrointestinal tract in individuals with poor iron status. Following absorption from any route of exposure, cadmium widely distributes throughout the body, with the highest concentrations found in the liver and kidney. Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. Absorbed cadmium is excreted very slowly, with urinary and fecal excretion being approximately equal. Approximately 0.007 and 0.009% of the body burden is excreted in the urine and feces, respectively, per day.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Cadmium metal and cadmium salts have low volatility and exist in air primarily as fine suspended particulate matter. When inhaled, some fraction of this particulate matter is deposited in the airways or the lungs, and the rest is exhaled. Large particles (greater than about 10 μm in diameter) tend to be deposited in the upper airway, while small particles (approximately 0.1 μm) tend to penetrate into the alveoli. While some soluble cadmium compounds (cadmium chloride and cadmium sulfate) may undergo limited absorption from particles deposited in the respiratory tree, the major site of absorption is the alveoli. Thus, particle size, which controls alveolar deposition, is a key determinant of cadmium absorption in the lung (Nordberg et al. 1985).

No direct data are available on cadmium deposition, retention, or absorption in the human lung. Data from animal studies indicate that lung retention is greatest after short-term exposure (5–20% after 15 minutes to 2 hours) (Barrett et al. 1947; Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986). The initial lung burden declines slowly after exposure ceases (Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986) due to absorption of cadmium and lung clearance of deposited particles. After longer periods of inhalation exposure to cadmium, somewhat lower lung retentions are found (Glaser et al. 1986). The absorption of cadmium in lung differs somewhat among chemical forms, but the pattern does not correlate with solubility (Glaser et al. 1986; Rusch et al. 1986).

Based on comparison of cadmium body burdens in human smokers and nonsmokers, cadmium absorption from cigarettes appears to be higher than absorption of cadmium aerosols measured in animals (Nordberg et al. 1985). The chemical form of cadmium in cigarette smoke is likely to be similar to that produced by other combustion processes, primarily cadmium oxide aerosols. The greater absorption of cadmium from cigarette smoke is likely due to the very small size of particles in cigarette smoke and the consequent very high alveolar deposition (Nordberg et al. 1985; Takenaka et al. 2004).

Based on the physiology of the human respiratory tree, a comprehensive model has been developed to predict the kinetics of inhaled cadmium in humans (Nordberg et al. 1985). Results of this model suggest that only about 5% of particles >10 μm in diameter will be deposited, up to 50% of particles <0.1 μm will be deposited, and between 50 and 100% of cadmium deposited in the alveoli will ultimately be absorbed (Nordberg et al. 1985).

3.4.1.2 Oral Exposure

Most ingested cadmium passes through the gastrointestinal tract without being absorbed (Kjellström et al. 1978). Measurement of gastrointestinal absorption is complicated by the fact that not all of a dose initially retained in the gastrointestinal system can be considered to be absorbed, because some portion may be trapped in the intestinal mucosa without crossing into the blood or lymph (Foulkes 1984). Thus, measures of whole-body cadmium retention may overestimate cadmium absorption (at least in the short-term). On the other hand, some absorbed cadmium may be excreted in urine or feces, so that retention may underestimate exposure. However, this underestimate is probably minor because excretion of absorbed cadmium is very slow (see Section 3.4.4.2).

Cadmium absorption has been estimated based on the retention of cadmium in the bodies of humans following ingestion of radioactive cadmium. Estimated cadmium absorption ranged from 1.1 to 10.6% (Flanagan et al. 1978; McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973; Shaikh and Smith 1980; Vanderpool and Reeves 2001). Although some studies have reported higher absorption levels (25–42%), this was based on cadmium retention measurements for 3–5 days after exposure that was probably too short to accurately measure cadmium transfer from the intestinal mucosa to circulation (Crews et al. 2000; Rahola et al. 1973). Using estimated cadmium intakes from national data and measured renal and urinary cadmium levels in healthy nonsmokers, cadmium absorption rates of 3–5% have been estimated (Ellis et al. 1979; Morgan and Sherlock 1984). In a balance study of women with high background cadmium intakes (mean urinary cadmium levels of 2.7–5.16 μg/g creatinine); the mean absorption rate in subjects examined for 7 days was 6.5% (Horiguchi et al. 2004).

The body store of iron influences cadmium absorption; subjects with low iron stores (assessed by serum ferritin levels) had an average absorption of 6 and 8.9%, while those with adequate iron stores had an average absorption of 2.3 and 2.4% (Flanagan et al. 1978; Shaikh and Smith 1980). A third study of anemic females with high background cadmium levels did not find a significant alteration in cadmium absorption, as compared to healthy females; however, cadmium absorption was lower in the anemic group (13.6%) than in healthy group (27.4%) (Horiguchi et al. 2004). It is not known if the differences in the methods used to estimate cadmium absorption (kinetic study using radiolabelled cadmium versus a balance study) or the high background cadmium intake in the Horiguchi study resulted in the discrepancy between the two studies. There is some indication that not all forms of cadmium are equally absorbed. Some populations with high dietary-cadmium exposure from Bluff oysters (McKenzie-Parnell et al. 1988)

or seal meat (Hansen et al. 1985) have been found not to have elevated blood-cadmium levels, perhaps due to the particular form of cadmium in these foods.

Crews et al. (2000) estimated that 42% of a cadmium dose incorporated into porridge was retained in the body 5 days after exposure (as measured by fecal excretion of radiolabelled cadmium); however, the fecal collection period was probably too short to accurately measure cadmium absorption. The investigators also attempted to measure cadmium absorption in 12-month-old infants; 18% of the labeled cadmium in the porridge was retained in the body after 4 days. As with the adult data, the collection period may have been too short to accurately measure cadmium absorption in the infants.

Most estimates of cadmium absorption in animals are somewhat lower than the values found from human studies, particularly after prolonged exposure. In mice, 0.27–3.2% of an oral dose of cadmium chloride was retained after 3–5 days (Bhattacharyya et al. 1981; Engstrom and Nordberg 1979), and in rats, 2–3% of a single oral dose of cadmium chloride was retained (Moore et al. 1973; Schafer et al. 1990). Following 30 days of oral exposure, 0.2–0.3% of an administered dose was retained in rats (Muller et al. 1986). After 4 weeks of dietary exposure to cadmium, absorption of cadmium was reduced to one-third the absorption of rats without pre-exposure to cadmium (Schafer et al. 1990). Cadmium pigments (cadmium sulfide and cadmium sulfoselenide) appear to be absorbed much less than cadmium chloride in rats (ILZRO 1977). Increases in absorption have been observed during gestation and lactation, 0.37 and 0.35% of cadmium administered via gavage was absorbed in mice on gestation days 8 and 15 and 0.56, 0.60, and 0.30% on lactation days 10, 17, and 24, as compared to 0.27% in nonpregnant controls; absorption was only significantly different from nonpregnant controls on lactation days 10 and 17 (Bhattacharyya et al. 1981). Similar findings were observed in mice continuously exposed to cadmium during pregnancy and/or lactation (Bhattacharyya et al. 1982, 1986).

The absorption of cadmium from the gastrointestinal tract has been extensively studied in rats and mice, and a number of factors are recognized that influence absorption. Absorption appears to take place in two phases: uptake from lumen into mucosa, and transfer into the circulation (Foulkes 1985). Phase 1 may involve sequestering of cadmium by metallothionein (Foulkes 1980), but any protective effect is overloaded at moderate doses (Kotsonis and Klaassen 1978). Uptake behaves like a saturable process with fractional absorption decreasing at high concentrations (Foulkes 1980). There is evidence, however, to suggest that this saturation results from charge neutralization at the membrane (Foulkes 1985), so that it need not be assumed that there is a specific system for carrying cadmium into the body. At doses high enough to damage gastrointestinal mucosa, fractional absorption is increased (Andersen et al. 1988; Goon

and Klaassen 1989; Lehman and Klaassen 1986). Cadmium bound to metallothionein was absorbed by rats to a lesser extent than cadmium added to the diet as cadmium chloride, but kidney cadmium content was only slightly less (Groten et al. 1990).

Maitani et al. (1984) compared the distribution of cadmium after oral administration of either cadmium ions or Cd-thionein in male CF-1 mice given 0.5 mg Cd/kg, per os (po), as cadmium chloride in saline, cadmium chloride in control rat liver homogenate, cadmium thionein in saline, Cd-TH in liver homogenate, or liver homogenate from Cd-treated rats. In all cases, 85–90% of the cadmium dose was present in feces within 24 hours. However, in groups receiving cadmium chloride, more cadmium was found in feces on days 2 and 3, compared to those receiving cadmium-thionein. In a companion study, tissue levels indicated that less cadmium was absorbed when rats received cadmium-thionein in saline than cadmium chloride in saline. Cadmium-thionein added to liver homogenate or liver homogenate containing cadmium-thionein increased the absorption of cadmium, resulting in renal cadmium levels similar to those in mice receiving cadmium chloride in saline. The kidney/liver cadmium concentration ratio (9) was the same for cadmium-thionein in all three media. Although Cd-TH gave much higher kidney/liver cadmium ratios than cadmium chloride (9 versus 2), renal cadmium concentrations were the same or lower than after cadmium chloride treatments. The authors concluded that the high kidney/liver cadmium ratio after cadmium-thionein treatment versus cadmium chloride was due to lower concentrations of cadmium in liver rather than marked increases in renal cadmium levels. While the chemical form of cadmium administered affects the absorption and distribution, the amount of cadmium reaching the kidney after cadmium-thionein administration is similar to that after cadmium chloride administration.

At moderate doses of cadmium, the presence of divalent and trivalent cations, such as calcium, chromium, magnesium, and zinc, may decrease cadmium uptake, probably by a nonspecific effect on the charge distribution of the intestinal brush border membrane (Foulkes 1985). However, the influence of cations on cadmium absorption is complex, because zinc can increase the amount of cadmium absorbed from the intestine (Jaeger 1990). A refined diet high in fat and protein increases cadmium absorption in mice, partially due to increased gastrointestinal passage time (Schafer et al. 1986). Studies in newborn rats and pigs also provide evidence that diet consituents influence cadmium absorption; absorption of cadmium chloride was higher when administered in water compared to cereal-based infant formula (Eklund et al. 2001, 2004). Diets low in iron increase cadmium absorption (Flanagan et al. 1978; Reeves and Chaney 2001, 2002; Schafer et al. 1990); a diet low in calcium will also increase cadmium absorption (Reeves and Chaney 2001, 2002). In contrast, low levels of dietary iron did not increase cadmium

absorption in suckling piglets; however, iron supplementation did increase cadmium absorption (Öhrvik et al. 2007); this difference may be due to the high cadmium dose used in the study. Zinc deficiency may result in an increased accumulation of cadmium in the intestinal wall, but does not affect transport into the blood (Foulkes and Voner 1981; Hoadley and Cousins 1985). The absorption of cadmium in rats depends on age, with measured absorption decreasing from 12 to 5 to 0.5% at 2 hours, 24 hours, and 6 weeks after birth, respectively (Sasser and Jarboe 1977). Sasser and Jarboe (1980) also reported that absorption of cadmium in the gastrointestinal tract of young guinea pigs was 20-fold higher than in adult guinea pigs. Thus, for a given individual, the absorption following oral exposure to cadmium is likely to depend on physiologic status (age; body stores of iron, calcium, and zinc; pregnancy history; etc.) and, also, on the presence and levels of ions and other dietary components ingested with the cadmium.

3.4.1.3 Dermal Exposure

A few measurements of dermal absorption of cadmium in animals have been made, with only one *in vitro* study using human skin to determine the percutaneous absorption of cadmium.

A study by Wester et al. (1992) evaluated the percutaneous absorption of cadmium from water and soil into and through human skin using *in vitro* skin cells. Radioactive cadmium (^{109}cadmium chloride) was made to a concentration of 116 ppb in water or 13 ppb in filtered soil (26% sand, 26% clay, 48% silt, 0.9% organic content). Cadmium chloride was administered either at 5 μL/cm^2 or 2 volumes of 2.5 μL/cm^2 (the same amount of cadmium apparently applied). Human cadaver skin dermatomed at 500 μm was placed in flow-through skin cells and perfused with human plasma. Approximately 0.1–0.6% of the cadmium chloride in water entered the plasma perfusate over the 16-hour perfusion period, while 2.4–12.7% of applied dose remained in the skin. Most of the cadmium (74–93%) remained unabsorbed and was recovered from the skin surface. Total recoveries ranged from 88±20 to 103±3. When cadmium-contaminated soil (13 ppb cadmium chloride) was applied to the skin surface, plasma levels ranged from 0.02 to 0.07% of the applied dose, while the skin contained 0.06–0.13% of applied dose. Surface wash ranged from 82 to 102% of applied dose. Total recoveries were from 83±33 to 106±2. The large differences between water and soil absorption into the plasma and retention in the skin were attributed to differences in cadmium partition coefficients, measured to be 3.61×10^1 for stratum corneum (powdered):water and 1.03×10^5 for soil:water. These measurements indicate that soil has a relatively higher affinity for cadmium than does the stratum corneum. The transfer of cadmium from soil to skin depends on the soil's binding capacity and water retention and variables describing the physical contact with the skin. When cadmium levels in the soil were increased from 6.5 to 65 ppb, skin levels

correspondingly increased, but plasma receptor fluid levels remained constant. This suggests that, with *in vitro* perfusion, the surface concentration of cadmium will influence skin cadmium concentration, but that absorption into plasma receptor fluid is relatively independent of the skin surface concentration. The authors offer the caveat that *in vitro* methods can influence results and therefore, the receptor fluid accumulation must be interpreted with caution. The authors calculate that a whole-body exposure to cadmium at 116 ppb in water with a 0.5% absorption will result in a daily systemic intake of about 10 µg cadmium.

A few animal studies are available that describe the percutaneous absorption of cadmium as estimated from the accumulation of cadmium in the liver and kidneys of mice and rabbits. Male rabbits (strain not specified) was dosed with cadmium chloride percutaneously with a 1% aqueous solution (6.1 mg cadmium) or 2% ointment (12.2 mg cadmium) over a 10-cm^2 shaved area (Kimura and Otaki 1972). Animals were treated 5 times over 3 weeks (duration of exposure not reported) and were killed 2 weeks after the last application. Only cadmium contents of liver and kidney were measured, so total absorption through the skin may have been greater. Accumulated amounts of cadmium in the liver and kidneys were found to be 0.4–0.61% 2 weeks after the end of cadmium exposure. This percentage was similar for aqueous solution or hydrocarbon ointment. Similarly, male hairless mice (strain not specified) were dosed with cadmium chloride percutaneously with a 2% ointment (containing 0.61 mg cadmium) 1 or 5 times in a week (duration of exposure not reported) and killed 1 week later (Kimura and Otaki 1972). Accumulated amounts of cadmium in the liver and kidneys were found to be 0.2–0.87%.

Cadmium was detected in liver, kidneys, and urine following dermal exposure in guinea pigs (Skog and Wahlberg 1964). The disappearance of cadmium from cadmium chloride in water applied to guinea pig skin was dependent on concentration, with a peak mean absorption of 1.8% over 5 hours at 0.239 molar cadmium (about a 2.7% solution). Less absorption occurred both at higher and lower concentrations of a cadmium chloride solution applied to the skin (Skog and Wahlberg 1964).

The results from all of these studies suggest that dermal absorption is slow, and would be of concern only in situations where concentrated solutions would be in contact with the skin for several hours or longer.

3.4.2 Distribution

Cadmium is widely distributed in the body, with the major portion of the body burden located in the liver and kidney. Animals and humans appear to have a similar pattern of distribution that is relatively independent of route of exposure, but somewhat dependent on duration of exposure.

3.4.2.1 Inhalation Exposure

Cadmium was found in autopsy samples from nearly all organs of a worker extensively exposed to cadmium dust, with greatest concentrations in the liver, kidney, pancreas, and vertebrae (Friberg 1950). In workers dying from inhalation of cadmium, lung-cadmium concentration was somewhat lower than liver or kidney cadmium concentration (Beton et al. 1966; Lucas et al. 1980; Patwardhan and Finckh 1976). The concentration of cadmium in the liver of occupationally exposed workers generally increases in proportion to intensity and duration of exposure to values up to 100 μg/g (Gompertz et al. 1983; Roels et al. 1981b). The concentration of cadmium in the kidney rises more slowly than in the liver after exposure (Gompertz et al. 1983) and begins to decline after the onset of renal damage at a critical concentration of 160–285 μg/g (Roels et al. 1981b).

In animals acutely exposed to cadmium carbonate aerosols, about 60% of the inhaled dose is found in the gastrointestinal tract, transported by mucociliary clearance (Moore et al. 1973). Following a 2-hour inhalation of approximately 100 mg/m^3 of cadmium, cadmium concentration in rat liver increased from an initial concentration of 0.8 μg/g in males and 1.9 μg/g in females immediately after exposure up to a peak of about 2 μg/g in males and 3.8 μg/g in females 1 week postexposure, then declined to 1.7 and 2.5 μg/g, respectively, by 30 days postexposure. The kidney concentrations were initially <0.5 μg/g in males and females, rising to approximately 8 μg/g in both sexes by 1 week postexposure and to 18 μg/g in males and 15 μg/g in females by 30 days postexposure (Rusch et al. 1986).

3.4.2.2 Oral Exposure

As discussed in Chapter 6, most nonoccupationally exposed people are exposed to cadmium primarily through the diet. Cadmium can be detected in virtually all tissues in adults from industrialized countries, with greatest concentrations in the liver and kidney (Chung et al. 1986; Sumino et al. 1975). Average cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40–50 μg/g wet weight) between ages 50 and 60, after which kidney concentrations plateau or decline (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984). Liver cadmium

concentrations also begin near zero at birth, increase to typical values of 1–2 μg/g wet weight by age 20–25, then increase only slightly thereafter (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984; Sumino et al. 1975).

Distribution of cadmium in animals after oral exposure is similar to that found in humans, with highest accumulation in the liver and kidneys, and lower levels spread throughout the rest of the body (Kotsonis and Klaassen 1978; Weigel et al. 1984). Liver and kidney cadmium concentrations are comparable after short-term exposure (Andersen et al. 1988; Jonah and Bhattacharyya 1989), but the kidney concentration exceeds the liver concentration following prolonged exposure (Kotsonis and Klaassen 1978), except at very high exposures (Ando et al. 1998; Bernard et al. 1980; Hiratsuka et al. 1999). In mice orally exposed to cadmium during lactation, 53% of the whole-body cadmium was found in the kidneys as compared to 27% in nonpregnant controls (Bhattacharyya et al. 1982).

Maitani et al. (1984) compared the distribution of cadmium in rats after an acute oral administration of either cadmium ions or cadmium bound to metallothionein. In all cases, 85–90% of the dose was present in the feces within 24 hours postexposure. More of the cadmium-thionein was retained after 2–3 days, and less of the cadmium-thionein was distributed to the liver than was the case for the ionic cadmium. Kidney levels were comparable.

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in a study in Czechoslovakia, the concentration of cadmium in the placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). In mice orally exposed to cadmium during pregnancy, maternal blood, placental, and fetal cadmium concentrations were essentially equal among control animals (with environmental cadmium exposure), but placental concentration increased with cadmium dose much more rapidly than either maternal blood or fetal cadmium concentration (Sorell and Graziano 1990). Thus, timing and level of cadmium exposure may influence the uptake of cadmium by the placenta, perhaps explaining the conflicting human studies.

Goyer and Cherian (1992) localized metallothionein in full-term human placenta and in fetal cells in human placenta. Metallothionein was present in trophoblasts (which facilitate transport of substances

entering the placenta from the maternal blood), Hofbauer cells (motile macrophages capable of phagocytosis and protein ingestion), amniotic epithelial cells (fetal derivatives), and decidual cells (endometrial stromal cells that have been transformed under hormonal influence into large pale cells, rich in glycogen). The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein.

Cadmium levels in human milk are 5–10% of levels in blood, possibly due to inhibited transfer from blood because of metallothionein binding of cadmium in blood cells (Radisch et al. 1987). Bhattacharyya et al. (1982) examined the maternal transfer of cadmium to pups during gestation and lactation in mice. Approximately 3, 11, and 25% of maternal cadmium was transferred to the pups following gestation-only exposure, lactation-only exposure, and gestation and lactation exposure, respectively.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to cadmium. Elevated levels of cadmium were found in the liver and kidneys of rabbits and mice dermally exposed to cadmium (Kimura and Otaki 1972).

3.4.3 Metabolism

Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. The cadmium (+2) ion does bind to anionic groups (especially sulfhydryl groups) in proteins (especially albumin and metallothionein) and other molecules (Nordberg et al. 1985). Plasma cadmium circulates primarily bound to metallothionein, and albumin (Foulkes and Blanck 1990; Roberts and Clark 1988).

3.4.4 Elimination and Excretion

Most cadmium that is ingested or inhaled and transported to the gut via mucociliary clearance is excreted in the feces. However, almost all excreted cadmium represents material that was not absorbed from the gastrointestinal tract. Most absorbed cadmium is excreted very slowly, with urinary and fecal excretion being approximately equal (Kjellström and Nordberg 1978). The half-time for cadmium in the whole body in humans was >26 years (Shaikh and Smith 1980) and half-times of several months up to

several years have been calculated in mice, rats, rabbits, and monkeys (Kjellström and Nordberg 1985). Half-times in the slowest phase were from 20 to 50% of the maximum life span of the animal (Kjellström and Nordberg 1985). In the human body, the main portion of the cadmium body burden is found in the liver and kidney and in other tissues (particularly muscle, skin, and bone). After reviewing the literature, Kjellström and Nordberg (1985) developed a range of half-times from their kinetic model of 6–38 years for the human kidney and 4–19 years for the human liver.

3.4.4.1 Inhalation Exposure

Cadmium excretion in urine of occupationally exposed workers increases proportionally with body burden of cadmium, but the amount of cadmium excreted represents only a small fraction of the total body burden unless renal damage is present; in this case, urinary cadmium excretion markedly increases (Roels et al. 1981b). Fecal excretion in workers occupationally exposed to cadmium reflects mainly cadmium dust swallowed from industrial air and/or incidentally ingested from contaminated hands (Adamsson et al. 1979).

In rats, following a 2-hour inhalation exposure to cadmium carbonate, cadmium was primarily eliminated in the feces, with a minor component (approximately 1% of fecal excretion) in the urine (Rusch et al. 1986). Cadmium excretion by both routes declined with time after exposure, with significantly elevated excretion found at 7 days, but not 30 days, after exposure (Rusch et al. 1986). Most of the cadmium initially excreted in the feces was probably not absorbed, but rather represented particles transported from the lung to the gastrointestinal tract (Moore et al. 1973).

3.4.4.2 Oral Exposure

Following oral exposure, the major proportion of administered cadmium is found in the feces, because absorption is so low (see Section 3.4.1.2) (Kjellström et al. 1978). Among five healthy adult volunteers, fecal excretion of a single dose of radiolabeled cadmium declined with time up to 45 days after ingestion, while urinary excretion remained at a low, near-constant level (Rahola et al. 1973). After about 20 days, fecal and urinary excretion appeared to be comparable (Rahola et al. 1973). In contrast, among four healthy adults ingesting cadmium in intrinsically labeled crabmeat, fecal excretion was 30 times higher than urinary excretion up to 10 weeks after ingestion of the test meal (Newton et al. 1984). In rats orally exposed to up to 0.35 mg/kg/day of cadmium in the diet for 60 days, no significant increase in urinary cadmium content was found (Weigel et al. 1984). The overall excretion of absorbed cadmium is

slow, with biological half-times of 70–270 days in rats or mice orally exposed to cadmium (Engstrom and Nordberg 1979; Moore et al. 1973).

In a comprehensive model developed for human cadmium toxicokinetics, parameters for urinary and fecal excretion were derived by adjustments to empirical data derived from human and animal studies (Kjellström and Nordberg 1978, 1985). Fecal excretion constitutes unabsorbed cadmium plus "true" excretion originating from blood via the intestinal wall (a function of cadmium body burden) and from bile via the liver (a function of cadmium liver burden) (Kjellström and Nordberg 1985). Urinary excretion depends on blood concentration and kidney concentration, and total excretion is assumed to equal daily intake at steady state. Using these methods and assumptions, daily fecal and urinary excretion is estimated to be 0.007 and 0.009% of body burden, respectively (Kjellström and Nordberg 1978, 1985). A whole-body retention half-time estimate of >26 years was obtained by Shaikh and Smith (1980) in a study using orally ingested radiolabelled cadmium and monitoring a subject for over 2 years.

Groups of 10 female outbred albino rats were exposed to cadmium in drinking water (as cadmium chloride) at 0 or 4.8 mg/kg/day for 10 weeks (at 4 weeks prior to mating, at 3 weeks of gestation, or 3 weeks into lactation). After weaning, exposure to cadmium was terminated. In dams, kidney concentrations exceeded liver concentrations, while in pups, the renal and liver concentrations were similar at all times during exposure. In pups, both hepatic and renal cadmium concentrations considerably increased only during the second half of the lactation period (Ld 11–21). The concentrations in the dams were several orders higher than in the offspring. After discontinuation of exposure, organ concentration slightly decreased in dams (2% in liver and 12% in kidneys), while in pups, the decrease was 84% in the liver and 62% in the kidneys. These values do not indicate cadmium elimination but rather dilution caused by growth (Kostial et al. 1993).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to cadmium. Cadmium was reportedly detected in urine in guinea pigs dermally exposed to aqueous cadmium chloride, but no details are available (Skog and Wahlberg 1964).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological

processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987a). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for cadmium exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

3.4.5.1 Summary of Cadmium PBPK Models

Several models have been reported to describe the kinetics of cadmium in mammalian systems. Of these models, the Nordberg-Kjellström model (Kjellström and Nordberg 1978; Nordberg and Kjellström 1979) has been the most widely used for cadmium risk assessment. Three of the most relevant cadmium models will be discussed here.

3.4.5.2 Cadmium PBPK Model Comparison

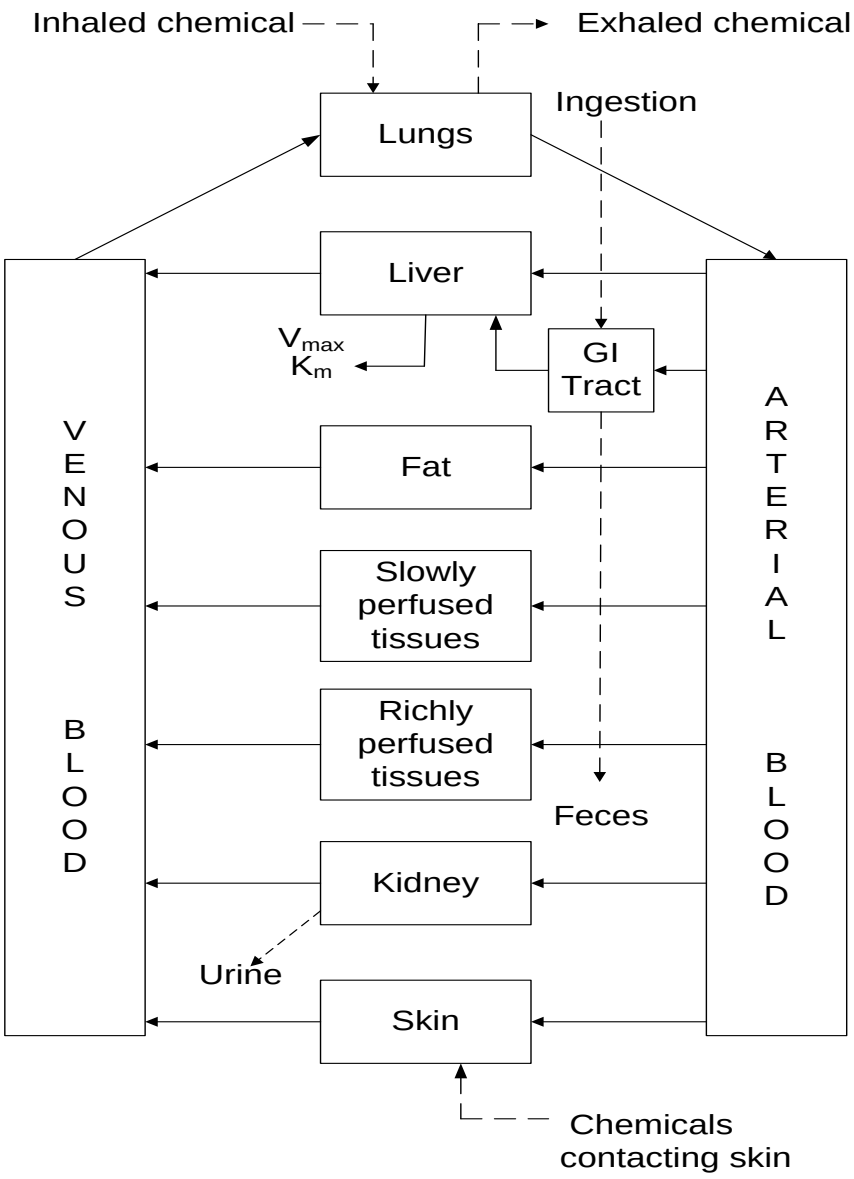
Although the Nordberg-Kjellström model (Kjellström and Nordberg 1978; Nordberg and Kjellström 1979) has its limitations, it provides the best overall description of cadmium toxicokinetics and is largely based on human data. The Shank (Shank et al. 1977) and Matsubara-Khan (Matsubara-Khan 1974) models are not as useful for human risk assessment applications, but they do provide useful insights into the absorption, distribution, and compartmentalization of cadmium in laboratory animals. These insights may have some future use in human risk assessment as PBPK models for cadmium continue to be refined.

3.4.5.3 Discussion of Cadmium Models

The Nordberg-Kjellström Model

The Nordberg-Kjellström model (Kjellström and Nordberg 1978; Nordberg and Kjellström 1979) is a linear multicompartment model that is the most commonly used model for cadmium risk assessment work today. The Nordberg-Kjellström schematic model diagram is shown in Figure 3-4.

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

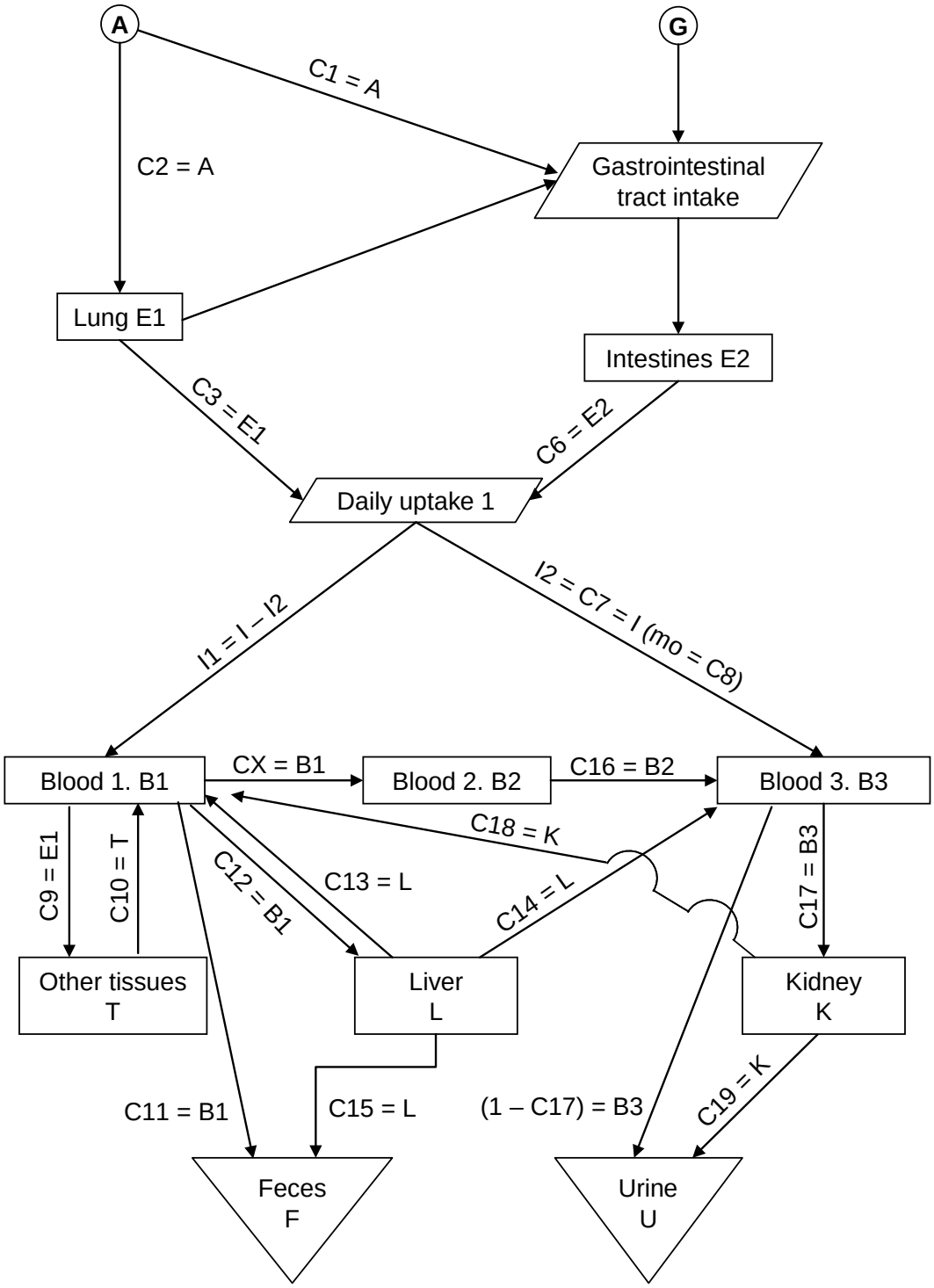
Source: adapted from Krishnan and Andersen 1994

Risk assessment. The Nordberg-Kjellström model has been demonstrated to be a useful model in human risk assessment work. Frazier (1994), however, noted that the model has two major limitations: (1) the linear nature of the model may not adequately allow a good description of known nonlinearities in biological responses to cadmium dosing, and (2) the phenomenological approach taken with this model does not provide a foundation for incorporating biological variability into the model parameters.

Description of the Model. The Nordberg-Kjellström model (see Figure 3-4) is a linear multi-compartment model that describes the disposition of cadmium via the oral and inhalation routes of exposure only. Dermal exposure and subsequent absorption through the skin were assumed to be negligible in this model. For inhalation exposures, the model accounts for different deposition patterns for different size particles in nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract. Particles with mass median aerodynamic diameter (MMAD) of 5 μm (i.e., cadmium-laden dust) were assumed to distribute mainly to the nasopharyngeal region (75%), with lesser amounts depositing in the alveolar (20%) and tracheobronchial (5%) regions. Particles of 0.05 μm MMAD (i.e., cigarette smoke) were assumed to deposit 50% in the alveolar compartment, 10% in the tracheobronchial compartment, and none in the nasopharyngeal compartment. The remaining amounts are exhaled. For all particle sizes initially deposited in the nasopharyngeal and tracheobronchial compartments, mucociliary clearance clears some particles from the respiratory tract to enter the oral compartment for absorption or out of the body and back to the environment. Assumed model coefficient values and the available physiological parameters are shown in Table 3-12.

For the oral route of exposure, cadmium may enter the gastrointestinal tract via food or water contaminated with cadmium, or as cadmium particles embedded in mucus from the respiratory tract via the mucociliary/tracheobronchial escalator. By either route of exposure, the model assumes that cadmium enters into any of three blood compartments (B) (see Figure 3-4). B1 is the plasma compartment where cadmium may bind to plasma components (i.e., albumin and other organic constituents). B2 is the red-blood cell compartment, which represents the accumulation of cadmium in erythrocytes, while B3 represents the binding of cadmium to metallothionein. The model does not take into account induction of metallothionein after cadmium exposure. From the blood, cadmium is calculated to distribute to either the liver, kidney, or "other tissues," the major accumulation sites. Elimination is either via the feces or in the urine. The transport of cadmium between the compartments is assumed to follow first-order exponential functions and is driven on concentration-dependent gradients.

Figure 3-4. A Schematic Representation of the Nordberg-Kjellström Model



Source: Kjellström and Nordberg 1978

Table 3-12. Assumed Model Parameters and Some Physiologic Parameters for the Nordberg-Kjellström Model

Coefficient or parameter	Assumed range	Unit[a]	Values fitting to empirical data
	Model parameters		
C1	0.1–0.2 (cigarette smoke)		0.1
	0.4–0.9 (factory smoke)		0.7
C2	0.4–0.6 (cigarette smoke)		0.4
	0.1–0.3 (factory smoke)		0.13
C3	0.01–1.0	day^{-1}	0.05
C4	0.1xC3 = 0.001–0.1	day^{-1}	0.005
C5	0.03–0.1		0.048
C6	0.05	day^{-1}	0.05
C7	0.2–0.4		0.25
C8	0.5–5.0	µg	1
C9	0.4–0.8		0.44
C10	0.00004–0.0002	day^{-1}	0.00014
C11	0.05–0.5		0.27
C12	0.1–0.4		0.25
C13	0–0.0001	day^{-1}	0.00003
C14	0.0001–0.0003	day^{-1}	0.00016
C15	0–0.0001	day^{-1}	0.00005
C16	0.004–0.015	day^{-1}	0.012
C17	0.8–0.98		0.95
C18	0–0.0001	day^{-1}	0.00001
C19	0.00002–0.0002	day^{-1}	0.00014
CX	0 01–0.05		0.04
C20	0.05–0.5		0.1
C21	0–0.000002	day^{-1}	0.0000011
	Physiologic parameters		
Average liver weight	1,500	gram	
Average blood volume	70	mL/kg	
Average blood specific gravity	1.06		
Average daily urine excretion (adult)	1.0	L	
Average daily urine excretion (aged)	0.9	L	
Average daily urine excretion (child)	0.5	L	

[a]Blanks indicate a unitless value

Source: Kjellström and Nordberg 1978; Nordberg and Kjellström 1979

Validation of the model. The Nordberg-Kjellström model was validated using several independent sets of human data from both Sweden and Japan. The data set by Friberg et al. (1974) estimated that smoking 20 cigarettes a day would result in an inhalation of 2–4 μg/day of cadmium, assuming smoking started at 20 years of age and daily cadmium intake from food was 16 μg/day. Based on the Friberg et al. (1974) data, the model predictions of cadmium concentrations in the kidney agreed well with the observed data from a study by Elinder et al. (1978); however, the model predicted higher than expected values for liver cadmium compared to the observed data from the Elinder study. The model's urinary excretion of cadmium (0.84 μg/24 hours for a 50-year-old person) agreed well with the observed data (0.56–0.8 μg/24 hours). The model predicted blood cadmium levels for Swedish smokers to be about 2 ng/g which compared well to the actual concentration of 1.6 ng/g.

The model was also validated against a data set for an average 45-year-old Japanese person living in Tokyo whose daily intake of cadmium is 40 μg via food and 2.7 μg via the inhalation route. Subjects were assumed to be smokers averaging 24 cigarettes a day starting at age 20. Based on these exposure conditions, the measured values for cadmium in the kidney, liver, and "other tissues" (in this case, muscle only) were reported to be 65, 3.4, and 0.2 μg/g, respectively, with the model predicting 48, 3.2, and 0.18 μg/g. For blood and urine, the measured values were 4.5 μg/g for blood and 1.1 μg/L for urine; the model predicted 3.4 μg/g and 1.3 μg/24 hours (assuming 1 L of urine output/day, the value would be 1.3 μg/L).

Another study of Japanese people reported cadmium concentrations in urine in relation to high cadmium concentrations in rice in their daily diet. For people who consumed rice containing 0.04 μg/g of rice (240 μg/day), the observed urinary level of cadmium was 7 μg/L; consumption of rice containing 1.1 μg cadmium/g of rice (660 μg/day), resulted in an observed value of 14 μg/L of urine. After making certain assumptions about the average daily consumption of rice containing an assumed amount of cadmium, and assuming an average urine production of 1 L/day, the model calculated urinary levels of 4.8 and 15.5 μg/L of urine, agreeing well with the observed values.

The model was also validated against a data set with high concentrations of cadmium in air (50 $\mu g/m^3$) (Piscator 1972) and blood cadmium concentrations ranging from 10 to 50 ng/g whole blood. Calculated blood, urine, liver, and kidney levels of cadmium agreed only roughly with the observed values; however, the authors concluded that the model predictions may not be accurate based on the observations that workers with long exposure histories had most likely experienced higher exposure levels in the past, skewing the data set, resulting in poor model predictions. Another data set by Piscator (1984) involved a

group of Swedish workers involved in polishing cadmium-plated objects, who were exposed to high concentrations of cadmium for ≤2 years. Cadmium levels were measured in the urine and blood. When this exposure data set was input into the model, the model could not adequately predict blood and urine levels for these workers.

Target tissues. The Nordberg-Kjellström model assumes that the kidney and liver are the two specific target tissues in which cadmium accumulates. The model also accounts for all other tissue accumulation in the "other tissues" compartment (i.e., muscle). The model assumes a human liver tissue half-life ($t_{1/2}$) of 4–19 years and a kidney $t_{1/2}$ of 6–38 years. For the "other tissue" compartments, $t_{1/2}$ was assumed to be 9–47 years. The Nordberg-Kjellström model does account for the loss of renal tubular epithelial cells leading to a loss of tubular reabsorptive capacity. This loss of cells could conceivably result in an increase in the excretion of cadmium from the tubules and an increase in the transport of cadmium from the tubules to the blood. This loss of cells is theorized to account for the large $t_{1/2}$ range for cadmium in the kidney. The model assumed that no changes in the movement of cadmium from the kidney to blood occurred with age and that the loss of cadmium from the kidney to the urine increased linearly after the age of 30.

The Nordberg-Kjellström model also accounted for differences in kidney and liver weights among different age groups and between peoples of different ethnic origins. The model corrected for differences in liver, kidney, blood, and "other tissue" weights with relation to age (1 and 79 years of age) and ethnicity (Japan and Sweden).

Species extrapolation. The Nordberg-Kjellström model was based solely on data collected from humans and was intended for human risk assessment applications. The model did not address any potential application for this model of cadmium in laboratory animals.

High-low dose extrapolation. The Nordberg-Kjellström model has been shown to adequately predict fluid and tissue concentrations via the oral and inhalation routes of exposure for humans exposed to low doses of cadmium. However, the model has difficulty in adequately predicting fluid and tissue concentrations in humans exposed to high concentrations of cadmium, especially for those individuals exposed to high concentrations via the inhalation route.

Interroute extrapolation. The Nordberg-Kjellström model adequately predicted the fate of cadmium in target tissues after exposure via the inhalation and oral routes. The dermal route of exposure was not incorporated into the model parameters and was considered an insignificant route of exposure in humans.

The Shank Model

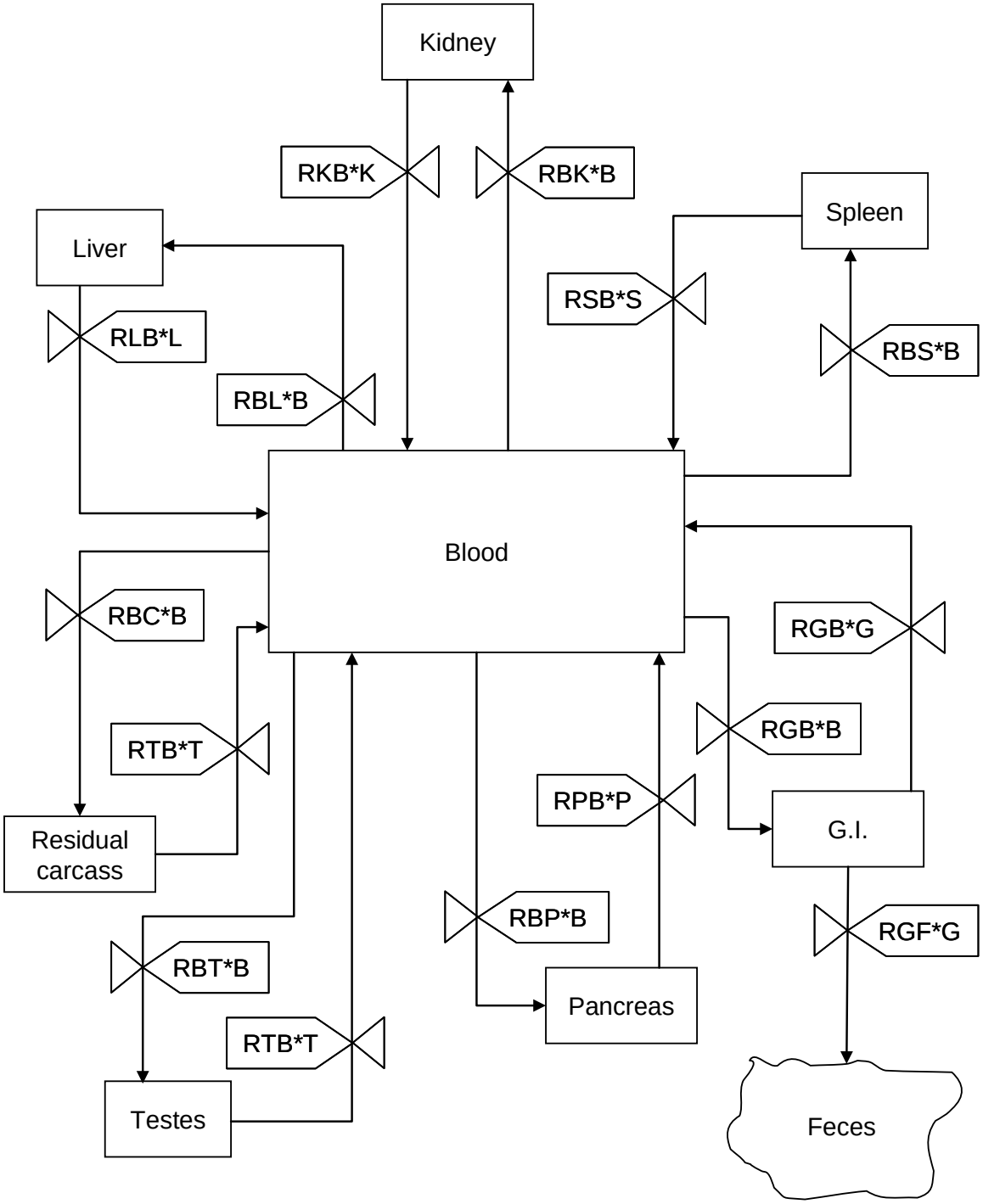
Risk assessment. The Shank model (Shank et al. 1977) may have the potential to serve as an alternative mathematical model for predicting the retention of cadmium in biological systems. Unfortunately, no human data were used to validate the Shank model for use as a risk assessment tool in cases of human exposure. In addition, the Shank model was validated only for the intravenous and subcutaneous routes of exposure; no data were presented for the oral, inhalation, or dermal routes of exposure.

Description of the model. A schematic representation of the Shank model is illustrated in Figure 3-5. The model mathematically represents the dynamic transport of cadmium between compartments in a mammalian biological system based on the male adult SW/NIH mouse as the test animal species. The intent was to predict the retention of cadmium in other species of animals (including humans) without requiring an adjustment of species-specific rate constants from within the model.

Male adult mice of the SW/NIH strain were dosed intravenously with ^{109}Cd as ^{109}Cd acetate. Mice received 1–3 intravenous injections spaced 48 hours apart. Animals in each group were sacrificed at 2 and 10 minutes and 1, 10, and 48 hours after the last dose. Tissues (liver, kidney, pancreas, spleen, gastrointestinal tract, testes, carcass, and feces) were harvested and the radioactivity recorded. A nine-compartment model was derived. Cadmium kinetics between compartments are described by first-order kinetics. The individual compartment retention values, obtained from the distribution study, were incorporated into the model equations and the rate constants derived.

Validation of the model. The Shank model was validated using three independent data sets. Mann (1973) dosed dogs, goats, and sheep with one intravenous injection of ^{109}Cd acetate (30 μCi), and the liver and kidneys were examined for cadmium content 8 weeks after administration. The Shank model's predicted values of cadmium retention in liver and kidneys at 8 weeks after a single administration were in good agreement with the observed values of the Mann (1973) study in all three species. Only data from the liver and kidneys were available for evaluation. A data set from a study by Gunn et al. (1968b) was used to evaluate the ability of the Shank model to predict the retention of cadmium in liver and

Figure 3-5. A Schematic Representation of the Shank Model



Source: Forrester 1968

kidney after a single subcutaneous administration of cadmium chloride. Animals in that study were sacrificed 2 weeks after administration, and the liver and kidneys were examined for cadmium content. The model values for the same time period were in very close agreement with observed values. Again, only data from the liver and kidneys were available for evaluation. Finally, a data set by Shanbaky (1973) was used to test the model's validity with multiple injections of cadmium acetate in rats. Five injections of cadmium acetate were administered over a 48-hour period; liver, kidneys, pancreas, spleen, and gastrointestinal tract were examined for cadmium content. The Shank model was found to be in close agreement with the arithmetic means of observed values found in the Shanbaky (1973) study.

No human data were presented to validate the model's effectiveness in predicting the cadmium retention in human target tissues after either a single or multiple dosing regime.

Target tissues. The target tissues for this model included the liver, kidney, pancreas, spleen, gastrointestinal tract, testes, and carcass of laboratory animals. No human tissue was used to derive cadmium retention in any of these tissues.

Species extrapolation. The model used goats, dogs, rats, mice, and sheep with various doses and dosing schemes of cadmium acetate and cadmium chloride and was found to serve as a good predictor of cadmium retention in the target tissues listed above. No human data were presented to determine if the model could satisfactorily predict the cadmium retention in human target tissues.

High-low dose extrapolation. High- and low-dose extrapolation was not specifically addressed by the Shank model.

Interroute extrapolation. Interroute extrapolations were addressed in a limited fashion by the Shank model. The model appeared to adequately predict the amount of cadmium retention in the target organs of laboratory animals, in particular the liver and kidney, when dosed by either the intravenous or subcutaneous routes. The inhalation and dermal routes of exposure, and other parenteral routes of exposure (intramuscular, intraperitoneal, intradermal, etc.) were not addressed by the Shank model. No human data were presented to determine if interroute extrapolations were valid.

The Matsubara-Khan Model

Risk assessment. The Matsubara-Khan model (Matsubara-Khan 1974) has not been used as a tool in risk assessment for humans. This model does demonstrate that cadmium kinetics and biological half-lives vary by tissue.

Description of the model. The Matsubara-Khan model is a simple model that attempted to fit cadmium elimination kinetic parameters into either a one- or two-compartment model. To obtain the data for the model, male and female ICR mice (8 weeks of age) were administered a single subcutaneous injection of a known amount of ^{109}cadmium chloride. Specific groups of mice were sacrificed at 1, 2, 4, 8, 16, 32, 64, or 128 days after injection. At the time of sacrifice, blood, liver, kidney, salivary gland, stomach wall and stomach contents, small intestine and small intestine contents, and colon wall and colon contents were removed and the amount of ^{109}Cd remaining in these tissues was determined.

An oral study was conducted in conjunction with the subcutaneous study described above. In the oral study, 8-week-old male mice (ddd x BALB/c; F_1) were orally administered ^{115m}cadmium chloride by gavage. Groups of mice were sacrificed at 1, 2, 4, 8, 16, 32, 64, or 128 days after injection. At the time of sacrifice, liver, kidney, salivary gland, stomach wall, gonad, and spleen were removed and the amount of ^{115m}Cd remaining in these tissues was determined.

The rate of uptake, rate constants, and biological half-lives determined for the subcutaneous and orally dosed mice are summarized in Table 3-13. Matsubara-Khan found that tissue kinetics in mice dosed subcutaneously with ^{109}cadmium chloride fit into either a one- or two-compartment model, depending on the tissue. The data from the digestive tract organs (stomach wall, small intestine, and colon) were best fitted into a 1-compartment model, with a strained fit of the data from the digestive tract contents (stomach, small intestine, and colon contents) to the one-compartment model. Data from the blood, liver, kidneys, and salivary glands were best fitted to the two-compartment model. Extremely small second-rate constants in the kidneys and salivary glands indicate that the elimination of cadmium from these tissues is very slow. For the oral study, similar findings were observed, with data from the gonads and spleen fitting the one-compartment model best. Biological half-lives were invariably longer for the subcutaneously dosed animals, while the rate constants were slightly smaller for the subcutaneously dosed animals. Sex-related differences in rate of uptake, rate constants, and biological half-lives were not found, except in the kidney data in which females had slightly smaller rate constants.

Table 3-13. Estimated Parameters, Rate of Uptake, Rate Constants, and Biological Half-Lives in Selected Mouse Organs After Subcutaneous and Oral Administrations of $^{109}CdCl_2$

	Rate of uptake (95% CL)		Rate constants b and c (95% CL)		Biological half-life (days)	
Organ	SC	PO	SC	PO	SC	PO
Liver	21	8.7	0.011 0.57	0.016 0.91	631.2	430.76
Kidney	22	1.4	0.0007 0.30	0.016 0.30	9902.3	4332.3
Salivary gland	21	0.33	0.0016 0.73	0.0047 0.78	4330.95	1500.89
Blood	0.15	NM	0.024 0.65	NM	291.1	NM
Stomach wall	1.7	0.36	0.0073	0.017	95	41
Stomach contents	0.68	NM	0.062	NM	11	NM
Small intestine	0.95	NM	0.01	NM	69	NM
Small intestine contents	2.5	NM	0.067	NM	10	NM
Colon	1.4	NM	0.013	NM	53	NM
Colon contents	4.1	NM	0.15	NM	4.6	NM
Gonad	NM	0.37	NM	0.012	NM	58
Spleen	NM	0.44	NM	0.0011	NM	630

CL = confidence limits; PO = oral; SC = subcutaneous; NM = not measured

Source: Matsubara-Khan 1974

Validation of the model. No independent data sets were used to validate the Matsubara-Khan model.

Target tissues. For the subcutaneous injection study, the Matsubara-Khan model used blood, liver, kidney, salivary gland, stomach wall and stomach contents, small intestine and small intestine contents, and colon wall and colon contents. For the oral study, the model used liver, kidney, salivary glands, stomach wall, gonads, and spleen.

Species extrapolation. No species extrapolations were performed in the Matsubara-Khan model.

High-low dose extrapolation. No high-low dose extrapolations were performed in the Matsubara-Khan model.

Interroute extrapolation. The Matsubara-Khan model compared the oral and subcutaneous routes and reported similar rate constants for many of the tissues examined. Biological half-lives varied considerably for the kidney and salivary gland, but were not much different for liver between the two routes of exposure.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Cadmium can be absorbed by the inhalation, oral, and dermal routes of exposure regardless of its chemical form (chloride, carbonate, oxide, sulfide, sulfate, or other forms). Absorption by the dermal route of exposure, however, is relatively insignificant for cadmium, although small amounts are absorbed percutaneously over a long period of time (Wester et al. 1992). Absorption is mainly of concern from inhalation and oral exposures.

Gastrointestinal tract absorption of cadmium (in any chemical form) is relatively low when compared to the total amount of cadmium absorbed via the inhalation route. In humans, cadmium absorption has been reported to be approximately 1–10% ((Flanagan et al. 1978; McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973; Shaikh and Smith 1980; Vanderpool and Reeves 2001). In other species, gastrointestinal tract absorption of cadmium has been determined to be 1–2% in mice and rats (Decker et al. 1958; Ragan 1977), 0.5–3.0% in monkeys (Friberg et al. 1974), 2% in goats (Miller et al. 1969), 5% in pigs and lambs (Cousins et al. 1973; Doyle et al. 1974), and nearly 16% in cattle (Miller et al. 1967).

Lehman and Klaassen (1986) investigated the dose-dependence of cadmium absorption and disposition in male Sprague-Dawley rats. Cadmium absorption was estimated to be 0.35 and 1% following oral exposure to 1 or 10,000 µg/kg, respectively. Goon and Klaassen (1989) measured absorption of cadmium in rat intestine *in situ* and reported that the intestinal absorption of cadmium is dosage independent at low dosages of cadmium (<10 µg/kg) and dosage dependent at high dosages (>10 µg/kg). They also evaluated the role of metallothionein and concluded that saturation of intestinal metallothionein is not a major determinant of the observed dosage-dependent absorption of cadmium.

Although the mechanism involved in the intestinal absorption of cadmium has not been fully elucidated, there is evidence that one or more transporter proteins are involved. Several studies have found evidence that divalent metal transporter I protein plays an important role in the gastrointestinal absorption of cadmium (Kim et al. 2007; Park et al. 2002; Ryu et al. 2004). However, studies in knockout mice suggest that other transporter proteins are involved with cadmium absorption (Min et al. 2008; Ryu et al. 2004; Suzuki et al. 2007).

In some cases, cadmium bound to metallothionein (as in food) is not absorbed or distributed from the gastrointestinal tract as readily as ionic cadmium. Mice had lower blood and liver cadmium levels from oral exposure to cadmium-metallothionein, compared to levels from cadmium chloride exposure for comparable doses, but the cadmium-metallothionein resulted in higher kidney cadmium levels. Sharma et al. (1983) reported that human exposure to very high intakes of cadmium during the consumption of oysters resulted in increases in whole blood and urine cadmium levels; however, the increase was not proportional to the level of intake.

A higher fraction of inhaled cadmium than ingested cadmium is absorbed. The total amount of cadmium absorbed by the body via the lungs depends on the particle size. Larger particles are deposited in the nasopharyngeal and tracheobronchial airways via impaction, and are largely cleared by mucociliary processes, leading to absorption by the gastrointestinal tract. Smaller particles reach the smaller airways and alveoli, and depending on the particle's solubility, are absorbed and distributed to the rest of the body. Solubility in lung fluids plays a role in absorption from the lung into the body of cadmium salts. Theoretically, the highly soluble salts, chloride, nitrate, acetate, and sulfate would be expected to give the highest blood levels following inhalation exposure to a given air concentration. The insoluble cadmium salts, the various sulfides, should yield the lowest blood level. The lung, however, is rich in carbon dioxide that is continuously transferred from the blood. Particles of the various cadmium sulfides within

the lung can react with this carbon dioxide. Lung tissue may then absorb and transfer solubilized or released cadmium ions to the blood.

No direct data, however, are available on cadmium deposition, retention, or absorption in the human lung. Data from animal studies indicate that lung retention is greatest after short-term exposure, 5–20% after 15 minutes to 2 hours (Barrett et al. 1947; Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986). The initial lung burden declines slowly after exposure ceases (Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986), due to the absorption of cadmium and the lung clearance of deposited particles. After longer periods of inhalation exposure to cadmium, somewhat lower lung retentions are found (Glaser et al. 1986). The absorption of cadmium in the lung differs somewhat among chemical forms, but the pattern apparently does not correlate well with solubility in water (Glaser et al. 1986; Rusch et al. 1986). Retention of cadmium has been reported to be >40% in rats (Moore et al. 1973), 40% in canines (Friberg et al. 1974), and 10–20% in mice (Potts et al. 1950).

The cadmium levels in cigarettes range from 0.28 to 3.38 μg (Elinder et al. 1985b; Watanabe et al. 1987); the mean in 38 U.S. brands was 1.07 μg (Watanabe et al. 1987). Approximately 10% of the cadmium in cigarettes is inhaled (Elinder et al. 1985b). Based on comparison of cadmium body burdens in human smokers and nonsmokers, cadmium absorption from cigarettes appears to be higher than absorptions of cadmium aerosols measured in animals (Nordberg et al. 1985). The chemical form of cadmium in cigarette smoke is likely to be similar to that produced by other combustion processes, primarily cadmium oxide aerosols. The greater absorption of cadmium from cigarette smoke is likely due to the very small size of particles in cigarette smoke and the consequent very high alveolar deposition (Nordberg et al. 1985).

Distribution and Metabolism. Absorbed cadmium is distributed throughout the body, with the highest concentrations found in the liver and kidneys. Cadmium is not known to undergo direct metabolic conversions. It has a high affinity for the sulfydryl groups of albumin and metallothionein (Nordberg et al. 1985). The interaction between cadmium and metallothionein plays a critical role in the toxicokinetices and toxicity, as discussed in Section 3.5.2, of cadmium. Metallothionein sequesters a large fraction of tissue cadmium (Shaikh 1982) and studies in metallothionein transgenic and metallothionein-null mice suggest that metallothionein influences tissue retention, but may not affect cadmium distribution to the liver, kidney, pancreas, or spleen (Liu and Klaassen 1996; Liu et al. 1996; Wong and Klaassen 1980a). Metallothionein turns over with half-lives of 2.8 days in the rat liver and 5 days in the kidney (Shaikh and Smith 1976); however, cadmium is retained in both organs bound

mainly to methallothionein. It has a retention half-time of 73 days in the liver and a life-time in the kidneys (Shaikh 1982).

Shaikh et al. (1993) report that disposition of cadmium in mouse liver, kidney, and testes is different for different strains, sex, or age. Different dose levels (i.e., subcutaneous doses in the 5–30 μmol/kg body weight range) also altered the disposition. Liver cadmium levels and metallothionein levels did not always correlate with hepatotoxicity. The difference in the tissue accumulation of cadmium may relate to variations in the hormonal or other intrinsic factors that affect cellular uptake of cadmium, subcellular distribution of cadmium, or metallothionein metabolism.

Excretion. Since a small fraction of the cadmium presented to the gastrointestinal tract is absorbed, most of the oral dose is excreted via the feces. After inhalation exposure to cadmium, the initial lung burden of cadmium-laden particles depositing in the nasopharyngeal or central airways will be cleared via the mucociliary mechanisms, possibly undergoing a small amount of absorption by the oral route. The remaining cadmium particles will be absorbed in the lung. Once absorbed cadmium has distributed throughout the body (primarily to the liver and kidney), the amounts of fecal and urinary excretion of cadmium are approximately equal. The amount of cadmium in the urine of occupationally exposed workers increases proportionally with body burden of cadmium, but the amount of cadmium excreted represents only a small fraction of the total body burden unless renal damage is present; in this case, urinary cadmium excretion increases markedly (Roels et al. 1981b).

Klaassen and Kotsonis (1977) evaluated biliary excretion of an intravenous bolus of cadmium chloride in the rat, rabbit, and dog. Marked species variation in biliary excretion was observed with rabbits at about 1/6th the rate of the rats, and dogs about 1/300th the rate of the rats. In the rat, the bile/plasma concentration ratio of cadmium was highly dose dependent, increasing with higher dose; at 0.1 mg/kg, the bile/plasma ratio was 2.6 and at 3.0 mg/kg, the bile/plasma ratio was 133. The bile/liver concentration ratio of cadmium was equal to or much lower than 1 decreasing to <1% for the low dose regimen.

3.5.2 Mechanisms of Toxicity

Cadmium is toxic to a wide range of organs and tissues; however, the primary target organs of cadmium toxicity are the kidneys; bone and lung (following inhalation exposure) are also sensitive targets of toxicity. Changes in the kidney due to cadmium toxicosis have been well established. Chronic exposure to cadmium by the oral or inhalation routes has produced proximal tubule cell damage, proteinuria

(mainly low-molecular weight proteins, such as β2-microglobulin), glycosuria, amino aciduria, polyuria, decreased absorption of phosphate, and enzymuria in humans and in a number of laboratory animal species. The clinical symptoms result from the degeneration and atrophy of the proximal tubules, or (in worse cases) interstitial fibrosis of the kidney (Stowe et al. 1972). Cadmium has been shown to perturb lipid composition and enhance lipid peroxidation (Gill et al. 1989b). Depletion of antioxidant enzymes, specifically glutathione peroxidase and superoxide dismutase, has been proposed as the mechanism of cadmium's cardiotoxic effects (Jamall and Smith 1985a), but subsequent studies showed that cardiotoxic mechanisms other than peroxidation are also present (Jamall et al. 1989). Cadmium has been shown to alter zinc, iron and copper metabolism (Petering et al. 1979) as well as selenium (Jamall and Smith 1985b). Xu et al. (1995) propose that an initiating step in cadmium-induced toxicity to the testes is cadmium interference with zinc-protein complexes that control DNA transcription which subsequently leads to apoptosis. Cadmium sequestration by metallothionein (or a chelator in the case of the Xu et al. [1995] study) prevents cadmium from disrupting zinc-dependent transcriptional controls.

Cardenas et al. (1992a) investigated a cadmium-induced depletion of glomerular membrane polyanions and the resulting increased excretion of high-molecular-weight proteins. Interference with glomerular membrane polyanionic charge may precede the tubular damage as a more sensitive and early response to cadmium (Roels et al. 1993). Acute or chronic doses of cadmium have also been reported to reduce hepatic glycogen stores and to increase blood glucose levels. Intralobular fibrosis, cirrhosis, focal mononuclear infiltrates, and proliferation of the smooth endoplasmic reticulum are among the nonspecific histopathological indicators of cadmium toxicity.

Cadmium complexed with metallothionein from the liver can redistribute to the kidney (Dudley et al. 1985). When metallothionein-bound cadmium is transported to the kidney, it readily diffuses and is filtered at the glomerulus, and may be effectively reabsorbed from the glomerular filtrate by the proximal tubule cells (Foulkes 1978). In the kidneys, exogenous metallothionein is degraded in lysosomes and released cadmium is sequested by the endogenous metallothionein as well as other proteins (Cherian and Shaikh 1975; Squibb et al. 1984; Vestergaard and Shaikh 1994). This non-metallothionein-bound cadmium can then induce new metallothionein synthesis in the proximal tubule (Squibb et al. 1984).

Early work indicated that metallothionein binding decreased the toxicity of cadmium, and the ability of the liver to synthesize metallothionein appeared to be adequate to bind all the accumulated cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978). The rate of metallothionein synthesis in the kidney is lower than in the liver (Sendelbach and Klaassen 1988), and is thought to be insufficient, at some point, to

bind the intrarenal cadmium (Kotsonis and Klaassen 1978). Renal damage is believed to occur when the localization of cadmium, or an excessive concentration of cadmium, is unbound to metallothionein. Acute exposure to low levels of cadmium bound to metallothionein produced an intracellular renal damage as described above (Squibb et al. 1984), but damage to brush-border membranes of the renal tubule has also been reported from metallothionein-bound cadmium (Suzuki and Cherian 1987) suggesting other toxic mechanisms may be present.

Dorian et al. (1992a) evaluated the intra-renal distribution of ^{109}cadmium-metallothionein injected (intravenously) into male Swiss mice at a nonnephrotoxic dose (0.1 mg Cd/kg) and concluded that cadmium-metallothionein-induced nephrotoxicity might be due, at least in part, to its preferential uptake of cadmium-metallothionein into the S1 and S2 segments of the proximal tubules, the site of cadmium-induced nephrotoxicity. In a companion study, Dorian et al. (1992b) reported that this preferential renal uptake was also observed after administration of various doses of [^{35}S]cadmium-metallothionein. In contrast to the earlier observed persistency of ^{109}cadmium in the kidney after ^{109}cadmium-metallothionein administration, however, ^{35}S disappeared rapidly (with a half-life of approximately 2 hours); 24 hours after injection of [^{35}S]cadmium-metallothionein, there was very little ^{35}S left in the kidneys. These observations indicate that the protein portion of cadmium-metallothionein is rapidly degraded after renal uptake of cadmium metallothionein and that the released cadmium is retained in the kidney.

The toxic effects and distribution of cadmium were compared after intravenous injection of ^{109}cadmium-metallothionein at 0.05–1 mg Cd/kg body w eight and ^{109}cadmium chloride at 0.1–3 mg/kg in male Swiss mice (Dorian et al. 1995). Cadmium-metallothionein increased urinary excretion of glucose, and protein indicated renal injury, with dosages as low as 0.2 mg Cd/kg. In contrast, renal function was unaltered by cadmium chloride administration, even at dosages as high as 3 mg Cd/kg. Cadmium-metallothionein distributed almost exclusively to the kidney, whereas cadmium chloride preferentially distributed to the liver. However, a high concentration of cadmium was also found in the kidneys after cadmium chloride administration (i.e., the renal cadmium concentration after administration of a high but nonnephrotoxic dose of cadmium chloride was equal to or higher than that obtained after injection of nephrotoxic doses of cadmium-metallothionein). Light microscopic autoradiography studies indicated that cadmium from cadmium-metallothionein preferentially distributed to the convoluted segments (S1 and S2) of the proximal tubules, whereas cadmium from cadmium chloride distributed equally to the various segments (convoluted and straight) of the proximal tubules. However, the concentration of cadmium at the site of nephrotoxicity, the proximal convoluted tubules, was higher after cadmium chloride than after cadmium-metallothionein administration. A higher cadmium concentration in both apical and basal parts of the

proximal cells was found after cadmium chloride than after cadmium-metallothionein administration. The authors suggest that cadmium-metallothionein is nephrotoxic, and cadmium chloride is not nephrotoxic because of a higher concentration of cadmium in the target cells after cadmium-metallothionein. Dorian and Klaassen (1995) evaluated the effects of zinc-metallothionein on ^{109}cadmium-metallothionein renal uptake and nephrotoxicity and concluded that zinc-metallothionein is not only nontoxic to the kidney at a dose as high as 5 μmole metallothionein/kg, but it can also protect against the nephrotoxic effect of cadmium-metallothionein without decreasing renal cadmium concentration.

To further test the hypothesis that nephrotoxicity produced from chronic cadmium exposure results from a cadmium-metallothionein complex, Liu et al. (1998) exposed metallothionein-null mice to a wide range of cadmium chloride doses, 6 times/week for up to 10 weeks. Renal cadmium burden increased with dose and duration up to 140 μg Cd/g kidney in control mice (i.e., metallothionein normal) with a 150-fold increase in renal metallothionein levels (800 μg metallothionein/g kidney). Renal cadmium was much lower in metallothionein-null mice (10 μg Cd/g), and metallothionein levels were not detectable. The maximum tolerated dose of cadmium (as indicated by routine urinalysis and histopathology measures) was approximately 8 times higher in control mice than in metallothionein-null mice. Lesions were more severe in metallothionein-null mice than in controls.

The critical concentration of cadmium in the renal cortex that is likely to produce renal dysfunction also remains a topic of intense investigation. Whether the critical concentration of urinary cadmium is closer to 5 or 10 μg Cd/g creatinine, corresponding to about 100 and 200 μg cadmium/g kidney, respectively, is the current focus of the debate. In one analysis, the critical concentration producing dysfunction in 10% of a susceptible population has been estimated to be approximately 200 μg cadmium/g kidney; 50% of the susceptible population would experience dysfunction with a kidney concentration of 300 μg/g (Ellis et al. 1984, 1985; Roels et al. 1983).

Studies in humans and animals have demonstrated that the bone is a sensitive target of cadmium toxicity. It is likely that cadmium acts by direct and indirect mechanisms, which can lead to decreased bone mineral density and increased fractures (Brzóska and Moniuszko-Jakoniuk 2005c, 2005d). Studies in young animals suggest that cadmium inhibits osteoblastic activity, resulting in a decrease in the synthesis of bone organic matrix and mineralization (Brzóska and Moniuszko-Jakoniuk 2005d). The decreased osteoblastic activity may also influence osteoclastic activity leading to increased bone resorption. During intense bone growth, effects on osteoblasts result in decreased bone formation; after skeletal maturity,

cadmium exposure results in increased bone resorption. Cadmium-induced renal damage can also result in secondary effects on bone (Brzóska and Moniuszko-Jakoniuk 2005c). Cadmium-induced renal damage interferes with the hydroxylation of 25-hydroxy-vitamin D to form 1,25-dihydroxy-vitamin D. Decreased serum concentration of 1,25-dihydroxy-vitamin D, along with impaired kidney resorptive function, result in calcium and phosphate deficiency (via decreased gastrointestinal absorption and increased calcium and phosphate urinary loss). To maintain calcium and phosphate homeostasis, parathyroid hormone is released, which enhances bone resorption.

3.5.3 Animal-to-Human Extrapolations

The effects of cadmium exposure have been studied in humans and in many laboratory animal species. The target organs are similar among species, with the kidneys, bone, and lungs (inhalation only) being the primary organs for cadmium induced toxicity. Absorption, distribution, and excretion of cadmium after oral and inhalation exposures are roughly similar among species; however, there are some notable differences and caveats. Most estimates of cadmium absorption in animals are somewhat lower than the values found from human studies, particularly after prolonged exposure. Differences in the breathing patterns between rats (obligatory nose breathers) and humans (mouth and nose breathers) may also result in radically different lung burden patterns (and hence, different absorption profiles) of cadmium particles in the lungs. Many of the common laboratory animals (in particular the mouse and rat) provide useful information on the toxic effects of cadmium; due to their relatively short lifespan, however, they may not be as useful from a risk assessment point of view in determining the human lifetime effects from inhaling cadmium in air, or ingesting it in food and water. Rates of synthesis and inducibility of metallothionein also differ among species, sex, and target organ.

Even within species there can be significant differences in metallothionein synthesis, and these differences correlate to the degree of cadmium toxicity observed (e.g., the mouse) (Shaikh et al. 1993). The Shaikh et al. (1993) study employed acute exposures. Strain differences in carcinogenic effects have also been reported for chronic exposures of subcutaneously administered cadmium chloride in male DBA and NFS mice. DBA mice developed lymphomas, while NFS mice developed hepatocellular adenomas and carcinomas, and sarcomas at the injection site. Both strains developed nonneoplastic testicular lesions (fibrosis and mineralization) (Waalkes and Rhem 1992).

Metal-metal interactions are also an important factor in cadmium kinetics and toxicity, and organ specific metal concentrations and metabolism can differ among species. It is thought that further development of

PBPK/PD models will assist in addressing these differences and in extrapolating the animal data to support risk assessments in humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997a). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to cadmium.

No *in vitro* studies were located regarding endocrine disruption of cadmium.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the

child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Occupational and environmental exposure studies in adults provide strong evidence that the lung (inhalation exposure only) and kidneys are sensitive targets of toxicity; it is likely that these effects would also be seen in children. Because cadmium is a cumulative toxin and has a very long half-time in the body, exposures to children in even low amounts may have long-term adverse consequences. Average cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40–50 μg/g wet weight) between the ages of 50 and 60 years, after which kidney concentrations plateau or decline (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984). There are limited data on the renal toxicity of cadmium in children. One study found significant associations between urinary and blood cadmium levels with urinary levels of NAG and retinol binding protein (de Burbure et al. 2006); however, the investigators cautioned that the early response observed in this group of children exposed to elevated levels of cadmium (and other metals) may reflect an early renal response that may be adaptive and/or reversible. Another study (Trzcinka-Ochocka et al. 2004) found higher urinary concentrations of β2-microglobulin and retinol binding protein in a population exposed to high levels of cadmium starting in childhood as compared to a group only exposed as adults even though urinary cadmium levels were lower (statistical comparisons of urinary cadmium levels were not made between the groups). These data suggest that adults exposed to cadmium as children may be more susceptible to the renal toxicity of cadmium than persons only exposed as adults. This is supported by the findings of Jacquillet et al. (2007) of renal damage in mature rats exposed to cadmium via gestation and lactation.

There are epidemiological data suggesting that the bone is also a sensitive target of cadmium toxicity (Åkesson et al. 2005; Alfvén et al. 2000, 2002a, 2004; Aoshima et al. 2003; Jin et al. 2004b; Nordberg et al. 2002; Staessen et al. 1999; Wang et al. 2003; Zhu et al. 2004). Epidemiology studies suggest that the elderly may be more susceptible than younger adults; however, no studies examined childhood exposure. Animal studies suggest that young animals are more susceptible than adult or elderly animals (Ogoshi et al. 1989).

A potential for cadmium to have adverse neurological effects is an important consideration. However, only a few studies have reported an association between environmental cadmium exposure and neuropsychological functioning. End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), and acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985). The usefulness of the data from these studies is limited, however, because of the potential confounding effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and inadequate quantification of cadmium exposure (i.e., the studies used hair cadmium as an index of exposure, which has some limitations because of potential confounding from exogenous sources). Several animal studies have reported alterations in performance on neurobehavioral tests in rats exposed to cadmium via gestation and lactation (Ali et al. 1986; Baranski et al. 1983; Desi et al. 1998; Nagymajtenyi et al. 1997). Several studies have examined the possible association between cadmium exposure and newborn birth weight, and most reliable studies have not found a significant association (Galicia-García et al. 1997; Mokhtar et al. 2002; Nishijo et al. 2002, 2004b; Zhang et al. 2004). Animal studies have found significant decreases in body weight or skeletal anomalies or malformations in the offspring of rats exposed to high doses of cadmium (Ali et al. 1986; Baranski 1985, 1987; Gupta et al. 1993; Kelman et al. 1978; Kostial et al. 1993; Machemer and Lorke 1981; Petering et al. 1979; Pond and Walker 1975; Schroeder and Mitchener 1971; Sorell and Graziano 1990; Sutou et al. 1980; Webster 1978; Whelton et al. 1988).

Oral cadmium exposure has also been reported to suppress the T-lymphocyte and macrophage-dependent humoral immune response of 6-week-old mice against sheep red blood cells (Blakley 1985), but not of 12-month-old mice (Blakley 1988). The investigators cautioned that “natural” age-related immune system dysfunction may have masked any cadmium suppressive effect.

Children are most likely to be exposed to cadmium in food or water. Most ingested cadmium passes through the gastrointestinal tract without being absorbed. In adults, only about 1/20 of the total ingested cadmium (in food or water) is absorbed (McLellan et al. 1978, Rahola et al. 1973; Shaikh and Smith

1980). The retention of cadmium in the gut slowly decreases over a period of 1–3 weeks after ingestion in adults (Rahola et al. 1973). The absorption of cadmium in rats depends on age, with measured absorption decreasing from 12 to 5 to 0.5% at 2 hours, 24 hours, and 6 weeks after birth, respectively (Sasser and Jarboe 1977). Sasser and Jarboe (1980) also reported that absorption of cadmium in the gastrointestinal tract of young guinea pigs was 20-fold higher than in adult guinea pigs.

Tissue distribution and retention of cadmium differed between 4- and 70-day-old rats. Cadmium was 3–6 times more concentrated in the newborn spleen, bone, brain, testes, and muscle than in the adult rat 2 hours after an intravenous administration of 1 mg Cd/kg body weight. Liver concentration of metallothionein was 20 times greater in the newborn than in the adult; kidney metallothionein concentrations were comparable, but liver cadmium was only 30% higher and kidney cadmium was 50% higher in the newborn. Nineteen days post-cadmium exposure, the retention of cadmium in the liver, kidney, and lung was similar in both the newborn and the adult rat (Wong and Klaassen 1980a). Goering and Klaassen (1984b) report that high levels of metallothionein in 10-day-old rats play an important role in their resistance to liver damage, presumably by binding and retaining cadmium. However, the tissue distribution data led Wong and Klaassen (1980a) to propose that metallothionein does not play a major role in the tissue distribution and retention of cadmium in the young.

Cadmium can be transferred to offspring in breast milk. Cadmium levels in human milk are 5–10% of levels in blood, possibly due to inhibited transfer from blood because of metallothionein binding of cadmium in blood cells (Radisch et al. 1987). A significant association between urinary cadmium levels and cadmium levels in breast milk was found in women environmentally exposed to cadmium (Nishijo et al. 2002). In female outbred albino rats exposed to cadmium in drinking water (as cadmium chloride) at 0 or 4.8 mg/kg/day for 10 weeks (at 4 weeks prior to mating, 3 weeks of gestation, or 3 weeks into lactation), kidney concentrations exceeded liver concentrations, while in their pups, the renal and liver concentrations were similar at all times during exposure. In pups, both hepatic and renal cadmium concentrations considerably increased only during the second half of the lactation period (Ld 11–21). The cadmium tissue concentrations in dams were several orders higher than in offspring. Another study found a positive correlation between cadmium levels in breast milk and cadmium levels in the pups' kidneys in rats receiving an intravenous injection of cadmium on lactation days 3–16 (Petersson Grawé and Oskarsson 2000).

Although studies on elimination of cadmium from the tissues of children are not available, the results of studies in animals provide some insight. Most cadmium that is ingested or inhaled and transported to the

gut via mucociliary clearance is excreted in the feces. Of the cadmium that is absorbed into the body, most is excreted very slowly, with urinary and fecal excretion being approximately equal (Kjellström and Nordberg 1978). Half-times for cadmium in the whole body of mice, rats, rabbits, and monkeys have been calculated to be from several months up to several years (Kjellström and Nordberg 1985). Half-times in the slowest phase were 20–50% of the maximum life span of the animal (Kjellström and Nordberg 1985). In the human body, the main portion of the cadmium body burden is found in the liver and kidney and in other tissues (particularly muscle, skin, and bone). After reviewing the literature, Kjellström and Nordberg (1985) developed a range of half-times from their kinetic model of between 6 and 38 years for the human kidney and between 4 and 19 years for the human liver. These high values indicate the persistence of cadmium in the body and the importance of minimizing exposures in children to prevent long-term accumulation and toxicity.

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in another study in Czechoslovakia, the concentration of cadmium in the placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). In mice orally exposed to cadmium during pregnancy, maternal blood, placental, and fetal cadmium concentrations were essentially equal among control animals (with environmental cadmium exposure), but placental concentration increased with cadmium dose much more rapidly than either maternal blood or fetal cadmium concentration (Sorell and Graziano 1990). Thus, timing and level of cadmium exposure may influence the uptake of cadmium by the placenta, perhaps explaining the conflicting human studies.

Of particular importance to the toxicokinetics and toxicity of cadmium is its interaction with the protein metallothionein. Metallothionein is a low-molecular-weight protein, very rich in cysteine, which is capable of binding as many as seven cadmium atoms per molecule and is inducible in most tissues by exposure to cadmium, zinc, and other metals (Waalkes and Goering 1990). Metallothionein binding decreases the toxicity of cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978). Goyer and Cherian (1992) localized metallothionein in full-term human placenta and in fetal cells in human placenta. Metallothionein was present in trophoblasts (which facilitate transport of substances entering the placenta from the maternal blood), Hofbauer cells (motile macrophages capable of phagocytosis and protein ingestion), amniotic epithelial cells (fetal derivatives), and decidual cells (endometrial stromal cells that

have been transformed under hormonal influence into large pale cells, rich in glycogen). The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein.

Chan and Cherian (1993) report that pregnancy in Sprague-Dawley rats previously administered cadmium chloride (1.0 mg Cd/kg body weight subcutaneously, daily for 8 days) leads to a mobilization of cadmium from the liver (40% decrease compared to nonpregnant cadmium treated controls) and an increase in the kidneys (60% increase). A similar pattern is seen for metallothionein. Plasma cadmium and metallothionein also increased in the pregnant group. Placental cadmium increased in the cadmium-treated rats compared to the untreated controls. In this rat model, then, pregnancy resulted in a transfer of hepatic cadmium and metallothionein via the blood to the kidney and placenta.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at http://www.cdc.gov/exposurereport/. The biomonitoring data for cadmium from this report is discussed in Section 6.5. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly

found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to cadmium are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by cadmium are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Cadmium

Cadmium levels in blood, urine, feces, liver, kidney, hair, and other tissues have been used as biological indicators of exposure to cadmium. A discussion of the utility and limitations of each for human biomonitoring is provided below.

Blood cadmium levels are principally indicative of recent exposure(s) to cadmium rather than whole-body burdens (Ghezzi et al. 1985; Järup et al. 1988; Lauwerys et al. 1994; Roels et al. 1989). The 50^{th} percentile of blood cadmium concentrations in adults living in the United States was 0.300 µg/L (CDC 2005). Environmental exposure can elevate blood cadmium concentration to above 10 µg/L (Kido et al. 1990a, 1990b; Shiwen et al. 1990). Workers occupationally exposed to cadmium by inhalation may have blood cadmium levels ranging up to 50 µg/L (Roels et al. 1981b).

Urine cadmium levels primarily reflect total body burden of cadmium, although urine levels do respond somewhat to recent exposure (Bernard and Lauwerys 1986). Use of a biokinetic model, such as the Nordberg-Kjellström model, allows estimation of cadmium dietary consumption or airborne cadmium

levels from urinary cadmium levels; these models are described in greater detail in Section 3.4.5.3. When the critical level for renal damage has been reached, urinary cadmium levels rise sharply because of the release of intrarenal cadmium along with decreased renal reabsorption of cadmium (Lauwerys et al. 1994; Roels et al. 1981b). In the U.S. general population, the geometric mean urinary cadmium level in adults is 0.273 μg/L (or 0.261 μg/g creatinine) (CDC 2005). In populations with substantial environmental or occupational exposure, values can range up to 50 μg/g creatinine, (Falck et al. 1983; Roels et al. 1981b; Tohyama et al. 1988). In environmentally exposed individuals, Buchet et al. (1990) report that abnormal values of various biomarkers are found in 5% of the population with urinary excretion of cadmium above the 2–4 μg Cd/24 hour level (approximately 1–3 μg/g creatinine). Significant correlations between total cadmium exposure and urinary cadmium levels have been found in environmentally exposed populations (Kido et al. 2004; Kobayashi et al. 2005; Shimbo et al. 2000). Among environmentally exposed subjects, there was good agreement between urinary cadmium levels measured at different times, suggesting that a single determination would be an accruement measure (Ikeda et al. 2005a).

Fecal cadmium may be used as a direct indicator of daily dietary intake of cadmium because dietary cadmium is poorly absorbed in the gastrointestinal tract (Kjellström et al. 1978). In workers exposed by inhalation, fecal cadmium has been used to estimate the amount of inhaled cadmium transported to the gastrointestinal tract and the amount of dust ingested incidentally at work (Adamsson et al. 1979). Fecal cadmium primarily reflects recently ingested cadmium and, therefore, is not a good indicator of past cadmium exposure (Shaikh and Smith 1984).

Liver and kidney tissues preferentially accumulate cadmium, and concentrations of cadmium in liver and kidney may be measured *in vivo* by neutron activation analysis or in the kidney by X-ray fluorescence analysis (Christoffersson et al. 1987; Scott and Chettle 1986). Levels in both tissues increase with age and level of cadmium exposure, but kidney cadmium concentration tends to peak around age 50–60, while liver cadmium concentration continues to rise. Typical values for a 60-year-old North American with average environmental cadmium exposure are 25–40 μg/g wet weight in kidney cortex and 1–3 μg/g wet weight in liver (Elinder 1985b). In workers exposed to cadmium by inhalation, values up to 300 μg/g wet weight in kidney and 100 μg/g wet weight in liver can be found (Christoffersson et al. 1987; Roels et al. 1981b). Because kidney cadmium content begins to decline after the onset of cadmium-induced renal dysfunction, liver cadmium may be a better indicator of cadmium exposure than kidney cadmium, and it has been suggested that kidney dysfunction is likely to appear at liver cadmium concentrations between 30 and 60 μg/g wet weight (Roels et al. 1981b). *In vivo* liver and kidney cadmium measurements involving neutron activation analysis or X-ray fluorescence require complex and costly equipment and

may pose a radiation hazard (Shaikh and Smith 1984), and those involving biopsy specimens (Lindqvist et al. 1989) require a painful and invasive procedure. Therefore, these methods for *in vivo* analysis are better suited for monitoring of occupationally exposed workers than environmentally exposed populations (Scott and Chettle 1986). Among cadmium workers, significant correlations of kidney cadmium levels with urinary and blood cadmium levels and liver cadmium with urinary cadmium levels were found (Börjesson et al. 1997, 2001). Similar correlations (urinary cadmium with renal cadmium) in an autopsy study of subjects without occupational exposure to cadmium; a urinary cadmium level of 1.7 μg/g creatinine was equivalent to a renal cadmium level of 50 μg/g (Orlowski et al. 1998).

Hair levels of cadmium have been used as a measure of cadmium exposure, although the possibility of exogenous contamination has led to substantial controversy concerning the reliability of hair levels as a measure of absorbed dose (Frery et al. 1993; Huel et al. 1984; Lauwerys et al. 1994, Shaikh and Smith 1984; Wilhelm et al. 1990). Recent evidence has shown a correlation between cadmium levels in the hair of newborn infants and their mothers (Huel et al. 1984) and between cadmium levels in scalp and pubic hair (Wilhelm et al. 1990), indicating that among environmentally exposed populations, external contamination may not be significant for hair samples taken close to the scalp. Under occupational conditions, external contamination may be a more substantial problem (Shaikh and Smith 1984).

On the other hand, Frery et al. (1993) evaluated hair levels in a male population with a high expected exposure to tobacco smoke and in a population of pregnant woman and their newborns; they concluded that cadmium hair analysis was a reliable indicator for the subjects with the highest exposure, but was not sensitive enough to resolve differences for low level exposures. Newborn cadmium hair levels were a more sensitive indicator than mother's hair, but the research was not able to determine if this was attributable to physiological changes or the lower reliability of the mother's head hair. Exogenous contamination is not considered a problem for newborn hair. The authors state that the variability introduced by exogenous contamination can be minimized by using the first 8 cm of hair from the scalp and by using careful washing techniques. There was also no significant difference between hair levels for passive or nonsmokers indicating that either the above mentioned precautions worked or that the passive smoke source of exposure was not significant.

Cadmium measurements have been made on a variety of other biological materials, including milk (Schulte-Lobbert and Bohn 1977; Sikorski et al. 1989), placenta (Kuhnert et al. 1982; Roels et al. 1978; Saaranen et al. 1989), nails (Takagi et al. 1988), teeth (Sharon 1988), and cataractous lenses (Racz and Erdohelyi 1988). Although in some cases it could be established that levels in these tissues were higher

among smokers than nonsmokers, the significance of cadmium levels as a marker of recent or total cadmium exposure has not been established for any of these tissues.

Studies in cadmium workers suggest that metallothionein levels may also be a biomarker of cadmium exposure. Elevated levels of metallothionein gene expression were observed in peripheral blood lymphocytes in highly exposed workers. The level of metallothionein gene expression was significantly correlated with blood and urinary cadmium levels (Lu et al. 2001). Urinary metallothionein correlates with cadmium concentrations in liver, kidney, and urine (Shaikh and Smith 1984; Tohyama et al. 1981). Relatively strong correlations have been found between urinary metallothionein and urinary cadmium levels in exposed humans (Kawada et al. 1990), and a dose-related increase in urinary metallothionein was found in rats exposed to cadmium in drinking water for up to 2 years (Shaikh et al. 1989). Hochi et al. (1995) also found a significant relationship between cadmium intake and urinary metallothionein levels among residents consuming cadmium-contaminated rice. However, the specificity of metallothionein for cadmium exposure may be questioned, because many other exposures are known to induce metallothionein (Waalkes and Goering 1990).

3.8.2 Biomarkers Used to Characterize Effects Caused by Cadmium

Acute inhalation exposure to high levels of cadmium causes respiratory damage and may lead to death. No information was located on biomarkers of respiratory effects in humans, but based on animal experiments, activity of alkaline phosphatase in the surfactant fraction of BALF has been suggested as a sensitive marker of pulmonary damage following acute cadmium inhalation (Boudreau et al. 1989). Such a biomarker of effect is not specific to cadmium exposure and would be most relevant to occupational exposures.

Renal dysfunction, usually first manifested as impaired tubular reabsorption of filtered solutes, is generally considered the primary toxic effect of chronic cadmium exposure (see Section 3.2). Impaired kidney function has been measured by increased levels of solutes (proteins, amino acids, uric acid, calcium, copper, phosphorous, etc.) in urine and/or serum. Excess urinary excretion of low-molecular-weight proteins and solutes is associated with decreased tubular reabsorption. Increased excretion of high-molecular-weight proteins or decreased serum clearance of creatinine reflect glomerular dysfunction, which is generally associated with progressive renal damage (Roels et al. 1989). A brief discussion of the utility and limitations of several measures of tubular damage as biomarkers of effects of

cadmium exposure is provided below. These biomarkers are normally found in the urine and elevated levels are not specific for cadmium.

Urinary β2-microglobulin, a low molecular weight protein, has been widely used as an indicator of tubular renal dysfunction (Arisawa et al. 1997; Piscator 1984; Roels et al. 1981a; Smith et al. 1980). However, tubular renal dysfunction can be caused by exposures and diseases other than cadmium, so β2-microglobulin is not a specific marker of cadmium-induced effects (Shaikh and Smith 1984). Practical considerations in using urinary β2-microglobulin as a marker of tubular renal dysfunction include the need to control the pH of samples to prevent the rapid degradation that occurs at pH values below 5.5 (Shaikh and Smith 1984), and the fact that urinary β2-microglobulin excretion normally rises with age (Roels et al. 1989).

Urinary retinol-binding protein is also considered to be a sensitive indicator of decreased tubular reabsorption, but it also is not specific for cadmium-induced damage in the kidney (Shaikh and Smith 1984; Topping et al. 1986). Retinol-binding protein is more stable in urine than β2-microglobulin (Bernard and Lauwerys 1981) and appears to be of approximately equal sensitivity and specificity for detecting tubular proteinuria in cadmium-exposed populations (Topping et al. 1986). Levels of both proteins fluctuate over time, so regular, repeated sampling may be necessary to establish abnormal levels (Ormos et al. 1985).

Human complex-forming glycoprotein (pHC, also referred to as α_1-microglobulin) is another sensitive marker of tubular renal dysfunction (Moriguchi et al. 2004, 2005a; Pless-Mulloli et al. 1998; Tohyama et al. 1986). As with retinol binding protein, pHC is more stable in urine than β2-microglobulin at room temperature and low urinary pH levels.

Urinary N-acetyl-β-D-glucosaminidase (NAG), a lysosomal enzyme present in high concentrations in the proximal tubule, has been shown to correlate with urinary cadmium levels in occupationally and environmentally exposed subjects (Jin et al. 1999; Kalahasthi et al. 2007) and has a better correlation with urinary cadmium levels than does β2-microglobulin at low cadmium exposure levels (urinary cadmium <10 μg/g creatinine) (Chia et al. 1989; Kawada et al. 1990; Mueller et al. 1989). However, increased urinary NAG activity can result from effects other than nephrotoxicity (Bernard and Lauwerys 1989). Jin et al. (1999) suggest that measurement of the B isozyme (NAG-B), which is released into the urine following tubular cell breakdown, may be a sensitive measure of renal damage.

Other enzymes, proteins, and amino acids in urine have been suggested as biological markers of incipient renal or liver damage resulting from cadmium exposure. Markers found to be sensitive indicators in exposed humans include trehalase (Iwata et al. 1988), alanine aminopeptidase (Mueller et al. 1989), and calcium (Buchet et al. 1990). Changes in urinary alkaline phosphatase, γ-glutamyl transferase, urate, and phosphate tend to be significant only after other markers of renal damage are clearly elevated (Mason et al. 1988). Several other enzymatic markers of cadmium-induced renal damage have been suggested based on animal studies (Bomhard et al. 1984; Gatta et al. 1989; Girolami et al. 1989). Aminoaciduria has been found to be more sensitive than proteinuria for renal damage in animal studies (Nomiyama et al. 1975), but less sensitive in humans (Axelsson and Piscator 1966). Recent work by Prozialeck et al. (2007) suggest that kidney injury molecule 1 may be a sensitive marker for renal dysfunction. At present, not enough information is available to determine which, if any, of these parameters provide sensitive and specific indicators of cadmium-induced renal damage.

At the present time, there is no single biological indicator for cadmium toxicity that is entirely adequate when considered alone. Measurement of cadmium levels in various biological materials can provide an indication of recent or total cadmium exposure, but the probability of adverse effects cannot be reliably predicted except at high exposure levels. Measurement of a variety of markers of renal dysfunction can provide a sensitive measure of early kidney toxicity, but cannot establish whether cadmium exposure was the cause.

There is also considerable controversy as to whether the critical concentration of urinary cadmium is closer to 5 or 10 μg Cd/g creatinine, corresponding to about 100 and 200 ppm in the kidney, respectively. Roels et al. (1993) correlated a number of markers with cadmium in blood and urine in a study population of workers occupationally exposed to cadmium from cadmium smelting operations. Three main groupings of thresholds were identified corresponding with different markers of effects: one around 2 μg Cd/g creatinine mainly associated with biochemical alterations (increased urinary 6-keto-prostaglandin F_{1x} and urinary sialic acid), a second around 4 μg Cd/g creatinine associated with increased excretion of high molecular weight proteins (possibly due to disruption of the glomerular membrane polyanionic charge) and tubular antigens or enzymes (BBA, NAG), and a third around 10 μg Cd/g creatinine associated with increased excretion of low molecular weight proteins and other indicators. The 10 μg Cd/g creatinine level had previously been proposed as the biological threshold for cadmium-induced nephropathy. Whether the earlier changes are indicative of irreversible adverse renal effects remains an area of continued investigation.

To further evaluate the reversibility of proteinuria, Roels et al. (1997) studied the progression of cadmium-induced renal tubular dysfunction in cadmium workers according to the severity of the microproteinuria at the time the exposure was substantially decreased. A total of 32 cadmium male workers were divided into two groups on the basis of historical records of urinary cadmium concentration (CdU) covering the period until 1984. The workers with CdU values of >10 μg Cd/g creatinine were subdivided further on the basis of the urinary concentration of β2-microglobulin (β2-MG-U) measured during the first observation period (1980–1984). In each group, the tubular microproteinuria as reflected by β2-MG-U and the concentration of retinol-binding protein in urine as well as the internal cadmium dose as reflected by the concentration of cadmium in blood and urine were compared between the first and second (1990–1992) observation periods. Increased microproteinuria was often diagnosed in cases with CdU values of >10 μg Cd/g creatinine. The progression of tubular renal function was found to depend on the extent of the body burden of cadmium (as reflected by CdU) and the severity of the initial microproteinuria at the time high cadmium exposure was reduced or ceased. When cadmium exposure was reduced and β2-MG-U did not exceed the upper reference limit of 300 μg/g creatinine, the risk of developing tubular dysfunction at a later stage was likely to be low, even in cases with historical CdU values occasionally >10 but always <20 μg Cd/g creatinine. When the microproteinuria was mild (β2-MG-U >300 and ≤1,500 μg/g creatinine) at the time exposure was reduced, and the historical CdU values had never exceeded 20 μg Cd/g creatinine, there was indication of a reversible tubulotoxic effect of cadmium. When severe microproteinuria (β2-MG-U >1,500 μg/g creatinine) was diagnosed in combination with historical CdU values exceeding 20 μg Cd/g creatinine, Cd-induced tubular dysfunction was progressive in spite of reduction or cessation of cadmium exposure.

For more information on biomarkers for renal and hepatic effects of chemicals see Agency for Toxic Substances and Disease Registry *Subcommittee Report on Biological Indicators of Organ Damage* (Agency for Toxic Substances and Disease Registry 1990a). For information on biomarkers for neurological effects see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

Cadmium toxicity can be influenced by a wide variety of other chemicals. In humans, dietary deficiencies of calcium, protein, and vitamin D are likely to account for increased susceptibility to bone effects following cadmium exposure (Kjellström 1986c). Iron deficiency has been shown to increase gastrointestinal absorption of cadmium in humans (Flanagan et al. 1978), while oral zinc supplementation

has been demonstrated to decrease the oral absorption of cadmium. No other information was located concerning interaction of cadmium with other chemicals in humans.

In animals, a few interactions following inhalation exposure have been evaluated. In rats exposed to cadmium chloride by inhalation, simultaneous exposure to zinc oxide prevents fatalities (Oldiges and Glaser 1986) and lung cancer (Oldiges et al. 1989). Exposure to an atmosphere containing 80% oxygen aggravated pulmonary damage from cadmium chloride inhalation in mice (Martin and Witschi 1985).

The toxicity of oral exposure to cadmium in animals has been shown to be influenced by several factors. In Japanese quail, cadmium toxicity was intensified by single or combined deficiencies of zinc, copper, iron, calcium, and protein (Fox et al. 1979). A calcium-deficient diet in animals has been shown to aggravate cadmium immunotoxicity (Chopra et al. 1984) and fetotoxicity (Pond and Walker 1975). Simultaneous exposure to lindane increased the developmental toxicity of cadmium in rats (Saxena et al. 1986). Female rats have an increased susceptibility to cadmium-induced bone loss due to multiple rounds of gestation and lactation (Bhattacharyya et al. 1988b) or ovariectomy (Bhattacharyya et al. 1988c), possibly related to associated effects on trace element status. Hopf et al. (1990) report that exposure to ethanol and cadmium in a liquid diet produced liver damage in rats at doses that were not separately hepatotoxic. In contrast, Kershaw et al. (1990) reported that ethanol pretreatment in male Sprague-Dawley rats substantially reduced the lethal and hepatotoxic properties of cadmium, possibly due to a reduced interaction between cadmium and target sites in liver organelles and cytosolic high-molecular-weight (HMW) proteins. Ethanol pretreatment in this study decreased (approximately 60%) the content of cadmium in nuclei, mitochondria, and endoplasmic reticulum, and nearly eliminated the association of cadmium with cytosolic HMW proteins. Reduction in the concentration of cadmium in potential target sites of intoxication was caused by a metallothionein-promoted sequestration of cadmium to the cytosol.

When cadmium is co-administered with ethanol in rats, there is a pronounced increase in cadmium accumulation in various regions of the brain (e.g., the corpus striatum and cerebral cortex). The cadmium is not bound to metallothionein, and there is a marked increase in lipid peroxidation and inhibition of membrane bound enzymes (Pal et al. 1993a, 1993b). Rats pretreated with acetaminophen are more sensitive to the renal toxicity of cadmium in water (Bernard et al. 1988a). Co-administration of lead and cadmium in the diet of rats had additive effects in reducing body weights, but neurologic toxicity was antagonized (Nation et al. 1990).

Numerous interactions have been demonstrated in animals using parenteral exposure, generally indicating that induction of metallothionein by pretreatment with zinc, selenium, or other metals, reduces toxicity of parenteral cadmium exposure (Gunn et al. 1968a, 1968b; Naruse and Hayashi 1989; Yamane et al. 1990). Zinc, calcium, or magnesium can prevent injection site, testicular, and prostatic cancers induced by subcutaneous or intramuscular injection of cadmium, but these interactions have been shown to be a complex phenomenon, dependent on dose, route, and target organ (Poirier et al. 1983; Waalkes et al. 1989). Mn(II) pretreatment reduces Cd(II)-induced lethality (Goering and Klaassen 1985). Cadmium has been noted to have an inhibitory effect on manganese uptake (Gruden and Matausic 1989). In addition, manganese appears to be capable of increasing the synthesis of the metal-binding protein metallothionein (Waalkes and Klaassen 1985). Data from a study by Goering and Klaasen (1985) suggest that manganese pretreatment increases the amount of Cd^{+2} bound to metallothionein, thereby decreasing hepatotoxicity due to unbound Cd^{+2}. The significance of these observations to humans exposed to cadmium and manganese by the oral or inhalation routes is not clear.

Induction of hepatic metallothionein by cold stress reduced the acute toxicity of cadmium given by gavage to mice (Baer and Benson 1987). In addition to effects on metallothionein induction, substances may interact with cadmium by altering the competition among metal ions for enzyme or regulatory protein binding sites. For example, simultaneous administration of garlic (which is high in reduced sulfhydryl groups) decreases oral cadmium renal toxicity in rats (Cha 1987).

Coexposure to selenium reduced the clastogenic effect of cadmium on mouse bone marrow (Mukherjee et al. 1988b). Selenium deficiency enhances cadmium-induced cardiotoxicity possibly mediated via lipid peroxidation indicated by a significant reduction in the activities of the selenoenzyme, glutathione peroxidase. Selenium supplements in the diet prevented cadmium's cardiotoxic effect (Jamall and Smith 1985a). Selenium has also been shown to prevent testicular damage in rats (Kar et al. 1960; Omaye and Tappel 1975). In testes, selenium as selenite given before or during cadmium administration was shown to divert the binding of cadmium from low molecular proteins to higher molecular weight proteins (Chen et al. 1975; Whanger 1992). In contrast, Jamall and Smith (1985c) report a shift in cadmium binding from metallothionein to lower weight proteins in kidney and liver from a diet supplemented with selenium compared to a selenium deficient diet. The selenium-cadmium interaction thus appears to be dependent on the duration and sequence of coexposure and possibly the organ-specific levels of selenoenzymes or other essential metals.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to cadmium than will most persons exposed to the same level of cadmium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in increased absorption, reduced detoxification or excretion of cadmium, or compromised function of organs affected by cadmium. Populations who are at greater risk due to their unusually high exposure to cadmium are discussed in Section 6.7, Populations with Potentially High Exposures.

Differences in individual sensitivity to cadmium have not been systematically studied, but based on what is known about cadmium toxicity, some inferences can be made. Populations with depleted stores of calcium, iron, or other dietary components due to multiple pregnancies and/or dietary deficiencies could be expected to have increased cadmium absorption from the gastrointestinal tract. Urinary cadmium levels have been shown to be correlated with iron status among pregnant women (Åkesson et al. 2002). However, a general population study of women living in Japan (Tsukahara et al. 2003) did not find significantly elevated levels of urinary cadmium, β2-microglobulin, or pHC among women with anemia or iron deficiency, as compared to healthy women. Populations with kidney damage from causes unrelated to cadmium exposure, including diabetes, some drugs and chemicals, and the natural age-related decline in kidney function, could be expected to exhibit nephrotoxicity at lower cadmium exposures than those of normal healthy adults (Buchet et al. 1990). There is also some evidence to suggest that diabetics may be more susceptible to the toxicity of cadmium (Åkesson et al. 2005; Buchet et al. 1990). Elevated levels of metallothionein-antibody have been significantly associated with excretion of biomarkers of tubular dysfunction among cadmium workers (Chen et al. 2006a), but not with urinary or blood cadmium levels. In a study of diabetics, metallothionein-antibodies were significantly associated with urinary levels of β2-microglobulin levels, which were indicative of cadmium toxicity but not with urinary albumin levels, which would be indicative of glomerular damage (Chen et al. 2006c).

A discussion of the susceptibility of children is found in Section 3.7, Children's Susceptibility.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to cadmium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to cadmium. When

specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to cadmium:

Caravati EM, McGuigan MA, MacGregor Whyte I, et al. Cadmium fume pneumonitis. In: Medical toxicology, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1411-1414.

Leikin JB, Paloucek FP. 2002. Cadmium. In: Poisoning and toxicology handbook. Hudson, OH: Lexi-Comp, Inc., 309-310.

Viccellio P. 1998. Cadmium, mercury, and arsenic. In: Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers, 379-380.

3.11.1 Reducing Peak Absorption Following Exposure

Inhalation exposure to high concentrations of cadmium can be particularly dangerous because initial symptoms are often as mild as those associated with low-level exposure, and exposed individuals who are unaware either of the presence of cadmium or of the dangers of inhaling cadmium may allow exposure to continue until a harmful or even fatal dose is received (Beton et al. 1966; Lucas et al. 1980). Severe respiratory symptoms that may develop within a few hours of high-dose inhalation exposure include tracheobronchitis, pneumonitis, and pulmonary edema, accompanied by additional nonspecific flu-like symptoms (sweating, shivering, malaise) (Beton et al. 1966). Aside from removing a victim to fresh air and providing supportive medical care, no effective means have been reported for reducing absorption following inhalation exposure to cadmium (Bronstein and Currance 1988; EPA 1989d). Supportive medical care of individuals with inhalation exposure to high levels of cadmium includes monitoring for respiratory distress, assisting ventilation as needed, and administering humidified oxygen (Bronstein and Currance 1988; EPA 1989d). If pulmonary edema develops, individuals may be treated with supplemental oxygen, positive-pressure mechanical ventilation, and administration of diuretics, intravenous fluids, and steroid medications. Antibiotic therapy and monitoring fluid balance (due to kidney function impairment) may also be required (Beton et al. 1966; Bronstein and Currance 1988; EPA 1989d; Haddad and Winchester 1990).

Oral exposure to cadmium is not an immediate threat because high doses are irritating enough to induce vomiting. In fact, the only known acute fatalities from oral exposure to cadmium followed intentional ingestion of high doses (Baker and Hafner 1961; Buckler et al. 1986; Frant and Kleeman 1941; Nordberg et al. 1973; Shipman 1986; Wisniewska-Knypl et al. 1971). Although inducing vomiting is sometimes recommended following ingestion of cadmium (Ellenhorn and Barceloux 1988; Stutz and Janusz 1988),

concentrated cadmium solutions may be caustic, and esophageal damage could result from spontaneous or induced vomiting. Administration of water or milk may be indicated for patients able to swallow (Bronstein and Currance 1988; EPA 1989d). Administration of cathartics such as sorbitol or magnesium sulfate to enhance elimination from the gastrointestinal tract has been recommended (EPA 1989d; Stutz and Janusz 1988); however, the administration of activated charcoal to bind unabsorbed cadmium does not appear to be effective (Agency for Toxic Substances and Disease Registry 1990b; Ellenhorn and Barceloux 1988).

The intestinal absorption of cadmium at levels below those leading to gastrointestinal damage is relatively low (5–10% of the administered dose) (Flanagan et al. 1978; McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973). Other polyvalent cations including calcium, magnesium, and zinc can interfere with cadmium uptake (Foulkes 1985), but administration of competing cations can in some cases increase rather than decrease cadmium absorption (Jaeger 1990), and is therefore not recommended for the treatment of cadmium ingestion. Oral administration of some compounds that chelate cadmium such as meso-2,3-dimercaptosuccinic acid has been found in rodent studies to reduce absorption following acute oral exposure to cadmium, but other chelators such as dithiocarbamates can increase toxicity (see Section 3.4.1.2). At present, no recommendations for chelation treatment to reduce absorption can be made (Jones and Cherian 1990). Administration of garlic (which is high in reduced sulfhydryl groups) has been shown to decrease oral cadmium toxicity in rats (Cha 1987). Thus, use of garlic could be an area of future research.

Dermal or ocular exposure to high levels of cadmium may cause irritation (Wahlberg 1977) and should be treated by removing contaminated clothing, washing the skin, and thoroughly flushing the eyes (EPA 1989d; Stutz and Janusz 1988). These measures will also reduce the relatively small potential for dermal absorption of cadmium (see Section 3.4.1.3).

3.11.2 Reducing Body Burden

A variety of chelating agents have been evaluated (Cantilena and Klaassen 1981; Jones et al. 1992, 1994; Kostial et al. 1996; Singh et al. 1996). Some of the more familiar chelators that are beneficial for other toxic metals actually increase cadmium toxicity by mobilizing the cadmium and substantially increasing the renal concentrations and toxicity (Agency for Toxic Substances and Disease Registry 1990b; Goldfrank et al. 1990; Jones and Cherian 1990). One such agent is the chelating agent dimercaprol (also known as BAL, British Anti-Lewisite), commonly used for treating cases of lewisite toxicosis. BAL is

widely recognized as harmful in treating cadmium exposures. Some sources recommend using ethylene-diamine tetraacetic acid (EDTA) salts (Cantilena and Klaassen 1980, 1981; Ellenhorn and Barceloux 1988; Stutz and Janusz 1988) or use of EDTA with caution about potential nephrotoxicity (EPA 1989d; Haddad and Winchester 1990). Other chelators that have reduced the cadmium burden in animal studies include diethylenetriaminepentaacetic acid (DTPA), 2,3-dimercaptosuccinic acid (DMSA), and various dithiocarbamates (Cantilena and Klaassen 1981, 1982b; Kamenosono et al. 2002a; Wang et al. 1999).

Cantilena and Klaassen (1982a) demonstrated the importance of rapid administration of DTPA, EDTA, or DMSA following acute cadmium exposure if they are to be effective. Waalkes et al. (1983) evaluated the role of metallothionein in the acute drop in chelator efficacy following cadmium poisoning in male Sprague-Dawley rats. Although the chelator, DTPA, reduced cadmium content in the various organs when given immediately after cadmium, it was ineffective at all later times. Increases in hepatic and renal metallothionein did not occur until 2 hours after cadmium, and did not coincide with the earlier drop in chelator efficacy. Blockade of metallothionein synthesis by actinomycin D treatment (1.25 mg/kg, 1 hour before Cd) failed to prolong the chelators effectiveness. Furthermore, newborn rats have high levels of hepatic metallothionein, which had no effect on the time course of chelator effectiveness since DTPA still decreased cadmium organ contents, if given immediately following cadmium, but had no effect if given 2 hours after cadmium. The authors concluded that metallothionein does not have an important role in the acute decrease in efficacy of chelation therapy for cadmium poisoning. The quick onset of chelator ineffectiveness may be due to the rapid uptake of cadmium into tissues, which makes it relatively unavailable of chelation.

Jones et al. (1992, 1994) investigated a series of monoalkyl and monoarakyl esters of meso-2,3-di-mercaptosuccinic acid. Monoisoamyl meso-2,3-dimercaptosuccinate (Mi-ADMS) was an effective chelating agent for reduction of kidney and liver cadmium when administered either parenterally or orally (Jones et al. 1992). This finding was supported by a study by Eybl et al. (1994), which showed that Mi-ADMS, administered orally every 48 hours for 12 days after acute cadmium exposure, was effective at reducing cadmium in the kidney and liver, but not in the testes and brain. Monophenylethyl-, mono(3-phenylpropyl)-, and mono(2-phenoxyethyl) meso-2,3-dimercaptosuccinic acid compounds successfully remove “aged” cadmium deposits and can be administered via a variety of routes (Jones et al. 1994).

Another area of chelation therapy research is in the use of multiple chelators. Blaha et al. (1995) evaluated the ability of two carbodithioate chelators, sodium N-(4-methylbenzyl)-4-O-(β-D-galacto-

pyranosyl)-D-glucamine-N-carbodithioate (MeBLDTC) and sodium 4-carboxyamidopiperidine-N-carbothioate (INADTC), singly or in combination to reduce cadmium burden from chronically exposed rats. The combination therapy resulted in a synergistic effect on increased biliary excretion and reduced renal cadmium that, in the case of biliary excretion, was more than doubled that expected for a simple additive interaction.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The toxic effects of cadmium are generally thought to be caused by "free" cadmium ions; that is, cadmium not bound to metallothionein or other proteins (Goyer et al. 1989). However, cadmium bound to metallothionein may have the capacity to directly damage renal tubular membranes during uptake (Suzuki and Cherian 1987). Free cadmium ions may have a number of adverse effects, including inactivation of metal-dependent enzymes, activation of calmodulin, and initiation of the production of active oxygen species (Palmer et al. 1986; Waalkes and Goering 1990).

Respiratory damage caused by acute, high-level inhalation exposure to cadmium can cause impaired lung function that can last many years after exposure (Barnhart and Rosenstock 1984; Townshend 1982). No treatments other than supportive care and avoidance of additional risk factors for lung injury are presently known.

The kidneys appear to be highly vulnerable to chronic cadmium exposure by either the oral or inhalation routes. The basis for the preferential sensitivity of the kidney is related to the filtering and reabsorption of circulating cadmium-metallothionein complex, which is then thought to be degraded in the tubular cell lysosomes and released as free intracellular cadmium. The toxic effect results from the limited ability of the kidney to synthesize new cytosolic metallothionein in response to an increasing cadmium load (Goyer et al. 1989). Cadmium bound to metallothionein, however, may also have nephrotoxic activity (Suzuki and Cherian 1987).

No treatments are currently available that specifically target free cadmium ions in the renal cortex, but zinc and calcium can stimulate metallothionein synthesis and may also compete with cadmium for enzyme binding sites. Thus, zinc, and/or calcium supplementation might help reduce renal cadmium toxicity, at least in zinc- or calcium-deficient individuals. It is not known whether administration of these compounds would be beneficial in individuals with adequate zinc and calcium intakes, and their clinical use is not currently recommended. Since one of the postulated mechanisms of cadmium toxicity is the

stimulation and production of active oxygen species, it is possible that increasing the cellular levels of antioxidants such as superoxide dismutase, reduced sulfur compounds (particularly glutathione), vitamin C, vitamin E, or β-carotene could reduce renal cadmium toxicity by scavenging active oxygen species prior to reaction with cellular components. Several animal studies have examined co-administration of several antioxidants on cadmium-induced kidney damage. Beneficial effects were found for vitamin E (Shaikh and Tang 1999; Shaikh et al. 1999a), N-acetyl cysteine (Kaplan et al. 2008; Shaikh et al. 1999a, 1999b), glycine (Shaikh and Tang 1999), glyceryrrhizin (Nomiyama and Nomiyama 1998), and a drug containing glyceryrrhizin, glycine, and cystein (Shaikh and Tang 1999; Shaikh et al. 1999a). However, antioxidants are not currently recommended for the treatment of cadmium-exposed humans.

Treatments for the cadmium-related effects on bone have not been evaluated. Although the mechanism of bone damage has not been fully elucidated, it is likely that calcium loss and altered vitamin D metabolism, which result from cadmium-induced kidney damage, play an important role. Thus, treatments that interfere with the renal damage will likely have a beneficial effect on bone.

Research in chelation therapy is promising for agents that can interfere or possibly reverse the toxic effects of cadmium. Xu et al. (1995, 1996) demonstrated that monoisoamyl meso-2,3-dimercapto-succinate, when administered within 1 hour after acute exposure, prevents the formation of cadmium-induced apoptotic DNA fragmentation and associated histopathological injury in the testes of rats. Perry et al. (1989) report a reversal of the cadmium induced hypertension in rats with the chelator d-myo-inositol-1,2,6-triphosphate.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cadmium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cadmium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would

reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Cadmium

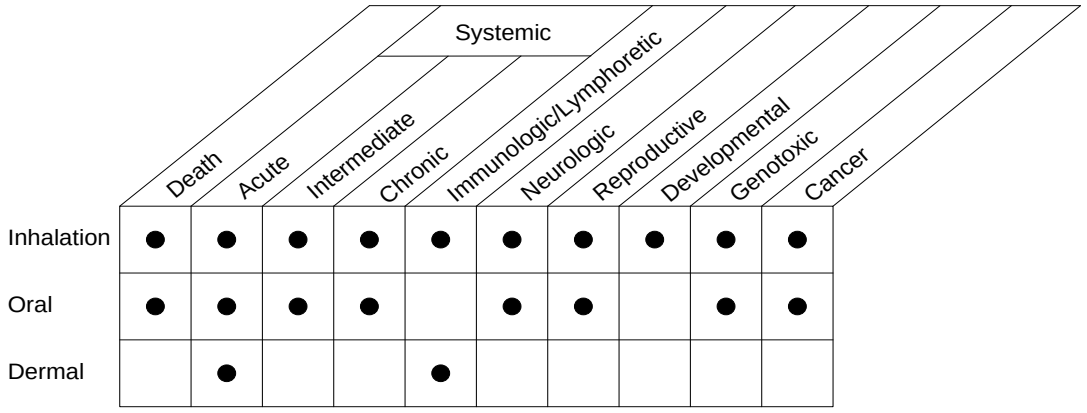
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to cadmium are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of cadmium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

There is a massive database regarding the health effects of cadmium. In humans, the majority of studies have involved workers exposed by inhalation or residents of cadmium-polluted areas exposed primarily in the diet. Quantitative estimates of exposure levels are not available for many of these studies; however, many studies provided information on urinary cadmium levels that would be reflective of the cadmium body burden. Lethality, systemic toxicity, genotoxicity, and cancer have been studied in humans more extensively than immunotoxicity or neurotoxicity, with less being known about reproductive or developmental toxicity of cadmium in humans following inhalation or oral exposure. In animals, effects following oral exposures have generally been more thoroughly investigated than those following inhalation exposure, and few studies of cadmium toxicity following dermal exposure in humans were located.

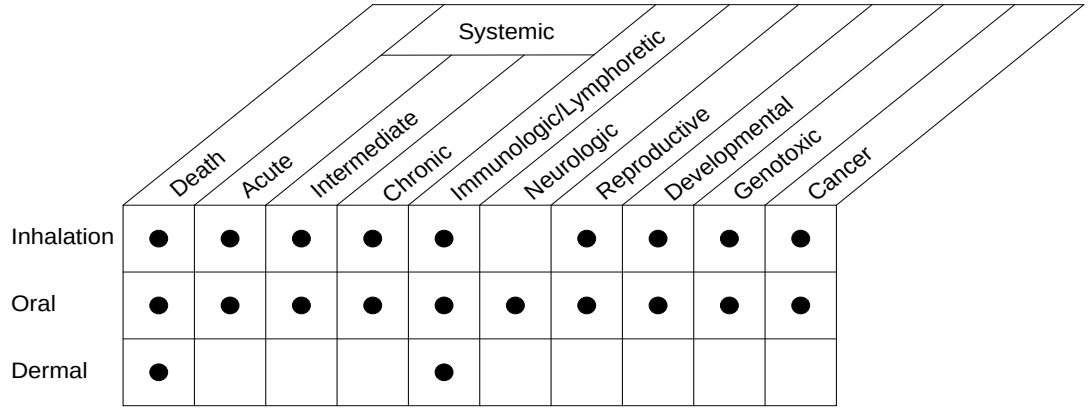
3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are limited data on the acute toxicity of cadmium in humans. Although there are numerous reports of respiratory effects in workers exposed to high concentrations of cadmium, there are no reliable estimates of levels associated with these effects. Animal studies provide

Figure 3-6. Existing Information on Health Effects of Cadmium



Human



Animal

● Existing Studies

support for identification of the respiratory tract as the most sensitive target of toxicity following inhalation exposure. Acute exposures to high levels of airborne cadmium has resulted in pneumonia, emphysema, and edema in laboratory animals (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart 1986; Henderson et al. 1979; NTP 1995; Palmer et al. 1986) and lower concentrations were associated with focal inflammation and minimal fibrosis (NTP 1995). A decreased immune response in mice was observed at similar cadmium concentrations (Graham et al. 1978; Krzystyniak et al. 1987). Other adverse effects observed at higher concentrations include erosions of the stomach, decreases in body weight, and reduced activity (Rusch et al. 1986). The available acute-duration animal data were considered adequate for derivation of an acute-duration inhalation MRL for cadmium.

There are no reliable human studies on the toxicity of cadmium following acute-duration oral exposure. In laboratory animals, acute exposure to high doses of cadmium resulted in a variety of effects, including altered hematological parameters, focal necrosis and degeneration of the liver, focal necrosis in renal tubular epithelium, necrosis and ulceration in the stomach and intestines, decreased motor activity, and testicular atrophy and necrosis (Andersen et al. 1988; Basinger et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989; Dixon et al. 1976; Kotsonis and Klaassen 1977; Machemer and Lorke 1981; Sakata et al. 1988; Shimizu and Morita 1990). There is some indication that developmental effects (delays in ossification and increased malformations) may occur at lower cadmium doses (Baranski 1985; Machemer and Lorke 1981). The acute-duration oral database was not considered adequate for derivation of an MRL because the results of the study that identified the lowest LOAEL (Baranski 1985) were inadequately reported and were inconsistent with a longer-duration study conducted by the same investigator. Although the data suggest that the developing organism is the most sensitive target, additional studies are needed to support this assumption. Studies characterizing the dose-response relationships for the most sensitive effects are needed for derivation of an acute-duration oral MRL.

No reliable information was located regarding toxicity following dermal exposure to cadmium, but based on the lack of reported effects in the workers handling cadmium compounds, it seems unlikely that dermal exposure could deliver a significant dose of cadmium.

Intermediate-Duration Exposure. There are limited data on the toxicity of cadmium in humans following intermediate-duration exposure.

Intermediate-duration inhalation studies in laboratory animals have identified several targets of toxicity including the respiratory tract (Glaser et al. 1986; Kutzman et al. 1986; NTP 1995; Prigge 1978a), reproductive effects (Baranski and Sitarek 1987; NTP 1995), and developing nervous system (Baranski 1984, 1985). At the lowest cadmium concentration tested, alveolar histiocytic infiltration and degeneration or metaplasia in the larynx were observed in mice (NTP 1995) and neurodevelopmental effects were observed in rats (Baranski 1984, 1985). These LOAELs were considered for derivation of an intermediate-duration inhalation MRL; however, an MRL based on the human equivalent concentration of the LOAELs would be lower than the chronic-duration inhalation MRL based on human data. Additional studies are needed to identify no-adverse-effect levels in animals for these sensitive targets of toxicity.

A number of studies have been conducted involving intermediate-duration oral exposure to laboratory animals. The results of these studies suggest that the growing bone is the most sensitive target. The skeletal effects observed in young rats include decreases in bone mineral density, impaired mechanical strength, increased fractures, and increased bone turnover (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b, 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c; Ogoshi et al. 1989). Developmental effects, including impaired renal function and neurodevelopmental alterations, have been observed at similar dose levels (Ali et al. 1986; Baranski et al. 1983; Jacquillet et al. 2007). At higher doses, observed effects included renal damage (proteinuria, tubular necrosis, and decreased renal clearance), liver necrosis, and anemia (Cha 1987; Gatta et al. 1989; Groten et al. 1990; Itokawa et al. 1974; Kawamura et al. 1978; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Prigge 1978a), altered immune response (Blakley 1985, 1986; Chopra et al. 1984), decreased motor activity (Kotsonis and Klaassen 1978; Nation et al. 1990), and necrosis and atrophy of seminiferous tubules and decreased sperm count and motility (Cha 1987; Saxena et al. 1989). The database of intermediate-duration animal studies was considered adequate for derivation an intermediate-duration oral MRL based on skeletal effects in growing rats.

No intermediate-duration dermal data were identified in humans or animals. Studies of possible toxicity in animals following intermediate-duration dermal exposure to cadmium are needed to evaluate potential health effects in humans exposed to cadmium primarily by the dermal route.

Chronic-Duration Exposure and Cancer. Data on the chronic toxicity of inhaled cadmium in humans come from numerous occupational exposure studies; no reliable animal studies examining noncancerous end points were identified. These studies have identified the respiratory tract (emphysema, impaired lung function) (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976) and

the kidney (tubular proteinuria, decreased glomerular filtration rate, increased excretion of low molecular weight proteins) (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985a; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Shaikh et al. 1987; Toffoletto et al. 1992; Verschoor et al. 1987) as the most sensitive targets of toxicity. Comparisons of the adverse effect levels for these two end points are difficult because the studies on respiratory effects typically reported air concentrations (current levels or estimated cumulative exposure) as the exposure biomarker and those examining renal effects typically used urinary cadmium levels as the exposure biomarker; based on limited data, the kidney appears to be the more sensitive target. Studies examining both end points in occupationally exposed populations would provide valuable information on sensitivity. None of the available human studies were considered adequate for derivation of an inhalation MRL because cadmium air concentrations were poorly characterized or no data were provided on the contribution of dietary cadmium to the cadmium body burden. However, the similarities on the toxicity and toxicokinetics of cadmium following inhalation and oral exposure allow for the use of the oral database to derive an inhalation MRL.

There is an extensive database of studies examining the chronic oral toxicity of cadmium in humans. These environmental exposure studies have identified two sensitive targets of cadmium toxicity—the skeletal system and the kidney. The skeletal effects included increased risk of osteoporosis and bone fractures and decreases in bone mineral density (Alfvén et al. 2000, 2004; Nordberg et al. 2002; Schutte et al. 2008; Staessen et al. 1999; Wang et al. 2003). Renal effects range from death due to renal failure (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 1995, 2004a, 2006) to increases in the prevalence of low molecular weight proteinuria (Buchet et al. 1990; Cai et al. 1990, 1992, 1998, 2001; Hayano et al. 1996; Ishizaki et al. 1989; Izuno et al. 2000; Järup et al. 2000; Jin et al. 2002, 2004a, 2004c; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002a; Monzawa et al. 1998; Nakashima et al. 1997; Nogawa et al. 1989; Noonan et al. 2002; Nordberg et al. 1997; Olsson et al. 2002; Oo et al. 2000; Osawa et al. 2001; Roels et al. 1981b; Suwazono et al. 2006; Teeyakasem et al. 2007; Trzcinka-Ochocka et al. 2004; Uno et al. 2005; Yamanaka et al. 1998; Wu et al. 2001). Animal studies confirm the identification of the kidney and bone as the most sensitive targets of cadmium toxicity (Akahori et al. 1994; Bernard et al. 1992; Bomhard et al. 1984; Brzóska and Moniuszko-Jakoniuk 2004a, 2004b; Fingerle et al. 1982; Mangler et al. 1988). Sufficient information from human studies is available to derive a chronic oral MRL. No information was located regarding dermal toxicity of chronic cadmium exposure in humans or animals, and studies of dermal toxicity are needed to evaluate risks to populations exposed to cadmium primarily by dermal contact.

The evidence of carcinogenicity from human studies is limited, due to uncertainties in cadmium exposure estimates and confounding factors including exposure to arsenic, a known human lung carcinogen, and smoking. Occupational exposure studies have found significant increases in lung cancer mortalities (Ades and Kazantzis 1988; Järup et al. 1998a; Kazantzis et al. 1988; Stayner et al. 1992a; Sorahan 1987; Sorahan and Waterhouse 1983; Thun et al. 1985). However, lung cancer deaths were often not significantly associated with cadmium exposure or duration. Other studies have not found increases in lung cancer deaths (Armstrong and Kazantzis 1983; Elinder et al. 1985c; Lamm et al. 1992, 1994; Sorahan and Esmen 2004; Sorahan and Lancashire 1997). Additional occupational exposure studies controlling for these exposures and providing more precise cadmium dose estimates are needed to provide more definitive evidence of the carcinogenic potential in humans of inhaled cadmium. Evidence for the carcinogenicity of cadmium by the inhalation route is available from studies in rats (Takenaka et al. 1983). Additional studies in animals are needed to evaluate the lack of an observed increase in lung cancer in mice and hamsters exposed to cadmium by inhalation (Heinrich et al. 1989). Cadmium has not been shown to be carcinogenic following oral exposure in humans (Bako et al. 1982; Hardell et al. 1994; Inskip et al. 1982; Lauwerys and De Wals 1981; Nakagawa et al. 1987; Shigematsu 1984). In rats, however, cadmium increased tumors of the prostate, testes, and hematopoietic system (Waalkes et al. 1992). Additional lifetime-exposure studies in rats, mice, and hamsters orally exposed to cadmium at sufficiently high doses are needed to further define the carcinogenic potential of cadmium.

Genotoxicity. The evidence for the genotoxicity of cadmium is mixed (see Tables 3-10 and 3-11). *In vitro* studies have provided both positive and negative results (Amacher and Paillet 1980; Bruce and Heddle 1979; Casto et al. 1979; Denizeau and Marion 1989; Depault et al. 2006; Fatur et al. 2002; Filipic and Hei 2004; Honma et al. 1999; Jianhua et al. 2006; Lopez-Ortal et al. 1999; Lutzen et al. 2004; Lynn et al. 1997; Mikhailova et al. 1997; Oberly et al. 1982; Rozgaj et al. 2002; Shiraishi et al. 1972; Terracio and Nachtigal 1988). Studies of chromosomal aberrations in humans (Bui et al. 1975; Deknudt and Leonard 1975; Fu et al. 1999; O'Riordan et al. 1978; Tang et al. 1990) and animals (Bruce and Heddle 1979; Desi et al. 2000; DiPaulo and Castro 1979; Fahmy and Aly 2000; Karmakar et al. 1998; Mukherjee et al. 1988a; Tan et al. 1990; Watanabe et al. 1979) exposed to cadmium have also found both positive and negative results. DNA damage has been consistently observed in *in vitro* studies (Devi et al. 2001; Fahmy and Aly 2000; Kasuba et al. 2002; Mukherjee et al. 1988a; Saplakoglu et al. 1997; Valverde et al. 2000; Wronska-Nofer et al. 1999; Zhou et al. 2004b). In animals, parenteral, but not inhalation or oral, cadmium exposure has been found to cause germ cell mutations (Gilliavod and Leonard 1975; Suter 1975; Sutou et al. 1980; Watanabe and Endo 1982; Zenick et al. 1982). Additional studies investigating

effects in exposed humans using larger populations with quantitative estimates of exposure would be useful to evaluate the human genotoxicity of cadmium.

Reproductive Toxicity. Only limited or conflicting evidence is available to evaluate the potential for cadmium exposure to cause reproductive toxicity in humans. Some studies report no effect on male fertility (Gennart et al. 1992), sex hormone levels (Mason 1990; Menke et al. 2008; Zeng et al. 2004a), sperm density (Noack-Fuller et al. 1993), or semen quality (Jurasović et al. 2004; Saaranen et al. 1989), while others report a reduction in sperm number or viability (Akinloye et al. 2006; Telišman et al. 2000; Xu et al. 1993a) or alterations in sex steroid hormone levels (Akinloye et al. 2006; Jurasović et al. 2004; Telišman et al. 2000). In one study, men occupationally exposed to cadmium at levels resulting in renal damage had no change in testicular function (Mason 1990). Adverse effects in animals from inhalation exposure have been reported including increased duration of the estrous cycle (Baranski and Sitarek 1987; NTP 1995; Tsvetkova 1970), and increased relative testes weight but no loss in reproductive success (Kutzman et al. 1986). Adverse reproductive effects in animals from high-dose, acute, oral cadmium exposure have been reported including testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989), and decreased fertility (Kotsonis and Klaassen 1978; Machemer and Lorke 1981). At lower doses and intermediate exposures, adverse effects have included necrosis and atrophy of seminiferous tubule epithelium (Cha 1987), increased testes weight (Pleasants et al. 1992, 1993), increased prostatic hyperplasias (Waalkes and Rehm 1992), significantly increased relative testes weight, decreased sperm count and motility, decreased seminiferous tubular diameter, seminiferous tubular damage (Saxena et al. 1989), and decreased fertility (Sutou et al. 1980). Other animal studies for lower dose intermediate exposures, however, report no adverse effects (Baranski et al. 1983; Bomhard et al. 1987; Groten et al. 1990; Kostial et al. 1993; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a; Pleasants et al. 1992; Pond and Walker 1975; Zenick et al. 1982). Additional studies in animals, as well as retrospective, case-matched studies of reproductive success of populations for which occupational or environmental exposure to cadmium has been estimated, are needed to further evaluate the potential reproductive toxicity of cadmium in humans. Additional studies would be useful (preferably with larger sample sizes) to evaluate the robustness of the association between cadmium and adverse effects on sperm.

Developmental Toxicity. The potential for cadmium exposure to cause developmental toxicity from pre- or postnatal exposures in humans is not known. One study in occupationally exposed women reported children with lowered birth weights, but with no increase in malformations (Tsvetkova 1970). However, no control was made for parity, maternal weight, gestational age, or other factors known to

influence birth weight. Many animal studies demonstrate that developmental toxicity may occur following cadmium exposure by oral routes with a relatively few studies reporting developmental effects following inhalation or oral exposure (Ali et al. 1986; Baranski 1985, 1987; Baranski et al. 1983; Gupta et al. 1993; Kelman et al. 1978; Kostial et al. 1993; Machemer and Lorke 1981; Petering et al. 1979; Pond and Walker 1975; Schroeder and Mitchener 1971; Sorell and Graziano 1990; Sutou et al. 1980; Webster 1978; Whelton et al. 1988). At lower inhalation and oral doses, impaired performance on neurobehavioral tests have been observed (Ali et al. 1986; Baranski et al. 1983; Desi et al. 1998; Nagymajtenyi et al. 1997). Retrospective, case-matched studies of developmental toxicity among children of women with known occupational or environmental exposure to cadmium are needed to evaluate the potential for cadmium exposure to cause human developmental toxicity such as skeletal malformations and neurobehavioral effects (as suggested in animal studies). Studies are also needed to follow-up on the results of increased susceptibility of young to bone damage (Ogoshi et al. 1989) or suppression of the immune response (Blakley 1985) reported in animals. The difference in the immune response (using the same protocol) between young mice (Blakley 1985) and older mice (Blakley 1988) should also be further evaluated. Studies of postnatal cadmium exposure to children, especially for children with diets deficient in calcium, protein, or iron, would be useful to evaluate whether increased cadmium absorption from the diet leads to developmental effects.

Immunotoxicity. A variety of immunologic effects have been found in animals exposed to cadmium by the oral or inhalation routes (Blakley 1988; Bouley et al. 1984; Cifone et al. 1989a). However, the biological significance of these effects is not clear, and there is little information available on immunotoxicity in humans. Investigations of immunologic function of populations occupationally or environmentally exposed to cadmium, and follow-up mechanistic studies in animals are needed to evaluate the potential immunotoxicity of cadmium exposure in humans.

Neurotoxicity. A few studies have suggested an association between cadmium exposure in humans and impaired neuropsychologic functioning at levels below those causing nephrotoxicity (Hart et al. 1989b; Marlowe et al. 1985; Thatcher et al. 1982). Neurotoxicity has also been found in animal studies (Nation et al. 1984; Wong and Klaassen 1982). Additional studies to investigate neurologic effects in populations with known cadmium exposure and studies of possible mechanisms of neurotoxicity in animals are needed to evaluate the potential neurotoxicity of cadmium exposure to humans. In addition, studies examining neurobehavioral end points in children would be useful.

Epidemiological and Human Dosimetry Studies. Cause/effect relationships for renal toxicity of cadmium have been derived from studies of workers occupationally exposed to cadmium by inhalation (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985b; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Kawada et al. 1989; Roels et al. 1993; Shaikh et al. 1987; Thun et al. 1989; Toffoletto et al. 1992; Verschoor et al. 1987) and of populations environmentally exposed to cadmium in the diet (Buchet et al. 1990; Cai et al. 1990, 1992, 1998, 2001; Hayano et al. 1996; Ishizaki et al. 1989; Izuno et al. 2000; Järup et al. 2000; Jin et al. 2002, 2004a, 2004c; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002b; Monzawa et al. 1998; Nakadaira and Nishi 2003; Nakashima et al. 1997; Nogawa et al. 1989; Noonan et al. 2002; Nordberg et al. 1997; Roels et al. 1981a; Olsson et al. 2002; Oo et al. 2000; Osawa et al. 2001; Suwazono et al. 2000; Teeyakasem et al. 2007; Trzcinka-Ochocka et al. 2004; Uno et al. 2005; Watanabe et al. 2002Wu et al. 2001; Yamanaka et al. 1998). There is also epidemiological evidence that chronic environmental exposure to cadmium can result in decreases in bone mineral density and increases in the risk of bone fractures and osteoporosis (Åkesson et al. 2005; Alfvén et al. 2000, 2004; Schutte et al. 2008; Staessen et al. 1999). Additional studies are needed to elucidate the mechanisms of these bone effects in humans and to determine if the skeletal system is a more sensitive target of cadmium toxicity than the kidney effects. Measurement of additional toxicity end points (reproductive, developmental, immunological, and neurological) in these well characterized populations are needed to evaluate whether any of these effects may occur at exposure levels below those leading to kidney damage. Additional development of PBPK/PD models is needed to evaluate human exposure scenarios. In its assessment of the U.S. population's exposure to environmental chemicals, the CDC measured urinary cadmium levels. If urinary cadmium levels are monitored in future assessments, it would be useful to also measure biomarkers of tubular dysfunction; these data would be useful in examining possible relationships between cadmium exposure and renal function in the general population.

Biomarkers of Exposure and Effect.

Exposure. Cadmium levels can be measured in a variety of tissues and fluids, including blood, urine, milk, liver, kidney, hair, and nails (Elinder and Lind 1985; Roels et al. 1981b; Sharma et al. 1982). Blood cadmium is a useful indicator of recent cadmium exposure, and urinary cadmium is a useful indicator of total body burden (Shaikh and Smith 1984). The most important indicator of the potential for toxicological injury is generally considered to be the cadmium concentration in the renal cortex, but individuals vary in the concentration causing renal effects (the "critical concentration") (Roels et al. 1981b). Methods for *in vivo* measurement of cadmium content in the kidney exist, but they are complex

and expensive, and involve some exposure to ionizing radiation (Scott and Chettle 1986). Efforts to develop easier, safer, and less costly methods for *in vivo* analysis are needed, as well as studies to determine factors influencing individual variation in critical concentrations. Although many studies correct urinary cadmium levels for creatinine concentration, several investigators (Alessio et al. 1985; Ikeda et al. 2003a; Moriguichi et al. 2005b) have questioned the validity of this approach due to wide intra- and interindividual variability and age-related decline in levels. Additional studies are needed to further investigate methods to account for dilution in urine spot samples.

Effect. A number of sensitive tests are available to detect early stages of renal dysfunction that are known to be caused by cadmium exposure. These include analysis of urinary excretion of β2-microglobulin, retinol-binding protein, metallothionein, or enzymes (Shaikh and Smith 1984). However, renal damage detected by these tests is not necessarily associated with cadmium exposure. Additional studies are needed to evaluate current or potentially new urinary or serum biomarkers in cadmium-exposed populations and their association with incipient injury to the kidney caused by cadmium. The bone is a sensitive target of cadmium toxicity, particularly during growth and in the elderly; studies are needed to develop sensitive biomarkers to detect early signs of bone damage.

Absorption, Distribution, Metabolism, and Excretion. Good information exists on cadmium toxicokinetics in humans and animals. PBPK/PD models have been developed to predict the critical organ dose as a function of route, duration, and level of exposure by the inhalation and oral routes (Kjellström and Nordberg 1978, 1985). Although general factors influencing absorption, distribution, metabolism, and excretion are known, additional studies are needed to provide information on metal metabolism and interactions that support quantitative evaluation of individual variations and resulting differences in renal cadmium accumulation. Very limited information exists on the dermal absorption of cadmium (Skog and Wahlberg 1964; Wester et al. 1992). Additional studies on the dermal absorption of cadmium are needed.

Comparative Toxicokinetics. Animal and human studies have generally reported comparable toxicokinetics of cadmium (Kjellström and Nordberg 1985; Nordberg et al. 1985), suggesting that rats, mice, and rabbits are suitable models for cadmium toxicity in humans. However, some concerns have been raised about the appropriateness of the rat model for cadmium-induced lung tumors in humans because of differences in the morphology of the rat respiratory tract and resulting differences in cadmium particle deposition patterns and target cell populations. This is especially of concern because cadmium appears to be a contact carcinogen for lung cancer. Additional studies on the differences between the rat

and human clearance rates, speciation at the level of the target cell, and protein transporters (as they relate to solubility and susceptibility) are needed to evaluate the appropriateness of the rat model for predicting cadmium-induced human lung cancers. Additional studies on differences in species, strain, sex, age, and other factors on cadmium kinetics and carcinogenic or other systemic effects are also needed to extrapolate the animal data to potential human toxicity. Additional studies establishing the toxicokinetics of cadmium in pregnant animals are needed to assess the relevance of the developmental effects observed in animals.

Methods for Reducing Toxic Effects. The mechanisms of cadmium absorption across epithelial layers are likely to be via nonspecific mechanisms (Foulkes 1989). No methods are known for influencing absorption across the lung, but absorption across the gastrointestinal tract may be influenced by dietary status (Flanagan et al. 1978). Studies to determine whether dietary adjustments might help decrease cadmium uptake from food or water are needed. Studies to determine the effects of dietary deficiencies in calcium are needed to further evaluate the risk of cadmium exposure to susceptible populations. Uptake across the skin is probably sufficiently slow that simple washing of exposed areas is adequate to prevent excessive absorption (Skog and Wahlberg 1964).

Once cadmium is absorbed, it tends to accumulate in the kidney, which is the main target tissue for chronic low-dose exposure. The cellular and molecular basis for the preferential accumulation in the kidney is only partially understood (Waalkes and Goering 1990), and additional studies to define the rate-limiting steps in renal uptake and renal clearance of cadmium are needed to design strategies for reducing the rate of cadmium accumulation in this tissue. Additional studies on existing and new chelating agents and different treatment regimens are needed to improve the clinical therapies for acute and chronic exposures to cadmium.

The mechanism of cadmium toxicity in renal cells and other tissues probably involves binding of free cadmium ions to key cellular enzymes and proteins (Waalkes and Goering 1990). Thus, any agent that prevents cadmium from binding might help prevent toxicity. The endogenous cadmium-binding protein can serve this function; however, metallothionein-cadmium complexes may have renal toxicity (Suzuki and Cherian 1987). Additional studies on the role of metallothionein in cadmium toxicity would be useful. Additional studies are needed on alternative substrate molecules or drugs that could interact with free cadmium and prevent binding to key cellular enzymes, as well as the ability of antioxidants to reduce damage from active-oxygen species produced by cadmium in tissues.

The impaired renal function that is the typical adverse effect of excessive cadmium exposure is neither clinically treatable nor reversible (Agency for Toxic Substances and Disease Registry 1990b; Roels et al. 1989). Studies on potential supportive treatment or remedies for cadmium-induced mild renal impairment would be valuable.

The bone is also a sensitive target of cadmium toxicity; however, methods for the treatment of the observed effects, decreased bone mineral density and increased fractures, have not been developed and are needed.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There is limited information on the toxicity of cadmium in children. Although it is likely that children will have similar effects as adults, there is some suggestive evidence that childhood exposure may result in increased renal toxicity, as compared to persons only exposed as adults (Trzcinka-Ochocka et al. 2004). Additionally, studies in animals suggest that young animals are more susceptible to cadmium-induced bone damage than adults (Ogoshi et al. 1989); this has not been investigated in humans. Studies are needed to evaluate whether there are age-specific differences in the toxicity of cadmium in humans. As discussed in the Developmental Toxicity section above, there are limited data on the developmental toxicity of cadmium in humans, particularly potential neurodevelopmental effects and additional studies are needed.

Additional research is needed on the toxicokinetics of cadmium during long-term, low-level exposures to determine the potential long-term tissue burdens that are likely to result especially for the susceptible tissues of liver, kidney, and bone. Data in animals suggest that children may absorb more cadmium than adults, but there are no human data examining these potential differences in the toxicokinetic properties of cadmium. Additional information is needed on cadmium transport across the blood-brain barrier in the developing fetus, and the role of metallothionein in the placenta.

Neurological and behavioral studies are needed that use the more sophisticated measures available today to evaluate children for *in utero*, acute, and longer term exposures. These studies should have the appropriate controls for confounding factors such as lead, parental use of ethanol, and living conditions.

Additional studies are needed to evaluate whether or not biomarkers of cadmium exposure and effects that have been developed for adults are also applicable to children. If not, new biomarkers of exposure and effect need to be developed.

The effects of nutritional status (iron, zinc, and calcium levels) on cadmium absorption and accumulation in children need further evaluation. Improved regimens and choices for chelation therapy are also needed.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

A number of research projects are in progress investigating the health effects of cadmium. These projects are summarized in Table 3-14.

Table 3-14. Ongoing Studies on Cadmium

Investigator	Study topic	Institution	Sponsor
Fadrowski, J	Determination if environmental cadmium exposure is associated with chronic kidney disease in children	John Hopkins University	National Institute of Environmental Health Sciences
Wande, LI	Examination of cadmium modulation of lysyl oxidase in the lung which may provide insight into the molecular mechanism of cadmium-induced emphysema.	Boston University	National Institute of Environmental Health Sciences
Nebert, DW	Characterization of the ZIPS transporter protein and the role of ZIPS in cadmium-induced renal damage	University of Cincinnati	National Institute of Environmental Health Sciences
Prozialeck, WC	Mechanisms of cadmium toxicity in epithelial cells	Midwestern University	National Institute of Environmental Health Sciences
Zahler, NH	Mechanisms involved in the cadmium-induced DNA damage and oxidative stress	University of Michigan, Ann Arbor	National Institute of Environmental Health Sciences
Thomas, DG and Kennedy TS	Examination of the possible association between cadmium levels in maternal blood and breast milk and cognitive development in infants	Oklahoma State University	National Research Initiative

Source: FEDRIP 2008

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Table 4-1 lists the common synonyms, trade names, and other pertinent identification information for cadmium and its most important compounds.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 4-2 lists important physical and chemical properties of cadmium and its most important compounds.

Table 4-1. Chemical Identity of Cadmium and Compounds[a]

Characteristic	Information		
Chemical name	Cadmium	Cadmium carbonate	Cadmium chloride
Synonym(s)	Colloidal cadmium	Otavite[b]; cadmium monocarbonate; carbonic acid; cadmium salt	Caddy[b]; Vi-Cad[b]; cadmium dichloride; dichlorocadmium
Registered trade name(s)	No data	No data	No data
Chemical formula	Cd[b]	$CdCO_3$[b]	$CdCl_2$[b]
Chemical structure	Cd[b]	$CdCO_3$[b]	$CdCl_2$[b]
Identification numbers:			
CAS registry	7440-43-9[b]	513-78-0[b]	10108-64-2
NIOSH RTECS	No data	No data	No data
EPA hazardous waste	D006	D006	D006
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	NA2570/IMCO 6.1
HSDB	282	1612	278
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Cadmium and Compounds[a]

Characteristic	Information		
Chemical name	Cadmium oxide	Cadmium sulfate	Cadmium sulfide
Synonym(s)	Aska-Rid[b]; cadmium fume; cadmium monoxide	Cadmium sulphate; sulfuric acid; cadmium (2+) salt	Cadmium monosulfide; cadmium yellow; cadmium orange; cadmopur yellow; greenockite[b]; capsebon[b]
Registered trade name(s)	No data	No data	No data
Chemical formula	CdO[b]	$CdSO_4$[b]	CdS[b]
Chemical structure	CdO[b]	$CdSO_4$[b]	CdS[b]
Identification numbers:			
CAS registry	1306-19-0[b]	10124-36-4[b]	1306-23-6[b]
NIOSH RTECS	No data	No data	No data
EPA hazardous waste	D006	D006	D006
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	UN2570/IMCO 6.1	No data	No data
HSDB	1613	274	1614
NCI	No data	No data	No data

[a]All information obtained from HSDB 2008 except where noted
[b]O'Neil et al. 2006

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Cadmium and Compounds[a]

Property	Cadmium	Cadmium carbonate
Molecular weight	112.41[b]	172.42[b]
Color	Silver-white[b]	White[c]
Physical state	Lustrous metal[b]	Powder or rhombohedral leaflets[b]
Melting point	321 °C[b]	Decomposes at 357 °C
Boiling point	765 °C[b]	No data
Density at 20 °C	8.65 g/cm^3 at 25 °C[b]	4.58 g/cm^3[f]
Odor	Odorless	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 20 °C	Insoluble[b]	Insoluble[f]
Organic solvents	Acids, NH_4NO_3[f]	Acids, especially HNO_3, concentrated NH_4 solution[c]
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure	7.5x10^{-3} mmHg at 257 °C	No data
Henry's law constant at 25 °C	No data	No data
Autoignition temperature	250 °C	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	No data	No data
Explosive limits	No data	No data

Table 4-2. Physical and Chemical Properties of Cadmium and Compounds[a]

Property	Cadmium chloride	Cadmium oxide
Molecular weight	183.32	128.41[b]
Color	White[c]	Dark brown[b]
Physical state	Rhombohedral crystals[b]	Infusible powder or cubic crystals[b]
Melting point	568 °C[b]	Decomposes at 950 ºC
Boiling point	960 °C[b]	Decomposes at 950 ºC
Density at 20 °C	4.047g/cm^3 at 25 °C[e]	Crystals 8.15 g/cm^3; amorphous powder 6.95 g/cm^3[c]
Odor	Odorless[c]	Odorless
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 20 °C	Soluble[b]	Insoluble[b]
Organic solvents	Acetone, slightly soluble in MEOH and ETOH[b]	Dilute acid, slowly soluble in NH_4 salts[b]
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure	10 mmHg at 656 °C[e], 40 mmHg at 736 °C[d], 760 mmHg at 967 °C[d]	1 mmHg at 1,000 °C[e]; 10 mm Hg at 1149 ºC; 40 mm Hg at 1257 ºC
Henry's law constant at 25 °C	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	No data	No data
Explosive limits	No data	No data

Table 4-2. Physical and Chemical Properties of Cadmium and Compounds[a]

Property	Cadmium sulfate	Cadmium sulfide
Molecular weight	208.47[b]	144.48[b]
Color	Colorless[c]	Light yellow or orange[b]; brown[c]
Physical state	Monoclinic crystals[b]	Cubic or hexagonal structure[b]
Melting point	1,000 °C[c]	1,750 °C[c]
Boiling point	No data	Sublimes in N_2 at 980 °C[c]
Density at 20 °C	4.69 g/cm[3b]	4.82 g/cm^3, hexagonal structure[b], 4.5 g/cm^3, cubic structure[b]
Odor	Odorless	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 20 °C	Soluble[c]	Soluble at 1.3 mg/L at 18 °C[b]
Organic solvents	Insoluble in alcohol[c], acetone, ammonia[f]	Concentrated or warm dilute mineral acids[b]
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure at 20 °C	No data	No data
Henry's law constant at 25 °C	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	No data	No data
Explosive limits	No data	No data

[a]All information from HSDB 2008, except where noted.
[b]O'Neil et al. 2006
[c]Sax and Lewis 2001
[d]Farnsworth 1980
[e]Sax and Lewis 2000
[f]Lide 2005

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Cadmium is a widely but sparsely distributed element found in the earth's crust at concentrations ranging from 0.1 to 5 ppm, primarily as sulfide minerals in association with zinc ores, zinc-bearing lead ores, and or complex copper-lead-zinc ores (Morrow 2001). Approximately 3 kg of cadmium for each ton of zinc are produced (OECD 1995). About 80% of cadmium production is associated with zinc production, while the other 20% is associated with lead and copper byproduct production and the recapture of cadmium from finished products (Morrow 2001). Between 2003 and 2006, the annual cadmium refinery production in the United States declined from 1,450 to 700 metric tons, dropping 52% between 2005 and 2006 (USGS 2007, 2008). Demand for cadmium in the nickel-cadmium (Ni-Cd) battery industry is strengthening as demand in other areas, like coatings and pigments, has been decreasing due to environmental concerns and regulations. Despite this demand, primary production of cadmium may decrease as zinc prices increase, since producers may choose to discard the cadmium byproduct instead of refining it (USGS 2008).

One company produced primary cadmium in the United States during 2007: Clarksville (Zinifex Ltd.), Clarksville, Tennessee. The Big River Zinc Corporation (Korea Zinc Co, Ltd), Sauget, Illinois operation was closed in 2006, citing mine closures and the increasing price of zinc concentrate (USGS 2008). In June 2006, it was purchased by ZincOx Resources plc, Surrey, United Kingdom (USGS 2007). A third company in Ellwood, Pennsylvania, International Metals Reclamation Co. Inc. (INMETCO), recovers cadmium from spent nickel-cadmium batteries, which began reclaiming cadmium in 1995 (USGS 2007). In 2005, it was estimated that the total cadmium recovery rate was only 12%, with an estimated 40,000 tons of cadmium being disposed of in municipal waste or held in household storage or industry stockpiles between 1996 and 2005 (USGS 2007).

The following companies are currently cited as major producers of cadmium compounds: GFS Chemicals Inc., Columbus, Ohio (cadmium chloride, cadmium sulfate); CERAC Inc., Milwaukee, Wisconsin (cadmium sulfide); and EP Scientific Products, LLC (cadmium sulfide) (SRI 2007). BASF Catalysts LLC, Louisville, Kentucky was specifically cited as a major producer of cadmium sulfide/ sulfoselenide pigments (SRI 2007).

Tables 5-1 and 5-2 list the facilities in each state that manufacture or process cadmium and cadmium compounds, respectively, the intended use, and the range of maximum amounts stored on site. The data

Table 5-1. Facilities that Produce, Process, or Use Cadmium

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	19	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	10	0	999,999	1, 2, 3, 5, 6, 8, 10, 12, 13
AZ	10	0	999,999	1, 2, 3, 4, 5, 7, 8, 10, 13
CA	40	0	99,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	7	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 12
CT	5	0	99,999	7, 8, 10, 11
FL	4	100	99,999	1, 2, 3, 4, 6, 7, 8, 10, 12
GA	6	0	999,999	1, 3, 6, 8, 13, 14
IA	8	0	99,999	1, 5, 7, 8, 12, 13
ID	5	10,000	999,999	1, 3, 5, 12, 13
IL	25	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14
IN	10	0	999,999	1, 2, 5, 7, 8, 9, 10, 12
KS	5	100	99,999	1, 3, 7, 8, 12
KY	12	0	999,999	1, 2, 3, 5, 6, 7, 8, 11, 14
LA	7	0	999,999	1, 3, 5, 6, 8, 10, 12, 13
MA	12	0	99,999	1, 2, 3, 4, 7, 8, 10
MD	5	100	49,999,999	1, 2, 4, 5, 6, 13
MI	19	0	99,999	1, 2, 3, 5, 6, 7, 8, 10, 12, 13, 14
MN	10	0	999,999	1, 3, 4, 7, 8, 9, 10, 11, 12, 13
MO	7	0	999,999	1, 2, 3, 4, 5, 6, 8, 14
MS	7	0	9,999	5, 7, 8, 12
NC	12	0	9,999,999	1, 5, 7, 8, 9, 10, 12, 14
NE	8	100	99,999	1, 2, 5, 7, 8, 12
NH	4	0	999	1, 3, 8, 12
NJ	18	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NM	1	10,000	99,999	12
NV	1	10,000	99,999	1, 5, 13
NY	19	0	9,999,999	2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14
OH	28	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	16	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
OR	6	0	9,999,999	1, 5, 8, 12
PA	34	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PR	1	0	99	8
RI	4	0	9,999	2, 3, 7, 8
SC	20	0	9,999,999	1, 3, 5, 6, 7, 8, 9, 10, 11, 12
TN	13	0	9,999,999	1, 2, 3, 4, 7, 8, 9, 11, 12, 13
TX	23	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14
UT	6	100	99,999	1, 5, 6, 7, 8, 12, 13
VA	11	0	99,999	1, 5, 7, 8, 10, 11, 13

Table 5-1. Facilities that Produce, Process, or Use Cadmium

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WA	4	0	9,999	1, 2, 3, 5, 10, 13
WI	12	100	49,999,999	3, 7, 8, 10, 11, 12
WV	3	100	99,999	7, 8, 12
WY	1	0	99	1, 13

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI06 2008 (Data are from 2006)

Table 5-2. Facilities that Produce, Process, or Use Cadmium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	11	100	499,999,999	1, 5, 7, 9, 11, 12, 14
AL	28	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
AR	17	100	999,999	1, 2, 3, 5, 7, 8, 12, 13, 14
AZ	24	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 12, 13, 14
CA	27	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
CO	7	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13
CT	27	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
DE	2	100	9,999	1, 5
FL	9	0	999,999	1, 2, 3, 5, 6, 8, 12, 13, 14
GA	12	0	999,999	1, 3, 5, 6, 7, 8, 13
IA	4	0	99,999	1, 5, 7, 8, 9, 12
ID	9	100	9,999,999	1, 5, 6, 7, 11, 14
IL	41	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14
IN	17	0	999,999	1, 5, 7, 8, 13, 14
KS	7	0	99,999	1, 7, 8, 11, 13
KY	19	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 12, 13
LA	11	0	999,999	1, 2, 3, 5, 7, 8, 12, 13
MA	12	0	999,999	1, 3, 4, 5, 6, 7, 8, 12, 13
MD	9	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 13
MI	24	0	99,999,999	1, 3, 5, 6, 7, 8, 10, 11, 12, 13
MN	10	100	999,999	1, 5, 7, 8, 9, 13
MO	14	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 13
MS	9	0	999,999	1, 5, 7, 8, 12
MT	3	1,000	9,999,999	1, 2, 3, 4, 5, 6, 13
NC	12	0	49,999,999	1, 7, 8, 13
NE	6	1,000	999,999	1, 2, 5, 8, 13, 14
NH	1	1,000	9,999	7, 10
NJ	34	0	9,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 12
NM	6	1,000	9,999,999	1, 5, 13
NV	21	100	49,999,999	1, 2, 3, 5, 6, 7, 9, 10, 12, 13, 14
NY	25	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
OH	76	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	17	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 13
OR	4	100	99,999	1, 5, 8
PA	58	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
PR	1	100	999	8
RI	8	100	99,999	2, 3, 7, 8, 11
SC	15	0	999,999	1, 4, 5, 6, 7, 8, 11, 12, 14

Table 5-2. Facilities that Produce, Process, or Use Cadmium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TN	30	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14
TX	32	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
UT	15	1,000	49,999,999	1, 5, 6, 7, 8, 12, 13
VA	11	0	99,999	1, 5, 7, 8, 12, 14
WA	13	0	999,999	1, 2, 3, 5, 6, 7, 8, 11, 12, 13
WI	11	100	49,999,999	1, 3, 5, 7, 8, 10, 11, 12
WV	7	1,000	999,999	1, 2, 3, 7, 8, 11, 13

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI06 2008 (Data are from 2006)

listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI) (TRI06 2008). Because only certain types of facilities were required to report, this is not an exhaustive list.

Cadmium metal is available in purities ranging from 99.5 to 99.999% in the following grades: technical, powder, pure sticks, ingots, slabs, and high-purity crystals (<10 ppm impurities) (HSDB 2008). Cadmium (as cadmium oxide) is obtained mainly as a byproduct during the processing of zinc-bearing ores (e.g., sphalerites), and also from the refining of lead and copper from sulfide ores (e.g., galena) (Morrow 2001). Cadmium oxide produced during roasting of ores is reduced with coke, and cadmium metal is separated by distillation or electrodeposition (Elinder 1985a). Commercial-grade cadmium oxide is available in purities ranging from 99 to 99.9999%; common impurities are lead and thallium (NTP 2005). Cadmium chloride is produced by reacting molten cadmium with chlorine gas at 600 °C or by dissolving cadmium metal or the oxide, carbonate, sulfide, or hydroxide in hydrochloric acid and subsequently vaporizing the solution to produce a hydrated crystal (HSDB 2008; IARC 1993). In preparing the anhydrous cadmium chloride salt, the hydrate is refluxed with thionyl chloride or calcined in a hydrogen chloride atmosphere (HSDB 2008). Commercial cadmium chloride is available as a hydrate mixture with a purity range of 95.0–99.999% (NTP 2005).

The commercial preparation of cadmium sulfate usually involves dissolution of the metal oxide, carbonate, or sulfide in sulfuric acid with subsequent cooling or evaporation (HSDB 2008). Anhydrous cadmium sulfate is prepared by oxidation of the sulfide or sulfite at elevated temperatures (Herron 2003); or by melting cadmium with ammonium or sodium peroxodisulfate (Schulte-Schrepping and Piscator 2002). Cadmium sulfate monohydrate, which is the cadmium compound most often marketed, is produced by evaporating a cadmium sulfate solution above 41.5 °C (Schulte-Schrepping and Piscator 2002). Cadmium sulfate is available in technical and C.P. (chemically pure) grades (Lewis 2001). Cadmium sulfide can be prepared by a direct reaction with hydrogen sulfide and cadmium vapor or between sulfur and cadmium metal or cadmium oxide (Herron 2003). Cadmium sulfide is available in technical, N.F. (national formulary grade), and high-purity (single crystals) (Lewis 2001). Cadmium carbonate is produced by heating an acidified solution of cadmium chloride and urea in a sealed tube at 200 °C, the slow absorption of carbon dioxide to cadmium oxide, or the precipitation of the hemihydrate from reaction of ammonium carbonate in cadmium ion solution (Herron 2003).

5.2 IMPORT/EXPORT

Imports of cadmium into the United States declined steadily from 1994 through 1998, dropping from 1,110 metric tons per year to an estimated 650 metric tons in 1998 (USGS 1999). In 1986, imports of cadmium metal for consumption increased significantly to 3,000 metric tons, but continually decreased into the 1990s. From 2003 to 2005, cadmium imports of metal, alloys, and scrap increased from 112 to 288 tons, 74–207 tons of which were metal-only imports (USGS 2008). Cadmium imports peaked in 2005 and then declined through 2007, with 172 tons of cadmium metal only and 174 tons of metal, alloys, and scrap imported (USGS 2008). The principal supplying countries were Australia (41%), Canada (20%), China (10%), and Peru (9%) (USGS 2008).

In the mid-1990s, exports varied widely from 38 metric tons in 1993, to 1,450 metric tons in 1994, to 550 metric tons in 1997. In 2003, cadmium exports (reported as metal, alloys, and scraps) were 615 tons, with exports decreasing to only 154 tons the following year (USGS 2008). Exports surged again in 2005 to 686 tons, but have since been steadily decreasing from 483 tons in 2006 to 304 tons in 2007 (USGS 2008).

5.3 USE

Cadmium, its alloys, and its compounds are used in a variety of consumer and industrial materials. The dominant use of cadmium is in active electrode materials in Ni-Cd batteries (83% of total cadmium use) (USGS 2008). Cadmium demand for other uses such as pigments for plastics, ceramics, and glasses; stabilizers for polyvinyl chloride (PVC) against heat and light; engineering coatings on steel and some nonferrous metals; and components of various specialized alloys have been decreasing. (Elinder 1992; IARC 1993; Thornton 1992; USGS 2008). Cadmium salts have been used in a limited capacity as a fungicide for golf courses and home lawns (EPA 2006d). Cadmium chloride is used in photography, photocopying, dyeing, calico printing, vacuum tube manufacture, pigment manufacture, galvanoplasty, lubricants, ice-nucleation agents, and in the manufacture of special mirrors (Herron 2003). However, the significance of cadmium chloride as a commercial product is declining (IARC 1993).

Cadmium-based colorants are used mainly in engineering plastics, ceramics, glasses, and enamels (IARC 1993; OECD 1995). Cadmium sulfide is especially important in this industry, especially in glasses and plastics; however, environmental and health concerns have contributed to a decrease in its production (Herron 2003). Cadmium sulfide (yellow) and cadmium selenide (red) are combined to create solid C.P. toners ranging in color from yellows and oranges to reds and maroons (Herron 2003). Cadmium

sulfide and cadmium telluride are used in solar cells and a variety of electronic devices which depend on cadmium's semiconducting properties (Herron 2003; IARC 1993; OECD 1995). The photoconductive and electroluminescent properties of cadmium sulfide have been applied in manufacturing a variety of consumer goods (IARC 1993). Cadmium sulfate solution is used in standard Weston cells (Herron 2003).

Though cadmium metal consumption for batteries has grown steadily since the 1980s and currently consumes 83% of the cadmium produced, other uses of cadmium began declining in the mid 1990s. Pigment, stabilizer, coating, and alloy markets for cadmium are decreasing due to environmental concerns (USGS 1997, 2008). Proposed legislation, particularly in the European Union, restricting cadmium in consumer products may have a negative effect on cadmium demand (USGS 2008). Excessive exports from Bulgaria and Russia in 1997 caused a drop in the average price of cadmium from $1.84 per pound in 1995 to $0.51 per pound in 1997. Also, Ni-Cd batteries have been replaced in some markets by lithium-ion and nickel metal hydride batteries (USGS 2008). As of 2006, Ni-Cd batteries made up 18% of the rechargeable battery market, down from 56% in 1996 with global sales decreasing 16% between 2005 and 2006 (USGS 2008). Despite this trend, demand for cadmium may increase due to new market opportunities for Ni-Cd batteries (USGS 2008). Regulations by local authorities have forced the recycling of cadmium in Ni-Cd batteries, further depressing the demand for primary cadmium metal (USGS 1999).

5.4 DISPOSAL

Cadmium-containing wastes are subject to regulations concerning their treatment, storage, and disposal (see Chapter 8) (EPA 1982a; HSDB 2008; U.S. Bureau of Mines 1990). In many states, the disposal of Ni-Cd batteries as municipal waste is prohibited (USGS 2007). Incineration of municipal wastes, particularly from older, poorly controlled facilities, is a potential environmental source of cadmium. In modern incineration plants, about 99.9% of cadmium was captured in boilers and control equipment (OECD 1995).

A range of physicochemical processes is available for treatment of cadmium in liquid waste process streams, including ion exchange, electrolysis, cementation, and adsorption. Both ion exchange and sulfide precipitation are used as alternate processes aimed at achieving low cadmium residuals in liquid wastes (UN 1985). Combining processes, for example, conducting the primary precipitation of cadmium as hydroxide followed by secondary precipitation of residual cadmium as sulfide, has also been adopted. The more general application of the sulfide precipitation technique, however, is constrained due to a

tendency for formation of colloidal precipitate, the toxicity and odor of hydrogen sulfide, and the necessity to oxidize residual sulfide occurring in emissions prior to discharge (UN 1985).

The most widely used treatment process involves the alkaline precipitation of cadmium as hydroxide or basic salts (UN 1985). Removal of specific metal species during hydroxide precipitation is pH-dependent, and some components of the waste stream can influence the solubility of cadmium hydroxide. After filtration, the sludge formed from the conversion of soluble cadmium compounds to insoluble compounds can be deposited in a suitable landfill (UN 1985).

Various cadmium-bearing wastes are subject to aggressive leaching in refuse media, particularly under aerobic conditions (UN 1985). While liquid wastes are banned from land disposal, the leaching tendency is accentuated in the presence of brine solutions. Also, the mobility of cadmium in landfill conditions could be enhanced in the presence of mineral acids, which tend to solubilize cadmium compounds, or amine-containing materials, which tend to complex cadmium ions. Waste containing mineral acids, cyanides, organic solvents, and amine-type substances should not be landfilled near cadmium-bearing wastes (UN 1985).

In the laboratory, a recommended method for recovering cadmium from small quantities of cadmium oxide wastes uses a minimum amount of concentrated nitric acid to form nitrates. The solution is evaporated in a hood to form a thin paste, and then diluted with water and saturated with hydrogen sulfide. After the filtration, the precipitate is washed, dried, and returned to the supplier (UN 1985).

Cadmium recovery from scrap metals and batteries is becoming increasingly popular, with the main emphasis being on recycling Ni-Cd batteries (Morrow 2001). Battery recycling is relatively easy and can be achieved using pyrometalllurigical (high temperature) or hydrometallurgical (wet chemical) processes (Morrow 2001). In these processes, the metallic waste that contains iron, nickel, cadmium, and their oxides and hydroxides are separated from the other battery components and then converted back to a metal that has a technical purity required for the production of new batteries (Morrow 2001). Cadmium-based coatings can be recycled using electric-arc furnace (EAF) dust, which is obtained through the re-melting of scrap steel that contains cadmium coatings and cadmium impurities (Morrow 2001). INMETCO in Ellwood, Pennsylvania recovers cadmium from spent Ni-Cd batteries, and has developed several collection programs to help facilitate battery recycling (USGS 2007). Although participation in battery recycling has increased in businesses, communities, and retailers, the total recovery of cadmium in 2005 was only 12% (USGS 2007).

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Cadmium has been identified in at least 1,014 of the 1,669 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). Cadmium compounds have been identified in at least 3 of the 1,669 hazardous waste sites. However, the number of sites evaluated for cadmium is not known. The frequency of these sites can be seen in Figures 6-1 and 6-2. Of the 1,014 sites where cadmium has been identified, 1,005 are located within the United States, 6 are located in the Commonwealth of Puerto Rico (not shown), 2 are located in Guam, and 1 is located in the Virgin Islands. All sites where cadmium compounds were detected are located in the United States.

Cadmium occurs in the earth's crust at an abundance of 0.1–0.5 ppm and is commonly associated with zinc, lead, and copper ores. It is also a natural constituent of ocean water, with average levels between <5 and 110 ng/L; with higher levels have been reported near coastal areas and in marine phosphates and phosphorites (Morrow 2001). Natural emissions of cadmium to the environment can result from volcanic eruptions, forest fires, generation of sea salt aerosols, or other natural phenomena (EPA 1985a; Morrow 2001; Shevchenko et al. 2003). Cadmium is refined and consumed for uses in batteries (83%), pigments (8%), coatings and platings (7%), stabilizers for plastics (1.2%), and nonferrous alloys, photovoltaic devices, and other uses (0.8%) (USGS 2008). Nonferrous metal mining and refining, manufacture and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal are the main anthropogenic sources of cadmium in the environment.

Cadmium can be released to the atmosphere through metal production activities, fossil fuel combustion, and waste incineration. The main cadmium compounds found in air are cadmium oxide, chloride, and sulfate, and these compounds are expected to undergo minimal transformation in the atmosphere (EPA 1980d). The major fate of cadmium in air is through transport and deposition. Cadmium can travel long distances in the atmosphere and then deposit (wet or dry) onto surface soils and water, which can result in elevated cadmium levels even in remote locations (Shevchenko et al. 2003). Results from the 2006 final report of EPA's Urban Air Toxic Monitoring program reported average daily cadmium levels of <0.01 $\mu g/m^3$ at several monitoring sites throughout the United States. These sites include: Bountiful, Utah; Northbrook, Illinois; Austin, Texas; St. Louis, Missouri; Indianapolis, Indiana; and Birmingham, Alabama (EPA 2007). Atmospheric concentrations of cadmium are generally highest in the vicinity of cadmium-emitting industries (Elinder 1985a; Pirrone et al. 1996). Due to advances in pollution control technology, cadmium emissions to air are not expected to increase, even though cadmium-emitting

Figure 6-1. Frequency of NPL Sites with Cadmium Contamination

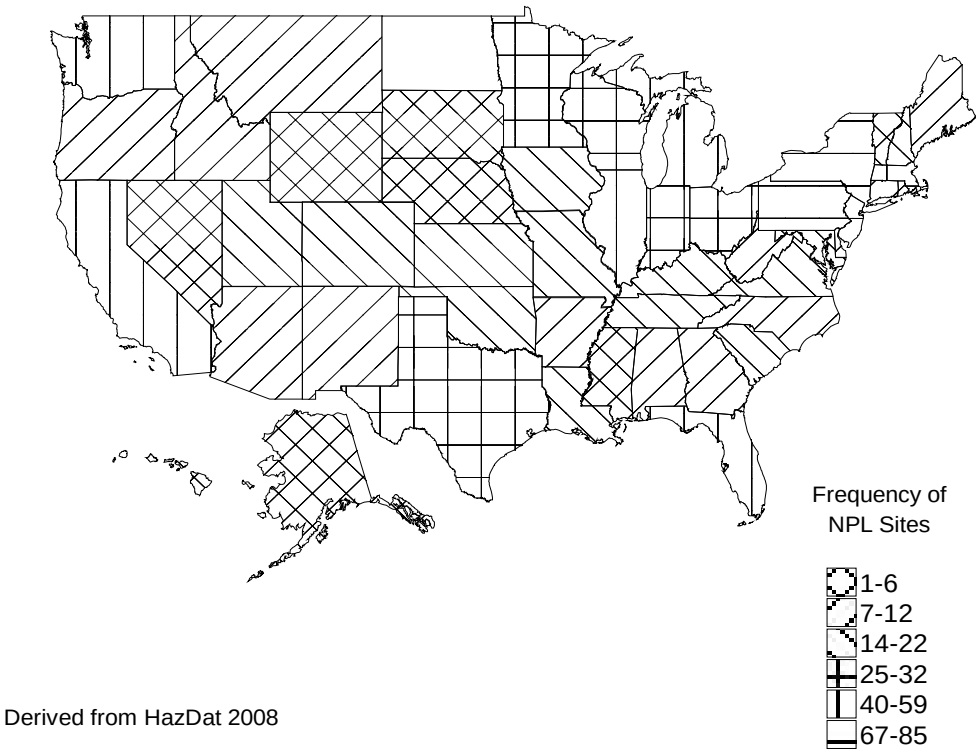
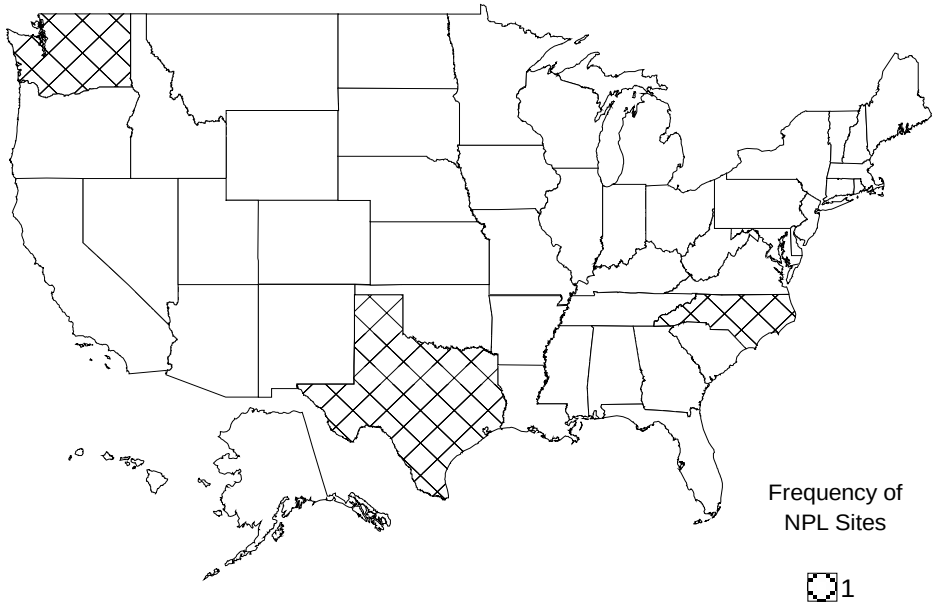


Figure 6-2. Frequency of NPL Sites with Cadmium Compounds Contamination



Derived from HazDat 2008

industries are expected to grow (Herron 2003; Morrow 2001; Schulte-Schrepping and Piscator 2002). Except for those who live near cadmium-emitting industries, inhalation of cadmium in the ambient air is not a major source of exposure.

The main sources of cadmium to soil include atmospheric deposition and direct application methods such as phosphate fertilizer use and sewage sludge disposal. Some phosphate fertilizers can contain up to 300 mg Cd/kg (Alloway and Steinnes 1999). Wet and dry deposition of cadmium from the atmosphere may also contribute sizable amounts of cadmium to soil in the areas surrounding sources of atmospheric emissions (EPA 1985a; Mielke et al. 1991). Cadmium's mobility in soil depends on several factors including the pH of the soil and the availability of organic matter. Generally, cadmium will bind strongly to organic matter and this will, for the most part, immobilize cadmium (Autier and White 2004). However, immobilized cadmium is available to plant life and can easily enter the food supply. Cadmium in soil tends to be more available when the soil pH is low (acidic) (Elinder 1992).

Water sources near cadmium-emitting industries, both with historic and current operations, have shown a marked elevation of cadmium in water sediments and aquatic organisms (Angelo et al. 2007; Arnason and Fletcher 2003; Brumbaugh et al. 2005; Mason et al. 2000; Paulson 1997). In surface water and groundwater, cadmium can exist as the hydrated ion or as ionic complexes with other inorganic or organic substances. While soluble forms may migrate in water, cadmium is relatively nonmobile in insoluble complexes or adsorbed to sediments. Cadmium is taken up and retained by aquatic and terrestrial plants and is concentrated in the liver and kidney of animals that eat the plants (Elinder 1985a).

For the U.S. population, cadmium exposure through the drinking water supply is of minor concern. EPA requires water suppliers to limit the cadmium concentration in water to <5 µg/L (EPA 2006a).

In the United States, the largest source of cadmium exposure for nonsmoking adults and children is through dietary intake (NTP 2005). Based on the mean cadmium daily intakes of males and females aged 6–60 years reported by Choudhury et al. (2001), age-weighted mean cadmium intakes of 0.35 µg/kg/day for males and 0.30 µg/kg/day for females were calculated for U.S. nonsmokers. Females generally absorb greater amounts of cadmium in the gastrointestinal tract (CDC 2005). In general, leafy vegetables, such as lettuce and spinach, and staples, such as potatoes and grains, contain relatively high values of cadmium. Peanuts, soybeans, and sunflower seeds have naturally high levels of cadmium (Morrow 2001). People who regularly consume shellfish and organ meats (liver and kidney) have an increased risk of cadmium exposure, as these organisms tend to accumulate cadmium (Elinder 1985a).

Tobacco leaves naturally accumulate large amounts of cadmium (Morrow 2001). Cadmium levels in cigarettes vary greatly depending on the source of production. Cigarettes produced in Mexico were found to have the highest level of cadmium per cigarette (arithmetic mean [AM] ± arithmetic standard deviation [ASD] = 2.03 µg/cigarette ±0.33), while cigarettes from India were found to have the lowest (arithmetic mean ± arithmetic standard deviation = 0.35 µg/cigarette ±0.09). The arithmetic mean for the United States was 1.07 µg/cigarette ±0.11 (Watanabe et al. 1987). It has been estimated that tobacco smokers are exposed to 1.7 µg cadmium per cigarette, and about 10% is inhaled when smoked (Morrow 2001; NTP 2005). The geometric mean blood cadmium level for the heavy smoker subgroup in New York City was reported as 1.58 µg/L, compared to the geometric mean of 0.77 µg/L for all New York City adults (McKelvey et al. 2007).

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

Additional releases of cadmium to the environment occur from natural sources and from processes such as combustion of fossil fuel, incineration of municipal or industrial wastes, or land application of sewage sludge or fertilizer (EPA 1985a). Quantitative information on releases of cadmium to specific environmental media is discussed below.

6.2.1 Air

Estimated releases of 5,308 pounds (~2.4 metric tons) of cadmium to the atmosphere from 74 domestic manufacturing and processing facilities in 2006, accounted for about 0.45% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). These releases are summarized in Table 6-1. Estimated releases of 8,908 pounds (~4.0 metric tons) of cadmium compounds to the atmosphere from 98 domestic manufacturing and processing facilities in 2006, accounted for about 0.31% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). These releases are summarized in Table 6-2.

Cadmium is released to the atmosphere from both natural and anthropogenic sources. Cadmium is widely distributed in the earth's crust (EPA 1985a) with concentrations reported between 0.1 and 0.5 ppm and higher levels in sedimentary rocks (Morrow 2001). Consequently, cadmium may be released to the air from entrainment of dust particles, volcanic eruptions, forest fires, or other natural phenomena (EPA 1985a; Morrow 2001). Cadmium exists in ocean waters at average levels ranging from <5 to 110 ng/L and may transport to the atmosphere through natural processes like generation of sea-salt aerosols (Morrow 2001; Shevchenko et al. 2003). Increased cadmium levels in the air over the Russian Arctic have been detected during the summer and autumn seasons and are believed to be attributed to natural processes, while the levels detected during the winter and spring seasons were due to anthropogenic sources (Shevchenko et al. 2003).

However, industrial activities are the main sources of cadmium release to air (EPA 1985a), and emissions from anthropogenic sources have been found to exceed those of natural origin by an order of magnitude (IARC 1993). Major industrial sources of cadmium emissions include zinc, lead, copper, and cadmium smelting operations; coal and oil-fired boiler; other urban and industrial emissions; phosphate fertilizer manufacture; road dust; and municipal and sewage sludge incinerators (Alloway and Steinnes 1999; Morrow 2001). Emission of cadmium through nonferrous metal production in 1995 was highest in Asia with 1,176 tonnes and North America emitting 191 tonnes. Estimated emissions of cadmium from municipal waste and sewage sludge incineration in North America were 8 and 7 tonnes/year, respectively, in the mid-1990s (Pacyna and Pacyna 2001). Additional sources that contribute negligible amounts of cadmium are rubber tire wear, motor oil combustion, cement manufacturing, and fertilizer and fungicide application (Wilber et al. 1992). Average cadmium emission factors for combustion of coal and oil are about 0.1 and 0.05 g/ton, respectively. Cement production releases an estimated 0.01 g/ton cement and

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Cadmium[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	2	87	4	0	39,510	750	39,663	754	40,417
AR	1	1	0	0	0	0	1	0	1
AZ	2	0	0	0	0	0	0	0	0
CA	9	575	1,002	0	29,248	4,593	17,193	18,475	35,668
FL	1	0	0	0	0	0	0	0	0
GA	2	5	0	0	5	250	5	255	260
IA	2	0	1	0	1	0	0	2	2
ID	1	50	0	0	282,046	0	282,096	0	282,096
KS	3	0	0	0	18	0	0	18	18
KY	2	28	0	0	250	0	28	250	278
LA	2	99	0	0	13,000	192	13,099	192	13,291
MI	5	0	0	0	14	0	0	14	14
MO	1	0	0	0	0	0	0	0	0
NC	2	67	0	0	0	0	67	0	68
NE	1	5	0	0	26,499	0	25,982	522	26,504
NY	4	1	0	0	85	27	17	112	129
OH	6	48	0	65,582	169,171	0	148,630	86,171	234,802
OK	2	6	0	0	18,652	0	18,305	353	18,658
OR	1	3	0	0	123,833	0	123,836	0	123,836
PA	3	0	0	0	986	1	0	987	987
PR	1	0	0	0	5	0	0	5	5
SC	2	19	0	0	0	3	19	3	22
TN	1	4,000	0	0	0	0	4,001	0	4,001
TX	13	297	0	50,347	11,514	26	62,180	26	62,206
UT	2	16	0	0	343,190	0	328,620	14,586	343,206
WI	2	0	0	0	0	0	0	0	0

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Cadmium[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WV	1	0	0	0	250	0	250	0	250
Total	74	5,308	1,008	115,929	1,058,277	5,842	1,063,993	122,725	1,186,719

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI06 2008 (Data are from 2006)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Cadmium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	3	128	5	0	62,879	1	63,012	1	63,014
AL	3	466	48	0	854,657	515	852,514	3,172	855,686
AR	3	44	3	0	23	20,935	47	20,958	21,005
AZ	2	634	755	0	457,303	5	450,837	7,860	458,697
CA	2	0	0	0	250	0	0	250	250
CT	1	0	0	0	0	0	0	0	0
FL	2	30	0	0	0	26	30	26	56
GA	1	7	5	0	0	0	9	3	12
IA	1	0	0	0	0	0	0	0	0
ID	2	2,971	10	0	319,827	0	322,808	0	322,808
IL	7	73	485	1,097	36,120	4,449	26,123	16,101	42,224
IN	4	263	17	0	32,229	12,000	270	44,239	44,509
KY	1	0	0	0	0	0	0	0	0
LA	2	5	0	0	36	0	41	0	41
MA	1	1	0	0	0	3,600	1	3,600	3,601
MD	1	0	0	0	0	0	0	0	0
MI	3	43	1	0	13,830	0	10,007	3,867	13,874
MO	2	1,024	123	0	9,088	0	10,186	49	10,235
MT	1	6	0	0	2,841	0	2,847	0	2,847
NC	3	0	0	0	12,205	35,789	0	47,994	47,994
NE	1	255	5	0	0	30,000	260	30,000	30,260
NH	1	0	0	0	0	0	0	0	0
NJ	2	5	1	0	11,293	185	5	11,479	11,484
NV	3	50	0	0	255,122	130	255,172	130	255,302
NY	2	27	53	0	2,505	3,931	2,559	3,957	6,516
OH	11	70	683	0	32,915	10,441	179	43,930	44,109
OK	2	501	0	32	0	293,634	533	293,634	294,167
PA	7	1,046	23	0	19,474	1,803	1,059	21,287	22,346
SC	1	19	1	0	0	0	20	0	20
TN	5	909	431	0	177,051	0	178,385	5	178,390
TX	9	57	80	0	146	5,374	57	5,600	5,657
UT	5	258	500	0	80,338	29,340	76,142	34,294	110,436
WA	2	4	0	0	102	3	106	3	109
WI	1	10	18	0	0	9	10	27	37

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Cadmium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WV	1	2	7	0	213	0	118	105	222
Total	98	8,908	3,255	1,129	2,380,447	452,170	2,253,338	592,572	2,845,910

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI06 2008 (Data are from 2006)

pig iron and steel production releases an estimated 0.1 g/ton (Pacyna and Pacyna 2001). Atmospheric cadmium exists mainly in the forms of cadmium oxide and cadmium chloride (Morrow 2001).

Cadmium emissions have decreased dramatically since the 1960s as primary cadmium producers now use the electrolytic process and pollution control technologies such as agglomerization, electrostatic purification of gas exhaust, and exhaust filtration have been implemented (Herron 2003; Morrow 2001; Schulte-Schrepping and Piscator 2002). In addition, EPA has proposed risk-based regulations for cadmium emissions from hazardous waste incinerators (EPA 1990a). Therefore, although there may be an increase in fossil fuel combustion and waste incineration, it does not appear likely that overall cadmium emissions to air will increase substantially.

There is a potential for release of cadmium to air from hazardous waste sites. Cadmium has been detected in air samples collected at 50 of the 1,014 NPL hazardous waste sites where cadmium has been detected in some environmental medium (HazDat 2008). Cadmium compounds have been detected in air samples collected at one of three NPL hazardous waste sites where cadmium compounds have been detected. The HazDat information used includes data from NPL sites only.

6.2.2 Water

Estimated releases of 1,008 pounds (~0.46 metric tons) of cadmium to surface water from 74 domestic manufacturing and processing facilities in 2006, accounted for about 0.085% of the estimated total environmental releases from facilities required to report to the TRI. This is estimate includes releases to wastewater treatment and publicly owned treatment works (TRI06 2008). These releases are summarized in Table 6-1. Estimated releases of 3,255 pounds (~1.5 metric tons) of cadmium compounds to surface water from 98 domestic manufacturing and processing facilities in 2006, accounted for about 0.11% of the estimated total environmental releases from facilities required to report to the TRI. This is estimate includes releases to wastewater treatment and publicly owned treatment works (TRI06 2008). These releases are summarized in Table 6-2.

Cadmium may be released to water by natural weathering processes, by discharge from industrial facilities or sewage treatment plants, atmospheric deposition, by leaching from landfills or soil, or phosphate fertilizers (EPA 1981a, 1985a; IJC 1989; Morrow 2001). Cadmium may also leach into drinking water supplies from pipes in the distribution system (Elinder 1985a). The average level of

cadmium in ocean water has been reported between <5 and 110 ng/L, with higher levels reported near coastal areas and in marine phosphates and phosphorites (Morrow 2001).

Smelting of nonferrous metal ores has been estimated to be the largest anthropogenic source of cadmium released into the aquatic environment. Cadmium contamination can result from entry into aquifers of mine drainage water, waste water, tailing pond overflow, and rainwater runoff from mine areas (IARC 1993). The upper Clark Fork River in Montana is contaminated with large amounts of cadmium from past mining activities between 1880 and 1972. While mining wastes are no longer released into the river, an estimated 14.5 million cubic meters of tailings have been incorporated into the river bed, floodplain, and reservoir sediments (Canfield et al. 1994). Other human sources include spent solutions from plating operations and phosphate fertilizers. Cadmium constitutes up to 35 mg/kg of phosphorous pentoxide in the United States (IARC 1993). Atmospheric fallout of cadmium to aquatic systems is another major source of cadmium to the environment (IARC 1993; Muntau and Baudo 1992).

A large proportion of the cadmium load in the aquatic environment is due to diffuse pollution originating from many different sources rather than from point sources. In the estuarine portion of the Hudson River, it has been found that more cadmium was released from agricultural and urban run-off than from industrial and municipal sewage treatment plants (Muntau and Baudo 1992). In an urban environment, there are also multiple sources of cadmium to waste water, based on an urban waste water study conducted in the United Kingdom. Cadmium was detected in the foul water originating from industrial, commercial, and private sectors, with the highest average cadmium concentration detected in the foul water of new (<5 years old) private housing (0.375 μg/L) (Rule et al. 2006).

There is also a potential for release of cadmium to water from hazardous waste sites. Cadmium has been detected in surface water samples collected at 354 of the 1,014 NPL hazardous waste sites, and in groundwater samples collected at 675 of the 1,014 NPL hazardous waste sites where cadmium has been detected in some environmental medium (HazDat 2008). The HazDat information used includes data from NPL sites only.

6.2.3 Soil

Estimated releases of 1,058,277 pounds (~480 metric tons) of cadmium to soils from (74) domestic manufacturing and processing facilities in 2006, accounted for about 89% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). An additional

115,929 pounds (~53 metric tons), constituting about 9.8% of the total environmental emissions, were released via underground injection and to Class I wells, Class II-V wells (TRI06 2008). These releases are summarized in Table 6-1. Estimated releases of 2,380,447 pounds (~1,080 metric tons) of cadmium compounds to soils from (98) domestic manufacturing and processing facilities in 2006, accounted for about 84% of the estimated total environmental releases from facilities required to report to the TRI. An additional 1,129 pounds (~53 metric tons), constituting about 0.040% of the total environmental emissions, were released via underground injection and to Class I wells, Class II-V wells (TRI06 2008). These releases are summarized in Table 6-2.

Major sources of cadmium to soil include atmospheric emissions, direct application, and accidental or fugitive contamination. Direct application emissions refer to phosphate fertilizers, phosphogypsum and other byproduct gypsums (from the manufacture of phosphoric acid and phosphorite), sewage sludges, composted municipal solid waste, and residual ashes from wood, coal, or other types of combustion. Contamination sources include industrial site contamination, mine waste dumps, and corrosion of metal structures (Alloway and Steinnes 1999).

EPA estimated that about 31% of the 11 billion pounds of sewage sludge produced annually in the United States is landspread (EPA 1985a). Estimated cadmium concentrations in sewage sludge range from <1 μg/g to >1,000 μg/g (EPA 1985a). Although EPA has set limits (EPA 1993c) on the cadmium content of sludge applied to land (maximum permitted cadmium concentration of 85 mg/kg in sewage sludge; maximum cadmium concentration of 39 mg/kg in "clean" sewage sludge; maximum annual cadmium loading of 1.9 kg-ha^{-1}·year^{-1}; and maximum cumulative cadmium loading of 39 kg/ha), significant amounts of cadmium are still likely to be transferred to soil by this practice. Sludges from treatment plants that serve cadmium industries (i.e., battery manufacturing) tend to have higher levels of cadmium (Alloway and Steinnes 1999).

Phosphate fertilizers are a major source of cadmium input to agricultural soils (EPA 1985a). The natural cadmium concentration in phosphates ranges from 3 to 100 μg/g (EPA 1985a; Singh 1994). Some can contain up to 300 mg Cd/kg (Alloway and Steinnes 1999). It is estimated that 880,000 pounds of phosphate fertilizer were used in the United States in 1980 (EPA 1985a). Any soil treated with these fertilizers will have a cadmium input, but exactly how much will vary (Alloway and Steinnes 1999). Continuous fertilization with a high rate of triple super-phosphate (1,175 kg P-ha-1·year^{-1}) for a period of 36 years resulted in a 14-fold increase in cadmium content of surface soils (Singh 1994).

Wet and dry deposition of cadmium from the atmosphere may also contribute sizable amounts of cadmium to soil in the areas surrounding sources of atmospheric emissions, such as incinerators and vehicular traffic, which may release cadmium from burned fuel and tire wear (EPA 1985a; Mielke et al. 1991). High-temperature sources, such as smelters and incinerators, release small particles that are ideal for long-range atmospheric transport. Also, vapors emitted from high temperature processes will preferentially condense onto smaller particles, thus making vapor emissions available for transport (Steinnes and Friedland 2006). Aerosols containing cadmium can be carried very long distances in the atmosphere before being deposited to soils. In the soils in southern Norway, most of the cadmium and other heavy metals that are deposited from the atmosphere originate from other parts of Europe (Alloway and Steinnes 1999). Long-range atmospheric deposition is more evident in organic-rich soils as they have a tendency to concentrate heavy metals (Steinnes and Friedland 2006).

There is also a potential for release of cadmium to soil from hazardous waste sites. Cadmium has been detected in soil samples collected at 606 of the 1,014 NPL hazardous waste sites and in sediment samples collected at 392 of the 1,014 NPL hazardous waste sites where cadmium has been detected in some environmental medium (HazDat 2008). The HazDat information used includes data from NPL sites only.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Cadmium is expected to partition mostly to soil (80–90%) when released to the environment. Although particulate and vapor cadmium may be released to the air, the net flux to soil will be positive as cadmium will eventually deposit onto soils (Morrow 2001; Wilber et al. 1992).

Cadmium and cadmium compounds have negligible vapor pressures (see Table 4-2) but can be released to the environment by emissions from municipal waste incinerators, nonferrous metal production, and other high-temperature processes (Morrow 2001). Cadmium emitted to the atmosphere from combustion processes condense onto very small particulates that are in the respirable range (<10 μm) and are subject to long-range transport (Steinnes and Friedland 2006; Wilber et al. 1992). These cadmium pollutants may be transported from a hundred to a few thousand kilometers and have a typical atmospheric residence time of about 1–10 days before deposition occurs (EPA 1980d). Larger cadmium-containing particles from smelters and other pollutant sources are also removed from the atmosphere by gravitational settling, with substantial deposition in areas downwind of the pollutant source. Cadmium-containing particulates may dissolve in atmospheric water droplets and be removed from air by wet deposition.

Cadmium is more mobile in aquatic environments than most other heavy metals (e.g., lead). In most natural surface waters, the affinities of complexing ligands for cadmium generally follow the order of humic acids > CO_3^{2-} > OH^- ≥ Cl^- ≥ SO_4^{2-} (EPA 1979). In unpolluted natural waters, most cadmium transported in the water column will exist in the dissolved state as the hydrated ion $Cd(H_2O)_6^{2+}$. Minor amounts of cadmium are transported with the coarse particulates, and only a small fraction is transported with the colloids. In unpolluted waters, cadmium can be removed from solution by exchange of cadmium for calcium in the lattice structure of carbonate minerals (EPA 1979). In polluted or organic-rich waters, adsorption of cadmium by humic substances and other organic complexing agents plays a dominant role in transport, partitioning, and remobilization of cadmium (EPA 1979). Cadmium concentration in water is inversely related to the pH and the concentration of organic material in the water (EPA 1979). Because cadmium exists only in the +2 oxidation state in water, aqueous cadmium is not strongly influenced by the oxidizing or reducing potential of the water. However, under reducing conditions, cadmium may form cadmium sulfide, which is poorly soluble and tends to precipitate (EPA 1983c; McComish and Ong 1988). Free (ionic) cadmium seems to be the toxic form and becomes much more prevalent at low salinity (Sprague 1986). Cadmium has a relatively long residence time in aquatic systems. In Lake Michigan, a mean residence time of 4–10 years was calculated for cadmium compared to 22 years calculated for mercury (Wester et al. 1992).

Precipitation and sorption to mineral surfaces, hydrous metal oxides, and organic materials are the most important processes for removal of cadmium to bed sediments. Humic acid is the major component of sediment responsible for adsorption. Sorption increases as the pH increases (EPA 1979). Sediment bacteria may also assist in the partitioning of cadmium from water to sediments (Burke and Pfister 1988). Both cadmium-sensitive and cadmium-resistant bacteria reduced the cadmium concentration in the water column from 1 ppm to between 0.2 and 0.6 ppm, with a corresponding increase in cadmium concentration in the sediments in the simulated environment (Burke and Pfister 1988). Studies indicate that concentrations of cadmium in sediments are at least one order of magnitude higher than in the overlying water (EPA 1979). The mode of sorption of cadmium to sediments is important in determining its disposition to remobilize. Cadmium associated with carbonate minerals, precipitated as stable solid compounds or co-precipitated with hydrous iron oxides, is less likely to be mobilized by resuspension of sediments or biological activity. Cadmium that is adsorbed to mineral surfaces such as clay, or to organic materials, is more easily bioaccumulated or released in the dissolved state when the sediment is disturbed (EPA 1979). Cadmium may redissolve from sediments under varying ambient conditions of pH, salinity, and redox potential (DOI 1985; EPA 1979; Feijtel et al. 1988; Muntau and Baudo 1992). Cadmium is not

known to form volatile compounds in the aquatic environment, so partitioning from water to the atmosphere does not occur (EPA 1979).

Debusk et al. (1996) studied the retention and compartmentalization of lead and cadmium in wetland microcosms. Differences between measured concentrations in inflow and outflow samples indicated that approximately half of the added cadmium was retained in the wetland microcosms. Experiments showed that nearly all trace metals were present in the sediments as sulfides, limiting their bioavailability and toxicity. The results of their analyses and a lack of noticeable biological effects suggested that in wetlands containing organic sediments, the sediment chemistry dominates cycling of the trace metals.

In soils, pH, oxidation-reduction reactions, and formation of complexes are important factors affecting the mobility of cadmium (Bermond and Bourgeois 1992; Herrero and Martin 1993). Cadmium can participate in exchange reactions on the negatively charged surface of clay minerals. In acid soils, the reaction is reversible. However, adsorption increases with pH and may become irreversible (Herrero and Martin 1993). Cadmium also may precipitate as insoluble cadmium compounds, or form complexes or chelates by interaction with organic matter. Available data suggest that organic matter is more effective than inorganic constituents in keeping cadmium unavailable (McBride 1995). Examples of cadmium compounds found in soil are $Cd_3(PO_4)_2$, $CdCO_3$, and $Cd(OH)_2$ (Herrero and Martin 1993). These compounds are formed as the pH rises. It has been found that about 90% of cadmium in soils remains in the top 15 cm (Anonymous 1994).

The mobility and plant availability of cadmium in wetland soils are substantially different from upland soils. Cadmium tends to be retained more strongly in wetland soils and is more available to plants under upland conditions (Gambrell 1994). Debusk et al. (1996) compared heavy metal uptake by cattails and duckweed wetland microcosms and found that duckweed, on a whole-plant basis, accumulates cadmium more effectively than cattail does. The potential cadmium removal rate for duckweed is 2–4 mg $Cd/m^2/day$.

Cadmium in soils may leach into water, especially under acidic conditions (Elinder 1985a; EPA 1979). Roy et al. (1993) demonstrated that Cl complexation in the leachate of ash from a municipal solid waste incinerator can result in a decrease in cadmium sorption by two common clays, kaolinite and illite. They also found that cationic competitive sorption enhances mobility in soils. Cadmium-containing soil particles may also be entrained into the air or eroded into water, resulting in dispersion of cadmium into these media (EPA 1985a). Contamination of soil by cadmium is of concern because the cadmium is taken

up efficiently by plants and, therefore, enters the food chain for humans and other animals. A low soil pH, which is becoming prevalent in many areas of the world due to acid rain, increases the uptake of cadmium by plants (Elinder 1992).

Aquatic and terrestrial organisms bioaccumulate cadmium (Handy 1992a, 1992b; Kuroshima 1992; Naqvi and Howell 1993; Roseman et al. 1994; Suresh et al. 1993). Cadmium concentrates in freshwater and marine animals to concentrations hundreds to thousands of times higher than in the water (EPA 1979). Reported bioconcentration factors (BCFs) range from <200 to 18,000 for invertebrates (van Hattum et al. 1989), from 3 to 4,190 for fresh water aquatic organisms (ASTER 1995), and from 5 to 3,160 for saltwater aquatic organisms (ASTER 1994). Bioconcentration in fish depends on the pH and the humus content of the water (John et al. 1987). Because of their high ability to accumulate metals, some aquatic plants have been suggested for use in pollution control. For example, it has been suggested that the rapidly-growing water hyacinth (*Eichhornia crassipes*) could be used to remove cadmium from domestic and industrial effluents (Ding et al. 1994; Muntau and Baudo 1992).

The data indicate that cadmium bioaccumulates in all levels of the food chain. Cadmium accumulation has been reported in grasses and food crops, and in earthworms, poultry, cattle, horses, and wildlife (Alloway et al. 1990; Beyer et al. 1987; Gochfeld and Burger 1982; Kalac et al. 1996; Munshower 1977; Ornes and Sajwan 1993; Rutzke et al. 1993; Sileo and Beyer 1985; Vos et al. 1990). The metal burden of a crop depends on uptake by the root system, direct foliar uptake and translocation within the plant, and surface deposition of particulate matter (Nwosu et al. 1995). In general, cadmium accumulates in the leaves of plants and, therefore, is more of a risk in leafy vegetables grown in contaminated soil than in seed or root crops (Alloway et al. 1990). He and Singh (1994) report that, for plants grown in the same soil, accumulation of cadmium decreased in the order: leafy vegetables > root vegetables > grain crops. Alloway et al. (1990) also demonstrated that uptake of cadmium decreased in the order: lettuces, cabbages, radishes, and carrots. Nwosu et al. (1995) investigated the uptake of cadmium and lead in lettuce and radish grown in loam soil spiked with known mixtures of $CdCl_2$ and $Pb(NO_3)_2$. They found that the mean uptake of cadmium by lettuce and radish increased as the concentrations of cadmium and lead in the soil increased. Their results supported previous findings that cadmium is absorbed by passive diffusion and translocated freely in the soil. The observed decline in cadmium uptake by lettuce at 400 mg/kg could be attributed to saturation of the active binding sites on the plant root system or by early toxicological responses of the plant root. The study also supported earlier findings that radish did not accumulate as much cadmium as lettuce.

Some studies have concluded that soil pH is the major factor influencing plant uptake of cadmium from soils (Smith 1994). Liming of soil raises the pH, increasing cadmium adsorption to the soil and reducing bioavailability (He and Singh 1994; Thornton 1992). One study found that in peeled potato tubers, potato peelings, oat straw, and ryegrass, cadmium concentrations generally decreased as simple linear functions of increasing soil pH over the range of pH values measured (pH 3.9–7.6) (Smith 1994). Soil type also affects uptake of cadmium by plants. For soils with the same total cadmium content, cadmium has been found to be more soluble and more plant-available in sandy soil than in clay soil (He and Singh 1994). Similarly, cadmium mobility and bioavailability are higher in noncalcareous than in calcareous soils (Thornton 1992). Oxidation-reduction potential may also have a large effect on soil-to-plant cadmium transport. The absorption of cadmium paddy rice is significantly affected by the oxidation-reduction potential of the soil. The oxidation-reduction potential of rice paddy soils shifts drastically compared to upland soils due to submerging and draining techniques. Cadmium to rice ratios (cadmium concentration in brown rice/cadmium concentration in soil) were the smallest when the rice was grown under submerged conditions during the whole growth period. The ratios were the largest when the soil (coarse Toyama soil) was drained after the tillering stage. This is due to changes in cadmium solubility. Under flooded conditions, cadmium sulfide formation increases, and thus, cadmium solubility decreases (Iimura 1981).

Since cadmium accumulates largely in the liver and kidneys of vertebrates and not in the muscle tissue (Harrison and Klaverkamp 1990; Sileo and Beyer 1985; Vos et al. 1990), and intestinal absorption of cadmium is low, biomagnification through the food chain may not be significant (Sprague 1986). In a study of marine organisms from the Tyrrhenian Sea, no evidence of cadmium biomagnification was found along pelagic or benthic food webs (Bargagli 1993). Although some data indicate increased cadmium concentrations in animals at the top of the food chain, comparisons among animals at different trophic levels are difficult, and the data available on biomagnification are not conclusive (Beyer 1986; Gochfeld and Burger 1982). Nevertheless, uptake of cadmium from soil by feed crops may result in high levels of cadmium in beef and poultry (especially in the liver and kidneys). This accumulation of cadmium in the food chain has important implications for human exposure to cadmium, whether or not significant biomagnification occurs.

Boularbah et al. (1992) isolated sic cadmium-resistant bacterial strains from a soil receiving dredged sediments and containing 50 mg Cd/kg. The isolates tolerated higher cadmium concentrations than the control strain and accumulated cadmium at concentrations ranging from 0 to 100 mg/L. One of the

isolates, *Bacillus brevis*, was found to be the most resistant to cadmium, with the ability to accumulate up to 70 mg Cd/g of cells dry weight, and may have some use in reclamation of metal-contaminated soils.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Little information is available on the atmospheric reaction of cadmium (EPA 1980d). The common cadmium compounds found in air (oxide, sulfate, chloride) are stable and not subject to photochemical reactions (EPA 1980d). Cadmium sulfide may photolyze to cadmium sulfate in aqueous aerosols (Konig et al. 1992). Transformation of cadmium among types of compounds in the atmosphere is mainly by dissolution in water or dilute acids (EPA 1980d).

6.3.2.2 Water

In fresh water, cadmium is present primarily as the cadmium(+2) ion and $Cd(OH)_2$ and $CdCO_3$ complexes, although at high concentrations of organic material, more than half may occur in organic complexes (McComish and Ong 1988). Some cadmium compounds, such as cadmium sulfide, cadmium carbonate, and cadmium oxide, are practically insoluble in water. However, water-insoluble compounds can be changed to water-soluble salts by interaction with acids or light and oxygen. For example, aqueous suspensions of cadmium sulfide can gradually photoxidize to soluble cadmium (IARC 1993). Cadmium complexation with chloride ion increases with salinity until, in normal seawater, cadmium exists almost entirely as chloride species ($CdCl^+$, $CdCl_2$, $CdCl_3^-$) with a minor portion as Cd^{2+}. In reducing environments, cadmium precipitates as cadmium sulfide in the presence of sulfide ions (McComish and Ong 1988). Photolysis is not an important mechanism in the aquatic fate of cadmium compounds (EPA 1983c), nor is biological methylation likely to occur (EPA 1979).

6.3.2.3 Sediment and Soil

Transformation processes for cadmium in soil are mediated by sorption from and desorption to water, and include precipitation, dissolution, complexation, and ion exchange (McComish and Ong 1988). Important factors affecting transformation in soil include the cation exchange capacity, pH, and content of clay minerals, carbonate minerals, oxides, organic matter, and oxygen (McComish and Ong 1988).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to cadmium depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of cadmium in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on cadmium levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring cadmium in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Cadmium levels in ambient air generally range from 0.1 to 5 ng/m^3 in rural areas, 2–15 ng/m^3 in urban areas, and 15–150 ng/m^3 in industrialized areas. Remote areas can contain lower levels of cadmium (Morrow 2001). Cadmium can undergo long-range atmospheric transport and deposition causing cadmium contamination in areas with no local cadmium inputs. Smoking can greatly affect indoor air concentrations of cadmium. In nonsmoking environments, there is little difference between indoor and outdoor air quality (Morrow 2001). Monitoring studies conducted for EPA's 2006 Final Report for the Urban Air Toxics Monitoring Program detected cadmium in ambient air at several monitoring sites throughout the United States. At all detection sites in Bountiful, Utah; Northbrook, Illinois; Austin, Texas; St. Louis, Missouri; Indianapolis, Indiana; and Birmingham, Alabama average daily cadmium levels in ambient air were <0.01 μg/m^3. In Bountiful, Utah average daily cadmium levels were reported as 0.0008 μg/m^3 (EPA 2007).

Emission rates of cadmium from solid waste incinerators have been found to range from 20 to 2,000 μg/m^3 from the stacks of traditional incinerators and from 10 to 40 μg/m^3 from advanced incinerators. Advances in pollution control and increased government regulations have resulted in decreased cadmium emissions to the environment (EPA 1990a; Herron 2003; Morrow 2001; Schulte-Schrepping and Piscator 2002). Although there may be an increase in fossil fuel combustion and waste incineration, it does not appear likely that overall cadmium emissions to air will increase substantially in the United States.

Cadmium levels in aerosols over Russian Arctic seas were measured in order to understand the magnitude of long-range atmospheric deposition. Ten-year average monthly mean concentrations ranged from 0.002 to 0.080 ng/m^3 in Franz Josef Land and from 0.0026 to 0.048 ng/m^3 in Sevemaya Zemlya. The

highest concentrations were reported in the spring season and the lowest concentrations reported in the autumn for both sampling sites. During the winter and spring months, it was estimated that >50% of the average air pollutant concentrations in the Russian Arctic are due to atmospheric pollution. The anthropogenic sources of cadmium to the Russian Arctic are the industrial areas of Northern Europe, Kola Peninsula, and the Urals and Norilsk regions (Shevchenko et al. 2003).

Atmospheric concentrations of cadmium are generally highest in the vicinity of cadmium-emitting industries such as smelters, municipal incinerators, or fossil fuel combustion facilities (Elinder 1985a; Pirrone et al. 1996). The mean annual concentration of airborne cadmium in an area about 1 km from a zinc smelter in Colorado was 0.023 μg/m^3 ($2.3x10^{-5}$ mg/m^3) (IARC 1993). Sweet et al. (1993) conducted a study of airborne inhalable particulate matter (PM-10) over a 2-year period in two urban/industrial areas (southeast Chicago and East St. Louis) and one rural area in Illinois. There was a significant difference between the cadmium levels in the urban areas and the cadmium levels in the rural area. Cadmium concentrations in the East St. Louis area were 5–10 times higher, with a range of <4 to 115 ng/m^3 (average 15[24] ng/m^3) for fine particles and a range of <4–97 ng/m^3 (average 10[18] ng/m^3) for course particles. In the Kikinda region of Serbia and Montenegro, where metal processing and construction industries are located, a mean annual atmospheric deposit of 36.0 μg/m^2 per day was reported in 1995. A period of decreased industrial production, which decreased atmospheric cadmium deposits by 93%, resulted in 17% cadmium reduction in cattle feed and 13% in milk (Vidovic et al. 2005). Moss studies conducted by Hasselbach et al. (2005) in the area of the Red Dog Mine in Alaska reported cadmium levels >24 mg/kg dry weight in moss adjacent to the ore haul road. Ore dust containing heavy metals escapes from the ore trucks on the haul road and can be deposited in the nearby area (Hasselbach et al. 2005).

Annual average concentrations of atmospheric cadmium over three Great Lakes reflect the influence of industrialization and urbanization; Lake Erie's levels of 0.6 ng/m^3 were higher than fine particle concentrations of 0.2 ng/m^3 over Lake Michigan and <0.2 ng/m^3 over Lake Superior (Sweet et al. 1998). In the Lake Michigan Urban Air Toxics Study of dry deposition of metals, the flux of cadmium on the south side of Chicago was reported at about 0.01 mg/m^2/day and levels in rural Michigan and over Lake Michigan were far lower (Holsen et al. 1993).

6.4.2 Water

The average level of cadmium in ocean water has been reported between <5 and 110 ng/L, with higher levels reported near coastal areas and in marine phosphates and phosphorites (Morrow 2001).

Thornton (1992) reports that waters from the vicinity of cadmium-bearing mineral deposits may have cadmium concentrations of ≥1,000 µg/L. The cadmium concentration of natural surface water and groundwater is usually <1 µg/L (Elinder 1985a, 1992). EPA requires water suppliers to limit the cadmium concentration in drinking water to <5 µg/L (EPA 2006a).

Groundwater in New Jersey has an estimated median level of 1 µg Cd/L with a high level of 405 µg/L. In a survey of groundwater surrounding waste sites, a concentration of 6,000 µg Cd/L was found (NTP 1994). The National Urban Runoff Program measured cadmium concentrations in urban storm water runoff; concentrations ranged from 0.1 to 14 µg/L in 55% of samples that were positive for cadmium (Cole et al. 1984). Cadmium in highway run-off has been detected at levels of 0.0–0.06 mg/L (0.0–60 µg/L).

In the estuarine portion of the Hudson River, more cadmium was released from agricultural and urban run-off than from industrial and municipal sewage treatment plants (Muntau and Baudo 1992). In an urban environment, there are also multiple sources of cadmium to waste water, based on an urban waste water study conducted in the United Kingdom. Cadmium was detected in the waste water originating from industrial, commercial, and private sectors, with the highest average cadmium concentration detected in the foul water of new (<5 years old) private housing (0.375 µg/L) (Rule et al. 2006). Cadmium was detected in the contaminated groundwater plume near in the Moon Creek watershed in the Couer D'Alene Mining District of Idaho at concentrations of ≤0.077 mg/L. The cadmium was transported to the creek with the plume where it was subsequently diluted (Paulson 1997). In the Spring River Basin of Kansas, Missouri, and Oklahoma, part of the Tri-State Mining District, cadmium was detected in surfaces waters at concentrations ranging from <1.0 to 24 µg/L (peak flow) and from <1.0 to 75.0 µg/L (base flow). It was detected in the sediment of the sampling sites at concentrations ranging from 0.62 to 300 µg/g dry weight in the <250 µm sediment fraction and from 0.89 to 180 µg/g dry weight in the <63 µm fraction (Angelo et al. 2007).

6.4.3 Sediment and Soil

Cadmium concentrations in soils not contaminated by anthropogenic sources range from 0.06 to 1.1 mg/kg, with a minimum of 0.01 mg/kg and a maximum of 2.7 mg/kg (Alloway and Steinnes 1999). Cadmium content in marine sediments ranges from 0.1 to 1.0 μg/g (ppm) in the Atlantic and Pacific oceans (Thornton 1992). Average cadmium concentration in agricultural soils of remote locations was reported as 0.27 mg/kg (Holmgren et al. 1993). Soils with parent materials such as black shale (cadmium content up to 24 mg/kg) may have higher concentrations of natural cadmium. Since the U.S. mandatory limit of cadmium in sewage sludge is <20 mg/kg, soils receiving sewage sludge should not have heightened cadmium levels (Alloway and Steinnes 1999). Topsoil concentrations are often more than twice as high as subsoil levels as the result of atmospheric fallout and contamination (Pierce et al. 1982). Cadmium will partition mostly to soil and sediment when released to the environment. Atmospheric deposition is a major source of surface soil contamination, which allows cadmium to be introduced into the food supply (Alloway and Steinnes 1999; Morrow 2001).

Markedly elevated levels may occur in topsoils near sources of contamination. Moss studies conducted by Hasselbach et al. (2005) in the area of the Red Dog Mine in Alaska reported cadmium levels >24 mg/kg dry weight in moss (n=151), as a measure atmospheric deposition onto soil surfaces, within 10 m of the ore haul road. Ore dust containing heavy metals escapes from the ore trucks during loading and unloading at the mine and port site settles on the surfaces of the trucks, which blow off the trucks during transport on the haul road and deposited in the nearby area. The mean cadmium concentrations in moss and subsurface soil throughout the entire study were 1.86 and 0.27 mg/kg dry weight, respectively. Cadmium concentrations in moss and subsurface soil were 0.08–24.30 and 0.07–0.75 mg/kg dry weight. There did not appear to be a connection between the elevated subsurface cadmium levels and the local geochemistry. Geospatial analysis showed that areas as far as 12 km north of the haul road may be affected by mining emission depositions (Hasselbach et al. 2005). In the vicinity of a smelter in Helena, Montana, average soil values were 72 ppm within 1 km and 1.4 ppm between 18 and 60 km (EPA 1981a). Total cadmium concentrations in soil samples taken from a Superfund site in southeast Kansas ranged from 15 to 86 mg/kg (ppm). In the same study, soil samples were extracted with diethylenetriamine-pentaacetic acid (DPTA) to approximate the plant-available metal concentrations. Extractable cadmium concentrations ranged from 0.6 to 10 mg/kg (ppm) (Abdel-Saheb et al. 1994). Soil cadmium levels in five Minnesota cities were highest in areas with the most vehicular traffic (>2 ppm in about 10% of inner-city samples) and also showed a pattern consistent with past deposition from a sewage-sludge incinerator

(Mielke et al. 1991). Cadmium levels >750 mg/kg have been found in sites polluted by nonferrous metal mining and smelting have been reported (Alloway and Steinnes 1999).

In the Spring River Basin of Kansas, Missouri, and Oklahoma, part of the Tri-State Mining District, cadmium was detected in surfaces waters at concentrations of <1.0–24 µg/L (peak flow) and <1.0–75.0 µg/L (base flow). Cadmium was detected in the sediment of the sampling sites at concentrations ranging from 0.62 to 300 µg/g dry weight in the <250 µm sediment fraction and from 0.89 to 180 µg/g dry weight in the <63 µm fraction (Angelo et al. 2007). A study conducted in 1999 at the Patroon Creek Reservoir in Albany County, New York sampled sediment cores for heavy metals, including cadmium. The watershed includes two industrial sites: one in operation from 1955 to present and the other operating from 1958 to 1984. Sediment samples in the interval of 0–1.68 m showed an average cadmium concentration of 1.69 mg/kg. This concentration is comparable to other stream and reservoir sediments impacted by industrial pollution (Arnason and Fletcher 2003). Sediments of the Sawmill River in Yonkers, New York contained the highest cadmium levels (6.9 mg/kg) in the Hudson River Basin during a sampling study conducted between 1992 and 1995 (USGS 1998b).

Surficial sediments collected from 18 locations in three major tributaries to Newark Bay, New Jersey, had a mean cadmium concentration of 10±6 mg/kg (ppm) dry weight (Bonnevie et al. 1994). The highest cadmium concentrations were found in the Ironbound section of the Passaic River, a heavily industrialized area (29 mg/kg and 14 mg/kg), and in the Arthur Kill on the northwest side of Prall's Island (15 mg/kg). An investigation of metals distribution in sediments along the Hudson River estuary revealed that cadmium concentrations in suspension were higher than in the bottom sediments by a factor of 30 (Gibbs 1994).

Soils derived from dredged material in confined disposal facilities in the Great Lakes Region had cadmium concentrations (dry weight) of <1.9–32 ppm (Beyer and Stafford 1993). In an analytical survey of sewage sludges from 16 large cities in the United States, cadmium concentrations ranged from 2.72 to 242 ppm (dry weight). Besides the sample with a cadmium concentration of 242 ppm, all other sludges had cadmium contents ≤14.7 ppm (Gutenmann et al. 1994).

6.4.4 Other Environmental Media

Cadmium levels in food can vary greatly depending on the type of food, agricultural and cultivating practices, and amount atmospheric deposition and other anthropogenic contamination. In general, leafy

vegetables, such as lettuce and spinach, and staples, such as potatoes and grains, contain relatively high values of cadmium. Peanuts, soybeans, and sunflower seeds have naturally high levels of cadmium. Meat and fish container lower amounts of cadmium, with the exception of animal organ meats, such as kidney and liver, as these organs concentrate cadmium (Morrow 2001).

As part of the U.S. Food and Drug Administration (FDA) Total Diet Study, average concentrations of cadmium in 14 food groups were analyzed from samples collected in 56 American cities. Cadmium was found in nearly all samples at varying concentrations. In general, the milk and cheese (no detection to <0.010 mg/kg) and fruits (no detection to 0.027 mg/kg) groups contained low concentrations of cadmium. Food items that contained high levels of cadmium were dry roasted peanuts (0.051 mg/kg); smooth peanut butter (0.056 mg/kg); shredded wheat cereal (0.057 mg/kg); boiled spinach (0.125 mg/kg); potato chips (0.062 mg/kg); and creamed spinach for infant and junior foods (0.090 mg/kg) (Capar and Cunningham 2000). Table 6-3 summarizes the data from this study.

Watanabe et al. (1996) measured the cadmium content in rice samples from various areas in the world during the period from 1990 to 1995. Twenty-nine samples collected in the United States had a geometric mean of 7.43 ng Cd/g, with a standard deviation of 2.11. Shellfish, liver, and kidney meats have higher concentrations than other fish or meat (up to 1 ppm) (Elinder 1985a; IARC 1993; Schmitt and Brumbaugh 1990). Particularly high concentrations of cadmium of 2–30 mg/kg (ppm) fresh weight have been found in the edible brown meat of marine shellfish (Elinder 1992). Cadmium concentrations up to 8 μg/g in oysters and 3 μg/g in salmon flesh have been reported (IARC 1993). Sprague (1986) has reviewed tissue concentrations of cadmium for marine molluscs and crustaceans. They found that drills were higher in cadmium (average, 26 μg/g dry weight) than almost all other mollusks, although scallops and whelks also tended to be high. Clams were relatively low in cadmium (average, 0.5–1.0 μg/g dry weight). Oysters from polluted areas averaged 18 μg/g dry weight. The average concentration of cadmium in clams from polluted areas was only 2.7 μg/g dry weight, but this was significantly higher than levels in clams from clean areas. In Fiscal Year (FY) 1985/1986, the FDA conducted a survey of cadmium, lead, and other elements in fresh clams and oysters collected from U.S. coastal areas used for shellfish production. Average cadmium levels (wet weight) were 0.09±0.06 mg/kg (ppm) (n=75) in hardshell clams, 0.05±0.04 mg/kg (n=59) in softshell clams, 0.51±0.31 mg/kg (n=104) in Eastern oysters, and 1.1±0.6 mg/kg (n=40) in Pacific oysters (Capar and Yess 1996). In FY91, FDA analyzed 5 samples of domestic clams and 24 samples of domestic oysters (collected from both coasts) for cadmium and found average concentrations of 0.06 and 0.62 mg/kg, respectively. Although no conclusions can be

Table 6-3. Mean Concentrations of Cadmium for FDA's Total Diet Study Market Baskets 91-3 through 97-1

Food product	Mean concentration range (mg/kg)[a]
Milk and cheese	Not detected–<0.010
Eggs	Not detected–<0.005
Meat, poultry, and fish	Not detected–0.077
Legumes and nuts	<0.005–0.056
Grain products	<0.005–0.030
Fruit	Not detected–0.027
Vegetables	<0.004–0.125
Mixed dishes and meals	<0.005–0.020
Desserts	Not detected–0.031
Snacks	<0.010–0.062
Condiments and sweeteners	Not detected–0.029
Fats and dressings	Not detected–<0.024
Beverages	Not detected–<0.003
Infant and junior foods	Not detected–0.090

[a]A < symbol indicates that manganese was detected, but at a level lower than the limit of quantification.

Source: Capar and Cunningham 2000

drawn in light of the small numbers of FY91 samples, these results to not appear to be appreciably different from those of the FY85/86 survey (Capar and Yess 1996).

Cadmium is accumulated mainly in the hepatopancreas (digestive gland) of the crab, and cadmium levels as high as 30–50 ppm have been detected in this edible part of the animal. Cadmium levels as high as 10 ppm also have been measured in some species of wild-growing edible mushrooms (Lind et al. 1995). Lind et al. (1995) conducted a feeding study in mice to determine the bioavailability of cadmium from crab hepatopancreas and mushroom in relation to organic cadmium. The cadmium accumulation in the liver and kidney of the mice was used as an estimate of the intestinal absorption. The group that was fed crab accumulated less cadmium in the liver and kidney than the groups fed mushrooms or inorganic cadmium salt. They concluded from the results of the study that cadmium from boiled crab has a lower bioavailability for absorption in the gastrointestinal tract of mice than inorganic cadmium and cadmium from dried mushrooms. Almost all (99%) of the cadmium in the boiled crab hepatopancreas was associated with insoluble ligands, probably denatured protein. In fresh crab hepatopancreas, most of the cadmium is in a soluble form bound to metallothionein (Lind et al. 1995).

Significant concentrations of cadmium have been observed in fish living in stormwater ponds in Florida, especially in the redear sunfish, a bottom feeder (Campbell 1994). The mean cadmium concentration in redear sunfish living in stormwater ponds was 1.64 mg/kg wet weight compared to 0.198 mg/kg for redear sunfish living in control ponds. Similarly, the mean cadmium concentration in largemouth bass living in stormwater ponds was 3.16 mg/kg wet weight compared to 0.241 mg/kg for largemouth bass living in control ponds. Red drum, flounder, and seatrout collected from South Carolina estuaries during the period 1990–1993 had consistently low cadmium levels throughout the sampling area and with respect to species (Mathews 1994). The mean concentration for all fillets and whole fish was 86.2 ppb wet weight, with 70.7% (n=164) of the samples having <25 ppb.

Cadmium and other heavy metals were detected in several of the freshwater invertebrates and fish of two Maryland streams. Due to their remote location and lack of source inputs, it is believed that the cadmium contamination was a result of long-range atmospheric deposition. Samples were taken from the Herrington Creek tributary (HCRT) and Blacklick Run (BLK) during October 1997, April 1998, and July 1998. Cadmium concentrations in the trout of BLK ranged from about 37 to 90 ng/g wet, with the older specimens having the higher cadmium concentrations. Cadmium concentrations in crayfish ranged from about 40 to 160 ng/g wet in BLK, with the younger specimens containing the highest levels of cadmium. Crayfish in HRCT ranged from 45 to 155 ng/g, with the highest levels in the middle age group. In

crayfish, cadmium strongly accumulates in the gills, while the kidney accumulates cadmium in trout (Mason et al. 2000).

Cadmium concentrations in the fish of the mining-contaminated waters of Oklahoma were reported by Brumbaugh et al. (2005). This area was part of the Tri-State Mining District that was extensively mined for lead and zinc from the mid-1800s to the 1950s, and contains nonremediated sites. Blood and carcass cadmium concentrations differed between species and sites, but were generally greatest in carp. Carcass cadmium in catfish were relatively low, with <0.1 μg/g dry weight in 34 of 36 samples.

Cadmium concentrations of ≥0.5 ppm have been found in rice grown in cadmium-polluted areas of Japan (Nogawa et al. 1989) and China (Shiwen et al. 1990). Tobacco also concentrates cadmium from the soil, and cadmium content of cigarettes typically ranges from 1 to 2 μg/cigarette (Elinder 1985a, 1992).

Some food crops, including confectionery sunflowers, have a propensity to take up cadmium from the soil in which they are grown and deposit it in the kernels. In a study to determine the cadmium burden of persons who report regular consumption of sunflower kernels, Reeves and Vanderpool (1997) analyzed 19 different lots of sunflower kernels from the 1995 crop grown in the northern Great Plains region of North Dakota and Minnesota. They found a range of 0.33–0.67 μg Cd/g, with a mean±standard deviation of 0.48±0.11 μg/g fresh weight. The study showed that high intakes of sunflower kernels increased the intake of cadmium. However, the amount of cadmium in whole blood or in red blood cells was not affected by cadmium intake. The authors pointed out that an increased intake of sunflowers will increase not only the cadmium intake, but also the intake of copper and phytate. In turn, this could reduce the availability of cadmium from this food source.

DOI (1985) examined the concentrations of cadmium in a variety of aquatic and terrestrial flora and fauna and identified six trends: (1) in general, marine biota contained significantly higher cadmium residues than their freshwater or terrestrial counterparts; (2) cadmium tends to concentrate in the viscera of vertebrates, especially in the liver and kidneys; (3) cadmium concentrations are higher in older organisms than in younger ones, especially in carnivores and marine vertebrates; (4) higher concentrations for individuals of a single species collected at various locations are almost always associated with proximity to industrial/urban areas or point-source discharges of cadmium-containing wastes; (5) background levels of cadmium in crops and other plants are generally <1.0 mg/kg (ppm); and (6) cadmium concentrations in biota are dependent upon the species analyzed, the season of collection, ambient cadmium levels, and the sex of the organism.

During a study monitoring cadmium levels in 331 cigarette packs from over 20 areas around the world it was found that the mean cadmium level per cigarette was 1.15 µg/cigarette ±0.43 (AM±ASD) or 1.06 µg/cigarette ±1.539 (geometric mean [GM]±geometric standard deviation[GSD]). Cigarettes from Mexico had the highest mean level of cadmium with an AM±ASD of 2.03 µg/cigarette ±0.33 or a GM±GSD of 2.00 µg/cigarette ±1.190. Cigarettes from India had the lowest mean levels of cadmium with an AM±ASD of 0.35 µg/cigarette ±0.09 or a GM±GSD of 0.34 µg/cigarette ±1.284. The arithmetic mean for the United States was 1.07 µg/cigarette ±0.11 and the GM±GSD was 1.06 µg/cigarette ±1.115 (Watanabe et al. 1987).

The cadmium content of coals varies widely; concentrations of 0.01–180 µg/g (ppm) have been reported for the United States (Thornton 1992; Wilber et al. 1992).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to cadmium through ingestion of food and drinking water, inhalation of particulates from ambient air or tobacco smoke, or ingestion of contaminated soil or dust. For nonsmokers, food is the major source of cadmium exposure (NTP 2005). Inhalation of cigarette smoke is the major source of cadmium exposure for smokers (CDC 2005). Cadmium is introduced to the food chain through agricultural soils, which may naturally contain cadmium, or from anthropogenic sources such as atmospheric deposition or direct application methods such as phosphate fertilizer application and municipal waste composting (Alloway and Steinnes 1999; Morrow 2001). Cadmium-plated utensils and galvanized equipment used in food processing and preparation; enamel and pottery glazes with cadmium-based pigments; and stabilizers used in food-contact plastics are also sources of food contamination (Galal-Gorchev 1993). Cadmium levels in soils are not a direct indicator of the level of cadmium in the food supply, with the exception of extreme contamination, as other factors such as the type of crop and farming methods are important (Morrow 2001).

Based on food intake rates and food-cadmium concentrations, the estimated geometric mean daily intake of cadmium for the U.S. population is 18.9 µg/day, down from an estimated 30 µg/day in the 1980s (Choudhury et al. 2001; Gartrell et al. 1986). Based on the mean cadmium daily intakes for males and females aged 6–60 years reported by Choudhury et al. (2001), age-weighted mean cadmium intakes of 0.35 µg/kg/day for males and 0.30 µg/kg/day for females were calculated for U.S. nonsmokers. The

average gastrointestinal absorption of dietary cadmium is about 5%, but it may be 5–10 times greater in young women (CDC 2005).

In the Third National Report on Human Exposures to Environmental Chemicals reported by the CDC (2005) results from the National Health and Nutrition Examination Survey (NHANES) 1999–2002 were reported. Cadmium levels in blood (see Table 6-4), urine (creatine corrected [see Table 6-5]), and urine (see Table 6-6) was evaluated for a variety age groups and ethnicities. Blood cadmium reflects both recent and cumulative exposures and urinary cadmium reflects cadmium exposure and the concentration of cadmium in the kidneys. Cadmium targets the kidneys in the body and high-dose chronic cadmium exposure can cause renal tubular damage and glomerular damage. Even relatively low levels of cadmium exposure have resulted in biomarkers of renal dysfunction or diminished bone mineral density (CDC 2005).

As a part of the New York City Health and Nutrition Examination Survey (NYC HANES), 2004 blood cadmium levels were evaluated in 1,811 New York City adults (age 20 years and older). The variables used in this study were sex, age, race/ethnicity, place of birth, family income, education, and smoking status (see Table 6-7 for detailed results of this study). The geometric mean blood cadmium concentration in New York City adults was 0.77 μg/L, slightly higher than the 1999–2000 estimated national mean of 0.47 μg/L with heavy smokers having the highest geometric mean blood cadmium level of 1.58 μg/L, higher than any other subgroup. The reason for the elevated blood cadmium levels in nonsmoking, New York City adults is not known, although it was speculated that higher shellfish consumption may be the cause of elevated blood cadmium levels in Asian subgroup (McKelvey et al. 2007).

Vahter et al. (1996) studied the dietary intake and uptake of cadmium in nonsmoking women consuming a mixed diet low in shellfish (n=34) or with shellfish once a week or more (n=17). The shellfish diets, with a median of 22 μg Cd/day, contained twice as much cadmium as the mixed diets, which had a median of 10.5 μg Cd/day. In spite of the differences in the daily intake of cadmium, there were no statistically significant differences in the blood cadmium concentrations of the shellfish group (0.25 μg/L) and the mixed diet group (0.23 μg/L) or in the urinary cadmium concentrations of the shellfish and mixed diet groups (0.10 μg/L in both groups). These results indicate a lower absorption of cadmium in the shellfish group than in the mixed diet group or a difference in kinetics. The authors suggested that a higher gastrointestinal absorption of cadmium in the mixed diet group could be explained in part by their lower body iron stores as measured by the concentrations of serum ferritin (S-fer). A median S-fer

Table 6-4. Geometric Mean and Selected Percentile Blood Concentrations (µg/L) of Cadmium in the U.S. Population From 1999 to 2002

Group	Survey years	Geometric mean[a] (95 percent confidence interval)	Selected percentiles (95 percent confidence interval)				Sample size
			50th	75th	90th	95th	
Total, age 1 and older	1999–2000	0.412 (0.378–0.449)	0.300 (0.300–0.400)	0.600 (0.500–0.600)	1.00 (0.900–1.00)	1.30 (1.20–1.40)	7,970
	2001–2002	Not calculated	0.300 (<LOD–0.300)	0.400 (0.400–0.500)	0.900 (0.900–1.10)	1.30 (1.20–1.60)	8,945,
Age group							
1–5 Years	1999–2000	Not calculated	<LOD	0.300 (<LOD–0.300)	0.400 (0.300–0.400)	0.400 (0.300–0.400)	723
	2001–2002	Not calculated	<LOD	<LOD	<LOD	0.300 (<LOD–0.300)	898
6–11 Years	1999–2000	Not calculated	<LOD	0.300 (<LOD–0.300)	0.400 (0.300–0.400)	0.400 (0.400–0.500)	905
	2001–2002	Not calculated	<LOD	<LOD	<LOD	0.400 (0.300–0.400)	1,044
12–19 Years	1999–2000	0.333 (0.304–0.366	0.300 (<LOD–0.300)	0.300 (0.300–0.400)	0.800 (0.600–0.900)	1.10 (0.900–1.10)	2,135
	2001–2002	Not calculated	<LOD	0.300 (<LOD–0.300)	0.400 (0.400–0.500)	0.800 (0.600–1.10)	2,231
20 Years and older	1999–2000	0.468 (0.426–0.513)	0.400 (0.300–0.400)	0.600 (0.600–0.700)	1.00 (1.00–1.10)	1.50 (1.40–1.60)	4,207
	2001–2002	Not calculated	0.300 (0.300–0.400)	0.600 (0.500–0.600)	1.10 (0.900–1.20)	1.60 (1.30–1.80)	4,772
Gender							
Males	1999–2000	0.403 (0.368–0.441)	0.400 (0.300–0.400)	0.600 (0.500–0.600)	1.00 (0.900–1.10)	1.30 (1.20–1.50)	3,913
	2001–2002	Not calculated	0.300 (<LOD–0.300)	0.400 (0.400–0.500)	0.900 (0.900–1.10)	1.40 (1.20–1.80)	4,339
Females	1999–2000	0.421 (0.386–0.460)	0.300 (0.300–0.400)	0.600 (0.500–0.600)	1.00 (0.800–1.00)	1.30 (1.10–1.40)	4,057
	2001–2002	Not calculated	0.300 (0.300–0.400)	0.500 (0.500–0.600)	1.00 (0.900–1.10)	1.40 (1.20–1.60)	4,606
Race/ethnicity							
Mexican Americans	1999–2000	0.395 (0.367–0.424)	0.400 (0.300–0.400)	0.400 (0.400–0.500)	0.700 (0.700–0.900)	1.10 (0.900–1.30)	2,742
	2001–2002	Not calculated	<LOD	0.300 (0.300–0.400)	0.600 (0.500–0.700)	1.00 (0.700–1.30)	2,268
Non-Hispanic blacks	1999–2000	0.393 (0.361–0.427)	0.300 (0.300–0.400)	0.600 (0.500–0.600)	1.00 (0.800–1.10)	1.40 (1.10–1.50)	1,842
	2001–2002	Not calculated	<LOD	0.400 (0.400–0.500)	1.00 (0.900–1.00)	1.40 (1.20–1.50)	2,219
Non-Hispanic whites	1999–2000	0.376 (0.470–0.209)	0.400 (0.300–0.400)	0.500 (0.500–0.600)	1.00 (0.900–1.10)	1.30 (1.20–1.40)	2,716
	2001–2002	Not calculated	<LOD	0.500 (0.500–0.600)	0.900 (0.900–1.10)	1.40 (1.20–1.80)	3,806

[a]The proportion of results below limit of detection was too high to provide a valid result.

Source: CDC 2003, 2005b

Table 6-5. Geometric Mean and Selected Percentile Urine Concentrations (Creatine Corrected) (µg/L) of Cadmium in the U.S. Population From 1999 to 2002

Group	Survey years	Geometric mean[a] (95 percent confidence interval)	Selected percentiles (95 percent confidence interval)				Sample size
			50th	75th	90th	95th	
Total, age 6 and older	1999–2000	0.181 (0.157–0.209)	0.219 (0.199–0.238)	0.423 (0.391–0.446)	0.712 (0.645–0.757)	0.933 (0.826–1.07)	2,257
	2001–2002	0.199 (0.181–0.218)	0.212 (0.194–0.232)	0.404 (0.377–0.440)	0.690 (0.630–0.754)	0.917 (0.813–0.998)	2,689
Age group							
6–11 Years	1999–2000	Not calculated	0.085 (0.063–0.107)	0.147 (0.123–0.182)	0.210 (0.171–0.316)	0.300 (0.184–0.607)	310
	2001–2002	0.075 (0.059–0.094)	0.100 (0.083–0.112)	0.166 (0.136–0.192)	0.233 (0.206–0.281)	0.291 (0.221–0.440)	368
12–19 Years	1999–2000	0.071 (0.051–0.098)	0.093 (0.084–0.106)	0.147 (0.130–0.163)	0.215 (0.204–0.240)	0.283 (0.222–0.404)	648
	2001–2002	0.078 (0.067–0.091)	0.091 (0.085–0.101)	0.136 (0.123–0.143)	0.191 (0.175–0.234)	0.280 (0.234–0.321)	762
20 Years and older	1999–2000	0.267 (0.247–0.289)	0.288 (0.261–0.304)	0.484 (0.433–0.545)	0.769 (0.727–0.818)	1.07 (0.927–1.17)	1,299
	2001–2002	0.261 (0.236–0.289)	0.273 (0.247–0.303)	0.481 (0.426–0.518)	0.776 (0.691–0.850)	0.979 (0.874–1.12)	1,559
Gender							
Males	1999–2000	0.154 (0.131–0.182)	0.174 (0.158–0.191)	0.329 (0.293–0.382)	0.617 (0.537–0.700)	0.788 (0.696–0.929)	1,121
	2001–2002	0.159 (0.143–0.177)	0.168 (0.157–0.182)	0.334 (0.304–0.364)	0.532 (0.491–0.653)	0.757 (0.690–0.856)	1,334
Females	1999–2000	0.211 (0.170–0.261)	0.267 (0.239–0.308)	0.473 (0.423–0.551)	0.783 (0.690–0.917)	1.09 (0.813–1.38)	1,136
	2001–2002	0.245 (0.216–0.278)	0.263 (0.228–0.297)	0.479 (0.414–0.541)	0.792 (0.687–0.884)	0.985 (0.876–1.16)	1,355
Race/ethnicity							
Mexican Americans	1999–2000	0.175 (0.137–0.223)	0.181 (0.144–0.225)	0.331 (0.266–0.418)	0.612 (0.441–0.828)	0.843 (0.674–1.13)	780
	2001–2002	0.156 (0.136–0.177)	0.170 (0.150–0.184)	0.282 (0.263–0.340)	0.501 (0.388–0.614)	0.693 (0.507–0.839)	682
Non-Hispanic blacks	1999–2000	0.183 (0.140–0.240)	0.201 (0.168–0.241)	0.414 (0.343–0.472)	0.658 (0.516–0.827)	0.873 (0.722–0.962)	546
	2001–2002	0.190 (0.156–0.232)	0.195 (0.174–0.225)	0.385 (0.336–0.449)	0.676 (0.559–0.850)	0.917 (0.725–1.08)	667
Non-Hispanic whites	1999–2000	0.175 (0.146–0.209)	0.219 (0.191–0.250)	0.432 (0.387–0.470)	0.729 (0.666–0.783)	1.00 (0.826–1.16)	760
	2001–2002	0.205 (0.184–0.229)	0.224 (0.208–0.242)	0.421 (0.382–0.470)	0.719 (0.668–0.784)	0.931 (0.806–1.05)	1,132

[a]The proportion of results below limit of detection was too high to provide a valid result.

Source: CDC 2003, 2005b

Table 6-6. Geometric Mean and Selected Percentile Urine Concentrations (µg/L) of Cadmium in the U.S. Population From 1999 to 2002

Group	Survey years	Geometric mean[a] (95 percent confidence interval)	Selected percentiles (95 percent confidence interval)				Sample size
			50th	75th	90th	95th	
Total, age 6 and older	1999–2000	0.193 (0.169–0.220)	0.232 (0.214–0.249)	0.475 (0.436–0.519)	0.858 (0.763–0.980)	1.20 (1.06–1.33)	2,257
	2001–2002	0.210 (0.189–0.235)	0.229 (0.207–0.255)	0.458 (0.423–0.482)	0.839 (0.753–0.919)	1.20 (1.07–1.28)	2,690
Age group							
6–11 Years	1999–2000	Not calculated	0.078 (0.061–0.101)	0.141 (0.115–0.173)	0.219 (0.178–0.233)	0.279 (0.211–0.507)	310
	2001–2002	0.061 (<LOD–0.081)	0.077 (0.067–0.092)	0.140 (0.112–0.160)	0.219 (0.184–0.262)	0.282 (0.260–0.326)	368
12–19 Years	1999–2000	0.092 (0.067–0.126)	0.128 (0.107–0.148)	0.202 (0.183–0.232)	0.329 (0.272–0.372)	0.424 (0.366–0.596)	648
	2001–2002	0.109 (0.087–0.136)	0.135 (0.114–0.157)	0.210 (0.189–0.247)	0.327 (0.289–0.366)	0.442 (0.366–0.480)	762
20 Years and older	1999–2000	0.281 (0.253–0.313)	0.306 (0.261–0.339)	0.551 (0.510–0.621)	0.979 (0.836–1.13)	1.31 (1.13–1.57)	1,299
	2001–2002	0.273 (0.249–0.299)	0.280 (0.261–0.308)	0.545 (0.493–0.607)	0.955 (0.855–1.06)	1.28 (1.20–1.43)	1,560
Gender							
Males	1999–2000	0.199 (0.165–0.241)	0.227 (0.193–0.263)	0.462 (0.381–0.539)	0.892 (0.748–1.15)	1.41 (0.980–1.83)	1,121
	2001–2002	0.201 (0.177–0.229)	0.223 (0.191–0.257)	0.445 (0.393–0.481)	0.870 (0.741–1.03)	1.22 (1.12–1.38)	1,335
Females	1999–2000	0.187 (0.153–0.229)	0.239 (0.220–0.255)	0.492 (0.456–0.540)	0.806 (0.705–0.980)	1.10 (1.01–1.19)	1,136
	2001–2002	0.219 (0.192–0.251)	0.234 (0.202–0.265)	0.466 (0.433–0.519)	0.817 (0.733–0.886)	1.17 (0.918–1.36)	1,355
Race/ethnicity							
Mexican Americans	1999–2000	0.191 (0.157–0.233)	0.202 (0.167–0.221)	0.438 (0.351–0.551)	0.813 (0.686–0.977)	1.12 (0.886–1.38)	780
	2001–2002	0.160 (0.135–0.189)	0.181 (0.171–0.198)	0.321 (0.285–0.362)	0.559 (0.430–0.733)	0.766 (0.633–1.15)	683
Non-Hispanic blacks	1999–2000	0.283 (0.208–0.387)	0.312 (0.243–0.412)	0.633 (0.498–0.806)	1.22 (0.892–1.38)	1.48 (1.30–1.72)	546
	2001–2002	0.277 (0.229–0.336)	0.302 (0.257–0.354)	0.580 (0.476–0.713)	1.04 (0.843–1.38)	1.51 (1.28–1.74)	667
Non-Hispanic whites	1999–2000	0.175 (0.148–0.206)	0.220 (0.194–0.246)	0.455 (0.388–0.510)	0.797 (0.714–1.01)	1.17 (0.963–1.47)	760
	2001–2002	0.204 (0.179–0.231)	0.221 (0.191–0.255)	0.445 (0.394–0.479)	0.813 (0.717–0.875)	1.17 (0.989–1.24)	1,132

[a]The proportion of results below limit of detection was too high to provide a valid result.

Source: CDC 2003, 2005b

Table 6-7. Blood Cadmium Concentrations, Geometric Means, Adjusted Proportional Change in Means, and 95th Percentiles in New York City Adults in Population Subgroups

		Results		
Variable	Number[a]	Crude weighted geometric mean blood cadmium (µg/L)	Adjusted proportional change in mean blood cadmium (µg/L)[b]	Crude weighted 95th percentile blood cadmium (µg/L)
Total:	1,811	0.77	—	1.88
Male	762	0.76	1.00	1.95
Female	1,049	0.79	1.07	1.83
20–39 years old	903	0.76	1.00	1.82
40–59 years old	673	0.84	1.16	2.19
≥60 years old	235	0.77	1.15	1.52
White, non-Hispanic[c]	529	0.73	1.04	1.71
Black, non-Hispanic[c]	390	0.80	1.11	1.97
Asian, non-Hispanic[c]	231	0.99	1.41	2.36
Hispanic[c]	630	0.73	1.00	1.73
Place of birth:				
United States	882	0.76	1.00	1.95
Outside the United States	923	0.79	1.02	1.73
Family income ($US):				
<20,000	610	0.86	1.00	2.33
20,000–49,999	566	0.77	0.94	1.76
50,000–74,999	256	0.74	0.92	1.76
≥75,000	304	0.69	0.91	1.43
Education:				
<Bachelor's	1,252	0.82	1.09	2.02
Bachelors or greater	551	0.69	1.00	1.43
Smoking status:				
Never smoked	1,036	0.66	1.00	1.28
Former smoker	310	0.71	1.07	1.32
Current smoker	449	1.22	1.88	3.00

[a]Totals do not all equal 1,811 because of missing data.
[b]The exponential β coefficient from a log-linear multiple regression that includes all covariates in the table. Sample size for adjust analysis is 1,707, after excluding study participants for whom covariate data are missing.
[c]Excludes 27 participants who self-classified as "other".

Source: McKelvey et al. 2007

concentration of 18 µg/L was measured for the mixed diet group compared to a median of 31 µg/L for the shellfish group.

Except in the vicinity of cadmium-emitting industries or incinerators, the intake of cadmium from drinking water or ambient air is of minor significance (Elinder 1985a). Cadmium is removed from waste water and sewage through precipitation to hydroxide or carbonate compounds and ultimate separation (Schulte-Schrepping and Piscator 2002). EPA requires water suppliers to limit the cadmium concentration in water to <5 µg/L (EPA 2006a).

IARC (1993) reports that the total body burden of non-occupationally exposed adult subjects has been estimated to range from 9.5 to 50 mg in the United States and Europe. People living near sources of cadmium pollution may be exposed to higher levels of cadmium. Ambient air cadmium concentrations in industrialized areas was been estimated between 15 and 150 ng/m^3 (Morrow 2001). During a study conducted in Germany between March and May 2000, cadmium levels in child-mother pairs, as a function of ambient air quality, were compared between populations in the urban, industrialized area of Duisberg and the rural area of North Rhine Westphalia. Cadmium levels in the ambient air of Duisburg-South ranged from 1.5 to 31 ng/m^3, compared to 0.5 ng/m^3 in the rural are of Westphalia. Cadmium levels in the blood and urine of mothers in the industrialized area were higher than in the rural areas. Cadmium levels in the blood and urine of the children did not differ between the two areas. In the industrialized area, regression analysis indicated a significant influence of cadmium in ambient air on cadmium in blood (Wilhelm et al. 2005).

It has been estimated that tobacco smokers are exposed to 1.7 µg cadmium per cigarette, and about 10% is inhaled when smoked (Morrow 2001; NTP 2005). Tobacco leaves naturally accumulate large amounts of cadmium (Morrow 2001). During a study monitoring cadmium levels in 331 cigarette packs from over 20 areas around the world, it was found that the mean cadmium level per cigarette was 1.15 µg/cigarette ±0.43 (AM±ASD) or 1.06 µg/cigarette ±1.539 GM±GSD. Cigarettes from Mexico had the highest mean level of cadmium with an AM±ASD of 2.03 µg/cigarette ±0.33 or a GM±GSD of 2.00 µg/cigarette ±1.190. Cigarettes from India had the lowest mean levels of cadmium with an AM±ASD of 0.35 µg/cigarette ±0.09 or a GM±GSD of 0.34 µg/cigarette ±1.284 (Watanabe et al. 1987). The amount of cadmium absorbed from smoking one pack of cigarettes per day is about 1–3 µg/day (Lewis et al. 1972a; Nordberg et al. 1985), roughly the same as from the diet. This large contribution is due to the greater absorption of cadmium from the lungs than from the gastrointestinal tract (Elinder 1985a). Direct measurement of cadmium levels in body tissues confirms that smoking roughly doubles

cadmium body burden in comparison to not smoking, with kidney concentrations averaging 15–20 μg/g wet weight for nonsmokers and 30–40 μg/g wet weight for heavy smokers at the age of 50–60 (Ellis et al. 1979; Hammer et al. 1973; Lewis et al. 1972a, 1972b). Ellis et al. (1979) found an increase in kidney cadmium of 0.11±0.05 mg per pack-year (AM±ASD) of smoking and an increase in liver cadmium concentration of 0.077±0.065 μg/g per pack-year (AM±ASD). Because excretion of cadmium is very slow, half-lives of cadmium in the body are correspondingly long (17–38 years) (Wester et al. 1992).

Workers in a variety of occupations may be exposed to cadmium and cadmium compounds. Occupations with potential exposure to cadmium are listed in Table 6-8 (IARC 1993).

Highest levels of occupational exposure would be expected to occur in operations involving heating cadmium-containing products by smelting, welding, soldering, or electroplating, and also in operations associated with producing cadmium powders (OSHA 1990). The primary route of occupational exposure is through inhalation of dust and fumes, and also incidental ingestion of dust from contaminated hands, cigarettes, or food (Adamsson et al. 1979).

Concentrations of airborne cadmium found in the workplace vary considerably with the type of industry and the specific working conditions. Processes that involve high temperatures can generate cadmium oxide fumes that are absorbed very efficiently through the lungs (IARC 1993). Deposition and absorption of dust containing different compounds depend upon particle size (IARC 1993). These exposures can be controlled through use of personal protective equipment and good industrial hygiene practices, and through operating procedures designed to reduce workplace emissions of cadmium (OSHA 1990).

Data from the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, estimated the number of workers potentially exposed to various chemicals in the workplace during the same period (NIOSH 1990); these data are summarized in Table 6-9.

The NOES database does not contain information on the frequency, level, or duration of exposure of workers to any of the chemicals listed. It provides only estimates of workers potentially exposed to the chemicals.

The OSHA final rule has established a permissible exposure limit (PEL) of 5 $\mu g/m^3$ for occupational exposure to airborne cadmium (OSHA 2007a). The American Conference of Governmental and

Table 6-8. Occupations with Potential Exposure to Cadmium and Cadmium Compounds

Occupation	
Alloy production[a]	Phosphorous production
Battery production[a]	Pigment production and use[a]
Brazing	Plastics production[a]
Coating	Plating
Diamond cutting	Printing
Dry color formulation	Semiconductor and superconductor production
Electroplating	Sensors production
Electrical contacts production	Smelting and refining[a]
Enameling	Solar cells production
Engraving	Soldering
Glasswork	Stabilizer production
Laser cutting	Textile printing
Metallizing	Thin film production
Paint production and use	Transistors production
Pesticide production and use	Welding

[a]Activity with high risk because atmospheric concentrations of cadmium are high and the number of workers employed is significant.

Source: IARC 1993

Table 6-9. Estimated Number of Workers Potentially Exposed to Various Chemicals in the Workplace in 1981–1983

Chemical	Number of workers potentially exposed
Cadmium sulfide	45,562
Cadmium oxide	15,727
Cadmium (pure)	335
Cadmium dust (form unknown)	3,893
Cadmium powder (form unknown)	486
Cadmium sulfate	1,313
1:1 Cadmium salt of carbonic acid	164
Cadmium (form unknown)	88,968
Total	153,486

Source: NIOSH 1990

Industrial Hygienists (ACGIH) has set their biological exposure index (BEI) at 10 μg/L (Aurelio et al. 1993).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are most likely to be exposed to cadmium in from ingestion of food (NTP 2005). There are no data on gastrointestinal absorption of cadmium in children, although very limited evidence exists that cadmium absorption from the gut may be greater in young animals. Oral absorption is discussed in more detail in Section 3.4.1.2. A study performed in Cincinnati, Ohio, investigated cadmium in human milk and found a mean concentration of 19 ppb (0.019 ppm) (Jensen 1983). The NHANES 1999–2002 reported cadmium levels in blood (see Table 6-4) and urine (see Table 6-5) for children in different age groups (CDC 2005). The NYC HANES did not test for blood cadmium levels in children, although the blood cadmium levels in adults were slightly higher than the national average (McKelvey et al. 2007). Results of the U.S. FDA Total Diet Study (Capar and Cunningham 2000) reported cadmium levels in infant and junior foods ranged from no detection to 0.090 mg/kg. According to the National Human Exposure Assessment Survey (NHEXAS), children in EPA Region V (Great Lakes Region) have a mean dietary cadmium exposure of 17 (±1.8) μg/kg for minority children and 21 (±2.2) μg/kg for non-minority children (Pellizzari et al. 1999).

Except in the vicinity of cadmium-emitting industries or incinerators, the intake of cadmium from drinking water or ambient air is of minor significance (Elinder 1985a). Ambient air cadmium concentrations in industrialized areas has been estimated between 15 and 150 ng/m^3 (Morrow 2001).

Cadmium levels in the ambient air of Duisburg-South, Germany ranged from 1.5 to 31 ng/m^3, compared to 0.5 ng/m^3 in the rural are of Westphalia. Cadmium levels in the blood and urine of mothers in the industrialized area were higher than in the rural areas. Cadmium levels in the blood and urine of the children did not differ between the two areas. In the industrialized area, regression analysis indicated a significant influence of cadmium in ambient air on cadmium in blood (Wilhelm et al. 2005). Children in the homes of parents who smoke also can be exposed to cadmium through the inhalation of environmental tobacco smoke. There is potential for cadmium originating from second-hand smoke to settle onto surfaces; thus, there is a possibility that children may ingest cadmium from contaminated surfaces by the hand-to-mouth pathway. Although no data were found, children playing near hazardous waste sites could be exposed to cadmium in soil by hand-to-mouth activity and/or soil pica. No case studies were found on accidental poisoning of children by swallowing cadmium-containing batteries or by ingesting cadmium-containing household pesticides, which also are potential routes of exposure. No information was found concerning differences in the weight-adjusted intakes of cadmium by children.

In the Workers' Home Contamination Study conducted under the Workers' Family Protection Act (DHHS 1995), several studies were identified that reported home contamination with cadmium originating from parental occupation in a lead smelter. In a study of 396 children of ages 1–9 years living <900 m from a primary lead smelter, 380 children (96%) had blood cadmium (CdB) levels >0.0089 μg/L (Carvalho et al. 1986). The geometric mean and standard deviation were 0.087 μmol/L and 2.5, respectively. No significant relationship was found between parental occupation in the smelter and CdB in children, but a significant relationship was found between presence of smelter dross in the house and elevated CdB in children. Higher CdB was significantly associated with shorter distance from the home to the smelter. In a similar study of 263 children (ages 1–9 years), living <900 m from a primary lead smelter, the mean cadmium in hair was significantly higher at 6.0 ppm for children whose fathers worked in lead smelters than the concentration of 3.7 ppm for children whose fathers had other jobs (Carvalho et al. 1989). In a study of 9 children from families of lead workers and 195 children (ages 4–17 years) from other families, the children from the families of lead workers had significantly higher geometric mean urinary cadmium (CdU) (0.34 μg/L ±2.6) than children from other families (0.13 μg/L ±2.2). The CdB levels of children from families of lead workers were higher than those of the children from other families, but the difference was not statistically significant (Brockhaus et al. 1988). Maravelias et al. (1989) measured the CdBs of 514 children (ages 5–12) from four schools located within various distances (500–1500 m) from a lead smelter. The geometric mean and geometric standard deviation CdB was 0.36 μg/L ±1.4, respectively, with a range of 0.1–3.1 μg/L. Children from the school closest to the

smelter had higher CdB levels than children from other schools, but no relationship was found between childrens' CdB and parental employment in the smelter.

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in a study in Czechoslovakia, the concentration of cadmium in the placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). Baranowska (1995) also measured the concentrations of cadmium and lead in human placenta and in maternal and neonatal (cord) blood to assess the influence of a strongly polluted environment on the content of metals in tissues and on the permeability of the placenta to cadmium and lead. Samples for the study were collected from women living in the industrial district of Upper Silesia, one of the most polluted regions in Poland. The mean (range) concentration of cadmium in the air was 11.3 (2.1–25.4) ng/m^3 (0.0113 [0.0021–0.0254] μg/m^3). The mean concentrations of cadmium were 4.90 ng/mL (0.00490 μg/mL) in venous blood, 0.11 μg/g in placenta, and 1.13 ng/mL (0.00113 μg/mL) in cord blood. The researcher concluded that the placenta is a better barrier for cadmium than for lead, based upon the relative decrease in metal concentrations from placenta to cord blood. The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein (Goyer and Cherian 1992). Timing and level of cadmium exposure may influence the uptake of cadmium by the placenta, perhaps explaining the conflicting human studies. Galicia-García et al. (1995) performed analyses of cadmium in maternal, cord, and newborn blood for 50 births in a Mexico City hospital. Multiple regression analyses applied to the data indicated a significant association between cord and newborn blood and between cord and maternal blood, but not among maternal and newborn blood. Birth weight of the newborns was found to be inversely associated with cord blood cadmium levels and smoking habits.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The greatest potential for above-average exposure of the general population to cadmium is from smoking, which may double the exposure of a typical individual. Smokers who are exposed to cadmium in the workplace are at highest risk (CDC 2005). Individuals living near zinc or lead smelting operations,

municipal incinerators, or other industrial processes emitting cadmium to the air will also have above-average exposure (Elinder 1985a). Exposures through inhalation are diminishing due to pollution controls at such facilities, but exposure resulting from soil contamination may continue to be significant. Persons who have corrosive drinking water and cadmium-containing plumbing, who habitually consume cadmium-concentrating foods (kidney, liver, and shellfish), or who ingest grains or vegetables grown in soils treated with municipal sludge or phosphate fertilizer all may have increased exposure (Elinder 1985a). The 2004 NYC HANES indicated that the New York City Asian population, especially those born in China, had higher concentrations of cadmium in blood. The authors speculate that this might be due to higher consumption of fish and shellfish (McKelvey et al. 2007).

Multiple pathways of exposure may exist for populations at hazardous waste sites contaminated with cadmium (ingestion of contaminated drinking water or garden vegetables, inhalation of airborne dust, incidental ingestion of contaminated soil).

Persons who consume large quantities of sunflower kernels can be exposed to higher levels of cadmium. Reeves and Vanderpool (1997) identified specific groups of men who were likely to consume sunflower kernels. The groups included baseball and softball players, delivery and long-distance drivers, and line workers in sunflower kernel processing plants.

Recreational and subsistence fishers that consume appreciably higher amounts of locally caught fish from contaminated waterbodies may be exposed to higher levels of cadmium associated with dietary intake (EPA 1993a). Cadmium contamination has triggered the issuance of several human health advisories. As of December 1997, cadmium was identified as the causative pollutant in five fish and shellfish consumption advisories in New York and another in New Jersey. EPA is considering including cadmium as a target analyte and has recommended that this metal be monitored in fish and shellfish tissue samples collected as part of state toxics monitoring programs. EPA recommends that residue data obtained from these monitoring programs be used by states to conduct risk assessments to determine the need for issuing fish and shellfish consumption advisories for the protection of the general public as well as recreational and subsistence fishers. Under the same program, EPA has issued a statewide advisory in Maine for cadmium in moose (EPA 1998).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cadmium is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cadmium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The chemical and physical properties of cadmium and its salts are known well enough to permit estimation of the environmental fate of the compounds (Elinder 1985a, 1992). Additional information on properties does not appear to be crucial for evaluating potential fate.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2006, became available in February of 2008. This database is updated yearly and should provide a list of industrial production facilities and emissions.

The production volume, producers, import/export quantities, and uses of cadmium in the United States are well documented (SRI 2007; USGS 2007, 2008). Recycling of cadmium from spent batteries is increasing, and there are some data to suggest that there is still a large portion of cadmium being disposed of as municipal waste (USGS 2007). More data concerning the amount of municipal disposal would be helpful. Disposal of cadmium-containing wastes is regulated by the federal government, and data are available for industrial disposal practices (EPA 1982a; HSDB 2008; U.S. Bureau of Mines 1990). Most releases of cadmium are not from production of the metal or its compounds, but from combustion or

smelter emissions, land application of sewage sludge and fertilizers, and other sources; estimates of these releases have been made (TRI06 2008).

Environmental Fate. Cadmium partitioning among media occurs, and this partitioning depends on local environmental conditions (Elinder 1985a, 1992). Cadmium may be subject to long-range transport in air and water (EPA 1980d). Cadmium is persistent in all media, although it may form organic complexes in soil and water under certain environmental conditions (EPA 1979). These processes, which are important for determining the environmental fate of cadmium, seem to be relatively well understood. Therefore, additional information on environmental fate does not appear to be essential to evaluate potential human exposure to cadmium.

Bioavailability from Environmental Media. Factors that control the bioavailability of cadmium from air, water, soil, and food have been investigated. Intestinal absorption of cadmium from food is low, about 5–10% (McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973), but the absorption of cadmium from soil is not known. Absorption from the lungs is somewhat greater, averaging about 25% (Nordberg et al. 1985). Estimates of dermal absorption of cadmium from soil and water on human skin have been made (Wester et al. 1992). There is some evidence that bioavailability of cadmium to plants and worms from contaminated soil is greater following remediation (Van Gestel et al. 1988). Additional information on the factors influencing bioavailability, particularly from remediated soil, are needed to assess residual risk to populations in the vicinity of reclaimed hazardous waste sites.

Food Chain Bioaccumulation. Sufficient data are available to indicate that cadmium is concentrated in plants, aquatic organisms, and animals (Alloway et al. 1990; Beyer 1986; Handy 1992a, 1992b; Kuroshima 1992; Naqvi and Howell 1993; Roseman et al. 1994; Suresh et al. 1993; Vos et al. 1990). In vertebrates, cadmium accumulates in the liver and kidneys (Harrison and Klaverkamp 1990; Sileo and Beyer 1985; Vos et al. 1990). There is strong evidence for food chain bioaccumulation, but the potential for biomagnification is uncertain. Additional studies on biomagnification are needed to provide data for more accurate evaluation of the environmental impact of cadmium contamination.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of cadmium in contaminated media at hazardous waste sites are needed so that the information obtained on levels of cadmium in the environment can be used in combination with the known body burden of cadmium to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Current ambient air quality surveys testing for cadmium concentrations in rural and urban locations in the United States is lacking. Since the major source of exposure to cadmium is through dietary intake and since cadmium emissions to air are not expected to increase, there may be less interest in these data. There are several long-range atmospheric transport studies, but since these were conducted Europe and Russia, they only illustrate the potential for cadmium contamination via atmospheric deposition in the United States (Reimann et al. 1997; Shevchenko et al. 2003; Vidovic et al. 2005). There is also minimal data on current levels of cadmium in agricultural soils of the United States and the identification of the sources of cadmium levels, whether they are native geochemistry, phosphate fertilizers, atmospheric deposition, etc. (Xue et al. 2000). Continuing monitoring efforts in all media would allow more precise estimation of current sources and levels of human exposure and would assist in identifying major sources contributing to current exposure.

Exposure Levels in Humans. Cadmium has been detected in human blood, urine, breast milk, liver, kidney, and other tissues, both in occupationally exposed individuals and in the general population (CDC 2005; McKelvey et al. 2007; NTP 2005; OSHA 1990). The NHANES and NYC HANES provide current data on the levels of cadmium in humans (CDC 2005; McKelvey et al. 2007). Other large-scale surveys concentrating on urban, agricultural, and suburban communities would be beneficial in understanding cadmium exposure to the U.S. population. Also, more information is needed on the specific exposure levels for different cadmium salts to determine if cadmium sulfides, for example, are associated with less harmful effects than cadmium oxides (Chettle and Ellis 1992).

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Cadmium has been measured in maternal and neonatal (cord) blood and in placenta (Baranowska 1995; Galicia-García et al. 1995; Kuhnert et al. 1982; Lauwerys et al. 1978; Roels et al. 1978; Truska et al. 1989), but the resulting data are sometimes conflicting with respect to the uptake of cadmium by the placenta. Research on the effects of timing and level of exposure on cadmium uptake by the placenta might help to explain these conflicting human studies. More recent data would be useful, both from women and children living in unpolluted areas (for background levels) and in polluted areas such as those near existing or former lead smelters.

There are some current data concerning cadmium exposure in children (Capar and Cunningham 2000; CDC 2005; Pellizzari et al. 1999). The NHANES 1999–2002 reported cadmium levels in blood (see

Table 6-4) and urine (see Table 6-5) for children in different age groups (CDC 2005). The NYC HANES did not test for blood cadmium levels in children, although the blood cadmium levels in adults were slightly higher than the national average (McKelvey et al. 2007). Results of the U.S. FDA Total Diet Study (Capar and Cunningham 2000) reported cadmium levels in infant and junior foods ranged from no detection to 0.090 mg/kg. According to the NHEXAS, children in EPA Region V (Great Lakes Region) have a mean dietary cadmium exposure of 17 (±1.8) μg/kg for minority children and 21 (±2.2) μg/kg for non-minority children (Pellizzari et al. 1999).

Some body burden data are available for children living near lead smelters (Lagerkvist and Lundstrom 2004; Leroyer et al. 2001; Jin et al. 2002). However, none of the studies took place in the United States. Body burden data from children living in polluted and unpolluted regions (for background levels) of the United States are needed.

Current information on whether children are different in their weight-adjusted intake of cadmium via oral, inhalation, and dermal exposures was not located. A study to determine this information would be useful. Also, no information was found on childhood specific means to reduce cadmium exposure.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. The State of New York has established the Heavy Metals Registry for surveillance of occupational heavy metals absorption. Cadmium levels >10 μg/L in blood and 5 μg/L in urine are reported to the registry. The number of adults with reportable levels has varies per year, but there have always been <50 adults reported per year. Between 1995 and 2003, the number of reportable adults was <5, and these exposures are do mostly to exposure for people working as jewelers and casting machine operators (NYS Dept of Health 2006).

No other exposure registries for cadmium were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2008) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-10.

Table 6-10. Ongoing Studies on Cadmium

Investigator	Affiliation	Research description	Sponsor
Birnbaum ER	Caldera Pharmaceuticals, Inc., Los Alamos, New Mexico	Biomarkers of response to environmental stressors	National Institute of Environmental Health Sciences
Chen Z	X-Ray Optical Systems, Inc. East Greenbush, New York	Direct measurement of trace elements in body fluids	National Center for Research Resources
Dweik BM	Giner, Inc., Newton, Massachusetts	Field-deployable monitor to assess personal exposure to multiple heavy metals	National Institute of Environmental Health Sciences
Fallin MD	Johns Hopkins University, Baltimore, Maryland	AGE-related epigenetic changes - environmental causes and disease consequences	National Institute of Environmental Health Sciences
Fox MA	Johns Hopkins University, Baltimore, Maryland	Environmental exposure to metal mixtures and kidney disease	National Institute of Environmental Health Sciences
Larkin PM	Ecoarray, Inc. Alachua, Florida	Developing and using sheepshead minnow microarrays for ecotoxicology	National Institute of Environmental Health Sciences
Mo J	Kumetrix, Inc, Union City, California	Automatic multi-analyte in-situ bioassay for monitoring exposure to toxic metals	National Institute of Environmental Health Sciences
Polette-Niewold LA	Mayan Pigments, Inc.	SBIR phase II: One-step environmentally-friendly synthesis of novel organic/inorganic hybrid pigments	National Science Foundation
Santra S	University of Central Florida	Selective detection of toxic heavy metal ions using highly sensitive quantum dot probes	National Science Foundation
Basta N; Raun WR	Oklahoma State University	Chemistry and bioavailability of waste constituents in soils	U.S. Department of Agriculture
Basta NT	Oklahoma State University	Heavy metal and trace element chemistry in soils: Chemical speciation and bioavailability	U.S. Department of Agriculture
Basta NT; Lower SK; Lanno R	Ohio State University	Heavy metal and trace element biogeochemistry in soils: Chemical speciation, bioavailability, and toxicity	U.S. Department of Agriculture
Bleam WF; Helmke PA	University of Wisconsin	Verifying and quantifying the specific complexation of metals to humic substances	U.S. Department of Agriculture
Chaney RL	Beltsville Agricultural Research Center	Characterization and remediation of potential trace element and phosphate risks from contaminated soils	U.S. Department of Agriculture
Chaney RL	Beltsville Agricultural Research Center	Risk assessment and remediation of soil and amendment trace elements	U.S. Department of Agriculture

Table 6-10. Ongoing Studies on Cadmium

Investigator	Affiliation	Research description	Sponsor
Chaney RL; Daniels WL	Virginia Polytechnic Institute	Effects of long-term biosolids applications on phytoavailability of soil cadmium and zinc	U.S. Department of Agriculture
Chang AC; Page AL	University of California, Riverside	Chemistry and bioavailability of waste constituents in soils	U.S. Department of Agriculture
Eick MJ	Virginia Polytechnic Institute	Trace element and ligand adsorption/ desorption from soil constituent surfaces	U.S. Department of Agriculture
Hopkins DG	North Dakota State University	Influence of geologic materials and pedogenic processes on trace elements in soil landscapes	U.S. Department of Agriculture
Hunt JR; Lykken GI	University of North Dakota	Whole body counting and radiotracer methods in research on mineral requirements in human nutrition	U.S. Department of Agriculture
Kpomblekou-Ademawou K; Ankumah RO	Tuskegee University	Trace elements in broiler littered soils: Fate and effects on nitrogen transformation	U.S. Department of Agriculture
Martinez CE	Pennsylvania State University	Chemical and biogeochemical processes involved in trace and toxic element cycling in soils	U.S. Department of Agriculture
Morrissey MT	Oregon State University	Characterization of the cadmium health risk, concentrations and ways to minimize cadmium residues in shellfish	U.S. Department of Agriculture
Schwab AP; Joern B; Johnston C	Purdue University	Chemistry and bioavailability of waste constituents in soils	U.S. Department of Agriculture
Sparks DL	University of Delaware	Rates and mechanisms of metal and metalloid sorption/surfaces	U.S. Department of Agriculture
Thomas, DG; Kennedy TS	Oklahoma State University	Maternal dietary nutrients and neurotoxins in infant cognitive development	U.S. Department of Agriculture
Williams PL	University of Georgia	Environmental health impacts of soil contamination	U.S. Department of Agriculture
	National Risk Management Research Laboratory	Biomonitoring of source water quality	U.S. Environmental Protection Agency
Petterson L	National Exposure Research Lab Environmental Sciences Division Characterization and Monitoring Branch	Efficient monitoring of heterogeneous media and electronic wastes	U.S. Environmental Protection Agency

Table 6-10. Ongoing Studies on Cadmium

Investigator	Affiliation	Research description	Sponsor
Petterson L	National Exposure Research Lab Ecosystems Research Division Ecosystems Assessment Branch	Geochemical and interfacial applications for assessing ecological toxicant exposures	U.S. Environmental Protection Agency
Nolan P	Office of Regional Administrator Office of Environmental Measurement and Evaluation	Lower Merrimack River fish tissue study	U.S. Environmental Protection Agency
Janes D	Office of Research and Development National Health and Environmental Effects Research Lab Mid-Continent Ecology Division	Risks of heavy metals to aquatic organisms from multiple exposure routes	U.S. Environmental Protection Agency

Sources: FEDRIP 2008; SI/EPA 2007

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring cadmium, its metabolites, and other biomarkers of exposure and effect to cadmium. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

The most common analytical procedures for measuring cadmium concentrations in biological samples use the methods of atomic absorption spectroscopy (AAS) and atomic emission spectroscopy (AES). In AAS analysis, the sample is heated by a flame or in a furnace until the element atomizes. In AES analysis, the emitted radiation resulting from the thermal energy from a flame or inductively coupled plasma discharge (ICP) is measured. These basic methods of analysis are well defined and generally accepted for the analysis of cadmium.

Samples are prepared for AAS and AES methods in a variety of ways. Digestion with nitric acid is most common (Roberts and Clark 1986; Sharma et al. 1982). Cadmium in blood and plasma measured by graphite furnace atomic absorption spectroscopy (GFAAS) facilitated by a wet ashing pretreatment of samples resulted in good accuracy and reproducibility. The sample detection limit using this method was 0.4 μg/L (Roberts and Clark 1986). This method was also precise and highly reproducible in determining cadmium in whole blood, urine, and hair with 99–99.4% recoveries reported (Sharma et al. 1982). The matrix may also be modified with diammonium hydrogen phosphate or other agents such as palladium (Pd)-based modifiers (Moreira et al. 1995). Detection limits as low as 0.1 μg/L with recoveries ranging from 93 to 111% are reported using this technique (Subramanian and Meranger 1981; Subramanian et al. 1983). If the concentration of cadmium in the dissolved sample is below the detection limit, preconcentration techniques, such as chelation and extraction, may be employed (Gross et al. 1976; Sharma et al. 1982). Since cadmium is a ubiquitous element, the risk of contamination during sampling, processing, and analysis must be minimized by strict laboratory procedures (Elinder and Lind 1985). In

procedures for micro-determination, all glass and plastic-ware should be acid-washed and subsequently rinsed with double-distilled water.

Current analytical improvements deal primarily with the methods of sample preparation and sample introduction to the analytical systems in order to lower the detection limits or decrease sample analysis time. Various improvements in the methods of extraction, preconcentration, chelation, complexation, and sample introduction have been developed for use with biological media. Detection limits as low as 0.003 µg/L were reported (Espinosa Almendro et al. 1992; Cordero et al. 1994; Jeng et al. 1994; Katskov et al. 1994; Komárek et al. 1991; Ma et al. 1994b; Welz et al. 1991).

The cadmium concentration in biological samples may also be measured by a number of other methods such as radiochemical neutron activation analysis (RNAA). One RNAA procedure involving a rapid two-step solvent extraction was used for determining cadmium in tissue samples (Tandon et al. 1994). Another method to determine cadmium in biological materials is based on the ion-exchange scheme developed by SAMSAHL where cadmium is trapped on an anion exchange resin. With this method, recovery of 98% and a detection limit of 4 µg/kg were reported. The accuracy of the method was estimated by three different approaches: analysis using radiotracers in inactive sample solutions; by analyzing standards, pipetted on filter paper, and processed as samples; and determination by RNAA (Woittiez and Tangonan 1992).

Cadmium concentration in tissue may be measured both *in vivo* (Ellis 1985; Scott and Chettle 1986) and *in vitro* (Lieberman and Kramer 1970) by neutron activation analysis (NAA). Direct *in vivo* assessment of body burden in humans focused on the measurements of cadmium in the kidney and liver by NAA. The detection limits reported are approximately 2 mg cadmium for the total kidney and 1.5 µg/g for the liver (Ellis 1985); 1.9 mg cadmium for the kidney; and 1.3 µg/g for the liver (Scott and Chettle 1986).

X-ray fluorescence is also used for *in vivo* measurement of cadmium in the kidney (Christoffersson et al. 1987; Nilsson and Skerfving 1993; Scott and Chettle 1986; Skerfving and Nilsson 1992). The *in vivo* techniques are used for clinical measurements of individuals occupationally exposed to cadmium. Additional methods applicable to the analysis of cadmium in biological media include inductively coupled plasma/mass spectrometry (ICP/MS) (Stroh 1993; Vanhoe et al. 1994) and high performance liquid chromatography (HPLC) (Chang and Robinson 1993; Steenkamp and Coetzee 1994). Electrothemal vaporization ICP/MS has been utilized for the analysis of dentin and enamel from teeth (Grünke et al. 1996). Electrochemical methods such as adsorptive cathodic stripping voltametry (ACSV)

and potentiometric stripping analysis (PSA) have been applied to hair analysis (Zhang et al. 1993), animal tissues (LaBar and Lamberts 1994), and body fluids (Ostapczuk 1993).

Table 7-1 summarizes some of the methods used for sample preparation and analysis of cadmium in biological samples.

7.2 ENVIRONMENTAL SAMPLES

Analysis for cadmium in environmental samples is usually accomplished by AAS or AES techniques, with samples prepared by digestion with acid, preconcentrated with a chelating resin, or direct aspiration with no preparation (APHA 1977a, 1977b; EPA 1983a, 1983b, 1997b; OSHA 2002a, 2004; USGS 1985). Since cadmium in air is usually associated with particulate matter, standard methods involve collection of air samples on glass fiber or membrane filters, acid extraction of the filters, and subsequent (APHA 1977a, 1977b; OSHA 2002a, 2002b). Inductively-coupled plasma spectrometry (ICP) analysis in standard methods is also popular. ICP analysis for water and air samples can be run in tandem with mass spectrometry (MS) or AES (EPA 1996b, 1997b, 2003b; NIOSH 2003; OSHA 2002b). ACSV (Nimmo and Fones 1994), differential pulse anodic stripping voltametry (DP-ASV) (Nam et al. 1994), and epithermal NAA (Landsberger and Wu 1993) have also been used for air analysis. The accuracy of the analysis of cadmium in acid digested atmospheric samples, measured by ACSV, was evaluated and compared with GFAAS and ICP/MS. The ASCV limit of detection for cadmium was 0.6 ng/mL, higher than that of GFAAS at 0.3 ng/mL, but lower than that of ICP-MS for a 1-minute collection period. ACSV has advantages for analysis of low concentrations of cadmium in aerosol acid digest samples (Nimmo and Fones 1994).

Several methods standardized by EPA (1983a, 1983b, 1994b, 1996a, 1996b, 1997b, 2000, 2003b) are used for measuring concentrations of cadmium in water. Techniques to compensate for chemical and matrix interferences in all three methods are described by EPA (1983a, 1983b, 1994b, 1996a, 1996b, 1997b, 2000, 2003b). After soils and solid wastes are extracted or solubilized by acid digestion, they may be analyzed for cadmium by the same AAS methods that are used for water (EPA 1986d, 1986e). Water can also be analyzed for cadmium by NAA methods (Saleh et al. 1993), PSA methods (Ostapczuk 1993), and anodic stripping voltametry (ASV) (Daih and Huang 1992).

Sediment and soil samples have been analyzed for cadmium using the methods of GFAAS (Klemm and Bombach 1995). Preparation of the samples is generally accomplished by treatment with HCl and HNO_3.

Table 7-1. Analytical Methods for Determining Cadmium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Digestion with nitric acid; chelation with APDC and extraction with MIBK	AAS	<1 ng/mL[a]	99	Sharma et al. 1982
Blood	Modification of matrix with diammonium hydrogen phosphate/Triton X-100	GFAAS	0.1 µg/L	100.8±4.3	Subramanian and Meranger 1981
Blood/plasma	Digestion with nitric acid; wet ashed	GFAAS	0.4 µg/L	No data	Roberts and Clark 1986
Serum	Dilution with ammonia/Triton X-100	ICP/MS	0.01 ng/mL	No data	Stroh 1993
Tissue and blood	Microwave digestion	FAAS/flow injection system	0.15 µg/L	No data	Welz et al. 1991
Human milk	Dilution with deionized and double distilled water	AAS	<0.01 ppb[a]	No data	Schulte-Lobbert and Bohn 1977
Hair	Digestion with nitric acid	AAS	0.07 µg/g[a]	99	Sharma et al. 1982
Kidney	None (*in vivo*)	XRF	170.1 µg/g	No data	Christoffersson et al. 1987
Kidney/liver	Chelation and extraction with solvent	AAS/direct aspiration	0.01 ppm[a] (liver) 1.9 mg (kidney)	No data	Gross et al. 1976
Kidney/liver	None (*in vivo*)	NAA	1.3 µg/g (liver) 1.9 mg (kidney)	No data	Scott and Chettle 1986
Muscle	Wet ashed with concentrated sulfuric acid	NAA	50 ppb	50–65	Lieberman and Kramer 1970
Urine	Dilution with nitric acid	ETAAS	0.045 µg/L	97–101	Komárek et al. 1991
Urine	Modification of matrix with diammonium hydrogen phosphate/nitric acid	GFAAS	0.09 ng/mL	92.7–111.1	Subramanian et al. 1983
Urine	Digestion with nitric acid	AAS	5.67 ng/mL[a]	99.4	Sharma et al. 1982
Biological materials	Microwave digestion followed by extraction with APTH in MIBK	ICP/AES	0.15 ng/mL	No data	Cordero et al. 1994
Biological materials	Digestion with acid	GFAAS/flow injection system	0.003 µg/L	No data	Ma et al. 1994a

Table 7-1. Analytical Methods for Determining Cadmium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Biological fluids (blood, urine)	Acidification	PSA	0.001 µg/kg	No data	Ostapczuk 1993
Biological materials	Dry tissues; irradiation followed by acid digestion	RNAA	4 µg/kg	98	Woittiez et al. 1992
Teeth, dentin, and enalmel	Digested in nitric acid, diluted with water	ETV-ICP-MS PN-ICP-MS	No data	No data	Grünke et al. 1996
Whole blood, urine	Modified with palladium based modifier	ETAAS	0.22 µg/L	No data	Moreira et al. 1995
Biological materials	Digested with nitric acid and hydrogen peroxide	B-9001-95; ICP-AES	No data	93	USGS 1996

[a]Lowest concentration found

AAS = atomic absorption spectroscopy; APDC = ammonium pyrrolidenedithiocarbamate; APTH = 13-bis[-(2-pyridyl)ethylidene]thiocarbonhydride; ETAAS = electrothermal atomic absorption spectroscopy; FAAS = flame atomic absorption; GFAAS = graphite furnace atomic absorption; ICPIAES = inductively coupled plasma atomic emission spectroscopy; ICPIMS = inductively coupled plasma mass spectrometry; MIBK = methyl isobutyl ketone; NAA = neutron activation analysis; PSA = potentiometric stripping analysis; RNAA = radio chemical neutron activation analysis; XRF = x-ray fluorescence

The most common method for analysis of cadmium in foods is AAS (Bruhn and Franke 1976; Dabeka 1979; Muys 1984), with GFAAS being one of the most common AAS methods used (Cabrera et al. 1995). The FDA's Total Diet Study 1991–1996 analyzed cadmium and other element concentrations in food by dry ash mineralization and GFAAS (Capar and Cunningham 2000). RNAA (Greenberg et al. 1979), differential pulse ASV (Satzger et al. 1982, 1984), and the calorimetric dithizone method (AOAC 1984) may also be employed. The AAS techniques appear to be most sensitive, with recoveries ranging from 94 to 109% (Bruhn and Franke 1976; Muys 1984). A method used to isolate cadmium by first extracting with bismuth diethyldithiocarbamate ($Bi[DDC]_3$) and then with zinc diethyldithiocarbamate ($Zn[DDC]_2$) in chloroform and then measuring by RNAA showed 94–106% recovery (Greenberg et al. 1979).

Table 7-2 summarizes some of the methods used for sample preparation and analysis of cadmium in environmental samples.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cadmium is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cadmium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

Table 7-2. Analytical Methods for Determining Cadmium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on glass fiber filter; ashed with hydrochloric and nitric acids	Method 311; AAS	0.005 µg/m^3	90	APHA 1977b
Air	Collection on membrane filter; ashed with hydrochloric and nitric acids	Method 7048; AAS	0.05 µg per sample	No data	NIOSH 1994
Air	Collection on membrane filter; digestion with nitric acid and perchloric acid	Method 7300; ICP	0.3 ng/mL	99.8–105.2	NIOSH 2003
Air	Collection using filters, wipes, or bulk materials; desorbed with water extractions and mineral acid digestions	Method 121; AAS/AES	0.004 µg/mL	99.5	OSHA 2002a
Air	Collection on membrane filter; digested in nitric acid, sulfuric acid, and hydrogen peroxide	Method 125G; ICP-AES	0.14 µg[a] 0.47 µg[b]	No data	OSHA 2002b
Air	Collection on membrane filter; digested with nitric acid and small amounts of hydrochloric acid	Method 189; AAS/ AAS-HGA	0.2 µg/m^3 (AAS)[a] 0.70 µg/m^3 (AAS)[b] 0.007µg/m^3 (AAS-HGA)[a] 0.025 µg/m^3 (AAS-HGA)[b]	No data	OSHA 2004
Air	Collection on membrane filter, wipe, or bulk material; digest with nitric and hydrochloric acids	Method 206; ICP-AES	0.0062 µg/mL[a] 0.0205 µg/mL[b]	No data	OSHA 1991
Air	Irradiation UF filters	Epithermal NAA	8 ng	No data	Landsberger et al. 1993
Air (aerosols)	Acid digestion with filters	ACSV	0.6 ng/mL	100	Nimmo and Fones 1994
Atmospheric particles	Direct analysis	ETV-ICP-MS	pg/m^3 range	No data	Lüdke et al. 1997
Water	Digestion with nitric acid	Method 213.1; AAS/direct aspiration	5 µg/L	94±24	EPA 1983a
Water	Digestion with nitric acid	Method 213.2; AAS/ GFAAS	0.1 µg/L	96–99	EPA 1983b

Table 7-2. Analytical Methods for Determining Cadmium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	On-line preconcentration with ion exchange or sorbent extraction columns	GFAAS/ flow injection system	0.8 ng/L	No data	Welz et al. 1992
Water	Digestion with nitric acid	Method 1637; chelation and GFAAS	0.0075 µg/L	No data	EPA 1996a
Water	Digestion with nitric acid	Method 1638; ICP-MS	0.025 µg/L	No data	EPA 1996b
Water	Preconcentrated with chelating resin	Method 1640; Online Chelation/ ICP-MS	0.0024 µg/L	No data	EPA 1997b
Water	Digested with hydrochloric and nitric acids	Method 200.5; AVICP-AES	0.1 µg/L	98±1.1	EPA 2003
Water and Wastes	Digestion with acids	Method 200.7; ICP-AES	1 µg/L (aqueous); 0.2 mg/kg (solids)	82–98	EPA 1994a
Various	Digestion with nitric and hydrochloric acids	Method 6010C; ICP-AES	No data	97	EPA 2000
Water and sediments	No preconcentration or pretreatment	I-1135; AAS	10 µg/L	No data	USGS 1985
Water	Digested with whole water	I-4471-97; ICP-OES	5 µg/L	No data	USGS 1998a
Various	Direct aspiration with no preconcentration or pretreatment	I-5135; AAS	10 µg/L	No data	USGS 1985
Soil	Digestion with nitric acid	Method 7130; AAS/direct aspiration	0.005 mg/L	No data	EPA 1986e
Soil	Digestion with nitric acid	Method 7131; GFAAS	0.1 µg/L	No data	EPA 1986d
Soil and sediment	Ultrasonic slurry in dilute nitric acid	GFAAS	No data	100±10	Klemm and Bombach 1995
Sediment	Digestion with hydrochloric and nitric acid	LEAFS	500 fg	No data	Zhou et al. 1998

Table 7-2. Analytical Methods for Determining Cadmium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil and sediment	Digestion with hydrofluoric acid and nitric acid; complexation with DDPA using on-line sorbent extraction system	GFAAS/ flow injection system	0.8 µg/L	No data	Ma et al. 1994b
Food	Dry ashed; oxidization with nitric acid	ASV/ differential pulse	1 ng/g	99–108	Satzger et al. 1984
Food	Dry ashed; complexation with APCD; extraction with isoamyl acetate	AAS	0.1 ng/g	97.5±2.5	Bruhn and Franke 1976
Food	Extraction with $Bi(DDC)_3$ then with $Zn(DDC)_2$ in chloroform	RNAA	0.029 µg/g[c]	94–106	Greenberg et al. 1979
Food (24 hour diet)	Microwave digestion with nitric acid and hydrogen peroxide	GFAAS	0.004 µg/g	94–101	Yang et al. 1995
Food	Dry ashed; complexation with NaDDTC; extraction with IBMK	GFAAS	0.1 ppb[c]	94–109	Muys 1984
Food	Homogenization followed by wet ashing	GFAAS	0.01 ppb	94–108	Zhang et al. 1997
Fruit	Homogenized fruit slurried with zirconia	ETAAS	0.3 ng/g	97.7±0.3	Cabrera et al. 1995

[a]Qualitative detection limit
[b]Quantitative detection limit
[c]Lowest concentration found

AAS = atomic absorption spectroscopy; ACSV = adsorptive cathodic stripping voltametry; APCD = ammonium pyrrolidino carbodithioate; ASV = anodic stripping voltametry; AVICP-AES = axially viewed inductively coupled plasma-atomic emission spectrometry; $Bi(DDC)_3$ = bismuth diethyldithiocarbamate; DDPA = ammonium diethyldithiophosphate; ETV-ICP-MS = electrothermal vaporization inductively coupled plasma mass spectrometry; GFAAS = graphite furnace atomic absorption; HGA = heated graphite atomizer; IBMK = isobutyl methyl ketone; ICP = inductively coupled plasma; LEAFS = laser-excited atomic fluorescence spectrometry; MS = mass spectrometry; NAA = neutron activation analysis; NaDDTC = sodiumdiethyl-dithiocarbomate; OES = optical emission spectroscopy; RNAA = radiochemical neutron activation analysis; $Zn(DDC)_2$ = zinc diethyldithiocarbamate

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Measurements of cadmium in liver and kidney are all useful biological indices for human exposure to cadmium (Roels et al. 1981b). Human milk, human placentas, and maternal and neonatal blood have been investigated as means to determine exposures of women and infants to cadmium (Baranowska 1995; Abadin et al. 1997). Sensitive and selective methods are available for the detection and quantitation of cadmium in these biological materials (Elinder and Lind 1985; Sharma et al. 1982). Improved methods for sample preparation and *in vivo* analysis of liver and kidney content are needed to assist in monitoring environmentally exposed populations.

Effect. Sensitive methods are also available for measuring biological markers of cadmium effect, particularly urine or serum concentration of β2-microglobulin, retinol-binding protein, metallothionein, and creatinine (Kawada et al. 1990; Roels et al. 1989; Topping et al. 1986). Additional studies to establish background levels of these indicators in unexposed populations are needed to evaluate the sensitivity of these biomarkers of effect.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Cadmium is ubiquitous in the environment and does not degrade. It is found in air, water, soil, sediments, and food. Analytical methods exist for the analysis of cadmium in all of these environmental media, and these methods have the sensitivity to measure background levels and detect elevated concentrations due to anthropogenic sources such as hazardous waste sites (EPA 1983a, 1983b, 1994b, 1996a, 1996b, 1997b, 2000, 2003b). Additional research to reduce chemical and matrix interferences are needed to improve the speed and accuracy of the analyses.

7.3.2 Ongoing Studies

The EPA is conducting a pilot program for comprehensive monitoring of human exposure.

The National Human Exposure Assessment Study (NHEXAS) is being conducted in three regions of the United States in order to establish relationships between environmental concentrations, exposure, dose, and health response and to determine the incidence and causes of high exposures, especially for biologically susceptible persons. One of the aims of the pilot study is to test measurement methodology for a variety of pollutants, including cadmium, in food, air, and water. As an adjunct to this pilot study,

the EPA and the State of Minnesota are conducting a study of children's exposure to toxic chemicals, including cadmium.

The information in Table 7-3 was found as a result of a search of the Federal Research in Progress database (FEDRIP 2008).

Table 7-3. Ongoing Analytical Methods Studies on Cadmium

Investigator	Affiliation	Research description	Sponsor
Parker D	University of California	Isotopic dilution methods for probing the bioavailability of trace elements in soils and sediments	U.S. Department of Agriculture
Pierzynski G	Kansas State University	Chemistry, bioavailability, and toxicity of constituents in residuals and residual treated soils	U.S. Department of Agriculture
Schwab AP; Joern B; Johnston C	Purdue University	Chemistry and bioavailability of waste constituents in soils	U.S. Department of Agriculture
Santra S	University of Central Florida	Selective detection of toxic heavy metal ions using highly sensitive quantum dot probes	National Science Foundation
Swain G	Michigan State University	Diamond microelectrode arrays: New materials for the electrochemical detection of aqueous analytes	U.S. Department of Agriculture

Source: FEDRIP 2008

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an acute-duration inhalation MRL of 0.03 μg Cd/m^3 for cadmium. This MRL is based on a LOAEL of 0.088 mg Cd/m^3 ($LOAEL_{HEC}$ of 0.01 mg Cd/m^3) for respiratory effects in rats exposed to cadmium oxide 6.2 hours/day, 5 days/week for 2 weeks (NTP 1995) and an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

ATSDR has derived a chronic-duration inhalation MRL of 0.01 μg Cd/m^3 for cadmium. This MRL is based on the 95% lower confidence limit of the urinary cadmium level associated with a 10% extra risk of low molecular weight proteinuria ($UCDL_{10}$) estimated from a meta-analysis of environmental exposure data. An air concentration that would result in this urinary cadmium level (0.5 μg/g creatinine), assuming a dietary cadmium intake of 0.3 μg/kg/day, was estimated using biokinetic models. The estimated air concentration of 0.1 μg Cd/m^3 was divided by an uncertainty factor of 3 for human variability and a modifying factor of 3.

The EPA has not established a reference concentration (RfC) for cadmium.

ATSDR has derived an intermediate-duration oral MRL of 0.5 μg Cd/kg/day for cadmium. This MRL is based on a $BMDL_{std1}$ of 0.05 mg Cd/kg/day for skeletal effects in young female rats exposed to cadmium chloride in drinking water for 6, 9, or 12 months (Brzóska and Moniuszko-Jakoniuk 2005d) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.1 μg Cd/kg/day for cadmium. This MRL is based on the $UCDL_{10}$ for low molecular weight proteinuria estimated from a meta-analysis of environmental exposure data. A cadmium intake that would result in the $UCDL_{10}$ (0.5 μg/g creatinine) at age 55 was estimated using pharmacokinetic models. The cadmium intake of 0.33 μg/kg/day was divided by an uncertainty factor of 3 for human variability.

The EPA has established a reference dose (RfD) of $5x10^{-4}$ mg/kg/day in water and $1x10^{-3}$ mg/kg/day in food (IRIS 2008). The RfD is based on a chronic intake that would result in a kidney concentration of 200 μg/g ww.

The international and national regulations, advisories, and guidelines regarding cadmium in air, water, and other media are summarized in Table 8-1.

Cadmium compounds are included on the list of 189 chemicals listed as hazardous air pollutants under Section 112 of the Clean Air Act as amended (EPA 2007). Cadmium also is on the list of chemicals appearing in the Emergency Planning and Community Right-To-Know Act of 1986 (EPA 2008g). Under Title III of this statute, owners and operators of facilities that manufacture, import, process, or otherwise use the chemicals on this list of report annually their release of those chemicals to any environmental media.

Cadmium and cadmium chloride are designed as hazardous substances under Section 311 of the Clean Water Act; any discharge of these chemicals over a specified threshold level into navigable waters is subject to reporting requirements (EPA 2008c).

Cadmium is a hazardous waste under the Resource Conservation and Recovery Act (RCRA) under several circumstances. Groundwater monitoring is required at municipal solid waste landfills (EPA 2008d) and cadmium is considered a priority persistent, bioaccumulative, and toxic (PBT) chemical under RCRA waste minimization chemical listing (EPA 1998).

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Cadmium

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2008
	Cadmium and cadmium compounds	Group 1[a]	
WHO	Air quality guidelines		WHO 2000
	Cadmium[b,c]	5 ng/m^3	
	Drinking water quality guidelines		WHO 2004
	Cadmium	0.003 mg/L	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	Biological exposure indices		ACGIH 2007
	Cadmium and inorganic compounds		
	Cadmium in urine	5 µg/g creatinine	
	Cadmium in blood	5 µg/L	
	TLV (8-hour TWA)		
	Cadmium	0.01 mg/m^3	
	Cadmium compounds (as Cd)[d]	0.002 mg/m^3	
	TLV basis (critical effects)		
	Cadmium	Kidney damage	
	Cadmium compounds (as Cd)	Kidney damage	
EPA	Second list of AEGL priority chemicals for guideline development		EPA 2008a
	Cadmium and compounds[e]	Yes	
	Hazardous air pollutant		EPA 2007 42 USC 7412
	Cadmium compounds	Yes	
NIOSH	REL (10-hour TWA)		NIOSH 2005
	Cadmium[f]	Potential occupational carcinogens	
	Cadmium oxide	Potential occupational carcinogens	
	IDLH		
	Cadmium (as Cd)	9 mg/m^3	
	Cadmium oxide (as Cd)	9 mg/m^3	
	Target organs		
	Cadmium	Respiratory system, kidneys, prostate, and blood	
	Cadmium oxide	Respiratory system, kidneys, and blood	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Cadmium

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NIOSH	Category of pesticides		NIOSH 1992b
	Cadmium carbonate	Group II pesticide[g]	
	Cadmium chloride	Group I pesticide[h]	
	Cadmium sulfate	Group II pesticide[g]	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2007a 29 CFR 1910.1027
	Cadmium (as Cd)	5 µg/m^3	
	PEL (8-hour TWA) for shipyard industry		OSHA 2007b 29 CFR 1915.1027
	Cadmium (as Cd)	5 µg/m^3	
	PEL (8-hour TWA) for construction industry		OSHA 2007c 29 CFR 1926.1127
	Cadmium (as Cd)	5 µg/m^3	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2008b 40 CFR 116.4
	Cadmium chloride	Yes	
	Drinking water standards and health advisories		EPA 2006b
	Cadmium		
	1-day health advisory for a 10-kg child	0.04 mg/L	
	10-day health advisory for a 10-kg child	0.04 mg/L	
	DWEL	0.02 mg/L	
	Lifetime	0.005 mg/L	
	National primary drinking water standards		EPA 2003a
	Cadmium		
	MCL	0.005 mg/L	
	Public health goal	0.005 mg/L	
	National recommended water quality criteria		EPA 2006c
	Cadmium[i]		
	Freshwater CMC	2.0 µg/L	
	Freshwater CCC	0.25 µg/L	
	Saltwater CMC	40 µg/L	
	Saltwater CCC	8.8 µg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2008c 40 CFR 117.3
	Cadmium chloride	10 pounds	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Cadmium

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Toxic pollutants designated pursuant to Section 307(a)(1) of the Clean Water Act		EPA 2008h 40 CFR 401.15
	Cadmium and compounds	Yes	
c. Food			
FDA	Bottled drinking water		FDA 2007 21 CFR 165.110
	Cadmium	0.005 mg/L	
	EAFUS	No data	FDA 2008
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2007
	Cadmium	A2[j]	
	Cadmium compounds (as Cd)	A2[j]	
EPA	Carcinogenicity classification		IRIS 2008
	Cadmium	Group B1[k]	
	Inhalation unit risk		
	Cadmium	1.8×10^{-3} per µg/m^3	
	RfC		
	Cadmium	No data	
	RfD		
	Cadmium		
	Food	1×10^{-3} mg/kg-day	
	Water	5×10^{-4} mg/kg-day	
	RCRA waste minimization PBT priority chemical list		EPA 1998 63 FR 60332
	Cadmium	Yes	
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list		EPA 2008d 40 CFR 264, Appendix IX
	Cadmium	Yes	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2008e 40 CFR 302.4
	Cadmium	Yes[l,m]	
	Cadmium and compounds	Yes[n]	
	Cadmium chloride	Yes[o]	
	Reportable quantity		
	Cadmium	10 pounds	
	Cadmium and compounds	None[p]	
	Cadmium chloride	10 pounds	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Cadmium

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Superfund, emergency planning, and community right-to-know		
	Effective date of toxic chemical release reporting		EPA 2008g 40 CFR 372.65
	Cadmium	01/01/1987	
	Cadmium compounds[q]	01/01/1987	
	Extremely Hazardous Substances		EPA 2008f 40 CFR 355, Appendix A
	Cadmium oxide		
	Reportable quantity	100 pounds	
	Threshold planning quantity	100/10,000 pounds	
NTP	Carcinogenicity classification	No data	NTP 2005
	Cadmium and cadmium compounds	Known to be human carcinogens	

[a]Group 1: The agent is carcinogenic to humans.
[b]The guideline value is based on the prevention of a further increase of cadmium in agricultural soils, which is likely to increase the dietary intake.
[c]TWA based on effects other than cancer or odor/annoyance using an averaging time of 1 year.
[d]Respriable fraction.
[e]Higher current priority chemical for guideline development.
[f]REL applies to all cadmium compounds (as Cd).
[g]Group II pesticide: Contains the pesticides that pose as significant risk of carcinogenic, teratogenic, neurotoxic, or reproductive effects
[h]Group I pesticide: Contains the pesticides that pose as significant risk of adverse acute health effects at low concentrations
[i]The CMC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed briefly without resulting in an unacceptable effect. The CCC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed indefinitely without resulting in an unacceptable effect.
[j]A2: Suspected human carciongen.
[k]Group B1: Probable human carcinogen based on limited evidence of carcinogenicity in humans.
[l]Designated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water Act.
[m]No reporting of releases of this hazardous substance is required if the diameter of the pieces of the solid metal released is larger than 100 micrometers (0.004 inches).
[n]Designated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water Act and Section 112 of the Clean Air Act.
[o]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.
[p]Indicates that no reportable quantity is being assigned to the generic or broad class.
[q]Cadmium compounds: Includes any unique chemical substance that contains cadmium as part of that chemical's infrastructure.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CCC = Criterion Continuous Concentration; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CMC = Criteria Maximum Concentration; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PBT = persistant, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cadmium
CAS Numbers: 7440-43-9
Date: July, 2008
Profile Status: Second Pre-Public Comment Draft
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 16
Species: Rat

Minimal Risk Level: 0.03 [ ] mg/kg/day [X] μg Cd/m^3

Reference: NTP. 1995. Cadmium oxide administered by inhalation to F344/N rats and B6C3F1 mice. National Toxicology Program, U.S. Department of Health and Human Services, Research Triangle Park, NC.

Experimental design: Groups of five male and five female F344 rats were exposed to 0, 0.1, 0.3, 1, 3, or 10 mg cadmium oxide/m^3 (0, 0.088, 0.26, 0.88, 2.6, or 8.8 mg Cd/m^3) 6.2 hours/day, 5 days/week for 2 weeks. The mean MMAD of the cadmium oxide particles was 1.5 μm with a geometric standard deviation of 1.6–1.8. The animals were observed twice daily and weighed on days 1 and 8, and at termination. Other parameters used to assess toxicity included organ weights (heart, kidney, liver, lungs, spleen, testis, and thymus) and histopathological examination (gross lesions, heart, kidney, liver, lungs, tracheobronchial lymph nodes, and nasal cavity and turbinates).

Effect noted in study and corresponding doses: All rats in the 8.8 mg Cd/m^3 group died by day 6; no other deaths occurred. A slight decrease in terminal body weights was observed at 2.6 mg Cd/m^3; however, the body weights were within 10% of control weights. Significant increases in relative and absolute lung weights were observed at 0.26 (males only), 0.88, and 2.6 mg Cd/m^3. Histological alterations were limited to the respiratory tract and consisted of alveolar histiocytic infiltrate and focal inflammation in alveolar septa in all rats exposed to ≥0.088 mg Cd/m^3, necrosis of the epithelium lining alveolar ducts in all rats exposed to ≥0.26 mg Cd/m^3, tracheobronchiolar lymph node inflammation at ≥0.88 mg Cd/m^3 (incidences in the 0, 0.088, 0.26, 0.88, 2.6, and 8.8 mg Cd/m^3 groups were 0/3, 0/5, 5/5, 5/5, and 3/4 in males and 0/4, 1/5, 1/5, 3/5, 5/5, and 3/5 in females), degeneration of the nasal olfactory epithelium at 0.88 mg Cd/m^3 (0/5, 0/5, 0/5, 2/5, 5/5, and 5/5 in males and 0/5, 0/5, 0/5, 4/5, 4/5, and 4/4 in females) and inflammation (0/5. 0/5. 0/5, 1/5, 5/5, and 3/5 in males and 0/5, 0/5, 0/5, 0/5, 4/5, and 3/4 in females) and metaplasia (0/5. 0/5. 0/5, 1/5, 0/5, and 5/5 in males and 0/5, 0/5, 0/5, 0/5, 4/5, and 4/4 in females)of the nasal respiratory epithelium at 2.6 mg Cd/m^3.

Dose and end point used for MRL derivation: The LOAEL of 0.088 mg Cd/m^3 was selected as the point of departure for derivation of the MRL; benchmark dose analysis was considered; however, the data were not suitable for benchmark dose analysis because the incidence data for alveolar histiocytic infiltration do not provide sufficient information about the shape of the dose-response relationship below the 100% response level.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

The $LOAEL_{HEC}$ was calculated using the equations below.

$$LOAEL_{HEC} = LOAEL_{ADJ} \times RDDR$$

The duration-adjusted LOAEL ($LOAEL_{ADJ}$) was calculated as follows:

$$LOAEL_{ADJ} = 0.088 \text{ mg Cd/m}^3 \times 6.2 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days}$$
$$LOAEL_{ADJ} = 0.016 \text{ mg Cd/m}^3$$

The regional deposited dose ratio (RDDR) for the pulmonary region of 0.617 was calculated with EPA's RDDR calculator (EPA 1994a) using the final body weight of 0.194 kg for the male rats exposed 0.088 mg Cd/m^3, the reported MMAD of 1.5 µm and the midpoint of the reported range of geometric standard deviations (1.7)

$$LOAEL_{HEC} = 0.016 \text{ mg Cd/m}^3 \times 0.617$$
$$LOAEL_{HEC} = 0.01 \text{ mg Cd/m}^3$$

Was a conversion used from intermittent to continuous exposure? Yes (see above)

Other additional studies or pertinent information that lend support to this MRL: The acute toxicity of airborne cadmium, particularly cadmium oxide fumes, was first recognized in the early 1920s and there have been numerous case reports of cadmium workers dying after brief exposures to presumably high concentrations of cadmium fumes (European Chemicals Bureau 2007). The initial symptoms, similar to those observed in metal fume fever, are usually mild but rapidly progress to severe pulmonary edema and chemical pneumonitis. Persistent respiratory effects (often lasting years after the exposure) have been reported in workers surviving these initial effects. There are limited monitoring data for these human reports; however, Elinder (1986b) estimated that an 8-hour exposure to 1–5 mg/m^3 would be immediately dangerous.

Animal studies support the findings in humans that acute exposure to cadmium results in lung damage. Single exposures to approximately 1–10 mg Cd/m^3 as cadmium chloride or cadmium oxide resulted in interstitial pneumonitis, diffuse alveolitis with hemorrhage, focal interstitial thickening, and edema (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart 1986; Henderson et al. 1979; Palmer et al. 1986). Repeated exposure to 6.1 mg Cd/m^3 1 hour/day for 5, 10, or 15 days resulted in emphysema in rats (Snider et al. 1973). At lower concentrations of 0.4–0.5 mg Cd/m^3 as cadmium oxide for 2–3 hours (Buckley and Bassett 1987b; Grose et al. 1987) or 0.17 mg Cd/m^3 as cadmium chloride 6 hours/day for 10 days (Klimisch 1993) resulted in mild hypercellularity and increases in lung weight. Alveolar histiocytic infiltration and focal inflammation and minimal fibrosis in alveolar septa were observed in rats exposed to 0.088 mg Cd/m^3 as cadmium oxide 6.2 hours/day, 5 days/week for 2 weeks (NTP 1995); in similarly exposed mice, histiocytic infiltration was observed at 0.088 mg Cd/m^3 (NTP 1995). At similar concentrations (0.19 or 0.88 mg Cd/m^3as cadmium chloride), decreases in humoral immune response were observed in mice exposed for 1–2 hours (Graham et al. 1978; Krzystyniak et al. 1987). Other effects that have been reported in animals acutely exposed to cadmium include erosion of the stomach, decreased body weight gain, and tremors in rats exposed to 132 mg Cd/m^3

as cadmium carbonate for 2 hours (Rusch et al. 1986) and weight loss and reduced activity in rats exposed to 112 mg Cd/m^3 as cadmium oxide for 2 hours (Rusch et al. 1986).

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cadmium
CAS Numbers: 7440-43-9
Date: July, 2008
Profile Status: Second Pre-Public Comment Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 63
Species: Human

Minimal Risk Level: 0.01 [ ] mg/kg/day [X] µg Cd/m^3

Reference: Buchet JP, Lauwerys R, Roels H, et al. 1990. Renal effects of cadmium body burden of the general population. Lancet 336:699-702.

Järup L, Hellstrom L, Alfven T, et al. 2000. Low level exposure to cadmium and early kidney damage: The OSCAR study. Occup Environ Med 57(10):668-672.

Suwazono Y, Sand S, Vahter M, et al. 2006. Benchmark dose for cadmium-induced renal effects in humans. Environ Health Perspect 114:1072-1076.

Experimental design: As detailed in the chronic oral MRL worksheet, a meta-analysis of select environmental exposure dose-response studies examining the relationship between urinary cadmium and the prevalence of elevated levels of biomarkers of renal function in environmentally exposed populations was conducted; for the inhalation MRL, the meta-analysis also included dose-response data from three occupational exposure studies (Chen et al. 2006a, 2006b; Järup and Elinder 1994; Roels et al. 1993). The meta-analysis was used to establish a point of departure for the urinary cadmium-response relationship and pharmacokinetic models (ICRP 1994; Kjellström and Nordberg 1978) were used to predict cadmium air concentrations.

Dose and end point used for MRL derivation: Analysis of the available environmental exposure studies and occupational exposure studies resulted in an estimation of a urinary cadmium level that would result in a 10% increase in the prevalence of β2-microglobulin proteinuria (UCD_{10}). The lowest UCD_{10} (1.34 µg/g creatinine) was estimated from the European environmental exposure studies (Buchet et al. 1990; Järup et al. 2000; Suwazono et al. 2006); the UCD_{10} values from the occupational exposure studies were 7.50 µg/g creatinine for the European cohorts (Järup and Elinder 1994; Roels et al. 1993) and 4.58 µg/g creatinine for the Chinese cohort (Chen et al. 2006a, 2006b). The UCD_{10} from the environmental exposure studies was selected as the basis of the MRL. The 95% lower confidence limit on this value ($UCDL_{10}$) of 0.5 µg/g creatinine was used as the point of departure for the MRL.

[ ] NOAEL [ ] LOAEL [X] $UCDL_{10}$

Deposition and clearance of inhaled cadmium oxide and cadmium sulfide particles were modeled using the ICRP Human Respiratory Tract Model (ICRP 1994). The ICRP model simulates deposition, retention, and absorption of inhaled cadmium particles of specific aerodynamic diameters, when specific parameters for cadmium clearance are used in the model (ICRP 1980). Cadmium-specific parameters represent categories of solubility and dissolution kinetics in the respiratory tract (e.g., slow, S; moderate, M; or fast, F). Cadmium compounds are classified as follows: oxides and hydroxides, S; sulfides, halides and nitrates, M; all other, including chloride salts, F.

Inhalation exposures (μg/m^3) to cadmium oxide or cadmium sulfide aerosols having particle diameters of 1, 5, or 10 μg (AMAD) were simulated using the ICRP model. Predicted mass transfers of cadmium from the respiratory tract to the gastrointestinal tract (i.e., mucocilliary transport) and to blood (i.e., absorption) were used as inputs to the gastrointestinal and blood compartments of the Kjellström-Nordberg pharmacokinetic model (1978) to simulate the kidney and urinary cadmium levels that correspond to a given inhalation exposure.

An airborne cadmium concentration of 1.8–2.4 μg/m^3 as cadmium oxide or 1.2–1.4 μg/m^3 as cadmium sulfide would result in a urinary cadmium level of 0.5 μg/g creatinine, assuming that the air was the only source of cadmium. This assumption is not accurate because the diet is a significant contributor to the cadmium body burden. Thus, inhalation exposures were combined with ingestion intakes to estimate an internal dose in terms of urinary cadmium. The age-weighted average intakes of cadmium in nonsmoking males and females in the United States are 0.35 and 0.30 μg Cd/kg/day, respectively (0.32 μg/kg/day for males and females combined) (Choudhury et al. 2001).

Based on the relationship predicted between chronic inhalation exposures to cadmium sulfide (AMAD=1 μm) and oral intakes that yield the same urinary cadmium level, exposure to an airborne cadmium concentration of 0.1 μg/m^3 and a dietary intake of 0.3 μg/kg/day would result in a urinary cadmium level of 0.5 μg/g creatinine.

Uncertainty Factors and Modifying Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans with dosimetric adjustment
[X] 3 for human variability

The uncertainty factor of 3 for human variability was used to account for the possible increased sensitivity of diabetics (Åkesson et al. 2005; Buchet et al. 1990).

[X] modifying factor of 3

The modifying factor of 3 was used to account for the lack of adequate human data that could be used to compare the relative sensitivities of the respiratory tract and kidneys.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? The pharmacokinetic model assumes continuous exposure.

Other additional studies or pertinent information that lend support to this MRL: Numerous studies examining the toxicity of cadmium in workers have identified the respiratory tract and the kidney as sensitive targets of toxicity. A variety of respiratory tract effects have been observed in cadmium workers including respiratory symptoms (e.g., dyspnea, coughing, wheezing), emphysema, and impaired lung function. However, many of these studies did not control for smoking, and thus, the role of cadmium in the induction of these effects is difficult to determine. Impaired lung function was reported in several studies that controlled for smoking (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976); other studies have not found significant alterations (Edling et al. 1986). The observed alterations include an increase in residual volume in workers exposed to air concentrations of cadmium

fumes ranging from 0.008 (in 1990) to 1.53 mg/m^3 (in 1975) (mean urinary cadmium level in the workers was 4.3 μg/L) (Cortona et al. 1992); alterations in several lung function parameters (e.g., forced expiratory volume, transfer factor, transfer coefficient) in workers exposed to 0.034–0.156 mg/m^3 (Davison et al. 1988); and decreased force vital capacity in workers exposed to >0.2 mg/m^3 (Smith et al. 1976). Additionally, Chan et al. (1988) found significant improvements in several parameters of lung function of workers following reduction or cessation of cadmium exposure.

The renal toxicity of cadmium in workers chronically exposed to high levels of cadmium is well established. Observed effects include tubular proteinuria (increased excretion of low molecular weight proteins), decreased resorption of other solutes (increased excretion of enzymes such as N-acetyl-β-glucosaminidase (NAG), amino acids, glucose, calcium, inorganic phosphate), evidence of increased glomerular permeability (increased excretion of albumin), increased kidney stone formation, and decreased glomerular filtration rate. The earliest sign of cadmium-induced kidney damage is an increase in urinary levels of low molecular weight proteins (particularly, β2-microglobulin, retinol binding protein, and human complex-forming glycoprotein [pHC]) in cadmium workers, as compared to levels found in a reference group of workers or the general population (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985a; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Shaikh et al. 1987; Toffoletto et al. 1992; Verschoor et al. 1987). Significant alterations in the prevalence of low molecular weight proteinuria among cadmium workers has been observed at urinary cadmium levels of 1.5 μg/g creatinine and higher (Chen et al. 2006a; Elinder et al. 1985a; Jakubowski et al. 1987; Järup and Elinder 1994).

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cadmium
CAS Numbers: 7440-43-9
Date: May, 2008
Profile Status: First Draft Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 33
Species: Rat

Minimal Risk Level: 0.5 [X] µg Cd/kg/day [ ] ppm

Reference: Brzóska MM, Moniuszko-Jakoniuk J. 2005d. Disorders in bone metabolism of female rats chronically exposed to cadmium. Toxicol Appl Pharmacol 202(1):68-83.

Brzóska MM, Majewska K, Moniuszko-Jakoniuk J. 2005a. Bone mineral density, chemical composition and biomechanical properties of the tibia of female rats exposed to cadmium since weaning up to skeletal maturity. Food Chem Toxicol 43(10):1507-1519.

Brzóska MM, Majewska K, Moniuszko-Jakoniuk J. 2005c. Weakness in the mechanical properties of the femur of growing female rats exposed to cadmium. Arch Toxicol 79(5):277-288.

Experimental design: Groups of 40 3-week-old female Wistar rats were exposed to 0, 1, 5, or 50 mg Cd/L as cadmium chloride in drinking water for 12 months. The investigators noted that cadmium intakes were 0.059–0.219, 0.236–1.005, and 2.247–9.649 mg Cd/kg/day in the 1, 5, and 50 mg/L groups, respectively. Using cadmium intake data presented in a figure, cadmium intakes of 0.2, 0.5, and 4 mg Cd/kg/day were estimated. Bone mineral density, bone mineral concentration, and mineralization area of the lumbar spine, femur and total skeleton (bone mineral density only) were assessed after 3, 6, 9, or 12 months of exposure. The mechanical properties of the femur and tibia were evaluated after 12 months of exposure. Markers for bone resorption (urinary and serum levels of C-terminal cross-linking telopeptide of type I collagen [CTX]) and bone formation (serum osteocalcin, total alkaline phosphatase, and cortical bone and trabecular bone alkaline phosphatase), and serum and urinary levels of calcium were also measured at 3, 6, 9, and 12 months.

Effect noted in study and corresponding doses: No significant alterations in body weight gain or food and water consumption were observed. Significant decreases in total skeletal bone mineral density was observed at ≥0.2 mg Cd/kg/day; the decrease was significant after 3 months in the 4 mg Cd/kg/day group, after 6 months in the 0.5 mg Cd/kg/day group, and after 9 months in the 0.2 mg Cd/kg/day group. Significant decreases in whole tibia and diaphysis bone mineral density were observed at ≥0.2 mg Cd/kg/day after 12 months of exposure. At 0.2 mg Cd/kg/day, bone mineral density was decreased at the proximal and distal ends of the femur after 6 months of exposure; diaphysis bone mineral density was not affected. At 0.5 mg Cd/kg/day, bone mineral density was decreased at the femur proximal and distal ends after 3 months of exposure and diaphysis bone mineral density after 6 months of exposure. At 4 mg Cd/kg/day decreases in femoral proximal, distal, and diaphysis bone mineral density were decreased after 3 months of exposure. Similarly, bone mineral density was significantly decreased in the lumbar spine in the 0.2 and 0.5 mg Cd/kg/day groups beginning at 6 months and at 3 months in the 4 mg Cd/kg/day group. Significant decreases in the mineralization area were observed in the femur and lumbar spine of rats exposed to 4 mg Cd/kg/day; lumbar spine bone mineral area was also affected at 0.5 mg Cd/kg/day. Significant decreases in tibia weight and length were observed at 4 mg Cd/kg/day. In tests of the mechanical properties of the tibia diaphysis, significant alterations in ultimate load, yield load, and

displacement at load were observed at ≥0.2 mg Cd/kg/day; work to fracture was also significantly altered at 4 mg Cd/kg/day. In the mechanical properties compression tests of the tibia, significant alterations were observed in ultimate load, ultimate load, and stiffness at 0.2 mg Cd/kg/day; displacement at yield and work to fracture at ≥0.5 mg Cd/kg/day; and displacement at ultimate at 4 mg Cd/kg/day. Multiple regression analysis showed that the cadmium-induced weakness in bone mechanical properties of the tibia was primarily due to its effects on bone composition, particularly the non-organic components, organic components, and the ratio of the ash weight to organic weight. The mechanical properties of the femur were strongly influenced by the bone mineral density (at the whole bone and diaphysis). A significant decrease in femur length was observed at 6 months of exposure to ≥0.2 mg Cd/kg/day; however, decreases in length were not observed at other time points in the 0.2 or 0.5 mg Cd/kg/day groups. Femur weight was significantly decreased at 4 mg Cd/kg/day. In tests of mechanical properties of the femoral neck and distal, decreases in yield load, ultimate load, displacement at ultimate, work to fracture (neck only), and stiffness (distal only) were observed at ≥0.2 mg Cd/kg/day. For the femoral diaphysis, significant alterations were observed for yield load, displacement at yield, and stiffness at ≥0.2 mg Cd/kg/day. Significant decreases in osteocalcin concentrations were observed in all cadmium groups during the first 6 months of exposure, but not during the last 6 months. Decreases in total alkaline phosphatase levels at 4 mg Cd/kg/day, trabecular bone alkaline phosphatase at 0.2 mg Cd/kg/day, and cortical bone alkaline phosphatase at 4 mg Cd/kg/day were observed. CTX was decreased at ≥0.2 mg Cd/kg/day. Total urinary calcium and fractional excretion of calcium were increased at ≥0.2 mg Cd/kg/day.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] $BMDL_{sd1}$

At the lowest dose tested, 0.2 mg Cd/kg/day, a number of skeletal alterations were observed including decreases in bone mineral density in the lumbar spine, femur, and tibia, alterations in the mechanical properties of the femur and tibia, decreases in osteocalcin levels, decreases in trabecular bone alkaline phosphatase, and decreases in CTX. Of these skeletal end points, the decrease in bone mineral density was selected as the critical effect because Brzóska et al. (2005a, 2005c) demonstrated that the bone mineral density was a stronger predictor of femur and tibia strength and the risk of fractures.

Available continuous models in the EPA Benchmark Dose Software (version 1.4.1c) were fit to data (Table A-1) for changes in bone mineral density of the femur and lumbar spine in female rats resulting from exposure to cadmium in the drinking water for 6, 9, or 12 months (Brzóska and Moniuszko-Jakoniuk 2005d). The BMD and the 95% lower confidence limit (BMDL) is an estimate of the doses associated with a change of 1 standard deviation from the control. The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest Akaike information criterion (AIC) for the fitted model is selected for BMD derivation. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the benchmark dose software (BMDS) to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the tests for both constant and non-constant variance are negative, then the data set is considered not to be suitable for BMD modeling.

Table A-1. Data Sets for Changes in Mineral Bone Density of the Femur and Lumbar Spine in Female Rats Exposed to Cadmium in Drinking Water for 6, 9, or 12 Months

	Dose (mg Cd/kg/day)			
Dataset[a]	0	0.2	0.5	4
Femur[b]				
6 month	329.7±3.6	317.6±2.7[c]	308.5±3.4[d]	303.4±3.4[e]
9 month	343.8±3.1	328.2±2.9[d]	322.8±3.0[e]	310.4±3.4[e]
12 month	354.3±3.7	338.0±1.9[d]	330.9±3.1[d]	318.7±3.4[e]
Lumbar spine[b]				
6 month	272.0±2.4	263.4±2.6[c]	258.3±2.7[d]	249.5±2.9[e]
9 month	282.4±2.3	271.8±1.6[d]	267.8±1.8[e]	259.5±2.7[e]
12 month	286.1±2.3	275.5±1.9[d]	269.1±1.9[e]	257.1±3.0[e]

[a]n=10
[b]mean±SE; standard errors were transformed to standard deviations for benchmark dose modeling via a function in the BMD software.
[c]Significantly different ($p \leq 0.05$) from the control group
[d]Significantly different ($p \leq 0.01$) from the control group
[e]Significantly different ($p \leq 0.001$) from the control group

Source: Brzóska and Moniuszko-Jakoniuk 2005d

The potential points of departures derived from the best fitting models for each dataset are summarized in Table A-2.

Table A-2. Summary of BMDs and BMDLs From the Best Fitting Models Predicting Changes in Bone Mineral Density in Female Rats After Cadmium Exposure From Drinking Water

Exposure Period (months)	Best-fitting model	Number of doses	BMD_{sd1}[a] (mg Cd/kg/day)	$BMDL_{sd1}$[a] (mg Cd/kg/day)
Femur				
6	Linear	3	0.24	0.17
9	Hill	4	0.11	0.05
12	Hill	4	0.09	0.05
Lumbar spine				
6	Hill	4	0.19	0.08
9	Hill	4	0.11	0.05
12	Hill	4	0.12	0.07

[a]BMDs and BMDLs from continuous data are associated with a 1 standard deviation change from the control.

The $BMDL_{sd1}$ of 0.05 mg Cd/kg/day estimated from the 9-month lumbar spine data set was selected as the point of departure for the MRL. In young female rats, the process of intense bone formation occurs during the first 7 months of life (the first 6 months of exposure in this study); thereafter, the increase in bone mineral density slows. In the lumbar spine of the control group, the changes in bone mineral density at 3–6 months, 6–9 months, and 9–12 months were 15, 4, and 1%, respectively. Thus, the 9-month data may best reflect the effect of cadmium on bone mineral density during the period of rapid skeletal growth. The lumbar spine data was selected over the femur data set because trabecular bone, which is abundant in the spine, appears to be more susceptible to cadmium toxicity than cortical bone.

For the 9-month lumbar spine data set, the simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. The Hill model was the only model that provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-3). Using the constant-variance Hill model, the BMD_{sd1} and $BMDL_{sd1}$ are 0.11 mg/kg and 0.05 mg Cd/kg/day, respectively (Figure A-1).

Table A-3. Model Predictions for Changes in Bone Mineral Density of the Lumbar Spine in Female Rats Exposed to Cd in Drinking Water for 9 Months

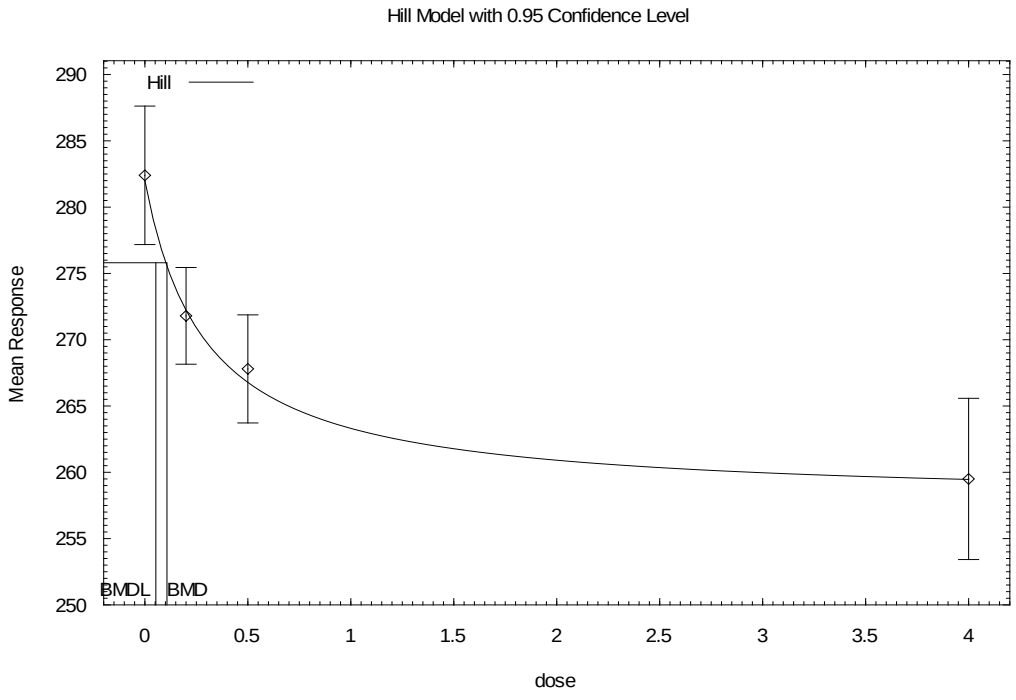
Model[a]	Variance p-value[b]	p-Value for the means[b]	AIC	BMD_{sd1} (mg Cd/kg/day)	$BMDL_{sd1}$ (mg Cd/kg/day)
Linear[c]	0.36	0.00	211.92	1.93	1.42
Polynomial (1-degree)[c]	0.36	0.00	211.92	1.93	1.42
Polynomial (2-degree)[c]	0.36	0.00	211.92	1.93	1.42
Polynomial (3-degree)[c]	0.36	0.00	211.92	1.93	1.42
Power	0.36	0.00	211.92	1.93	1.42
Hill	**0.36**	**0.60**	**197.21**	**0.11**	**0.05**

[a]Constant variance assumed for all models
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Restriction = non-positive

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; p = p value from the Chi-squared test; Std1 = a 1 standard deviation change from the control.

Source: Brzóska and Moniuszko-Jakoniuk 2005d

Figure A-1. Predicted and Observed Incidence of Changes in Lumbar Spine Bone Mineral Density in Female Rats Exposed to Cadmium in Drinking Water for 9 Months (Brzóska and Moniuszko-Jakoniuk 2005d)*



*BMDs and BMDLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg Cd/kg/day.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Investigators estimated doses based on body weight and water consumption.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: There are limited data on the toxicity of cadmium in humans following intermediate-duration exposure. Numerous animal studies have examined the systemic, immunological, neurological, reproductive, and developmental toxicity of cadmium. The most sensitive systemic effect following intermediate-duration oral exposure to cadmium appears to be damage to growing bone. Exposure to 0.2 mg Cd/kg/day as cadmium chloride in drinking water for 3–12 months resulted decreases in bone mineral density, impaired mechanical strength of the lumbar spine, tibia, and femur bones, increased bone turnover, and increased incidence of deformed or fractured lumbar spine bone in young female rats (3 weeks of age at study initiation) (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c); similar findings were observed in young male rats exposed to 0.5 mg Cd/kg/day for up to 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b). Decreases in bone strength were also observed in young rats exposed to 0.8 mg Cd/kg/day as cadmium chloride in drinking water for 4 weeks (Ogoshi et al. 1989); however, no skeletal effects were observed in adult or elderly female rats exposed to doses >20 mg Cd/kg/day for 4 weeks (Ogoshi et al. 1989).

Renal effects have been observed at higher doses than the skeletal effects. Vesiculation of the proximal tubules was observed in rats exposed to 1.18 mg Cd/kg/day as cadmium chloride in drinking water for 40 weeks (Gatta et al. 1989). At approximately 3–8 mg Cd/kg/day, proteinuria, tubular necrosis, and decreased renal clearance were observed in rats (Cha 1987; Itokawa et al. 1974; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Prigge 1978a). Liver necrosis and anemia (Cha 1987; Groten et al. 1990; Kawamura et al. 1978) were observed at similar cadmium doses.

A number of developmental effects have been observed in the offspring of rats exposed to cadmium during gestation and lactation. Decreases in glomerular filtration rates and increases in urinary fractional excretion of phosphate, magnesium, potassium, sodium, and calcium were observed in 60-day-old offspring of rats administered via gavage 0.5 mg Cd/kg/day on gestation days 1–21 (Jacquillet et al. 2007). Neurodevelopmental alterations have also been observed at the low maternal doses. Delays in the development of sensory motor coordination reflexes and increased motor activity were observed at 0.706 mg Cd/kg/day (gestation days 1–21) (Ali et al. 1986), decreased motor activity at 0.04 mg Cd/kg/day (5–8 weeks of pre-gestation exposure, gestation days 1–21) (Baranski et al. 1983), decreased ambulation and rearing activity and altered ECG at 14 mg Cd/kg/day (gestation days 5–15, lactation days 2–28, postnatal days 1–56) (Desi et al. 1998) or 7 mg Cd/kg/day (F_2 and F_3 generations) (Nagymajtenyi et al. 1997) have been observed. Decreases in pup body weight were observed at ≥5 mg Cd/kg/day (Baranski 1987; Gupta et al. 1993; Kostial et al. 1993; Pond and Walker 1975) and decreases in fetal body weight or birth weight were observed at ≥2.4 mg Cd/kg/day (Petering et al. 1979; Sorell and Graziano 1990; Webster 1978; Sutou et al. 1980). Another commonly reported developmental effect was alterations in hematocrit levels or anemia in the offspring of animals exposed to ≥1.5 mg Cd/kg/day

(Kelman et al. 1978; Baranski 1987; Webster 1978). Increases in the occurrence of malformations or anomalies is limited to a study by Sutou et al. (1980), which reported a significant delay in ossification in rats exposed to 10 mg Cd/kg/day.

The animal studies identify several sensitive targets of toxicity following intermediate-duration exposure to cadmium; these include skeletal mineralization in young female rats exposed for at least 3 months to 0.2 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c), decreased glomerular filtration in young rats exposed during gestation to maternal doses of 0.5 mg Cd/kg/day (Jacquillet et al. 2007), and neurodevelopmental effects following gestational exposure to 0.04 mg Cd/kg/day (Baranski et al. 1983). Although the Baranski et al. (1983) study reported the lowest LOAEL, it was not selected as the principal study for derivation of an intermediate-duration MRL. For locomotor activity, a significant decrease in activity was observed in female offspring exposed to 0.04, 0.4, and 4 mg Cd/kg/day, as compared to controls; however, no significant differences were found between the cadmium groups despite the 100-fold difference in doses. Locomotor activity was also decreased in males exposed to 0.4 or 4 mg Cd/kg/day. For the rotorod test, a significant decrease in the length of time the rat stayed on the rotorod was observed in males exposed to 0.04 and 0.4 mg Cd/kg/day, but not to 4 mg Cd/kg/day and in females exposed to 0.4 and 4 mg Cd/kg/day; no differences between the cadmium groups were observed in the males and females. The results were poorly reported and the investigators did not explain the lack of dose-response of the effects or the discrepancy between genders.

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cadmium
CAS Numbers: 7440-43-9
Date: July, 2008
Profile Status: Second Pre-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 105
Species: Human

Minimal Risk Level: 0.1 [X] µg Cd/kg/day [ ] µg Cd/m^3

Reference: Buchet JP, Lauwerys R, Roels H, et al. 1990. Renal effects of cadmium body burden of the general population. Lancet 336:699-702.

Järup L, Hellstrom L, Alfven T, et al. 2000. Low level exposure to cadmium and early kidney damage: The OSCAR study. Occup Environ Med 57(10):668-672.

Suwazono Y, Sand S, Vahter M, et al. 2006. Benchmark dose for cadmium-induced renal effects in humans. Environ Health Perspect 114:1072-1076.

Experimental design: ATSDR conducted a meta-analysis of select environmental exposure dose-response studies examining the relationship between urinary cadmium and the prevalence of elevated levels of biomarkers of renal function (Buchet et al. 1990; Järup et al. 2000; Jin et al. 2004c; Kobayashi et al. 2006; Shimizu et al. 2006; Suwazono et al. 2006; Wu et al. 2001). The studies were selected based on the following qualitative criteria: (1) the study measured an urinary cadmium as indicator of internal dose; (2) the study measured reliable indicators of low molecular weight (LMW) proteinuria; (3) a dose-response relationship was reported in sufficient detail so that the dose-response function could be reproduced independently; (4) the study was of reasonable size to have provided statistical strength to the estimates of dose-response model parameters (i.e., most studies selected included several hundred to several thousand subjects); and (5) major co-variables that might affect the dose-response relationship (e.g., age, gender) were measured or constrained by design and included in the dose-response analysis. No attempt was made to weight selected studies for quality, statistical power, or statistical uncertainty in dose-response parameters. Studies using a cut-off value for β2-microglobulin of ≥1,000 µg/g creatinine were eliminated from the analysis based on the conclusions of Bernard et al. (1997) that urinary β2-microglobulin levels of 1,000–10,000 µg/g creatinine were indicative of irreversible tubular proteinuria, which may lead to an age-related decline in glomerular filtration rate. Additionally, an attempt was made to avoid using multiple analyses of the same study population.

The individual dose-response functions from each study were implemented to arrive at estimates of the internal dose (urinary cadmium expressed as µg/g creatinine) corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (urinary cadmium dose, UCD_{10}). Estimates were derived from the seven environmental exposure studies listed above. When available, male and female data were treated separately; thus, 11 dose-response relationships were analyzed. For studies that did not report the UCD_{10}, the value was estimated by iteration of the reported dose response relationship for varying values of urinary cadmium, until an excess risk of 10% was achieved. For studies that reported the dose-response relationship graphically, but did not report the actual dose-response function, a function was derived by least squares fitting based on data from a digitization of the graphic

Dose and end point used for MRL derivation: Aggregate UCD_{10} estimates and the estimates stratified by location (i.e., Europe, Japan, China) are presented in Table A-4. The lowest UCD_{10} (1.34 µg/g creatinine) was estimated from the European database; and the 95% lower confidence limit on this UCD_{10} ($UCDL_{10}$) of 0.5 µg/g creatinine was considered as the point of departure for the MRL.

Table A-4. Estimates of the UCD_{10} and Cadmium Intake from Environmental Exposure Dose-Response Studies

	UCD_{10}[a] (µg Cd/g creatinine)	Cadmium intake[b] (µg/kg/day)	
		Females	Males
Europe (n=4)[c]			
Mean	1.34	0.97	2.24
Median	—	—	—
95% CI	0.50, 2.18	0.33, 1.75	0.70, 3.94
Japan (n=4)[d]			
Mean	5.23	4.59	10.1
Median	—	—	—
95% CI	4.24, 6.21	3.67, 5.49	8.07, 12.0
China (n=3)[e]			
Mean	9.55	8.60	18.8
Median	—	—	—
95% CI	2.96, 16.1	2.48, 14.7	5.51, 31.9
All (n=11)			
Mean	4.99	4.37	9.58
Median	4.20	3.63	7.99
95% CI	1.44, 6.60	1.06, 5.86	2.45, 12.8

[a]Estimates of urinary cadmium level corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (UCD_{10})
[b]UCD was transformed into estimates of chronic cadmium intake that would result in the UCD at age 55 using a modification (Choudhury et al. 2001; Diamond et al. 2003) of the Kjellström and Nordberg (1978) model.
[c]Dose-response function data from Buchet et al. (1990), Suwazono et al. (2006), and Järup et al. (2000); dose response data from males and females in the Buchet et al. (1990) study were treated separately.
[d]Dose-response function data from Kobayashi et al. (2006) and Shimizu et al. (2006); dose response data from males and females were treated separately.
[e]Dose-response function data from Jin et al. (2004c) and Wu et al. (2001); dose response data from males and females in the Jin et al. (2004c) study were treated separately.

UCD = urinary cadmium dose

[ ] NOAEL [ ] LOAEL [X] $UCDL_{10}$

The $UCDL_{10}$ of 0.5 µg/g creatinine was transformed into estimates of chronic cadmium intake (expressed as µg/kg/day) that would result in the $UCDL_{10}$ at age 55 (approximate age of peak cadmium concentration in the renal cortex associated with a constant chronic intake). The dose transformations were achieved by simulation using a modification of the Kjellström and Nordberg (1978) model. The following modifications (Choudhury et al. 2001; Diamond et al. 2003) were made to the model: (1) the equations describing intercompartmental transfers of cadmium were implemented as differential equations in Advanced Computer Simulation Language (acslXtreme, version 2.4.0.9); (2) growth algorithms for males

and females and corresponding organ weights (O'Flaherty 1993) were used to calculate age-specific cadmium concentrations from tissue cadmium masses; (3) the cadmium concentration in renal cortex (RC, μg/g) was calculated as follows:

$$RC = 1.5 \cdot \frac{K}{KW}$$

where K is the age-specific renal cadmium burden (μg) and KW is the age-specific kidney wet weight (g) (Friberg et al. 1974)

(4) the rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was calculated from the relationship between lean body mass (LBM) and Cr_{ur}); and (5) absorption of ingested cadmium was assumed to be 5% in males and 10% in females. The rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was estimated from the relationship between LBM (kg) and Cr_{ur}:

$$LBM = 27.2 \cdot Cr_{ur} + 8.58$$

where the constants 27.2 and 8.58 are the sample size-weighted arithmetic mean of estimates of these variables from eight studies reported in (Forbes and Bruining 1976). Lean body mass was estimated as follows (ICRP 1981):

$$LBM = BW \cdot 0.85, adult\ females$$
$$LBM = BW \cdot 0.88, adult males$$

where the central tendency for adult body weight for males and females were assumed to be 70 and 58 kg for adult European/American males and females, respectively.

Dose units expressed as cadmium intake (μg/kg/day), urinary cadmium excretion (μg/g creatinine), or kidney tissue cadmium (μg/g cortex) were interconverted by iterative pharmacokinetic model simulations of constant intakes for the life-time to age 55 years, the age at which renal cortex cadmium concentrations are predicted to reach their peak when the rate of intake (μg/kg/day) is constant.

The dietary cadmium intakes which would result in urinary cadmium levels of 1.34 and 0.5 μg/g creatinine (UCD_{10} and $UCDL_{10}$) are 0.97 and 0.33 μg/kg/day in females and 2.24 and 0.70 μg/kg/day in males.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 3 for human variability

The UCD is based on several large-scale environmental exposure studies that likely included sensitive subpopulations; however, there is concern that individuals with diabetes may be especially sensitive to the renal toxicity of cadmium (Åkesson et al. 2005; Buchet et al. 1990) and diabetics were excluded from a number of human studies, and thus, an uncertainty factor of 3 was used.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: The results of numerous studies of environmentally exposed populations provide strong evidence that the kidney, and possibly bone, is the most sensitive target of toxicity following chronic exposure to cadmium. Most of the studies have focused on subclinical alterations of kidney function, as measured by the urinary excretion of several biomarkers including low molecular weight proteins (β2-microglobulin, pHC, retinol binding protein), intracellular tubular enzymes (NAG), amino acids, high molecular weight proteins (albumin), and electrolytes (potassium, sodium, calcium). Significant associations between urinary cadmium levels and an increased prevalence of abnormal levels of these biomarkers have been found in populations living in areas with moderate or high cadmium pollution or low cadmium pollution (Buchet et al. 1990; Cai et al. 1990, 1992, 1998, 2001; Hayano et al. 1996; Horiguchi et al. 2004; Ishizaki et al. 1989; Izuno et al. 2000; Järup et al. 2000; Jin et al. 2002, 2004a, 2004c; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002a; Monzawa et al. 1998; Nakashima et al. 1997; Nogawa et al. 1989; Noonan et al. 2002; Nordberg et al. 1997; Olsson et al. 2002; Oo et al. 2000; Osawa et al. 2001; Roels et al. 1981b; Suwazono et al. 2006; Teeyakasem et al. 2007; Trzcinka-Ochocka et al. 2004; Uno et al. 2005; Yamanaka et al. 1998; Wu et al. 2001). Increases in the prevalence of abnormal biomarker levels appear to be the most sensitive indicator of cadmium toxicity and alterations have been observed at urinary cadmium levels ranging from 1 μg/g creatinine (Järup et al. 2000) to 9.51 μg/g creatinine (Jin et al. 2004a).

Several studies have examined the possible association between exposure to cadmium and bone effects. Significant associations between urinary cadmium levels and an increased risk of bone fractures at urinary cadmium levels of ≥0.7 μg/g creatinine (Alfvén et al. 2004; Staessen et al. 1999; Wang et al. 2003), increased risk of osteoporosis at urinary cadmium levels of ≥1.5 μg/g creatinine (Alfvén et al. 2000; Jin et al. 2004b; Wang et al. 2003), and decreased bone mineral density at urinary cadmium levels of ≥0.6 μg/g creatinine (Nordberg et al. 2002; Schutte et al. 2008).

The adverse effect levels for renal effects were similar to those observed for skeletal effects. Because the renal effects database is stronger, it was used for derivation of a chronic-duration oral MRL for cadmium. Three approaches were considered for derivation of the MRL: (1) NOAEL/LOAEL approach using a single environmental exposure study finding an increased prevalence of abnormal renal effect biomarker levels, (2) selection of a point of departure from a published benchmark dose analysis, or (3) selection of a point of departure on an analysis of the dose-response functions from a number of environmental exposure studies.

In the first approach, all studies in which individual internal doses for subjects were estimated based on urinary cadmium were considered. The Järup et al. (2000) study identified the lowest adverse effect level; the investigators estimated that a urinary cadmium level of 1 μg/g creatinine would be associated with a 10% increase in the prevalence of abnormal pHC levels above background prevalence (approximately a 10% added risk). The European Chemicals Bureau (2007) recalculated the probability of HC proteinuria because the reference population and the study population were not matched for age (40 versus 53 years, respectively). They estimated that the probability of HC proteinuria (13%) would be twice as high as the reference population at a urinary cadmium concentration of 0.5 μg/g creatinine. For the second approach, five published benchmark dose analyses were evaluated (Jin et al. 2004b; Kobayashi et al. 2006; Shimizu et al. 2006; Suwazono et al. 2006; Uno et al. 2005). The lower 95% confidence interval of the benchmark dose (BMDL) for low molecular weight proteinuria ranged from 0.7 μg/g creatinine (Uno et al. 2005) to 9.9 μg/g creatinine (Kobayashi et al. 2006). The third approach involved a meta-analysis of selected environmental exposure dose-response studies. Using individual dose-response

functions from each study, estimates of the internal cadmium dose corresponding to probabilities of 10% excess risk of low molecular weight proteinuria were calculated. The lowest UCD_{10} (1.34 µg/g creatinine) was estimated from the European database; and the 95% lower confidence limit on this UCD_{10} ($UCDL_{10}$) of 0.5 µg/g creatinine was considered as a potential point of departure for the MRL.

The points of departure selected using the three different approaches are similar: 0.5 µg/g creatinine from the Järup et al. (2000) study (using the European Chemicals Bureau 2007 recalculation), 0.7 µg/g creatinine from the Uno et al. (2005) benchmark dose analysis, and 0.5 µg/g creatinine from the dose-response analysis. The third approach was selected for the derivation of the MRL because it uses the whole dose-response curves from several studies rather than data from a single study.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

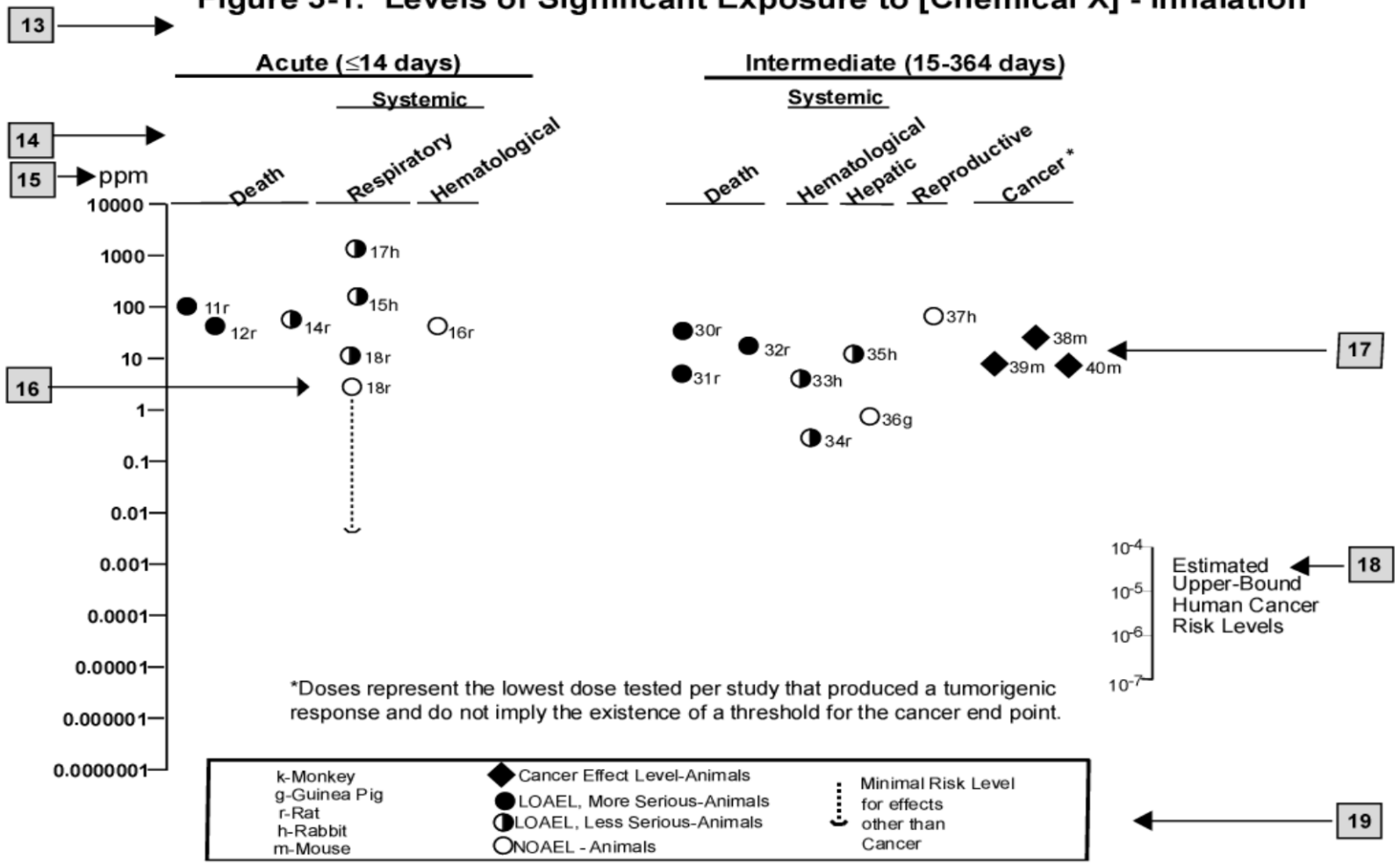
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11 ↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX

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TOXICOLOGICAL PROFILE FOR CHLOROFORM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

A Toxicological Profile for chloroform was released in April 1993. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

David Satcher, M.D., Ph.D.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on April 29, 1996 (61 FR 18744). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

PEER REVIEW

A peer review panel was assembled for chloroform. The panel consisted of the following members:

1. Dr. Richard Bull, Senior Staff Scientist, Battelle Pacific Northwest Laboratories, Richland, Washington;

2. Dr. Derek Hodgson, Provost and Vice-president, Academic Affairs, Mississippi State University, Mississippi State, Mississippi; and

3. Dr. Nancy Reiches, Private Consultant, Bexley, Ohio.

These experts collectively have knowledge of chloroform's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about chloroform and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and the sites are targeted for long-term federal cleanup. Chloroform has been found in at least 717 of the 1,430 current or former NPL sites, including 6 in Puerto Rico and 1 in the Virgin Islands. However, it's unknown how many NPL sites have been evaluated for this substance. As more sites are evaluated, the sites with chloroform may increase. This is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to chloroform, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS CHLOROFORM?

Chloroform is also known as trichloromethane or methyltrichloride. It is a colorless liquid with a pleasant, nonirritating odor and a slightly sweet taste. Most of the chloroform found in the environment comes from industry. It will only burn when it reaches very high temperatures. Chloroform was one of the first inhaled anesthetics to be used during surgery, but it is not used for anesthesia today. Nearly all the chloroform made in the United States

1. PUBLIC HEALTH STATEMENT

today is used to make other chemicals, but some is sold or traded to other countries. We also import chloroform.

Chloroform enters the environment from chemical companies and paper mills, It is also found in waste water from sewage treatment plants and drinking water to which chlorine has been added. Chlorine is added to most drinking water and many waste waters to destroy bacteria. Small amounts of chloroform are formed as an unwanted product during the process of adding chlorine to water. Chloroform can enter the air directly from factories that make or use it and by evaporating from water and soil that contain it. It can enter water and soil when waste water that contains chlorine is released into water or soil. It may enter water and soil from spills and by leaks from storage and waste sites. There are many ways for chloroform to enter the environment, so small amounts of it are likely to be found almost everywhere. You will find more information about what chloroform is, how it is used, and where it comes from in Chapters 3 and 4.

1.2 WHAT HAPPENS TO CHLOROFORM WHEN IT ENTERS THE ENVIRONMENT?

Chloroform evaporates very quickly when exposed to air. Chloroform also dissolves easily in water, but does not stick to the soil very well. This means that it can travel down through soil to groundwater where it can enter a water supply. Chloroform lasts for a long time in both the air and in groundwater. Most chloroform in the air eventually breaks down, but this process is slow. The breakdown products in air include phosgene, which is more toxic than chloroform, and hydrogen chloride, which is also toxic. Some chloroform may break down in soil. Chloroform does not appear to build up in great amounts in plants and animals, but we may find some small amounts of chloroform in foods. You will find more information about where chloroform comes from, how it behaves, and how long it remains in the environment in Chapter 5.

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1.3 HOW MIGHT I BE EXPOSED TO CHLOROFORM?

You are probably exposed to small amounts of chloroform in your drinking water and in beverages (such as soft drinks) made using water that contains chloroform. You can also get chloroform in your body by eating food, by breathing air, and by skin contact with water that contains it. You are most likely to be exposed to chloroform by drinking water and breathing indoor or outdoor air containing it. The amount of chloroform normally expected to be in the air ranges from 0.02 to 0.05 parts of chloroform per billion parts (ppb) of air and from 2 to 44 ppb in treated drinking water. However, in some places, chloroform concentrations may be higher than 44 ppb. It is estimated that the concentration of chloroform in surface water is 0.1 ppb, the concentration in untreated groundwater is 0.1 ppb, and the amount in soil is 0.1 ppb. As much as 610 ppb was found in air at a municipal landfill and up to 88 ppb was found in treated municipal drinking water. Drinking water derived from well water near a hazardous waste site contained 1,900 ppb, and groundwater taken near a hazardous waste site also contained 1,900 ppb. Surface water containing 394 ppb has also been found near a hazardous waste site; however, no more than 0.13 ppb has been found in soil at hazardous waste sites. Chloroform has been found in the air from all areas of the United States and in nearly all of the public drinking water supplies. We do not know how many areas have surface water, groundwater, or soil that contains chloroform.

The average amount of chloroform that you might be exposed to on a typical day by breathing air in various places ranges from 2 to 5 micrograms per day μg/day) in rural areas, 6 to 200 μg/day in cities, and 80 to 2,200 μg/day in areas near major sources of the chemical. The estimated amount of chloroform you probably are exposed to in drinking water ranges from 4 to 88 μg/day. We cannot estimate the amounts that you may be exposed to by eating food and by coming into contact with water that has chloroform in it. People who swim in swimming pools absorbed chloroform through their skin. People who work at or near chemical plants and factories that make or use chloroform can be exposed to higher-thannormal amounts of chloroform. Higher exposures might occur in workers at drinking-water treatment plants, waste water treatment plants, and paper and pulp mills. People who operate waste-burning equipment may also be exposed to higher than normal levels. The National

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Institute for Occupational Safety and Health (NIOSH) estimated that 95,778 persons in the United States have occupational exposure to chloroform. You will find more information about how you can be exposed to chloroform in Chapter 5.

1.4 HOW CAN CHLOROFORM ENTER AND LEAVE MY BODY?

Chloroform can enter your body if you breathe air, eat food, or drink water that contains chloroform. Chloroform easily enters your body through the skin. Therefore, chloroform may also enter your body if you take a bath or shower in water containing chloroform. In addition, you can breathe in chloroform if the shower water is hot enough for chloroform to evaporate. Studies in people and in animals show that after you breathe air or eat food that has chloroform in it, the chloroform can quickly enter your bloodstream from your lungs or intestines. Inside your body, chloroform is carried by the blood to all parts of your body, such as the fat, liver, and kidneys. Chloroform usually collects in body fat; however, its volatility ensures that it will eventually be removed once the exposure has been removed. Some of the chloroform that enters your body leaves unchanged in the air that you breathe out, and some chloroform in your body is broken down into other chemicals. These chemicals are known as breakdown products or metabolites, and some of them can attach to other chemicals inside the cells of your body and may cause ha.rmful effects if they collect in high enough amounts in your body. Some of the metabolites also leave the body in the air you breathe out. Only a small amount of the breakdown products leaves the body in the urine and stool.

You can find more information about the behavior of chloroform in the body in Chapter 2.

1.5 HOW CAN CHLOROFORM AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

1. PUBLIC HEALTH STATEMENT

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

In humans, chloroform affects the central nervous system (brain), liver, and kidneys after a person breathes air or drinks liquids that contain large amounts of chloroform. Chloroform was used as an anesthetic during surgery for many years before its harmful effects on the liver and kidneys were recognized. Breathing about 900 parts of chloroform in a million parts of air (900 ppm or 900,000 ppb) for a short time causes fatigue, dizziness, and headache. If you breathe air, eat food, or drink water containing elevated levels of chloroform, over a long period, the chloroform may damage your liver and kidneys. Large amounts of chloroform can cause sores when the chloroform touches your skin.

We do not know whether chloroform causes harmful reproductive effects or birth defects in people. Miscarriages occurred in rats and mice that breathed air containing elevated levels (30 to 300 ppm) of chloroform during pregnancy and in rats that ate chloroform during pregnancy. Abnormal sperm were found in mice that breathed air containing elevated levels (400 ppm) of chloroform for a few days. Offspring of rats and mice that breathed chloroform during pregnancy had birth defects.

Results of studies of people who drank chlorinated water showed a possible link between the chloroform in chlorinated water and the occurrence of cancer of the colon and urinary bladder. Cancer of the liver and kidneys developed in rats and mice that ate food or drank water that had large amounts of chloroform in it for a long time. We do not know whether liver and kidney cancer would develop in people after long-term exposure to chloroform in drinking water. Based on animal studies, the Department of Health and Human Services (DHHS) has determined that chloroform may reasonably be anticipated to be a carcinogen (a

substance that causes cancer). The International Agency for Research on Cancer (IARC) has determined that chloroform is possibly carcinogenic to humans (2B). The EPA has determined that chloroform is a probable human carcinogen.

You can find a more complete discussion about how chloroform affects your health in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CHLOROFORM?

Although we can measure the amount of chloroform in the air that you breathe out, and in blood, urine, and body tissues, we have no reliable test to determine how much chloroform you have been exposed to or whether you will experience any harmful health effects. The measurement of chloroform in body fluids and tissues may help to determine if you have come into contact with large amounts of chloroform. However, these tests are useful only a short time after you are exposed to chloroform because it leaves the body quickly. Because it is a breakdown product of other chemicals (chlorinated hydrocarbons), chloroform in your body might also indicate that you have come into contact with those other chemicals. Therefore, small amounts of chloroform in the body may indicate exposure to these other chemicals and may not indicate low chloroform levels in the environment. From blood tests to determine the amount of liver enzymes, we can tell whether the liver has been damaged, but we cannot tell whether the liver damage was caused by chloroform.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop

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recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for chloroform include the following:

The EPA sets rules for the amount of chloroform allowed in water. The EPA limit for total trihalomethanes, a class of chemicals that includes chloroform, in drinking water is 100 micrograms per liter (μg/L, 1 μg/L = 1 ppb in water). Furthermore, EPA requires that spills of 10 pounds or more of chloroform into the environment be reported to the National Response Center.

OSHA sets the levels of chloroform allowed in workplace air in the United States. A permissible occupational exposure limit is 50 ppm or 240 mg/m^3 (ceiling value) in air during an 8-hour workday, 40-hour workweek.

1. PUBLIC HEALTH STATEMENT

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance
Phone: (404) 639-6000
Fax: (404) 639-6315 or 6324

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of chloroform. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure --inhalation, oral, and dermal; and then by health effect--death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant, dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt

at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects (Cancer Effect Levels, CELs) of chloroform are indicated in Figure 2-2. Because cancer effects could occur at lower exposure levels, Figures 2-l and 2-2 also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for chloroform. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute-, intermediate-, and chronic-duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990b), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions,

asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

Most of the data regarding inhalation exposure to chloroform in humans were obtained from clinical reports describing health effects in patients under anesthesia. In some instances, the results may have been confounded by the concurrent administration of other drugs with chloroform or by artificial respiration of patients under chloroform anesthesia. Furthermore, most of the studies did not provide any information regarding actual exposure levels for observed effects. Nonetheless, chloroforminduced effects in humans are supported by those observed in animals under experimental conditions.
The human studies cited in the profile provide qualitative information on chloroform toxicity in humans.

2.2.1.1 Death

Information on the exposure levels of chloroform leading to death in humans was obtained from clinical reports of patients exposed to chloroform as a method of anesthesia. It should be noted that when examining the ability of chloroform to cause death, these clinical reports may be misleading, in that many of these patients had pre-existing health conditions that may have contributed to the cause of death and that chloroform toxicity may not have been the only factor involved in the death of the patient. Older clinical case reports suggested that concentrations of ≈40,000 ppm, if continued for several minutes, may be an overdose (Featherstone 1947). When a cohort of 1,502 patients, ranging in age from 1 to 80 years, exposed under anesthesia to less than 22,500 ppm chloroform was evaluated, no indication of increased mortality was found (Whitaker and Jones 1965). In most patients, the anesthesia did not last longer than 30 minutes; however, a few received chloroform for more than 2 hours. Several studies reported deaths in women after childbirth when chloroform anesthesia had been used (Royston 1924; Townsend 1939). No levels of actual exposure were provided in either study. Death was caused by acute hepatotoxicity. Prolonged labor with starvation, dehydration, and exhaustion contributed to the chloroform-induced hepatotoxicity.

Levels of acute exposure resulting in animal deaths are generally lower than those reported for human patients under anesthesia; however, the exposure durations are generally longer in the animal studies. An inhalation LC_{50} (lethal concentration, 50% kill) of 9,770 ppm for a 4-hour exposure was reported for female rats (Lundberg et al. 1986). One rat died after 6 exposures in one report where groups of 9-12 pregnant female rats exposed to chloroform at doses as high as 4,117 ppm for 1 hour a day for 8 days (Newell and Dilley 1978). However, exposure to 8,000 ppm for 4 hours was lethal to albino rats (Smyth et al. 1962). Male mice appear to be more sensitive than female mice. Following exposure to 1,024 ppm for l-3 hours, 15 of 18 male mice died within 11 days; however, most of the female mice similarly exposed survived for several months (Deringer et al. 1953). Male mice that died had kidney and liver damage, while females did not. An exposure as low as 692 ppm for 1-3 hours resulted in the death of 3 of 6 male mice within 8 days. When exposed to 4,500 ppm chloroform for 9 hours, 10 of 20 female mice died (Gehring 1968). Increased mortality was observed in male rats exposed to 85 ppm chloroform for 6 months (Torkelson et al. 1976). The deaths were attributed to interstitial pneumonia. Rats of either sex exposed to 50 ppm survived. Exposure to 85 ppm for 6 months did not increase mortality in rabbits and guinea pigs. Similarly, no deaths were reported in dogs exposed to 25 ppm chloroform for the same time period.

The LC_{50} and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-l and plotted in Figure 2-I.

2.2.1.2 Systemic Effects

No studies were located regarding dermal or ocular effects in humans or animals after inhalation exposure to chloroform.

The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l.

Respiratory Effects. Changes in respiratory rate were observed in patients exposed to chloroform via anesthesia (exposure less than 22,500 ppm) (Whitaker and Jones 1965). Increased respiratory rates were observed in 44% of 1,502 patients who were exposed to light chloroform anesthesia. Respiratory rates were depressed, however, during deep and prolonged anesthesia when chloroform concentrations

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Albino)	4 hr				8000 (5/6 died)	Smyth et al. 1962
2	Rat (Sprague-Dawley)	4 hr				9770 F (LC_{50})	Lundberg et al. 1986
3	Rat (Sprague-Dawley)	8 d Gd 7-14 1 hr/d				4117 F (death; 1 animal on Gd 12)	Newell and Dilley 1978
4	Mouse (Swiss-Webster)	9 hr				4500 F (10/20 died)	Gehring 1968
5	Mouse (C3H)	1-3 hr				692 M (3/6 died)	Deringer et al. 1953
Systemic							
6	Human	113 min	Cardio			8000 (arrhythmia)	Smith et al. 1973
			Gastro		8000 (vomiting)		
			Hemato		8000 (increased prothrombin time)		
			Hepatic			8000 (increased sulfobromophthalein sodium retention)	

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
7	Human	0.5-2 hr	Resp		22,500	(changes in respiratory rate)			Whitaker and Jones 1965
			Cardio				22,500	(cardiac arrhythmia, bradycardia)	
			Gastro		22,500	(vomiting)			
			Hepatic		22,500	(transient jaundice in 1 patient)			
8	Rat (Sprague-Dawley)	8 d Gd 7-14 1 hr/d	Bd Wt	2232 F			4117 F	(60% decreased maternal body weight gain)	Newell and Dilley 1978
9	Rat (Sprague-Dawley)	4 hr	Hepatic	76 F	153 F	(SDH-enzyme levels increased)			Lundberg et al. 1986
10	Rat (Wistar)	10 d Gd 7-16 7 hr/d	Hepatic	300 F					Baeder and Hofmann 1988
			Renal	300 F					
			Bd Wt		30 F	(18% decreased weight gain of dams)	100 F	(24% decreased weight gain of dams)	
			Other		30 F	(decrease in feed consumption)			
11	Rat (Wistar)	8 hr	Hepatic		50 M	(elevated liver triglycerides and liver GSH)			Ikatsu and Nakajima 1992
12	Rat (Fischer- 344)	7 d 6 hr/d	Resp	3.1 M	10.4 M	(degeneration of Bowman's gland; new bone formation; increased number of S-phase nuclei)			Mery et al. 1994
			Bd Wt	100 M	271 M	(unspecified decrease in body weight)			

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
13	Rat (Fischer- 344)	7 d 6 hr/d	Resp	3.1 M	10.4 M (epithelial goblet cell hyperplasia and degeneration of Bowman's glands in olfactory mucosa)		Larson et al. 1994c
			Hepatic	100 M	271 M (swelling and mild centrilobular vacuolation)		
			Renal	10.4 M	29.3 M (increased number of S-phase nuclei for tubule cells in the cortex)		
			Bd Wt	3.1 M	10.4 M (decreased weight gain)		
14	Rat (Wistar)	6 hr	Hepatic	100 M	500 M (increased plasma GOT and GPT; decreased hepatic GSH)		Wang et al. 1994
15	Rat (Wistar)	6 hr	Hepatic	100	500 (incr. plasma GOT activity)		Wang et al. 1995
16	Mouse (CBA; W.H.)	2 hr	Hepatic		246 (fatty changes)		Culliford and Hewitt 1957
			Renal	246 F		246 M (tubular necrosis in males)	
17	Mouse (NS)	4 hr	Hepatic		100 F (fatty changes)		Kylin et al. 1963
18	Mouse (C3H)	1-3 hr	Resp	1106			Deringer et al. 1953
			Hepatic	1106 F		942 M (liver necrosis in males that died)	
			Renal	1106 F		692 M (tubular necrosis in males that died)	

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
19	Mouse (CF1)	8 d Gd 1-7, Gd 6-15, or Gd 8-15 7 hr/d	Hepatic		100 F (increased SGPT activity; increased absolute and relative liver weights)		Murray et al. 1979
			Bd Wt		100 F (unspecified decreased weight gain in dams)		
20	Mouse (Swiss-Webster)	9 hr	Hepatic		4500 F (increased SGPT activity)		Gehring 1968
21	Mouse (B6C3F1)	7 d 6 hr/d	Resp	3 F	10 F (increased number of S-phase nuclei)		Mery et al. 1994
			Bd Wt	29.5 F	101 F (unspecified decr. in body weight)		
22	Mouse (B6C3F1)	7 d 6 hr/d	Resp	288 F			Larson et al. 1994c
			Hepatic	3[b] F	10 F (mild to moderate vacuolar changes in centrilobular hepatocytes)	101 F (centrilobular hepatocyte necrosis and severe diffuse vacuolar degeneration of midzonal and periportal hepatocytes)	
			Renal	101 F	288 F (proximal tubules lined by regenerating epithelium)		
			Bd Wt	288 F			

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
23	Mouse (B6C3F1)	4 d 6 hr/d	Resp	2 F	10 F (mild, transient, proliferative responses & bone thickening in the periosteum and posterior ventral areas)		Larson et al. 1996
			Musc/skel	88 F			
			Hepatic	30 F	88 F (increased relative liver weights; hepatocyte lipid vacuolization & scattered individual hepatocyte necrosis; significant increase in hepatic LI)		
			Renal	88 F			
	Immunological/Lymphoreticular						
24	Rat (Wistar)	10 d Gd 7-16 7 hr/d		300 F			Baeder and Hofmann 1988
25	Mouse (C3H)	1-3 hr		1106			Deringer et al. 1953
	Neurological						
26	Human	3 min			920 (dizziness, vertigo)		Lehman and Hasegawa 1910
27	Human	113 min				8000 (narcosis)	Smith et al. 1973
28	Human	0.5-2 hr				22,500 (narcosis)	Whitaker and Jones 1965
29	Mouse (NS)	0.5-2 hr		2500		3100 (slight narcosis)	Lehmann and Flury 1943
30	Cat (NS)	5-93 min				7,200 (disturbed equilibrium)	Lehmann and Flury 1943

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Reproductive							
31	Rat (Sprague-Dawley)	10 d Gd 6-15 7 hr/d		100 F		300 F (73% decreased conception rate; increased incidence of fetal resorptions)	Schwetz et al. 1974
32	Rat (Wistar)	10 d Gd 7-16 7 hr/d				30 F (empty implantations in 2/20 dams)	Baeder and Hofmann 1988
33	Mouse (CF1)	8 d Gd 1-7, Gd 6-15, or Gd 8-15 7 hr/d				100 F (increased incidence of resorptions; decrease in % pregnancies)	Murray et al. 1979
34	Mouse (C57B1/ C3H)F1	5 d 4 hr/d				400 M (increased percentage of abnormal sperm)	Land et al. 1979
Developmental							
35	Rat (Sprague-Dawley)	10 d Gd 6-15 7 hr/d			30 (delayed ossification and wavy ribs)	100 (missing ribs; acaudate fetuses with imperforate anus)	Schwetz et al. 1974
36	Rat (Wistar)	10 d Gd 7-16 7 hr/d			30 (slight growth retardation)		Baeder and Hofmann 1988
37	Mouse (CF1)	8 d Gd 1-7, Gd 6-15, or Gd 8-15 7 hr/d				100 (cleft palate, decreased ossification)	Murray et al. 1979

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Death							
38	Rat (NS)	6 mo 5 d/wk 7 hr/d				85 M (increased mortality; 4/10 died)	Torkelson et al. 1976
Systemic							
39	Human	1-6 mo	Gastro		14 (nausea; vomiting)		Phoon et al. 1983
			Hepatic		14[c] (toxic hepatitis)		
40	Rat (NS)	6 mo 5 d/wk 7 hr/d	Resp	50 M 85 F	85 M (interstitial pneumonia)		Torkelson et al. 1976
			Hemato	85			
			Hepatic		25 (degenerative changes)		
			Renal		25 (cloudy swelling)		
			Bd Wt	25 M 85 F	50 M (decreased body weight in males)		
41	Mouse (B6C3F1)	3 wk 7 d/wk 6 hr/d	Resp	88			Larson et al. 1996
			Musc/skel	88			
			Hepatic	10	29.6 (hepatocyte vacuolation and swelling; variations in nuclear size)		
			Renal	10 M 88 F	29.6 M (nephropathy of epithelial cells of the proximal convoluted tubules)		
			Bd Wt	88			

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
42	Mouse (B6C3F1)	6 wk 7 d/wk 6 hr/d	Resp	88			Larson et al. 1996
			Musc/skel	88			
			Hepatic	10 F	29.6 F (16.1% increase in relative liver weights; mild degenerative changes in hepatocytes; increase in liver LI)		
			Renal	88			
			Bd Wt	88 F			
43	Mouse (B6C3F1)	13 wk 7 d/wk 6 hr/d	Resp	88			Larson et al. 1996
			Musc/skel	88			
			Hepatic	10	29.6 (vacuolation and swelling of hepatocytes; variations in nuclear size)		
			Renal	1.99 M	10 M (nephropathy & enlarged nuclei of the epithelial cells of the proximal convoluted tubules; mineralization in the cortex)		
				88 F			
			Bd Wt	88			

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
44	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d	Resp	88			Larson et al. 1996
			Musc/skel	88			
			Hepatic	29.6	88 (increased relative liver weights; vacuolation & swelling of hepatocytes & enlarged nuclei; increased liver LI)		
			Renal	1.99 M	10 M (nephropathies and enlarged nuclei in epithelial cells of the proximal convoluted tubules; mineralization within the cortex; increased cortical and medullary tissue LIs)		
				88 F			
			Bd Wt	29.6			
45	Dog (NS)	6 mo 5 d/wk 7 hr/d	Hemato	25			Torkelson et al. 1976
			Hepatic	25			
			Renal	25 M	25 F (cloudy swelling of tubular epithelium)		
46	Rabbit (NS)	6 mo 5 d/wk 7 hr/d	Resp	50 M	25 F (interstitial pneumonia) 85 M (pneumonitis)		Torkelson et al. 1976
			Hemato	85			
			Hepatic		25 (centrilobular granular degeneration and necrosis)		
			Renal		25 (interstitial nephritis)		

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
47	Gn pig (NS)	6 mo 5 d/wk 7 hr/d	Hemato	85			Torkelson et al. 1976
			Hepatic		25 (centrilobular granular degeneration)		
			Renal		25 (tubular and interstitial nephritis)		
Immunological/Lymphoreticular							
48	Rat (NS)	6 mo 5 d/wk 7 hr/d		25			Torkelson et al. 1976
Reproductive							
49	Rat (NS)	6 mo 5 d/wk 7 hr/d		25 M			Torkelson et al. 1976

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
CHRONIC EXPOSURE							
Systemic							
50	Human	10-24 mo	Gastro		22 F (nausea)		Challen et al. 1958
			Hepatic	71			
51	Human	1-4 yr	Hepatic		2[d] (hepatomegaly)		Bomski et al. 1967
52	Human	3-10 yr	Gastro		77 F (nausea)		Challen et al. 1958
			Hepatic	237 F			
53	Human	1-15 yr	Hepatic		29.5 (elevated serum prealbumin and transferrin)		Li et al. 1993
			Renal	13.5			
Immunological/Lymphoreticular							
54	Human	1-4 yr			2 (splenomegaly)		Bomski et al. 1967
Neurological							
55	Human	3-10 yr			77 F (exhaustion, irritability, depression, lack of concentration)		Challen et al. 1958
56	Human	10-24 mo			22 F (exhaustion)		Challen et al. 1958

Table 2-1. Levels of Significant Exposure to Chloroform - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
57	Human	1-15 yr			13.49 (dizziness, fatigue, somnolence, insomnia, increased dreaming, hypomnesia, anorexia, and palpitations)		Li et al. 1993

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.1 ppm; concentration is converted to a human equivalent concentration and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive an intermediate-duration inhalation MRL of 0.05 ppm; concentration is divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

[d]Used to derive a chronic-duration inhalation MRL of 0.02 ppm; concentration is divided by an uncertainty factor 100 (10 for use of a LOAEL and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = female; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; GOT = glutamic oxalotransaminase; GPT = glutamic pyruvic transaminase; GSH = glutathione; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; LI = labeling index; M = male; min = minute(s); mo = moth(s); musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; SDH = sorbitol dehydrogenase; SGPT = serum glutamic pyruvic transaminase; wk = week; yr = year(s)

Figure 2-1. Levels of Significant Exposure to Chloroform - Inhalation

Acute (≤14 days)

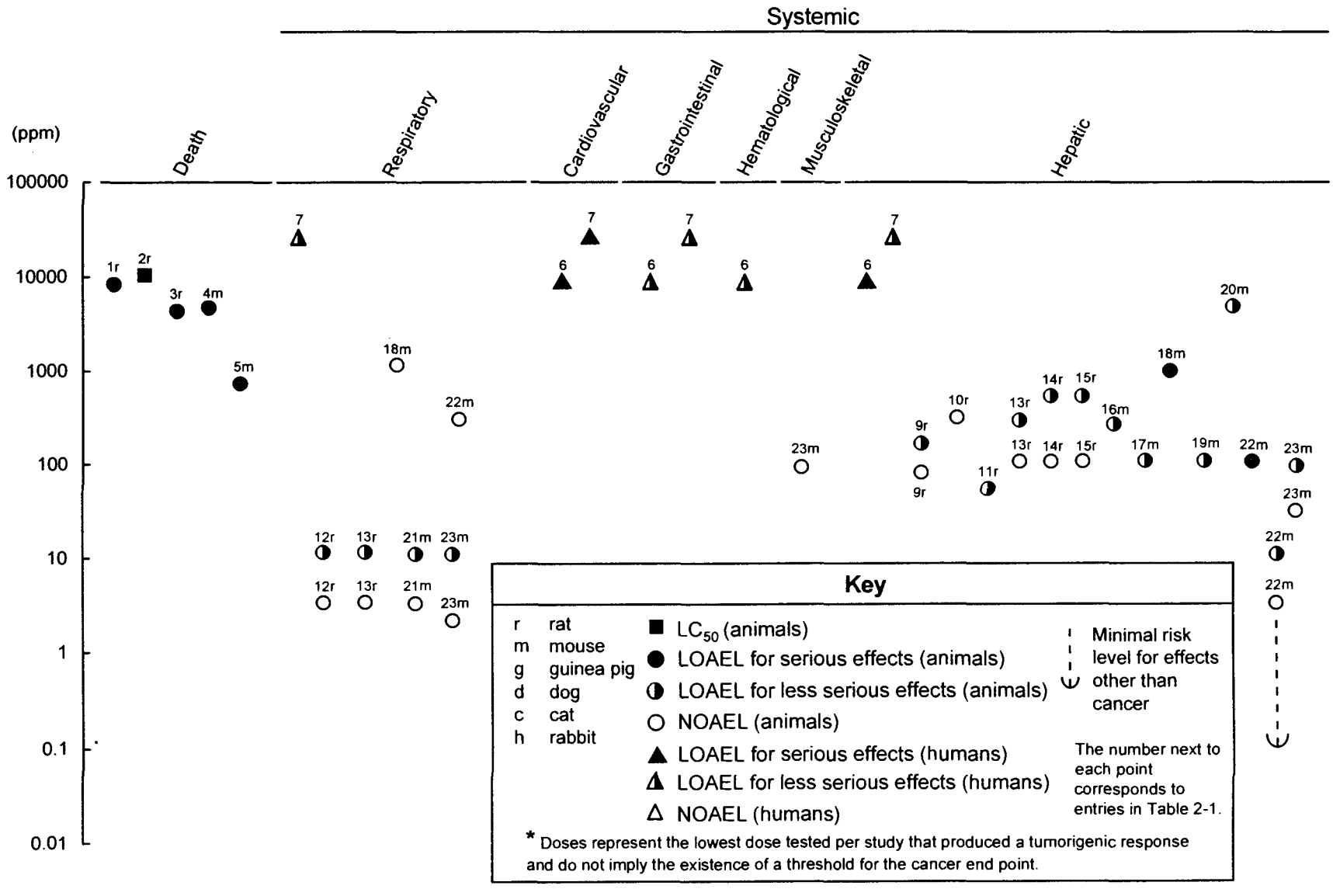


Figure 2-1. Levels of Significant Exposure to Chloroform - Inhalation (cont.)

Acute (≤14 days)

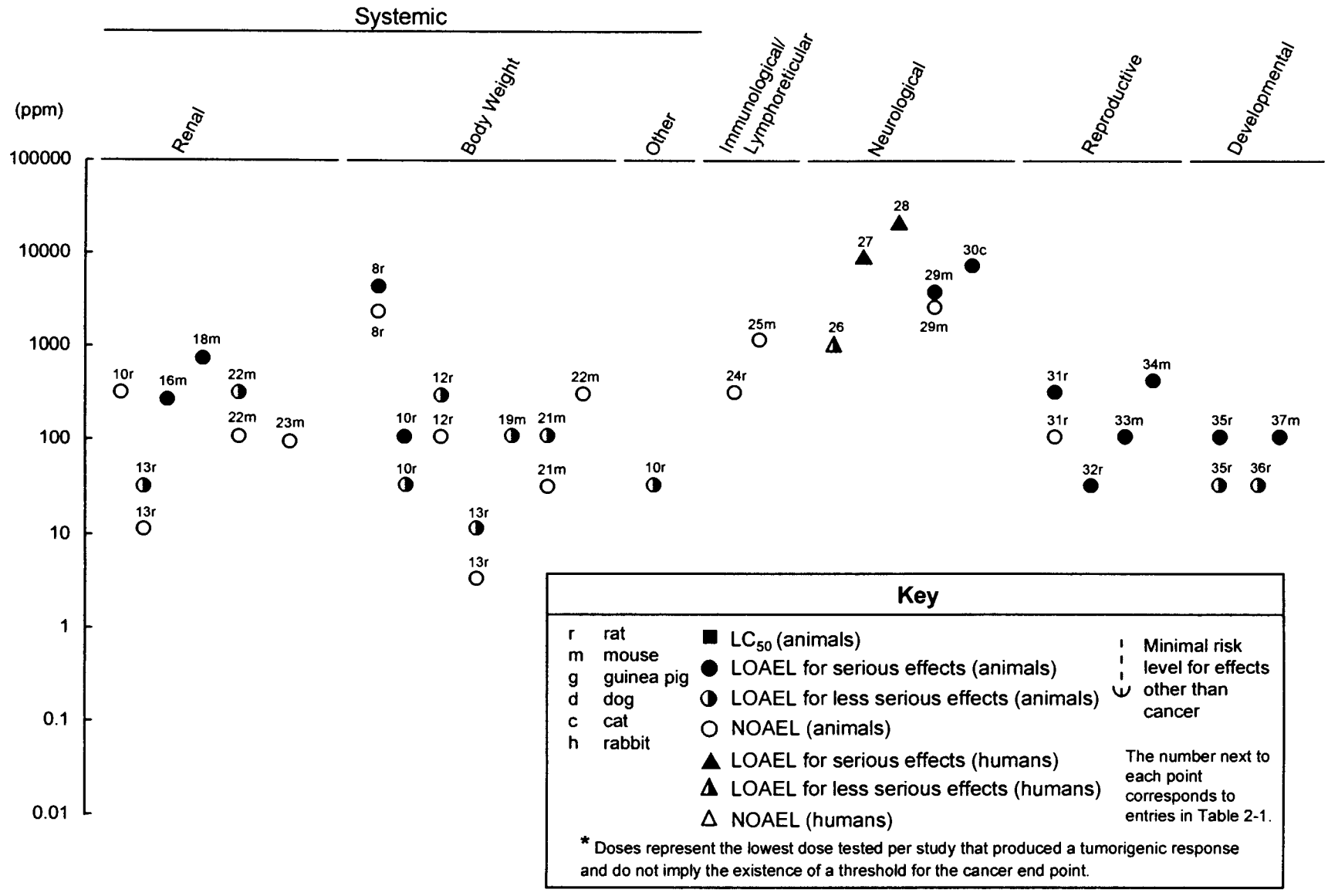


Figure 2-1. Levels of Significant Exposure to Chloroform - Inhalation (cont.)

Intermediate (15-364 days)

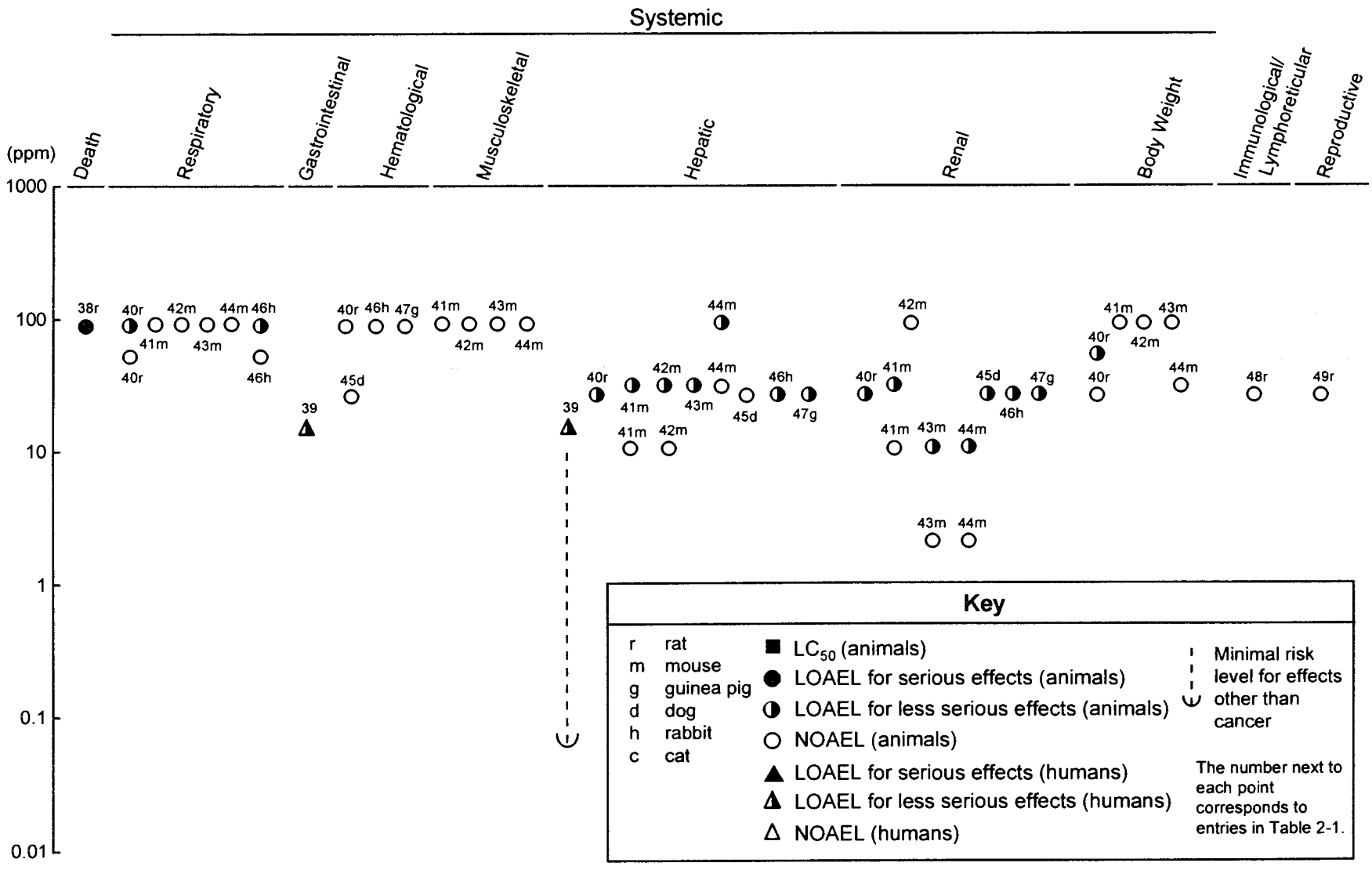
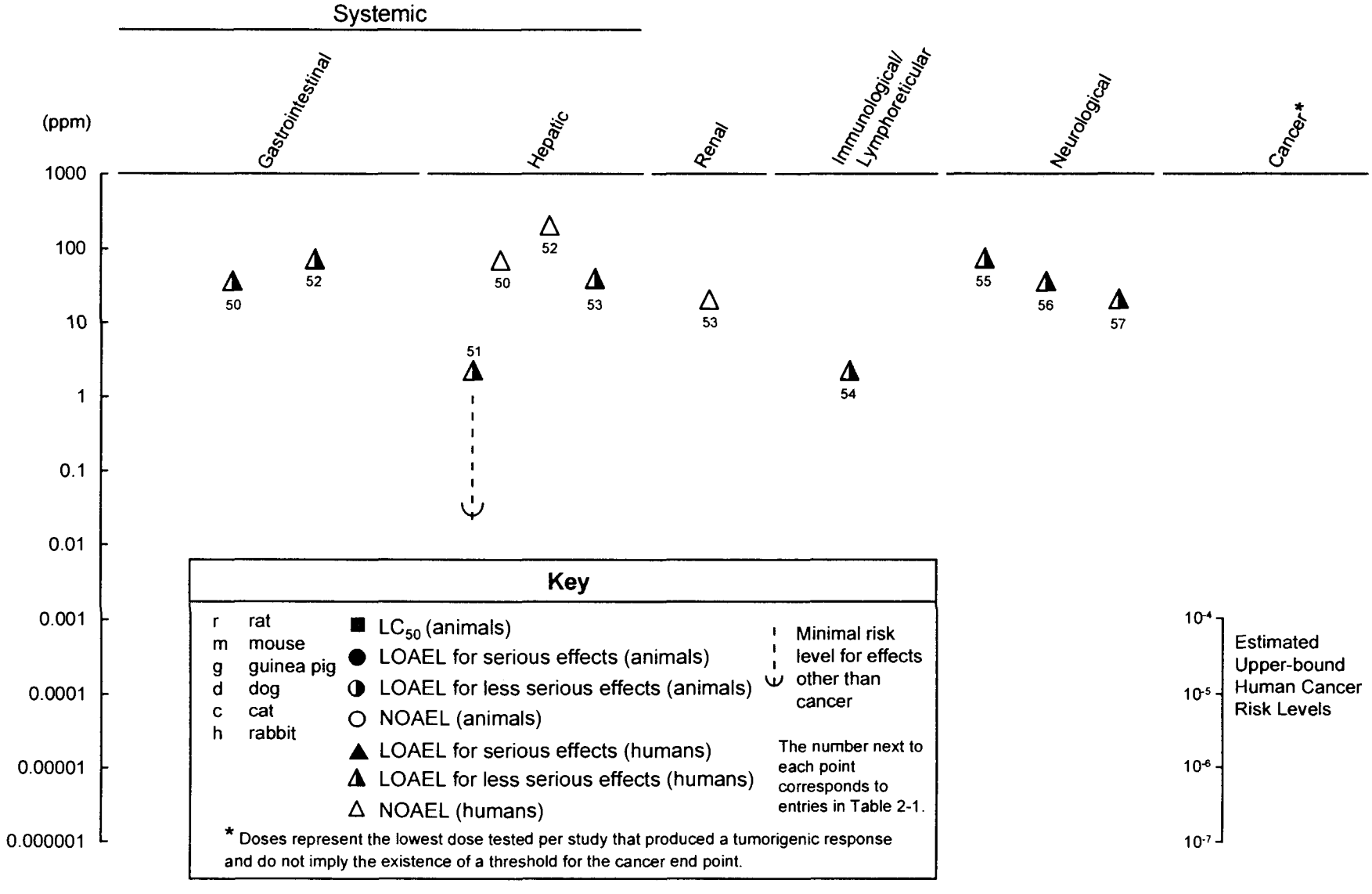


Figure 2-1. Levels of Significant Exposure to Chloroform - Inhalation (cont.)

Chronic (≥365 days)



did not exceed 2.25%. No other studies were located regarding respiratory effects in humans after inhalation exposure to chloroform.

Larson et al. (1996) investigated the ability of acute exposure to chloroform vapors to produce toxicity and regenerative cell proliferation in the liver, kidneys, and nasal passage of female B6C3F_1 mice. Groups of 5 animals were exposed to 0, 0.3, 2, 10, 30, or 90 ppm chloroform via inhalation for 6 hours a day for 4 consecutive days. Animals were administered bromodeoxyuridine (BrdU) via implanted osmotic pump for the last 3.5 days. At necropsy, livers and kidneys were removed, weighed, examined macroscopically, and prepared for microscopic evaluation. The nasal cavities were also removed and prepared for microscopic evaluation. Cell proliferation was quantitated as the percentage of cells in S-phase (labeling index = LI) measured by immunohistochemical detection of BrdU-labeled nuclei. This study found no overt clinical signs of toxicity in female mice exposed to chloroform for 4 days; however, some mild, transient changes occurred in the posterior ventral areas of nasal tissue in female mice exposed to the 10, 30, and 90 ppm concentrations of chloroform. The lesions were characterized by mild proliferative responses in the periosteum consisting of a thickening of the bone. The adjacent lamina also exhibited loss of acini of Bowman's glands and vascular congestion. No microscopic changes were noted in nonnasal bones, nor were nonnasal bone LIs significantly different from those of controls.

Another similar study by Larson et al. (1994c) using a wider range of inhaled doses investigated the ability of chloroform vapors to produce toxicity and regenerative cell proliferation in the liver and kidneys of female B6C3F_1, mice and male Fischer 344 rats, respectively. Nasal passages were also examined for toxic response. Groups of 5 animals were exposed to 0, 1, 3, 10, 30, 100, or 300 ppm chloroform via inhalation for 6 hours a day for 7 consecutive days. Actual exposure concentrations measured were 0, 1.2, 3, 10, 29.5, 101, and 288 ppm for mice; and 0, 1.5, 3.1, 10.4, 29.3, 100, and 271 ppm and for rats. Animals were administered BrdU via implanted osmotic pump for the last 3.5 days to quantitate S-phase cell proliferation using an LI method. Necropsies were performed on day 8. No histopathological lesions were observed in the nasal passages of female mice at any exposure concentration. In the nasal passages of rats, chloroform concentrations of 10 ppm and above induced histopathological changes that exhibited a clear concentration-related response. These lesions consisted of respiratory epithelial goblet cell hyperplasia and degeneration of Bowman's glands in olfactory mucosa with an associated osseous hyperplasia. of the endo- and ectoturbinates in the periphery of the ethmoid region.

2. HEALTH EFFECTS

Acute exposure to chloroform clearly can induce site-specific as well as biochemical changes in the nasal region of female $B6C3F_1$, mice and male Fischer 344 rats (Mery et al. 1994). To demonstrate the biochemical alterations, mice were exposed to 1.2, 3, 10, 29.5, 101, and 288 ppm chloroform and rats were exposed to 1.5, 3.1, 10.4, 29.3, 100, and 27 1 ppm for 6 hours a day for 7 days to determine the nasal cavity site-specific lesions and the occurrence of cell induction/proliferation associated with these varying concentrations of chloroform. In male rats, the respiratory epithelium of the nasopharyngeal meatus exhibited an increase in the size of goblet cells at 100 and 271 ppm chloroform, in addition to an increase in both neutral and acidic mucopolysaccharides. Affected epithelium was up to twice its normal thickness. New bone formation within the nasal region was prominently seen at 10.4 ppm and above, and followed a concentration response curve. At 29.3 and 100 ppm, new osseous spicules were present at the beginning of the first endoturbinate, while at 271 ppm, the width of the new bone was almost doubled compared to controls. The Bowman's glands were markedly reduced in size. Cytochrome P-450-2El staining was most prominent in the cytoplasm of olfactory epithelial sustentacular cells and in the acinar cells of Bowman's glands in control animals. In general, increasing the chloroform concentration tended to decrease the amount of P-450 staining in exposed animals. Exposure to chloroform resulted in a dramatic increase in the number of S-phase nuclei, with the proliferative response confined to activated periosteal cells, including both osteogenic (round) and preosteogenic (spindle) cells. The proximal and central regions of the first endoturbinate had the highest increase of cell proliferation. Interestingly, the only detectable treatment-related histologic change observed in female mice was a slight indication of new bone growth in the proximal part of the first endoturbinate in one mouse exposed to 288 ppm chloroform. The S-phase response was observed at chloroform concentrations of 10.4 ppm and higher. If similar nasal cavity changes occur in humans, the sense of smell could potentially be altered.

In some animal species, the lung may be a target organ when inhalation exposure to chloroform is of intermediate duration. Interstitial pneumonitis was observed in male rats and rabbits exposed to 85 ppm and in female rabbits exposed to 25 ppm chloroform for 6 months (Torkelson et al. 1976). The NOAEL was 50 ppm for male rats and rabbits. No respiratory changes were reported in guinea pigs and dogs exposed to 85 and 25 ppm chloroform, respectively.

Larson et al. (1996) investigated the ability of intermediate exposure to chloroform vapors to produce toxicity and regenerative cell proliferation in the nasal passage of male and female $B6C3F_1$, mice. Groups of 8 animals of each sex were exposed to 0, 0.3, 2, 10, 30, or 90 ppm chloroform via

inhalation for 6 hours a day, 7 days a week for 3, 6, or 13 weeks; additional groups of 8 animals of each sex were exposed for 6 hours a day, 5 days a week for 13 weeks. Animals were administered BrdU via implanted osmotic pump and cell proliferation was quantitated as the percentage of cells in S-phase using LI (measuring by immunohistochemical detection of BrdU-labeled nuclei). At necropsy, the nasal cavities were removed and prepared for microscopic evaluation. No alterations in nasal tissues were noted at any exposure level in either sex after exposures of 3, 6, or 13 weeks.

Cardiovascular Effects. Epidemiologic studies indicate that chloroform causes cardiac effects in patients under anesthesia. In a cohort of 1,502 patients (exposure less than 22,500 ppm), dose-related bradycardia developed in 8% of the cases, and cardiac arrhythmia developed in 1.3% of the cases (Whitaker and Jones 1965). Hypotension was observed in 27% of the patients and was related to the duration of the anesthesia and to pretreatment with thiopentone. Chloroform anesthesia (exposure 8,000-10,000 ppm) caused arrhythmia (nodal rhythm, first degree atrio-ventricular block, or complete heart block) in 50% of the cases from the cohort of 58 patients and hypotension in 12% (Smith et al. 1973). It should be noted that the effects seen may be secondary to surgical stress or the underlying disease which necessitated the surgical procedure.

No studies were located regarding cardiovascular effects in animals after inhalation exposure to chloroform.

Gastrointestinal Effects. Nausea and vomiting were frequently observed side effects in humans exposed to chloroform via anesthesia (exposure 8,000-22,500 ppm) (Royston 1924; Smith et al. 1973; Townsend 1939; Whitaker and Jones 1965). Nausea and vomiting were observed in male and female workers exposed solely to 14-400 ppm chloroform for l-6 months (Phoon et al. 1983). Similarly, gastrointestinal symptoms (nausea, dry mouth, and fullness of the stomach) were reported in female workers occupationally exposed to 22-71 ppm chloroform for lo-24 months and 77-237 ppm chloroform for 3-10 years (Challen et al. 1958).

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to chloroform.

Hematological Effects. The hematological system does not appear to be a significant target after inhalation exposure to chloroform. Except for increased prothrombin time in some individuals after

anesthesia exposure to 8,000 ppm, no hematological effects were observed in humans after inhalation exposure to chloroform (Smith et al. 1973). This effect reflects the hepatotoxicity of chloroform because prothrombin is formed in the liver.

No hematological effects were observed in rats, rabbits, and guinea pigs exposed to 85 ppm chloroform or in dogs exposed to 25 ppm chloroform for intermediate durations (Torkelson et al. 1976).

Musculoskeletal Effects. Few musculoskeletal effects have been reported in the literature after an acute, intermediate, or chronic exposure to chloroform in humans or in laboratory animals. Larson et al. (1996) investigated the ability of acute- and intermediate-duration exposure to chloroform vapor to produce toxicity and regenerative cell proliferation in various tissues of female $B6C3F_1$, mice. Using the methods described in previous sections of this profile, Larson et al. (1996) found that, after acute exposure, no microscopic changes were noted in nonnasal bones, nor were non nasal bone LIs different from those of controls. In the intermediate duration studies, no alterations in nonnasal bone tissues were noted at any exposure level in either sex after exposures of 3, 6, or 13 weeks.

Hepatic Effects. Chloroform-induced hepatotoxicity is one of the major toxic effects observed in both humans and animals after inhalation exposure. Increased sulfobromophthalein retention was observed in some patients exposed to chloroform via anesthesia (exposure 8,000-10,000 ppm), indicating impaired liver function (Smith et al. 1973). Serum transaminase, cholesterol, total bilirubin, and alkaline phosphatase levels were not affected. Transient jaundice has also been reported in one study (Whitaker and Jones 1965), while several earlier studies report acute hepatic necrosis in women exposed to chloroform via anesthesia (exact exposure not provided) during childbirth (Lunt 1953; Royston 1924; Townsend 1939). The effects observed in the women included jaundice, liver enlargement and tenderness, delirium, coma, and death. Centrilobular necrosis was found at autopsy in those who died. Workers exposed to 14-400 ppm chloroform for l-6 months developed toxic hepatitis and other effects including jaundice, nausea, and vomiting, without fever (Phoon et al. 1983). The workers were originally diagnosed with viral hepatitis; however, in light of epidemiologic data, the diagnosis was changed to toxic hepatitis. No clinical evidence of liver injury was observed in workers exposed to as much as 71 and 237 ppm chloroform for intermediate and chronic durations, respectively; however, liver function was not well characterized (Challen et al. 1958). In contrast, toxic hepatitis (with hepatomegaly, enhanced serum glutamic pyruvic transaminase [SGPT] and serum

glutamic oxaloacetic transaminase [SGOT] activities, and hypergammaglobulinemia) was observed in workers exposed to 2-205 ppm chloroform (Bomski et al. 1967). Co-exposure to trace amounts of other solvents was also detected, however. Elevated serum prealbumin and transferrin were noted in another study (Li et al. 1993); however, the data is questionable as the exposed individuals most likely received exposures to toxic substances other than just chloroform. An intermediate-duration inhalation MRL of 0.05 ppm was derived from the LOAEL of 14 ppm from the data presented by Phoon et al. (1983); a chronic-duration inhalation MRL of 0.02 ppm was derived from the LOAEL of 2 ppm from the data presented by Bomski et al. (1967). More information on these MRLs and how they were derived is located in the footnote to Table 2-1, Section 2.5 and in Appendix A of this profile.

A study by Aiking et al. (1994) examined the possible hepatotoxicity of chloroform exposure in competitive swimmers who trained in indoor chlorinated swimming pools (n=l0) compared to those who trained in outdoor chlorinated swimming pools (n=8). The actual amount of chloroform inhaled was not determined; however, the mean concentration of chloroform was determined to be 24 μg/L in the indoor pools and 18.4 μg/L in the outdoor pools. Mean blood chloroform concentration in the indoor pool swimmers was found to be 0.89 μg/L, while the control group and the outdoor pool swimmers had blood chloroform concentrations of less than 0.5 μg/L, suggesting that the chloroform could not be removed by environmental air currents (resulting in higher exposure dose) as it did in an outdoor pool environment. No significant differences in liver enzyme function was seen between any of the groups.

Chloroform-induced hepatotoxicity in various animal species has been reported in several studies. No changes in SGPT activity were observed in rats exposed to 300 ppm chloroform during gestation days (Gd) 6-15 (Schwetz et al. 1974). No changes in liver weights were found in pregnant Wistar rats that were exposed to 0, 30, 100, or 300 ppm chloroform via inhalation during Gd 7-16, followed by termination on day 21 (Baeder and Hofmann 1988). In contrast, serum sorbitol dehydrogenase (SDH) activity was increased in rats exposed to 153 ppm and above for 4 hours (Lundberg et al. 1986) and SGPT levels were increased in mice exposed to 100 ppm, 7 hours a day for 8 days during various stages of pregnancy (Murray et al. 1979) and 4,500 ppm for 9 hours (Gehring 1968). These increased enzyme levels in serum indicate hepatoceliular necrosis. Fatty changes were observed microscopically in male and female mice after acute exposure to chloroform concentrations ≥100 ppm (Culliford and Hewitt 1957; Kylin et al. 1963). Elevated liver triglycerides and liver glutathione (GSH) have also been reported (Ikatsu and Nakajima 1992). Liver necrosis was observed in female rats exposed to

4,885 ppm chloroform for 4 hours (Lundberg et al. 1986) and in male mice that died after acute exposure to 692-1,106 ppm chloroform (Deringer et al. 1953). Centrilobular granular degeneration was observed in rats, rabbits, and guinea pigs exposed to 25 ppm chloroform for 6 months, but not in dogs exposed to 25 ppm for the same time period (Torkelson et al. 1976); however, these pathological findings were not observed in the 50 ppm exposure group of rabbits and guinea pigs, or in the 85 ppm exposure group of guinea pigs. Although the liver effects in rabbits and guinea pigs were not doserelated, the small number of surviving animals in the higher exposure group may have biased the results of the study and may not fully describe the pathological effects of chloroform at the higher dose.

In two separate studies, Wang et al. (1994, 1995) investigated the effect of ethanol consumption or fasting, respectively, on the metabolism and toxicity of chloroform administered by inhalation of an acute duration. In the first study, male Wistar rats were pretreated with either ethanol, 2,000 mg/kg, or water. Eighteen hours later, the animals were exposed to air containing chloroform at concentrations of 0, 50, 100, or 500 ppm for 6 hours (5 rats a group). At 24 hours postexposure, animals were anesthetized, blood samples were collected for determination of SGOT and SGPT levels; livers were harvested and processed for determination of GSH levels. Chloroform produced dosedependent hepatotoxicity, and ethanol pretreatment enhanced this effect. In rats exposed by inhalation, hepatotoxicity was only evident at the highest dose (500 ppm); SGOT and SGPT values in treated rats were 47 and 24 international units per liter (IV/L) versus 30 and 16 IU/L in controls, respectively. GSH concentrations in rats exposed to chloroform were lowered in a dose-dependent manner. Significant ($p<0.05$) reductions were seen at the 500 ppm dose in rats exposed by inhalation. In the second study, rats were divided in two groups: those fasted over night and those allowed free access to food. The following day, 5 rats per group were exposed to chloroform once by inhalation at 0, 50, 100, or 500 ppm for 6 hours. Twenty-four hours after exposure, blood samples were collected for SGOT and SGPT determinations. Chloroform tended to produce hepatotoxicity in a dose-dependent manner, and fasting tended to potentiate the toxicity. Plasma SGOT activity was significantly elevated in the fasting group at 100 and 500 ppm and the fed group at 500 ppm as compared to controls. SGPT levels in the fasting group exposed to 500 ppm chloroform (212 IU/L) significantly exceeded those of the fasting control group (16 IU/L). GSH levels in the fasting group exposed to 500 ppm chloroform (2.22 mg/g) were significantly lower than those of the fasted control group (2.51 mg/g).

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Larson et al. (1996) investigated the ability of acute chloroform vapor exposure to produce toxicity and regenerative cell proliferation in the liver of female B6C3F_1 mice. Groups of 5 animals were exposed to 0, 0.3, 2, 10, 30, or 90 ppm chloroform via inhalation for 6 hours a day for 4 consecutive days. Animals were administered BrdU via an implanted osmotic pump, and cell proliferation was quantitated as the percentage of cells in S-phase (LI) measured by immunohistochemical detection of BrdU-labeled nuclei. At necropsy, livers were removed, weighed, examined macroscopically, and prepared for microscopic evaluation. Exposure to 90 ppm chloroform resulted in increased relative liver weights. Female mice exposed to chloroform for 4 days experienced a dose-dependent mild response of uniform hepatocyte lipid vacuolization. Scattered individual hepatocyte necrosis also occurred in a dose-dependent manner. Hepatic LI was significantly elevated in female mice in the 90 ppm dose group after 4 days exposure (9-fold; $p<0.05$).

In an earlier study, Larson et al. (1994c) investigated the ability of chloroform vapors to produce toxicity and regenerative cell proliferation in the liver and kidneys of female B6C3F_1 mice and male Fischer 344 rats, respectively. Groups of 5 animals were exposed to 0, 1, 3, 10, 30, 100, or 300 ppm chloroform via inhalation for 6 hours a day for 7 consecutive days. Actual exposure concentrations measured for mice were 0, 1.2, 3, 10, 29.5, 101, and 288 ppm and for rats were 0, 1.5, 3.1, 10.4, 29.3, 100, and 271 ppm. Necropsies were performed on day 8. Animals were administered BrdU via implanted osmotic pump for the last 3.5 days in order to measure S-phase cell proliferation using an LI method. Female mice exposed to 101 or 298 ppm exhibited centrilobular hepatocyte necrosis and severe diffuse vacuolar degeneration of mid-zonal and periportal hepatocytes, while exposure to 10 or 29.5 ppm resulted in mild-to-moderate vacuolar changes in centrilobular hepatocytes. Specifically, decreased eosinophilia of the centrilobular and mid-zonal hepatocyte cytoplasm relative to periportal hepatocytes was observed at 29.5 ppm. Livers of mice in the 1 and 3 ppm groups did not differ from controls. Slight, dose-related increases in the hepatocyte LIs were observed in the 10 and 30 ppm dose groups, while the LI was increased more than 30-fold in the 101 and 288 ppm groups. Relative liver weights were increased in a dose-dependent manner at exposures of 3 ppm and above. Livers from mice exposed to 101 or 288 ppm were enlarged and pale. In male rats, swelling and mild centrilobular vacuolation was observed only in the livers of rats exposed to 271 ppm. Necrosis was minimal and confined to individual hepatocytes immediately adjacent to the central vein; livers were dark red and congested. The hepatocyte LI in rats were increased only at 101 and 271 ppm, 3- and 7-fold over controls, respectively. An acute-duration inhalation MRL of 0.1 ppm was based on the

NOAEL of 3 ppm for hepatic effects in mice. More information on this MRL and how it was derived is located in the footnote to Table 2-1, Section 2.5 in Appendix A this profile.

Larson and coworkers (1996) investigated the ability of intermediate-duration chloroform vapor exposure to produce toxicity and regenerative cell proliferation in the liver of male and female $B6C3F_1$ mice. Groups of 8 animals of each sex were exposed to 0, 0.3, 2, 10, 30, or 90 ppm chloroform via inhalation for 6 hours a day, 7 days a week for 3, 6, or 13 weeks; additional groups of 8 animals of each sex were exposed for 6 hours a day, 5 days a week for 13 weeks. Animals were administered BrdU via implanted osmotic pump and cell proliferation was quantitated as the percentage of cells in S-phase. At necropsy, livers were removed, examined macroscopically, and then prepared for microscopic evaluation. In mice exposed for 3 weeks, no changes in relative liver weights occurred in males at any dose level, whereas females exposed to 90 ppm chloroform experienced a significant increase (10.7%; $p<0.05$) in relative liver weights. Liver lesions were noted in males and females at exposures of 30 and 90 ppm. Lesions were characterized by vacuolation and swelling of hepatocytes and variations in nuclear size. Cell proliferation was elevated in the livers of females and males at 30 and 90 ppm exposures, respectively. In mice exposed for 6 weeks, exposure to 90 ppm chloroform resulted in a significant increase (16.1%; $p<0.05$) in relative liver weights. Liver lesions were noted in females at exposures of 30 and 90 ppm; these lesions were characterized by mild degenerative changes in hepatocytes. An increase in liver LI was also noted in the females exposed to 30 and 90 ppm chloroform. In mice exposed 7 days a week for 13 weeks, relative liver weights increased in males exposed to 30 and 90 ppm chloroform and in females exposed to 90 ppm chloroform ($p<0.05$). Liver lesions were elevated above background in males and females at exposures of 30 and 90 ppm. Lesions were characterized by vacuolation and swelling of hepatocytes and variations in nuclear size. Cell proliferation was elevated in the livers of females and males at exposed to 90 ppm chloroform. Hepatic alterations in mice exposed 5 days a week for 13 weeks were similar to those of mice exposed 7 days a week; however, the severity of the lesions was diminished with significant effects seen only at the 90 ppm exposure level.

Renal Effects. Several studies regarding kidney toxicity effects in humans after inhalation exposure to chloroform were found. No biochemical renal anomalies were reported in one study examining factory workers in China exposed to varying levels of chloroform (Li et al. 1993). One report was obtained from case reports of death among women exposed to chloroform via anesthesia during childbirth (Royston 1924). The fatty degeneration of kidneys observed at autopsy indicated

chloroform-induced damage. A study by Aiking et al. (1994) examined the possible renal toxicity of chloroform exposure in competitive swimmers who trained in indoor and outdoor chlorinated swimming pools in the Netherlands. Although no significant differences in liver enzyme function were seen between any of the groups, the study did determine that β-2-microglobulin was elevated in the indoor pool swimmers (after controlling for possible age bias using multiple regression analysis), suggesting some degree of renal damage due to higher inhaled air concentrations of chloroform present in the air of indoor swimming pools.

In animals, the kidney is one of the target organs of inhalation exposure to chloroform. Groups of 20 female Wistar rats were exposed to 0, 30, 100, or 300 ppm chloroform via inhalation during Gd 7-16 and terminated on day 21 showed no changes in kidney weights compared to control animals (Baeder and Hofmann 1988). Larson et al. (1996) investigated the ability of acute chloroform vapor exposure to produce toxicity and regenerative cell proliferation in the kidneys of female $B6C3F_1$ mice. Groups of 5 animals were exposed to 0, 0.3, 2, 10, 30, or 90 ppm chloroform via inhalation for 6 hours a day for 4 consecutive days. At necropsy, kidneys were removed, weighed, examined macroscopically, and prepared for microscopic evaluation. Relative kidney weights were similar to controls at all chloroform exposure levels. Kidneys of female mice exposed to chloroform were not different from those of controls at any dose. Exposure to chloroform did not significantly affect the kidney cortex LI in females at any dose.

In an earlier study, Larson et al. (1994~) examined the ability of chloroform vapors to produce toxicity and regenerative cell proliferation in the liver and kidneys of female $B6C3F_1$ mice and male Fischer 344 rats, respectively. Groups of 5 animals were exposed to 0, 1, 3, 10, 30, 100, or 300 ppm chloroform via inhalation for 6 hours a day for 7 consecutive days. Actual exposure concentrations measured for mice were 0, 1.2, 3, 10, 29.5, 101, and 288 ppm and for rats were 0, 1.5, 3.1, 10.4, 29.3, 100, and 271 ppm. Necropsies were performed on day 8. The kidneys of mice were affected only at the 300 ppm exposure, with approximately half of the proximal tubules lined by regenerating epithelium and an increased LI of tubule cells of 8-fold over controls. In the kidneys of male rats exposed to 300 ppm, about 25-50% of the proximal tubules were lined by regenerating epithelium. The LI for tubule cells in the cortex was increased at 30 ppm and above.

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Tubular necrosis was observed in male mice after acute exposure to chloroform concentrations ≥246 ppm (Culliford and Hewitt 1957; Deringer et al. 1953). Tubular calcifications were observed in mice that survived the exposure and were terminated after a 12-month recovery period.

In a study of intermediate duration, increased kidney weight (both sexes) and cloudy swelling (males) were observed in rats exposed to chloroform concentrations ≥25 ppm chloroform (Torkelson et al. 1976). Results were not consistent in rabbits and guinea pigs under the same exposure conditions. Cloudy swelling, and tubular and interstitial nephritis were observed in groups of rats exposed to 25 ppm chloroform, but not in groups exposed to 50 ppm. The results in rabbits and guinea pigs, however, may be biased due to the low survival rate at the higher exposure level.

Larson and coworkers (1996) also investigated the ability of intermediate-duration chloroform vapor exposure to produce toxicity and regenerative cell proliferation in the kidneys of male and female $B6C3F_1$ mice. Groups of 8 animals of each sex were exposed to 0, 0.3, 2, 10, 30, or 90 ppm chloroform via inhalation for 6 hours a day, 7 days a week for 3, 6, or 13 weeks; additional groups of 8 animals of each sex were exposed for 6 hours a day, 5 days a week for 13 weeks. At necropsy, kidneys were removed, examined macroscopically, and prepared for microscopic evaluation. In mice exposed for 3 weeks, no changes were noted in relative kidney weights in either sex at any exposure level. While kidneys of female mice did not differ from those of controls at any dose, those of males were significantly affected by chloroform exposures of 30 ppm or more. Lesions were mainly in the epithelial cells of the proximal convoluted tubules, with 25 and 50% of cells affected in the 30 and 90 ppm groups, respectively. Cell proliferation was elevated in males at the 30 ppm exposure level, while female kidney LIs were not affected at any exposure level. In mice exposed for 6 weeks, no changes were noted in relative kidney weights at any exposure level. Kidneys from exposed females were not histologically different from controls at any exposure level, and kidney LIs were similar to control values at all exposure levels. In mice exposed 7 days a week for 13 weeks, no changes were noted in relative kidney weights in either sex at any exposure level. While kidneys of female mice did not differ from those of controls at any dose, those of males were significantly affected by chloroform exposures of 10 ppm or more. Lesions were mainly in the epithelial cells of the proximal convoluted tubules, with 25 and 50% of cells affected in the 30 and 90 ppm groups, respectively. Mineralization within the cortex and enlarged nuclei in the epithelial cells were also noted. Cell proliferation was elevated in the cortical tissues of males at the 30 and 90 ppm exposure level; in contrast, female

kidney LIs were not affected at any exposure level. In contrast, exposure to chloroform vapors 5 days a week for 13 weeks produced no adverse renal effects.

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to chloroform.

Larson et al. (1994c) noted that in female B6C3F_1 mice and male Fischer 344 rats exposed to 0, 1, 3, 10, 30, 100, or 300 ppm chloroform via inhalation for 6 hours a day for 7 consecutive days that body weight gains were significantly decreased relative to controls in mice exposed to 101 and 288 ppm (1% weight loss at 101 and 288 ppm). Body weight gain was significantly decreased in a concentration-dependent manner in rats exposed to 10 ppm of chloroform and above (2% weight loss at 271 ppm; weight gains of 9-12% at 10.4-101 ppm, as compared to 18% weight gain by controls).

A dose-dependent reduction in feed consumption, resulting in decreased body weight gain, was observed in pregnant female rats exposed to 30 ppm chloroform (7 hours a day for 10 days) and above during gestation (Baeder and Hofmann 1988). Newell and Dilley (1978) report that maternal body weights decreased in Sprague-Dawley rats when the chloroform concentration reached 4,117 ppm when exposed for 1 hour a day during Gd 7-14. Similarly, decreased body weight was observed in pregnant mice exposed to 100 ppm chloroform during gestation (Murray et al. 1979). Decreased body weight was reported in male rats exposed to chloroform at 271 ppm for 6 hours a day for 7 days; however, no discernable decrease in body weight was noted at concentrations from 1.5 to 100 ppm. Decreases in body weight were also noted in female mice exposed to 101 ppm chloroform for the same duration (Mery et al. 1994). Decreased body weight also occurred in male rats exposed to 50 ppm for 6 months (Torkelson et al. 1976).

Larson and coworkers (1996) also investigated the effect of intermediate exposure to chloroform vapor on body weight in male and female B6C3F_1 mice. Groups of 8 animals of each sex were exposed to 0, 0.3, 2, 10, 30, or 90 ppm chloroform via inhalation for 6 hours a day, 7 days a week for 3, 6, or 13 weeks; additional groups of 8 animals of each sex were exposed for 6 hours a day, 5 days a week for 13 weeks. In mice exposed 7 days a week for 3 weeks, body weights in females were unaffected, while those of males exposed to 90 ppm chloroform were significantly lower compared to controls (2% weight loss versus 6% weight gain). Exposure to chloroform 7 days a week for 6, or 13 weeks did not affect body weights in males or females; however, when exposed 5 days a week for 13 weeks,

body weight gains in males and females exposed to 90 ppm chloroform were slightly reduced compared to their respective controls (93 and 91%, respectively).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to chloroform.

Gearhart et al. (1993) studied the interactions of chloroform exposure with body temperature in mice. Male mice were exposed to chloroform concentrations up to 5,500 ppm chloroform for 6 hours and their core body temperature monitored. The largest decrease in core body temperature was observed in the 5,500 ppm exposure group, followed by the 2,000, 800, and 100 ppm groups. There was no significant decrease in *in vitro* cytochrome P-450 activity at any temperature tested. The data collected were used to develop a PBPK model, which is discussed in more detail in Section 2.3.5. Decreased feed consumption also been reported at chloroform doses as low as 30 ppm in rats (Baeder and Hofmann 1988).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding in-depth immunological effects in humans after inhalation exposure to chloroform. Only one study (Bomski et al. 1967) described the health effects of a group of 68 workers occupationally exposed to chloroform for 1-4 years in a pharmaceutical plant. Chloroform air concentrations ranged from 0.01 to 1 mg/L, and other solvents were also reported in the air in trace amounts. Splenomegaly was the only immunologically detected health effect in a small percentage of these cases.

Chloroform appears to have little effect on the spleen of laboratory animals. No histological changes were found in the spleen of mice exposed to chloroform concentrations as high as 1,106 ppm for l-3 hours (Deringer et al. 1953) or in male rats receiving 25 ppm of chloroform for 6 months (Torkelson et al. 1976). Female Wistar rats exposed to 0, 30, 100, or 300 ppm chloroform for 10 days via inhalation during Gd 7-16 also failed to show a change in maternal spleen organ weights (Baeder and Hofmann 1988).

Other information on the immunotoxicity of chloroform is limited to one study on effects of chloroform on host resistance in CD-l mice. A single exposure to 10.6 ppm chloroform for 3 hours

did not increase the mortality rate after streptococcal challenge and did not alter the ability of alveolar macrophages to destroy bacteria in these mice (Aranyi et al. 1986). After repeated chloroform exposure (3 hours a day for 5 days), the mortality rate significantly increased, but the bactericidal activity of macrophages was not suppressed compared to control animals.

2.2.1.4 Neurological Effects

The central nervous system is a major target for chloroform toxicity in humans and in animals. Chloroform was once widely used as an anesthetic during surgery in humans, but is not currently used as a surgical inhalant anesthetic in modern-day medical practice. Levels of 3,000-30,000 ppm were used to induce anesthesia (Featherstone 1947; Smith et al. 1973; Whitaker and Jones 1965). Concentrations of ≈40,000 ppm, if continued for several minutes, could result in death (Featherstone 1947). To induce anesthesia, increasing the concentration of chloroform gradually to 25,000 or 30,000 ppm during the first 2 or 3 minutes with maintenance at much lower levels was recommended. Concentrations <1,500 ppm are insufficient to induce anesthesia; concentration of 1,500-2,000 ppm cause light anesthesia (Goodman and Gilman 1980).

Dizziness and vertigo were observed in humans after exposure to 920 ppm chloroform for 3 minutes; headache and slight intoxication were observed at higher concentrations (Lehmann and Hasegawa 1910). Exhaustion was reported in 10 women exposed to ≥22 ppm chloroform during intermediateand chronic-duration occupational exposures (Challen et al. 1958). Chronic exposure to chloroform concentrations ≥77 ppm caused exhaustion, lack of concentration, depression, or irritability in 9 of 10 occupationally exposed women. A case report of an individual addicted to chloroform inhalation for ≈12 years reported psychotic episodes, hallucinations and delusions, and convulsions (Heilbrunn et al. 1945). Withdrawal symptoms, consisting of pronounced ataxia and dysarthria, occurred following an abrupt discontinuation of chloroform use. Moderate, unspecified, degenerative changes were observed in the ganglion cells in the putamen and the cerebellum at autopsy. Death resulted from an unrelated disease.

A study of 61 workers exposed for l-l5 years (average 7.8 years) attempted to delineate a possible exposure-effect relationship and to determine the toxicity of chloroform after long-term exposures at a low concentrations in factories in China (Li et al. 1993). Concentrations of chloroform ranged from 0.87 to 28.9 ppm. Dizziness, fatigue, somnolence, insomnia, increased dreaming, hypomnesia,

anorexia, and palpitations were significantly elevated in these individuals. Depression, anger, and fatigue were also reported to be significantly elevated. Significant changes were found in neurologic testings of Simple Visual Reaction Time, Digital Symbol Substitution, Digit Span, Benten Retention and Aim Pursuiting in some workers. A limitation of this study was that the exposed group, based on information indicating where the exposed groups originated, indicated that these individuals probably inhaled much more than just chloroform (i.e., other solvents, drugs, pesticides, etc.) and all the effects attributed to chloroform may be attributable to other chemicals in addition to chloroform.

Evidence of central nervous system toxicity in animals includes disturbed equilibrium in cats exposed to 7,200 ppm chloroform for 5 minutes, deep narcosis in cats exposed to 21,500 ppm for 13 minutes, deep narcosis in mice exposed to 4,000 ppm for 30 minutes, slight narcosis in mice exposed to 3,100 ppm for 1 hour, and no obvious effects in mice exposed to 2,500 ppm for 2 hours (Lehmann and Flury 1943). Memory retrieval was affected in mice exposed to chloroform via anesthesia (concentration not specified) (Valzelli et al. 1988). The amnesic effect was not long-lasting.

The highest NOAEL value and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to chloroform.

Several studies indicate that inhalation exposure to chloroform may cause reproductive effects in animals. Rats exposed to chloroform during gestation had decreased conception rates after exposure to 300 ppm, but not after exposure to 100 ppm (Schwetz et al. 1974). Studies by Baeder and Hofmann (1988) indicated that exposure to as little as 30 ppm chloroform resulted in increased fetal resorptions. Similarly, a decreased ability to maintain pregnancy, characterized by an increased number of fetal resorptions and decreased conception rates, was observed in mice exposed to 100 ppm chloroform (Murray et al. 1979). In addition to the reproductive effects described above, a significant increase in the percentage of abnormal sperm was observed in mice exposed to 400 ppm chloroform for 5 days (Land et al. 1979).

In males, groups of 10-12 male rats (strain not reported) were exposed to 0, 25, 50, or 85 ppm chloroform for 6 months. Adjusted testicular weights in the 50 and 85 ppm groups were greater than those of their respective controls, but were not different from those of other control groups within the same colony. Additionally, no histological changes were noted in testicular tissues of treated animals. The significant increase in testes weights reported in this study was considered to be spurious not likely a direct effect of chloroform exposure (Torkelson et al. 1976).

The highest NOAEL value and all reliable LOAEL values for reproductive effects in each species in the acute-duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to chloroform.

Chloroform-induced fetotoxicity and teratogenicity were observed in experimental animals. The offspring of rats exposed during gestation had delayed ossification and wavy ribs (30 ppm), acaudate fetuses with imperforate anus and missing ribs (100 ppm), and decreased fetal body weight and crownrump length, and increased fetal resorptions (300 ppm) (Schwetz et al. 1974). Slight growth retardation of live fetuses at 30 ppm was observed in rats exposed during gestation; no major teratogenic effects were observed (Baeder and Hofmann 1988). The offspring of mice exposed to 100 ppm chloroform during gestation had increased incidences of cleft palate, decreased ossification, and decreased fetal crown-rump length (Murray et al. 1979). The observed malformations occurred in the fetuses that were exposed during organogenesis (days 8-15). Increased resorptions were observed in dams exposed during Gd 1-7.

In another study using relatively higher doses, female Sprague-Dawley rats were exposed to 0, 942, 2,232, or 4,117 ppm chloroform 8 days during Gd 7-14, for 1 hour a day. The number of resorptions was enhanced (45% resorptions) and average fetal body weights declined in the highest exposure group only, with no adverse effects noted in the 2,232 ppm and lower doses. The average fetal weight was decreased at the highest dose. No gross teratologic effects or anomalies in ossification were observed in the offspring of exposed dams (Newell and Dilley 1978).

All reliable LOAEL values for developmental effects in each species in the acute-duration category are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to chloroform.

Inhalation exposure to 400 ppm chloroform for 5 days increased the percentage of abnormal sperm in mice (Land et al. 1979). Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to chloroform.

Studies in animals indicate that oral exposure to chloroform causes cancer (see Section 2.2.2.8). Because chloroform is carcinogenic in animals exposed orally and because chloroform has identical toxicological end points following oral or inhalation exposure, EPA (1985a) derived a q_1* for inhalation exposure to chloroform based on mouse liver tumor data from a chronic gavage study (NCI 1976). EPA considered the NCI (1976) study to be appropriate to use in the inhalation risk estimate because there are no inhalation cancer bioassays and no pharmacokinetic data to contraindicate the use of gavage data (IRIS 1995). The geometric mean of the estimates for male and female mice in the NCI (1976) study, $8x10^{-2}$ $(mg/kg/day)^{-1}$, was recommended as the inhalation q_l* for chloroform. EPA (1985a) combined the estimates for both data sets because the data for males includes observations at a lower dose, which appear to be consistent with the female data. Expressed in terms of air concentration, the q_l* is equal to $2.3x10^{-5}$ $(\mu g/m^3)^{-1}$ or $l.lx10^{-4}$ parts per billion $(ppb)^{-1}$

The air concentrations associated with individual, lifetime upper-bound risks of 10^{-4} to 10^{-7} are $4.3x10^{-3}$ to $4.3x10^{-6}$ mg/m^3 ($8.8x10^{-4}$ to $8.8x10^{-7}$ ppm), assuming that a 70-kg human breathes 20 m^3 air/day. The 10^{-4} to 10^{-7} levels are indicated in Figure 2- 1.

2.2.2 Oral Exposure

2.2.2.1 Death

Information regarding mortality in humans after oral exposure to chloroform is limited. In one report, a man died of severe hepatic injury 9 days after reportedly drinking ≈6 ounces of chloroform (3,755 mg/kg) (Piersol et al. 1933). He was admitted to a hospital in a deep coma within 15 minutes of ingestion. This man was also noted to be a long-time user of chloroform in his occupation and a heavy drinker, suggesting that damage inflicted by previous use of chloroform and alcohol over a long period of time may have been contributing factors in his death. In contrast, a patient who ingested 4 ounces (≈2,410 mg/kg) recovered from toxic hepatitis (Schroeder 1965). The recovery may have been due to better therapeutic handling of the case. Fatal doses have been reported to be as low as 10 mL (14.8 grams) or 212 mg/kg (Schroeder 1965).

Oral LD_{50}, (lethal dose, 50% kill) values in animals vary greatly. No deaths occurred in rats exposed to once 0.1-0.5 mL/kg chloroform by gavage in oil (Nakajima et al. 1995). Acute LD_{50} values of 2,000 mg/kg chloroform (Torkelson et al. 1976) and 2,180 mg/kg chloroform (Smyth et al. 1962) were reported for rats. LD_{50} values in male rats varied with age: 446 mg/kg for 14-day-olds, 1,337 mg/kg for young adults, and 1,188 mg/kg for old adults (Kimura et al. 1971). LD_{50} values were different for male rats (908 mg/kg/day) and female rats (1,117 mg/kg/day) (Chu et al. 1982b). Similarly, the LD_{50} for male mice was lower (1,120 mg/kg) than for female mice (1,400 mg/kg) (Bowman et al. 1978). In general, young adult males had lower survival rates. In another study, an acute oral LD_{50} value of 1,100 mg/kg/day was reported for male and female mice (Jones et al. 1958). Decreased survival rates were also observed in male mice exposed to 250 mg/kg/day chloroform for 14 days, but not in mice exposed to 100 mg/kg/day. Female mice, however, survived 500 mg/kg/day chloroform treatment (Gulati et al. 1988). Increased mortality was noted in 5 of 12 male mice exposed to 277 mg/kg/day in corn oil by gavage for 4 days (Larson et al. 1994d). Pregnant animals may be more susceptible to chloroform lethality. Increased mortality was observed in pregnant rats exposed to 516 mg/kg/day. Rabbits exposed to 63, 100, 159, 25 1, and 398 mg/kg/day chloroform during Gd 6-l 8 had increasing rates of mortality as the dose of chloroform increased (Thompson et al. 1974).

There was a high rate of mortality in rats exposed to 142 mg/kg/day chloroform in drinking water for 90 days and during a 90-day observation period. Histopathological examination revealed atrophy of

the liver and extensive squamous debris in the esophagus and gastric cardia. These changes suggested to the authors that the rats had died of starvation. Mortality was not increased in the 44 mg/kg/day group (Chu et al. 1982a). The vehicle and mode of administration may influence the lethality of chloroform in mice. In 90-day studies in mice, no effect on mortality was observed in groups treated by gavage with doses up to 250 mg/kg/day chloroform in oil (Munson et al. 1982) or with 435 mg/kg/day in drinking water (Jorgenson and Rushbrook 1980). The maximum tolerated dose of chloroform in drinking water was calculated as 306 mg/kg/day for mice (Klaunig et al. 1986). Survival was affected in mice exposed by gavage to 400 mg/kg/day chloroform in oil for 60 days, but not in those exposed to 100 mg/kg (Balster and Borzelleca 1982). Exposure to 150 mg/kg/day chloroform in toothpaste by gavage for 6 weeks caused death in 8 of 10 male mice (Roe et al. 1979). No death occurred in mice exposed to 149 mg/kg/day chloroform in oil for 30 days; there was an increased incidence of death in males exposed to 297 mg/kg/day (Eschenbrenner and Miller 1945a). No deaths occurred in dogs exposed to 120 mg/kg/day chloroform in toothpaste capsules for 12-18 weeks (Heywood et al. 1979).

Decreased survival was observed in rats exposed by gavage to concentrations ≥90 mg/kg/day chloroform in oil for 78 weeks and in female mice exposed to 477 mg/kg/day, but not in male mice exposed to 277 mg/kg/day time-weighted average (TWA) during the same time period (NCI 1976). In addition, no increase in compound-related mortality was observed in mice exposed by gavage to 60 mg/kg/day chloroform in toothpaste (Roe et al. 1979) in rats or mice exposed to ≥160 mg/kg/day chloroform in drinking water for chronic durations (Jorgenson et al. 1985; Klaunig et al. 1986). Similarly, mortality was not affected in dogs exposed to 30 mg/kg/day chloroform in toothpaste capsules for 7.5 years (Heywood et al. 1979).

The LD_{50} and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No credible studies were located regarding ocular effects in humans or animals after oral exposure to chloroform. The other systemic effects of oral exposure to chloroform are discussed below. The highest NOAEL values and all reliable LOAEL values for each effect in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Table 2-2. Levels of Significant Exposure to Chloroform - Oral

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	once (GO)				908 M (LD_{50})	Chu et al. 1982b
						1117 F (LD_{50})	
2	Rat (Sprague-Dawley)	once (G)				1337 M (LD_{50} for young adults)	Kimura et al. 1971
						1188 M (LD_{50} for old adults)	
						446 M (LD_{50} for 14-day olds)	
3	Rat (Wistar)	once (G)				2180 F (LD_{50})	Smyth et al. 1962
4	Rat (Sprague-Dawley)	10 d Gd 6-15 1-2 x/d (GO)				516 F (4/6 died)	Thompson et al. 1974
5	Rat (NS)	once (G)				2000 M (LD_{50})	Torkelson et al. 1976
6	Mouse (ICR Swiss)	once (GO)				1120 M (LD_{50})	Bowman et al. 1978
						1400 F (LD_{50})	
7	Mouse (CD-1)	14 d 1 x/d (GO)				250 M (5/8 died)	Gulati et al. 1988
8	Mouse (Swiss)	once (GO)				1100 (LD_{50})	Jones et al. 1958
9	Mouse (B6C3F1)	4 d 1 x/d (GO)				277 M (Unscheduled deaths; 5/12 mice)	Larson et al. 1994d

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
10	Rabbit (Dutch Belted)	13 d Gd 6-18 2 x/d (GO)				100 F (3/5 died)	Thompson et al. 1974
	Systemic						
11	Human	once (IN)	Resp		2410 M (respiratory tract obstruction)		Schroeder 1965
			Cardio			2410 M (arrhythmia)	
			Gastro		2410 M (vomiting)		
			Musc/skel		2410 M (muscle relaxation)		
			Hepatic			2410 M (jaundice and toxic hepatitis)	
			Renal			2410 M (oliguria)	
12	Rat (Sprague-Dawley)	once (GO)	Hemato		546 (reduced hemoglobin and hematocrit by 10-12%)		Chu et al. 1982b
			Renal		546 F (increased kidney weight)		
13	Rat (Fischer- 344)	once (GO)	Hepatic		34 M (elevated SDH, ALT and AST; scattered necrotic foci)		Larson et al. 1993
			Renal			34 M (renal proximal tubule necrosis)	
			Bd Wt	477 M			
14	Rat (Fischer- 344)	4 d 1 x/d (GO)	Hepatic	10 M	34 M (slight to mild centrilobular sinusoidal leukostasis)		Larson et al. 1995a
			Renal	10 M	34 M (degeneration of renal proximal tubules)		
			Bd Wt	90 M	180 M (decreased body weight gain)		

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
15	Rat (Fischer- 344)	4 d 1 x/d (W)	Hepatic	33.2 M	68.1 M (mild hepatocyte vacuolation)		Larson et al. 1995a
			Renal	57.5 M			
			Bd Wt		57.5 M (decreased body weight gain)		
16	Rat (Fischer- 344)	4 d (GO)	Resp		34 F (new bone formation; periosteal hypercellularity; degeneration of the olfactory epithelium and superficial Bowman's glands)		Larson et al. 1995b
			Hepatic	34 F		400 F (mild centrolobular vacuolization; sinusoidal leucostasis; mild to focally severe centrilobular hepatocyte degeneration and necrosis; diffuse centrolobular swelling)	
			Renal	100 F		200 F (distal nephrons with hyaline casts; proximal tubules lined with degenerated, necrotic or regenerating epithelium)	
			Bd Wt	34 F	400 F (weight loss approximately 14%)		
17	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)	Hemato		100 F (decreased hemoglobin and hematocrit)		Ruddick et al. 1983
			Hepatic		100 F (increased liver weight)		
			Renal	200 F	400 F (increased kidney weight)		
			Bd Wt			100 F (32% decreased body weight gain)	

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
18	Rat (Sprague-Dawley)	10 d Gd 6-15 1-2 x/d (GO)	Gastro			516 F (gastric erosions)	Thompson et al. 1974
			Hepatic			516 F *(acute toxic hepatitis)*	
			Renal			516 F (acute toxic nephrosis)	
			Bd Wt	79 F	126 F (decreased body weight gain)		
19	Rat (Sprague-Dawley)	10 d Gd 6-15 2 x/d (GO)	Dermal	50 F	126 F (alopecia)		Thompson et al. 1974
			Bd Wt	20 F	50 F (decreased maternal body weight gain)		
20	Rat (Wistar)	once (GO)	Hepatic		100 M (increased plasma GOT and GPT)		Wang et al. 1994
21	Rat (Wistar)	once (GO)	Hepatic		100 (increased plasma GOT & GPT activity)		Wang et al. 1995
22	Mouse (CD-1)	14 d 1x/d (GO)	Dermal	50	100 (rough hair coat)		Gulati et al. 1988
			Bd Wt	100 M	250 M (12% weight loss)	500 M (32% weight loss)	
23	Mouse (Swiss-Webster)	once (GO)	Hepatic		35 (midzonal fatty changes)	350 (centrilobular necrosis)	Jones et al. 1958
24	Mouse (B6C3F1)	once (GO)	Hepatic	34 F	238 F (small randomly scattered foci of hepatocyte necrosis)		Larson et al. 1993
25	Mouse (B6C3F1)	4 d 1 x/d (GO)	Hepatic	90 F	238 F (centrilobular vacuolar degeneration; increased hepatic cell proliferation)		*Larson et al. 1994b*

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
26	Mouse (B6C3F1)	4 d (W)	Hepatic	26[b] F	53 F (pale pink tinctorial changes in centrilobular hepatocytes)		Larson et al. 1994b
			Bd Wt		81 F (approximately 20% decreased body weight)		
27	Mouse (B6C3F1)	4 d 1 x/d (GO)	Hepatic		34 M (pale livers; mild centrilobular hepatocyte swelling, pale eosinophilc staining; periportal hepatocyte vacuolation)	138 M (centrilobular hepatocyte degeneration; scattered necrosis)	Larson et al. 1994d
			Renal			34 M (extensive acute necrosis, proximal convoluted tubule)	
			Bd Wt	277 M			
28	Mouse (CFLP-Swiss)	once (G)	Hepatic	59.2 M	199 M (increased SGPT)		Moore et al. 1982
			Renal	59.2 M		199 M (tubular necrosis; increased thymidine uptake)	
29	Mouse (CFLP Swiss)	once (GO)	Hepatic	65.6 M	273 M (increased thymidine uptake, increased SGOT)		Moore et al. 1982
			Renal	17.3 M		65.6 M (tubular necrosis)	
30	Mouse (CD-1)	14 d 1 x/d (GO)	Hemato	250			Munson et al. 1982
			Hepatic	125	250 (increased SGPT and SGOT levels)		
			Bd Wt	125 M	250 M (16% decreased body weight)		

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
31	Mouse (B6C3F1)	5 or 12 d 5 d/wk 1 x/d (GO)	Hepatic			263 F (necrotic, hydrotropic, swollen, and rounded hepatocytes; macrophage and neutrophil infiltration)	Pereira 1994
			Bd Wt	263 F			
32	Mouse (B6C3F1)	5 d 24 hr/d (W)	Hepatic		67.1 F (29% decreased relative liver weight; smaller hepatocytes with dense nonvacuolated and basophilic cytoplasm)		Pereira 1994
			Bd Wt	67.1 F			
			Other		67.1 F (decreased water consumption)		
33	Mouse (B6C3F1)	12 d 24 hr/d (W)	Hepatic		625.4 F (vacuolated hepatocytes)		Pereira 1994
			Bd Wt	625.4 F			
34	Rabbit (Dutch Belted)	13 d Gd 6-18 1 x/d (GO)	Gastro		20 F (diarrhea)		Thompson et al. 1974
			Bd Wt	35 F	50 F (decreased maternal body weight gain)		
	Immunological/Lymphoreticular						
35	Rat (Sprague-Dawley)	once (GO)		765 F	1071 F (reduced lymphocytes)		Chu et al. 1982b
36	Mouse (CD-1)	14 d 1 x/d (GO)			50 (suppressed humoral immunity)		Munson et al. 1982
	Neurological						
37	Human	once (IN)				2410 M (deep coma)	Schroeder 1965

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
38	Mouse (ICR)	14 d 1 x/d (GO)		31.1 M			Balster and Borzelleca 1982
39	Mouse (ICR)	once (GO)			484 M (calculated ED_{50} for motor performance)		Balster and Borzelleca 1982
40	Mouse (ICR Swiss)	once (GO)				500 (ataxia, incoordination, and anesthesia; brain hemorrhage)	Bowman et al. 1978
41	Mouse (CD-1)	14 d 1 x/d (GO)		100 M	250 M (hunched posture, inactivity)		Gulati et al. 1988
42	Mouse (Swiss)	once (GO)				350 (calculated ED_{50} for narcosis)	Jones et al. 1958
43	Mouse (CD-1)	10 d 1 x/d (GO)		10 M	30 M (taste aversion)		Landauer et al. 1982
	Reproductive						
44	Rat (Sprague-Dawley)	10 d Gd 6-15 1-2 x/d (GO)		300 F		316 F (increased resorptions)	Thompson et al. 1974
45	Rabbit (Dutch Belted)	13 d Gd 6-18 2 x/d (GO)		25 F		63 F (abortion; no viable concepti)	Thompson et al. 1974
	Developmental						
46	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)		200	400 (19% decreased fetal weight)		Ruddick et al. 1983

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
47	Rat (Sprague-Dawley)	10 d Gd 6-15 1-2 x/d (GO)		300	316 (decreased fetal weight)		Thompson et al. 1974
48	Rat (Sprague-Dawley)	10 d Gd 6-15 2 x/d (GO)		50	126 (decreased fetal weight)		Thompson et al. 1974
49	Rabbit (Dutch Belted)	13 d Gd 6-18 2 x/d (GO)		100			Thompson et al. 1974

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	INTERMEDIATE EXPOSURE						
	Death						
50	Rat (Sprague-Dawley)	90 d (W)				142.2 (high mortality during exposure and during recovery period)	Chu et al. 1982a
51	Mouse (Schofield)	6 wk 6 d/wk (G)				150 M (8/10 died)	Roe et al. 1979
	Systemic						
52	Rat (Sprague-Dawley)	90 d (W)	Hemato	149.8			Chu et al. 1982a
			Bd Wt	44.9	142.2 (25% decreased body weight gain)		
53	Rat (Sprague-Dawley)	28 d (W)	Hemato	22.8 M	193 M (decreased neutrophils)		Chu et al. 1982b
			Hepatic	193 M			
			Renal	193 M			
54	Rat (Osborne-Mendel)	90 d (W)	Resp	160 M			Jorgenson and Rushbrook 1980
			Gastro	160 M			
			Hemato	160 M			
			Hepatic	160 M			
			Renal	160 M			
			Bd Wt	81 M	160 M (11-17% decreased body weight)		

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
55	Rat (Fischer- 344)	3 wk 5 d/wk 1 x/d (GO)	Hepatic	90 M	180 M (degeneration of centrilobular hepatocytes)		Larson et al. 1995a
			Renal	90 M	180 M (progressive degeneration of the proximal tubules)		
			Bd Wt	180 M			
56	Rat (Fischer- 344)	3 wk 7 d/wk 1 x/d (W)	Hepatic	62.3 M	106 M (mild hepatocyte vacuolation)		Larson et al. 1995a
			Renal	6.0 M	17.4 M (increased numbers of focal areas of regenerating renal proximal tubular epithelium and cell proliferation)		
			Bd Wt	62.3 M	106 M (25% decrease in weight gain - taken from graph)		
57	Rat (Fischer- 344)	3 wk 5 d/wk (GO)	Resp		34 F (new bone formation; periosteal hypercellularity)		Larson et al. 1995b
			Hepatic	100 F	400 F (diffuse vacuolar change; focal centrilobular degeneration)		
			Renal	34 F	100 F (proximal tubule epithelial regeneration, dilation and mineralized concretions)		
			Bd Wt		100 F (significant decrease in weight gain)		

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference
58	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (G)	Hemato	150	410	(increased cellular proliferation in bone marrow)			Palmer et al. 1979
			Hepatic	30	150	(increased relative liver weight)	410	(fatty changes, necrosis)	
			Renal	30	150	(increased relative kidney weight)			
59	Mouse (B6C3F1)	90 d 1 x/d (GO)	Hepatic		60	(fatty changes)	270	(cirrhosis)	Bull et al. 1986
			Bd Wt	130 M	270 M	(15% decreased body weight)			
60	Mouse (Strain A)	30 d 1 x/d (GO)	Hepatic	297			594	(cirrhosis)	Eschenbrenner and Miller 1945a
61	Mouse (CD-1)	105 d 1 x/d (GO)	Resp	41					Gulati et al. 1988
			Hepatic	16 F	41 F	(increased liver weight and hepatocellular degeneration)			
			Renal	41					
62	Mouse (B6C3F1)	90 d (W)	Resp	435 F					Jorgenson and Rushbrook 1980
			Gastro	435 F					
			Hemato	435 F					
			Hepatic	32 F	64 F	(fatty changes)			
			Renal	435 F					

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
63	Mouse (B6C3F1)	52 wk 7 d/wk (W)	Resp	257 M			Klaunig et al. 1986
			Hepatic		86 M (focal necrosis)		
			Renal			86 M (tubular necrosis)	
			Bd Wt		86 M (15% decreased body weight gain)		
64	Mouse (B6C3F1)	3 wk 5 d/wk 1 x/d (GO)	Hepatic		34 F (vacuolation of the centrilobular and midzonal hepatocytes; increased ALT and SDH)		Larson et al. 1994b
			Renal	477 F			
65	Mouse (B6C3F1)	3 wk 7 d/wk (W)	Hepatic		82 F (increased liver weight)		Larson et al. 1994b
			Renal	329 F			
66	Mouse (B6C3F1)	3 wk 5 d/wk 1 x/d (GO)	Hepatic	34 M	90 M (centrilobular hepatocyte swelling; loss of eosinophilia)	138 M (centrilobular and periportal hepatocyte degeneration and necrosis)	Larson et al. 1994d
			Renal		34 M (regenerating proximal convoluted tubules)	277 M (degeneration & necrosis of the proximal tubules)	
			Bd Wt	138 M	277 M (15-20% decrease in body weight)		
67	Mouse (CD-1)	90 d 1 x/d (GO)	Hepatic		50 (hydropic degeneration)		Munson et al. 1982
			Renal		50 (chronic inflammation of lymphocytes)		
			Bd Wt	250			

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
68	Mouse (B6C3F1)	33 or 159 d 5 d/wk 1 x/d (GO)	Hepatic		263 F	(30.1-38.2% increase in relative liver weight; focal areas of necrotic, swollen, rounded, and pale hepatocytes and a low number of mononuclear cells)	Pereira 1994
			Bd Wt	263 F			
69	Mouse (B6C3F1)	33 d 24 hr/d (W)	Hepatic	438.5 F			Pereira 1994
			Bd Wt	438.5 F			
70	Mouse (B6C3F1)	159 d 24 hr/d (W)	Hepatic		363.5 F	(31.4% increase in relative liver weight)	Pereira 1994
			Bd Wt	386 F			
71	Dog (Beagle)	6 wk 6 d/wk 1 x/d (C)	Hepatic	15[c]	30	(significantly increased SGPT activity)	Heywood et al. 1979
Immunological/Lymphoreticular							
72	Mouse (CD-1)	90 d 1 x/d (GO)			50	(depressed humoral immunity)	Munson et al. 1982
Neurological							
73	Mouse (ICR)	90 d 1x/d (GO)		31.1 M			Balster and Borzelleca 1982
74	Mouse (ICR)	60 d 1x/d (GO)			100 M	(operant behavior affected)	Balster and Borzelleca 1982

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Reproductive						
75	Rat (Osborne-Mendel)	90 d (W)		160 M			Jorgenson and Rushbrook 1980
76	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (G)		150		410 (gonadal atrophy)	Palmer et al. 1979
77	Mouse (CD-1)	105 d 1 x/d (GO)		41			Gulati et al. 1988
	Developmental						
78	Mouse (ICR)	6-10 wk 1 x/d (GO)		31.1			Burkhalter and Balster 1979
79	Mouse (CD-1)	105 d 1 x/d (GO)			41 M (increased epididymal weights, degeneration of epididymal epithelium in F_1)		Gulati et al. 1988
80	Mouse (CD-1)	105 d 1 x/d (GO)			41 F (increased liver weight and hepatocellular degeneration in F_1 females)		Gulati et al. 1988
	Cancer						
81	Mouse (Strain A)	30 d 1 x/d (GO)				594 (CEL: hepatomas)	Eschenbrenner and Miller 1945a

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	CHRONIC EXPOSURE						
	Death						
82	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)				90 M (decreased survival)	NCI 1976
						100 F	
83	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)				477 F (decreased survival)	NCI 1976
	Systemic						
84	Human	1-5 yr	Hepatic	0.96			De Salva et al. 1975
			Renal	0.96			
85	Human	10 yr 1 x/d (IN)	Hemato		21 M (decreased erythrocytes)		Wallace 1950
			Hepatic			21 M (increased sulfobromophthalein sodium retention)	
			Renal			21 M (albuminuria)	
86	Rat (Osborne-Mendel)	104 wk 7 d/wk (W)	Renal	160 M			Jorgenson et al. 1985
			Bd Wt	38 M	81 M (decreased body weight)		

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
87	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)	Resp	200 F			NCI 1976
			Cardio	200 F			
			Gastro	200 F			
			Hemato	200 F			
			Musc/skel	200 F			
			Hepatic	100 F	200 F (necrosis of hepatic parenchyma)		
				180 M			
			Renal	200 F			
			Bd Wt		90 M (15% decreased weight gain)		
88	Rat (Wistar)	180 wk 7 d/wk (W)	Hepatic			200 (adenofibrosis)	Tumasonis et al. 1985, 1987
			Bd Wt			200 M (50% decreased body weight gain)	
89	Mouse (B6C3F1)	104 wk 7 d/wk (W)	Bd Wt	130 F	263 F (decreased body weight)		Jorgenson et al. 1985
90	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)	Resp		238 F (pulmonary inflammation)		NCI 1976
			Cardio		238 F (cardiac thrombosis)		
			Gastro	477 F			
			Hemato	477 F			
			Musc/skel	477 F			
			Hepatic			138 M (nodular hyperplasia of the liver)	
						238 F	
			Renal	477 F			
			Bd Wt	477 F			

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
91	Mouse (ICI)	80 wk 6 d/wk (G)	Resp	60			Roe et al. 1979
			Hepatic		17 (fatty degeneration)		
			Renal	60			
			Bd Wt	60			
92	Dog (Beagle)	7.5 yr 6 d/wk (C)	Cardio	30			Heywood et al. 1979
			Hemato	30			
			Hepatic		15[d] (increased SGPT activity)		
			Renal	15	30 (fatty changes)		
			Bd Wt	30			
	Neurological						
93	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)		200 F			NCI 1976
94	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)		477 F			NCI 1976
95	Mouse (ICI)	80 wk 6 d/wk (G)		60			Roe et al. 1979
	Reproductive						
96	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)		200 F 180 M			NCI 1976

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
97	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)		477 F 277 M				NCI 1976
98	Dog (Beagle)	7.5 yr 6 d/wk (C)		30				Heywood et al. 1979
	Cancer							
99	Rat (Osborne-Mendel)	104 wk 7 d/wk (W)				160 M	(CEL: tubular cell adenoma)	Jorgenson et al. 1985
100	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)				90 M 200 F	(CEL: tubular cell adenoma and carcinoma; tubular cell neoplasms in 4/50) (CEL: kidney tubular cell neoplasms in 2/48)	NCI 1976; Dunnick and Melnick 1993
101	Rat (Wistar)	180 wk 7 d/wk (W)				200 F	(CEL: hepatic neoplastic nodules)	Tumasonis et al. 1985, 1987
102	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)				138 M 238 F	(CEL: hepatocellular adenomas or carcinomas in 18/50 mice) (CEL: hepatocellular adenomas or carcinomas in 36/45 mice)	NCI 1976; Dunnick and Melnick 1993

Table 2-2. Levels of Significant Exposure to Chloroform - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
103	Mouse (ICI)	80 wk 6 d/wk (G)				60 M	(CEL: epithelial tumors of the kidney)	Roe et al. 1979

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an acute oral minimal risk level (MRL) of 0.3 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

[c]Used to derive an intermediate oral MRL of 0.1 mg/kg/day; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

[d]Used to derive an chronic oral MRL of 0.01 mg/kg/day; dose adjusted for intermittent exposure and divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

ALT = alanine amino transferase; ST = aspartate amino transferase; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); ED_{50} = effective dose for a given effect in 50% of animals; F = female; F_1 = first filial generation; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; Hemato = hematological; hr = hour(s); (IN) = ingestion; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL= no-observed-adverse-effect level; NS = not specified; Resp = respiratory; SDH = sorbitol dehydrogenase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; (W) = drinking water; wk = week; x = time(s); yr = year(s)

Figure 2-2. Levels of Significant Exposure to Chloroform - Oral

Acute (≤14 days)

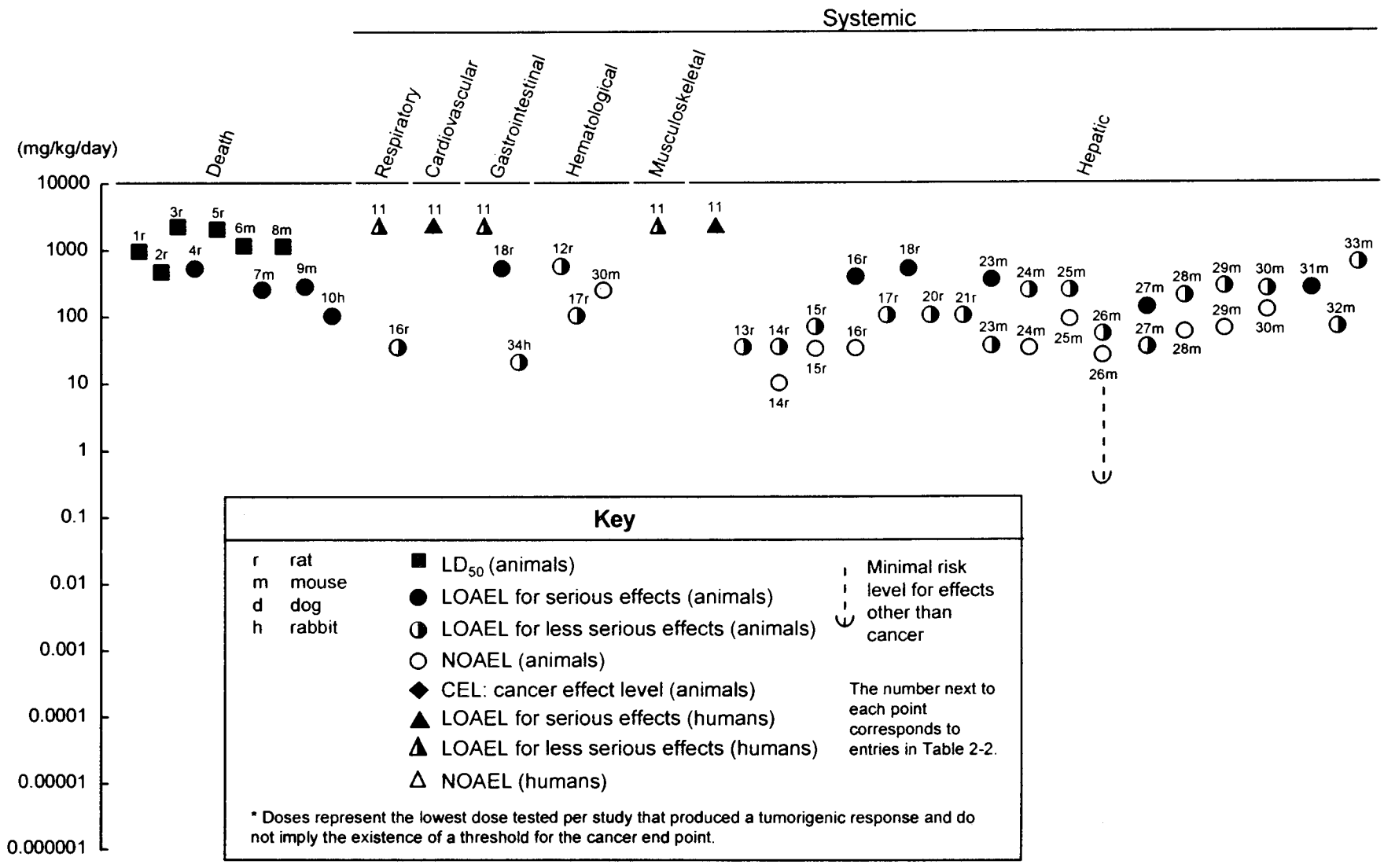


Figure 2-2. Levels of Significant Exposure to Chloroform - Oral (cont.)

Acute (≤14 days)

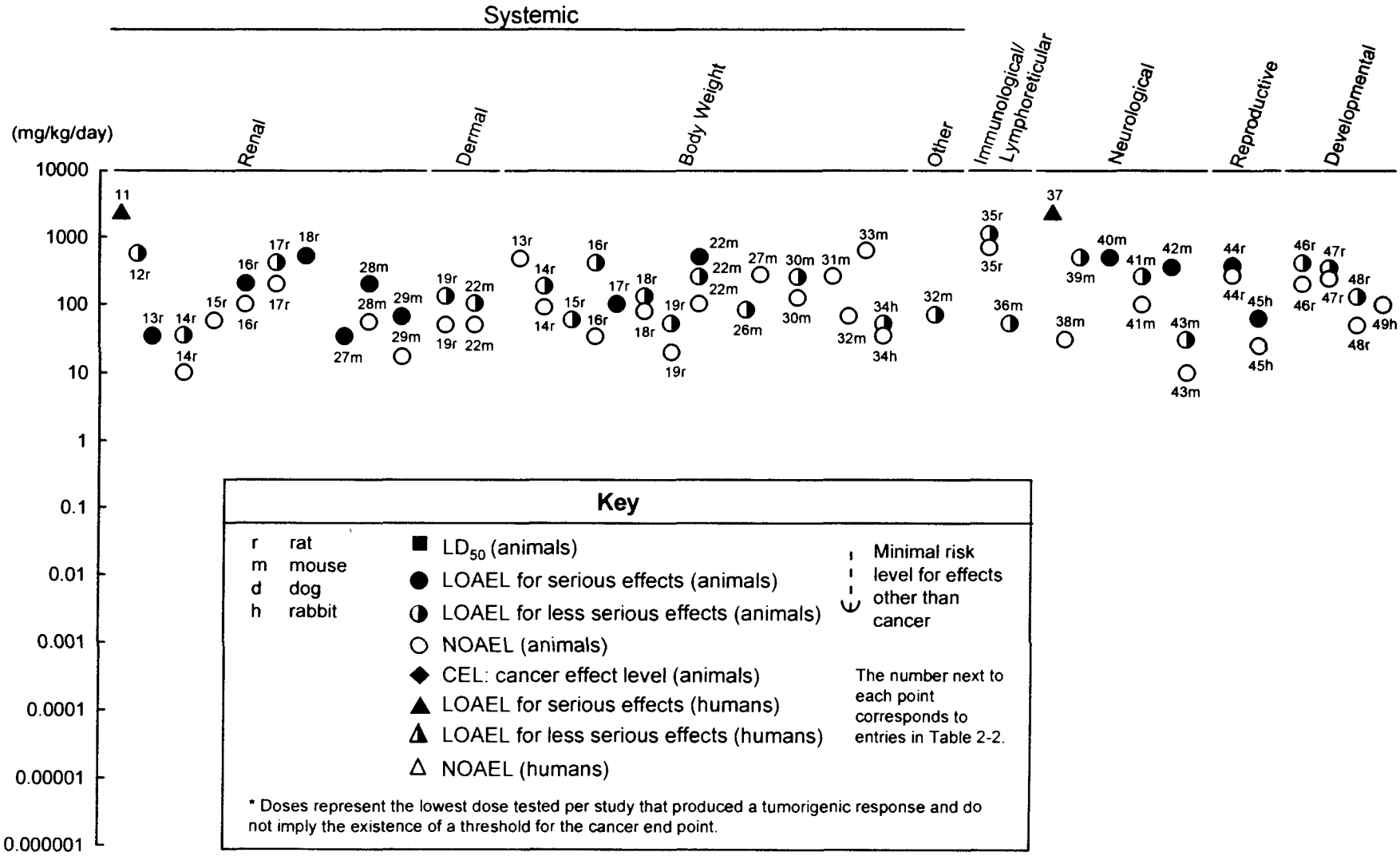


Figure 2-2. Levels of Significant Exposure to Chloroform - Oral (cont.)

Intermediate (15-364 days)

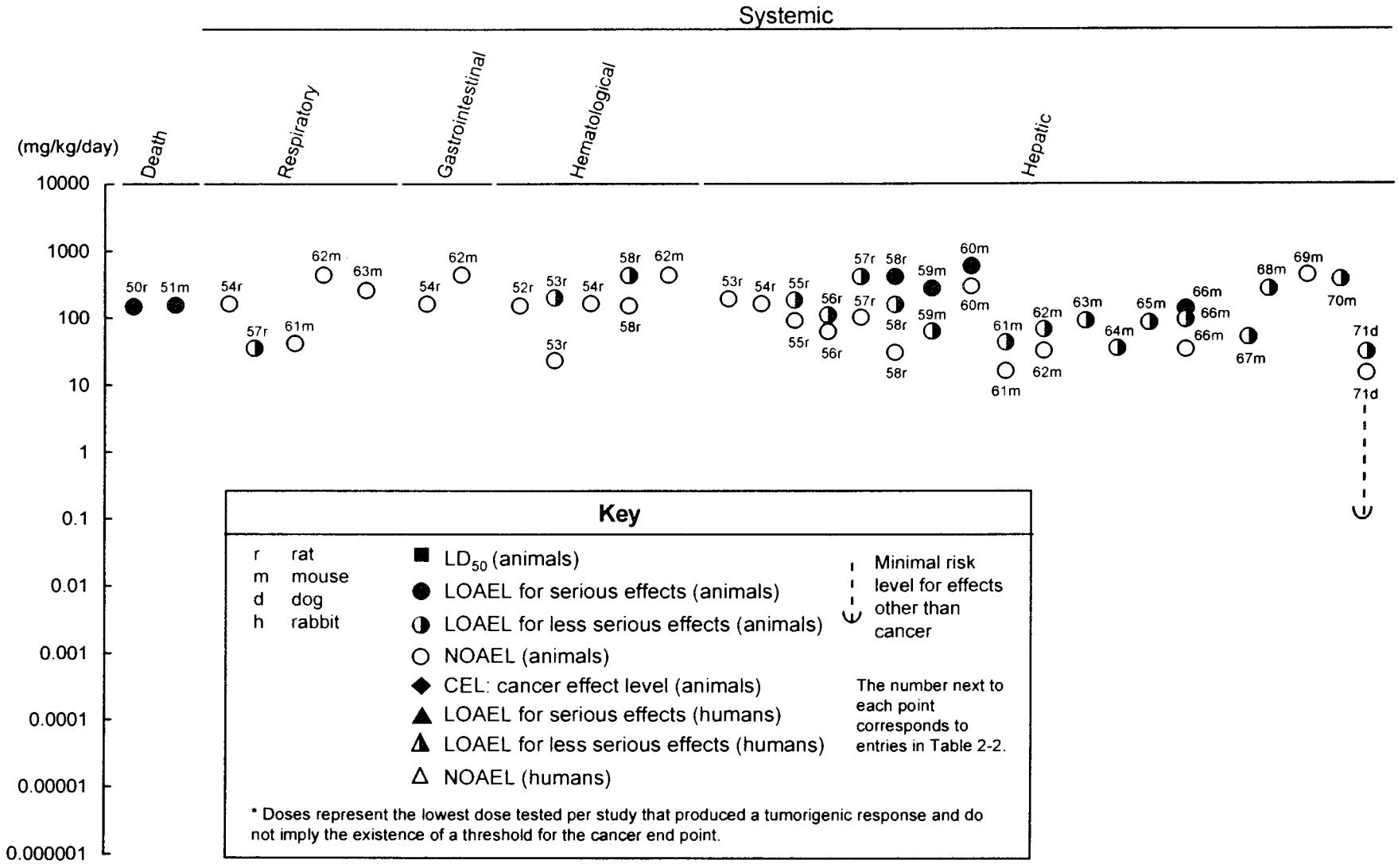


Figure 2-2. Levels of Significant Exposure to Chloroform - Oral (cont.)

Intermediate (15-364 days)

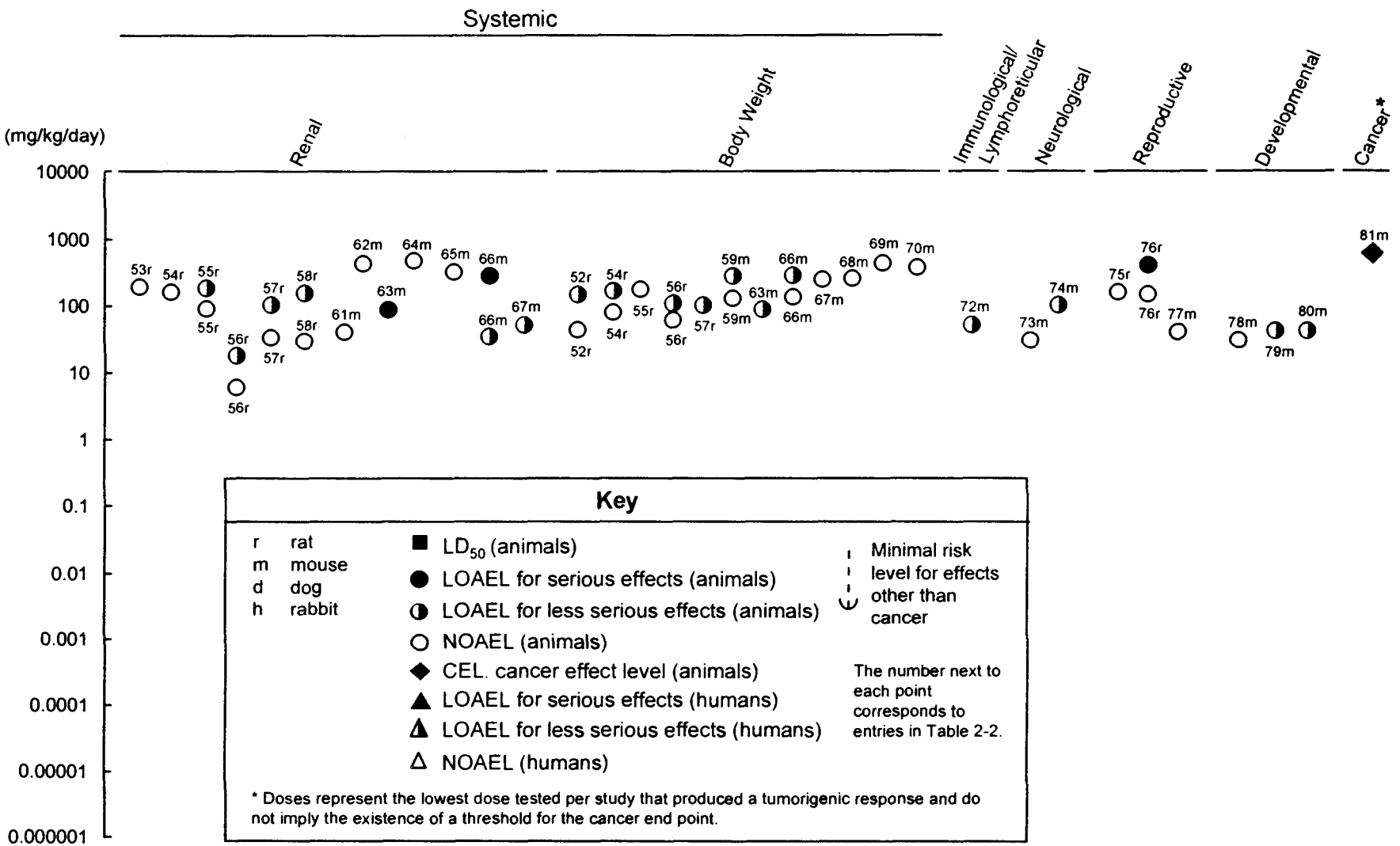
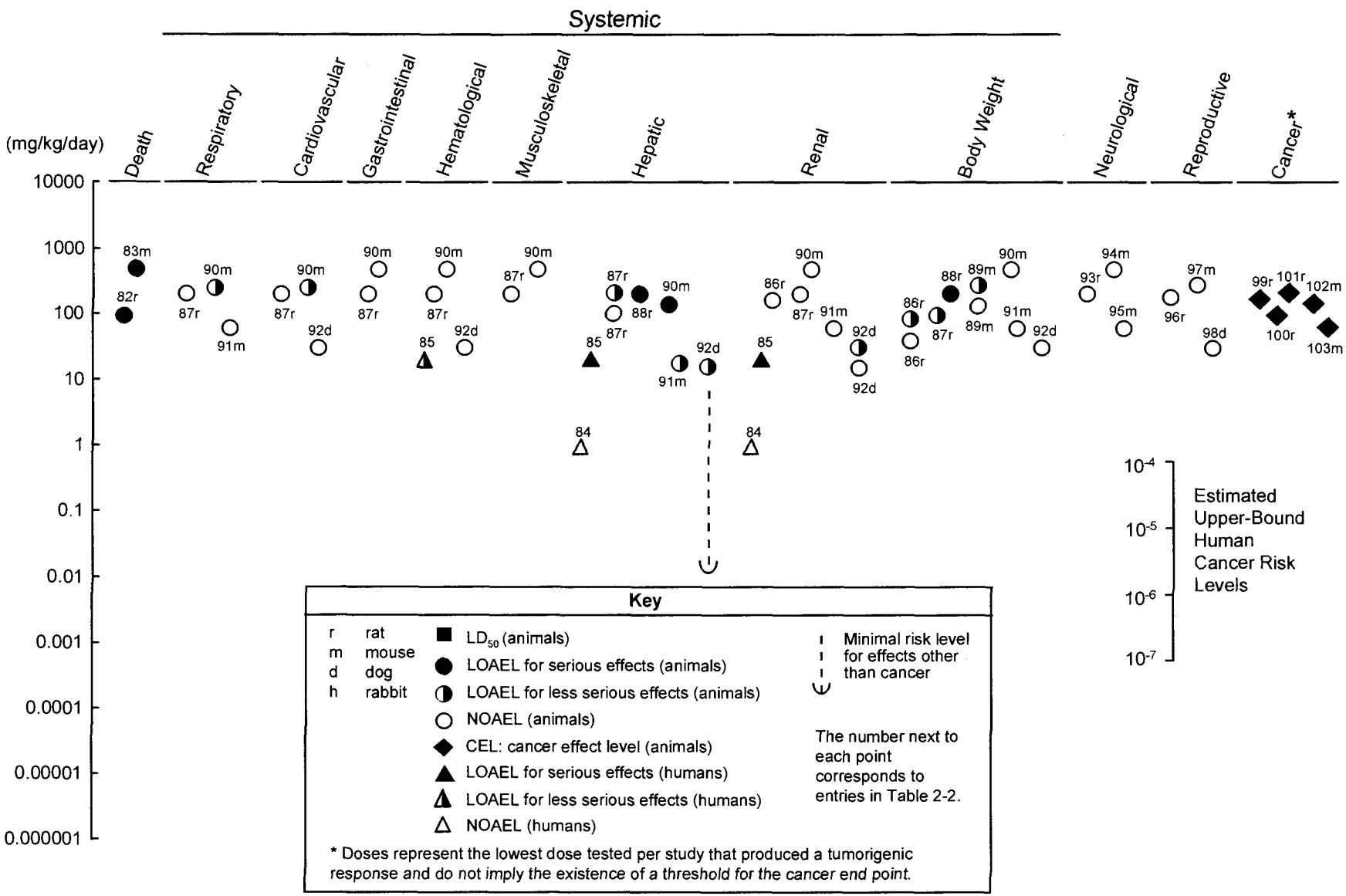


Figure 2-2. Levels of Significant Exposure to Chloroform - Oral (cont.)

Chronic (≥365 days)



2. HEALTH EFFECTS

Respiratory Effects. Information regarding respiratory effects in humans after oral exposure to chloroform is limited. Upper respiratory tract obstruction due to muscular relaxation was observed in a patient who accidentally ingested ≈2,410 mg/kg chloroform (Schroeder 1965). Congested lungs and scattered patches of pneumonic consolidation were found at autopsy in a man who committed suicide by drinking ≈6 ounces (3,755 mg/kg) of chloroform (Piersol et al. 1933). In both of these case studies, very large doses of chloroform were consumed. Thus, the respiratory effects noted may not be characteristic of those seen after ingestion of more moderate doses.

The majority of animal data suggest that the respiratory system is not a target of chloroform-induced toxicity after oral exposure. However, in one study, female Fisher 344 rats administered chloroform by gavage in corn oil at doses of 34, 100, 200, or 400 mg/kg/day for 4 days or 3 weeks did exhibit dose-dependent nasal lesions consisting of early phases of new bone formation, periosteal hypercellularity, and degeneration of the olfactory epithelium and superficial Bowman's glands (Larson et al. 1995b). In other studies, no treatment-related histopathological changes were found in the lungs of rats exposed to 160 mg/kg/day or mice exposed to 435 mg/kg/day chloroform in drinking water in a 90-day study (Jorgenson and Rushbrook 1980), in mice exposed by gavage to 41 mg/kg/day chloroform in oil for 105 days (Gulati et al. 1988), or in mice exposed to 257 mg/kg/day in drinking water for 1 year (Klaunig et al. 1986).

Following chronic exposure, no histopathological changes were observed in rats exposed by gavage to 200 mg/kg/day TWA chloroform in oil (NCI 1976). Respiratory disease was observed in all chloroform-exposed groups of rats (≥15 mg/kg/day); however, no histopathological changes were observed in a 60 mg/kg/day exposure group during another experiment by the same investigators (Palmer et al. 1979). No histopathological changes were observed in the lungs of male mice exposed by gavage to 277 mg/kg/day TWA chloroform in oil for 78 weeks (NCI 1976) or to 60 mg/kg/day in toothpaste for 80 weeks (Roe et al. 1979).

Cardiovascular Effects. Information regarding cardiovascular effects after oral exposure to chloroform is limited to case report studies. On admission to the hospital, the blood pressure was 140/90 mm Hg and pulse was 70 beats per minute (bpm) in a patient who accidentally ingested ≈2,410 mg/kg chloroform (Schroeder 1965). Electrocardiography showed occasional extra systoles and a slight S-T segment depression. The patient recovered with no persistent cardiovascular change, In another individual, blood pressure was 100/40 mm Hg and pulse was 108 bpm after ingestion of an

unknown quantity of chloroform and alcohol (Storms 1973). In both of these case studies, other factors (e.g., age, consumption of alcohol, suicidal/agitated state) may have contributed to the cardiovascular effects seen. Thus, it would appear that no studies exist which reliably indicate the presence of cardiovascular effects after oral chloroform exposure in humans.

Information regarding cardiovascular effects in animals after oral exposure to chloroform is limited; the data suggest that, at the doses utilized, the cardiovascular system was not a target for chloroform toxicity. No histopathological changes were observed in rats and mice chronically exposed by gavage to 200 and 477 mg/kg/day TWA chloroform, respectively, for 78 weeks (NCI 1976). In this study, cardiac thrombosis was observed in low-dose female mice, but was not seen in high-dose female or male mice or either sex of rat at any dose. Similarly, no cardiovascular changes were observed in dogs exposed to 30 mg/kg/day chloroform in toothpaste capsules for 7.5 years (Heywood et al. 1979).

Gastrointestinal Effects. Retrostemal soreness, pain on swallowing, and gastric distress with vomiting were reported in cases of intentional and accidental ingestion of chloroform (Piersol et al. 1933; Schroeder 1965). At autopsy, congestion with patchy necrosis of the mucosa was observed in the stomach and duodenum of a man who died after drinking ≈3,755 mg/kg chloroform (Piersol et al. 1933). The colonic mucosa was edematous, and the rectosigmoid junction was hemorrhagic. A 16-year-old female who ingested an unknown of amount of chloroform arrived at a hospital semiconscious and with repeated vomiting. She was treated with gastric lavage, antacids, intravenous glucose, and antiemetics. She had apparently recovered and was released. Seven days later, she presented with hepatomegaly, slightly depressed hemoglobin, and an abnormal liver sonogram, but no gastric side-effects (Hakim et al. 1992).

The effects of chronic oral exposure to chloroform, as a by-product of the chlorination of drinking water, were evaluated in four epidemiology studies (Alavanja et al. 1978; Cantor et al. 1978; Saurez-Varela et al. 1994; Young et al. 1981). The association between the incidence of gastrointestinal cancer in humans and the chlorination of drinking water is discussed in Section 2.2.2.8. The data from these studies should be viewed with caution as many other known or suspected carcinogens are known to exist in chlorinated drinking water.

Gastrointestinal irritation has been observed in some animals after oral exposure to chloroform. Gastric erosions were observed in pregnant rats gavaged with 516 mg/kg chloroform in oil during

gestation (Thompson et al. 1974). Rabbits exposed by gavage to 20 mg/kg/day chloroform in oil during gestation had diarrhea; no histological results were provided. In a 90-day drinking-water study, no histopathological changes were observed in rats and mice exposed to 160 and 435 mg/kg/day chloroform, respectively (Jorgenson and Rushbrook 1980). Vomiting was observed in dogs exposed to 30 mg/kg/day chloroform in toothpaste capsules for 12-18 weeks (Heywood et al. 1979). In a chronic exposure study, no histopathological changes in gastrointestinal tissue were observed in rats and mice exposed by gavage to 200 and 477 mg/kg/day TWA chloroform, respectively (NCI 1976).

Hematological Effects. The only information regarding hematological effects in humans after chronic oral exposure to chloroform was reported in a case study. Decreased erythrocytes and hemoglobin were observed in a subject who ingested ≈21 mg/kg/day chloroform in a cough medicine for 10 years (Wallace 1950). The lack of detail and the potential for confounding factors in this study does not allow a firm conclusion regarding the hematological effects of oral exposure to chloroform in humans.

Hematological effects have been observed in some animals after oral exposure to chloroform. Hemoglobin and hematocrit decreased in male and female rats after a single oral dose of 546 mg/kg chloroform in oil (Chu et al. 1982b) and in female rats exposed to 100 mg/kg/day chloroform during gestation (Ruddick et al. 1983). However, no hematological changes were observed in mice exposed to 250 mg/kg/day for 14 days (Munson et al. 1982). In an intermediate-duration study, decreased neutrophils were observed in rats exposed to 192.98 mg/kg/day in drinking water (Chu et al. 1982b); however, no hematological changes were observed in rats and mice exposed to 160 and 435 mg/kg/day chloroform, respectively, for 90 days in drinking water (Chu et al. 1982a; Jorgenson and Rushbrook 1980). Increased cellular proliferation in the bone marrow was observed in rats exposed by gavage for 13 weeks to 410 mg/kg chloroform in toothpaste (Palmer et al. 1979). No hematological changes were observed, however, in rats similarly exposed to 165 and 60 mg/kg/day chloroform by gavage for 52 and 80 weeks, respectively. Moreover, no histopathological changes in hematopoietic tissues were observed in rats and mice after chronic exposure to 200 and 477 mg/kg/day TWA chloroform in oil, respectively (NCI 1976). No hematological effects were observed in dogs exposed to 30 mg/kg/day chloroform in toothpaste in capsules for 7.5 years (Heywood et al. 1979). In conclusion, no consistent hematological effects were noted in human or animal studies of oral exposure to chloroform.

2. HEALTH EFFECTS

Musculoskeletal Effects. The only information regarding musculoskeletal effects in humans after oral exposure to chloroform was reported in a case study. Muscular relaxation of the jaw caused upper respiratory obstruction in a man who accidentally ingested approximately 2,410 mg/kg chloroform (Schroeder 1965), reflecting the neurological effects of chloroform exposure.

Only one report detailing musculoskeletal effects in animals after oral exposure to chloroform was located. In that study, no histopathological changes were observed in the musculoskeletal system of rats and mice after chronic gavage exposure to 200 and 477 mg/kg/day TWA chloroform in oil, respectively (NCI 1976).

Hepatic Effects. The liver is a primary target of chloroform toxicity in humans, with some evidence that suggests that the damage may be reversible (Wallace 1950). Hepatic injury occurred in patients within 1-3 days following chloroform ingestion (Piersol et al. 1933; Schroeder 1965; Storms 1973). Jaundice and liver enlargement and tenderness developed in all patients. The clinical observations were supported by blood biochemistry results with increased SGOT, SGPT, and lactate dehydrogenase (LDH) activities and increased bilirubin levels. At autopsy, fatty degeneration and extensive centrilobular necrosis were observed in one fatal case (Piersol et al. 1933).

A 16-year-old female who ingested an unknown of amount of chloroform and arrived at a hospital semiconscious and with repeated vomiting was reported by Hakim et al. (1992). She was treated with gastric lavage, antacids, intravenous glucose, and antiemetics. She had apparently recovered and was released. Seven days later, she presented with hepatomegaly, slightly depressed hemoglobin, and an abnormal liver sonogram, suggesting toxic hepatic disease due to chloroform toxicosis. A 33-year-old female had injected herself intravenously with 0.5 mL of chloroform and then became unconscious. When she awoke approximately 12 hours later, she then drank another 120 mL of chloroform. She was treated with hyperbaric oxygen, cimetidine (to inhibit cytochrome P-450 and formation of phosgene), and N-acetylcystine (to replenish GSH stores). Liver serum enzymes alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and LDH were elevated in a pattern that suggested liver cell necrosis. Generally, these enzymes were noted to peak by day 4 and decrease by day 11. Total bilirubin and direct bilirubin did not change appreciably. GGT (gamma glutamyltransferase, also known as gamma glutamyl transpeptidase), alpha-feto protein and retinol binding protein showed increases between 6 and 8 days after ingestion, but still within normal ranges for humans (Rao et al. 1993).

2. HEALTH EFFECTS

Increased sulfobromophthalein retention indicated impaired liver function in an individual who ingested 21 mg/kg/day chloroform in a cough medicine for 10 years (Wallace 1950). The changes reversed to normal after exposure was discontinued. Biochemical tests indicate that liver function in male and female humans was not affected by the use of mouthwash providing 0.96 mg/kg/day chloroform for ≤5 years (De Salva et al. 197.5).

The liver is also a target organ for chloroform toxicity in animals. In acute studies, hepatitis was observed in pregnant rats exposed by gavage to 516 mg/kg/day chloroform in oil (Thompson et al. 1974), while increased maternal liver weight without any histopathological changes was observed in pregnant rats similarly exposed to 100 mg/kg/day chloroform (Ruddick et al. 1983). Increased serum levels of transaminases, indicative of liver necrosis, were observed in mice treated with a single gavage dose of 199 mg/kg chloroform in toothpaste, 273 mg/kg in oil (Moore et al. 1982), or 250 mg/kg/day in oil for 14 days (Munson et al. 1982). Similar results were reported for rats treated with a single gavage dose of 100 mg/kg (Wang et al. 1994, 1995) or 0.1 mL/kg (Nakajima et al. 1995) Centrilobular necrosis of the liver with massive fatty changes was also observed in mice after a single dose of 350 mg/kg chloroform in oil (Jones et al. 1958). At a dose of 35 mg/kg, minimal lesions consisting of mid-zonal fatty changes were observed in mice.

Similar results were reported by Larson et al. (1993) in male rats in order to identify target tissues for the acute effects of chloroform in rats and mice and to establish the time-course of chloroform-induced histopathologic and proliferative responses. Rats were given 34, 180, or 477 mg/kg once in corn oil by gavage and sacrificed 24 hours after administration (acute-duration study). In a related time-course study (which focused on histologic changes in tissues over time), rats received 180 mg/kg chloroform in corn oil by gavage and were sacrificed at 0.5, 1, 2, 4, and 8 days after treatment, or received 477 mg/kg in corn oil by gavage and were sacrificed either 1 or 2 days after administration. In the acute study, gross liver to body weight ratios were unaffected at all doses. Histologically, chloroform caused hepatic injury, in a dose-related manner, producing morphologic changes generally limited to the centrilobular hepatocytes. Liver enzymes (SDH, ALT, and AST) were slightly elevated above controls in the 34 and 180 mg/kg group, but were significantly higher in the 477 mg/kg group for all three enzymes. In the time-course study, 1 day after dosing, about 50% of the hepatocytes adjacent to the central veins were degenerated or necrotic in the 180 mg/kg treatment group. Larger vessels had perivascular edema, influx of neutrophils and eosinophils. Only scattered hepatocyte necrosis was seen

by day 2 after treatment. By eight days however, the livers were not histologically different from controls.

In a similar study, mice were administered 34, 238, or 477 mg/kg once in corn oil by gavage and sacrificed 24 hours after administration (acute study) or 350 mg/kg chloroform in corn oil by gavage and sacrificed at 0.5, 1, 2, 4, and 8 days after treatment (time-course study). Livers of female mice were much more sensitive than the kidneys to the toxic effects of chloroform. In the acute study, livers of mice receiving 34 mg/kg chloroform were not histologically different from controls; however, those treated with 238 mg/kg had few small randomly scattered foci of hepatocyte necrosis. Livers from the 477 mg/kg group had centrilobular coagulative necrosis of 50% of the lobule. In the timecourse study, a significant increase in liver weights and liver to body-weight ratios was observed in mice at 2 and 4 days after treatment with the 350 mg/kg dose of chloroform. At 12 hours after treatment, mice had marked swelling of the centrilobular hepatocytes, affecting about 50% of the lobule. One day after treatment, the hepatocytes adjacent to the central vein were necrotic. Two days after chloroform treatment, centrilobular sinusoids were dilated with inflammatory cells associated with centrilobular necrosis. At eight days after treatment, the livers from the treated mice were not histologically different from those of control animals. Serum liver enzymes (SDH and ALT) were elevated in the groups sacrificed at 0.5, 1, 2, and 4 days after treatment, but not in controls or in those animals sacrificed 8 days after treatment.

Another study by Larson et al. (1994d) identified the relationships among chloroform-induced cytolethality, regenerative cell proliferation, and tumor induction in male B6C3F_1 mice dosed with 0, 34, 90, 138, or 277 mg/kg/day chloroform by gavage in corn oil. Mice exposed to 90 mg/kg/day experienced prominent centrilobular hepatocyte swelling with loss of cytoplasmic eosinophilia. Mice exposed to 138 and 277 mg/kg/day experienced increasing levels of centrilobular hepatocyte swelling and degeneration, as well as scattered necrosis and inflammatory cell accumulation. Dose-dependent increases in hepatocyte proliferation were seen in all dose groups after exposure to chloroform for 4 days.

Differences in chloroform toxicity have been noted in female mice when chloroform was administered in different vehicles and by different dosing regimes (Larson et al. 1994b). Mice were treated orally with 3, 10, 34, 90, 238, or 477 mg/kg/day of chloroform in corn oil, or with 16, 26, 53, 81, or 105 mg/kg/day in the drinking water, for 4 days. Chloroform treatment resulted in significant

increases in liver weights of mice at the 238 and 477 mg/kg/day dose levels. Mice treated with 238 mg/kg chloroform had moderate centrilobular vacuolar degeneration of hepatocytes and scattered centrilobular and subcapsular hepatocyte necrosis. At the 477 mg/kg dose, severe centrilobular coagulative necrosis with small number of inflammatory cells in the necrotic areas was also observed. Dose-dependent increases in both ALT and SDH were also observed. At daily doses of 90 mg/kg or less, no increase in hepatic cell proliferation was noted. Dose-dependent increases in hepatic cell proliferation and cells observed to be in S-phase occurred in the 238 and 477 mg/kg/day doses. For mice dosed with 16, 26, 53, 81, or 105 mg/kg/day in the drinking water, serum ALT or SDH were not different from controls at any dose. In the 53, 81, and 105 mg/kg/day treatment groups, the livers had changes that were characterized by pale cytoplasmic eosinophilic staining of centrilobular hepatocytes compared to the periportal hepatocytes and controls. Livers from mice treated with 26 mg/kg/day chloroform or less failed to showed significant histologic changes when compared to controls. Cell proliferations in the liver were not found at any dose or duration. An acute oral MRL of 0.3 mg/kg/day was calculated using the 26.4 mg/kg/day NOAEL based on the hepatic effects in these animals from this study. More information on this MRL and how it was derived is located in the footnote to Table 2-2, Section 2.5, and in Appendix A of this profile.

Larson et al. (1995a) examined the dose-response relationships for the induction of cytolethality and regenerative cell proliferation in the livers of male Fischer 344 rats given chloroform by gavage. Groups of 12 rats were administered oral doses of 0, 3, 10, 34, 90, and 180 mg/kg/day chloroform in corn oil by gavage for 4 days. BrdU was administered via an implanted osmotic pump to label cells in S-phase. Cells having incorporated BrdU were visualized in tissue sections immunohistochemically and the LI evaluated as the percentage of S-phase cells. Necropsies and histopathological examinations were performed at death. The relative liver weights were increased at doses of 10 mg/kg/day and above at 4 days posttreatment. Rats treated with 34, 90, or 180 mg/kg/day by gavage for 4 days had mild-to-moderate degeneration of centrilobular hepatocytes. The livers of rats given 90 mg/kg/day for 4 days had a slight increase in centrilobular pallor and necrosis of hepatocytes surrounding the central vein; the remaining central and some mid-zonal hepatocytes were swollen and displayed a cytoplasmic granularity. In the 180 mg/kg/day dose group, the livers had scattered individual cell necrosis throughout the central and mid-zonal regions. The cytoplasm of the centrilobular hepatocytes were pale, eosinophilic and mildly vacuolated. Dose-dependent increases in both ALT and SDH were observed at 4 days in the 90 and 180 mg/kg/day dose groups and at 3 weeks

in the 180 mg/kg/day dose group only. A dose-dependent increase in LI was seen in rat liver after 4 days of treatment with 90 and 180 mg/kg/day by gavage.

Larson et al. (1995a) also examined the toxicological effects of chloroform administered in the drinking water in rats. Groups of 12 rats were administered chloroform *ad libitum* in drinking water at concentrations of 0, 60, 200, 400, 900, and 1,800 ppm for 4 days. BrdU was administered via an implanted osmotic pump to label cells in S-phase. Cells having incorporated BrdU were visualized in tissue sections immunohistochemically and the LI evaluated as the percentage of S-phase cells. Necropsies and histopathological examinations were performed at death. Average daily doses of chloroform ingested from drinking water were: 0, 6.6, 19.3, 33.2, 68.1, and 57.5 mg/kg/day for 0, 60, 200, 400, 900, and 1,800 ppm concentration levels, respectively. Only mild hepatocyte vacuolation was observed in rats given 900 or 1,800 ppm in water for 4 days; no increase in the hepatic LI was observed at any time point.

In another study by Larson et al. (1995b), female Fisher 344 rats administered 400 mg/kg chloroform by gavage in corn oil for 4 days exhibited hepatic lesions consisting of mild centrolobular vacuolization, scattered necrotic hepatocytes, sinusoidal leucostasis, mild-to-focally severe centrilobular hepatocyte degeneration and necrosis, and diffuse centrolobular swelling. Rats in the 100 and 200 mg/kg groups had only slight centrolobular changes, while those in the 34 mg/kg group did not differ from controls.

Pereira (1994) investigated the effects of chloroform exposure in different vehicles and by different dosing regimes on hepatic cell proliferation in female B6C3F_1 mice. Animals received either 263 mg/kg/day chloroform by gavage in corn oil or 1,800 ppm chloroform in drinking water, 24 hours a day and were sacrificed at 5 or 12 days. When administered by gavage, chloroform exposure resulted in significantly increased relative liver weights at 5 days (53%; $p<0.05$), but not at 12 days. The livers of mice exposed to chloroform for 5 days exhibited toxicity consisting of necrotic hepatocytes, infiltration of macrophages and neutrophils in the central zone, and hydrotropic, swollen, and rounded hepatocytes of a pale ground glass appearance in the midzone. Hepatotoxicity was less severe at 12 days. Cell proliferation was significantly increased at both 5 and 12 days. In contrast, chloroform administered in drinking water for 5 days reduced absolute and relative liver weight while exposure for 12 days had no effect on relative liver weights. The livers of mice exposed to chloroform in drinking water exhibited limited toxicity after 5 days consisting of smaller hepatocytes

with dense nonvacuolated and basophilic cytoplasm; hepatotoxicity after 12 days was limited to vacuolated hepatocytes. Cell proliferation, was significantly reduced ($p<0.05$) at 5 and 12 days as compared to controls.

Liver effects in animals have been reported in numerous oral studies of intermediate duration (Chu et al. 1982b; Eschenbrenner and Miller 1945a; Larson et al. 1995b). Larson et al. (1994b) exposed female mice to 3, 10, 34, 90, 238, and 477 mg/kg/day of chloroform in corn oil via gavage 5 days a week for 3 weeks. Chloroform treatment resulted in significant increases in liver weights of mice at the 90, 238, and 477 mg/kg/day doses. Doses of 34 mg/kg/day resulted in pale cytoplasmic eosinophilia of the centrilobular hepatocytes and mild vacuolation of the centrilobular and mid-zonal hepatocytes relative the periportal hepatocytes and livers from control mice. At the 238 mg/kg/day dose, the livers were characterized by a severe centrilobular hepatocyte necrosis. At 477 mg/kg/day, the central zone of the liver was populated by degenerate vacuolated hepatocytes and regenerating hepatocytes with markedly basophilic cytoplasm and,small round nuclei with clumped chromatin and prominent nucleoli. Significant dose-dependent increases in ALT and SDH were observed at doses of 34 mg/kg/day and greater. Cell proliferation was markedly increased in the liver at the 238 and 477 mg/kg/day doses. Mice dosed with 16, 43, 82, 184, or 329 mg/kg/day of chloroform in the drinking water for 7 days a week for 3 weeks resulted in no histological changes in livers at all doses studied. Liver weights were significantly increased at 82, 184, and 329 mg/kg/day.

Larson et al. (1995a) examined the dose-response relationships for the induction of cytolethality and regenerative cell proliferation in the livers of male Fischer 344 rats given chloroform by gavage. Groups of 12 rats were administered oral doses of 0, 3, 10, 34, 90, and 180 mg/kg/day chloroform in corn oil by gavage for 5 days a week for 3 weeks. BrdU was administered via an implanted osmotic pump to label cells in S-phase. Cells having incorporated BrdU were visualized in tissue sections immunohistochemically and the LI evaluated as the percentage of S-phase cells. Necropsies and histopathological examinations were performed at death. The relative liver weights were increased at doses of 90 mg/kg/day and greater at 3 weeks. After 3 weeks of exposure, livers of rats in the 34 or 90 mg/kg/day dose groups did not differ from controls. In the 180 mg/kg/day dose group, effects were similar to those seen at 4 days after exposure. Dose-dependent increases in both ALT and SDH were observed after 3 weeks in the 180 mg/kg/day dose group only.

Larson et al. (1995a) also examined the toxicological effects of chloroform administered in the drinking water in rats. Groups of 12 rats were administered chloroform *ad libitum* in drinking water at concentrations of 0, 60, 200, 400, 900, and 1,800 ppm for 7 days a week for 3 weeks. BrdU was administered via an implanted osmotic pump to label cells in S-phase. Cells having incorporated BrdU were visualized in tissue sections immunohistochemically and the LI evaluated as the percentage of S-phase cells. Necropsies and histopathological examinations were performed at death. Average daily doses of chloroform ingested from drinking water were: 0, 6, 17.4, 32, 62.3, and 106 mg/kg/day for 3 weeks exposure for 0, 60, 200, 400, 900, and 1,800 ppm concentration levels, respectively. Only mild hepatocyte vacuolation was observed in rats given 1,800 ppm in water for 3 weeks. No increase in the hepatic LI was observed at any time point.

Larson et al. (1995b) further examined the dose-response relationship for chloroform-induced cytotoxicity and cell proliferation in the liver of female Fisher 344 rats via gavage. Animals received chloroform in corn oil at doses of 0, 34, 100, 200, or 400 mg/kg/day for 3 weeks (5 days a week). At completion of dosing, animals were sacrificed, the livers were evaluated microscopically and cell proliferation was quantitated. Exposure to 400 mg/kg chloroform resulted in hepatic lesions consisting of slight to mild diffuse vacuolar change and focal centrilobular degeneration. Rats in the 200 mg/kg groups had only slight centrilobular vacuolation, while those in the 100 and 34 mg/kg dose groups did not differ from controls.

Pereira (1994) provided further evidence of the effect of dosing method (gavage versus drinking water) and vehicle (corn oil versus water) on hepatic cell proliferation in female B6C3F$_1$ mice. Animals received either 263 mg/kg/day chloroform by gavage in corn oil or 1,800 ppm chloroform in drinking water, 24 hours a day and were sacrificed at 33 or 159 days. When administered by corn oil gavage, chloroform exposure resulted in increased relative liver weights at 33 and 159 days (30.1 and 38.2% increases, respectively). The livers of mice exposed to chloroform for 33 or 159 days exhibited limited toxicity consisting of focal areas of necrotic hepatocytes and a limited number of mononuclear cells and swollen, rounded, pale hepatocytes. Cell proliferation was significantly increased at both 33 and 159 days as compared to controls. In contrast, administration of chloroform in drinking water had no effect on absolute or relative liver weights after 33 days, while exposure for 159 days resulted in significantly increased relative liver weights (3 1.4%; $p<0.05$). However, the livers of mice exposed for either 33 or 159 days exhibited no signs of toxicity. In addition, cell proliferation was not significantly affected by exposure to chloroform in drinking water for either 33 or 159 days.

2. HEALTH EFFECTS

Fatty changes, necrosis, increased liver weight, and hyperplasia have been observed in rats exposed to ≥150 mg/kg/day chloroform in a toothpaste vehicle via gavage for 13 weeks (Palmer et al. 1979). An increased incidence of sporadic, mild, reversible, liver changes occurred in rats exposed to chloroform in the drinking water at doses of 0.64-150 mg/kg/day for 90 days, but the incidences were not significantly higher than the incidences in controls (Chu et al. 1982a). The effect- and no-effect-levels in the study are clearly defined. Fatty and hydropic changes, necrosis, and cirrhosis were observed in mice treated by gavage with ≥50 mg/kg/day chloroform in oil for 90 days (Bull et al. 1986; Munson et al. 1982) or 86 mg/kg/day in drinking water for 1 year (Klaunig et al. 1986). In contrast, centrilobular fatty changes observed in mice at 64 mg/kg/day chloroform in drinking water for 90 days appeared to be reversible (Jorgenson and Rushbrook 1980), and no liver effects were found in mice treated with ≥50 mg/kg/day chloroform in aqueous vehicles (Bull et al. 1986). In addition, hepatocellular degeneration was induced in F_1 females in a 2-generation study in which mice were treated by gavage with 41 mg/kg/day chloroform in oil (Gulati et al. 1988). Significantly increased ($p<0.05$) SGPT activity occurred in dogs beginning at 6 weeks of exposure to chloroform in toothpaste in capsules at a dose of 30 mg/kg/day in a 7.5-year study (Heywood et al. 1979). SGPT activity was not increased at 15 mg/kg/day until week 130. Therefore, 15 mg/kg/day was the NOAEL for intermediate-duration exposure. This NOAEL was used to derive an intermediate-duration oral MRL of 0.1 mg/kg/day. More information on this MRL and how it was derived is located in the footnote to Table 2-2, Section 2.5, and in Appendix A of this profile.

The relationships among chloroform-induced cytolethality, regenerative cell proliferation, and tumor induction in male B6C3F_1 mice dosed with chloroform by gavage in corn oil has also been studied. Mice received chloroform at doses of 0, 34, 90, 138, or 277 mg/kg for 4 consecutive days or 5 days a week for 3 weeks. To monitor cell proliferation, mice were administered BrU via implanted osmotic pump for the last 3.5 days. Chloroform treatment for 3 weeks also resulted in a small (<10%) but significant increase in relative liver weight of mice at the highest dose level. Macroscopically, pale livers and kidneys were noted at all dose levels after 3 weeks of chloroform exposure; treatment with 138 or 277 mg/kg for 3 weeks resulted in the formation of white subcapsular foci. After 3 weeks of chloroform exposure, the livers of all mice in the 34 mg/kg/day group and 3 of 5 mice in the 90 mg/kg/day group were histologically similar to those of controls. Livers of 2 mice in the 90 mg/kg/day group exhibited centrilobular hepatocyte swelling with loss of eosinophilia. Mice dosed with 138 mg/kg/day experienced marked centrilobular hepatocyte swelling, mild to moderate periportal vacuolation, and scattered centrilobular and periportal degeneration and necrosis. Mice dosed with

277 mg/kg/day experienced marked centrilobular hepatocyte degeneration and necrosis. Cell proliferation was significantly elevated in the 138 and 277 mg/kg dose groups only.

In chronic-duration exposure studies, liver effects have been observed in rats, mice, and dogs after oral exposure to chloroform. Male and female ICI mice were exposed to 17 or 60 mg/kg/day chloroform by gavage using toothpaste as a vehicle for 80 weeks followed by 13-24-week observation period. No significant histopathological findings (noncancerous) were recorded in the kidneys or lung tissues. Moderate or severe fatty degeneration of the liver was slightly more prevalent among treated animals than controls (statistical significance not provided) beginning at the 17 mg/kg/day. Necrosis was observed in female rats treated by gavage with 200 mg/kg/day chloroform in oil for 78 weeks (NCI 1976). Nodular hyperplasia occurred in all groups of male and female mice similarly treated at 138 and 238 mg/kg/day, respectively. Fibrosis of the liver was observed in both sexes of rats exposed to 200 mg/kg/day chloroform in the drinking water for ≤180 weeks (Tumasonis et al. 1985, 1987). Increased SGPT was observed in dogs given chloroform in toothpaste capsules for 7.5 years (Heywood et al. 1979). The lowest oral dose administered to animals in chronic studies was 15 mg/kg/day, which increased SGPT in dogs. This LOAEL was used to derive a chronic oral MRL of 0.01 mg/kg/day. More information on this MRL and how it was derived is located in the footnote to Table 2.2, Section 2.5, and in Appendix A of this profile.

Renal Effects. The kidney is also a major target of chloroform-induced toxicity in humans. Oliguria was observed 1 day after the ingestion of ≈3,755 or 2,410 mg/kg chloroform (Piersol et al. 1933; Schroeder 1965). Increased blood urea nitrogen (BUN) and creatinine levels also indicated renal injury. Albuminuria and casts were detected in the urine. Histopathological examination at autopsy revealed epithelial swelling and hyaline and fatty degeneration in the convoluted tubules of kidneys in one fatal case of oral exposure to chloroform (Piersol et al. 1933). Numerous hyaline and granular casts and the presence of albumin were observed in the urine of one subject who ingested 21 mg/kg/day chloroform in cough medicine for 10 years (Wallace 1950). The urinalysis results reversed to normal after discontinuation of chloroform exposure. No indications of renal effects were observed in humans who ingested estimated doses of 0.34-0.96 mg/kg/day chloroform in mouthwash for 5 years (De Salva et al. 1975).

The renal toxicity of chloroform in animals has been reported in many studies of acute duration. Larson et al. (1993) studied the effects of dose and time after chloroform administration on the renal

toxicology of chloroform in male rats. Rats were given 34, 180, or 477 mg/kg once in corn oil by gavage and sacrificed 24 hours after administration. In a related time-course study (which focused on histologic changes in tissues over time), rats received 180 mg/kg chloroform in corn oil by gavage and were sacrificed at 0.5, 1, 2, 4, and 8 days after treatment; others received 477 mg/kg in corn oil by gavage and were sacrificed either 1 or 2 days after administration. Histologically, chloroform caused extensive renal damage and, to a much lesser extent, hepatic injury, in a dose-related manner. One day after treatment with a single dose of chloroform of 34 mg/kg or greater, the kidneys of male rats developed tubular necrosis that was restricted to the proximal convoluted tubules. The severity of these lesions occurred in a dose-dependent manner. Rats given 34 mg/kg had scattered necrotic tubules affecting less than 10% of the midcortical nephrons. In the 180 mg/kg group, 25% of the proximal convoluted tubules were necrotic. Nearly all segments of the proximal tubules had necrosis in the rats receiving 477 mg/kg chloroform. Despite extensive renal injury, increases in BUN or in urinary protein or glucose were not observed. In the time-course study, the kidneys, after 12 hours of treatment, had a diffuse granularity of cytoplasm of the epithelium lining of the proximal convoluted tubules in the 180 mg/kg group. Damage was severe after 1 day, and after 2 days, 100% of the proximal tubules were lined by necrotic epithelium. After 8 days, the kidneys had returned to normal appearance. No increases in BUN or urinary protein or glucose were noted at any time after treatment.

Larson et al. (1995a) also examined the toxicological effects of chloroform administered in the drinking water in rats. Groups of 12 rats were administered chloroform *ad libitum* in drinking water at concentrations of 0, 60, 200, 400, 900, and 1,800 ppm for 4 days. BrdU was administered via an implanted osmotic pump to label cells in S-phase. Cells having incorporated BrdU were visualized in tissue sections immunohistochemically and the LI evaluated as the percentage of S-phase cells. Necropsies and histopathological examinations were performed at death. Average daily doses of chloroform ingested from drinking water were: 0, 6.6, 19.3, 33.2, 68.1, and 57.5 mg/kg/day for 4 days exposure for the 0, 60, 200, 400, 900, and 1,800 ppm concentration levels, respectively. When chloroform was administered in the drinking water, no microscopic alterations were seen in the kidneys after 4 days of treatment. The overall renal LI was not increased at any dose.

The same study (Larson et al. 1995a) examined the dose-response relationships for the induction of cytolethality and regenerative cell proliferation in the kidneys of male Fischer 344 rats given chloroform by gavage. Groups of 12 rats were administered oral doses of 0, 3, 10, 34, 90, and

180 mg/kg/day chloroform in corn oil by gavage for 4 days. BrdU was administered via an implanted osmotic pump to label cells in S-phase. Cells having incorporated BrdU were visualized in tissue sections immunohistochemically and the LI evaluated as the percentage of S-phase cells. Necropsies and histopathological examinations were performed at death. Rats treated with 34, 90, or 180 mg/kg/day by gavage for 4 days had mild-to-moderate degeneration of renal proximal tubules. After 4 days of dosing with 34 mg/kg/day, the proximal convoluted tubule epithelial cells had increased numbers and prominence of apical cytoplasmic vacuoles. Likewise, rats given 90 mglkglday for 4 days displayed swelling and vacuolation of 25-50% of the proximal tubules. Progressive degeneration of the proximal tubules was observed in rats exposed to 180 mg/kg/day. At 4 days, swollen and vacuolated cytoplasm in approximately 10-20% of proximal tubule epithelium was observed. LI were increased in the kidney cortex only in the rats treated with 180 mg/kg/day for 4 days.

The dose-response relationship for chloroform-induced cytotoxicity and cell proliferation in the kidneys of female Fisher 344 rats has also been elucidated. Animals received 34, 100, 200, or 400 mg/kg chloroform by gavage in corn oil for 4 days. At completion of dosing, kidneys were prepared for microscopic evaluation, and cell proliferation was quantitated. Rats in the high dose group had 50-75% of proximal tubules lined with necrotic or attenuated regenerating epithelium, as well as distal nephrons containing hyaline casts. Rats in the 200 mg/kg group had kidneys with 25-50% of proximal tubules lined with degenerated, necrotic or regenerating epithelium. Kidneys from rats in the 2 lowest dose groups were similar to those of controls (Larson et al. 1995b).

Acute toxic nephrosis was observed in female rats exposed to 516 mg/kg/day chloroform by gavage in oil during Gd 6-15, with maternal lesions characterized by tubular swelling, hydropic or fatty degeneration and necrosis (Thompson et al. 1974). Increased kidney weight was observed in female rats after a single gavage dose of 546 mg/kg chloroform (Chu et al. 1982b). Similarly, rats exposed to 400 mg/kg/day by gavage during gestation had increased kidney weight (Ruddick et al. 1983). No increase in kidney weight was found in the rats treated with 200 mg/kg/day during gestation. Renal necrosis in convoluted tubules was observed in male mice after a single dose of 199 mg/kg chloroform in toothpaste or 65.6 mg/kg chloroform in oil (Moore et al. 1982).

The relationships among chloroform-induced cytolethality, regenerative cell proliferation, and tumor induction in male $B6C3F_1$ mice dosed with chloroform by gavage in corn oil of acute duration has

also been reported. Mice received chloroform at doses of 0, 34, 90, 138, or 277 mg/kg/day by gavage for 4 consecutive days. To monitor cell proliferation, mice were administered BrdU via implanted osmotic pump for the last 3.5 days. After four days of exposure, 2 of 4 mice dosed with 34 mg/kg/day and all mice dosed with 90 mg/kg/day or more experienced extensive (>75% of tissue) acute necrosis of the proximal convoluted tubule, characterized by a thin layer of eosinophilic necrotic cellular debris lining the tubular basement membrane. Distal tubules and collecting ducts were filled with hyaline casts. The remaining 2 mice in the 34 mg/kg/day dose group experienced scattered necrosis in proximal convoluted tubules. In the kidneys, significant increases in cell proliferation were noted in all dose groups given chloroform for 4 days. The authors concluded that the results of this study confirmed the sensitivity of the male mouse, relative to the female mouse, to the nephrotoxic effects of chloroform (Larson et al. 1994d).

In intermediate-duration exposures, several studies suggest that mice appeared to be more sensitive than rats to the nephrotoxic effects of chloroform. Rats exposed to 193 mg/kg/day for 28 days (Chu et al. 1982b) or to 160 mg/kg/day chloroform for 90 days (Jorgenson and Rushbrook 1980) in drinking water had no kidney effects. Increased relative kidney weight was observed in rats exposed by gavage to 150 mg/kg/day for 13 weeks, but not in rats exposed to 30 mg/kg/day (Palmer et al. 1979). Chronic inflammatory changes were observed in the kidneys of mice exposed to 50 mg/kg/day chlorofoorm (dissolved in an emulsion prepared with emulphor in water) by gavage (Munson et al. 1982); however, no changes were observed in mice exposed to 41 mg/kg/day by gavage (Gulati et al. 1988) or in mice exposed to 435 mg/kg/day chloroform in drinking water (Jorgenson and Rushbrook 1980). Nonetheless, exposure to 86 mg/kg/day in drinking water for 1 year caused tubular necrosis in mice (Klaunig et al. 1986).

Larson et al. (1995b) examined the dose-response relationship for chloroform-induced cytotoxicity and cell proliferation in the kidneys of female Fisher 344 rats using a wide range of doses. Animals received 34, 100, 200, or 400 mg/kg chloroform by gavage in corn oil for 3 weeks (5 days a week). At completion of dosing, the kidneys were prepared for microscopic evaluation, and cell proliferation was quantitated. Rats in the 100, 200, and 400 mg/kg dose groups had 50-75% of proximal tubules lined with regenerating epithelium; many of the tubules were dilated and contained mineralized concretions. Kidneys from rats in the lowest dose group were similar to those of controls.

2. HEALTH EFFECTS

Lipsky et al. (1993) studied groups of male Fischer 344 rats gavaged with either 90 or 180 mg/kg/day of chloroform in corn oil or water for 5 days a week for 4 weeks. Rats exposed to chloroform by gavage in corn oil displayed acute cell injury and necrosis, primarily in the epithelial cells lining the S2 segment of the proximal tubule, with some apparent damage/necrosis occurring in the Sl segment as well. This injury was present in all rats exposed to the 180 mg/kg/day dose and in less than half of the animals exposed to the 90 mg/kg/day dose. There was also a dose-dependent increase in the total BrdU labeling of nuclei in renal cells of the chloroform-treated oil-gavaged animals compared to controls. The largest increase in DNA BrdU labeling was in the cells of the S2 segment. The 90 mg/kg/day dose of chloroform also produced increase in DNA labeling in the S3 segment, but not for the 180 mg/kg/day dose of chloroform. Animals exposed to chloroform in water showed minimal histopathologic alterations in the kidneys. Mild injury and necrosis was seen in cells of the S2 segment in 1 of 6 animals in the 180 mg/kg/day group, while none were seen in the 90 mg/kg/day dose group. Little to no change in DNA labeling of renal cells was seen in the water-gavaged rats.

Larson et al. (1995a) examined the dose-response relationships for the induction of cytolethality and regenerative cell proliferation in the kidneys of male Fischer 344 rats given chloroform by gavage. Groups of 12 rats were administered oral doses of 0, 3, 10, 34, 90, and 180 mg/kg/day chloroform for 5 days a week for 3 weeks. BrdU was administered via an implanted osmotic pump to label cells in S-phase. Cells having incorporated BrdU were visualized in tissue sections immunohistochemically and the LI evaluated as the percentage of S-phase cells. Necropsies and histopathological examinations were performed at death. Relative kidney weights were increased after 3 weeks in the 180 mg/kg/day dose group only. Rats treated with 34, 90, or 180 mg/kg/day by gavage for 4 days had mild-to-moderate degeneration of renal proximal tubules. These alterations were absent or slight after 3 weeks of treatment, except at the highest dose level. After 4 days of dosing with 34 mg/kg/day, the proximal convoluted tubule epithelial cells had increased numbers and prominence of apical cytoplasmic vacuoles, but these changes were not observed at 3 weeks. Likewise, rats given 90 mg/kg/day for 4 days displayed swelling and vacuolation of 25-50% of the proximal tubules, at 3 weeks only 1 of 3 rats had vacuolated and degenerated epithelium. Progressive degeneration of the proximal tubules was observed in rats exposed to 180 mg/kg/day. At 4 days, swollen and vacuolated cytoplasm in approximately 10-20% of proximal tubule epithelium was observed, while at 3 weeks the percentage was 25-50%. At 3 weeks, scattered tubules also had mineral concretions that appeared subepithelial. LI was increased in the kidney cortex only in the rats treated with 180 mg/kg/day for 4 days.

Larson et al. (1995a) also examined the toxicological effects of chloroform administered in the drinking water in rats. Groups of 12 rats were administered chloroform *ad libitum* in drinking water at concentrations of 0, 60, 200, 400, 900, and 1,800 ppm for 7 days a week for 3 weeks. BrdU was administered via an implanted osmotic pump to label cells in S-phase. Cells having incorporated BrdU were visualized in tissue sections immunohistochemically and the LI evaluated as the percentage of S-phase cells. Necropsies and histopathological examinations were performed at death. Average daily doses of chloroform ingested via drinking water were 0, 6, 17.4, 32, 62.3, and 106 mg/kg/day for 3 weeks exposure for 0, 60, 200, 400, 900, and 1,800 ppm concentration levels, respectively. As a general observation, rats treated for 3 weeks with 200 ppm chloroform and greater had slightly increased numbers of focal areas of regenerating renal proximal tubular epithelium and cell proliferation than were noted in controls, but no clear dose-response relationship was evident. The overall renal LI was not increased at any dose or time point.

Larson et al. (1994b) exposed female mice to 3, 10, 34, 90, 238, and 477 mg/kg/day of chloroform in corn oil via gavage for 5 days a week for 3 weeks. Mice were also dosed with 16, 43, 82, 184, or 329 mg/kg/day of chloroform in the drinking water for 7 day a week for 3 weeks. In both studies, no increases in cell proliferation were noted and no significant changes in renal histopathology were reported.

In another study by Larson et al. (1994d) the possible relationships among chloroform-induced cytolethality, regenerative cell proliferation, and tumor induction were identified in male $B6C3F_1$ mice dosed with chloroform by gavage in corn oil. Mice received chloroform at doses of 0, 34, 90, 138, or 277 mg/kg/day for 5 days a week for 3 weeks. To monitor cell proliferation, mice were administered BrdU via implanted osmotic pump for the last 3.5 days. Renal lesions were similar to, but less severe than, lesions seen in mice exposed for 4 days and were characterized by extensive tubular regeneration. The kidneys of mice dosed with 34-138 mg/kg/day chloroform exhibited dose-dependent increases in regenerating proximal convoluted tubules. The kidneys of mice dosed with 277 mg/kg/day chloroform exhibited severe nephropathy characterized by degeneration, necrosis, and regeneration of the proximal tubules. The renal interstitium was swollen due to fibroplasia, edema, and inflammatory cell infiltration. After 3 weeks of exposure, renal cell proliferation was still elevated relative to controls at doses of ≥90 mg/kg/day, but LI values declined from levels seen after 4 days of exposure.

In chronic oral studies, no definite renal effects were observed in rats exposed to ≤200 mg/kg/day or mice exposed to <477 mg/kg/day TWA (Heindel et al. 1995; Jorgenson et al. 1985; NCI 1976; Roe et al. 1979). In dogs, however, fat deposition in renal glomeruli was observed at a dose of 30 mg/kg!day chloroform for 7.5 years, but not at 15 mg/kg/day (Heywood et al. 1979).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to chloroform.

Alopecia was observed in pregnant rats exposed to 126 mg/kg/day chloroform in oil (Thompson et al. 1974). Rough coats were observed in mice exposed to 100 mg/kg/day chloroform in oil for 14 days (Gulati et al. 1988).

Ocular Effects. Only one reference was located that discussed the ocular effects of chloroform after oral ingestion. Li et al. (1994) examined the effects of chloroform administered in drinking water to guinea pigs with cedar pollen-induced allergic conjunctivitis, prepared by passive cutaneous anaphylaxis. Groups of 5 male Hartley guinea pigs were given drinking water with chloroform concentrations of 0.01, 0.1, 1, 10, 100, or 1,000 ppm 48 hours before applying an antigen eye drop (starting on the 8th day after antiserum administration). One control group was not administered chloroform and another control group was not administered the antiserum (chloroform alone) for every dose level. The light absorption rate of Evans blue extracted from conjunctiva was used as an index of the relative intensity of allergic conjunctivitis. In a separate experiment, using the dose level which caused the most intense aggravating effect in the above testing, groups of 3 male guinea pigs were given 1 ppm chloroform in drinking water for 48 hours and the residual effect on the allergic conjunctivitis was examined. Animals were examined immediately after, and 1, 2, 4, 7, and 14 days after exposure; antigen eye drops were applied 10 days after the antiserum administration. Water intake was monitored and blood chloroform concentrations were measured. At 0.1 ppm chloroform, significant aggravation of allergic conjunctivitis was observed. Allergic conjunctivitis was most intensely aggravated at I ppm chloroform. At higher doses (10 and 100 ppm) the aggravation was still noticeable, yet less significant. At 1,000 ppm chloroform, the aggravating effect was not present. Rlood chloroform concentrations increased as the concentration in drinking water increased from 0.01 to 1,000 ppm.

2. HEALTH EFFECTS

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to chloroform.

Several studies were located regarding body weight changes in animals after oral exposure to chloroform; however, the effect of chloroform on body weight is variable and depends somewhat on the dose and dosing method. Body weight was unaffected in male Wistar rats receiving single doses of chloroform ranging from 0.1 to 0.5 mL/kg (Nakajima et al. 1995), in female B6C3F$_1$ mice exposed to 263 mg/kg/day chloroform by gavage in corn oil for 5 or 12 days (Pereira 1994), and in male rats exposed once to 477 mg/kg day of chloroform (Larson et al. 1993), or for 4 days in male mice dosed at 277 mg/kg/day by gavage (Larson et al. 1994d). When female mice were exposed to 1,800 ppm chloroform in drinking water (24 hours a day) for 5 or 12 days, body weight initially declined; however, this was attributed to decreased water consumption (Pereira 1994). A dose-related decrease in body weight gain was observed in rats exposed to 100 mg/kg/day and in rabbits exposed to 50 mg/kg/day chloroform by gavage in oil during gestation (Ruddick et al. 1983; Thompson et al. 1974). In addition, decreased body weight was observed in male mice after acute exposure to 250 mg/kg/day chloroform by gavage in oil (Gulati et al. 1988; Munson et al. 1982). Others have reported similar reductions in body weight after oral dosing with chloroform (Davis and Berndt 1992, 1994b, 1995a, 1995b; Reddy et al. 1992).

In studies of intermediate duration, dose-related decreases in body weight or body weight gain were observed in rats exposed to ≥81 mg/kg/day in water (Jorgenson and Rushbrook 1980) or in oil (Larson et al. 1994b, 1995b; NCI 1976) and in mice (Bull et al. 1986; Klaunig et al. 1986; Roe et al. 1979). Similar effects were found in rats exposed to ≥60 mg/kg/day regardless of the vehicle (Jorgenson et al. 1985; Larson 1995a; NCI 1976; Palmer et al. 1979; Tumasonis et al. 1985) and mice exposed to 263 mg/kg/day in water (Jorgenson et al. 1985) in studies of chronic exposure; taste aversion may have been a complicating factor in these studies. In contrast, no effect on body weight was observed in mice treated with 477 mg/kg/day by gavage in oil (NCI 1976) or dogs treated with 30 mg/kg/day chloroform (Heywood et al. 1979) in studies of chronic duration. Food and/or water consumption were decreased in chloroform-exposed animals in some studies (Chu et al. 1982a; Jorgenson and Rushbrook 1980), but others reported fluctuating food intake unrelated to chloroform exposure (Palmer et al. 1979) or no significantly depressed food consumption at the lowest LOAEL level for body weight effects (Thompson et al. 1974). The effects chloroform has on changes in body weight and water consumption when administered orally in different vehicles and varying doses have also been

reported in female mice (Pereira 1994). In this study, female $B6C3F_1$ mice received 263 mg/kg/day chloroform by gavage in corn oil or 1,800 ppm/day chloroform in their drinking water, and animals were sacrificed at 5, 12, 33, or 159 days. Chloroform administered by gavage did not affect body weight; however, when administered in drinking water, body weights in exposed animals initially declined, but increased by day 33 to control levels. This was attributed to changes in drinking-water consumption, which was suppressed during the first 5 days but was greater than that of controls from days 6-12.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to chloroform. Information regarding immunological effects in animals after oral exposure to chloroform is limited to three studies. Reduced lymphocyte counts were observed in female rats after a single gavage dose of 1,071 mg/kg chloroform (Chu et al. 1982b); no effects were observed in the 765 mg/kg group. Humoral immunity, defined as antibody-forming cells (AFC)/spleen x 100,000, was depressed in both sexes of mice after oral dosing with 50 mg/kg/day chloroform for 14 days (Munson et al. 1982). In contrast, hemagglutination titer was not significantly influenced, and no changes in cell-mediated immunity were recorded. Similar results were obtained in a 90-day experiment (Munson et al. 1982). Depressed humoral immunity was observed in mice exposed to 50 mg/kg/day chloroform. Cellmediated immunity (delayed-type hypersensitivity) was affected in the high-dose (250 mg/kg/day) group of females. The chloroform-induced changes were more marked in the 14-day study than in the 90-day study. Although the data are limited, there are indications that the immune system is a target of chloroform-induced toxicity after oral exposure. The data also indicate that humoral immunity may be more severely affected than cell-mediated immunity. These conclusions, however, should be viewed with caution due to the small number of studies.

Li et al. (1994) examined the effects of chloroform administered in drinking water to guinea pigs with cedar pollen-induced allergic conjunctivitis, prepared by passive cutaneous anaphylaxis. Groups of 5 male Hartley guinea pigs were given drinking water with chloroform concentrations of 0.01, 0.1, 1, 10, 100, or 1,000 ppm 48 hours before applying an antigen eye drop (starting on the 8th day after antiserum administration). At 0.1 ppm chloroform, significant aggravation of allergic conjunctivitis was observed. Allergic conjunctivitis was most intensely aggravated at 1 ppm chloroform. At higher

doses (10 and 100 ppm) the aggravation was still noticeable, yet less significant. At 1,000 ppm chloroform, the aggravating effect was not present.

The highest NOAEL value and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

The data regarding neurological effects in humans after oral exposure to chloroform were obtained from clinical case reports. Deep coma occurred immediately after exposure to 2,410 or 3,755 mg/kg in all cases of intentional or accidental ingestion of chloroform (Piersol et al. 1933; Schroeder 1965; Storms 1973). All reflexes were abolished, and pupil size varied. All patients survived the first coma and became fully conscious; however, one patient died in coma several days later due to extensive liver necrosis (Piersol et al. 1933). Mild cerebellar damage (instability of gait, intentional tremor) was observed in one patient, but reversed to normal in two weeks (Storms 1973).

The central nervous system in animals is a target of chloroform toxicity after oral exposure to chloroform. High single doses of chloroform caused ataxia, incoordination, and anesthesia in mice (Balster and Borzelleca 1982; Bowman et al. 1978). Sprague-Dawley rats administered a single 200 mg/kg dose of chloroform gavage experienced significant decreases in midbrain 5-hydroxyindolacetic acid (5-HIAA) levels and significant increases in hypothalamic dopamine concentrations 2 hours after dosing ($p<0.05$) (Kanada et al. 1994). The calculated ED_{50} (dose is effective on 50% of animals) for motor performance was 484 mg/kg chloroform (Balster and Borzelleca 1982). The effects disappeared within 90 minutes postexposure. A minimal narcotic dose for 50% of the treated mice was calculated to be 350 mg/kg (Jones et al. 1958). Hunched posture and inactivity were observed in male mice exposed by gavage to 250 mg/kg chloroform in oil for 14 days (Gulati et al. 1988). No effects were observed after exposure to 100 mg/kg day. Hemorrhaging in the brain was observed during gross pathological examinations of mice that died under chloroform anesthesia following doses ≥500 mg/kg/day (Bowman et al. 1978). Lower concentrations of chloroform-induced taste aversion to a saccharin solution in mice exposed by gavage for 10 days to 30 mg/kg/day in oil, but not in mice exposed to 10 mg/kg/day (Landauer et al. 1982). No signs of behavioral toxicity were observed in mice exposed to 31.l mg/kg/day chloroform for 14, 60, or 90 days, or in mice exposed to 100 mg/kg for 30 days (Balster and Borzelleca 1982). Operant behavior in mice was affected after exposure to

100 mg/kg/day for 60 days (Balster and Borzelleca 1982). The most severe effects were observed early in the experiment; partial tolerance was observed later. No histopathological changes were observed in the brains of rats after chronic exposure to 200 mg/kg/day, in the brains of mice after chronic exposure to 477 mg/kg/day (NCI 1976) or in the brains of mice after chronic exposure to 60 mg/kg/day (Roe et al. 1979).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No definitive studies were located regarding reproductive effects in humans after oral exposure to chloroform. However, in a study by Bove et al. (1995), the effects of drinking-water consumption on birth outcomes were evaluated in women giving birth in northern New Jersey during the period of Jan 1, 1985 to Dec 31, 1988. A total of 80,938 live births and 594 fetal deaths were studied. Exposure to total trihalomethane (TTHM) levels >0.l ppm resulted in a 70.4 g reduction in mean birth weight among term babies, increased odds ratio (OR) for low birth weight among term births (1.42), an increased OR for reduced size at gestational age birth (1.50) and an increased OR for oral cleft defects (3.17). In addition, exposure to TTHM of >0.08 ppm resulted in an increased OR for central nervous system defects (2.59) and neural tube defects (2.96). The results of this study should be viewed with caution since the outcomes data were not correlated directly with chloroform concentrations, but rather with TTHM concentrations; hence, the effects observed may be due to exposure to other THMs. The authors of this study also acknowledged the presence of other non-THM contaminants, and that some or all of these contaminants may have contributed to the observed effects as well.

In rats, increased resorptions were observed at a dose of 316 mg/kg/day chloroform during gestation but not at 300 mg/kg/day; increased resorptions were also observed in rabbits exposed to 100 mg/kg/day during gestation (Thompson et al. 1974). Furthermore, abortions (not otherwise specified) were observed in rabbits exposed to 63 mg/kg/day chloroform during gestation (Thompson et al. 1974). No histopathological changes were observed in the testes of rats exposed to 160 mg/kg/day chloroform in drinking water for intermediate durations (Jorgenson and Rushbrook 1980). Gonadal atrophy was observed in both sexes of rats treated by gavage with 410 mg/kg/day

chloroform in toothpaste (but not with 150 mg/kg/day) (Palmer et al. 1979). In a 2-generation reproductive study in mice, exposure to 41 mg/kg/day of chloroform by gavage in oil did not affect the fertility in either generation (Gulati et al. 1988). No remarkable histopathological differences regarding the reproductive system were observed in dogs receiving up to 30 mg/kg/day of chloroform delivered in toothpaste capsules for 7.5 years (Heywood et al. 1979). No histopathological changes were observed in the reproductive organs of male and female rats and mice chronically exposed to 200 and 477 mg/kg/day chloroform via gavage (NCI 1976).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

One study (Kramer et al. 1992) was located regarding developmental effects in humans after oral exposure to chloroform via the drinking water. The study was conducted to determine whether water supplies containing relatively high levels of chloroform and other THMs within the state of Iowa are associated with low birth weight, prematurity, or intrauterine growth retardation (the most sensitive end point). Subjects selected include 159 low-birth-weight infants, 342 premature infants, and 187 grow-thretarded infants; however, case definitions were not mutually exclusive. Infants studied were divided into three groups: those who lived in areas where the water supply had undetectable amounts of chloroform, those who lived in areas where the water supply had l-9 μg/L chloroform, and those who lived in areas where the water supply had more than 10 μg/L. The estimated relative risk of low birth weight associated with drinking-water sources having chloroform levels of greater than or equal to 10 μg/L was 30% higher than the risk for sources with undetectable levels of chloroform. Prematurity was not associated with chloroform/THM exposure. The estimated relative risk of intrauterine growth retardation associated with drinking-water supplies with chloroform concentration of >10 μg/L was 80% more than the risk for those sources with undetectable levels of chloroform. Sources with intermediate chloroform levels (l-9 μg/L) had an elevated risk of 30%. The authors concluded that there is an increased risk of intrauterine growth retardation associated with higher concentrations of waterborne chloroform and dichlorobromomethane; however, it also should be noted that other organic halides that can co-occur in chlorinated drinking water (haloacetic acids and haloacetonitriles) produce developmental effects in animals.

No teratological effects or skeletal anomalies in rats or rabbits after oral exposure to chloroform were reported in developmental studies (Ruddick et al. 1983; Thompson et al. 1974). Decreased fetal weight was observed in the offspring of rats exposed by gavage to 400 mg/kg/day chloroform during gestation, but not in those exposed to 200 mg/kg/day (Ruddick et al. 1983). In a preliminary dosefinding study, decreased fetal weight and increased resorptions were observed in rats exposed to 316 mg/kg/day chloroform during gestation (Thompson et al. 1974). In the principal study, reduced birth weight of the offspring was reported in the 126 mg/kg/day group; no effects were observed in the 50 mg/kg/day exposure group. No behavioral effects were observed in the offspring of the F_0 generation mice treated for 6-10 weeks with 31.l mg/kg chloroform (Burkhalter and Balster 1979).

In a 2-generation reproductive study, increased epididymal weights and degeneration of epididymal ductal epithelium were observed in mice in the F_1 generation dosed with 41 mg/kg/day in oil (Gulati et al. 1988). The production and viability of sperm was not affected, however. Swiss mice given drinking water containing a mixture of contaminants including 7 ppm chloroform experienced no significant developmental effects. In the same study, Sprague-Dawley rat pups of the F_l generation had lower body weights from birth through mating; however, this was likely an artifact of decreased water intake. No other developmental effects were noted (Heindel et al. 1995). These data are limited by the possible interactions caused by the concurrent exposure to other water contaminants.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to chloroform.

Unscheduled DNA synthesis (UDS) in hepatocytes was not increased in rats exposed to chloroform at gavage doses ≥400 mg/kg in oil (Mirsalis et al. 1982). Exposure to 200 mg/kg/day chloroform in oil by gavage for 4 days increased sister chromatid exchange frequency in bone marrow cells of mice (Morimoto and Koizumi 1983). Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

Epidemiology studies suggest an association between cancer in humans and the consumption of chlorinated drinking water, but the results are not conclusive at this time (Alavanja et al. 1978; Cantor et al. 1978; Ijsselmuiden et al. 1992; McGeehin et al. 1993; Young et al. 1981; Zierler et al. 1988). Such an association implicates chloroform because chloroform is a known animal carcinogen (see below) and is the predominant THM in chlorinated drinking water (see Chapter 5); however, it is important to note that some of the many chemicals produced in the process of water chlorination are highly mutagenic and/or carcinogenic. Although attempts were made to control for various demographic variables in all of these studies (e.g., social class, ethnic group, marital status, occupation, urban or rural, etc.), many confounding effects remained unaccounted for, most notably the likelihood that numerous chemicals other than chloroform were present in the drinking water, as stated above. Furthermore, the studies differed regarding the type of cancer associated with consumption of chlorinated water. Bladder cancer was reported to have the strongest association with chlorinated water in several studies (Cantor et al. 1978; McGeehin et al. 1993; Zierler et al. 1988), but only colon cancer had an elevated OR (3.6) in another study (Young et al. 1981). In addition, Ijsselmuiden et al. (1992) found the use of municipal water to be associated with pancreatic cancer. All these studies superficially suggest that low-level oral chloroform consumption may increase the risk of some cancers in humans; however, it is equally important to note that most of these studies had confounding factors that make it difficult to definitively state that chloroform is the chemical chiefly responsible for the induction of these specific types of cancer. Confounding factors, such as the presence of other THMs (i.e., brominated THMs), haloacetic acids, haloacetonitriles, halogenated aldehydes, ketones and furanones, and chlorine content (both free and total), all of which may vary widely from one chlorinated drinking-water source to another, may have a large influence on the incidence of these cancers. In addition, many of these studies did not account for migration and historical exposures to any THMs, the wide ranges of potential exposure doses, occupational exposures to other chemicals, and the lack of a direct measurement of chloroform (or other THM) consumption in the drinking-water source (Cantor et al. 1978; Ijsselmuiden et al. 1992; Young et al. 1981; Zierler et al. 1988). Overall, the human data are insufficient to support any conclusion regarding the carcinogenic potential of orally consumed chloroform in humans.

Differing results on the carcinogenic capabilities of chloroform have been demonstrated in laboratory animals. Chloroform is carcinogenic in laboratory animals after oral exposure in some studies of

intermediate durations. An increased incidence of hepatomas was observed in mice exposed by gavage for 30 days to 594 mg/kg/day chloroform in oil, but not in mice exposed to 297 mg/kg/day (Eschenbrenner and Miller 1945a). An 8-week exposure to 1,800 mg/kg/day chloroform in oil by gavage did not induce lung tumors in mice (Stoner et al. 1986). Chloroform in corn oil acted as a promoter rather than an initiator of preneoplastic foci in a rat liver bioassay (Deml and Oesterle 1985). In addition, no increase in tumors was found in mice exposed to 257 mg/kg/day chloroform in drinking water for 52 weeks (Klaunig et al. 1986). Interestingly, Reddy et al. (1992) dosed male rats with 14, 25, 52, and 98 mg/kg/day of chloroform in the drinking water for 12 weeks. The study conclusively showed that chloroform, at the doses administered and routes studied in the rat, reduced the number of preneoplastic enzyme-altered foci (gamma-glutamyltranspeptidase-positive and GSH S-transferase-positive) in the liver of male rats after induction of foci with diethylnitrosamine in a dose-related fashion. The exact mechanism behind this effect was not determined.

Chloroform was found to be carcinogenic in several chronic animal studies of oral exposure. Renal tumors (tubular cell adenoma and carcinoma) were observed in male Osborne-Mendel rats after a 78-week exposure to 90 mg/kg/day chloroform by gavage in corn oil (NCI 1976). Dunnick and Melnick (1993) demonstrated the incidence of liver and kidney tumors in rats and mice dosed by gavage in corn oil for 5 days a week for 78 weeks. In rats, kidney tubular cell neoplasms did not occur in controls but were observed at 90 mg/kg/day (4 of 50) and at 180 mg/kg/day (12 of 50) in males, and at 200 mg/kg/day (2 of 48) in females. In male mice, hepatocellular neoplasms were rarely seen in controls (1 of 18), but were frequently observed in the 138 mg/kg group (18 of 50) and 277 mg/kg group (44 of 45). In female mice, no hepatocellular neoplasms were recorded in controls but were observed in the 238 mg/kg group (36 of 45) and 477 mg/kg group (39 of 41). The incidence of hepatic neoplastic nodules was increased in female Wistar rats chronically exposed to 200 mg/kg/day chloroform in drinking water (Tumasonis et al. 1987). An increased incidence of tubular cell adenoma and carcinoma was observed in the kidneys of Osborne-Mendel rats chronically exposed to 160 mg/kg/day chloroform in drinking water but not in those exposed to 81 mg/kg/day (Jorgenson et al. 1985). The 160 mg/kg/day dose in this study also resulted in decreased water consumption (taste aversion). In contrast, no increase in the incidence of tumors was observed in Sprague-Dawley rats exposed by gavage to 60 and 165 mg/kg/day chloroform in toothpaste for 80 and 52 weeks, respectively (Palmer et al. 1979). Hepatocellular carcinoma was observed in all groups of male $B6C3F_1$ mice exposed to gavage doses ≥138 mg/kg/day chloroform in oil for 78 weeks (NCI 1976). An increased incidence of kidney tumors was observed in ICI mice chronically exposed to

60 mg/kg/day chloroform by gavage, but not in those exposed to 17 mg/kg/day (Roe et al. 1979). Under the same experimental conditions, chloroform exposure had no effect on the frequency of tumors in C57BL, CBA, and CF-1 mice. Moreover, no increase in tumor incidence was observed in $B6C3F_l$ mice exposed to 263 mg/kg/day chloroform in drinking water for 2 years (Jorgenson et al. 1985). Cancer was not observed in dogs exposed to 30 mg/kg/day chloroform in toothpaste capsules for 7.5 years (Heywood et al. 1979). From these data it would appear that the method of dosing (e.g., gavage versus drinking water) and the vehicle utilized may influence outcomes in chronic trials. The CELs (cancer effect levels) are recorded in Table 2-2 and plotted in Figure 2-2. EPA (IRIS 1995) selected the study by Jorgenson et al. (1985) as the basis for the q_l* for oral exposure to chloroform because administration via drinking water better approximates oral exposure in humans than does administration in corn oil by gavage as used in the NCI (1976) study. Based on the incidence of renal tumors in male Osborne-Mendel rats, the q_1 * was calculated to be $6.1x10^{-3}$ $(mg/kg/day)^{-1}$. The oral doses associated with individual lifetime upper-bound risks of 10^{-4} to 10^{-7} are $1.6x10^{-2}$ to $1.6x10^{-5}$ mg/kg/day, respectively, and are plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to chloroform.

No deaths resulted from dermal exposure of rabbits exposed to doses of up to 3,980 mg/kg chloroform for 24 hours (Torkelson et al. 1976).

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or ocular effects in humans or animals after dermal exposure to chloroform.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to chloroform.

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No hepatic effects were observed in rabbits when 3,980 mg/kg chloroform was applied to the abdominal skin for 24 hours (Torkelson et al. 1976). The NOAEL for hepatic effects is recorded in Table 2-3.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to chloroform.

Renal degenerative tubular changes were observed in rabbits when 1,000 mg/kg chloroform was applied to the abdominal skin for 24 hours (Table 2-3) (Torkelson et al. 1976).

Dermal Effects. Completely destroyed stratum corneum was observed in the skin of 2 young volunteers exposed to chloroform for 15 minutes on 6 consecutive days (Malten et al. 1968). Milder changes were observed in two older individuals. Chloroform was applied in a glass cylinder (exact exposure was not specified).

A clinical study of 21 females and 21 males used to determine the efficacy of using aspirin dissolved in chloroform which was then applied topically to patients infected with herpes zoster and post--therapeutic neuralgia with painful skin lesions has been reported. When an aspirin/chloroform combination (approximately 43.3 mg/mL) was applied, the only reported side-effect was an occasional burning sensation on the skin as the chloroform evaporated from the skin surface; however, the possible impact on other major body organs (liver, kidney, etc.) was not investigated (King 1993).

Application of 0.01 mL chloroform for 24 hours to the skin of rabbits caused only slight irritation (Smyth et al. 1962). Skin necrosis was observed in rabbits dermally exposed to 1,000 mg/kg chloroform for 24 hours (Torkelson et al. 1976). These LOAEL values are recorded in Table 2-3.

Body Weight Effects. No studies were located regarding body weight effects in humans after dermal exposure to chloroform.

Dermal exposure to 1,000 mg/kg chloroform for 24 hours caused weight loss in rabbits (Table 2-3) (Torkelson et al. 1976).

Table 2-3. Levels of Significant Exposure to Chloroform - Dermal

Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL	LOAEL				Reference
				Less Serious		Serious		
ACUTE EXPOSURE								
Systemic								
Rabbit (New Zealand)	24 hr	Dermal		0.01mL M	(slight skin irritation)			Smyth et al. 1962
Rabbit (NS)	24 hr	Hepatic	3980 mg/kg					Torkelson et al. 1976
		Renal		1000 mg/kg	(degenerative tubular changes)			
		Dermal				1000 mg/kg	(necrosis)	
		Bd Wt		1000 mg/kg	(unspecified weight loss)			

Bd Wt = body weight; hr = hour(s); LOAEL = lowest-observed-adverse-effect-level; M = male; NOAEL = no-observed-adverse-effect-level; NS = not specified

2. HEALTH EFFECTS

No credible studies were located regarding the following health effects in humans or animals after dermal exposure to chloroform:

2.2.3.3 Immunological and Lymphoreticular Effects

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genatoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to chloroform.

2.3 TOXICOKINETICS

Overview. Sufficient information exists on the absorption, distribution, metabolism, and excretion of chloroform, with most information on the pharmacokinetics being derived from animal data. Generally, chloroform is absorbed easily into the blood from the lungs after inhalation exposures. Following oral exposure, peak blood levels are achieved within 5-6 minutes, depending on the dosing vehicle and dosing frequency used. The chemical properties of chloroform also permit percutaneous absorption without difficulty. After absorption, chloroform has been reported to distribute to adipose tissues, brain, liver, kidneys, blood, adrenals, and embryonic neural tissues. Higher levels of chloroform can be found in the renal cortex of male animals than in female animals, a finding apparently mediated by the presence of testosterone. Approximately 50% of a dose of chloroform is eventually metabolized to carbon dioxide in humans; however, an intermediate toxic metabolite, phosgene, is formed in the process in the liver. Chloroform undergoes metabolism primarily in the liver and may undergo covalent binding to both lipid and microsomal protein. Chloroform is excreted from the body either unchanged by pulmonary desorption or in the form of carbon dioxide, with small amounts of either detectable in the urine and feces.

2. HEALTH EFFECTS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Chloroform absorption depends on the concentration in inhaled air, the duration of exposure, the blood/air partition coefficient, the solubility in various tissues, and the state of physical activity which influences the ventilation rate and cardiac output. Pulmonary absorption of chloroform is also influenced by total body weight and total fat content, with uptake and storage in adipose tissue increasing with excess body weight and obesity.

In inhalation exposures, the arterial blood concentration of chloroform is directly proportional to the concentration in inhaled air. At anesthetic concentrations (8,000-10,000 ppm), steady-state arterial blood concentrations of chloroform were 7-16.2 mg/mL (Smith et al. 1973). Total body equilibrium with inspired chloroform concentration required at least two hours in normal humans at resting ventilation and cardiac output (Smith et al. 1973).

The amount of chloroform absorbed and exhaled from the body in alveolar air from male and female swimmers in indoor swimming pools in Italy was measured by Aggazzotti et al. (1993). Alveolar air samples were collected from both swimmers and observers present in indoor chlorinated swimming pools. Of all the nonexposed subjects, 47% had chloroform concentrations below the detection limit of the assay, and the remainder of this control group had low concentrations (75.39 nmol/m^3) of chloroform present in their alveolar air. Median alveolar chloroform concentrations for persons exposed to the indoor swimming pools (swimmers and observers), were significantly higher than those of nonexposed subjects (median=695.02 nmol/m^3). No differences were found between males and females in any exposure group.

Cammann and Huebner (1995) attempted to correlate chloroform exposure with blood and urine chloroform concentrations in persons using indoor swimming pools. Water and air samples were collected from three swimming pools in Germany, with blood and urine samples collected from attendants, normal swimmers, and agonistic swimmers before and after environmental exposure. Pool water chloroform levels ranged from 3.04 to 27.8 μg/L, while air concentrations ranged from 7.77 to 191 ug/m3. In general, blood chloroform levels increased with exposure. Blood levels were lowest in attendants (0.13-2.45 μg/L), followed by normal swimmers (0.56-l.65 μg/L) and agonistic swimmers

(1.14-5.23 μg/L). Based upon the differences seen in the two swimming groups, the authors concluded that increased physical activity leads to increased absorption and/or ingestion of chloroform.

In a similar study, Levesque et al. (1994) attempted to quantitate the body burden of chloroform following exposure in an indoor pool. Scuba divers were exposed to chloroform-laden water and air on each of seven days. On each exposure day, the subjects exercised for a 55-minute period; alveolar air samples were collected before exercise and after 35 or 55 minutes of exercise. Pre-exercise alveolar levels of chloroform averaged 52.6 ppb; this was attributed to air contamination in the locker room. Alveolar air concentrations of chloroform after 35 and 55 minutes of exercise increased steadily through day 5, averaging 100-950 and 104-1,093 ppb, respectively. On day 6, when scuba gear was worn by the subjects, alveolar air concentrations after 35 and 55 minutes of exercise were 196 and 209 ppb, respectively. The authors concluded from this data that the average proportion of body burden due to inhalation after 35 and 55 minutes exercise was 76 and 78%, respectively.

Nashelsky et al. (1995) described one non-fatal assault and three deaths-in which chloroform was utilized. Blood and/or tissue concentrations of chloroform were determined in the assault victim and one decedent within 24 hours, within 10 days in another decedent who was frozen for the majority of that period, and after 5 months without preservation in the last decedent. Blood concentrations in 2 decedents were 2 and 3 μg/mL; fat concentrations were 10 and 42 μg/mL; brain concentrations were 3 and 46 μg/mL; and the liver concentration in one decedent was 24 μg/mL. Due to the nature of the tissues analyzed, these data should be regarded as qualitative indicators of chloroform absorption only.

No studies were located regarding absorption in animals after inhalation exposure to chloroform. Evidence that chloroform is absorbed after inhalation exposure is provided in toxicity studies (see Section 2.2.1), but the rate and extent cannot be determined from the toxicity data.

2.3.1.2 Oral Exposure

In one case report, a 33-year-old female (weight not reported) injected herself intravenously with 0.5 mL of chloroform and became unconscious. She awoke approximately 12 hours later and drank another 120 mL of chloroform. Plasma chloroform levels were determined 18 hours after ingestion by gas chromatography (GC) and showed a blood chloroform level of 0.66 mg/dL. Subsequent serum

samples were analyzed for chloroform content and were reported to have been less than this level, steadily declining over time (Rao et al. 1993).

Absorption of an oral dose of ^{13}C-labeled chloroform (0.5 grams in a gelatin capsule) was rapid in volunteers, reaching peak blood levels in 1 hour (Fry et al. 1972). Almost 100% of the dose was absorbed from the gastrointestinal tract.

Experiments in mice, rats, and monkeys indicate that oral doses (60 mg/kg) of ^{14}C-labeled chloroform in olive oil were almost completely absorbed as indicated by a 80-96% recovery of radioactivity in expired air, urine, and carcass (Brown et al. 1974a; Taylor et al. 1974). Absorption in mice and monkeys was rapid; the peak blood levels were reached 1 hour after oral administration of 60 mg/kg chloroform in olive oil.

Intestinal absorption of chloroform in either water or corn oil administered intragastrically to rats was rapid with both vehicles, but the rate and extent of absorption varied greatly (Withey et al. 1983). The peak concentration of chloroform in blood was 39.3 μg/mL when administered in water and 5.9 μg/mL when administered in corn oil. The greater degree of absorption following administration in water can be explained by the faster partitioning of a lipophilic compound such as chloroform with mucosal lipids from an aqueous vehicle. Peak blood concentrations were reached somewhat more rapidly with the water vehicle (5.6 minutes as opposed to 6 minutes for corn oil). The uptake from a corn oil solution was more complex (pulsed) than from aqueous solution. A possible explanation for this behavior is that the chloroform in corn oil was broken up into immiscible globules, some of which did not come into contact with the gastric mucosa. Another possible explanation was that intragastric motility may have separated the doses into aliquots that were differentially absorbed from the gastrointestinal tract. In a similar study, Pereira (1994) investigated the uptake and protein binding of chloroform in the liver and kidney in female $B6C3F_1$ mice. Animals received single doses of chloroform by gavage in either water or corn oil. Uptake of chloroform from water into the liver peaked in 1.5 minutes, and hepatic uptake during the first 20 minutes exceeded that of chloroform delivered in oil. During the first 20 minutes after dosing, binding of chloroform to macromolecules in the liver was greater when water vehicle was utilized; beyond 20 minutes, the amount of binding was equivalent between the 2 vehicle groups. Renal uptake of chloroform from water exceeded uptake of chloroform from oil over the entire 4-hour period. The extent of binding to macromolecules in

kidneys was consistently greater in the group given chloroform in water. Differences in chloroform toxicity based on the vehicle have also been recently reported elsewhere (Larson et al. 1994b, 1995a)

2.3.1.3 Dermal Exposure

A limited number of experimental studies were located regarding dermal absorption of chloroform in humans. Levesque et al. (1994) attempted to quantitate the body burden of chloroform following dermal and inhalation exposure in an indoor swimming pool. Male scuba divers were exposed to chloroform-laden water and air on each of seven days. On each exposure day the subjects exercised for a 55-minute period. On day 6 of the experiment, subjects wore scuba gear so as to determine the percentage body burden due to dermal exposure. On day 6, when scuba gear was worn by the subjects, alveolar air concentrations after 35 and 55 minutes of exercise were 196 and 209 ppb, respectively. From this data it would appear that the average proportion of body burden due to dermal exposure after 35 and 55 minutes exercise was 24 and 22%, respectively.

Cammann and Huebner (1995) attempted to correlate chloroform exposure with blood and urine chloroform concentrations in persons using indoor swimming pools. Water and air samples were collected from three pools in Germany, and blood and urine samples were collected from attendants, normal swimmers and agonistic swimmers before and after exposure. Pool water chloroform levels ranged from 3.04 to 27.8 μg/L, while air concentrations ranged from 7.77 to 191 $\mu g/m^3$. Blood chloroform levels generally increased with higher chloroform exposure levels. Blood levels were lowest in attendants (0.13-2.45 μg/L), followed by normal swimmers (0.56-1.65 μg/L) and agonistic swimmers (1.14-5.23 μg/L). Based upon the differences seen in the two swimming groups, the authors concluded that increased physical activity leads to increased absorption and/or ingestion. With the exception of the inclusion of attendants, the authors did not attempt to differentiate between inhalation and dermal absorption of chloroform. However, the increased blood concentrations seen in the swimmers seems to indicate that dermal absorption did indeed occur

Dick et al. (1995) examined the absorption of chloroform through human skin *in vivo* using volunteers and *in vitro* using fresh, excised abdominal skin. In the *in vivo* study, the ventral forearm skin of four male volunteers was dosed with a solution of chloroform in either water or ethanol. The solution remained on the skin for eight hours. When administered in water, the total absorbed dose was 8.2%. In contrast, the total absorbed dose was only 1.68% when chloroform was administered in ethanol. In

the *in vitro* study, two doses were applied to the skin and remained there for four hours. At study termination, the percentages of the low and high doses of chloroform absorbed were 5.6 and 7.1%, respectively.

According to dermal absorption studies with solvents other than chloroform, the absorption of such solvents in guinea pigs is more rapid than the metabolism or pulmonary excretion (Jakobson et al. 1982). A dermal absorption rate of 329 nmol/minute/cm^2 (±60 nmol/minute/cm^2) was calculated for the shaved abdominal skin of mice (Tsuruta 1975). This is equivalent to a human absorption rate of 29.7 mg/minute, assuming that a pair of hands are immersed in liquid chloroform (Tsuruta 1975). However, this calculation was based on the assumptions that the rate of chloroform penetration is uniform for all kinds of skin and that the total surface area of a pair of human hands is 800 cm^2; the former assumption is especially dubious. Islam et al. (1995) investigated the fate of topically applied chloroform in male hairless rats. For exposures under 4 minutes, chloroform-laden water was applied to shaved back skin; for exposures of 4-30 minutes, rats were submerged in baths containing chloroform-laden water. Selected skin areas were tape-stripped a various number of times after various delay periods. It appeared that there was an incremental build-up of chloroform in the skin over the first four minutes. When compared to uptake measured by bath concentration differences, approximately 88% of lost chloroform was not accounted for in the stratum corneum and was assumed to be systemically absorbed.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Chloroform is lipid soluble and readily passes through cell membranes, causing narcosis at high concentrations. Blood chloroform concentrations during anesthesia (presumed concentrations 8,000-10,000 ppm) were 7-16.2 mg/mL in 10 patients (Smith et al. 1973). An arterial chloroform concentration of 0.24 mg/mL during anesthesia corresponded to the following partition coefficients: blood/gas, 8; blood/vessel rich compartment, 1.9; blood/muscle compartment, 1.9; blood/fat compartment, 31; blood/vessel poor compartment, 1; and blood/liver, 2 (Feingold and Holaday 1977). Recently, partition coefficients were calculated for humans based on results in mice and rats, and in human tissues *in vitro:* blood/air, 7.4; liver/air, 17; kidney/air, 11; and fat/air, 280 (Corley et al. 1990).

2. HEALTH EFFECTS

The chloroform levels in 7 patients who died after excessive administration during anesthesia were: brain, 372-480 mg/kg; lungs, 355-485 mg/kg; and liver, 190-275 mg/kg (Gettler and Blume 1931). The chloroform levels in patients under anesthesia who died from other causes were: brain, 120-182 mg/kg; lungs, 92-145 mg/kg; and liver, 65-88 mg/kg tissue wet weight. Nashelsky et al. (1995) describe one nonfatal assault and three deaths in which chloroform was utilized. Blood and/or tissue concentrations of chloroform were determined in the assault victim and one decedent within 24 hours, within 10 days in another decedent who was frozen for the majority of that period, and after 5 months without preservation in the last decedent. Blood concentrations in 2 decedents were 2 and 3 μg/mL; fat concentrations were 10 and 42 μg/mL; brain concentrations were 3 and 46 μg/mL; and the liver concentration in one decedent was 24 μg/mL.

After whole-body autoradiography to study the distribution of ^{14}C-labeled chloroform in mice, most of the radioactivity was found in fat immediately after exposure, while the concentration of radioactivity in the liver increased during the postanesthetic period, most likely due to covalent binding to lipid and protein in the liver (Cohen and Hood 1969). Partition coefficients (tissue/air) for mice and rats were 21.3 and 20.8 for blood; 19.1 and 21.1 for liver; 11 and 11 for kidney; and 242 and 203 for fat, respectively (Corley et al. 1990). Arterial levels of chloroform in mongrel dogs reached 0.35-0.40 mg/mL by the time animals were in deep anesthesia (Chenoweth et al. 1962). Chloroform concentrations in the inhaled stream were not measured, however. After 2.5 hours of deep anesthesia, there were 392 mg/kg chloroform in brain tissue, 1,305 mg/kg in adrenals, 2,820 mg/kg in omental fat, and 290 mg/kg in the liver.

Radioactivity from ^{14}C-labeled chloroform was detected in the placenta and fetuses of mice shortly after inhalation exposure (Danielsson et al. 1986). In early gestation, accumulation of radioactivity was observed in the embryonic neural tissues, while the respiratory epithelium was more involved in chloroform metabolism in the late fetal period.

Due to its lipophilic character, chloroform accumulates to a greater extent in tissues of high lipid content. As shown by the results presented above, the relative concentrations of chloroform in various tissues decreased as follows: adipose tissue > brain > liver > kidney > blood.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to chloroform.

High concentrations of radioactivity were observed in body fat and livers of rats, mice, and squirrel monkeys given oral doses of 60 mg/kg ^{14}C-labeled chloroform (Brown et al. 1974a). The maximum levels of radioactivity in the blood appeared within 1 hour and were 3 μg equivalents chloroform/ml for mice and 10 μg equivalents chloroform/ml for monkeys, which represented ≈0.35 and l%, respectively, of the total radioactivity. In monkeys, bile concentrations peaked within 6 hours. The distribution of radioactively labeled chloroform was studied in three strains of mice (Taylor et al. 1974). No strain-related differences were observed; however, higher levels of radioactivity were found in the renal cortex of males and in the liver of females. The renal binding of radioactive metabolites may have been altered by variations in the testosterone levels as a result of hormonal pretreatment in females or castration in males. Sex-linked differences in chloroform distribution were not observed in rats or monkeys (Brown et al. 1974a). Chloroform accumulates in the adipose tissue of rats after oral exposure of intermediate duration (Pfaffenberger et al. 1980).

2.3.2.3 Dermal Exposure

A limited number of studies were located regarding distribution in humans or animals after dermal exposure to chloroform.

Dick et al. (1995) examined the absorption of chloroform through human skin in *vivo* using volunteers and *in vitro* using fresh, excised abdominal skin. In the *in vivo* study, the ventral forearm skin of four male volunteers was dosed with a solution of chloroform in either water or ethanol. The solution remained on the skin for eight hours. When administered in water, urinary excretion was 0.42%, while excretion from the lungs over the first 48 hours postexposure averaged 7.8%. Tape-stripping data indicated that only 0.01% of the dose remained in the skin after 3 days. When chloroform was administered in ethanol, urinary excretion was 0.07% while excretion from the lungs over the first 48 hours postexposure averaged 0.83%. Tape-stripping data indicated that the percentage of the dose remaining in the skin after three days was non detectable. In the *in vitro* study, two doses were applied to the skin and remained there for four hours. At study termination, the majority of the

absorbed dose was found in the perfusate (7.0%), with only minor amounts remaining in the skin (0.14%).

Islam et al. (1995) investigated the fate of topically applied chloroform in male hairless rats. For exposures under 4 minutes, chloroform-laden water was applied to shaved back skin; for exposures of 4-30 minutes, rats were submerged in baths containing chloroform-laden water. Selected skin areas were tape-stripped a various number of times after various delay periods. The authors found that the accumulated amount of chloroform declined rapidly with depth of stratum corneum. As the time of exposure decreased, smaller amounts of chloroform were found in the deeper layers of stratum comeum; by five minutes postexposure, the amount of chloroform at the first tape strip (skin surface) dropped to negligible levels. It appeared that there was an incremental build-up of chloroform in the skin over the first four minutes. When compared to uptake measured by bath concentration differences, approximately 88% of the chloroform dose was not accounted for in the stratum comeum and was assumed to be systemically absorbed.

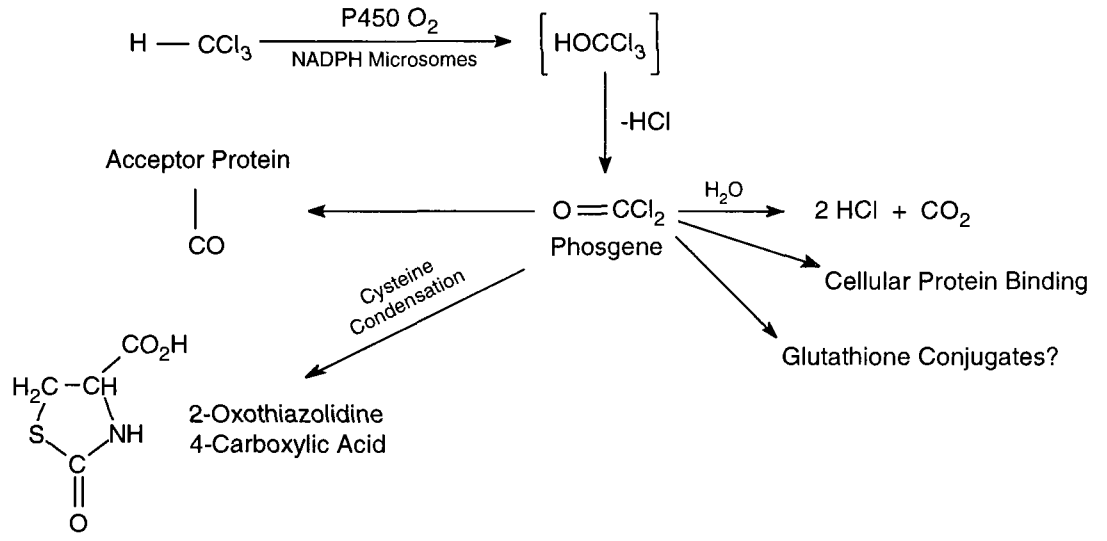
2.3.3 Metabolism

The metabolism of chloroform is well understood. Approximately 50% of an oral dose of 0.5 grams of chloroform was metabolized to carbon dioxide in humans (Fry et al. 1972). Metabolism was dose-dependent, decreasing with higher exposure. A first-pass effect was observed after oral exposure (Chiou 1975). Approximately 38% of the dose was converted in the liver, and ≤17% was exhaled unchanged from the lungs before reaching the systemic circulation. On the basis of pharmacokinetic results obtained in rats and mice exposed to chloroform by inhalation, and of enzymatic studies in human tissues *in vitro, in vivo* metabolic rate constants ($V_{max}C$ = 15.7 mg/hour/kg, Km = 0.448 mg/L) were defined for humans (Corley et al. 1990). The metabolic activation of chloroform to its toxic intermediate, phosgene, was slower in humans than in rodents.

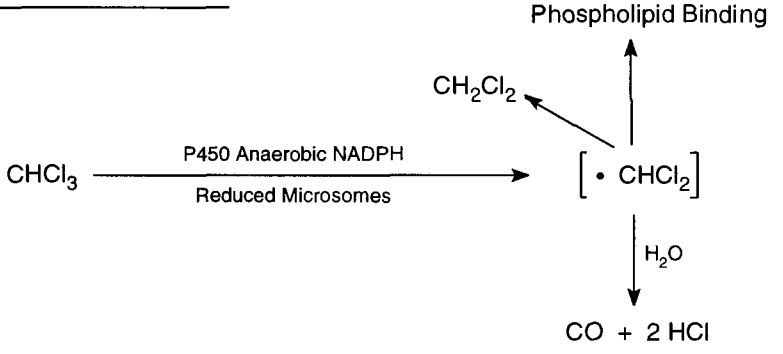
Metabolic pathways of chloroform biotransformation are shown in Figure 2-3. Metabolism studies indicated that chloroform was, in part, exhaled from the lungs or was converted by oxidative dehydrochlorination of its carbon-hydrogen bond to form phosgene (Pohl et al. 1981; Stevens and Anders 1981). This reaction was mediated by cytochrome P-450 and was observed in the liver and kidneys (Ade et al. 1994; Branchflower et al. 1984; Smith et al. 1984). In renal cortex microsomes of

Figure 2-3. Metabolic Pathways of Chloroform Biotransformation

MAJOR AEROBIC PATHWAY



MINOR ANAEROBIC PATHWAY



DBA/2J mice, the majority of chloroform metabolism was oxidative under ambient oxygen conditions, while anoxic conditions resulted in reductive metabolism (Ade et al. 1994). Phosgene may react with two molecules of GSH to form diglutathionyl dithiocarbonate, which is further metabolized in the kidneys, or it may react with other cellular elements and induce cytotoxicity (Pohl and Gillette 1984). *In* vitro studies indicate that phosgene and other reactive chloroform metabolites bind to lipids and proteins of the endoplasmic reticulum proximate to the cytochrome P-450 (Sipes et al. 1977; Wolf et al. 1977). The metabolism of chloroform to reactive metabolites occurs not only in microsomes but also in nuclear preparations (Gomez and Castro 1980). Covalent binding of chloroform to lipids can occur under anaerobic and aerobic conditions, while binding to the protein occurs only under aerobic conditions (Testai et al. 1987). It was further demonstrated that chloroform can induce lipid peroxidation and inactivation of cytochrome P-450 in rat liver microsomes under anaerobic conditions (De Groot and No11 1989). Covalent binding of chloroform metabolites to microsomal protein *in vitro* was intensified by microsomal enzyme inducers and prevented by GSH (Brown et al. 1974b). It was proposed that the reaction of chloroform metabolites with GSH may act as a detoxifying mechanism. When GSH is depleted, however, the metabolites react with microsomal protein, and may cause necrosis. This is supported by observations that chloroform doses that caused liver GSH depletion produced liver necrosis (Docks and Krishna 1976). In fasted animals, chloroform has been found to be more hepatotoxic (Brown et al. 1974b; Docks and Krishna 1976) even though animals were found to have lower blood chloroform concentrations (Wang et al. 1995); this phenomenon would apparently be explained by a decreased GSH content and resultant inability to bind toxic metabolites. This may explain the clinical finding of severe acute hepatotoxicity in women exposed to chloroform via anesthesia during prolonged parturition. Evidence that chloroform is metabolized at its carbonhydrogen bond is provided by experiments using the deuterated derivative of chloroform (Branchflower et al. 1984; McCarty et al. 1979; Pohl et al. 1980a). Deuterated chloroform was onehalf to one-third as cytotoxic as chloroform, and its conversion to phosgene was much slower. The results confirmed that the toxicity of chloroform is primarily due to its metabolites.

A recent *in vitro* study of mice hepatic microsomes indicated that a reductive pathway may also play an important role in chloroform hepatotoxicity (Testai et al. 1990). It was demonstrated that radical chloroform metabolites bind to macromolecules (proteins, lipids) and the process can be inhibited by reduced GSH.

2. HEALTH EFFECTS

The final product of the aerobic metabolic pathway of chloroform is carbon dioxide (Brown et al. 1974a; Fry et al. 1972). This carbon dioxide is mostly eliminated through the lungs, but some is incorporated into endogenous metabolites and excreted as bicarbonate, urea, methionine, and other amino acids (Brown et al. 1974a). Chloride ions are an end product of chloroform metabolism found in the urine (Van Dyke et al. 1964). Carbon monoxide was a minor product of the anaerobic metabolism of chloroform in vitro (Ahmed et al. 1977) and *in vivo* in rats (Anders et al. 1978).

A sex-related difference in chloroform metabolism was observed in mice (Taylor et al. 1974). Chloroform accumulated and metabolized in the renal cortex of males to a greater extent than in females, while liver chloroform concentrations were greater in females than in males; the results may have been influenced by testosterone levels. This effect was not observed in any other species and may explain why male mice were more susceptible to the lethal and renal effects of chloroform than were females (Deringer et al. 1953).

Wang et al. (1994) found that, in male Wistar rats, pretreatment with ethanol increased chloroform metabolism about I S-fold but did not affect hepatic microsomal protein of cytochrome P-450 content. In addition, intraperitoneal administration of chloroform resulted in greater blood concentrations, peak values, and area of the curves (AUCs), as compared to oral administration. AUCs in rats administered chloroform orally ranged from 0.34 to 6.45 versus 0.58 to 8.78 in rats administered chloroform intraperitoneally. The authors concluded that differences between route groups in hepatotoxicity were due to differences in the proportion of dose exposed to first-pass metabolism. Since oral dosing results in the greatest first-pass exposure, this route resulted in the greatest hepatotoxicity. The degree of hepatic exposure also influenced the enhancing effect of ethanol; the group receiving chloroform orally was affected the most by ethanol pretreatment. The authors also concluded that intraperitoneal exposure produced data which most like that of inhalation exposure, presumably due to the smaller proportion of dose going through first-pass metabolism.

Interspecies differences in the rate of chloroform conversion were observed in mice, rats, and squirrel monkeys, with species differences in metabolism being highly dose-dependant. The conversion of chloroform to carbon dioxide was highest in mice (80%) and lowest in squirrel monkeys (18%) (Brown et al. 1974a). Similarly, chloroform metabolism was calculated to be slower in humans than in rodents. Therefore, it was estimated that the exposure to equivalent concentrations of chloroform would lead to a much lower delivered dose in humans (Corley et al. 1990).

2. HEALTH EFFECTS

A study by Gearhart et al. (1993) was conducted to determine the interactions of chloroform exposure with body temperature, gas uptake, and tissue solubility in mice as possible explanations for the difficulty in fitting a physiologically based pharmacokinetic/pharmacodynamic (PBPK) model to chloroform gas-uptake data to derive *in vivo* metabolic constants. Male mice were exposed to air concentrations of 100, 800, 2,000, or 5,500 ppm chloroform for 6 hours and their core body temperatures monitored frequently over the exposure period. After exposure, blood, liver, thigh muscle, and fat tissues were removed for tissue/air and tissue/blood partition coefficient analysis at 3 temperatures (25, 31, and 37 °C). For all tissues, tissue/air partition coefficients exhibited temperature-dependent decreases with increasing temperature. The rate of decrease was greatest for the blood/air partition coefficient. Average body temperatures for each exposure group decreased as the exposure concentrations increased. Temperature dependent decreases in core body temperature were hypothesized to decrease overall metabolism of chloroform in mice. The data collected were also used to develop a PBPK model for chloroform disposition.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Chloroform was detected in the exhaled air of volunteers exposed to a normal environment, to heavy automobile traffic, or to air in a dry cleaning establishment (Gordon et al. 1988). Higher chloroform levels in the breath corresponded to higher exposure levels. The calculated biological half-time for chloroform was 7.9 hours.

Excretion of radioactivity in mice and rats was monitored for 48 hours following exposure to ^{14}C-labeled chloroform (Corley et al. 1990). In general, 92-99% of the total radioactivity was recovered in mice, and 58-98% was recovered in rats; percentage of recovery decreased with increasing exposure. With increasing concentration, mice exhaled 80-85% of the total radioactivity recovered as ^{l4}C-labeled carbon dioxide, 0.4-8% as ^{14}C-labeled chloroform, and 8-l1 and 0.6-1.4% as urinary and fecal metabolites, respectively. Rats exhaled 48-85% of the total radioactivity as ^{14}C-labeled carbon dioxide, 2-42% as ^{14}C-labeled chloroform, and 8-l 1 and 0.1-0.6% in the urine and feces, respectively. A 4-fold increase in exposure concentration was followed by a 50- and 20-fold increase in the amount of exhaled, unmetabolized chloroform in mice and rats, respectively.

2.3.4.2 Oral Exposure

Following a single, oral exposure, most of the 0.5 grams of radioactively labeled chloroform administered to volunteers was exhaled during the first 8 hours after exposure (Fry et al. 1972). A slower rate of pulmonary excretion was observed during the first eight hours in volunteers who had more adipose tissue than the other volunteers. Up to 68.3% of the dose was excreted unchanged, and up to 50.6% was excreted as carbon dioxide. A positive correlation was made between pulmonary excretion and blood concentration. Less than 1% of the radioactivity was detected in the urine.

Approximately 80% of a single dose of 60 mg/kg ^{14}C-labeled chloroform was converted within 24 hours to ^{14}C-labeled carbon dioxide in mice (Brown et al. 1974a; Taylor et al. 1974), while only ≈66% of the dose was converted to ^{14}C-labeled carbon dioxide in rats (Brown et al. 1974a). Eight hours after administration of 100-150 mg/kg of ^{14}C-labeled chloroform, 49.6 and 6.5% of radioactivity was converted to carbon dioxide, 26.1 and 64.8% was expired as unmetabolized parent compound, and 4.9 and 3.6% was detected in the urine in mice and rats, respectively (Mink et al. 1986). These results indicate that mice metabolize high doses of chloroform to a greater degree than rats do. Only 18% of a chloroform dose was metabolized to ^{14}C-labeled carbon dioxide in monkeys, and ≈79% was detected as unchanged parent compound or toluene soluble metabolites (Brown et al. 1974a). Within 48 hours after exposure, ≈2, 8, and 3% of the administered radioactivity was detected in the urine and feces of monkeys, rats, and mice, respectively.

2.3.4.3 Dermal Exposure

One study was located regarding excretion in humans after dermal exposure to chloroform. Dick et al. (1995) examined the fate of chloroform applied to human skin *in vivo* using volunteers and *in vitro* using fresh, excised abdominal skin. In the *in vivo* study, the ventral forearm skin of four male volunteers was dosed with a solution of chloroform in either water or ethanol. The solution remained on the skin for eight hours. When administered in water, urinary excretion was 0.42%, while excretion from the lungs over the first 48 hours postexposure averaged 7.8%. Tape-stripping data indicated that only 0.01% of the dose remained in the skin after three days. When chloroform was administered in ethanol, urinary excretion was 0.07% while excretion from the lungs over the first 48 hours postexposure averaged 0.83%. Tape-stripping data indicated that the percentage of the dose remaining in the skin after three days was non detectable. In the *in vitro* study, two doses were

applied to the skin and remained there for four hours. At study termination, the majority of the absorbed dose was found in the perfusate (7%), with only minor amounts remaining in the skin (0.14%).

No animal studies were located regarding the excretion of chloroform after dermal exposure to chloroform.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: model representation, model parameterization, model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular chemical substance require estimates of the

chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true. complexities of biological systems. This simplification, however, is desirable if the uptake and disposition of the chemical substance(s) is adequately described because data are often unavailable for many biological processes and using a simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is therefore of great importance and thus model validation must be critically considered.

PBPK models improve the pharmacokinetic extrapolation aspects of the risk assessment process, which seeks to identify the maximal (i.e., safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based upon the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

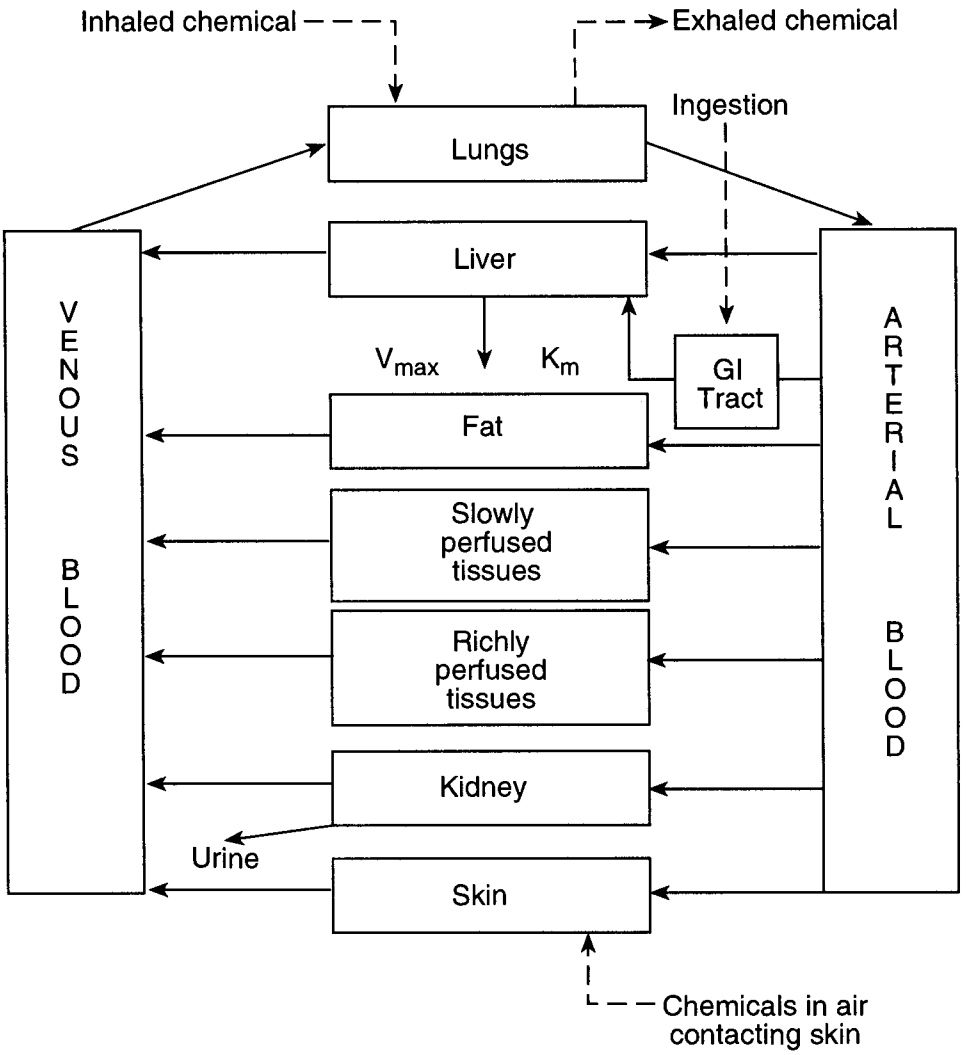
If PBPK models for chloroform exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

2.3.5.1 Summary of PBPK/PD Models

Several rodent and human models have been used to predict the absorption (oral, inhalation, and dermal) from water and air, distribution, metabolism, and excretion of chloroform.

In a PBPK model that used simulations with mice, rats, and humans (Corley et al. 1990), the tissue delivered dose from equivalent concentrations of chloroform was highest in the mouse, followed by rats and then humans. The authors suggest that this behavior is predicted by the model because of the lower relative rates of metabolism, ventilation, and cardiac output (per kg of body weight) in the

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1992

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

larger species. Assuming that equivalent target doses produce equivalent toxicities in target tissues, the relative sensitivities of the three species used in the study (mouse > rat > human) predicted by the model under identical exposure conditions are quite different from the relative sensitivity to chloroform assumed by the “uncertainty factor.”

In a PBPK/PD model based closely on the Corley model, Reitz et al. (1990) described a pharmacodynamic end point (cytotoxicity) in the livers of chloroform-exposed animals produced by phosgene, the reactive metabolite of chloroform.

In gas-uptake experiments, Gearhart et al. (1993) demonstrated a dose-dependent decrease in core body temperature with increased inhaled concentrations of chloroform. The decrease in body temperature could account for decreased *in vivo* chloroform metabolism, partition coefficients, pulmonary ventilation, and cardiac output rates in mice.

Chinery and Gleason (1993) used a shower model for chloroform-contaminated water to predict breath concentration (as a quantifiable function of tissue dose) and actual absorbed dose from a measured water supply concentration following exposure while showering. The model ’ s predictions demonstrated that dose information based only on dermal absorption (without considering an inhalation component) may underestimate actual dose to target organs in dosimetric assessment for chloroform in water supplies during shower. The model also predicted a steady-state *stratum corneum* permeability of chloroform in human skin in the range of 0.16-3.6 cm/hour with the most likely value being 0.2 cm/hour. The authors suggest that the results predicted by this model could be used to estimate household exposures to chloroform or other exposures which include dermal absorption.

McKone (1993) demonstrated that chloroform in shower water had an average effective dermal permeability between 0.16 and 0.42 cm/hour for a 10-minute shower. The model predicted that the ratio of chloroform dermally absorbed in the shower (relative to chloroform-contaminated water concentration) ranged between 0.25 and 0.66 mg per mg/L. In addition, the McKone model demonstrated that chloroform metabolism by the liver was not linear across all dermal/inhalation exposure concentrations and became nonlinear at higher (60-100 mg/L) dose concentrations.

2.3.5.2 Chloroform PBPK Model Comparison

Five chloroform PBPK models that describe the disposition of chloroform in animals and humans have been identified from the recent open literature (early 1980s-1994). Based on the information presented in these five models, there appears to be sufficient evidence to suggest that PBPK models for chloroform are fairly refined and have a strong potential for use in human risk assessments. The PBPK model developed by Corley et al. (1990) has provided a basic model for the fate of chloroform in humans and laboratory animals. Using this model as a template, other more sophisticated and refined models have been developed that can be used in human risk assessment work. The models of Corley et al. (1990) and Reitz et al. (1990) have described several aspects of chloroform metabolism and disposition in laboratory animals and humans; however, they do not address the dermal routes of exposure. The models of McKone (1993) and Chinery and Gleason (1993) address both the inhalation and dermal exposure routes in humans the Chinery and Gleason model uses a 3-compartment skin component which may more accurately reflect the flux of chloroform through the skin after dermal only or dermal plus inhalation exposure scenarios, while the McKone model uses a single compartment within the skin to describe chloroform flux. Further discussion of each model and its application in human risk assessments is presented below.

2.3.5.3 Discussion of Chloroform Models

The Corley Model

The Corley model (Corley et al. 1990) was the first chloroform PBPK model to describe and ultimately predict the fate of chloroform in several species (including humans) under a variety of exposure conditions. Many subsequent PBPK models for chloroform (Chinery and Gleason 1993; McKone 1993) are based on the Corley model. The Corley model has been used for cancer risk assessment (Reitz et al. 1990).

Risk Assessment. This model successfully described the disposition of chloroform in rats, mice and humans following various exposure scenarios and developed dose surrogates more closely related to toxicity response. With regard to target tissue dosimetry, the Corley model predicts the relative order of susceptibility to chloroform toxicity consequent to binding to macromolecules (MMB) to be mouse > rat > human. Linking the pharmacokinetic parameters of this model to the pharmacodynamic

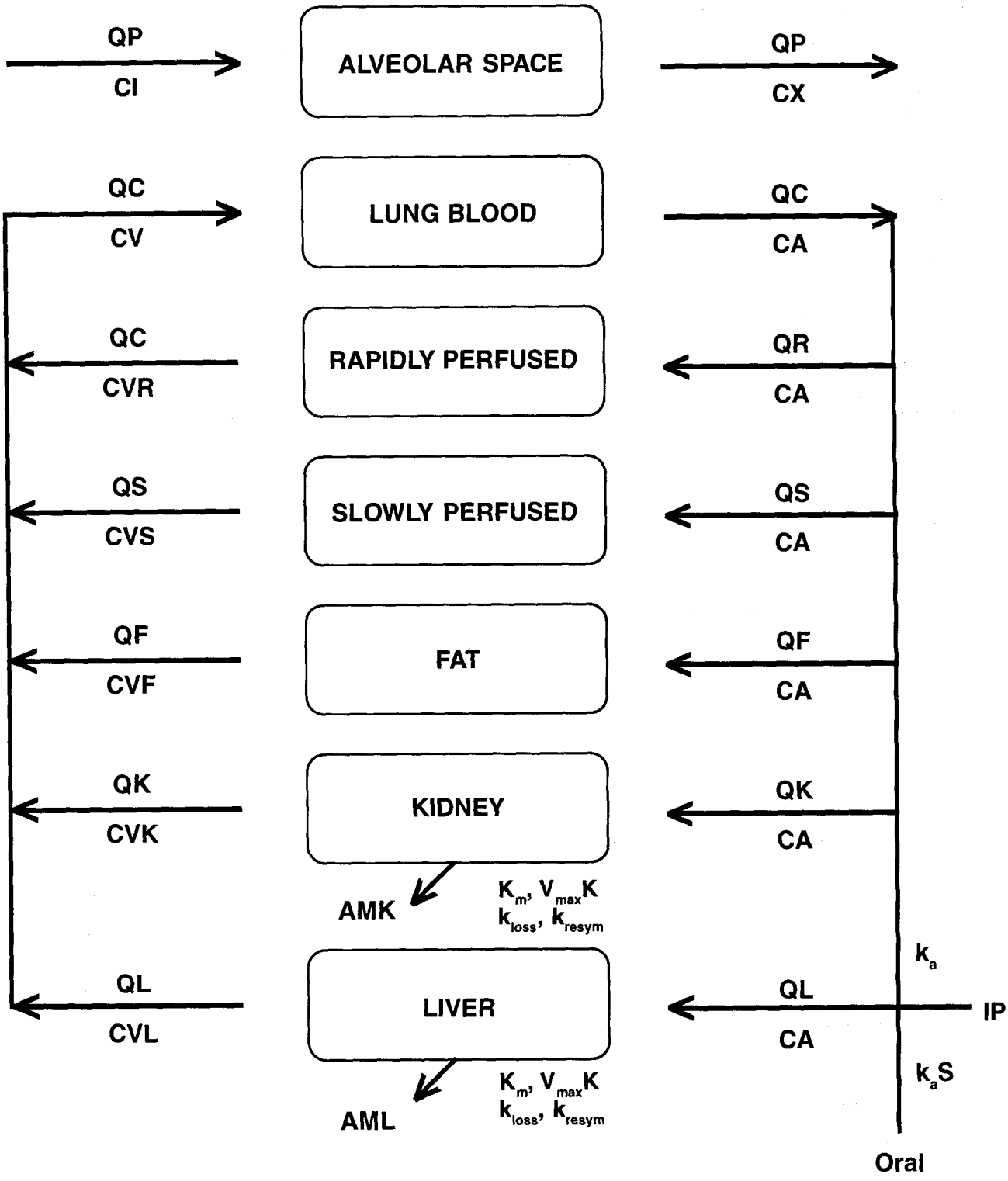
cancer model of Reitz et al. (1990) provides a biologically based risk assessment model for chloroform.

Description of the Model. The Corley chloroform PBPK model was based on an earlier PBPK model developed by Ramsey and Andersen (1984) to describe the disposition of styrene exposure in rats, mice, and humans. A schematic representation of the Corley model (taken from Corley et al. 1990) is shown in Figure 2-5 with oral, inhalation, and intraperitoneal routes represented. The dermal route of exposure is not represented in this model; however, others have modified the Corley model to include this route of exposure (see below). Liver and kidney are represented as separate compartments since both are target organs for chloroform.

The physiologic, biochemical constants and partition coefficients required for the model are shown in Table 2-4. Physiologic constants (organ weight, blood flows, etc) were similar to those used by Andersen et al. (1987) or were taken from other literature sources. Tissue and blood partition coefficients were determined in tissues by vial equilibration techniques in the rat and human, with extrapolated values used for the mouse. All metabolism of chloroform was assumed to occur only in the liver and kidneys through a single metabolic pathway (mixed function oxidase) that followed simple Michaelis-Menten kinetic parameters. Metabolic rate constants were obtained from the gasuptake experiments. Human metabolic rate constants were obtained from *in vitro* human microsomal fractions of liver and kidney samples using $^{14C}CHCL_3$ as the substrate. Binding of chloroform metabolites (phosgene) to MMBs was assumed to occur in bioactivating tissues (liver and kidney) in a non-enzymatic, nonspecific, and dose-independent fashion. Macromolecular binding constants for the liver and kidney were estimated from *in vivo* MMB data obtained from rats and mice exposed to $^{14C}CHCL_3$ via inhalation.

The gas-uptake data for rats were well described using a single Michaelis-Menten equation to describe metabolism. For the mouse inhalation studies, a simple Michaelis-Menten equation failed to adequately describe the chloroform-metabolizing capacity based on the data collected and model constants. The authors suspected that, following the administration of chloroform (particularly at higher concentrations), destruction of microsomal enzymes and subsequent resynthesis of microsomal enzymes was important in the mouse. This phenomenon has been documented in phenobarbitalinduced but not naive rats. To account for this phenomenon, a first-order rate constant for the loss and subsequent regeneration of metabolic capacity was incorporated into the model for mice only.

Figure 2-5. Parameters Used in the Corley PBPK Model



Physiological model used to describe the pharmacokinetics of chloroform in rats, mice, and humans during inhalation, oral, and intraperitoneal exposures.

AMK = amount metabolized in kidney; AML = amount metabolized in liver

Table 2-4. Parameters Used in the Corley PBPK Model

Parameters	Mouse	Rat	Human
	Weights (kg):		
Body	0.02858	0.230	70.0
	Percentage of Body Weight		
Liver	5.86	2.53	3.14
Kidney	1.70	0.71	0.44
Fat	6.00	6.30	23.10
Rapidly perfused tissues	3.30	4.39	3.27
Slowly perfused tissues	74.14	77.07	61.05
	Flows (L/hr/kg)		
Alveolar ventilation	2.01	5.06	347.9
Cardiac output	2.01	5.06	347.9
	Percentage of Cardiac Output		
Liver	25.0	25.0	25.0
Kidney	25.0	25.0	25.0
Fat	2.0	5.0	5.0
Rapidly perfused tissues	29.0	26.0	26.0
Slowly perfused tissues	19.0	19.0	19.0
	Partition Coefficients		
Blood/air	21.3	20.8	7.43
Liver/air	19.1	21.1	17.00
Kidney/air	11.0	11.0	11.00
Fat/air	242.0	203.0	280.00
Rapidly perfused/air	19.1	21.1	17.0
Slowly perfused/air	13.0	13.9	12.0
	Metabolic and macromolecular binding constants		
V_{max} C (mg/hr/kg)	22.8	6.8	15.7
K_m (mg/L)	0.352	0.543	0.448
K_{loss} (l/mg)	$5.72x10^{-4}$	0	0
K_{resyn} (hr^{-1})	0.125	0	0
A (kidney/liver)	0.153	0.052	0.033
fMMB (hr^{-1}), liver	0.003	0.00104	0.00202
fMMB (hr^{-1}), kidney	0.010	0.0086	0.00931
	Gavage Absorption Rate Constants		
k_{aS} (hr^{-1}), corn oil	0.6	0.6	0.6
k_{aS} (hr^{-1}), water	5.0	5.0	5.0
	Intraperitoneal Injection Absorption Rate Constant		
k_a (hr^{-1})	1.0	1.0	1.0

The model also provided a good description of the *in vivo* levels of MMB in both rats and mice, with good agreement between observed and predicted values.

Validation of the Model. The Corley model was validated using chloroform data sets from oral (Brown et al. 1974a) and intraperitoneal (Ilett et al. 1973) routes of administration and from human pharmacokinetic studies (Fry et al. 1972). Metabolic rate constants obtained from the gas-uptake experiments were validated by modeling the disposition of radiolabeled chloroform in mice and rats following inhalation of chloroform at much lower doses. For the oral data set, the model accurately predicted the total amounts of chloroform metabolized for both rats and mice.

Target Tissues. The model provided excellent predictions of MMB in both the target tissues of chloroform (liver and kidney) after intraperitoneal administration in mice (rat data was not generated). The model adequately predicted the amount of unchanged material exhaled at infinite time and the total amount metabolized by groups of male and female humans of widely varying age and weight.

Species Extrapolation. The Corley model used species-specific information to outline the model parameters; little extrapolation of information among mice, rats and humans was required. Certain parameters previously reported in the scientific literature were assumed, however, such as body weight, percentage of body weight, and percentage of blood from the heart (i.e., percentage of cardiac output of body organs, see Table 2-4).

High-low Dose Extrapolation. The Corley model was designed to facilitate extrapolations from high doses (similar to those used for chronic rodent studies) to low doses that humans may potentially be exposed to at home or in the workplace.

Interroute Extrapolation. The Corley model used three routes of administration, intraperitoneal, oral and inhalation, in rats and mice to describe the disposition of chloroform. This data was validated for humans by comparing the model output using the animal data with actual human data from human oral chloroform pharmacokinetic studies. Using the human pharmacokinetic constants from the *in* vitro studies conducted by Corley, the model made adequate predictions of the amount of chloroform metabolized and exhaled in both males and females.

The Reitz Model

Risk Assessment. The Reitz model is based on the assumption that cytotoxicity and reparative hyperplasia are responsible for liver neoplasia. Dose-surrogates, a more sophisticated and more accurate measure of target tissue dose derived from measuring a pharmacodynamic effect, were used.

Description of the Model. The Reitz PBPK model was largely based on the Corley et al. (1990) model, but differed in the use of a pharmacodynamic end point, cytotoxicity in the livers of chloroform-exposed animals (mice) produced by phosgene (the reactive metabolite of chloroform). The Reitz model focused on the liver as the target organ for chloroform, hence the kidney compartment toxicity was not addressed. The kidney compartment was combined with the rapidly perfused tissue group. The Reitz model used two types of dose measurement, referred to as dose surrogates. One type of dose surrogate used was covalent binding to MMBs (average daily macromolecular binding, AVEMMB), a rate independent parameter. The second type of dose surrogate was cytotoxicity (PTDEAD), a rate dependent parameter that measured cell death (by histopathological analysis and ^{3H}thymidine uptake) due to the formation of reactive chloroform metabolites (i.e., phosgene). Model calculations of PTDEAD were based on several assumptions: that liver cells have a finite capability for repairing damage caused by $CHCl_3$ metabolites; that liver cells differ from cell to cell in their capabilities to repair this damage; and that induction of cytotoxicity in liver cells does not occur instantaneously.

Validation of the Model. The model simulations of PTDEAD were compared with two experimental measures of cytotoxicity: the percentage of nonviable cells observed microscopically in mice gavaged with solutions of chloroform in corn oil, and the rate of incorporation of ^{3H}thymidine into normal DNA during compensatory cell replication (CCR). CCR was measured following exposure of mice to chloroform vapor for 5-6 hours. Model predictions were in good agreement (within 10%) with observed percentages of dead liver cells evaluated microscopically. Agreement between predicted and observed values of cell killing based on CCR was less satisfactory.

Target Tissues. The Reitz model only applies to the metabolism of chloroform and the induction of cytotoxicity in liver tissue following exposure by inhalation, drinking water, and gavage routes using rat and mouse data.

Species Extrapolation. The Reitz model used the same species and physiologic parameters that the Corley model utilized (average body weights, organ percentage of body weight, blood flow, etc.) for model predictions. See Table 2-4 for these parameters. However, the model assumed equivalent intrinsic sensitivity of mouse and human hepatocytes.

High-low Dose Extrapolation. The Reitz model was designed to facilitate extrapolations from high doses (similar to those used for chronic rodent studies) to low doses that humans may potentially be exposed to at home or in the workplace.

Interroute Extrapolation. Inhalation and oral routes of administration were examined in the Reitz model; however, interroute extrapolations were not specifically addressed in the Reitz model.

The Gearhart Model

Risk Assessment. The Gearhart model provided strong evidence that temperature changes play an important role in predicting chloroform metabolism in mice and also provided a testable hypothesis for the lack of fit of the Corley model prediction with respect to the mouse data. These data strengthen the Corley model and its implications for human risk assessment (see the Corley model description above).

Description of the Model. Gearhart et al. (1993) developed a PBPK model that described the effects of decreased core body temperature on the analysis of chloroform metabolic data. Experimental data showed that when male B6C3F_1 mice were exposed for 6 hours to chloroform vapor concentrations of l00-5,500 ppm, a dose-dependent drop in core body temperature occurred, with the least amount of temperature drop occurring at the 100 ppm concentration and the most dramatic drop in temperature occurring at the 5,500 ppm level. The Gearhart model incorporated a model previously used by Ramsey and Andersen (1984) (the same model and parameters the Corley model was based on) in conjunction with a separate model reflecting changes in body core temperature to drive equations accounting for changes in partition coefficients, cardiac output, minute ventilation volumes, and rate of chloroform metabolism.

The model predicted that the V_{max} for chloroform metabolism without correcting for core temperature effects was 14.2 mg/hour/kg (2/3 of that reported in the Corley model) and the K_m was 0.25 mg/L.

Without body temperature corrections, the model underpredicted the rate of metabolism at the 5,500 ppm vapor concentration. Addition of a first-order kinetic rate constant (kf=l.86 $hour^{-1}$) to account for liver metabolism of chloroform at high doses of chloroform did provide a small improvement in model predictions at 5,500 ppm, but was still considered inadequate for predicting metabolism at high concentrations.

Validation of the Model. The Gearhart model was not validated against a comparable data set. Corrections for the temperature effects (V_{max} increased to 15.1 mg/hour/kg) and inclusion of a firstorder metabolism correction equation provided an accurate prediction of chloroform metabolism across all concentrations tested.

Target Tissues. The liver was the target tissue for this model.

Species Extrapolation. No species extrapolation was specifically addressed by the Gearhart model.

High-low Dose Extrapolation. No high-low dose extrapolation was specifically addressed by the Gearhart model.

Interroute Extrapolation. No interroute extrapolation was specifically addressed by the Gearhart model.

The Chinery-Gleason Model

Risk Assessment. The Chinery-Gleason model has the greatest potential for use in estimating exposures to chloroform in a household environment as well as for occupational exposures that result from dermal exposure.

Description of the Model. The Chinery and Gleason (1993) PBPK model is a combination of the Corley et al. (1990) model and other existing models that includes a multicompartment skin component similar to that of Shatkin and Szejnwald-Brown (1991). This compartment is used to simulate penetration of chloroform into the skin while showering for 10 minutes with water containing chloroform. The skin module for this new model assumed a physiologic skin compartment consisting

of three linear compartments: the dilute aqueous solution compartment; the stratum corneum (the primary barrier to the absorption of most chemicals, including chloroform); and the viable epidermis.

Validation of the Model. The model was validated using published data an experimentally derived exhaled breath concentrations of chloroform following exposure in a shower stall (Jo et al. 1990a).

Target Tissues. Based on the data set of Jo et al. (1990a), the Chinery-Gleason model predicted the stratum comeum permeability coefficient for chloroform to be 0.2 cm/hour (range, 0.6 and 2.2) and the estimated ratio of the dermally and inhaled absorbed doses to be 0.75 (range, 0.6 and 2.2) cm/hour. This new model showed that a simple steady-state model can be used to predict the degree of dermal absorption for chloroform. It was also shown that the model would be useful in predicting the concentrations of chloroform in shower air and in the exhaled breath of individuals exposed both dermally and by inhalation routes while showering with water containing low amounts (20 μg/L) of chloroform. At this concentration, the model predicted a dermal absorption dose of 0.0047 mg and inhalation of 0.0062 mg. In addition, the model also demonstrated that as the concentration of chloroform rises due to increases in chloroform vapor, the absorbed inhalation dose increases faster and becomes larger than the absorbed dermal dose.

Species Extrapolation. No species extrapolation was specifically addressed by the this model.

High-low Dose Extrapolation. No high-low dose extrapolation was specifically addressed by this model.

Interroute Extrapolation. The Chinery-Gleason model examined two routes of exposure, inhalation-only exposure and inhalation/dermal exposure. The model was useful in predicting the concentration of chloroform in shower air and in the exhaled breath of individuals exposed by the dermal and inhalation routes.

The McKone Model

Risk Assessment. The McKone model has some use in human chloroform risk assessments, in that the model defined the relationship between the dermal and inhalation exposure to measures of dose and the amounts that can be metabolized by the liver by each route. The model also provided

information about the inhalation and dermal exposure concentrations at which chloroform metabolism becomes nonlinear in humans.

Description of the Model. The McKone (1993) PBPK model addressed potential exposure to chloroform by the inhalation and dermal routes. McKone revised existing shower-compartment, dermal uptake and PBPK models to produce a revised PBPK model for simulating chloroform breath levels in persons exposed in showers by the inhalation route only and by the inhalation and dermal routes combined. Parameters used by this model were taken primarily from two main sources, Jo et al. (1990a) and Corley et al. (1990).

The model was also used to assess the relationship of dermal and inhalation exposure to metabolized dose in the liver, as well as to determine the tap-water concentrations at which hepatic metabolism of dermal and inhalation doses of chloroform become nonlinear. This information is especially useful for risk assessment on persons exposed to a wide range of chloroform concentrations. Experimentally measured ratios of chloroform concentrations in air and breath to tap water concentration (Jo et al. 1990a) were compared with the model predictions.

Validation of the Model. The McKone model used one data set to evaluate the model results (Jo et al. 1990a). The McKone model results were also compared to other existing chloroform models, with an in-depth discussion of similarities an differences between those models.

Target Tissues. The skin and lung were the target tissues studied in this model. Based on the information presented, the McKone model is appropriate for simulating chloroform breath levels in persons exposed in showers by both exposure routes. A major difference between the McKone model and the Chinery-Gleason model is that the McKone model assumes the skin to be a one compartment organ, whereas the Chinery-Gleason model assumed three compartments within the skin. The McKone model indicated that the ratio of chloroform dermally absorbed in the shower to the concentration in tap water ranges from 0.25 to 0.66 mg/L, and that chloroform can effectively permeate through the skin at a rate of 0.16-0.42 cm/hour during a 10-minute shower.

Species Extrapolation. The human was the only species addressed by the McKone model. No extrapolation between species was addressed in this model.

High-low Dose Extrapolation. For tap-water concentrations below 100 mg/L, the model predicted a linear relationship between potential dose (i.e., amounts present in the drinking water, inhaled in a shower, or skin surface contact) and the cumulative metabolized dose. At tap-water concentrations greater than 100 mg/dL for inhalation-only showers and 60 mg/L or normal showers, however, the relationship was no longer linear and modifications to this model may be required.

Interroute Extrapolation. The dermal and inhalation routes were addressed in this model. The McKone model did not specifically address interroute extrapolations for chloroform.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. In humans and laboratory animals, chloroform is generally absorbed quickly. Primarily because of its high blood/air partition coefficient, it passes with some ease through most tissue and cellular barriers in the body. Chloroform can be absorbed by inhalation and ingestion, and by dermal routes of exposure. Inhalation studies were performed by Corley et al. (1990) on groups of mice exposed to various concentrations of chloroform for 6 hours and sacrificed 48 hours after the last exposure. Chloroform absorption by the lungs varied by concentration and was generally 34-46%. An earlier study by Von Oettingen (1964) found that when dogs were exposed to 15,000 ppm chloroform, the concentration of chloroform in the blood rose quickly and leveled off, apparently establishing a steady-state concentration in the blood at 80-100 minutes after inhalation exposures began. The average steady-state concentration in the blood was 0.4 mg/mL. Less information is available on the absorption of chloroform by inhalation in humans. Humans exposed to 10,000 ppm of chloroform during surgical anesthesia showed a rapid absorption of chloroform detected in arterial blood samples, with peak concentrations occurring within 2 hours after initiation of anesthesia. The average arterial blood concentration of chloroform was reported to be about 0.1 mg/mL (Smith et al. 1973). Dick et al. (1995) examined the absorption of chloroform through human skin *in vivo* using volunteers and *in vitro* using fresh, excised abdominal skin. In the *in vivo* study, the ventral forearm skin of four male volunteers was dosed with a solution of chloroform in either water or ethanol. The solution remained on the skin for eight hours. When administered in water, the total absorbed dose was 8.2%. In contrast, the total absorbed dose was only 1.68% when chloroform was administered in ethanol. In the *in vitro* study, two doses were applied to the skin and remained there for four hours.

At study termination, the percentages of the low and high doses of chloroform absorbed were 5.6 and 7.1%, respectively.

Rats and mice exposed to 60 mg/kg ^{14}C-chloroform orally demonstrated that absorption was practically complete within 48 hours for mice and within 96 hours in rats. Peak blood levels occurred within 1 hour after the oral dose (Brown et al. 1974a). Humans dosed orally with 0.5 grams of ^{13}C-chloroform delivered as a capsule containing olive oil showed near complete absorption of chloroform within 8 hours after administration. Peak blood levels generally occurred at approximately 1 hour after dosing, with ^{13}C-chloroform concentrations in blood ranging from 1 to 5 μg/mL (Fry et al. 1972).

Chloroform can also permeate the stratum corneum of rabbit skin (Torkelson et al. 1976) and mouse skin (Tsuruta 1975). Percutaneous absorption of chloroform across mouse skin was calculated to be approximately 38 μg/min/cm^2, indicating that the dermal absorption of chloroform occurs fairly rapidly in mice. No reliable studies report the percutaneous absorption of chloroform in humans; however, a few clinical reports indicate that chloroform is used as a vehicle for drug delivery (King 1993). Islam et al. (1995) investigated the fate of topically applied chloroform in male hairless rats. For exposures under 4 minutes, chloroform-laden water was applied to shaved back skin; for exposures of 4-30 minutes, rats were submerged in baths containing chloroform-laden water. Selected skin areas were tape-stripped a various number of times after various delay periods. It appeared that there was an incremental build-up of chloroform in the skin over the first four minutes. When compared to uptake measured by bath concentration differences, approximately 88% of lost chloroform was not accounted for in the stratum corneum and was assumed to be systemically absorbed.

Distribution. Radiolabeled chloroform in mice, once absorbed, is widely distributed to most organs and tissues, specifically the liver, kidney, lungs, spleen, body fat, muscle, and nervous tissue, as reported by Cohen and Hood (1969) and Bergman (1979). Significant accumulations were noted 48 hours after inhalation exposure in the central nervous system, particularly in the cerebellar cortex, spinal nerves, and meninges. When administered orally (Brown et al. 1974a), rats and squirrel monkeys showed significant accumulations of ^{14}C-chloroform in the brain, lung, muscle, and kidney in both species, with an unusual accumulation of chloroform in the gall bladder of the monkey. When administered orally to mice, similar accumulations of chloroform occurred in the liver, kidney, lung,

muscle, blood, intestines, and gall bladder (Taylor et al. 1974). Little current information on the distribution of chloroform in humans was available for review.

Chloroform (or phosgene) tends to accumulate to a significantly higher degree in the kidneys of male mice than in those of female mice given equivalent doses, which leads to a higher degree of chloroform nephrotoxicity in male mice. The sex differences seen with the renal cortical accumulation of chloroform or phosgene can be halted if chloroform is administered to castrated males; the sex difference can be reversed if chloroform is administered to females pretreated with testosterone prior to dosing with chloroform. This difference in chloroform accumulation is obviously dependent on the presence of testosterone and is very consistent with a body of evidence that indicates chloroform is more nephrotoxic to male mice than to female mice (Ilett et al. 1973; Pohl et al. 1984; Smith et al. 1973). Although this sex-related toxic effect is known to occur in mice, it is not known at present if a similar effect occurs in humans.

Excretion. Chloroform is largely excreted either in the parent form or as the end metabolite (carbon dioxide, CO_2) in the bodies of both laboratory animals and humans. Corley et al. (1990) demonstrated that mice exposed to 10 or 89 ppm of chloroform by inhalation excreted 99% of the chloroform body burden as CO_2 in exhaled air. As the chloroform concentrations in the air rose however, the amount of chloroform metabolized to CO_2 decreased and the amount of unchanged chloroform rose in the exhaled air, indicating that chloroform metabolism in mice is a saturable process. Rats exposed in a similar manner to 93, 356, and 1,041 ppm chloroform excreted 2, 20, and 42.5%, respectively, of the total body burden of chloroform as unchanged parent compound, indicating that chloroform is metabolized to CO_2 in rats but to a lesser degree than in mice.

In humans, Fry et al. (1972) administered 500 mg of chloroform orally in olive oil in capsular form and found that 17-67% of the total dose of chloroform was exhaled as unchanged parent compound, and that the extent of pulmonary elimination of chloroform was governed inversely by the amount of adipose tissue on the individual ingesting the chloroform. The study also found that most of the chloroform tended to be exhaled between 40 minutes and 2 hours after dosing, which coincided with peak blood levels of chloroform produced at approximately 1 hour after dosing.

2. HEALTH EFFECTS

Chloroform in humans tends to be eliminated in a biphasic manner. After ingesting 500 mg of chloroform orally, an initial (a) half-life in the blood of 9-21 minutes was reported, with the second (p) half-life ranging from 86 to 96 hours.

2.4.2 Mechanisms of Toxicity

Chloroform is widely distributed to many tissues of the body in laboratory animals and, presumably, in humans; however, many studies have demonstrated that chloroform does not tend to accumulate in the body for extended periods. Chloroform may accumulate to some degree in the body fat stores; however, it quickly partitions out the fat and is excreted by the normal routes and mechanisms. The liver (primary) and kidneys (secondary) are considered to be the target organs for chloroform toxicity in both humans and laboratory animals. Thus, humans (and animals) with existing hepatic or renal disease who are exposed to chloroform, particularly by the oral or inhalation routes, are more likely to be at risk to the toxic effects of chloroform. Reproductive/developmental effects due to chloroform's presence in the drinking water of both humans and laboratory animals has been reported, thereby placing women of childbearing age at a potentially higher risk of reproductive organ anomalies than those women past menopausal age.

Chloroform is largely metabolized in many tissues (particularly the liver and kidney) to CO_2, in humans and animals (Brown et al. 1974a; Corley et al. 1990; Fry et al. 1972). Chloroform metabolism is catalyzed by cytochrome P-450, initiating an oxidative cleavage of the C-H bond producing trichloromethanol. Trichloromethanol is unstable and is rapidly transformed to phosgene ($COCl_2$). Phosgene may react with water to form CO_2, which can be exhaled by the lung or excreted in the urine as carbonate or bicarbonate, and hydrochloric acid. Phosgene can also react with other molecules such as cysteine, deplete hepatic GSH (Docks and Krishna 1976; Pohl et al. 1981) and form adducts with microsomal proteins (Corley et al. 1990).

Chloroform toxicity can be attributed to the presence of both the parent compound and the formation of phosgene in most instances of toxicosis. High doses of inhaled chloroform have been reported to cause death (due to respiratory depression), ataxia, narcosis, and central nervous system depression, and are due to the direct effects of the parent compound. Lower doses of chloroform in the air, feed, or water, or administered by gavage, with variable exposure times, may induce toxicity due to the presence of the parent compound or to production of phosgene during metabolism. It appears that the

metabolite is responsible for hepatocellular damage, resulting in the ultimate elevation of hepatic enzymes (SGPT, SGOT, GGT, etc.) and cell damage/necrosis. The accumulation of chloroform in the renal cortex of mice with the subsequent metabolism to phosgene most likely contributes to the renal toxicity of chloroform seen in male mice. Tubular necrosis, calcification, nephritis, increased kidney weight, alterations in Na/K excretion, and other cellular anomalies were observed in response to one or both of these toxicants. Although the sex-related nephrotoxic effect is known to occur in mice, it is not known at present if a similar effect occurs in humans or other laboratory animals.

2.4.3 Animal-to-Human Extrapolations

Many laboratory animal models have been used to describe the toxicity and pharmacology of chloroform. By far, the most commonly used laboratory animal species are the rat and mouse models. Generally, the pharmacokinetic and toxicokinetic data gathered from rats and mice compare favorably with the limited information available from human studies. PBPK models have been developed using pharmacokinetic and toxicokinetic data for use in risk assessment work for the human. The models are discussed in depth in Section 2.3.5. As mentioned previously, male mice have a sex-related tendency to develop severe renal disease when exposed to chloroform, particularly by the inhalation and oral exposure routes. This effect appears to be species-related as well, since experiments in rabbits and guinea pigs found no sex-related differences in renal toxicity.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview. Data are available regarding health effects in humans and animals after inhalation, oral, and dermal exposure to chloroform; however, data regarding dermal exposure are quite limited. Chloroform was used as a general anesthetic, pain reliever, and antispasmodic for more than a century before its toxic effects were fully recognized. High levels of chloroform (23-400 ppm) (Challen et al. 1958; Phoon et al. 1983) in the air are found specifically in highly industrialized areas. Exposure of the general population to chloroform can also occur via the drinking water as a result of the chlorination process. Occupational exposure is another source of inhalation and/or dermal exposure for humans.

Most of the presented information regarding chloroform toxicity following inhalation exposure in humans was obtained from clinical case reports of patients undergoing anesthesia. In some instances,

the results in these studies may have been confounded by unreported data, such as the intake of other drugs or the use of artificial respiration during anesthesia.

The target organs of chloroform toxicity in humans and animals are the central nervous system, liver, and kidneys. There is a great deal of similarity between chloroform-induced effects following inhalation and oral exposure. No studies were located regarding reproductive effects in humans after exposure to chloroform alone; however, Bove et al. (1995) studied the effects of drinking-water consumption on birth outcomes and found that exposure to TTHM at levels >0.l ppm resulted in reduced birth weight and size as well as an increased risk of oral cleft, central nervous system, and neural tube defects. Since the authors did not specifically monitor chloroform levels, the effects seen may be due to exposure to other THMs. In addition, non-THM contaminants in the drinking water may have contributed to the observed effects as well. Only one study was located regarding the developmental effects of chloroform in humans. Animal studies indicate that chloroform can cross the placenta and cause fetotoxic and teratogenic effects. Chloroform exposure has also caused increased resorptions in animals. Epidemiology studies suggest a possible risk of colon and bladder cancer in humans that is associated with chloroform in drinking water. In animals, chloroform was carcinogenic after oral exposure.

Minimal Risk Levels for Chloroform.

Inhalation MRLs.

- An MRL of 0.1 ppm has been derived for acute-duration inhalation exposure (14 days or less) to chloroform.

The MRL was based on a hepatic NOAEL of 3 ppm chloroform administered for 6 hours a day for 7 consecutive days to mice (Larson et al. 1994c). Female mice exposed to 100 or 300 ppm exhibited centrilobular hepatocyte necrosis and severe diffuse vacuolar degeneration of midzonal and periportal hepatocytes, while exposure to 10 or 30 ppm resulted in mild-to-moderate vacuolar changes in centrilobular hepatocytes. Decreased eosinophilia of the centrilobular and midzonal hepatocyte cytoplasm relative to periportal hepatocytes was observed at 30 ppm. Livers of mice in the 1 and 3 ppm groups did not differ significantly from control animals and were considered to be NOAELs for liver effects. The NOAEL of 3 ppm was converted to the Human Equivalent Concentration (HEC) as described in Equation 4-10 in Interim Methods for Development of Inhalation Reference

Concentrations (EPA 1990b). This calculation resulted in a $NOAEL_{[HEC]}$, of 3 ppm. An uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability) was applied to the $NOAEL_{[HEC]}$, value, which resulted in an MRL of 0.1 ppm.

Reports regarding chloroform hepatotoxicity in animals are numerous (Larson et al. 1993, 1994a, 1994b, 1994c). Liver damage has been reported in several other studies, and was usually indicated by liver biochemical/enzyme alterations in rats (Lundberg et al. 1986) and mice (Gehring 1968; Murray et al. 1979) after acute inhalation exposure. Fatty changes (Culliford and Hewitt 1957; Kylin et al. 1963) and liver necrosis (Deringer et al. 1953) were observed histologically in mice after acute inhalation exposure. Histological findings indicative of liver toxicity were also observed in other laboratory animals following inhalation exposure of intermediate duration, but the findings were not dose-related (Torkelson et al. 1976). The 17.3 mg/kg dose was also a NOAEL for kidney effects, but tubular necrosis occurred at 65.6 mg/kg/day.

- An MRL of 0.05 ppm has been derived for intermediate-duration inhalation exposure (15 days to 364 days) to chloroform.

The MRL was based on a LOAEL of 14 ppm in workers exposed to concentrations of chloroform of up to 400 ppm for less than 6 months (Phoon et al. 1983). Vomiting and toxic hepatitis were noted to occur at an inhaled chloroform concentration of 14 ppm. The LOAEL of 14 ppm was divided by an uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability) and a modifying factor of 3 (insufficient diagnostic data to determine the seriousness of hepatotoxic effects) to arrive at the MRL of 0.05 ppm. Alterations in liver functions have been reported in several studies in both humans and animals, and is discussed in more detail in the chronic-duration inhalation MRL section immediately below.

- An MRL of 0.02 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to chloroform.

The MRL was based on a LOAEL of 2 ppm in workers exposed to concentrations of chloroform ranging from 2 to 205 ppm for l-4 years (Bomski et al. 1967). The LOAEL of 2 ppm was divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability) to arrive at the MRL of 0.02 ppm. Hepatomegaly was found in 25% of chloroform-exposed workers. Toxic hepatitis was found in 5.6% of the liver enlargement cases. Hepatosteatosis (fatty liver) was detected in 20.6%

of liver-enlargement cases. Chloroform-exposed workers had a higher frequency of jaundice over the years than the control group. Alterations in liver functions have been reported in several studies in both humans and animals. In humans, impaired liver function was indicated by increased sulfobromophthalein retention in some patients exposed to chloroform via anesthesia (Smith et al. 1973), in addition to acute toxic hepatitis developing after childbirth in several women exposed to chloroform via anesthesia (Lunt 1953; Royston 1924; Townsend 1939). In contrast, no clinical evidence of liver toxicity was found in another study among chloroform workers exposed to ≤237 ppm (Challen et al. 1958).

Oral MRLs.

- An MRL of 0.3 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to chloroform.

The MRL was based on a NOAEL of 26 mg/kg/day in the drinking water for 4 days for hepatic effects in mice (Larson et al. 1994b). The NOAEL of 26.4 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to arrive at the MRL of 0.3 mg/kg/day. A study performed by Moore et al. (1982) found renal effects in CFLP Swiss mice dosed at 65.5 mg/kg/day by gavage in oil. Another study by Larson et al. (1993) found both hepatic (elevated SDH, ALT and AST, hepatocyte necrosis) and renal (proximal tubule necrosis) lesions in Fischer 344 rats and hepatic lesions only in $B6C3F_1$ mice induced by chloroform administered at 34 mg/kg/day once by gavage in oil. Lesions in the Larson et al. (1993) study were ranked as less serious LOAELs.

- An MRL of 0.1 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to chloroform.

This MRL is based on a NOAEL of 15 mg/kg/day for hepatic effects in dogs dosed with chloroform in a capsule 1 time a day, 6 days a week for 6 weeks (Heywood et al. 1979). The NOAEL of 15 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to arrive at the MRL of 0.1 mg/kg/day. Clinical chemistry parameters showed significantly increase SGPT in the 30 mg/kg/day group beginning at 6 weeks. SGPT activity was not increased in the 15 mg/kg/day group until week 130. Liver effects in animals have been reported in numerous oral studies of intermediate duration. Fatty changes, necrosis,

increased liver weight, and hyperplasia have been observed in rats exposed to ≥150 mg/kg/day chloroform in drinking water for 90 days (Palmer et al. 1979). An increased incidence of sporadic, mild, reversible liver changes occurred in mice exposed to chloroform in drinking water at doses of 0.3-l14 mg/kg/day for 90 days, but the incidences were not significantly higher than the incidences in controls (Chu et al. 1982a). Fatty and hydropic changes, necrosis, and cirrhosis were observed in mice treated by gavage with ≥50 mg/kg/day chloroform in oil for 90 days (Bull et al. 1986; Munson et al. 1982) or at 86 mg/kg/day in drinking water for 1 year (Klaunig et al. 1986). In contrast, centrilobular fatty changes observed in mice at 64 mg/kg/day chloroform in drinking water for 90 days appeared to be reversible (Jorgenson and Rushbrook 1980), and no liver effects were found in mice treated with ≥50 mg/kg/day in aqueous vehicles (Bull et al. 1986). In addition, hepatocellular degeneration was induced in F_1 females in a 2-generation study in which mice were treated by gavage with 41 mg/kg/day chloroform in oil (Gulati et al. 1988).

- An MRL of 0.01 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to chloroform.

This MRL is based on a LOAEL of 15 mg/kg/day for hepatic effects in dogs dosed with chloroform 6 days a week for 7.5 years (Heywood et al. 1979). The LOAEL of 15 mg/kg/day was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability) to arrive at the MRL of 0.01 mg/kg/day. SGPT activity was not increased in the 15 mg/kg/day group until week 130, providing the LOAEL on which this MRL was based. Numerous chronic oral studies examined hepatic and renal end points as well as neurological and cancer effects. Serious effects occurred at higher doses; 15 mg/kg/day was the lowest dose used in available animals studies. A NOAEL of 2.46 mg/kg/day for liver and kidney effects (SGPT, SGOT, BUN and SAP) was found in humans who used a dentifrice containing 0.34% or a mouthwash containing 0.43% chloroform for l-5 years (DeSalva et al. 1975).

The reader is advised to exercise caution in the extrapolation of toxicity data from animals to humans. Species-related differences in sensitivity must be accounted for. Some studies utilized to derive MRLs or otherwise extrapolate data, is dated; however, they do represent the body of knowledge regarding chloroform toxicity. In addition, many of the human studies quoted involved clinical case reports in which chloroform was utilized either as an anesthetic or as an agent of suicide. Such doses are clearly

excessive and would not be encountered by the general population. These and other issues are addressed in Section 2.10.

Death. Chloroform levels of ≈40,000 ppm cause death in patients under chloroform anesthesia (Featherstone 1947; Whitaker and Jones 1965). Death is usually due to severe respiratory depression/ failure or disturbances in cardiac rhythm. Accidental or intentional ingestion of large doses of chloroform may lead to death (Piersol et al. 1933). Death in humans after oral exposure to chloroform is usually caused by respiratory obstruction by the tongue due to jaw relaxation, central respiratory paralysis, acute cardiac failure, or severe hepatic injury (Piersol et al. 1933; Schroeder 1965).

The levels of chloroform exposure that cause death in animals are usually lower than those administered to patients to induce anesthesia; however, the duration of exposure in animals is generally longer. Following acute exposure to high concentrations of chloroform, all male mice died; however, most females survived the exposure for several months (Deringer et al. 1953). Survival was associated with lower testosterone levels, as suggested by the higher mortality rate in noncastrated adult males. This conclusion is supported by similar observations of higher survival rates in female rats, compared to male rats, after intermediate-duration exposure to chloroform (Torkelson et al. 1976). In regard to LC_{50} values in rats, survival rates were highest among females and lowest among young adult males. The correlation between mortality rates and male hormone levels is evident. Deaths were apparently potentiated by starvation, dehydration, and exhaustion (Ekstrom et al. 1986, 1988; Royston 1924; Townsend 1939). Increased mortality was also observed in rats and mice after oral exposure of intermediate and chronic duration (Balster and Borzelleca 1982; Chu et al. 1982a; Jorgenson et al. 1985; Klaunig et al. 1986; NCI 1976; Palmer et al. 1979; Roe et al. 1979). Deaths were caused by toxic liver and kidney effects, and tumors. Deaths after dermal exposures in either humans or laboratory animals have not been reported.

Chloroform concentrations in air and drinking water in the general environment or near hazardous waste sites are not likely to be high enough to cause death in humans after acute exposure. Whether chronic exposure to low levels of chloroform in the environment, drinking water, or hazardous wastes could shorten the life span of humans is not currently known. Currently available epidemiologic findings about the chronic exposure to chloroform are inconsistent at best which, in large part, may be due to study design issues.

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Systemic Effects.

Respiratory Effects. The respiratory failure observed in patients under chloroform anesthesia was probably due to a direct effect of chloroform on the respiratory center of the central nervous system. A decline of the systolic pressure in the cerebral vessels may also contribute to respiratory failure, as demonstrated in animals: when respiration had stopped under chloroform anesthesia, the animals (species not specified) breathed again if positioned head down (Featherstone 1947). Upper respiratory tract obstruction can occur in patients after inhalation exposure to chloroform via anesthesia (Featherstone 1947) and after chloroform ingestion (Schroeder 1965). Few autopsy reports were located in the literature. Hemorrhage into the lungs, without any signs of consolidation, was reported in a case study involving death after inhalation exposure (Royston 1924); however, congested lungs with pneumonic consolidation were observed in a man who died after drinking chloroform (Piersol et al. 1933).

In addition to lower respiratory tract effects, chloroform has been demonstrated to induce changes in the nasal region of rats and mice after inhalation and oral exposure. Increased sizes of goblet cells and nasal epithelium, degeneration of the nasal epithelium and Bowman's glands, changes in the proliferation rates of cells, new bone formation, and changes in biochemical parameters (especially cytochrome P-450-2El) have been reported (Larson et al. 1995b, 1996; Mery et al. 1994), indicating that chloroform can adversely affect the upper as well as the lower respiratory tract at low concentrations. The incidence of respiratory lesions after oral (gavage) administration also indicates a systemic mechanism of action for chloroform-induced toxicity.

Interstitial pneumonitis was observed in male rats and rabbits after inhalation exposure to 85 or 50 ppm chloroform, respectively, for 6 months (Torkelson et al. 1976). In most oral studies, no exposure-related histopathological changes were observed in the lungs of exposed animals (Gulati et al. 1988; Jorgenson and Rushbrook 1980; NCI 1976; Palmer et al. 1979; Roe et al. 1979).

Respiratory effects are more likely to occur after inhalation exposure to high concentrations of chloroform. It has been demonstrated that chloroform has a destructive influence on the pulmonary surfactant (Enhorning et al. 1986). This effect is probably due to the solubility of phospholipids in the surfactant monolayer and can cause collapse of the respiratory bronchiole due to the sudden increase in inhalation tension. Immediate death after chloroform inhalation may be due principally to this effect

in the lungs (Fagan et al. 1977). It is unlikely that exposure levels of chloroform in the general environment or at hazardous waste sites would be high enough to cause these severe respiratory effects.

Cardiovascular Effects. Chloroform induces cardiac arrhythmia in patients exposed to chloroform via anesthesia (Smith et al. 1973; Whitaker and Jones 1965). Similarly, heart effects were observed upon electrocardiography of an individual who accidentally ingested chloroform (Schroeder 1965). Hypotension was observed in 12-27% of patients exposed to chloroform via anesthesia (Smith et al. 1973; Whitaker and Jones 1965) and also was observed in a patient who ingested chloroform (Storms 1973).

No studies were located regarding cardiovascular effects in animals after inhalation exposure to chloroform. No histopathological changes were observed in the heart of rats, mice (NCI 1976), or dogs (Heywood et al. 1979) chronically exposed to chloroform; however, cardiovascular function was not assessed in these studies. It has been demonstrated in an *in vitro* study on heart-lung preparations of guinea pigs that chloroform may cause a permanent contractile failure of the heart (Doring 1975). The effect is due to structural damage of the transverse tubular system and is accompanied by increased storage of adenosine triphosphate (ATP) and phosphocreatine. The *in vitro* induction of changes showed that contractile failure is a direct effect on the cardiovascular system rather than an indirect cardiovascular effect on the central nervous system. This mechanism may operate in humans exposed to high vapor concentrations such as those used in anesthesia or in humans exposed to high oral doses from accidental or intentional ingestion. It is unlikely, however, that concentrations of chloroform in the environment would be high enough to cause overt cardiovascular effects.

Cytotoxicity of chloroform (1,000 ppm) in male Sprague-Dawley rat cardiac myocytes has been examined *in vitro*. Cell viability was measured using the criterion of Trypan blue exclusion as well as counting the number of rod and spherical cells in the media. Creatinine phosphokinase (CPK) leakage was measured as an indirect measurement of heart cell function. Myocytes treated with chloroform showed statistically significant decreases in cell viability and significant decreases in rod-shaped cells compared to controls. Significant increases in enzyme leakage of CPK from myocytes were noted (El-Shenawy and Abdel-Rahman 1993b). The effects of various concentrations of chloroform on the *in vitro* transfer of dyes between cardiac myocytes from Sprague-Dawley rats has also been examined (Toraason et al. 1992). The cells were exposed to one of 11 concentrations of chloroform in dimethyl

sulfoxide (DMSO), and Lucifer yellow CH dye injected the cells, and the rate of transfer of dye from the injected myocyte to the non-injected myocyte recorded. As the cells were exposed to increasing concentrations of chloroform, the number of cells that transferred the dye decreased to zero. Heart cells also tended to beat slower or stop beating completely when exposed to chloroform but resumed normal spontaneous beating when chloroform was washed out. This *in vitro* data suggest that incorporation of halocarbons in the membrane may block intercellular communication through modification of the immediate environment of gap junctions. The data from these two studies indicate that chloroform exposure may induce reversible toxicity in the heart.

Gastrointestinal Effects. Nausea and vomiting were not only frequently observed side effects in patients exposed to chloroform via anesthesia (Hakim et al. 1992; Royston 1924; Smith et al. 1973; Townsend 1939; Whitaker and Jones 1965), but also occurred in humans exposed to lower chloroform concentrations (22-237 ppm) in occupational settings (Challen et al. 1958; Phoon et al. 1983). Vomiting, gastric distress, and pain were observed in individuals who intentionally or accidentally ingested high doses of chloroform (Piersol et al. 1933; Schroeder 1965; Storms 1973).

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to chloroform. Vomiting in dogs (Heywood et al. 1979) and gastric erosions in rats (Thompson et al. 1974) were observed in oral studies of intermediate duration. These results suggest that severe gastrointestinal irritation in humans and animals is due to direct damage of the gastrointestinal mucosa caused by ingesting high concentrations of chloroform (Piersol et al. 1933; Schroeder 1965; Thompson et al. 1974). Nausea and vomiting experienced by occupationally exposed individuals is likely due to neurotoxicity. Since toxic hepatitis may occur at occupational levels as low as 2 ppm (Bomski et al. 1967), it is possible that levels of chloroform in the air at hazardous waste sites may be high enough to cause some liver effects with secondary gastrointestinal effects, if exposure is prolonged.

Hematological Effects. Information regarding hematological effects in humans exposed to chloroform is limited. Increased prothrombin time was observed in some patients, following exposure to chloroform via anesthesia (Smith et al. 1973). This effect, however, reflects chloroform hepatotoxicity, because prothrombin is formed in the liver. Decreased erythrocytes and hemoglobin were observed in a patient who was chronically exposed to chloroform in a cough medicine (Wallace 1950).

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No hematological effects were observed in rats, rabbits, guinea pigs, or dogs after inhalation exposure to chloroform for intermediate durations (Torkelson et al. 1976). Studies report conflicting results regarding hematological effects in animals after oral exposure to chloroform.

No conclusion about hematological effects in humans after exposure to chloroform can be made on the basis of one case study in humans. From the experimental data in animals, it is evident that all hematological effects observed in rats were due to oral exposure of acute, intermediate, or chronic duration. It is possible that the hematological effects observed in rats are transient. Human exposure to chloroform in the environment, drinking water, or at hazardous waste sites is likely to cause few or no hematological effects.

Musculoskeletal Effects. Little data is available that examines the effects of chloroform toxicity on the musculoskeletal system; however, it appears that chloroform has few significant toxic effects on this system.

Hepatic Effects. The liver is a primary target organ of chloroform toxicity in humans and animals after inhalation and oral exposure, with some evidence that suggests that the damage may be reversible (Wallace 1950). Impaired liver function was indicated by increased sulfobromophthalein retention in some patients exposed to chloroform via anesthesia (Smith et al. 1973). Acute toxic hepatitis developed after childbirth in several women exposed to chloroform via anesthesia (Lunt 1953; Royston 1924; Townsend 1939). Upon autopsy, centrilobular necrosis was observed in the women who died; however, the hepatotoxicity was associated with exhaustion from prolonged delivery, starvation, and dehydration, indicating improper handling of the delivery procedure by an obstetrician. Toxic hepatic disease, characterized by hepatomegaly and abnormal liver sonograms as late as seven days after an unknown amount of oral chloroform, has been reported (Hakim et al. 1992). Elevated liver enzymes and changes in GGT, alpha-feto protein and retinol binding protein were reported in a female who injected herself intravenously and also consumed chloroform orally during a 12-hour period (Rao et al. 1993). During occupational exposure to concentrations ranging from 14 to 400 ppm, chloroform hepatotoxicity was characterized by jaundice (Phoon et al. 1983), hepatomegaly, enhanced SGPT and SGOT activities, and hypergammaglobulinemia following exposure to concentrations ranging from 2 to 205 ppm (Bomski et al. 1967). In contrast, no clinical evidence of liver toxicity was found in another study among chloroform workers exposed to ≤237 ppm (Challen et al. 1958). Case reports of intentional and accidental ingestion of high doses (≥2,410 mg/kg) of chloroform indicate severe liver

injury (Piersol et al. 1933; Schroeder 1965; Storms 1973). The diagnosis was supported by clinical and biochemical results: fatty degeneration and extensive centrilobular necrosis were observed in one patient who died (Piersol et al. 1933). Liver damage was induced by chronic use of a cough medicine containing chloroform (Wallace 1950), but not by chronic exposure to chloroform in mouthwash (De Salva et al. 1975). An intermediate-duration inhalation MRL of 0.05 ppm was derived from the LOAEL of 14 ppm from the data presented by Phoon et al. (1983); a chronic-duration inhalation MRL of 0.02 ppm was derived from the LOAEL of 2 ppm from the data presented by Bomski et al. (1967).

Reports regarding chloroform hepatotoxicity in animals are numerous (Larson et al. 1993, 1994a, 1994b, 1994c, 1995b, 1996; Nakajima et al. 1995; Pereira 1994; Wang et al. 1994, 1995). An acute-duration inhalation MRL of 0.1 ppm was based on a NOAEL for hepatic effects in mice exposed to 3 ppm chloroform for 6 hours a day for 7 days (Larson et al. 1994c).

Liver damage was indicated by biochemical changes in rats (Lundberg et al. 1986; Nakajima et al. 1995; Wang et al. 1994, 1995) and mice (Gehring 1968; Murray et al. 1979) after acute inhalation exposure. Fatty changes (Culliford and Hewitt 1957; Kylin et al. 1963) and liver necrosis (Deringer et al. 1953; Larson et al. 1995b, 1996; Pereira 1994) were observed histologically in mice and rats after acute inhalation exposure. Histological findings indicative of liver toxicity were also observed in rabbits and guinea pigs following inhalation exposure of intermediate duration, but the findings were not dose-related (Torkelson et al. 1976). Liver effects have been observed in many species (rats, mice, and dogs) that were tested by the oral route by various methods of administration (gavage or drinking water) and durations (acute, intermediate, or chronic). Observed effects include increased liver weight, increased serum levels of transaminases indicative of liver necrosis, and histological evidence of swelling, fatty changes, hydropic changes, vacuolation, necrosis, hyperplasia, cirrhosis, macrophage and neutrophil infiltration, and toxic hepatitis (Bull et al. 1986; Chu et al. 1982b; Heindel et al. 1995; Heywood et al. 1979; Jones et al. 1958; Jorgenson and Rushbrook 1980; Klaunig et al. 1986; Larson et al. 1993, 1994b, 1995b, 1996; Nakajima et al. 1995; NCI 1976; Pereira 1994; Tumasonis 1985, 1987). Two acute oral studies define a LOAEL and a NOAEL for liver effects in mice. Fatty infiltration was observed in mice given a single gavage dose of 35 mg/kg/day chloroform in oil (Jones et al. 1958). No toxic effects on the livers of mice occurred after a single dose of 17.3 or 59.2 mg/kg chloroform in oil, but increased SGPT occurred at 199 mg/kg (Moore et al. 1982). The 17.3 mg/kg dose was also a NOAEL for kidney effects, but tubular necrosis occurred at 65.6 mg/kg/day. In a 7.5-year study in which dogs were administered chloroform in toothpaste, SGPT activity was

significantly increased at 30 mg/kg/day beginning at 6 weeks (Heywood et al. 1979). SGPT activity was not increased at 15 mg/kg/day until 130 weeks. Therefore, 15 mg/kg/day was a NOAEL for intermediate-duration exposure and a LOAEL for chronic-duration exposure. The 15 mg/kg/day dose was used to derive MRL values of 0.1 and 0.01 mg/kg/day for intermediate- and chronic-duration oral exposure, respectively.

Data regarding chloroform-induced hepatotoxicity were also supported by results obtained after acute intraperitoneal exposure in rats (Bai et al. 1992; Ebel et al. 1987; El-Shenawy and Abdel-Rahman 1993a; Lundberg et al. 1986; Wang et al. 1994), mice (Klaassen and Plaa 1966), dogs (Klaassen and Plaa 1967), and gerbils (Ebel et al. 1987). No hepatic effects were observed in rabbits when chloroform was applied to their skin for 24 hours (Torkelson et al. 1976). The toxicity of chloroform on laboratory animal hepatocytes *in vitro* has been reported (Azri-Meehan et al. 1992, 1994; Bai and Stacey 1993; El-Shenawy and Abdel-Rahman 1993a; Suzuki et al. 1994).

As discussed in Section 2.3.3, the mechanism of chloroform-induced liver toxicity may involve metabolism to the reactive intermediate, phosgene, which binds to lipids and proteins of the endoplasmic reticulum, lipid peroxidation, or depletion of GSH by reactive intermediates. Because liver toxicity has been observed in humans exposed to chloroform levels as low as 2 ppm in the workplace and in several animal species after inhalation and oral exposure, it is possible that liver effects could occur in humans exposed to environmental levels, to levels in drinking water, or to levels found at hazardous waste sites.

Endocrine Effects. No reports of chloroform toxicity to endocrine organs have been reported.

Renal Effects. Clinical reports indicate that the renal damage observed in women exposed to chloroform via anesthesia during prolonged parturition most likely occurs when chloroform anesthesia is associated with anoxia. Competitive swimmers who swim in indoor pools have been reported to have elevated β-2microglobin, suggesting some degree of renal damage (Aiking et al. 1994). Case studies of individuals who intentionally or accidentally ingested high doses of chloroform report biochemical changes indicative of kidney damage, as well as fatty degeneration at autopsy (Piersol et al. 1933; Schroeder 1965). Albuminuria and casts were also reported in a case of chronic use of a cough medicine containing chloroform (Wallace 1950); however, no renal effects were observed in individuals chronically exposed to chloroform in a mouthwash (De Salva et al. 1975).

Renal effects of chloroform after inhalation have also been examined in animals (Larson et al. 1994b, 1994c, 1996). Kidney effects in animals after inhalation exposure to chloroform include tubular necrosis, tubular calcification, increased kidney weight, cloudy swelling, mineralization of the cortex, and interstitial nephritis. Animal studies regarding renal toxicity after oral exposure are numerous. Effects include acute toxic nephrosis, tubular dilation, necrosis and regeneration, chronic inflammation, mineralized concretions, hyaline cast formation, and fatty degeneration. The effects of dose and vehicle have been examined (Heindel et al. 1995; Larson et al. 1993, 1995b; Lipsky et al. 1993).

Mice seem to be more sensitive to chloroform-induced renal toxicity than other experimental animals. Certain strains of male mice are susceptible to chloroform-induced nephrotoxicity, while female mice appear to be somewhat resistant (Culliford and Hewitt 1957; Eschenbrenner and Miller 1945b; Larson et al. 1996). Castrated mice were no longer susceptible to the effect, and testosterone treatment increased the severity of kidney damage in females, suggesting the role of hormones in chloroforminduced nephrotoxicity. It has been demonstrated that sensitivity to kidney damage is related to the capacity of the kidney to metabolize chloroform to phosgene (Pohl et al. 1984). The activation of chloroform to its reactive metabolites appeared to be cytochrome P-450-dependent: the covalent binding to microsomal protein required nicotinamide adenine dinucleotide phosphate (NADPH) and oxygen, and could be inhibited by carbon monoxide (Hook and Smith 1985; Smith and Hook 1983, 1984; Smith et al. 1984). Furthermore, administration of chloroform to male mice caused a depletion of renal GSH, indicating that GSH can react with reactive intermediates, thereby reducing the extent of the reaction with tissue MMBs and kidney damage.

The renal toxicity of chloroform in rats after intraperitoneal dosing has also been reported (Kroll et al. 1994a, 1994b).

It is likely that kidney effects may occur in humans after inhalation or oral exposure to high levels of chloroform; however, it is not known whether such effects would occur at the levels of chloroform found in the environment, in drinking water, or at hazardous waste sites.

Dermal Effects. No reports are available on the toxicity of chloroform to skin after inhalation and oral exposures in humans. Stratum comeum damage was reported after a topical exposure of chloroform of 15 minutes duration for 6 consecutive days (Malten et al. 1968). Chloroform was used as a vehicle for the topical application of aspirin for the treatment of painful herpes zoster lesions in

male and female humans. The only reported side-effect was an occasional burning sensation to the skin as the chloroform evaporated after application (King 1993).

Few reports exist on the dermal effects of chloroform in animals after inhalation or oral exposures. Alopecia has been observed in pregnant rats (Thompson et al. 1974) and in mice (Gulati et al. 1988). Skin irritation and necrosis and been reported in rabbits after topical application of chloroform (Smyth et al. 1962; Torkelson et al. 1976).

Ocular Effects. No studies were located regarding the ocular effects of chloroform in humans or animals.

Body Weight Effects. Decreased body weight has been observed frequently in animals after inhalation or oral exposure to chloroform, although the degree of body weight changes are somewhat variable and may be linked to taste aversion (in oral studies) (Chu et al. 1982b; Larson et al. 1995b, 1996; Munson et al. 1982; Newell and Dilley 1978; Torkelson et al. 1976; Tumasonis et al. 1985, 1987). The degree of decreased weight gain was often dose-related and was caused by chloroform toxicity. Decreased weight gain generally occurred at exposure levels similar to or lower than those that induced liver and kidney effects in animals. The possibility of effects on body weight in humans exposed to ambient or elevated levels of chloroform cannot be dismissed.

Immunological and Lymphoreticular Effects. No studies were located regarding immunological effects in humans after inhalation, oral, or dermal exposure to chloroform.

Information about immunological effects in animals is limited. After repeated inhalation exposure to chloroform, mortality was increased in mice challenged with streptococcus infection, suggesting increased susceptibility (Aranyi et al. 1986). However, the bacterial activity of alveolar macrophages was not suppressed in this study. After acute oral exposure, reduced lymphocyte counts were observed in rats (Chu et al. 1982b). Furthermore, humoral immunity was depressed in mice exposed to 50 mg/kg/day chloroform for acute or intermediate durations (Munson et al. 1982). In contrast, cell-mediated immunity was influenced only at high chloroform concentrations administered orally for intermediate durations; however, the chloroform-induced immunological changes appeared to be more severe following acute exposure. *In vitro* treatment of serum with chloroform resulted in a loss of complement activity (Stefanovic et al. 1987). Immunological effects may result from the ability of

chloroform to dissociate antigen-antibody complexes, since it can cause dissociation of certain enzymeinhibitor complexes (Berger et al. 1983). Every day, humans are exposed to very low levels of chloroform in the environment, mainly via inhalation and oral exposure (Hajimiragha et al. 1986; Peoples et al. 1979; Wallace et al. 1987a, 1989). There is a risk of chloroform exposure at or near hazardous waste sites. Although no evidence that chloroform can cause immunological effects in humans was located in the literature, the possibility remains that these effects may result from exposure to chloroform.

Neurological Effects. Neurological effects in humans after acute inhalation exposure to chloroform are well documented because chloroform has been used as an anesthetic for surgery. Inhaled chloroform acts as a depressant on the central nervous system. Chronic inhalation exposure to chloroform resulted in exhaustion, lack of concentration, depression, and irritability in occupationally exposed people (Challen et al. 1958). In a case study, chloroform inhalation for 12 years resulted in psychotic episodes, hallucinations, and convulsions (Heilbrunn et al. 1945). Central nervous system toxicity was observed in humans after oral exposure to chloroform, which suggests that the effects of inhalation and oral exposure are similar. In case reports of patients who intentionally or accidentally ingested several ounces of chloroform, deep coma with abolished reflexes occurred within a few minutes (Piersol et al. 1933; Schroeder 1965; Storms 1973).

Inhalation exposure to high chloroform concentrations induced narcosis (Lehmann and Flury 1943; Sax 1979) and reversible impairment of memory retrieval in animals. High, single, oral doses of chloroform caused ataxia, incoordination, anesthesia, and brain hemorrhage in mice (Balster and Borzelleca 1982; Bowman et al. 1978). Behavioral effects were observed at lower oral doses.

Chloroform concentrations from 1.5 to 6 mmol chloroform were used to determine how chloroform may modify glutamate receptor agonist responses in mouse brain cortical wedges. The two agonists examined were N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA). Responses were determined by measuring electrical responses within the cortical slices. Three mmol of chloroform selectively inhibited AMPA but did not affect NMDA responses. Higher concentrations of chloroform failed to inhibit the AMPA or NMDA content in the wedges (Carla and Moroni 1992). Male Sprague-Dawley rats administered a single 200 mg/kg dose of chloroform experienced a significant decrease in midbrain 5-HIAA levels and a significant increase in hypothalamic dopamine concentrations (Kanada et al. 1994).

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The clinical effects of chloroform toxicity on the central nervous system are well documented. However, the molecular mechanism of action is not well understood. It has been postulated that anesthetics induce their action at a cell-membrane level due to lipid solubility. The lipid-disordering effect of chloroform and other anesthetics on membrane lipids was increased by gangliosides (Harris and Groh 1985), which may explain why the outer leaflet of the lipid bilayer of neuronal membranes, which has a large ganglioside content, is unusually sensitive to anesthetic agents. Anesthetics may affect calcium-dependent potassium conductance in the central nervous system (Caldwell and Harris 1985). The blockage of potassium conductance by chloroform and other anesthetics resulted in depolarization of squid axon (Haydon et al. 1988).

Based upon existing data, the potential for neurological and behavioral effects in humans exposed to chloroform at levels found in the environment, in drinking water, or at hazardous waste sites is very minimal.

Reproductive Effects. It has not been definitively determined whether chloroform exposure induces reproductive effects in humans. No studies were located regarding reproductive effects in humans after inhalation or dermal exposure to chloroform. Only one study was located regarding reproductive effects in humans after oral exposure to chloroform. Bove et al. (1995) studied the effects of drinking-water consumption on birth outcomes and found that exposure to TTHM at levels >0.l ppm resulted in reduced birth weight and size as well as an increased risk of oral cleft, central nervous system, and neural tube defects. These results should be viewed with caution since the authors did not specifically monitor chloroform levels. The effects seen may be due to exposure to other THMs or non-THM contaminants in the drinking water.

Studies indicate that exposure to chloroform causes reproductive effects in animals. Dose-related increases of embryonal resorptions were observed in rats and mice after inhalation or oral exposure to chloroform during gestation. A significant increase in the incidence of abnormal sperm was observed in mice after acute inhalation exposure (Land et al. 1979, 1981). Gonadal atrophy was observed in male and female rats treated by gavage (Palmer et al. 1979). Fertility was not affected in either generation of mice exposed orally to chloroform in a 2-generation study (Gulati et al. 1988). In contrast, a 2-generation study in Sprague-Dawley rats and Swiss mice demonstrated significant decreases in combined live pup weights and in the proportion of male pups born live (rats), a significant reduction in sperm concentrations and sperm head counts, and increased numbers of unclear

or no estrous cycles (mice). However, the animals in this study were administered drinking water containing a mixture of 25 contaminants; thus, other toxicants may have elicited these effects. Oral exposure to chloroform did not induce histopathological changes in the reproductive organs of rats exposed for intermediate durations (Jorgenson and Rushbrook 1980) or in rats and mice (NCI 1976) and dogs (Heywood et al. 1979) exposed for chronic durations.

Developmental Effects. One study regarding developmental effects in humans after oral exposure to chloroform has been reported (Kramer et al. 1992). The estimated relative risk of low birth weight associated with drinking-water sources having chloroform levels of ≥10 μg/L was 30% higher than sources with undetectable levels of chloroform. Prematurity was not associated with chloroform/THM exposure. The estimated relative risk of intrauterine growth retardation associated with drinking-water supplies with chloroform concentrations of >l0 μg/L was 80% higher than the risk for sources with undetectable levels of chloroform. Sources with intermediate chloroform levels (l-9 μg/L) had an elevated risk of 30%. There seems to be reasonable evidence to suggest that some correlation with an increased risk of intrauterine growth retardation associated with higher concentrations of waterborne chloroform and dichlorobromomethane does exist.

Inhalation exposure to chloroform during gestation induced fetotoxicity and teratogenicity in rats (Schwetz et al. 1974) and mice (Murray et al. 1979). Decreased fetal crown-rump length, decreased ossifications, imperforate anus (rats), and cleft palate (mice) were observed in the offspring of exposed dams. In contrast, fetotoxicity (decreased fetal weight), but not teratogenicity, was observed in rats after oral exposure to chloroform (Ruddick et al. 1983; Thompson et al. 1974). Increased resorptions were observed in rats and rabbits (Thompson et al. 1974). In a 2-generation oral study, degeneration of the epididymal ductal epithelium was observed in mice of the F_1 generation (Gulati et al. 1988). Due to its chemical nature, chloroform can cross the placenta easily, as demonstrated by its detection in the placenta and fetuses of mice a short time after inhalation exposure (Danielsson et al. 1986). Chloroform may accumulate in the amniotic fluid and fetal tissues. Various developmental effects may result from exposure, depending on the period of *in utero* exposure. Although no studies have conclusively reported developmental effects in humans, chloroform (or in tandem with other organic halomethanes) may have the potential to cause developmental effects in humans. Whether such effects could occur from exposure to levels in the environment, in drinking water, or at hazardous waste sites is not known.

Genotoxic Effects. *In vivo* and *in vitro* studies of the genotoxic effects of chloroform are summarized in Tables 2-5 and 2-6. Information regarding genotoxic effects after *in vivo* exposure to chloroform is limited. Mice exposed to chloroform by gavage had an increase in sister chromatid exchange frequency in bone marrow cells (Morimoto and Koizumi 1983). No sperm-head abnormalities were noted in mice after receiving 5 daily intraperitoneal injections of chloroform in concentrations up to 0.25 mg/kg/day in corn oil (Topham 1980). Oral exposure to chloroform did not increase UDS in rat hepatocytes (Mirsalis et al. 1982). Chloroform exposure caused mitotic arrest in grasshopper embryos (Liang et al. 1983) and a nonsignificant increase in the recessive lethals in *Drosophila melanoguster* (Gocke et al. 1981). In general, most of the assays for chloroform genotoxicity are negative. Therefore, it seems that chloroform is a weak mutagen and that its potential to interact with DNA is low.

In *in vitro* experiments, chloroform did not cause reverse mutations in *Salmonella typhimurium* (Gocke et al. 1981; San Augustin and Lim-Sylianco 1978; Simmon et al. 1977; Uehleke et al. 1977; Van Abbe et al. 1982; Varma et al. 1988) or in *Escherichia coli* (Kirkland et al. 1981) with or without metabolic activation. Inconclusive results were obtained in *Saccharomyces cerevisiae* and *Schistozosaccharomyces pombe* (Callen et al. 1980; De Serres et al. 1981). Chloroform, however, induced Aneuploidia in *Aspergillus niduluns* (Crebelli et al. 1988). Chloroform caused forward mutations in L5 178Y mouse lymphoma cells after metabolic activation (Mitchell et al. 1988), but did not cause mutations at 8-azaguanine locus in Chinese hamster lung fibroblasts (Sturrock 1977) or sister chromatid exchange in Chinese hamster ovary cells (White et al. 1979). A study performed in mice examined the ability of chloroform to induce UDS in hepatocytes *in vitro* from 15-week-old female $B6C3F_1$ mice. Chloroform concentrations ranged from 0.01 to 10 mmol. Mice were sacrificed at 2 and 12 hours postdosing to determine if and when UDS began to occur. Dimethylnitrosamine, a known inducer of UDS, was used as a positive control and did induce UDS in these hepatic cells. No induction of DNA repair was observed at any concentration of chloroform at either the 2-hour or 12-hour posttreatment groups. All concentrations of chloroform added to the cell cultures of mouse hepatocytes proved to be toxic. The study showed that chloroform is not directly genotoxic in hepatocytes of female mice, either *in vivo* or *in vitro*, despite the fact that it is the target organ of chloroform carcinogenesis (Larson et al. 1994a). In human lymphocytes, chloroform did not induce UDS (Peroccio and Prodi 1981) and did not increase the frequency of sister chromatid exchange and chromosome aberrations (Kirkland et al. 1981). In contrast, increases in sister chromatid exchange were reported after metabolic activation in another study (Morimoto and Koizumi 1983).

Table 2-5. Genotoxicity of Chloroform *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Rat hepatocytes	Unscheduled DNA synthesis	-	Mirsalis et al. 1982
Mouse bone marrow	Sister chromatid exchange	-	Morimoto and Koizumi 1983
Mouse	Sperm-head abnormalities	-	Topham 1980
Mouse	Sperm abnormalities	+	Land et al. 1981
Grasshopper embryo	Mitotic arrest	+	Liang et al. 1983
Drosophila melanogaster	Recessive lethals	-	Gocke et al. 1981
Host-mediated assays:			
Salmonella typhimurium TA1535 (mouse host-mediated assay)	Reverse mutation	-	San Agustin and Lim-Sylianco 1978
S. typhimurium TA1537 (mouse host-mediated assay) (males only)	Reverse mutation	+	San Agustin and Lim-Sylianco 1978

- = negative result; + = positive result; DNA = Deoxyribonucleic acid

Table 2-6. Genotoxicity of Chloroform *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organism:				
Salmonella typhimurium TA98	Reverse mutation	-	-	Gocke et al. 1981
S. typhimurium TA100	Reverse mutation	-	-	Gocke *et al. 1981*
S. typhimurium TA1535	Reverse mutation	-	-	Gocke et al. 1981
S. typhimurium TA1535	Reverse mutation	-	-	Uehleke et al. 1977
S. typhimurium TA1538	Reverse mutation	-	-	Uehleke et al. 1977
S. typhimurium TA98	Reverse mutation	-	-	Simmon *et al. 1977*
S. typhimurium TA100	Reverse mutation	-	-	Simmon et al. 1977
S. typhimurium TA1535	Reverse mutation	-	-	Simmon et al. 1977
S. typhimurium TA1537	Reverse mutation	-	-	Simmon et al. 1977
S. typhimurium TA98	Reverse mutation	-	-	Van Abbe *et al. 1982*
S. typhimurium TA100	Reverse mutation	-	-	Van Abbe et al. 1982
S. typhimurium TA1535	Reverse mutation	-	-	Van Abbe et al. 1982
S. typhimurium TA1537	Reverse mutation	-	-	Van Abbe et al. 1982
S. typhimurium TA1538	Reverse mutation	-	-	Van Abbe *et al. 1982*
S. typhimurium TA98	Reverse mutation	-	(+)	Varma et al. 1988
S. typhimurium TA100	Reverse mutation	+	(+)	Varma et al. 1988
S. typhimurium TA1535	Reverse mutation	-	(+)	Varma et al. 1988
S. typhimurium TA1537	Reverse mutation	-	(+)	Varma *et al.* 1988
S. typhimurium TA98	Reverse mutation	Not tested	-	San Augustin and Lim-Sylianco 1978
S. typhimurium TA1535	Reverse mutation	Not tested	-	San Augustin and Lim-Sylianco 1978
S. typhimurium TA1537	Reverse mutation	Not tested	-	San Augustin and Lim-Sylianco 1978

Table 2-6. Genotoxicity of Chloroform *In Vitro* (continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Escherichia coli	Reverse mutation	-	-	Kirkland et al. 1981
Aspergillus nidulans	Aneuploidia	+	Not tested	Crebelli et al. 1988
Saccharomyces cerevisiae	Reverse mutation	-	(+)	De Serres et al. 1981
Schizosaccharomyces pombe	Recombinations	-	(+)	Callen et al. 1980
Eukaryotic organisms:				
Mammalian cells:				
L5178Y mouse lymphoma cells	Forward mutation	+	-	Mitchell et al. 1988
Chinese hamster lung fibroblasts	Mutation at 8-azaquonine		-	Sturrock 1977
Chinese hamster ovary cells	Sister chromatid exchange		-	White et al. 1979
Human lymphocytes	Unscheduled DNA synthesis	-	-	Perocco and Prodi 1981
Human lymphocytes	Sister chromatid exchange	-	+	Morimoto and Koizumi 1983
Human lymphocytes	Sister chromatid exchange	-	-	Kirkland et al. 1981
Human lymphocytes	Chromosome aberrations		-	Kirkland et al. 1981

- = negative result; + = positive result; (+) = weakly positive; DNA = Deoxyribonucleic acid

2. HEALTH EFFECTS

Cancer. No studies were available regarding cancer in humans or animals after inhalation exposure to chloroform. Epidemiology studies suggest an association between chronic exposure to chlorinated drinking-water sources and increased incidences of colon cancer (Young et al. 1981), pancreatic cancer (Ijsselmuiden et al. 1982) and bladder cancer (Cantor et al. 1978; McGeehin et al. 1993; Zierler et al. 1988). However, numerous other potential toxicants known to exist in chlorinated drinking water may easily account for these effects.

The carcinogenic potential of chloroform has been tested in animal studies. A dose-related increase in the incidence of hepatomas was observed in mice exposed to chloroform for intermediate durations (Eschenbrenner and Miller 1945a). Chronic-duration exposure induced an increased incidence of renal adenoma and carcinoma in rats exposed to chloroform in drinking water (Jorgenson et al. 1985). Increased incidence of neoplastic nodules in the liver was observed in female Wistar rats ingesting chloroform in drinking water (Tumasonis et al. 1987). In addition, hepatocellular carcinoma was observed in $B6C3F_1$ mice given chloroform in oil by gavage (NCI 1976), and kidney tumors were observed in male ICI mice exposed by gavage to chloroform in toothpaste (Roe et al. 1979). The incidence of liver and kidney tumors in male and female rats given chloroform in a chronic-duration study has been reported (Dunnick and Melnick 1993; NCI 1976). While no hepatocellular or large intestine neoplasms were noted in either sex of rat, kidney tubular cell neoplasms were observed at 90 mg/kg/day and 180 mg/kg/day in male rats and at 200 mg/kg/day in female rats. In a another study by the same authors, using male and female mice dosed with similar amounts of chloroform, no kidney tubular cell neoplasms or large intestine neoplasms were reported in either sex of mice, while hepatocellular neoplasms were recorded in both sexes. In a similar study, Jorgenson et al. (1985) examined the carcinogenic effects of chloroform administered chronically (104 weeks) in drinking water to male Osborne-Mendel rats and female B6C3Fl mice. While no treatment related enhancement of tumor formation was observed in mice, kidney tubular cell neoplasms were observed in male rats exposed to 160 mg/kg/day chloroform.

The data concerning mouse liver tumors are conflicting. In contrast to the increased incidence of liver tumors observed in $B6C3F_l$ mice exposed by gavage to chloroform in oil (NCI 1976), no increased incidence of liver tumors was observed in female $B6C3F_1$ mice exposed to chloroform in drinking water (Jorgenson et al. 1985). This result is consistent with the absence of liver tumor effects in four other strains of mice exposed by gavage to chloroform in toothpaste (Roe et al. 1979). In a pharmacokinetic study, chloroform was absorbed more slowly and to a lesser extent from corn oil than

water (Withey et al. 1983), suggesting that pharmacokinetic effects are not responsible for the differences in liver tumor responses. Nevertheless, data from historical controls indicate that corn oil alone is not responsible for the increased incidence of liver tumors (Jorgenson et al. 1985).

The corn oil vehicle effect on the induction of mouse liver neoplasms may be due to an interaction between the vehicle and chloroform (Bull et al. 1986; Jorgenson et al. 1985), possibly resulting in altered pharmacokinetics. Larson et al. (1994b) demonstrated that female $B6C3F_1$ mice developed increased hepatocyte toxicity after gavage dosing in oil with chloroform concentrations of 238 and 477 mg/kg/day for 4 days or 3 weeks (as determined by BrdU-labelling of hepatocytes). However, there was no increase in LI in the liver of the same strain of female mice administered up to 1,800 ppm in the drinking water for 4 days or 3 weeks. The actual doses for the mice administered at 1,800 ppm were 105 and 329 mg/kg/day, respectively. Other studies have shown similar intake dose difference due to vehicle effect (Jorgenson et al. 1985; NCI 1976). The difference in results are most likely due to the method of dosing and the vehicle used, both having effects on the pharmacokinetics of chloroform and hence the degree of hepatotoxicity (and perhaps the renal toxicity in males) that chloroform may induce in these mice. Gavaged animals typically receive a large dose of chloroform all at one time over a period of several days, while the animals in the drinking-water studies consume somewhat equal amounts of chloroform; however, it is consumed in small sips (Larson et al. 1994b). It seems clear that the design of the gavage studies inherently results in repeated and relatively massive doses of chloroform to the liver (and other susceptible cells) over a short period of time that likely overwhelm the liver defense mechanisms for chloroform detoxification, resulting in hepatotoxicity, cell death, or both. Conversely, drinking-water studies expose the liver to continuous, low doses of chloroform, resulting in detoxification, elimination, and few apparent signs of hepatocellular damage. Clearly, further studies that describe the differences in pharmacokinetics between dosing method (gavage as opposed to drinking water) and vehicle effects (oil as opposed to water) need to be performed to correctly estimate human risk to orally consumed chloroform.

The possible association between cell proliferation as a result of cytotoxicity and chemical carcinogenesis has been the subject of considerable debate (Melnick et al. 1996). Chemically induced cell proliferation does play an important role in the carcinogenic process; however, the relationship between induced cell proliferation and tumorigenesis is not a direct cause-and-effect relationship (Farber 1995). Based on short-term exposures studies (4, 7, or 21 days), Larson et al. (1994b) suggest that chloroform causes cancer by inducing cytotoxicity, followed by cell regeneration. However, a

review by Chiu et al. (1996), correlating chloroform-induced short-term and long-term cytotoxicity studies with cancer in target tissues, suggests that the mode of action of chloroform carcinogenesis can not be concluded with the currently available data.

There is a qualitative correlation between short-term toxicological end points of cytotoxicity and the occurrence of neoplasia in the liver of B6C3F$_1$ mice exposed to chloroform either by corn oil gavage or in the drinking water. However, the association between cytotoxicity and cancer is lacking in other test systems. For example, short-term cytotoxicity (4 days) was observed in the kidneys of B6C3F$_1$ mice (Larson et al. 1994d) without an observable increase in neoplasia in male B6C3F$_1$ mice exposed to chloroform in corn oil by gavage for 78 weeks at similar doses (NCI 1976). These data indicate that increased cell proliferation may not always be sufficient to cause increased tumor incidence.

Some studies suggest that the carcinogenic response in male rat kidneys (Jorgensen and Rushbrook 1980; Jorgensen et al. 1985) may not be mediated by a mechanism involving necrosis and regenerative cell proliferation. This observation is supported by the fact that chloroform exposure, by either drinking water or corn oil gavage, induced kidney neoplasia in male Osborne-Mendel rats without any reported short-term and long-term cytotoxicity. There was no treatment-reIated biochemical and microscopic/gross histopathological changes in the kidneys of the rats at 30, 60, or 90 days after receiving chloroform in the drinking water (Jorgensen and Rushbrook 1980). Neither necrosis nor tubular cell hyperplasia was found in the kidneys of male Osborne-Mendel rats treated with chloroform by gavage or drinking water in the 2-year bioassays (Jorgensen et al. 198.5; NCI 1986).

In the liver bioassay for GGTase positive foci, chloroform had neither an initiating effect nor a promoting effect when administered in drinking water (Herren-Freund and Pereira 1987), but had a promoting effect of these loci initiated by diethylnitrosamine if given in a corn oil vehicle (Deml and Oesterle 1985); both studies were performed in rats. Moreover, chloroform enhanced the growth of experimentally inoculated tumors in mice (Cape1 et al. 1979). In contrast, chloroform had an inhibiting effect on the growth of tumors induced by known carcinogens (1,2-dimethylhydrazine and ethylnitrosurea) in rats (Daniel et al. 1989; Herren-Freund and Pereira 1987).

In epidemiologic studies, chloroform is not identified as the sole or primary cause of excess cancer rates, but it is one of many organic contaminants found in chlorinated drinking water, many of which are considered to have carcinogenic potential. These studies are often flawed by a lack of measured

chloroform concentrations in drinking water; lack of data concerning concentrations of other organics, limited information concerning personal drinking-water consumption, long latency periods, and effects of migration, making it difficult to quantify exposure. Although human data suggest a possible increased risk of cancer from exposure to chloroform in chlorinated drinking water, the data are too weak to draw a conclusion about the carcinogenic potential of chloroform in humans. Based on animal studies, chloroform has been classified as a probable human carcinogen by EPA (IRIS 1995), as a possible human carcinogen by IARC (1987), and as a substance that may reasonably be anticipated to be carcinogenic in humans (NTP 1989).

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to chloroform are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health

impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by chloroform are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a pre-existing disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Chloroform

Chloroform concentrations measured in tissue and/or air samples can not be currently be used as specific biomarkers for chloroform exposure; however, they may indicate exposure to chloroform or other halogenated compounds that have undergone metabolism to chloroform. Methods for measuring chloroform in biological fluids, tissues, and exhaled breath are available; however, there is relatively little quantitative information relating monitored chloroform levels in tissues or fluids to exposure. The presence of chloroform or its metabolites in biological fluids and tissues may result from the metabolism of other chlorinated hydrocarbons; thus, elevated tissue levels of chloroform or its metabolites may reflect exposure to other compounds. The relationship between chloroform concentration in inspired air and resulting blood chloroform levels is the most well defined measure of exposure due to the extensive use of chloroform as a surgical anesthetic. A mean arterial blood concentration of 9.8 mg/dL (range 7-16.6 mg/dL) was observed among 10 patients receiving chloroform anesthesia at an inspired air concentration of 8,000-10,000 ppm (Smith et al. 1973). Monitoring of blood levels in workers experiencing toxic jaundice due to chloroform exposure revealed that when workroom air concentrations were estimated to be >400 ppm, the blood samples of 13 workers with jaundice were 0.10-0.3 μg/l00 mL blood (Phoon et al. 1983). In another group of 18 workers with toxic hepatitis, blood samples revealed chloroform in some but not all workers, and workroom air contained 14.4-50.4 ppm on various days. These data suggest an association between

increased blood concentrations and increased exposure concentrations, but the blood levels varied too greatly to establish a direct quantitative relationship.

Environmental exposure to chloroform in humans probably represents a combination of inhalation exposure (from the air polluted with volatile halogenated hydrocarbons) and oral exposure (from chlorinated water sources), in addition to a dermal absorption route for chloroform from contaminated water sources (from showering, bathing, or swimming). The chloroform levels detected in human blood varied according to geographical areas. Chloroform levels ranged from 13 to 49 μg/L in serum samples taken from 10 individuals in Florida (Peoples et al. 1979). The level of environmental exposure was not reported. The mean blood chloroform concentration was 1.5 μg/L in blood samples taken from 250 individuals in Louisiana; exposure levels were not reported (Antoine et al. 1986).

Chloroform was found in breath samples from large cohorts of people from New Jersey, North Carolina, and North Dakota (Wallace et al. 1987a). The levels of chloroform in breathing zone (personal) air were consistently higher than outdoor concentrations and correlated with chloroform concentrations in the exhaled breath samples. Some activities such as visiting the dry cleaners (an industry associated with high chloroform levels) or showering were associated with increased chloroform breath levels (Jo et al. 1990a, 1990b; Wallace et al. 1989). Chloroform was detected in 7 of 42 samples of human milk collected in 4 geographical areas in the United States (Pellizzari et al. 1982).

Tissue levels of chloroform obtained at autopsy reflected environmental exposure levels in other studies. The levels ranged from 20 to 49 μg/kg of chloroform from adipose tissue extracted into hexane from samples taken from 10 individuals in Florida (Peoples et al. 1979). In 30 autopsy cases in Germany, the adipose tissue contained a mean of 23.4 μg/kg wet tissue; 24.8 μg/kg perinephric fat; 10.8 μg/kg liver tissue; 9.9 μg/kg lung tissue; and 10 μg/kg muscle tissue (Alles et al. 1988). The maximum chloroform content increased with age and was not dependent on the volume of fat in the tissues.

No correlation has been made between the exact environmental levels of chloroform and the amount of chloroform in the exhaled breath or in the blood. Furthermore, chloroform also can be detected in the breath after exposure to carbon tetrachloride and other chlorinated hydrocarbons (Butler 1961). Therefore, chloroform levels cannot be used as reliable biomarkers of exposure to this chemical.

2.6.2 Biomarkers Used to Characterize Effects Caused by Chloroform

The primary targets of chloroform toxicity are the central nervous system, liver, and kidney. The signs and symptoms of central nervous system effects (e.g., dizziness, fatigue, headache) are easily recognized. Monitoring liver and kidney effects induced by exposure to low levels of chloroform requires the testing of organ functions. Liver effects are commonly detected by monitoring for elevated levels of liver enzymes in the serum or testing for sulfobromophthalein retention. Urinalysis and measurements of BUN and β-2-microglobin are used to detect abnormalities in kidney function. Because many toxic chemicals can cause adverse liver and kidney effects, these tests are not specific for chloroform. No specific biomarkers used to characterize effects caused specifically by chloroform were located.

For more information on biomarkers for renal and hepatic effects of chemicals see *ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.7 INTERACTIONS WITH OTHER CHEMICALS

The interactions of chloroform with other chemicals are an issue of great importance; as with many chemicals, exposure to chloroform alone seldom occurs. This is especially true when considering exposure to chlorinated water, which usually contains other trihalomethanes and may contain other potential toxicants.

Clinical reports of patients who underwent chloroform anesthesia indicated that premeditation with morphine caused serious respiratory depression when chloroform was co-administered. Thiopentone (thiopental Na, an ultra-short-acting barbiturate anesthetic) was associated with increased incidences of hypotension in chloroform-anesthetized patients (Whitaker and Jones 1965).

Several animal studies indicate that chloroform interacts with other chemicals within the organism. The lethal and hepatotoxic effects of chloroform were increased by dicophane (DDT) (McLean 1970) and phenobarbital (a long-acting barbiturate) in rats (Ekstrom et al. 1988; McLean 1970; Scholler 1970). Increased hepatotoxic and nephrotoxic effects were observed after interaction with ketonic solvents and ketonic chemicals in rats (Hewitt and Brown 1984; Hewitt et al. 1990) and in mice

(Cianflone et al. 1980; Hewitt et al. 1979). The hepatotoxicity of chloroform was also enhanced by co-exposure to carbon tetrachloride in rats (Harris et al. 1982) and by co-exposure to ethanol in mice (Kutob and Plaa 1962). Furthermore, ethanol pretreatment in rats enhanced chloroform-induced hepatotoxicity (Wang et al. 1994) and increased the in vitro metabolism of chloroform (Sato et al. 1981).

A mixture of cadmium and chloroform potentiated the cytotoxicity of each in *in vitro* experiments in rat hepatocytes (Stacey 1987a, 1987b). In contrast, mirex did not increase chloroform toxicity in mice (Hewitt et al. 1979). Disulfiram, an inhibitor of microsomal enzymes, decreases the hepatotoxicity of chloroform (Masuda and Nakayama 1982; Scholler 1970). Diethyldithiocarbamate and carbon disulfide pretreatment also protect against chloroform hepatotoxicity (Gopinath and Ford 1975; Masuda and Nakayama 1982, 1983), presumably by inhibiting microsomal enzymes. In general, chloroform toxicity can be influenced by chemicals that alter microsomal enzyme activity or hepatic GSH levels.

The role that dichloroacetate (DCA) and trichloroacetate (TCA) play in chloroform toxicity was studied in rats (Davis 1992). TCA and DCA are formed in conjunction with chloroform during the chlorination of drinking water; therefore, animals drinking chlorinated water may be exposed to all three compounds simultaneously. It was found that DCA increases the hepatotoxicity and nephrotoxicity of chloroform in rats, that TCA increases the nephrotoxicity of chloroform, and that these effects were gender-specific, occurring mainly in females. The effects of monochloroacetate (MCA) on chloroform toxicity has also been investigated, with the combination (MCA + chloroform) shown to have toxic effects on the liver and kidneys of rats (Davis and Bemdt 1992). The effect of chloroform and other organic halides (i.e., dichlorobromomethane) on intrauterine growth retardation has also been explored (Kramer et al. 1992).

Ikatsu and Nakajima (1992) studied the effect of low-dose inhalation of chloroform with or without co-exposure to carbon tetrachloride on hepatotoxicity when rats were or were not previously exposed to ethanol. Groups of control or ethanol-pretreated rats inhaled 0, 50, or 100 ppm chloroform alone; 0, 25, or 50 ppm chloroform with 5 ppm carbon tetrachloride; or 0, 10, 25, or 50 ppm chloroform with 10 ppm carbon tetrachloride. Exposures to either 50 or 100 ppm of chloroform alone did not significantly change SGOT, SGPT, liver, or serum malondialdehyde (MDA) concentrations. In the rats pretreated with ethanol, SGOT and SGPT levels were significantly elevated above control animals at 100 ppm chloroform and SGOT levels were increased at 50 ppm chloroform as well. There was no

change in either serum or liver concentrations of MDA in either exposure group. Liver triglycerides and GSH levels were significantly elevated above those of control animals for both exposure levels for animals not pretreated with ethanol; however, overall liver weights were elevated at only 100 ppm chloroform. In rats pretreated with ethanol, there was no significant change in liver triglyceride concentrations at either dose; however, liver GSH and liver weights were significantly elevated above control at both exposure concentrations. In chloroform and carbon tetrachloride treated rats not pretreated with ethanol, elevations in SGOT (10 ppm $CC1_4$ plus 10 and 50 ppm $CHC1_3$), SGPT (5 ppm $CC1_4$ plus 50 ppm $CHC1_3$, 10 ppm $CC1_4$ plus 25 ppm $CHC1_3$, and plasma MDA (10 ppm $CC1_4$ plus 10, 25, and 50 ppm $CHC1_3$ were observed. In chloroform and carbon tetrachloride-treated rats pretreated with ethanol, elevations in SGOT (all doses), SGPT (all doses except 5 ppm $CC1_4$ + 25 ppm $CHCl_3$), liver MDA (all doses), and plasma MDA (5 and 10 ppm $CC1_4$ + 50 ppm $CHC1_3$, 10 ppm $CC1_4$ + 25 ppm $CHC1_3$,) were observed. In chloroform and carbon tetrachloride treated rats not pretreated with ethanol, elevations in liver triglyceride (all doses) and GSH (5 ppm $CC1_4$ + 50 ppm $CHC1_3$, 10 ppm $CC1_4$ + 10 and 50 ppm $CHC1_3$) were observed. In chloroform and carbon tetrachloride treated rats pretreated with ethanol, elevations in liver triglyceride (all chloroform doses at 10 ppm CCl_4) and GSH (all doses except 5 ppm $CC1_4$ + 25 ppm $CHC1_3$ were observed. The results suggest that chloroform enhances carbon tetrachloride-induced hepatotoxicity.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to chloroform than will most persons exposed to the same level of chloroform in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of chloroform, or compromised function of target organs affected by chloroform. Populations who are at greater risk due to their unusually high exposure to chloroform are discussed in Section 5.6, Populations With Potentially High Exposure.

Since the liver and kidney are the two main organs responsible for chloroform metabolism, individuals who have hepatic or renal impairment may be more susceptible to chloroform toxicity; one such population would be those who abuse alcohol (Wang et al. 1994; Kutob and Plaa 1962). Also, exhaustion and starvation may potentiate chloroform hepatotoxicity, as indicated in some human clinical reports (Royston 1924; Townsend 1939) and in animal studies (Ekstrom et al. 1988; McMartin

et al. 1981). Animal studies indicate that male mice and rats may be more susceptible to the lethal and renal effects of chloroform than female mice and rats (Deringer et al. 19.53; Torkelson et al. 1976). The greater susceptibility of adult male animals is associated with testosterone levels in the animals (Deringer et al. 1953). Evidence also exists for age-related effects; young male mice were less susceptible to the lethal effects of chloroform compared to adult males (Deringer et al. 1953). Kimura et al. (1971) noted similar differences between young and old adult rats, but also found that chloroform was significantly more toxic in 14-day-old rats than in adult rats. Whether or not these subpopulations in humans would be more susceptible than their respective counterparts is not presently known.

2.9. METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chloroform. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to chloroform. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to chloroform:

Ellenhom, MJ and Barceloux, DG, (eds.) (1988). Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Elsevier Publishing, New York, NY., pp. 972-974.

Dreisback, RH, (ed.) (1987). Handbook of Poisoning. Appleton and Lange, Norwalk, CT.

Haddad, LM and Winchester, JF, teds.) (1990). Clinical Management of Poisoning and Drug Overdose. 2nd edition, WB Saunders, Philadelphia, PA.

Aaron, CK and Howland, MA (eds.) (1994). Goldfrank’s Toxicologic Emergencies. Appleton and Lange, Norwalk, CT.

2.9.1 Reducing Peak Absorption Following Exposure

Human exposure to chloroform may occur by inhalation, ingestion, or by dermal contact. General recommendations for reducing absorption of chloroform include removing the exposed individual from the contaminated area and removing the contaminated clothing. If the eyes and skin were exposed, they should be flushed with water. In order to reduce absorption of ingested chloroform, emesis may

be considered unless the patient is comatose, is convulsing, or has lost the gag reflex. Controversy exists concerning use of emesis because of the rapid onset of central nervous system depression, the risk of aspiration of stomach contents into the lungs, and the relative ineffectiveness of this method. In comatose patients with absent gag reflexes, an endotracheal intubation may be performed in advance to reduce the risk of aspiration pneumonia. Gastric lavage may also be used.

2.9.2 Reducing Body Burden

Chloroform is not stored to any appreciable extent in the human body and is mostly metabolized to phosgene and eventually CO_2 (see Section 2.3); however, some chloroform may be stored in fat depots in the body. The half-life of chloroform in humans has been calculated to be 7.9 hours following inhalation exposure (Gordon et al. 1988). Furthermore, an oral-exposure study found most of the chloroform dose being eliminated within 8 hours postexposure (Fry et al. 1972). Hepatic and pulmonary first-pass effect was reported in humans (Chiou 1975).

Despite a relatively fast clearance of chloroform from the body, toxic effects may develop in exposed individuals. No method is commonly practiced to enhance the elimination of the absorbed dose of chloroform. Although there is evidence that ethanol pretreatment of rats can increase the in vitro metabolism of chloroform (Sato et al. 1981), such treatment would not be recommended (Kutob and Plaa 1962) because it would increase the toxicity of chloroform and it is a very poor practice generally.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Target organs of chloroform toxicity are the central nervous system, liver, and kidneys (see Section 2.2). Respiratory, cardiovascular, and gastrointestinal toxic effects have also been reported. Studies in animals also indicated that chloroform exposure may induce reproductive and developmental effects and cause cancer. Several studies investigated the possible mechanism for chloroform-induced toxicity (see Section 2.5). Proposed mechanisms of chloroform toxicity and potential mitigations based on these mechanisms are discussed below. The potential mitigation techniques mentioned are all experimental.

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One of the possible mechanisms of chloroform toxicity is thought to be linked to its high lipid solubility and its ability to bind covalently to lipids (Testai et al. 1987). For example, neurotoxic and respiratory effects of chloroform may be due to the interaction of chloroform with gangliosides in neuronal membranes (Harris and Groh 1985) and phospholipids in the surfactant monolayer of the lower respiratory tract (Enhorning et al. 1986), respectively. Another proposed reaction of chloroform and lipids would result in the formation of conjugated dienes which are indicative of lipid peroxidation (De Groot and Noll 1989). Some authors reported that conjugated dienes may play a key role in the hepatotoxicity induced by haloalkanes (Comporti 1985; Recknagel et al. 1982). Others, however, argue that lipid peroxidation alone is not responsible for all changes found in the liver following chloroform exposure (Brown et al. 1974b; Lavigne and Marchand 1974). Instead, it was proposed that the mechanism of chloroform-induced liver and kidney toxicity involved metabolism to the reactive intermediate, phosgene, which binds to proteins of the endoplasmatic reticulum (Pohl et al. 1980a, 1980b). While this is true in the rat, it has not been established in other species, including humans.

The toxicity of chloroform is increased by inducers of cytochrome P-450 such as phenobarbital (Scholler 1970). The involvement of cytochrome P-450 is further supported by the finding that disulfiram (Scholler 1970) and methoxsalen (Letteron et al. 1987), both inhibitors of microsomal enzymes, decreased the liver injury caused by chloroform in rats and mice, respectively. In addition, pretreatment with diethyldithiocarbamate and carbon disulfide protected mice against chloroform hepatotoxicity as indicated by biochemical and histopathological results (Gopinath and Ford 1975; Masuda and Nakayama 1982, 1983). Similarly, pretreatment of mice with methoxsalen (Letteron et al. 1987) and piperonyl butoxide (Kluwe and Hook 1981) reduced the chloroform-induced nephrotoxicity. Further research to determine which isozymes of P-450 are involved in metabolism to the more harmful metabolite, phosgene, as well as which isozymes are involved in enhancing the elimination of chloroform, could lead to the development of strategies designed to selectively inhibit specific P-450 isozymes, and thus reduce the toxic effects of chloroform.

Administration of chloroform to laboratory animals resulted in the depletion of renal GSH, indicating that GSH reacts with reactive intermediates, thus reducing the kidney damage otherwise caused by the reaction of these intermediates with tissue MMBs (Hook and Smith 1985; Smith and Hook 1983, 1984; Smith et al. 1984). Similarly, chloroform treatment resulted in the depletion of hepatic GSH and alkylation of MMBs (Docks and Krishna 1976). Other studies demonstrated that sulfhydryl compounds such as L-cysteine (Bailie et al. 1984) and reduced GSH (Kluwe and Hook 1981) may

provide protection against nephrotoxicity induced by chloroform. The sulfhydryl compound N-acetylcysteine is an effective antidote for poisoning by acetaminophen, which, like chloroform, depletes GSH and produces toxicity by reactive intermediates.

All mitigations of the chloroform-induced toxicity cited above are experimental. Further studies would be needed for implications of any of these methods to humans.

2.10 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chloroform is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chloroform.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.10.1 Existing Information on Health Effects of Chloroform

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chloroform are summarized in Figure 2-6. The purpose of this figure is to illustrate the existing information concerning the health effects of chloroform. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR

defines a data gap more broadly as any substance-specific information missing from the scientific literature.

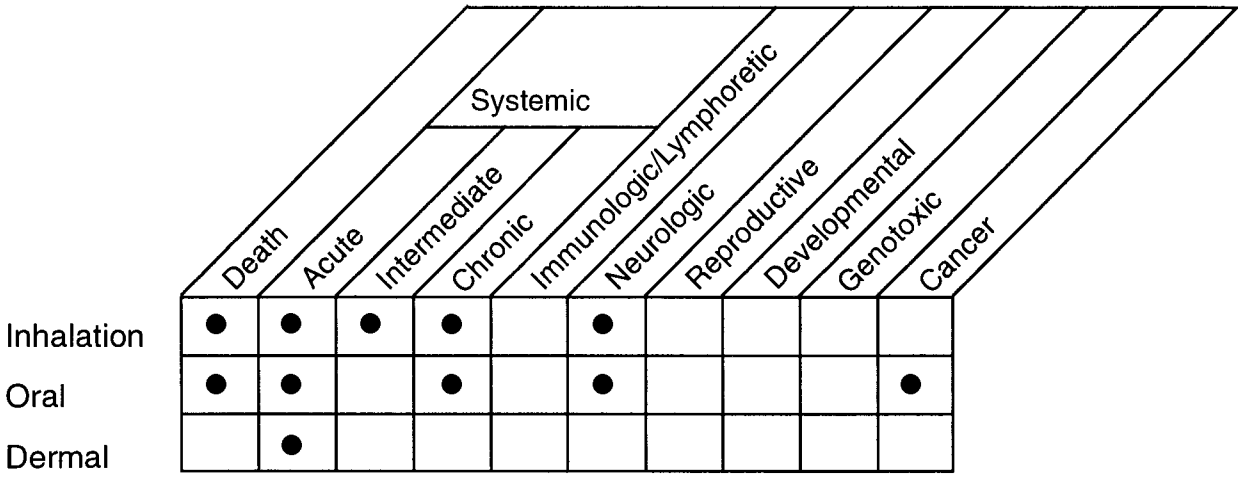
As seen from Figure 2-6, information is available regarding death, systemic effects, and neurological effects in humans after inhalation and oral exposure to chloroform. In addition, information is available regarding carcinogenic effects in humans after oral exposure to chlorinated drinking water. Limited information is available regarding dermal effects in humans after exposure to chloroform.

Inhalation and oral studies in animals provide data on death, systemic effects after acute- and intermediate-duration exposure, immunological effects, neurological effects, developmental effects, reproductive effects, and genotoxic effects. Information is available regarding systemic effects and carcinogenic effects in animals after oral exposure to chloroform. The carcinogenic effects after oral exposure is inconsistent and not totally conclusive. In addition, data regarding death and acute systemic effects in animals after dermal exposure to chloroform were located in the available literature.

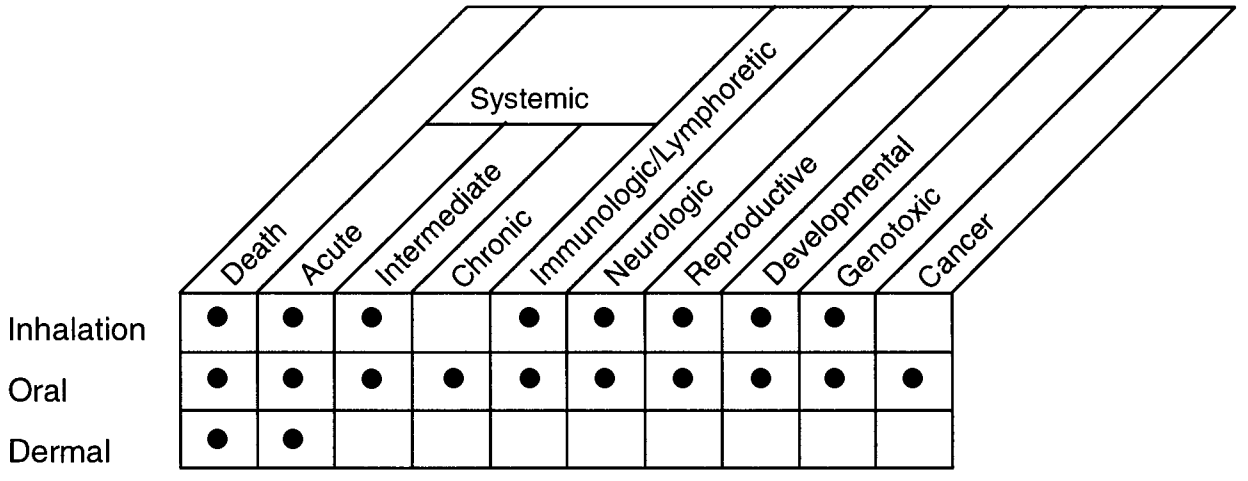
2.10.2 Identification of Data Needs

Acute-Duration Exposure. Clinical reports indicate that the central nervous system, cardiovascular system, stomach, liver, and kidneys in humans are target organs of chloroform toxicity after inhalation and oral exposure to chloroform (Schroeder 1965; Smith et al. 1973; Whitaker and Jones 1965). These findings are supported by results obtained from acute inhalation and oral-exposure studies in animals in which target organs identical to those observed in human studies (central nervous

Figure 2-6. Existing Information on Health Effects of Chloroform



Human



Animal

● Existing Studies

system, liver, and kidney) were identified (Culliford and Hewitt 1957; Jones et al. 1958; Lehmann and Flury 1943; Lundberg et al. 1986; Moore et al. 1982). The data are sufficient to derive an MRL for acute oral exposure. An acute inhalation MRL was derived based on a NOAEL for hepatic effects in mice (Larson et al. 1994c). Lethality studies were conducted in rats and mice after acute inhalation exposure (Deringer et al. 1953; Gehring 1968; Lundberg et al. 1986; Smyth et al. 1962). Similarly, lethal doses were identified after single oral exposure in rats and mice (Bowman et al. 1978; Chu et al. 1982b; Jones et al. 19.58; Kimura et al. 1971; Smyth et al. 1962). Information regarding dermal effects in humans and animals after exposure to chloroform is limited. Degenerative changes in the kidney tubules of rabbits were reported in one dermal study (Torkelson et al. 1976). Toxicokinetic data regarding dermal exposure are very limited; however, there is evidence that chloroform can be absorbed through the skin (Tsuruta 1975). Due to its lipophilic quality after dermal exposure, chloroform is likely to be distributed in the organism in patterns similar to those for inhalation and oral exposure. Information regarding acute dermal exposure in rodents would be useful to identify target organs and threshold levels of chloroform toxicity. Several *in vitro* skin models are available that would be adequate for describing the absorption of chloroform through the skin and the effects that differing concentrations of chloroform would have on skin histology.

Intermediate-Duration Exposure. An occupational study suggests that the liver is a target organ of chloroform toxicity after inhalation exposure of intermediate duration (Phoon et al. 1983). No data were located regarding intermediate-duration oral and dermal exposure in humans. Several studies were located regarding chloroform toxicity in animals after oral exposure (including 3 90-day studies in rats, 3 90-day studies in mice, and a ≥6-week oral study in dogs) (Bull et al. 1986; Chu et al. 1982a, 1982b; Heywood et al. 1979; Jorgenson and Rushbrook 1980; Klaunig et al. 1986; Munson et al. 1982; Palmer et al. 1979); fewer data were located regarding inhalation exposure (Torkelson et al. 1976), and no data were located regarding dermal exposure. In animals, the target organs for chloroform toxicity were identified as the central nervous system, liver, and kidneys.

An intermediate-duration oral MRL was derived based on liver effects in dogs (Heywood et al. 1979). An intermediate-duration inhalation MRL was derived based on toxic hepatitis which occurred in humans (Phoon et al. 1983). Pharmacokinetic data regarding dermal exposure to chloroform are limited, but it is known that chloroform can be absorbed through the skin. Intermediate-duration dermal studies in animals would provide information about chloroform toxicity via this exposure route.

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The information would be useful for populations living at or near hazardous waste sites, who may be exposed to chloroform for intermediate durations.

Chronic-Duration Exposure and Cancer. Information regarding chronic-exposure inhalation exposure to chloroform in humans is limited to occupational studies (Bomski et al. 1967; Challen et al. 1958). The liver and central nervous system are target organs of chloroform toxicity. Regarding chronic-duration oral exposure in humans, limited information is available from a case study reporting hematological, hepatic, and renal effects in an individual who used a cough medicine containing chloroform for 10 years (Wallace 1950) and from a follow-up study of individuals who used a mouthwash containing chloroform for 15 years (De Salva et al. 1975). Animal data indicate that the central nervous system, liver, and kidneys are target organs of chloroform toxicity after chronic oral exposure (Heywood et al. 1979; Jorgenson et al. 1985; NCI 1976; Roe et al. 1979; Tumasonis et al. 1985, 1987). The data are sufficient to derive a chronic oral MRL. No studies were located regarding chloroform toxicity in humans and animals after dermal exposure to chloroform and in animals after inhalation exposure to chloroform. Considering the similar pattern of chloroform toxicity after inhalation and oral exposures for acute and intermediate durations, similar target organs in animals after chronic inhalation exposure to chloroform may be predicted. Nonetheless, studies designed to assess the chronic toxicity of chloroform in animals after inhalation and dermal exposure would be useful to establish dose-response relationships. This information is important to humans occupationally exposed or exposed to contaminated air, water, or soil at or near hazardous waste sites.

Epidemiology studies suggest a possible association between chloroform in drinking water and cancer risk. Increased incidences of colon and bladder cancer were identified in separate populations exposed to chlorinated water. However, as mentioned before, other toxic compounds have also been identified in chlorinated drinking water, making the role of chloroform in cancer induction questionable. Studies in rats and mice indicate that oral exposure to chloroform causes cancer (Jorgenson et al. 1985; NCI 1976; Roe et al. 1979; Tumasonis et al. 1985, 1987); however, some of these studies utilized gavage dosing instead of drinking water. No data were located regarding carcinogenicity in humans and animals following inhalation and dermal exposure to chloroform. Nonetheless, pharmacokinetic data indicate similar toxicokinetics of chloroform after inhalation and oral exposure; therefore, similar targets for carcinogenic effects may be predicted. Data were located suggesting different effects of chloroform depending on the vehicle and method of oral administration. Chloroform in corn oil administered by gavage caused an increased incidence of liver tumors (NCI 1976) while

administration of the same dose in drinking water did not (Jorgenson et al. 1985). It was demonstrated, however, that chloroform uptake is much slower from the oil vehicle (Withey et al. 1983). Therefore, the higher cancer incidence cannot be explained merely by the levels of chloroform in tissues. Furthermore, chloroform acted as a promoter rather than an initiator of preneoplastic foci in a rat liver bioassay (Deml and Oesterle 1985). In contrast, some studies indicate that chloroform inhibits the growth of tumors induced by known carcinogens (Daniel et al. 1989; Herren-Freund and Pereira 1987). Animal studies also suggest an epigenetic mechanism for the carcinogenicity of chloroform. Because of these differences, further studies on the possible mechanism of chloroform carcinogenicity would be useful.

Genotoxicity. Chloroform has been tested for genotoxicity in several *in vitro* and *in vivo* experiments. Its potency to induce mutations seems to be weak. No induction of reverse mutations was observed in prokaryotic systems (Gocke et al. 1981; Kirkland et al. 1981; San Augustin and Lim-Sylianco 1978; Simmon et al. 1977; Uehleke et al. 1977; Van Abbe et al. 1982; Vat-ma et al. 1988). Mixed results were obtained in the induction of mutations in human lymphocytes and Chinese hamster cells *in vitro* (Kirkland et al. 1981; Mitchell et al. 1988; Peroccio and Prodi 1981; White et al. 1979). Nonetheless, an increase in sperm anomalies and sister chromatid exchanges in the bone marrow of rodents was observed after *in vivo* exposure (Land et al. 1979, 1981; Morimoto and Koizumi 1983). Cytogenetic analysis of peripheral lymphocytes from exposed individuals would provide useful information about the ability of chloroform to induce mutations in-humans if a suitable population can be identified.

Reproductive Toxicity. No information was located regarding reproductive effects in humans exposed to chloroform via any route or in animals exposed by the dermal route. Increased resorptions were observed in rats and mice after inhalation exposure to chloroform during gestation (Murray et al. 1979; Schwetz et al. 1974) and in rats and rabbits after oral exposure (Thompson et al. 1974). In addition to effects in dams, abnormal sperm were found in mice after inhalation exposure (Land et al. 1979, 1981). Furthermore, exposure-related gonadal atrophy was observed in both sexes of rats following oral exposure to chloroform (Palmer et al. 1979). The results suggest that reproductive organs are a target of chloroform toxicity in animals; however, some inhalation and oral studies in animals do not report any effects. More studies assessing the reproductive function in animals would be useful for the purpose of extrapolating the data to human exposure.

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Developmental Toxicity. Only one study was located regarding developmental effects in humans exposed to chloroform via an oral route. Animal data indicate that chloroform can cross the placenta. Fetotoxicity effects (decreased birth weight, decreased fetal crown-rump length, increased resorptions) and teratogenicity (acaudate fetuses with imperforate anus, cleft palates) were observed in rats and mice after inhalation exposure to chloroform (Murray et al. 1979; Schwetz et al. 1974). Oral exposure to chloroform-induced fetotoxicity in rats and rabbits (Ruddick et al. 1983; Thompson et al. 1974). Degeneration of the epididymal ductal epithelium (not affecting the fertility) was observed in mice in the F_1 generation in a 2-generation oral reproductive study (Gulati et al. 1988). No information is available regarding the developmental toxicity of chloroform after dermal exposure. More data regarding developmental toxicity both in humans and in experimental animals (especially after oral and dermal exposure) would be useful to identify the possible risk for humans.

Immunotoxicity. No data were located regarding immunological effects in humans after inhalation, oral, or dermal exposure to chloroform. The data obtained from animal studies are limited to one inhalation study in mice and three oral studies in rats and mice (Aranyi et al. 1986; Chu et al. 1982b; Munson et al. 1982). Depressed humoral and cell-mediated immunity were detected; however, the chloroform-induced changes were more serious in the acute exposure study than in the intermediateduration study, indicating that the changes may be transient. Studies regarding skin sensitization with chloroform were not performed. A battery of immune function tests has not been performed in humans or in animals, but would provide helpful information to support or refute the limited evidence for chloroform immunotoxicity.

Neurotoxicity. The central nervous system is a target organ for chloroform toxicity in humans after inhalation and oral exposure. The neurotoxic effect is well documented in studies of patients exposed to chloroform via anesthesia (Featherstone 1947; Smith et al. 1973; Whitaker and Jones 1965) or of individuals who intentionally and accidentally ingested the chemical (Piersol et al. 1933; Schroeder 1965; Storms 1973). Lower chloroform doses produced neurological effects during occupational exposure (Challen et al. 1958). Similarly, neurotoxicity is reported in animal studies involving inhalation and oral exposure to chloroform (Bowman et al. 1978; Jones et al. 1958; Lehmann and Flury 1943). A battery of neurobehavioral tests was conducted in mice after oral exposure to chloroform (Balster and Borzelleca 1982). No data were located regarding chloroform neurotoxicity in humans or animals after dermal exposure to chloroform. Animal studies involving dermal exposure to chloroform would be useful for risk assessment of occupational exposure. Continued research on the

toxicity of inhaled and dermally absorbed chloroform in humans when exposed to water sources containing elevated concentrations of chloroform during showering would also be useful. More information regarding the mechanism of chloroform-induced neurotoxicity and structural alterations produced in the central nervous system would be helpful.

Epidemiological and Human Dosimetry Studies. Populations may be exposed to chloroform in the workplace, near hazardous waste sites containing chloroform, from chlorinated water, and from various consumer products that contain chloroform. Limited information was obtained from occupational studies reporting central nervous system and liver effects in exposed workers (Bomski et al. 1967; Challen et al. 1958; Phoon et al. 1983). Reliable dosimetry data correlating occupational exposure with signs of toxic effects would be useful. Epidemiology studies suggest an association between elevated chloroform levels in drinking water and colon, rectal, and bladder cancer in humans (Alavanja et al. 1978; Cantor et al. 1978; Young et al. 1981). All of these studies were limited by a lack of attention to important details (e.g., migration, exposure to other carcinogens). Better designed and better conducted epidemiology studies of occupational exposure would be helpful. The information can be useful to populations living near hazardous waste sites where chloroform is present. In addition, further refining of the PBPK/PD models would further advance our understanding of chloroform tissue dosimetry in humans and animals.

Biomarkers of Exposure and Effect.

Exposure. Methods for detecting chloroform in exhaled breath, blood, urine, and tissues are available. Nevertheless, it is difficult to correlate chloroform levels in biological samples with exposure, because of the volatility and short half-life of chloroform in biological tissues. Several studies monitored chloroform levels in environmentally exposed populations (Antoine et al. 1986; Hajimiragha et al. 1986; Peoples et al. 1979); however, the measured levels probably reflect both inhalation and oral exposure. Moreover, increased tissue levels of chloroform or its metabolites may reflect exposure to other chlorinated hydrocarbons. Studies to better quantitate chloroform exposure would enhance the database.

Effect. No biomarkers were identified that are particularly useful in characterizing the effects induced by exposure to chloroform. The target organs of chloroform toxicity are the central nervous system, the liver, and kidneys; however, damage to these organs may result from exposure to other chemicals.

More effort to identify subtle biochemical changes to serve as biomarkers of effects of chloroform exposure would be useful in detecting early, subtle signs of chloroform-induced damage.

Absorption, Distribution, Metabolism, and Excretion. Human data indicate that chloroform absorption from the lungs is rapid and fairly complete (Smith et al. 1973). The data also indicate that absorption after oral exposure is fairly complete for both animals and humans (Brown et al. 1974a; Fry et al. 1972; Taylor et al. 1974). Although there are no experimental data regarding dermal absorption in humans, some data have been extrapolated from mouse studies (Tsuruta 1975). The rate of absorption following oral or inhalation exposure is rapid (within l-2 hours). Additional animal studies investigating the rate of dermal absorption would be useful to quantitate dermal absorption and to compare information from oral and inhalation studies.

Data are available regarding the distribution of chloroform in animals after inhalation and oral exposure to chloroform (Brown et al. 1974a; Chenoweth et al. 1962; Cohen and Hood 1969; Corley et al. 1990; Danielsson et al. 1986; Taylor et al. 1974); however, data regarding the distribution of chloroform in humans is very limited (Feingold and Holaday 1977) and warrants further investigation. It appears that distribution following oral exposure is similar to that following inhalation exposure. Another well conducted animal study focusing on distribution and excretion after dermal exposure would be useful to assess exposure via this route.

The metabolic pathways of chloroform metabolites are well understood. It appears that both the mode of oral administration and the vehicle affect metabolism. Additional data investigating the mode and vehicle of administration would be useful in order to understand the role of these factors in the mechanism of chloroform’s toxicity. The co-administration of other compounds (e.g., ethanol) has been shown to alter chloroform metabolism and toxicity. Further investigations of the hazards associated with exposure to complex mixtures containing chloroform would be useful.

The excretion of chloroform and its metabolites is understood, based on human and animal data derived from oral and inhalation studies (Brown et al. 1974a; Corley et al. 1990; Fry et al. 1972; Taylor et al. 1974). The major route of chloroform elimination is pulmonary, but minor pathways are through enterohepatic circulation, urine, and feces as parent compound or metabolites. There are no human or animal data regarding excretion of dermally applied chloroform.

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Comparative Toxicokinetics. Target organs for chloroform distribution appear to be similar in humans and animals, according to inhalation studies (Corley et al. 1990; Feingold and Holaday 1977). Nonetheless, human and animal studies indicate that there are large interspecies differences in chloroform metabolism and tissue partition coefficients (Brown et al. 1974a; Corley et al. 1990). Marked sex-related differences in tissue distribution and covalent binding to tissue MMBs in mice also have been observed (Taylor et al. 1974). Excretion data indicate that humans and nonhuman primates excrete chloroform in the breath primarily as unchanged chloroform; mice eliminated almost 80% of an oral chloroform dose as CO_2, (Brown et al. 1974a). Thus, toxicokinetic data indicate that it may be difficult to compare the toxicokinetics of chloroform in animals with that in humans. There are a large number of oral studies, relatively few inhalation studies, and almost no dermal studies regarding the toxicokinetics of chloroform. Quantitative toxicokinetic studies in several animal species involving exposure to chloroform via all three routes, especially inhalation and dermal, would help complete the database.

Methods for Reducing Toxic Effects. Protective clothing and protective breathing devices may be used to prevent exposure to large amounts of chloroform, although for everyday low exposures to chloroform, these methods are obviously impractical. General procedures such as flushing the skin with water following dermal exposure and emesis or gastric lavage following oral exposure may be used to reduce absorption of chloroform. However, specific medical treatments that prevent absorption of chloroform have not been identified. Such mechanisms might be beneficial because they might be more effective than general procedures and might involve less risk than procedures such as emesis. Ways to enhance elimination of chloroform from the body are not known. Although chloroform is eliminated fairly rapidly, methods to accelerate elimination without producing toxic metabolites would be helpful in reducing toxicity. The mechanism by which chloroform produces toxicity appears to involve metabolism by phenobarbital-inducible isozymes of cytochrome P-450 to phosgene (Pohl et al. 1980a, 1980b). Development of methods to selectively inhibit the P-450 isozymes responsible for this reaction might reduce chloroform toxicity. There is also evidence that GSH conjugates with reactive products of chloroform metabolism, providing protection from damaging effects (Docks and Krishna 1976; Hook and Smith 1985). Development of a method to maintain high tissue GSH levels following exposure to chloroform might have a mitigating effect on toxicity. Therefore, although no treatments are currently available to block the toxic action of chloroform or repair damage caused by this chemical, there are indications that further research in this area would enable identification of such treatments.

2.10.3 Ongoing Studies

A few ongoing studies involving chloroform have been identified. The effects of volatile anesthetics on the N-methyl-D-aspartate (NMDA) receptor-channel complex are being studied. Specific aims are to determine the effects of several volatile anesthetics (halothane, enflurane, isoflurane, diethyl ether, cyclopropane, nitrous oxide, and chloroform) on ligand binding to glutamate binding sites on the NMDA receptor complex; to study ligand binding to the glycine modulatory site, glutamate, glycine, divalent cation, and spermidine activation of NMDA receptor ion channels; and to examine NMDAreceptor mediated changes in calcium content of rat brain microvesicles (Aronstam 1994). Mechanistic work on the hepatotoxicity and toxigenic sequence will be studied *in vitro* with suspensions of hepatocytes exposed to carbon tetrachloride and other agents known to alter calcium homeostasis and stimulate phospholipase A_2 (bromotrichloromethane and chloroform) (Glende 1994). Mechanisms of toxic chemical interactions in the liver resulting in hepatotoxicity will utilize the hepatotoxic effects of chloroform to explore interactions among metals and organics in the induction of stress response proteins such as metallothionein, heme oxygenase, and nitric oxide synthase, and the induction of inflammatory cytokines (i.e., tumor necrosis factor-alpha, interleukin-1, and interleukin-6). Work by Swenburg will determine if exposure to environmental carcinogens, including 1,1,2-trichloroethylene, 1,1,2,2-tetrachloroethylene, 1,1,2-trichloroethane, chloroform, and carbon tetrachloride, induces or modulates the formation and/or repair of cyclic DNA adducts. Work by Benjamin (1995) will also continue to study the phenomenon of hepatic cell proliferation, and the effect that this response has on the initiation and promotion of cancer. Other research will investigate the toxicity and bioaccumulation of a mixture of sediment contaminants (trichlorethylene, lead, benzene, chloroform, phenol, chromium, and arsenic) in several species of invertebrates and fish. Uptake and depuration will be measured in chironomids *(Chironomus riparius)*, and pharmacokinetic models will be developed to describe bioaccumulation of these sediment contaminants (Clements 1994). Studies by Yang (1994) will continue to evaluate age- and dosing-related changes in pharmacokinetics, biochemical markers, liver cell proliferation, and histopathology in male Fischer 344 rats chronically exposed (up to 2 years) to low levels of a chemical mixture of 7 organic and inorganic groundwater pollutants (including arsenic, benzene, chloroform, chromium, lead, phenol, trichloroethylene). Also, this research will further explore the pharmacokinetic modeling of chemical mixtures and incorporate time-course information on biochemical markers, cell proliferation and histopathology into pharmacokinetic and pharmacodynamic modeling. A study by the Japan Industrial Safety and Health Association (Japan Bioassay Lab) that explores the toxicity of chloroform inhaled over a 2-year period

(6 hours a day, 5 days a week) in male and female Fischer 344 rats and BDF_1 mice is reportedly close to completion (Matsushima 1994). Efforts are also being made to develop a high-efficiency activated carbon granule for drinking-water treatment that can remove water contaminants, including chloroform (Mieville 1992).

3. CHEMICAL AND PHYSICAL INFORMATION

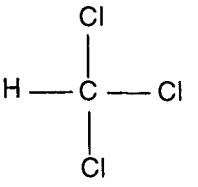
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of chloroform is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of chloroform is located in Table 3-2.

Table 3-1. Chemical Identity of Chloroform

Characteristic	Information	Reference
Chemical name	Trichloromethane	SANSS 1990
Synonym(s)	Methenyl chloride, methane trichloride, methyl trichloride, formyl trichloride	IARC 1979
Registered trade name(s)	Freon 20, R 20, R 20 refrigerant	IARC 1979
Chemical formula	$CHCl_3$	Weast 1988
Chemical structure		IARC 1979
Identification numbers:		
CAS registry	67-66-3	Weast 1988
NIOSH RTECS	FS 9100000	HSDB 1996
EPA hazardous waste	UO44	HSDB 1996
OHM/TADS	7216639	HSDB 1996
DOT/UN/NA/IMCO shipping	Chloroform; UN 1888; IMO 6.1	HSDB 1996
HSDB	56	HSDB 1996
NCI	CO2686	HSDB 1996

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-2. Physical and Chemical Properties of Chloroform

Property	Information	Reference
Molecular weight	119.38	Deshon 1979
Color	Colorless	Hawley 1981
Physical state	Liquid	Deshon 1979
Melting point	-63.2 °C -64 °C -63.5 °C	Deshon 1979 Verschueren 1983 Weast 1988
Boiling point	61.3 °C 62 °C 61.7 °C	Deshon 1979 Verschueren 1983 Weast 1988
Density: at 20 °C	1.485 g/cm^3 1.4832 g/cm^3	Hawley 1981 Weast 1988
Odor	Pleasant, ethereal, nonirritating Pleasant, sweet	Deshon 1979 NFPA 1994
Odor threshold:		
Water	2.4 ppm (w/v)	Amoore and Hautala 1983
Air	85 ppm (v/v)	Amoore and Hautala 1983
Solubility: Water at 25 °C	7.22x10^3 mg/L 9.3x10^3 mg/L 7.43 x 10^3 mg/L	Banerjee et al. 1980 Verschueren 1983 Merck 1989
Organic solvent(s)	Miscible with principal organic solvents Miscible with alcohol, benzene, ether, petroleum ether, carbon tetrachloride, carbon disulfide, oils	Deshon 1979 Merck 1989
Partition coefficients:		
Log K_{ow}	1.97	Hansch and Leo 1985, Verschueren 1983
Log K_{oc}	1.65 2.40	Sabljic 1984 Aster 1996
Vapor pressure at 20 °C	159 mm Hg 160 mm Hg 160 mm Hg	Boublik et al. 1984 Verschueren 1983 NFPA 1994
Henry's law constant:		
at 20 °C	3.0x10^{-3} atm-m^3/mol	Nicholson et al. 1984
at 24.8 °C	3.67x10^{-3} atm-m^3/mol	Gossett 1987
at 25 °C	4.06x10^{-3} atm-m^3/mol	SRC 1994a

Table 3-2. Physical and Chemical Properties of Chloroform (continued)

Property	Information	Reference
Decomposition rates	Negligible rate of hydrolysis Half-life of 80 days in air with photochemically produced hydroxyl radicals	Mabey and Mill 1978 Hampson 1980
	Residence time in air 116 days	Singh et al. 1981
Hydrolysis rate constant at 25 °C for pH>8	6.44×10^{-5} L/mol-sec	SRC 1994b
Autoignition temperature	>1,000 °C	Deshon 1979
Flashpoint	None	Deshon 1979
Flammability limits	No data	No data
Conversion factors in air (20 °C) in air (20 °C)	 1 ppm (v/v)=4.96 mg/m^3 1 mg/m^3=0.20 ppm (v/v)	 Calculated Calculated
Other	Reacts with strong alkalies and aluminum *Oxidized by strong oxidizing agents* such as chromic acid, with formation of phosgene and chlorine gas	NFPA 1994 *HSDB 1996*
Explosive limits	No data	No data

v/v = volume per volume; w/v = weight per volume

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Chloroform is used primarily in the production of chlorodifluoromethane (hydrochlorofluorocarbon-22 or HCFC-22) used as a refrigerant for home air conditioners or large supermarket freezers and in the production of fluoropolymers (CMR 1995). Chloroform has also been used as a solvent, a heat transfer medium in fire extinguishers, an intermediate in the preparation of dyes and pesticides, and other applications highlighted below. Its use as an anesthetic has been largely discontinued. It has limited medical uses in some dental procedures and in the administration of drugs for the treatment of some diseases.

4.1 PRODUCTION

The chlorination of methane and the chlorination of methyl chloride produced by the reaction of methanol and hydrogen chloride are the two common methods for commercial chloroform production (Ahlstrom and Steele 1979; Deshon 1979). The Vulcan Materials Co., Wichita, Kansas, was documented as still using the methanol production process during the late 1980s with all other facilities in the United States at that time using the methyl chloride chlorination process (SRI 1990).

One U.S. manufacturer began chloroform production in 1903, but significant commercial production was not reported until 1922 (IARC 1979). Since the early 1980s, chloroform production increased by 20-25%, due primarily to a higher demand for HCFC-22, the major chemical produced from chloroform. The Montreal Protocol established goals for phasing out the use of a variety of ozonedepleting chemicals, including most chlorofluorocarbons (CFCs). HCFC-22 was one of the few fluorocarbons not restricted by the international agreement. Chloroform is used in the manufacture of HCFC-22, and an increase in the production of this refrigerant has led to a modest increase in the demand for chloroform (CMR 1989). These increasing trends in U.S. production, based on information compiled in the trade journal Chemical & Engineering News for period from 1983 though 1994 (CEN 1995), are summarized in Table 4-l.

The manufacturers and sites of major chloroform production facilities identified for 1993 (SRI 1993) include the following: Dow Chemical U.S.A., Freeport, Texas, and Plaquemine, Louisiana; Occidental Petroleum Corp., Belle, West Virginia; and Vulcan Materials Co., Geismar, Louisiana, and Wichita, Kansas. Estimated annual production capacity (SRI 1993) from these facilities as of January 1, 1993,

Table 4-1. U.S. Production of Chloroform

Year	U.S. production (in millions of pounds)	U.S. production (in millions of kg)
1983	362	164
1984	405	183
1985	275	124
1986	422	191
1987	462	209
1988	524	237
1989	588	266
1990	484	219
1991	505	229
1992	na	na
1993	476	215
1994	565	254

Taken from Chemical & Engineering News 1995

was 460 million pounds (208 million kg). By early 1995, the Occidental Petroleum Corporation facility in West Virginia had ceased its chloroform production operations (CMR 1995; SRI 1995). While precise production figures for the 4 remaining sizable U.S.-based facilities are not available, the annual production capacity estimate for the Dow plant in Freeport, Texas, was 135 million pounds (61.8 million kg); capacity for the Dow plant at Plaquemine, Louisiana, was 150 million pounds (67.5 million kg); capacity at the Vulcan plant at Geismar, Louisiana, was 90 million pounds (40.5 million kg); and capacity at the Vulcan plant at Wichita, Kansas, was 145 million pounds (62.3 million kg); for a total United States annual production capacity of around 520 million pounds (234 million kg) from these 4 large plants (CMR 1995). An estimate of actual production (CEN 1995) in the United States during 1994 was 565 million pounds (254 million kg).

Table 4-2 lists the facilities in each state that manufacture or process chloroform, the intended use, and the range of maximum amounts of chloroform that are stored on site. The data listed in Table 4-2 are derived from the Toxics Release Inventory (TRI93 1995). Only plants from 3 states (associated with the 4 plants noted above) actually generate chloroform as an end-product for sale or distribution. In most cases, chloroform is a chemical intermediary, impurity, or waste by-product at the 172 facilities included in the TRI survey. Only certain types of facilities were required to report; therefore, this is not an exhaustive list. In some cases, facility names are not available or numeric values for amounts of chloroform produced, stored, transferred, or released are missing. This complicates making comparisons between the TRI listings and information from other information sources.

4.2 IMPORT/EXPORT

In 1985, the United States imported 27.6 million pounds (12.5 million kg) of chloroform; 24 million pounds (10.8 million kg) of chloroform were imported into the United States in 1988 (CMR 1989; HSDB 1996). More recent U.S. import figures from the National Trade Data Bank (NTDB 1995) are:

U.S. Imports for Year	Quantity (kg)
1990	10,624,006
1991	9,460,747
1992	6,038,483
1993	8,467,294
1994	2,398,668

Table 4-2. Facilities That Manufacture or Process Chloroform

State[a]	Number of facilities	Range of maximum amounts on site in thousands of pounds [b]	Activities and uses [c]
AK	2	0-1	1, 5, 6
AL	12	0-1000	1, 5, 6, 7, 12
AR	6	0-1000	1, 5, 6, 7, 13
AZ	1	0-1	1, 5
CA	2	0-0	1, 6, 13
CO	1	10-100	2, 6, 11
CT	1	100-1000	11
FL	7	0-100	1, 5, 6, 13
GA	6	0-10	1, 5, 6
ID	1	1-10	1, 5
IL	2	10-1000	11
IN	3	1-100	11, 13
KS	2	100-10000	1, 3, 4, 7, 13
KY	7	0-10000	1, 3, 5, 6, 7, 10, 13
LA	16	0-50000	1, 2, 3, 4, 5, 6, 7, 11, 13
MA	1	10-100	12
MD	1	0-1	1, 5
ME	7	0-1	1, 5, 6
MI	5	0-10000	1, 5, 6, 7, 11, 12, 13
MN	3	0-100	1, 5, 8, 12
MO	2	10-100	8, 10, 11
MS	2	0-1	1, 6
MT	1	0-1	1, 5
NC	4	0-1000	1, 5, 6, 11
NH	1	0-1	1, 5
NJ	4	0-1000	1, 5, 7, 8, 11
NY	3	0-100	1, 5, 6, 11, 13
OH	3	0-100	1, 6, 10, 11
OK	1	0-0	1, 5
OR	3	0-10	1, 6, 11
PA	7	0-1000	1, 5, 6, 11
PR	6	0-1000	11, 12, 13
SC	5	0-10	1, 5, 6, 8, 10
TN	2	0-1	1, 5, 6
TX	17	0-50000	1, 2, 4, 5, 6, 7, 9, 12, 13
VA	4	0-1000	1, 5, 11
VT	1	10-100	8
WA	7	0-10	1, 5, 6

Table 4-2. Facilities That Manufacture or Process Chloroform (continued)

State[a]	Number of facilities	Range of maximum *amounts on site* in thousands of pounds [b]	Activities and uses [c]
WI	11	0-100	1, 5, 6, 7, 11, 13
WV	3	10-10000	1, 4, 5, 9, 11, 13

Source: TRI93 1995

[a] Post office state abbreviations used
[b] Data in TRI are maximum amounts on site at each facility
[c] Activities/Uses:

1. *Produce*
2. Import
3. For on-site use/processing
4. For sale/distribution
5. As a by-product
6. As an impurity
7. As a reactant
8. *As a formulation component*
9. As a product component
10. For repackaging only
11. As a chemical processing aid
12. As a manufacturing aid
13. Ancillary or other uses

These import statistics suggest a slight decrease in chloroform imports from the late 1980s into the 1990s. Additional data would be needed to evaluate properly the drastic decrease in imports for 1994.

In 1985, 33.5 million pounds (15.2 million kg) of chloroform were exported (HSDB 1994); for 1988, exports of 40 million pounds (18.1 million kg) were estimated (CMR 1989). More recent export figures from the National Trade Data Bank (NTDB 1995) are:

U.S. Exports for Year	Quantity (kg)
1989	26,756,412
1990	21,897,011
1991	23,709,482
1992	20,133,535
1993	31,620,815
1994	42.320,259

These statistics suggest an overall increase in export levels from the mid-1980s through the mid-1990s.

4.3 USE

The major use for chloroform (CMR 1989) is in the manufacture of the refrigerant HCFC-22. Chloroform has been used in the past as a solvent or an extraction solvent for fats, oils, greases, resins, lacquers, rubber, alkaloids, gums, waxes, gutta-percha, penicillin, vitamins, flavors, floor polishes, and adhesives in artificial silk manufacture. It is also used as a dry cleaning spot remover, in fire extinguishers, as an intermediate in the manufacture of dyes and pesticides, and as a fumigant (Deshon 1979). Chloroform was previously used as an anesthetic, but it has been replaced by safer and more versatile materials (Deshon 1979). The U.S. Food and Drug Administration (FDA) banned chloroform use in drug, cosmetic, and food packaging products in 1976 (see Chapter 7). This ruling did not include drug products that contain chloroform in residual amounts resulting from its use as a processing solvent in manufacturing or its presence as a by-product from the synthesis of drug ingredients (IARC 1979). Chloroform can still apparently be used as a local anesthetic and solvent in certain dental endodontic (gutta-percha root canal) surgery procedures (McDonald and Vire 1992).

Topically applied aspirin-chloroform mixtures are also used to relieve pain from severe cases of herpes zoster (shingles) or posttherapeutic neuralgia (King 1993).

A recent summary of major domestic uses for chloroform noted the following percentage breakdowns typical of the early to mid-1990s (CMR 1995): use for manufacture of HCFC-22, 98% (refrigerants, 70%; fluoropolymers, 30%); other miscellaneous uses, including laboratory reagents and ‘extraction solvents for pharmaceuticals, 2%.

As discussed in Chapter 5, the most common chloroform exposure opportunities for members of the general population are related less to any commercially produced form of the chemical than to chloroform generated when organic materials come in contact with chlorinated oxidants (e.g., chlorine or hypochlorous acid) widely used to purify water or remove pathogens from waste materials.

4.4 DISPOSAL

According to the 1993 TRI, the amount of chloroform released to land is only a small fraction (less than 1%) of the total amount of chloroform released to the environment by facilities that produce and process the chemical (see Section 5.2.3) (TR193 1995). TRI also documents 2,386,285 pounds (1,073,828 kg) transferred to off-site waste handling sites in 1993, a level amounting to around 17% the total releases to environmental media and larger than any releases to environmental media other than air (TR193 1995). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Chloroform has been identified as a hazardous waste by EPA, and disposal of this waste is regulated under the Federal Resource Conservation and Recovery Act (RCRA) (EPA 1988a, 1989b). Specific information regarding federal regulations on chloroform disposal on land is available in the Code of Federal Regulations (EPA 1988a, 1989b). Ultimate disposal of chloroform, preferably mixed with another combustible fuel, can be accomplished by controlled incineration. Complete combustion must be ensured to prevent phosgene formation, and an acid scrubber should be used to remove the haloacids produced. Chloroform also is a potential candidate for liquid injection incineration. Because chloroform has been used in some pesticides, the disposal of containers for these pesticides may be relevant. Combustible containers from organic or many metallo-organic pesticides could be disposed of in pesticide incinerators or in specified landfill sites. Noncombustible containers could be disposed

of in a designated landfill or recycled (HSDB 1996). Except for the TRI statistics, no data were located regarding the approximate amounts of chloroform disposed or released to environmental media. Chapter 7 provides more details on federal or state regulations governing the disposal of chloroform.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chloroform is both a synthetic and naturally occurring compound, although anthropogenic sources are responsible for most of the chloroform in the environment. Chloroform is released into the environment as a result of its manufacture and use; its formation in the chlorination of drinking water, municipal and industrial waste water, and swimming pool and spa water; and from other water treatment processes involving chlorination. Under anaerobic conditions, some bacteria can dehalogenate carbon tetrachloride to release chloroform. Most of the chloroform released into the environment will eventually enter the atmosphere. In the atmosphere, chloroform may be transported long distances before ultimately being degraded by indirect photochemical reactions with such free radicals as hydroxyl. The compound has been detected in ambient air in locations that are remote from anthropogenic sources. Chemical hydrolysis is not a significant removal process. While microbial biodegradation can take place, such reactions are generally possible only at fairly low concentration levels due to chloroform's toxicity. Microbial biodegradation of chloroform may also be inhibited due to high levels of other aromatics (e.g., toluene), chlorinated hydrocarbons (e.g., trichloroethylene [TCE]), or heavy metals (e.g., zinc). Because of its low soil adsorption and slight, but significant, water solubility, chloroform will readily leach from soil into groundwater. In groundwater, chloroform is expected to persist for a long time.

The general population is exposed to chloroform by ingesting water and food, inhaling contaminated air, and possibly through dermal contact with chloroform-containing water. Generalizations can be made concerning the chloroform concentrations in the environment. Background air concentrations appear to be in the sub-ppb range, but certain urban, indoor, and source-dominated areas may show elevated concentrations when compared to background concentrations. Drinking water levels as high as 311 ppb have been reported in public water supplies, although most of the reported concentrations are less than 50 ppb, typically ranging between 2 and 44 ppb. Levels in drinking water derived from groundwater contaminated with leachate from landfills and hazardous waste sites can sometimes be much higher. Except for a few special surveys, regular testing for chloroform or other trihalomethanes (THMs) has focused on larger community water treatment systems serving at least 10,000 people. Very limited information was located regarding the concentrations found in ambient soil. Chloroform has also been detected in the ppb range in certain foods.

5. POTENTIAL FOR HUMAN EXPOSURE

Occupational exposure to higher than background levels of chloroform can be expected to occur in some occupations although few quantitative exposure data were located. Populations with the highest potential' exposures appear to be workers employed in or persons living near industries and facilities that manufacture or use chloroform; operators and individuals who live near municipal and industrial waste water treatment plants and incinerators, and paper and pulp plants; and persons who derive their drinking water from groundwater sources contaminated with leachate from hazardous waste sites.

Chloroform has been identified in at least 717 of 1,428 current or past EPA National Priorities List (NPL) sites (HazDat 1996). However, the number of sites evaluated for chloroform is not known. Figure 5-l shows the distribution of sites in the continental United States; there are 710 such sites. In addition, there are 6 sites in the Commonwealth of Puerto Rico and one site in the Virgin Islands (not shown in Figure 5-l).

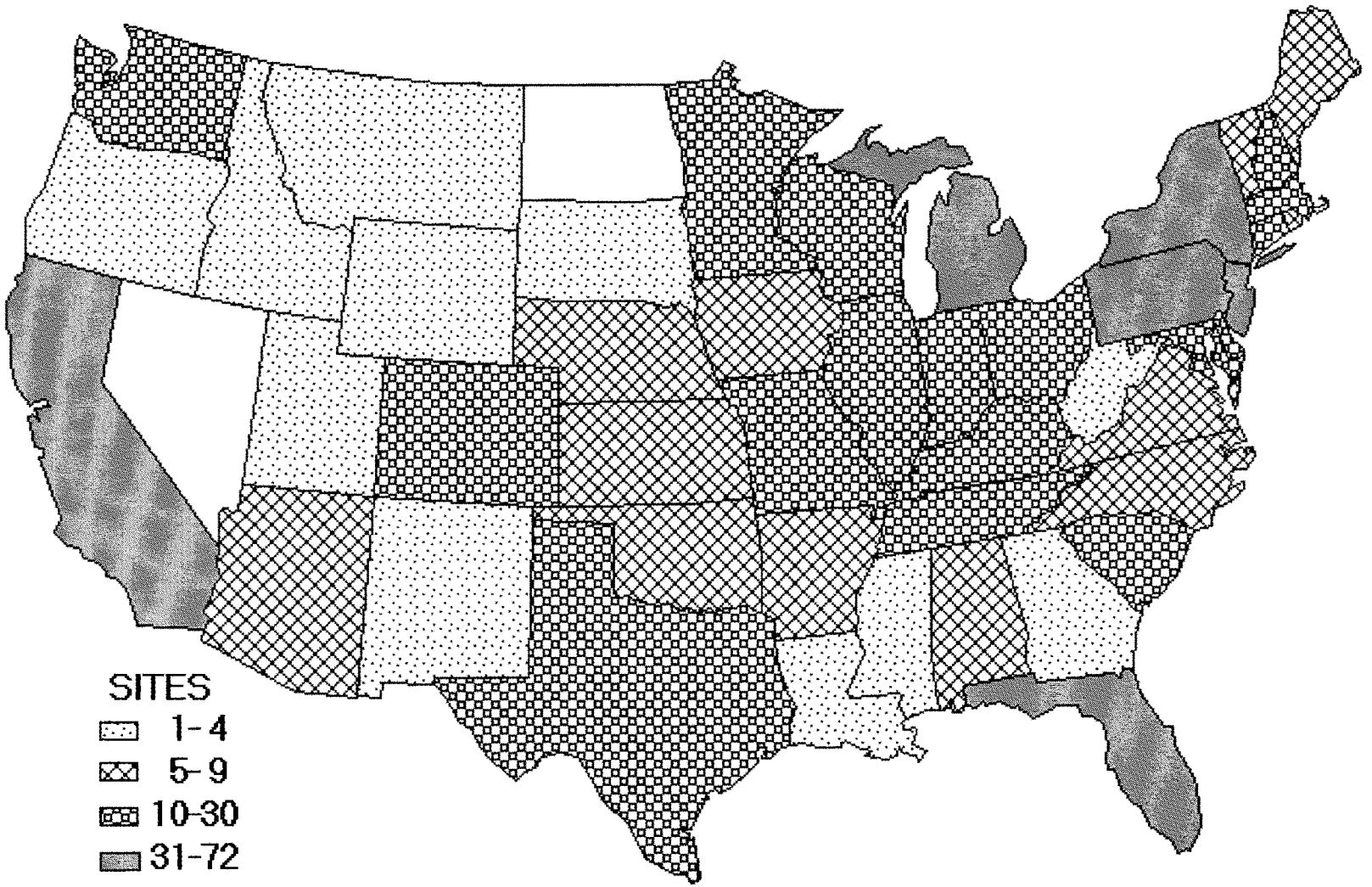
5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

According to the 1991 Toxic Chemical Release Inventory (TR191 1993), releases of chloroform to the air from 182 large processing facilities were 17,034,926 pounds (8,413,971 kg). This represented about 95% of the total releases to environmental media. For TRI information from 1993 (TR193 1995), 13,485,992 pounds (6,068,696.4 kg) were reported as released to the air from 172 facilities, which represents around 97.1% of the total releases to environmental media. Since there was a slight decrease in overall chloroform production in 1993 as compared with 1991 (CEN 1995), it is difficult to attribute this decrease in releases to the air to improved pollution prevention measures as opposed to short-term fluctuations related to production capacity utilization factors. The releases of chloroform to air from facilities that manufactured and processed it in the United States during 1993 are reported in Table 5-l (TR193 1995). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Current comprehensive quantitative data or estimates of chloroform releases to the atmosphere are lacking. Some direct releases to the atmosphere are expected to occur during the manufacture, loading, and transport of chloroform (EPA 1985a, 1985b). Indirect chloroform releases have resulted from its use in the manufacture of hydrochlorofluorocarbon-22, fluoropolymers, pharmaceuticals,

Figure 5-1. Frequency of NPL Sites with Chloroform Contamination



Derived from HazDat 1996

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Chloroform

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground injection	Total environment[c]	POTW transfer	Off-site waste transfer
AK	2	140697-240000	19000-40869	0	0	181566-259000	0	0
AL	12	250-620000	0-16000	0-2000	0	250-636000	0	0-132346
AR	6	1-229000	0-3600	0-5	0	1-229960	0	0-250
AZ	1	23000	0	22400	0	45400	0	0
CA	2	0-3150	0-3600	0	0	0-6750	0	0
CO	1	500	0	0	0	500	250	67000
CT	1	2250	14400	0	0	16650	0	242520
FL	7	62-235000	0-11100	0-3700	0	62-239120	0-53580	0-18500
GA	6	21199-329000	0-4500	0-750	0	21949-333273	0	0-130
ID	1	88000	750	5	0	88755	0	0
IL	2	108-2150	0	0	0	108-2150	0-500	12242-160130
IN	3	250-9700	0-30	0	0	250-9730	0	5-99000
KS	2	40000-44662	0	0	0-37950	40000-82612	0	781-7726
KY	7	0-150000	0-7200	0-5	0	0-157205	0-849	0-89630
LA	16	3-280000	0-16600	0-250	0-15	34-284950	0	0-72280
MA	1	17650	0	0	0	17650	0	975
MD	1	17000	0	0	0	17000	32000	0
ME	7	28933-441000	650-2200	0-130	0	30377-441756	0	0-370
MI	5	2475-55000	2-570	0-79	0	2500-55600	0-15000	0-596
MN	3	8400-140000	0-4000	0-7	0	12407-140000	0-18417	0-1600
MO	2	8750-105000	0	0	0	8750-105000	250-3400	32100-114500
MS	2	25510-292000	1269-15000	1-5	0	26780-307005	0	0
MT	1	49800	700	0	0	50500	0	0
NC	4	98000-730000	0-3200	0	0	98000-730650	0-5	0-730
NH	1	36953	79	18	0	37050	0	0
NJ	4	150-18200	0-439	0	0	150-18639	0-13350	0-44300
NY	3	10-11000	0-250	0	0	10-11250	0-12	250-28729
OH	3	406-22100	0-820	0	0	406-22920	0	0-4037

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Chloroform (continued)

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground injection	Total environment[c]	POTW transfer	Off-site waste transfer
OK	1	93200	700	550	0	94450	0	0
OR	3	1000-143800	0-3000	0	0	1000-146800	0-100000	250-16000
PA	7	10700-231000	0-2900	0-15	0	10700-232705	0-70000	0-55700
PR	6	0-92072	0	0	0	0-92072	0-161519	0-306374
SC	5	500-136540	0-5649	0	0	500-138440	0-5	0-500
TN	2	38000-47763	1900-7441	0-160	0	39900-55364	0	0-3
TX	17	5-600000	0-5350	0-900	0-74	5-600000	0-112000	0-377935
VA	4	55950-187000	31-2600	0-170	0	57979-187063	0	0
VT	1	4	0	0	0	4	0	168700
WA	7	5036-196000	0-15000	0-5	0	12275-200500	0	0
WI	11	1000-150000	0-4900	0-250	0	1000-152500	0-13	0-51000
WV	3	870-22276	0-654	0-200	0	870-23130	0-1	0-1328

Source: TRI93 1995

[a] Data in TRI are maximum amounts released by each facility.
[b] Post office state abbreviations used
[c] The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

POTW = publicly owned treatment works

ethylene dichloride, dyes, and fumigants (Deshon 1979; EPA 1985a, 1985b; HSDB 1996). Chloroform releases result from its formation and subsequent volatilization from chlorinated waters including drinking water, municipal and industrial waste waters, process waters and effluent from the bleaching of pulp in pulp and paper mills, cooling-tower water, and swimming-pool and whirlpool-spa water (Benoit and Jackson 1987; EPA 1985a, 1985b; Hoigne and Bader 1988). Increased release rates of the chloroform in waters can be expected from chloroform-containing waters that are heated (e.g., water used for cooking, showers, swimming pools, and spas). Aeration and use of groundwater contaminated with chloroform are a potential source of emission to the atmosphere (Crume et al. 1990). Chloroform is released as a result of hazardous and municipal waste treatment processes. The chloroform released may have initially been present in the waste or possibly formed during chlorination treatment (Corsi et al. 1987; EPA 1990b; Namkung and Rittmann 1987). Releases may also occur from hazardous waste sites and sanitary landfills where chloroform was disposed, and from municipal and hazardous waste incinerators that bum chloroform-containing wastes or produce chloroform during the combustion process (LaRegina et al. 1986; Travis et al. 1986).

In the past, minor releases may have resulted from the use of consumer products (e.g., certain air deodorizers and cleaning products) that contained chloroform as a component or residual product (Bayer et al. 1988; Wallace et al. 1987a). Chloroform is widely used in laboratory work as an extractant. It is also still used in certain medical procedures, such as dental root canal surgeries (McDonald and Vire 1992), and in combination with aspirin as an experimental treatment for serious cases of herpes zoster (King 1993). These medical uses are extremely limited and would contribute very minor amounts of chloroform as releases to the air.

5.2.2 Water

In 1991, releases of chloroform to the water from as many as 167 large processing facilities were 654,452 pounds (323,250 kg) (TR191 1993), amounting to about 3.6% of total releases to all environmental media. TRI information from 1993 (TR193 1995) indicates releases of chloroform to water from as many as 165 facilities were 335,032 pounds (150,764.4 kg) (TR193 1995), or about 2.4% of the total releases to all environmental media. The releases of chloroform to water from facilities that manufactured and processed it in the United States during 1993 are reported in Table 5-l (TR193 1995). The TRI data indicate that only a small fraction of the chloroform released to the

environment is released to water. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Current, more comprehensive quantitative data or estimates of chloroform releases to natural waters are lacking. Direct releases to water are expected via waste waters generated during chloroform manufacture and its use in the manufacture of other chemicals and materials (EPA 1985a). Direct discharge sources are expected to be relatively minor contributors to total chloroform emissions to water relative to the formation of chloroform resulting from the chlorination of drinking water or chlorination to eliminate pathogens in discharged wastes or other process waters (EPA 1985a). Since chlorination to disinfect water supplies is nearly universal, chloroform contamination resulting from chlorination will also be widespread (see discussion on levels monitored or estimated in water in Section 5.4.2).

Other chloroform emission sources tend to be relatively isolated point sources. Chlorination of municipal and industrial waste waters at municipal and industrial waste water-treatment plants, process waters and effluent from the bleaching of pulp in pulp and paper mills, cooling-tower water, and swimming-pool and whirlpool-spa water will also result in chloroform formation (Benoit and Jackson 1987; Comba et al. 1994; EPA 1985a, 1985b, 1990a; Hoigne and Bader 1988). The use of modern treatment facilities may reduce the amounts of chloroform released to environmental waters. This has been demonstrated at a modern kraft pulp mill (Paasivirta et al. 1988); however, much of the chloroform removed from the waste water may be released to the atmosphere by volatilization. Release of chloroform to groundwater has resulted from improper disposal of chloroform-containing waste at hazardous waste sites (Clark et al. 1982; Dewalle and Chian 1981; Harris et al. 1984; Sawhney 1989). An additional minor source of water contamination may be atmospheric rainout since chloroform has been found in rainwater (Kawamura and Kaplan 1983). Other sources of chloroform release to surface water include breweries, thermal combustion of plastics, reaction of dissolved chlorine with sediment and other materials in water, biological production by marine algae, and the reaction of chlorinated pollutants with humic materials in natural waters (EPA 1985a).

5.2.3 Soil

In 1991, releases of chloroform to the land from as many as 137 large processing facilities were 28,582 pounds (14,117 kg), which amounts to less than 1% of the total releases to all environmental

media (TR191 1993). TRI information from 1993 (TR193 1995) indicates releases to the land from as many as 124 facilities was 32,926 pounds (14,816.7 kg), which is less than 1% of the total releases to all environmental media. The releases of chloroform to soil from facilities that manufactured and processed it in the United States during 1993 are reported in Table 5-l (TR193 1995). The TRI data indicate that only a very small fraction of the chloroform released to the environment is released to land. The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Current comprehensive quantitative data or estimates of chloroform releases to soil are lacking. Chloroform releases to soil have occurred at hazardous waste sites containing improperly disposed wastes where chloroform has leached through soil to groundwater (Clark et al. 1982; Dewalle and Chian 1981; Harris et al. 1984; Sawhney 1989). Land disposal of sludge from municipal and industrial waste water-treatment plants may also result in chloroform releases to soil (EPA 1990a). Direct land disposal of chloroform-containing wastes may have occurred in the past, but land disposal of chloroform wastes is currently subject to restrictive regulations (EPA 1988a, 1989b). An additional minor source of soil contamination may be atmospheric rainout since chloroform has been found in rainwater (Kawamura and Kaplan 1983).

Chloroform has been used as a carrier or solvent for some pesticides (HSDB 1996). It is still used as a carrier for at least one pesticide formulation with dichlorvos as the active ingredient (Petrelli et al. 1993). Application of pesticides using chloroform in the carriers could have resulted in releases of chloroform to the land. It is impossible to quantify the magnitude of such releases, and the chloroform could be expected to be transported to either the atmosphere through volatilization or, if dissolved in water, carried into surface waters or groundwater.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Based upon a vapor pressure of 159 mm Hg at 20 °C, chloroform is expected to exist almost entirely in the vapor phase in the atmosphere (Boublik et al. 1984; Eisenreich et al. 1981). Large amounts of chloroform in the atmosphere may be removed by wet deposition since chloroform has significant solubility in water. This is confirmed by its detection in rainwater (Kawamura and Kaplan 1983).

5. POTENTIAL FOR HUMAN EXPOSURE

Most of the chloroform removed in precipitation, however, is likely to reenter the atmosphere by volatilization. Trace amounts of chloroform have been documented in air samples from remote, often relatively pristine, areas of the world (Class and Ballschmidter 1986). Since chloroform is relatively nonreactive in the atmosphere, long-range transport within the atmosphere is possible. The detections in remote areas may also mean that the chloroform is produced as the result of more localized transformation processes, possibly including the reaction of naturally generated chlorinated oxidants with organic matter.

The dominant fate process for chloroform in surface waters is volatilization. Chloroform present in surface water is expected to volatilize rapidly to the atmosphere. An experimental half-disappearance range of 18-25 minutes has been measured for volatilization of chloroform from a 1 ppm solution with a depth of 6.5 cm that was stirred with a shallow pitch propeller at 200 rpm at 25 ºC under still air (≈0.2 mph air currents) (Dilling 1977; Dilling et al. 1975). Using the Henry's law constant, a halflife of 3.5 hours was calculated for volatilization from a model river 1 meter deep flowing at 1 meter/second, with a wind velocity of 3 m/second, and neglecting adsorption to sediment (Lyman et al. 1982). A half-life of 44 hours was estimated for volatilization from a model pond using EXAMS (1988).

Based on a measured soil organic carbon sorption coefficient (K_{oc}) of 45 (or a log [K_{oc}]of 1.65), chloroform is not expected to adsorb significantly to sediment or suspended organic matter in surface water (Sabljic 1984). This prediction is supported by sediment monitoring data that indicate that this compound has not been detected (or was detected at very low concentrations) in sediment samples (Bean et al. 1985; Ferrario et al. 1985; Helz and Hsu 1978). Little or no chloroform concentration was observed on peat moss, clay, dolomite limestone, or sand added to water (Dilling et al. 1975). Chloroform slightly adsorbed to aquifer solids in laboratory studies utilizing different amounts of two different aquifer materials with K_{oc} values ranging from 63.4 to 398. The authors reported higher adsorption with increasing organic content of the solids (Uchrin and Mangels 1986). K_{oc} values ranging from 45 to 80 in soil have been experimentally determined for chloroform (Sabljic 1984; Wilson et al. 1981).

Chloroform does not appear to bioconcentrate in higher aquatic organisms, based upon measured bioconcentration factors (BCF) of 6 and 8 for bluegill sunfish *(Lepomis macrochirus)* (Barrows et al. 1980; Veith et al. 1980). Information from EPA's ASTER (1996) database document a calculated

BCF for the fathead minnow of 14, a low value suggesting little potential for bioconcentration in fish. A BCF of 690 experimentally determined for the bioconcentration of chloroform in the green algae *Selenastrum capricornutum* suggests that the compound has a moderate tendency to concentrate in nonvascular aquatic plants (Mailhot 1987). No data regarding the biomagnification potential of chloroform were found. Based upon the observed BCF, however, significant biomagnification of chloroform is apparently unlikely.

In soil, the dominant transport mechanism for chloroform near the surface will probably be volatilization because of its high volatility and low soil adsorption. Volatilization rates seem relatively constant over a wide variety of soil types (Park et al. 1988). In other laboratory studies, 75% of the chloroform initially present in water volatilized when applied to a fine sandy soil, and 54% of the chloroform volatilized from a soil column during a percolation study utilizing a sandy soil (Piwoni et al. 1986; Wilson et al. 1981). All or nearly all of the remaining chloroform traveled through the soil because of its low adsorption onto soil. Another laboratory study of 15 common volatile or semivolatile organic chemicals reported a disappearance half-life for chloroform of 4.1 days, which assumed first-order kinetic decay (Anderson et al. 1991). The leaching potential of chloroform is further confirmed by the detection of chloroform in groundwater, especially at hazardous waste sites (Clark et al. 1982; Dewalle and Chian 1981; Harris et al. 1984; Sawhney 1989).

5.3.2 Transformation and Degradation

For air, the major degradation process involves reactions with free radicals such as hydroxyl groups (Atkinson 1985). For other media, it is clear that chloroform can be mineralized through both abiotic and biotic processes. Information in the available literature (Bouer and McCarty 1983; Rhee and Speece 1992) documents the disappearance of chloroform in water and soil media under both aerobic and anaerobic conditions as well as identification of the end products.

5.3.2.1 Air

The vapor-phase reaction of chloroform with photochemically generated hydroxyl radicals is the dominant degradation process in the atmosphere. The rate constant for this process at 25 °C has been experimentally determined as 1.0×10^{-13} cm^3/molecule-second, which corresponds to a half-life of ≈80 days based upon a 12-hour sunlit day in a typical atmosphere containing 1×10^6 hydroxyl

radicals/cm^3 (Hampson 1980; Singh et al. 1981). Breakdown products from reaction with hydroxyl radicals probably include phosgene and hydrogen chloride (Atkinson 1985). Chloroform is more reactive in photochemical smog conditions where the approximate half-life is 11 days (Dimitriades and Joshi 1977). Direct photolysis of chloroform will not be a significant degradation process in the atmosphere. Chloroform solutions sealed in quartz tubes and exposed to sunlight for one year degraded at almost the same rate as solutions in sealed tubes stored in the dark, which indicated that very little or no photodegradation of the compound had occurred (Dilling et al. 1975). This is expected because chloroform does not show significant light absorbance at wavelengths >290 nm (Hubrich and Stuhl 1980).

5.3.2.2 Water

Hydrolysis will not be a significant degradation process in water based upon rate constants experimentally determined at 25 °C that correspond to half-lives ranging from 1,850 to 3,650 years at pH 7, and from 25 to 37 years at pH 9 (Jeffers et al. 1989; Mabey and Mill 1978). Direct photolysis of chloroform will not be a significant degradation process in surface waters because, as noted above, the compound does not absorb light at wavelengths >290 nm (Hubrich and Stuhl 1980). The reaction rate of chloroform with hydrated electrons photochemically produced from dissolved organic matter has been predicted to correspond to a near-surface half-life of ≈44 days based upon an experimentally determined rate constant and a hydrated electron concentration of $1.2x10^{-17}$ mol of hydrolyzed electrons/L (Zepp et al. 1987). This latter process is probably too slow to effectively compete with volatilization as a removal process from surface waters.

Biological degradation of chloroform has been studied primarily with an eye to batch process operation at waste water treatment plants or remediation possibilities at hazardous waste disposal sites. Above certain dosage levels, chloroform becomes toxic to anaerobic and aerobic microorganisms. This is especially noticeable for biological treatment facilities that use anaerobic digestion systems, where sustained inputs with chloroform concentrations approaching 100 mg/L can all but eliminate methanogenic (methane-fermenting) bacteria (Rhee and Speece 1992). Other studies have shown appreciable inhibition of methanogenesis with levels of chloroform in the range of 1 mg/L (Hickey et al. 1987). Other chlorinated hydrocarbons, and particularly such common 2-carbon chlorinated aliphatics as TCE, can similarly inhibit bacteria found in sewage sludges (Long et al. 1993; Rhee and Speece 1992). Similar inhibition effects can be the result of heavy metal toxics, zinc being

particularly stressful to methanogenic bacteria (van Beelen et al. 1994; van Vlaardingen and van Beelen 1992). Studies of actual natural waters or waste waters, where it is difficult to control the levels of specific chemicals or preclude inputs of other toxicants, yield a wide variety of results on the efficiencies of chloroform biodegradation. For instance, little or no degradation was observed during 25 weeks in aqueous aerobic screening tests utilizing primary sewage effluent inocula (Bouwer et al. 1981a). No chloroform degradation was observed in aerobic biofilm column studies (Bouwer et al. 1981b). Significant degradation of chloroform (46-49% loss in 7 days, at least some of which was apparently due to volatilization) in aerobic screening tests utilizing settled domestic waste water as inoculum was reported (Tabak et al. 1981). Under the proper conditions, chloroform appears to be much more susceptible to anaerobic biodegradation. Degradation of chloroform under anaerobic conditions was more rapid at lower chloroform concentrations (81 and 99% degradation after 2 and 16 weeks, respectively, at 16 ppb); a more gradual degradation was observed at higher concentrations and 78% degradation after 2 and 16 weeks, respectively, at 157 ppb) (Bouwer et al. 1981a). No degradation was observed, however, when chloroform was incubated with aquifer material under anaerobic conditions for 27 weeks (Wilson et al. 1981).

In the absence of toxicity from other solvents, chlorinated hydrocarbons, or heavy metals, and where chloroform concentrations can be held below approximately 100 ppb, both aerobic and anaerobic bacteria can biodegrade chloroform, with removal rates well over 80% in a period of 10 days (Long et al. 1993). Deviations from these ideal conditions can lead to lower removal efficiencies. These biodegradation reactions generally lead to the mineralization of the chloroform to chlorides and carbon dioxide (Bouwer and McCarty 1983; Rhee and Speece 1992). One study, however, documents the production of the toxicant methylene chloride (dichloromethane) from the breakdown of chloroformcontaining wastes in a mixed culture of bacteria from sewage sludge (Rhee and Speece 1992 citing results from work at Tyndall AFB, Florida). Caution should be exercised in making generalizations without site-specific evidence, however, since commercial grades of chloroform will often contain methylene chloride as an impurity (HSDB 1996). In waters containing mixtures of different chlorinated aliphatics, biodegradation may produce new chloroform, at least as a temporary by-product, the breakdown of carbon tetrachloride into chloroform having been confirmed in laboratory studies (ATSDR 1994; Long et al. 1993; Picardal et al. 1993).

5.3.2.3 Sediment and Soil

Little information was located regarding the degradation of chloroform in soil. Based upon data for degradation in water, chemical degradation in soil is not expected to be significant. The available soil data suggest that chloroform biodegradation rates in soil may vary, depending upon conditions. In soil column studies, the chloroform present in the influent secondary waste water appeared to pass through the column nearly unchanged even though some of the other organic compounds present were apparently biodegraded, which indicated that the waste water was not too toxic to the microorganisms in the soil (Bouwer et al. 1981b). In contrast to these studies, significant degradation of chloroform (33% removed in 6 days) was observed in fine sandy soil in sealed bottles; however, the chloroform may have been co-metabolized by methylotropic bacteria already present in the soil. The aerobic degradation was even faster in methane-enriched soil (Henson et al. 1988). Such bio-oxidation of chloroform was also observed under methanogenic conditions in batch experiments using an inoculum derived from activated sludge and in a continuous-flow laboratory scale column, using a methanogenic fixed film derived from primary sewage effluent (Bouwer and McCarty 1983). Overall, biodegradation in soil is not expected to compete with the predicted rapid rate of volatilization from soil (Park et al. 1988). As with biodegradation in water, concentrations of chloroform above certain threshold levels may inhibit many bacteria, especially methane-fermenting bacteria under anaerobic or near-anaerobic conditions (Hickey et al. 1987).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Data from the most recent study located (1982-85 air samples) reported that the background level of chloroform concentrations over the northern Atlantic ocean ranges from $2x10^{-5}$ to $5x10^{-5}$ ppm (Class and Ballschmidter 1986). This range does not differ significantly from the range reported for 1976-79 ($1.4\text{-}4x10^{-5}$ ppm) and the range reported from the 1987 update of the National Ambient Volatile Organic Compounds Database (NAVOCDB), which was $2x10^{-5}$ ppm (Brodzinsky and Singh 1982; EPA 1988b; Singh 1977; Singh et al. 1979). The maximum and background levels found in 7 U.S. cities between 1980 and 1981 were $5.1x10^{-3}$ and $2x10^{-5}$ ppm, respectively (Singh et al. 1982). Average atmospheric levels in U.S. cities ranged from $2x10^{-5}$ to $2x10^{-3}$ ppm between 1980 and 1981, The median concentration reported between 1977 and 1980 was $7.2x10^{-5}$ ppm, and the median

reported in the 1987 update of the NAVOCDB was $6x10^{-5}$ ppm (Brodzinsky and Singh 1982; EPA 1988b; Singh et al. 1981, 1982; Wallace et al. 1986a, 1986b, 1988). A recent update to EPA's volatile organic compounds (VOC) databases on background ambient air concentrations for hazardous air pollutants (Kelly et al. 1994) estimated a chloroform background ambient level for chloroform in the United States as $4x10^{-5}$ ppm.

The median concentration for source-dominated areas in the United States is $8.2x10^{-4}$ ppm for data reported between 1977 and 1980, and this figure does not differ significantly from the 5.1×10^{-4} ppm values reported in the 1987 update of the NAVOCDB (Brodzinsky and Singh 1982; EPA 1988b). Certain source-dominated areas contained much higher chloroform levels. The ambient air concentrations outside homes in Love Canal, New York, in 1978, ranged from $2x10^{-4}$ to $2.2x10^{-2}$ ppm, and the maximum concentration found in ambient air at 20 California municipal landfills was 0.61 ppm (Barkley et al. 1980; Wood and Porter 1987). Concentrations ranging from $2.9x10^{-4}$ to $6x10^{-3}$ ppm were found in air samples taken from 5 hazardous waste sites in New Jersey (LaRegina et al. 1986). Ambient air samples measured near a hazardous waste landfill contained $\leq 1x10^{-3}$ ppm chloroform. All these data indicate that chloroform levels in air can be much higher in areas near hazardous waste sites (Stephens et al. 1986). Other source-dominated areas that may have ambient air chloroform concentrations significantly higher than background levels include areas near facilities that treat hazardous and municipal waste, as well as areas near contaminated groundwater, and municipal- and hazardous-waste incinerators (Corsi et al. 1987; EPA 1990a; LaRegina et al. 1986; Namkung and Rittmann 1987; Travis et al. 1986).

Typical median indoor air concentrations of chloroform range from $\approx 2x10^{-4}$ to $4x10^{-3}$ ppm (Barkley et al. 1980; Pellizzari et al. 1986; Wallace et al. 1987c, 1989). Chloroform concentration ratios of indoor air to outdoor air range from <l to 25 (Pellizzari et al. 1986). One of the most significant indoor sources of chloroform is chlorinated tap water, and taking showers (and breathing air where chloroform has been released from the shower water) is expected to contribute a substantial amount to the indoor chloroform levels (Andelman 1985a, 1985b; Wallace 1987). A recent study investigating typical levels of various VOCs in the air in Canadian homes noted median chloroform concentrations of $4x10^{-4}$ ppm (Otson et al. 1994).

The air around swimming pools may also contain chloroform. This is especially likely in heated, indoor pools, which can approximate the conditions found in shower stalls. Concentrations ranging

from $3.5x10^{-2}$ to $19.9x10^{-2}$ ppm (440-2,335 nmol/m^3) have been reported for environmental air at an indoor swimming pool (Aggazzotti et al. 1990, 1993).

Chloroform has been identified in at least 717 of 1,428 current or past NPL sites (HazDat 1996). Chloroform has been detected in air samples taken at an estimated 57 of the 717 NPL hazardous waste sites where chloroform was detected.

5.4.2 Water

Recent monitoring data regarding the presence of chloroform in surface water, sediments, and groundwater were not located. The most recent monitoring data that were obtained involved chloroform levels in drinking water. Finished drinking water collected in 1988 from 3.5 sites across the United States contained median concentrations of chloroform ranging from 9.6 to 15 μg/L (Krasner et al. 1989). In an analysis of available monitoring data from raw water supplies, the maximum detected value was 136 ppb (EPA/AMWA 1989). Data from earlier studies indicate a wide range of concentrations have been found in drinking-water supplies. The reported chloroform concentrations that were detected ranged from trace levels to 311 ppb, with one study reporting a median concentration of 16.7 ppb and another study reporting a geometric mean concentration of 1.81 ppb. Most of the concentrations ranged between 22 and 68 ppb (Brass et al. 1977; EPA/AMWA 1989; Furlong and D'Itri 1986; Kasso and Wells 1981; Krasner et al. 1989; Rogers et al. 1987; Symons et al. 1975). Chloroform can be expected to exist in virtually all chlorinated drinking-water supplies. The main source of chloroform found in municipal drinking water is the chlorination of naturally occurring humic materials found in raw-water supplies (Bellar et al. 1974; Cech et al. 1982). Factors that can increase the amount of chloroform in drinking water include seasonal effects (high summer values) and increased contact time between chlorine and humic material. Sources of water with high humic material content will contain higher levels of chloroform, The chloroform concentration increases with time, indicating that concentrations of the compound increase as the water moves through the distribution system (Kasso and Wells 1981). Drinking water derived from groundwater, especially groundwater at or near some hazardous waste sites and landfills, may contain higher levels of chloroform than normally encountered in drinking water derived from surface water. Chloroform levels ranging from 2.1 to 1,890 ppb have been observed in drinking water derived from wells near a hazardous waste dump (Clark et al. 1982). The leachate from one solid waste landfill contained 21,800 ppb chloroform; drinking water obtained from wells in the vicinity of the landfill had

chloroform levels of 0.3-1.6 ppb (Dewalle and Chian 1981). Data from the most recent study of Kansas groundwater sampled in 1986 indicate concentrations ranging from ≈0.3 to 91 ppb in both raw and treated groundwater; the average and median concentrations in the treated water were 7.6 and 0.5 ppb, respectively (Miller et al. 1990). Of the sample sites in a national groundwater supply survey, 45% had detectable levels of chloroform, and median and maximum concentrations were 1.5 and 300 ppb, respectively (Westrick et al. 1989).

In addition to drinking water, chlorinated oxidants reacting with organic materials will lead to the formation of chloroform in swimming pools. Since swimming pools are not routinely analyzed for their chloroform content, data are limited and derived from special studies. Such studies will often cover the broader family of THMs, and while chloroform levels in blood or alveolar air samples will be reported, the environmental agents will often simply be recorded in terms of TI-IMs. A rule of thumb (Copaken 1990) is that up to 90% of the THMs in chlorinated water samples will be chloroform. Recorded concentrations in samples from public pools fall in a range of 25-137 ppb (Aiking et al. 1994; Barnes et al. 1989; Copaken 1990). In poorly tended or very crowded public or private pools, where there are large inputs of organic materials or heavy use of chlorinating agents, chloroform levels as high as 163 ppb have been documented (Barnes et al. 1989). Chloroform production in swimming pools can be increased where the pools are treated with copper-containing algicides. In tests on chlorinated water using various doses of chlorine, copper (cupric valence form) from different copper-containing salts, and varying levels of humic acid (Barnes et al. 1989), chloroform concentrations after a given reaction time were generally 50% or more higher in samples treated with copper, which acts as a catalyst in the reactions with the humic acids.

Current reviews of surface water monitoring data in the peer reviewed literature are lacking. The highest concentrations observed in surface waters of the United States sampled before 1984 were 394 and 120 ppb. These concentrations were observed in rivers in highly industrialized cities (Ewing et al. 1977; Pellizzari et al. 1979). Typical concentrations for most sites that are not heavily industrialized appear to range from trace levels to ≈22 ppb (Ohio River Valley Sanitation Commission 1980, 1982). Data from EPA’s STORET database indicate that chloroform was detected in 64% of 11,928 surface water sample data points at a median concentration of 0.30 ppb (Staples et al. 1985).

Chloroform at 0.25 ppb has been found in rainwater collected in Los Angeles, California, during 1982 (Kawamura and Kaplan 1983).

5. POTENTIAL FOR HUMAN EXPOSURE

Chloroform has been detected in surface-water samples taken at an estimated 139 of 717 current or past NPL sites where chloroform was detected (HazDat 1996). Detections in groundwater are documented at 552 sites. From the available information found in HazDat (1996), groundwater appears to be the most common environmental medium at NPL sites where chloroform might be encountered.

5.4.3 Sediment and Soil

Chloroform has been found in sediment samples. Chloroform was found in sediment samples taken in 1980 from the 3 passes of Lake Pontchartrain, Louisiana, at concentrations ranging from 1.7 to 18 ng/kg (w/w [weight per weight] basis) (Ferrario et al. 1985). Chloroform was found at concentrations ranging from 30 to 80 ng/kg (dry weight basis) in sediment samples exposed to chlorinated electrical power plant cooling water; the control samples that were not exposed to cooling water contained nearly the same amounts of chloroform (Bean et al. 1985). Data from EPA's STORET database indicate that chloroform was detected in 8% of 425 sediment sample data points at a median concentration of <5.0 μg/kg (Staples et al. 1985).

Routine sediment sampling for chloroform does not seem common in the United States, and sampling at relatively unpolluted ambient monitoring sites may overlook the levels possible in more restricted hotspots. Anaerobic biodegradation of chlorinated hydrocarbons may generate chloroform, especially in harbors, shipping canals, or areas receiving large amounts of industrial discharges. Where the sediments contain large concentrations of zinc, which is widely used to galvanize metal or as an ingredient in common industrial rust inhibitors, methanogenic bacteria populations may be adversely affected, thus preventing the mineralization of chloroform. Chloroform in interstitial water may then build up to levels as high as 50 ppb (van Beelen et al. 1994; van Vlaardingen and van Beelen 1992).

Soil monitoring data in the peer reviewed literature could not be located. It can be predicted that chloroform contamination occurs at hazardous waste sites where chloroform-containing leachate moves through the soil to groundwater. An explanation of the lack of data results from the fact that any chloroform in the soil is expected to either rapidly volatilize or leach. Laboratory studies using a variety of different soil types document the effectiveness of volatilization in removing chloroform from soils (Park et al. 1988).

5. POTENTIAL FOR HUMAN EXPOSURE

Chloroform has been found in soil samples taken at an estimated 213 of the 717 current or past NPL where chloroform was detected (HazDat 1996). Detections in sediment samples are documented for 79 current or past NPL sites. Detections on soil gas obtained from soil samples were documented at 18 sites.

5.4.4 Other Environmental Media

Chloroform has been detected in various foods at the following concentrations: soft drinks and beverages (2.7-178 μg/kg), dairy products (7-1,110 μg/kg), oils and fats (traces <12 μg/kg), dried legumes (6.1-57.2 μg/kg), and grains and milled grain products (1.4-3,000 μg/kg) (Abdel-Rahman 1982; Entz et al. 1982; Graham and Robertson 1988; Heikes 1987; Heikes and Hopper 1986; Lovegren et al. 1979). In a study of various foods, 41% of 231 samples contained chloroform at levels ranging from 4 to 312 μg/kg; the average level was 52 μg/kg (Daft 1988a). In another broad study, 55% of 549 samples contained between 2 and 830 μg/kg. The average level in this study was 71 μg/kg (Daft 1989). The chloroform concentration observed in other foods ranged from 6.1 to 1,110 μg/kg. The highest amounts were found in butter (1,110 μg/kg), mixed cereal (220μg/kg), infant/junior food (230 μg/kg), and cheddar cheese (83 μg/kg) (Heikes 1987).

Chloroform has been detected in the air above outdoor and indoor pools and in spas at maximum concentrations of $2.8x10^{-2}$, $5.0x10^{-2}$, and $5.2x10^{-2}$ ppm, respectively; water concentrations ranged between 4 and 402, 3 and 580, and <0.1 and 530 ppb, respectively (Armstrong and Golden 1986). In another study, air samples above whirlpool spas treated with chlorine disinfectant contained chlorofom at concentrations ranging from $8x10^{-4}$ to $1.5x10^{-l}$ ppm; the concentration in the water ranged from 15 to 674 ppb (Benoit and Jackson 1987). Chloroform has been detected at ≤37 ppb in the cooling water of a nuclear reactor; a concentration of 50 ppb was detected 0.75 miles downstream from the reactor cooling tower in one study (Hollod and Wilde 1982).

Since chloroform is highly volatile and shows little tendency to bioconcentrate or bioaccumulate in higher life forms such as fishes, it is not ordinarily included in the types of persistent pollutants that are the focus of state fish consumption advisory programs. Information from HazDat (1996) does document detections of chloroform in tissues from fishes from at least 3 current or past NPL sites.

5. POTENTIAL FOR HUMAN EXPOSURE

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is probably exposed to chloroform through drinking water and beverages, eating food, inhaling contaminated air, and through dermal contact with water (e.g., while showering, bathing, cleaning, washing, swimming). All humans are expected to be exposed to at least low levels of chloroform. Accurate, current estimates of the daily intake of chloroform by various exposure routes are not available, or possible, due to the lack of appropriate current monitoring data. Typical levels of atmospheric exposure in remote, urban, and source-dominated areas range from $2x10^{-5}$ to $5x10^{-5}$, $6x10^{-5}$ to $2x10^{-3}$, and $8.2x10^{-4}$ to $2.2x10^{-2}$ ppm, respectively (Barkley et al. 1980; Brodzinsky and Singh 1982; Class and Ballschmidter 1986; EPA 1988a; Singh et al. 1981, 1982; Wallace et al. 1986a, 1986b, 1988; Wood and Porter 1987). Exposure via ingestion of contaminated drinking water is expected to be extensive since most U.S. community drinking-water supplies are chlorinated (see Singer 1994 for an overview of the entire topic of disinfection by-products in drinking water). Typical levels in drinking water range from 2 to 68 ppb (Brass et al. 1977; EPA/AMWA 1989; Furlong and D'Itri 1986; Kasso and Wells 1981; Krasner et al. 1989; Rogers et al. 1987; Symons et al. 1975). Although data regarding levels in food are rather scant, typical average chloroform levels in certain foods are estimated to range from 52 to 71 μg/kg (Daft 1988a, 1988b, 1989).

Although data are available from various studies regarding concentrations of chloroform found in human tissues, blood, and expired air, only limited data are available that compare these concentrations to measured or estimated environmental exposure levels. Furthermore, no correlation has been made between these measured human tissue concentrations and the corresponding environmental exposure levels (see Section 2.5.1 for a discussion of the relationship between chloroform exposure levels and concentrations found in humans). Much of the data available is from the Total Exposure Assessment Methodology (TEAM) studies (see Andelman 1990 or Wallace 1995 for succinct overviews) in which the concentration of chloroform was measured in personal air samples and exhaled human breath (Wallace 1987; Wallace et al. 1984, 1986a, 1986b, 1988). For example, in one TEAM study, the ratios of the concentrations of chloroform detected in personal air samples to those found in human exhaled breath air varied from 0.66:1 to 13.3:1 (Wallace 1987) (see Section 2.5.1 for more data regarding concentrations found in humans, including data obtained during autopsies). Recent studies supported through IARC on swimmers using indoor pools in Europe showed good correlations between the chloroform concentrations in alveolar air and blood plasma concentrations (Aggazzotti et al. 1990, 1993). Plasma levels ranging from 0.8 to 25.1 nmol/L were observed. Statistical analysis

showed the plasma levels to be significantly correlated with concentrations of chloroform in the pool water, time spent swimming, the number of swimmers in the pool, and the chloroform concentration in the environmental air.

Limited current data were located regarding occupational exposure to chloroform. Although some of the exposure levels encountered in workplaces may be comparable to exposure the worker receives in his own home, there are probably many specific jobs that expose the workers to significantly higher levels of chloroform. These occupations include work at or near source-dominated areas such as chemical plants and other facilities that manufacture or use chloroform, operation of chlorination processes in drinking-water plants, work at or near waste water-treatment plants and paper and pulp plants, and other facilities where large amounts of chloroform are released (e.g., hazardous and municipal-waste incinerators). Persons working at waste water and other treatment plants can be exposed to significant levels of chloroform. A maximum level of $3.8x10^{-3}$ ppm was found in the air at an activated sludge waste-water treatment plant (Lurker et al. 1983). Maintenance workers, attendants, and life guards at indoor pools and spas may encounter maximum concentrations of $5.0x10^{-2}$ and $1.5x10^{-1}$ ppm, respectively (Armstrong and Golden 1986; Benoit and Jackson 1987). Persons who use tap water often, especially if it is heated and/or sprayed (e.g., water used for cleaning, washing clothes and dishes, showering, and cooking), may be exposed to higher than background levels. For example, levels in personal air samples as high as $2.2x10^{-2}$ and $1.1x10^{-2}$ ppm have been measured during household cleaning activities and showering (Wallace et al. 1987d). While the use of activated carbon filters may provide some reduction in the tap water levels for cold water feeds, such filters are not effective with hot water where the elevated temperatures will induce volatilization from the filter media. Persons using certain cleaning agents and pesticides in enclosed spaces with poor ventilation or persons working where these materials are used may be exposed to relatively high levels of chloroform.

A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 95,778 workers in the United States are potentially exposed to chloroform (NOES 1991). In the absence of more recent national occupational exposure data, the NOES information still has some value. The NOES database does not contain information on the frequency, concentration, or exposure duration of workers; it only provides estimates of the number of workers potentially exposed to chemicals in the workplace. Of the 151 different occupational groups with potential chloroform exposure risks listed in the NOES database, approximately 50% of the potentially exposed workers fall

into the following Standard Industrial Classification (SIC) categories: Funeral Service and Crematory Technicians from SIC category 7261; Biological, Engineering or Chemical Technicians and Chemists from the Research and Development Laboratory SIC category 7391; Adhesive and Sealant Chemical Technicians from SIC category 2891; Assemblers from SIC category 3679 (Electronic Components) and SIC Category 3622 (Industrial Controls); Petroleum Refining Machine Operators and other Workers from SIC category 2911; and General Medical and Surgical Hospital Clinical Laboratory Technologists and Technicians from SIC category 8062.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

All humans are exposed to low concentrations of chloroform. Those with potentially high exposures are workers employed in chloroform manufacturing and use industries. Persons living in certain source-dominated areas may be at risk for higher than background exposures to chloroform. These may include persons living near industries and facilities that manufacture and use chloroform, municipal and industrial waste water-treatment plants and incinerators, paper and pulp plants, and persons who derive their drinking water from groundwater sources contaminated with chloroformcontaining leachate from hazardous waste sites.

Previously reported air monitoring data from landfills and other waste sites (see Section 5.4.1) suggest that potentially high exposure may occur via inhalation of contaminated air near hazardous waste sites. Other possibilities include drinking water from wells contaminated with chloroform that leached from the sites and, perhaps, living in homes built directly on top of former waste sites. Although some of the drinking-water supplies contaminated solely by leached chloroform (e.g., levels ≤1.6 ppb from a water well near a site with documented chloroform contamination) (Dewalle and Chian 1981) have shown levels lower or comparable to that in normal chlorinated drinking water, where chloroform levels in the range of 2-44 ppb are common (EPA/AMWA 1989), much higher levels (1,890 ppb) have been found in water from wells near a waste dump (Clark et al. 1982). HazDat (1996) documents 239 current or past NPL sites where specific concentration levels for groundwater are contained in the database. At least 97 current or past NPL sites show groundwater samples where values are 100 ppb or higher. A drinking-water standard of 100 ppb for total trihalomethanes (TTHMs) (where chloroform is usually the predominant constituent) is EPA’s current requirement for treated water systems serving 10,000 or more consumers (see Chapter 7 below).

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5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chloroform is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chloroform.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. As reported in Table 3-2, the physical and chemical properties of chloroform have been characterized sufficiently to permit estimation of its environmental fate.

Production, Import/Export, Use, Release, and Disposal. Data regarding the production methods and current, past, projected future production capacity volumes, and current import and export volumes are available (Ahlstrom and Steele 1979; CEN 1995; Deshon 1979; NTDB 1994; SRI 1993, 1994; TR192 1994). However, these statistics will generally not include all instances where chloroform is generated as a chemical intermediate or waste product. With the exception of the partial coverage provided in the Toxics Release Inventory (TR191 1993; TR193 1995) comprehensive information regarding current release and disposal patterns, are lacking. General disposal information is adequately detailed in the literature, and information regarding disposal regulations of chloroform is available (EPA 1988a, 1988b). Production, release, and disposal data are useful to determine where environmental exposure to chloroform may be high. A major data need is to achieve a better understanding of why a substantial number of NPL sites show chloroform levels in groundwater at or above concentrations of 100 ppb. There are 239 sites in HazDat (1996) where groundwater

concentration levels are documented. At least 36 sites show signs of groundwater contamination with levels of 1,000 ppb (or 1 ppm) or higher, levels high enough to suggest disposal or spills of wastes containing very high concentrations of chloroform. Sixty-one (61) sites show groundwater levels in a range from 100 to 1,000 ppb, and the remaining 142 sites show levels below 100 ppb. While some sites show very low levels comparable to the concentrations associated with many chlorinated public drinking-water supplies, the substantial number of sites with values at or slightly above the community drinking-water standard for TTHMs of 100 ppb deserves some scrutiny. Is the chloroform at such sites the result of past disposal of chloroform-laden wastes, or are some other sources (e.g., *in situ* generation of chloroform as the result of chemical or biochemical transformation of other on-site wastes) for the chloroform contamination involved? Present data sources are lacking to explain adequately the large number of NPL sites showing elevated levels of chloroform in such media as groundwater that pose major off-site exposure risks.

Environmental Fate. Experimental data are available regarding the transport and partitioning properties of chloroform in surface waters (Bean et al. 1985; Clark et al. 1982; Class and Ballschmidter 1986; Dilling 1977; Ferrario et al. 1985; Piwoni et al. 1986; Sawhney 1989). Chloroform partitions mainly into the atmosphere and into groundwater. Empirical measurements or model predictions on half-disappearance times in such media as soil could not be identified in the literature. Chloroform can be transported long distances in air. Data are available regarding the degradation of chloroform in the atmosphere, but less is known about degradation rates in water and soil (Anderson et al. 1991; Bouwer et al. 1981a, 1981b; Dilling et al. 1975; Hampson 1980; Henson et al. 1988; Jeffers et al. 1989; Park et al. 1988; Singh et al. 1981; Tabak et al. 1981; Wilson et al. 1981). Hydrolysis and direct photodegradation are not significant removal processes. Although data regarding biodegradation rates in natural media are lacking, volatilization is expected to dominate over biodegradation as a removal process from surface water and near-surface soil. Chloroform seems relatively persistent in the atmosphere and groundwater. The environmental fate of chloroform releases related to most common anthropogenic sources appears to be sufficiently determined by the available data. In light of the documented occurrence (Class and Ballschmidter 1986) of chloroform in remote, often pristine, areas, however, further study is warranted to help quantify the relative role of long-range transport processes as opposed to a variety of more localized potential chemical transformation processes. These more localized processes could include the reaction of naturally generated chlorinated oxidants with organic materials to yield chloroform. More data would be useful on the half-lives of chloroform in such media as soils.

5. POTENTIAL FOR HUMAN EXPOSURE

Bioavailability from Environmental Media. Chloroform is absorbed following inhalation, oral, and dermal contact. Toxicity studies of exposure to chloroform in air, water, and food demonstrated the bioavailability of chloroform by these routes. Data regarding its bioavailability from soil are lacking, but near-surface soil concentrations can be expected to be low due to volatilization (Piwoni et al. 1986; Wilson et al. 1981).

Food Chain Bioaccumulation. Data are available that indicate that chloroform does not bioconcentrate in aquatic organisms (Barrows et al. 1980; Veith et al. 1980); however, data are lacking for plants and other animals (e.g., vacuolar plants, shellfish, or macroinvertebrates) as well as for the biomagnification potential of chloroform in terrestrial and aquatic food chains. Additional information on bioconcentration and biomagnification could be useful in establishing the significance of food chain bioaccumulation as a route of human exposure.

Exposure Levels in Environmental Media. All humans are exposed to at least low levels of chloroform via inhalation of contaminated air, and most humans are exposed by drinking contaminated water. Estimates from intake via inhalation and ingestion of drinking water, based on limited data, are available (see Section 5.5). Exposure from foods cannot be estimated, due to the lack of data. Current information on exposure to chloroform from water, air, and foods, especially for workers or people who live near manufacturing and use facilities, water and waste water-treatment plants, municipal and industrial incinerators, hazardous waste sites, and other sources of significant release, in addition to data regarding exposure levels in indoor air would be useful.

Exposure Levels in Humans. Data regarding exposure levels in humans are incomplete and are usually the result of limited, special studies. Chloroform has been found in human blood and expired air of both occupationally and nonoccupationally exposed groups, and in breast milk of nonoccupationally exposed groups (Hajimiragha et al. 1986; Pellizzati et al. 1982; Wallace et al. 1987a). A detailed recent database of exposure would be helpful in determining the current exposure levels, thus allowing an estimation of the average daily dose associated with various scenarios, such as living near a point source of release, drinking contaminated water, or working in a contaminated place. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for chloroform were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure

Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 Ongoing Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environment Health Laboratory Sciences Division of the National Center for Environment Health, Centers for Disease Control and Prevention, will be analyzing human urine samples for chloroform (Needham et al. 1990). These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

Research at Colorado State University (FEDRIP 1994) will investigate toxicity and bioaccumulation potential of chloroform and other organic and inorganic chemicals. The laboratory studies will use a simple food chain containing larval invertebrates and fish. The results would be applicable to many natural systems with fish foraging on insect larvae in contaminated sediments.

Another research project at Colorado State University (FEDRIP 1994) will study the microbial degradation kinetics of pollutant mixtures, which will include chloroform. One aspect of this research will focus on both the degradation of chloroform as well as its inhibitory effects when present above certain threshold concentrations.

A project at the University of Arizona (FEDRIP 1996) will study microbial dehalogenation of several compounds, including chloroform. A major part of the study will focus on the facultative anaerobic bacteria *Shewanellu putrefaciens* sp., which is known to catalyze the transformation of carbon tetrachloride to chloroform and other as yet unidentified products. The organic substrates will also contain metals. It is hoped that the end-products from the biochemical treatment can be subjected to a photolytic finishing process that will completely mineralize any remaining halogenated compounds.

A project at the University of Idaho (FEDRIP 1996) will study the biodegradation of several halogenated hydrocarbons in soils amended with plant residues from various Brussicu cultivars (e.g., rape seed). These residues contain chemicals that may help catalyze the degradation of some

chlorinated hydrocarbons. Work to date has shown the potential for phrophyrins metallated with cobalt or nickel to cause the breakdown of carbon tetrachloride into such products as chloroform, dichlormethane, and carbon monoxide.

A project at the University of California at Berkeley (FEDRIP 1996) will study factors affecting the rates of degradation for several chlorinated hydrocarbons by soil microbial populations. Chloroform will be included as one of the organic chemicals studied.

A project conducted by the USDA (FEDRIP 1996) at its Western Regional Research Center in Albany, California, will study the use of ozone or peroxide treatment as an alternative to chlorinated bleaching in the preparation of walnuts intended for in-the-shell sales. There are concerns that the current use of hypochlorite bleaching agents can adversely impact taste as well as leaving behind THM residues containing chloroform.

A project at the University of California at Riverside (FEDRIP 1996) will study factors affecting the biodegradation in soils of several pesticides and halogenated organics by such microbes as *Methanobacterium thermoautotrophicum.* This anaerobic bacterium shows the potential for very rapid oxidation of several organics, including chloroform. In practice, however, one or more limiting factors dramatically reduces the expected degradation kinetics.

A project at the USDA's Western Research Center in Albany, California, will study ways to reduce exposures to chloroform for workers at poultry processing plants (FEDRIP 1994). At various points in the processing of poultry, the carcasses are rinsed in chiller-water baths that kill pathogens. Currently, chlorine is the only USDA-approved sanitizing agent. This study will investigate the potential of such alternative agents as chlorine dioxide to achieve comparable germicidal effects while reducing the levels of chloroform generated.

The United States Geological Survey (FEDRIP 1996) is conducting a study on the Mississippi River and its major tributaries focused on the transport and degradation of organic substances. Experiments will be conducted at 12 stations to determine the THM and organic halide formation potentials. The results will be summarized in a chapter on water purification by-products in a Report to Congress on the Mississippi River.

5. POTENTIAL FOR HUMAN EXPOSURE

Remedial investigations and feasibility studies at NPL sites that contain chloroform will also provide further information on environmental concentrations and human exposure levels near waste sites.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring chloroform in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify chloroform. Rather, the intention is to identify well established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect chloroform in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Methods for analyzing chloroform in the biological matrices (breath, blood, urine, and tissues) are listed in Table 6-l. None of these methods has been standardized by an organization or federal agency, although the blood method of Ashley et al. (1992) was developed at the Centers for Disease Control and Prevention (CDC). Sample preparation methods are based on headspace analysis, purgeand-trap, or solvent extraction. Sample preparation for breath samples typically utilizes an adsorbent followed by thermal desorption or direct analysis of an aliquot of breath. These methods all use gas chromatography (GC) with various detection methods as an analytical technique. Cardinali et al. (1994) describe a procedure for the production of blank water for use with analysis of organic compounds in human blood at the parts per trillion (ppt) level; the availability of such blank samples is very important if reliable results are to be obtained. With limits of detection (LODs) in the low-ppt range, these methods are sufficiently sensitive to measure background levels of chloroform in the general population as well as chloroform levels at which health effects might occur after short-term or long-term exposure. However, many studies do not report the method detection limit and/or the recovery percentage for the method. For more information regarding the use of GC methods and detectors, see Section 6.2.

Table 6-1. Analytical Methods for Determining Chloroform in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Exhaled air (breath)	Collection in Tedlar bag; preconcentration by Tenax-GC; thermal desorption	HRGC/FID and HRGC/MS	No data	No data	Krotoszynski et al. 1979
Alveolar air	Collection of exhaled air using a specially-designed device to provide pure air for inhalation. Breath collected into duplicate evacuated canisters.	GC/MS	0.5 μg/m^3 (0.5 ppt, w/v)	112 (8% RSD) at 5.1 μg/m^3	Raymer et al. 1990
Alveolar air	Collection directly into an evacuated canister	GC/MS	No data	No data	Pleil and Lindstrom 1995
Exhaled air	Collection of whole breath into a sampling bag; collected sample pulled through a Tenax cartridge	GC/Electrolytic conductivity	13 ng on cartridge	63 ± 13	Jo et al. 1990
Alveolar air	Collection onto carbonaceous sorbent; thermal desorption	GC/ITMS	No data	No data	Phillips and Greenberg 1992
Alveolar air	Collection of end-expired air into glass tube	GC/ECD, GC/MS	8.4 nmol/m^3 (1 μg/m^3; 1 ppt, w/v)	No data	Aggazzotti et al. 1993
Whole blood	Purge-and-trap pre-concentration (with isotopically-labelled internal standard)	GC/Isotope dilution MS	0.040 ppb	105 at 0.054 ppb	Ashley et al. 1992
Whole blood	Headspace analysis	GC/FID	0.02 μg/mL (0.02 ppm, w/v)	No data	Seto et al. 1993
Whole blood	Purge-and-trap preconcentration; thermal desorption	GC/MS	<0.5 μg/L	No data	Antoine et al. 1986
Adipose tissue and serum	Purge-and-trap pre-concentration; thermal desorption	GC/Hall with GC/MS confirmation	No data	100 at 0.6 μg/L (serum); No data (tissue)	Peoples et al. 1979

Table 6-1. Analytical Methods for Determining Chloroform in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Whole blood	Solvent extraction	HRGC/ECD with HRGC/MS confirmation	No data	99 at 50 µg/L	Kroneld 1986
Serum and adipose tissue	Purge-and-trap pre-concentration; thermal desorption	GC/Hall with GC/MS confirmation	0.05 µg/L for serum	No data	Pfaffenberger et al. 1980
Water, serum, and urine	Solvent extraction	HRGC/ECD	1 µg/L for serum and urine	100.3 at 50 µg/L (water); 103 at 2.5 µg/L (serum); 141 at 2.3 µg/L (urine)	Reunanen and Kroneld 1982
Blood, urine	Blood collected into vacutainers containing EDTA. Two-mL aliquots of blood or urine dispensed into headspace vials for analysis	Headspace GC/ECD	No data	No data	Cammann and Hübner 1995
Blood, urine, and tissues	Addition of sample to internal standard; addition of proteolytic enzyme; equilibration at elevated temperature; analysis of headspace gas	GC/ECD	At least 1 ppm	No data	Streete et al. 1992
Blood, urine, and tissue	Purge-and-trap pre-concentration; thermal desorption	GC/HSD or GC/MS	0.10 µg/L (blood and urine)	No data	*EPA 1985a*

ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; Hall = Hall electrolytic conductivity detector; HRGC = high-resolution gas chromatography; HSD = Halogen-specific electrolytic conductivity conductor; MS = mass spectrometry; RSD = relative standard deviation; w/v = weight:volume

6. ANALYTICAL METHODS

Chloroform is transformed by mammalian P-450 enzymes in *vivo* to trichloromethanol which undergoes spontaneous dechlorination to yield phosgene ($COC1_2$) (Pohl et al. 1977), a highly reactive electrophile (Mansuy et al. 1977). Phosgene can react with cysteine to form 2-oxothiazolidine-4-carboxylic acid (Pohl et al. 1977, 1980b), with two molecules of glutathione to form diglutathionyl dithiocarbonate (Pohl et al. 1981), or with water to produce chloride ion and carbon dioxide (Pohl et al. 1980b). Although 2-oxothiazolidine-4-carboxylic acid and diglutathionyl dithiocarbonate have been measured in liver microsomal preparations (Pohl et al. 1977, 1980b, 1981), the applicability of these methods to human tissues is unknown. Phosgene can also be formed from bromotrichloromethane and carbon tetrachloride (Pohl et al. 1981), so the formation of phosgene and any subsequent products cannot be related exclusively to exposure to chloroform.

6.2 ENVIRONMENTAL SAMPLES

Analytical methods for determining chloroform in environmental samples are presented in Table 6-2. As with all extremely volatile chemicals, it is essential to take precautions during sampling, storage, and analysis to avoid loss of chloroform. Methods commonly used for the determination of chloroform concentrations in air are based on either adsorption onto a sorbent column followed by thermal or solvent desorption with subsequent analysis using GC (EPA 1988f; NIOSH 1994; OSHA 1979) or on cryogenic concentration of chloroform directly from a parcel of air (Bureau International Technique des Solvants Chlores 1976; EPA 19888, 19881) followed by GC. The disadvantages of the sorption tubes are that sorption and desorption efficiencies may not be 100%, and that the background impurities in the sorbent tubes may limit the detection limit for samples at low concentrations (Cox 1983). In addition, storage of sorbent tubes before desorption and analysis can result in losses of chloroform (OSHA 1979), and poor retention of chloroform by the sorbent can result in poor LODs (EPA 1988h). Determination of chloroform using isolation methods based on cryogenic trapping can be limited by moisture condensation in the trap (EPA 1988g). Evacuated canisters used to collect air samples in the field for transport to the laboratory must be carefully cleaned to avoid contamination of the sample (EPA 1988i).

Solid phase microextraction (SPME) has been shown to be useful for the determination of chloroform in air (Chai and Pawliszyn 1995). This technique is based upon the absorption of chloroform into a polymer coated on a silica fiber. Following equilibration of the fiber with the atmosphere, chloroform is released via thermal desorption in the injection port of a gas chromatograph. Sample preparation is

Table 6-2. Analytical Methods for Determining Chloroform in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Adsorption onto carbon molecular sieve; thermal desorption	GC/MS (EPA Method TO2)	No data	91 (15% RSD) at 89 ng/L	EPA 1988f
Air	Cryogenic preconcentration; thermal transfer to GC	GC/ECD (EPA Method TO3)	No data	100 (5.8% RSD) at 3.5 ppb	EPA 1988g
Air	Collection into SUMMA polished canister	GC/FID/ECD or GC/MS (EPA Method TO14)	No data	No data	EPA 1988i
Air	Adsorption onto charcoal; desorption with carbon disulfide	GC/FID (OSHA Method 05)	0.11 ppm for 10 L sample	96 (8.5% RSD)	OSHA 1979
Air	Adsorption onto charcoal; desorption with carbon disulfide, containing internal standard if desired	GC/FID (NIOSH method 1003)	0.7 mg/m^3 for 15 L sample	97 at 120–493 mg/m^3	NIOSH 1994
Ambient air and stacks	Adsorption onto Tenax; thermal desorption	GC/FID or ECD	No data	No data	Parsons and Mitzner 1975
Air	Collection in flask; transfer to GC by syringe	GC/ECD	1.5 $\mu g/m^3$	No data	Bureau International Technique des Solvants Chlores 1976
Air	Solid Phase Microextraction; transfer to GC via thermal desorption of fiber.	GC/ion trap MS	2 ppb (v/v); 6% RSD	No data	Chai and Pawliszyn 1995
Air	Exposure of passive sampler (3M 3500 OVM) for four weeks. Extraction with carbon disulfide.	GC/ECD/FID	4 ng/m^3	98 (10.0% inter-day RSD)	Begerow et al. 1995

Table 6-2. Analytical Methods for Determining Chloroform in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (phosgene)	Phosgene collection in an impinger containing a solution of aniline (forming carbanilide); evaporation of solvent; dissolution of residue in acetonitrile	HPLC/UV (EPA Method TO6)	0.1 ppb (v/v)	100 at 3 ppb (v/v); 15% RSD	EPA 1988n
Air (phosgene)	Phosgene collection onto Chromosorb coated with 1-(2-pyridyl)-piperazine; elution of derivative with acetonitrile	HPLC/UV	0.005 ppm (w/v)	100 over range 0.02–1 ppm (w/v)	Rando et al. 1993
Air (phosgene)	Passage of air through a tube filled with magnesium perchlorate (for water removal); cryogenic trapping	GC/ECD	7 ppt (v/v)	No data	Bächmann and Polzer 1989
Air, water	Solid phase microextraction (from air, water, or headspace over water)	GC/ECD	0.9 ppb (v/v) gas phase; 30 ng/L (30 ppt, w/v) liquid phase	No data	Chai et al. 1993
Drinking water	Direct injection or purge-and-trap pre-concentration	GC/ECD, GC/Hall	1 µg/L (1 ppb, w/v direct); 0.1 µg/L (0.1 ppb, w/v with purge-and-trap)	103–126 at 35–70 µg/L (direct); 91–106 at 35–70 µg/L (purge-and-trap)	Nicholson et al. 1977
Drinking water	Purge-and-trap pre-concentration; thermal desorption	GC/MS	0.1 µg/L (0.1 ppb, w/v)	No data	Coleman et al. 1976
Drinking water	Direct injection	GC/MS	0.1 µg/L (0.1 ppb, w/v)	No data	Fujii 1977

Table 6-2. Analytical Methods for Determining Chloroform in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Seawater and freshwater	Solvent extraction with pentane; extract dried with sodium sulfate	GC/ECD	80 ng/L (0.08 ppb, w/v)	No data	Bureau International Technique des Solvants Chlores 1976
Water	Permeation through a silicon polycarbonate membrane into an inert gas stream and into GC port	GC/FID	74.0 µg/L (74 ppb, w/v)	No data	Blanchard and Hardy 1986
Drinking water	Acidification and dechlorination; extraction with methyl-t-butyl ether; direct injection of extract	GC/ECD or GC/MS (EPA Method 551)	0.002 µg/L (0.002 ppm, w/v)	100 (13% RSD) at 0.005 µg/L	EPA 1990g
Drinking water, waste water	Purge-and-trap pre-concentration; thermal desorption	GC/MS (Standard Method 6210)	< 0.1 µg/L (reagent water) using narrow bore capillary column	105 (3% RSD) narrow bore column	Greenberg et al. 1992
Tap water	Solvent extraction	HRGC/ECD with HRGC/MS confirmation	No data	No data	Kroneld 1986
Water	Solvent extraction	HRGC/ECD	1 µg/L (ppb, w/v)	100.3 at 50 µg/L	Reunanen and Kroneld 1982
Drinking water	Purge-and-trap pre-concentration onto Tenax/ silica/charcoal; thermal desorption	GC with PID and Hall in series	0.02 µg/L	98 (2.5% RSD)	Ho 1989
Finished drinking/raw source water	Purge-and-trap pre-concentration onto Tenax/ silica/charcoal; thermal desorption	GC/Hall (EPA method 502.1)	No data	0.90C+3.44 where C = true concentration (µg/L)	EPA 1991a

Table 6-2. Analytical Methods for Determining Chloroform in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Finished drinking/raw source water	Purge-and-trap pre-concentration onto Tenax/silica/charcoal; thermal desorption	GC with PID and HSD in series (EPA method 502.2)	0.10 µg/L (0.1 ppb, w/v)	98 (2% RSD)	EPA 1991b
Finished drinking/raw source water	Purge-and-trap pre-concentration onto Tenax/ silica/charcoal; thermal desorption	Subambient programmable HRGC/MS (EPA method 524.1)	0.2 µg/L (0.2 ppb, w/v)	103 at 1.0 µg/L	EPA 1991c
Finished drinking/raw source water	Purge-and-trap pre-concentration onto Tenax/ silica/charcoal; thermal desorption	Cryofocusing (wide or narrow bore); HRGC/MS (EPA method 524.2)	0.03 µg/L (0.03 ppb, w/v) with wide bore column; 0.02 µg/L (0.02 ppb, w/v) with narrow bore column	90 (6.1% RSD) at 0.5–10 µg/L (wide bore); 95 (3.2% RSD) at 0.1 µg/L with narrow bore column	EPA 1992a
Groundwater, liquid, and solid matrices	Direct injection of head-space gas (EPA method 5020) or purge-and-trap pre-concentration and thermal desorption (EPA method 5030)	GC/HSD (EPA method 8010)	0.5 µg/L (ppb, w/v) for groundwater, 0.5 µg/g (ppm, w/w) for low-level soil, 500 µg/L (ppb, w/v) for water-miscible liquid waste, 1,250 µg/g (ppm, w/w) for soil, sludge, and non-water-miscible waste	Water: 0.93C -0.39 where C = true concentration in µg/L.	EPA 1986a
Waste water	Purge-and-trap pre-concentration; thermal desorption	GC/HSD or MS (EPA methods 601 and 624)	0.05 µg/L (for HSD); 1.6 µg/L (for MS)	102 at 0.44–50 µg/L (for HSD); 101 at 10–100 µg/L (for MS)	EPA 19982a

Table 6-2. Analytical Methods for Determining Chloroform in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Solid and liquid waste, soil	Dispersion in glycol; purge-and-trap pre-concentration onto Tenax/ silica/charcoal; thermal desorption	GC/ECD and FID in series	No data	105 at 5 µg/L	Lopez-Avila et al. 1987
Sediment	Extraction into methanol; dilution with water; purge-and-trap pre-concentration	GC/FID/ECD	0.1 µg/g (0.1 ppm, w/w)	99 (4% RSD) at 0.8 µg/mL (0.8 ppm, w/v)	Amaral et al. 1994
Bulk oils	Purge-and-trap pre-concentration (with deuterated internal standards) onto Tenax; thermal desorption	GC/MS	1 ppb (w/v)	88 (6.7% RSD) at 93 ppb	Thompson 1994
Food	Extraction of composited, table-ready food with isooctane or acetone-isooctane; micro-Florisil clean-up (if fat content 21–70%); direct injection into GC	GC-ECD/Hall	5 ng/g (ECD); 5 ng/g (Hall)	15–161	Daft 1988a, 1989
Volatile food components	Direct injection of head-space gas	GC/ECD or MS	4.2 µg/kg (4.2 ppb, w/w in beverages); 12.5 µg/kg (12.5 ppb, w/w in dairy products); 18 µg/kg (meats); 28 µg/kg (fats/oils)	No data No data No data No data	Entz et al. 1982

ECD = electron capture detector; EPA = Environmental Protection Agency; FID = flame ionization detector; GC = gas chromatography; Hall = Hall electrolytic conductivity detector; HPLC/UV = high performance liquid chromatography with ultraviolet absorbance detection; HRGC = high-resolution gas chromatography; HSD = halogen-specific electrolytic conductivity detector; MS = mass spectrometry; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PID = photo-ionization detector; RSD = relative standard deviation; v/v = volume/volume; w/v = weight/volume

very easy and fast (90 seconds for chloroform) with this technique although sample collection conditions and thermal desorption conditions must be carefully controlled for the best precision. Samples containing very volatile analytes, like chloroform, must be analyzed quickly after sample collection to avoid analyte loss with storage.

Phosgene has been identified as an atmospheric decomposition product of several chlorinated compounds, including chloroform (Bachmann and Polzer 1989). Phosgene can be determined in air samples using, for example, capillary GC with electron capture detection (ECD) (Bachmann and Polzer 1989), high-performance liquid chromatography (HPLC) after the conversion of phosgene to carbanilide (EPA 1988n), and HPLC after the reaction of phosgene with 1-(2-pyridyl)-piperazine (Rando et al. 1993). Chloroformates can interfere in the carbanilide analysis (EPA 1988n). In the method of Rando et al. (1993), the apparent recovery of phosgene was nearly quantitative from air at up to 25% relative humidity; this decreased to about 65% at 95% humidity.

The most common method for the determination of chloroform levels in water, sediment, soil, and foods is the purging of the vapor from the sample, or its suspension in a solvent with an inert gas and trapping (purge-and-trap) the desorbed vapors onto a sorbent trap (EPA 1991 a, 1991b, 1991c, 1992; Greenberg et al. 1992; Ho 1989; Lopez-Avila et al. 1987). SPME is a method that combines the ease of headspace analysis with some of the concentration benefits of purge-and-trap (Chai et al. 1993). Subsequent thermal desorption is used for the quantification of chloroform concentrations. Solvent extraction is also used in a number of methods (Amaral et al. 1994; Daft 1988a, 1989; EPA 1990g; Kroneld 1986; Reunanen and Kroneld 1982). No methods were found for phosgene in water, sediment, soil, and foods.

All of the methods listed above for the analysis of environmental samples use GC with various detection methods. The two methods that provide the lowest detection limits are halide-specific detectors (e.g., Hall electrolytic conductivity detector or electron capture detector) and the mass spectrometer (EPA 1986a; Ho 1989; Lopez-Avila et al. 1987; Ramus et al. 1984). The advantage of halide specific detectors is they are not only very sensitive, but are also specific for halide compounds. The mass spectrometer, on the other hand, provides additional confirmation of the presence of a compound through its ionization pattern and is desirable when a variety of compounds are required to be identified and quantified. The disadvantage of halide-specific detectors is their inability to detect and quantify nonhalogen compounds, if nonhalogenated compounds are of interest also; this can be

greatly overcome by using other detectors (e.g., photoionization detector) in series (Lopez-Avila et al. 1987). High-resolution gas chromatography (HRGC) with capillary columns coupled with mass spectrometry (MS) provides better resolution and increased sensitivity for volatile compounds than packed columns. In methods such as EPA method TO14 (EPA 198Si), desorbed compounds are cryogenically trapped onto the head of the capillary column. Such HRGC/MS methods overcome some common problems involved in analyses of excessively complex samples, samples with large ranges of concentrations, and samples that also contain high-boiling compounds (Dreisch and Munson 1983; EPA 1986a). LODs in the sub-parts per billion (ppb) range are routinely possible in both air and liquid/solid matrices. Numerous standard methods exist.

Methods for rapid sample introduction to an ion trap mass spectrometer have been developed for the determination of organic compounds, including chloroform, in aqueous samples. In the method of Bauer and Solyom (1994) a polymeric membrane is placed into contact with the sample, the organics dissolve in the membrane and diffuse to the other side where they are swept directly into the mass spectrometer. This technique, known as membrane introduction mass spectrometry (MIMS) was shown to be sensitive to chloroform in water to 0.025 ppb. Another sample introduction technique known as inertial spray extraction nebulizes an aqueous sample (water, blood) into a small chamber where a countercurrent stream of helium sweeps any released volatile organic compounds (VOCs) into a jet separator at the inlet of an ion trap mass spectrometer (St-Germain et al. 1995). Up to 1 mL of sample can be introduced and the released VOCs are detected by the MS. Although both of these techniques provide for high throughput, no separation step is employed and this can result in interferences from ions formed by compounds other than the target analytes. These methods have great utility in selected applications.

A fiber-optic device has been described that can monitor chlorinated hydrocarbons in water (Gobel et al. 1994). The sensor is based on the diffusion of chlorinated hydrocarbons into a polymeric layer surrounding a silver halide optical fiber through which is passed broad-band mid-infrared radiation. The chlorinated compounds concentrated in the polymer absorb some of the radiation that escapes the fiber (evanescent wave); this technique is a variant of attenuated total reflection (ATR) spectroscopy. A LOD for chloroform was stated to be 5 mg/L (5 ppm). This sensor does not have a high degree of selectivity for chloroform over other chlorinated aliphatic hydrocarbons, but appears to be useful for continuous monitoring purposes.

6. ANALYTICAL METHODS

The reproducibilities of the methods listed in Table 6-2 are generally acceptable, but will vary, depending on the laboratories doing the analyses. Probable interferences for the methods of analysis include contamination from chloroform vapors in the laboratory. For this reason, it is often recommended that the laboratories doing the analysis should not contain chloroform or any other solvent to be measured in the sample (EPA 1986a). Plastic or rubber system components should be avoided as they can contaminate a sample or result in carryover from one analysis to the next (EPA 1992). The formation of aerosols and foam during purge-and-trap of liquid samples can contaminate the analytical system, so precautions must be taken (Thompson 1994; Vallejo-Cordoba and Nakai 1993). The use of field blanks is extremely important to correct for chloroform that might have diffused into the sample during shipping and storage (EPA 1986a). Other interferences include those volatile compounds that have similar retention times in the various GC columns used. This problem is often eliminated by analyzing the samples with two different types of GC columns such that the retention times will not be coincidental in both columns. Mass spectrometric detection can also help to overcome interferences resulting from incomplete chromatographic resolution. Refer to the references cited in Table 6-2 and the text for specific information regarding reproducibility and potential interferences.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chloroform is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chloroform.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met w,ould reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods are available for the determination of chloroform in breath (Aggazzotti et al. 1993; Jo et al. 1990; Krotoszynski et al. 1979; Phillips and Greenberg 1992; Pleil and Lindstrom 1995; Raymer et al. 1990), blood (Antoine et al. 1986; Ashley et al. 1992; Cammann and Htibner 1995; EPA 1985a; Kroneld 1986; Peoples et al. 1979; Pfaffenberger et al. 1980; Reunanen and Kroneld 1982; Seto et al. 1993; Streete et al. 1992), and other fluids and tissues such as urine and adipose (Cammann and Htibner 1995; EPA 1985a; Peoples et al. 1979; Pfaffenberger et al. 1980; Reunanen and Kroneld 1982; Streete et al. 1992). Sub-ppb limits of detection have been shown (e.g., Ashley et al. 1992; Pfaffenberger et al. 1980) and the methods are adequate for the determination of chloroform concentrations in samples from the general population. No biomarker that can be associated quantitatively with chloroform exposure has been identified (see Sections 2.5.1 and 6.1). Although chloroform levels can be determined in biological samples, the relationship between these levels and the exposure levels has not been adequately studied. In one study, the concentrations of chloroform in alveolar air of people attending activities at an indoor swimming pool were found to be proportional to the concentrations in air (Aggazzotti et al. 1993). Such proportionality was observed, in part, because the alveolar air samples were taken soon after exposure termination. Good correlations have also been measured between chloroform concentrations measured in blood and breath with those in air or water after exposure to water/air during showering (Jo et al. 1990) and swimming (Cammann and Htibner 1995; Lévesque et al. 1994). The studies of Jo et al. (1990) and Lévesque et al. (1994) demonstrated and quantified the uptake of chloroform via dermal absorption. Correlations of alveolar air concentrations with exposure air concentrations based on breath samples at unknown postexposure times will be complicated by metabolism and other factors, such as activity, important in the elimination of chloroform from the body (see PBPK discussion, Chapter 2). Furthermore, the presence of chloroform, or a transformation product of chloroform such as phosgene and reaction products of phosgene, in a biological sample may have resulted from the metabolism of another chlorinated hydrocarbon. If a biomarker of exposure for this compound in a human tissue or fluid was available and a correlation between the level of the biomarker and exposure existed, it could be used as an indication of the extent of chloroform exposure. Further information regarding the accuracy of sample recovery for the methods of chloroform analysis would be useful in interpreting monitoring data.

6. ANALYTICAL METHODS

No biomarker of effect that can be associated quantitatively and directly to chloroform exposure has been identified (see Section 2.5.2). If biomarkers of effect were available for this compound and a correlation between the level or intensity of the biomarker of effect and the exposure level existed, it could be used as an indication of the levels and extent of chloroform exposure. However, in cases where an exposure to chloroform has been known to occur, measurements of chloroform in breath or blood can indicate body burden.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining chloroform in the environment are available. These include methods for drinking water (Blanchard and Hardy 1986; EPA 199Og, 1991a, 1991b, 1991c, 1992; Greenberg et al. 1992; Ho 1989; Kroneld 1986; Nicholson et al. 1977), air (Bergerow et al. 1995, Chai and Pawliszyn 1995, EPA 1988f, 1988g, 198831, 19881; NIOSH 1994; OSHA 1979; Parsons and Mitzner 1975), and foods (Daft 1988a, 1989; Entz et al. 1982; Thompson 1994). These three media are of most concern for human exposure. The precision, accuracy, reliability, and specificity of the methods are well documented and well suited for the determination of low levels of chloroform and levels at which health effects occur. For example, the MRL for acute-duration inhalation is 0.1 ppm (weight per volume [w/v] or 0.0099 mg/m^3) so any method used must have a limit of detection equal to or less than this. The methods of Chai et al. (1993), Chai and Pawliszyn (1995), and Bergerow et al. (1995) report limits of detection of 0.9 ppb volume per volume (v/v), 2 ppb, and 4 ng/m^3, respectively, and are adequate for the measurement of chloroform in air. Although no limits of detection were reported for EPA methods TO2 and TO3 (EPA 1988f, 1988g), recoveries were acceptable for low-ppb concentrations of chloroform in air and thus these methods should certainly be applicable to concentrations at the acute-duration inhalation MRL. Similarly, the chronic-duration oral MRL is 0.01 mg/kg/day, which converts to 0.7 mg/day for a 70-kg person. For a 2 L/day water consumption, this translates into a required method limit of detection of 0.35 mg/L. This concentration is easily measured by the methods of EPA (199Og) (limit of detection 0.002 μg/L), Greenberg et al. (1992) (1imit of detection 0.1 μg/L), and Chai et al. (1993) (limit of detection 30 ng/L). Assuming a food intake of 2 kg/day, this oral MRL translates to a needed method limit of detection in food of 0.35 mg/kg. The methods of Entz et al. (1982) and Daft (1988a, 1989) provide limits of detection of less than 0.028 mg/kg and are adequate. Method sensitivities are clearly adequate for matrices in which the higher acute-duration oral MRL is of concern. There is not much information regarding the degradation products of chloroform in the environment. Although phosgene can be produced in the environment and its high reactivity suggests that it would not persist, several

methods were found for the quantification of phosgene in ambient air (Bachmann and Polzer 1989; EPA 1988n; Rando et al. 1993). No methods were found for phosgene in other environmental matrices and it is not likely that it would be found in matrices other than air.

6.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control and Prevention, is developing methods for the analysis of chloroform and other VOCs in blood. These methods use purge-and-trap methodology, HRGC, and magnetic sector mass spectrometry which gives detection limits in the low-ppt range (see Ashley et al. 1992).

The following information was obtained form a search of Federal Research in Progress (FEDRIP, 1996). Researchers at Physical Sciences, Inc. are developing an imaging infrared spectrometer that can rapidly screen field sites to detect the presence of VOCs, including chloroform, from remote locations (either in the air or on the ground). The following research projects were identified as having objectives that might require the development or modification of methods to measure chloroform. Researchers at Colorado State University are studying the biodegradation of pollutants, including chloroform, in bioreactors. Researchers at the University of California at Berkeley and Riverside are conducting studies on the biodegradation of organic compounds, including chloroform, in soil.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding chloroform in air, water and other media are summarized in Table 7- 1.

An MRL of 0.1 ppm has been derived for acute-duration inhalation exposure to chloroform. The MRL is based on a NOAEL of 3 ppm for hepatic effects in mice (Larson et al. 1994c).

An MRL of 0.05 ppm has been derived for intermediate-duration inhalation exposure to chloroform. The MRL is based on a LOAEL of 14 ppm for toxic hepatitis in workers exposed to up to 400 ppm for less than 6 months (Phoon et al. 1983).

An MRL of 0.02 ppm has been derived for chronic-duration inhalation exposure to chloroform. The MRL was based on a LOAEL of 2 ppm for hepatic effects in workers exposed to concentrations of chloroform ranging from 2 to 205 ppm for l-4 years (Bomski et al. 1967).

An MRL of 0.3 mg/kg/day has been derived for acute-duration oral exposure to chloroform. The MRL is based on a NOAEL of 26.4 mg/kg/day for hepatic effects in mice (Larson et al. 1994b).

An MRL of 0.1 mg/kg/day has been derived for intermediate-duration oral exposure to chloroform. The MRL is based on a NOAEL of 15 mg/kg/day for liver effects (increased SGPT) in dogs exposed to chloroform in toothpaste for ≥6 weeks (Heywood et al. 1979).

An MRL of 0.01 mg/kg/day has been derived for chronic-duration oral exposure to chloroform based on a LOAEL for liver effects (increased SGPT) in dogs administered 15 mg/kg/day chloroform in toothpaste in capsules for 7.5 years (Heywood et al. 1979).

The chronic-duration oral reference dose (RfD) for chloroform is also 0.01 mg/kg/day, based on the LOAEL for liver effects in dogs administered 15 mg/kg/day chloroform (Heywood et al. 1979; IRIS 1996).

No reference concentration (RfC) exists for the compound.

7. REGULATIONS AND ADVISORIES

The EPA has determined that chloroform is a probable human carcinogen; corresponding group B2 (IRIS 1996). Gavage studies conducted by the NTP were positive for carcinogenicity in female mice and male mice and rats, but negative for female rats (NTP 1995).

The International Agency for Research on Cancer (IARC) has determined that chloroform is possibly carcinogenic to humans; Group 2B classification (IARC 1987).

Chloroform is regulated by the Clean Water Act Effluent Guidelines for the following industrial point sources: electroplating; organic chemicals; steam electric, asbestos, and timber products processing; paving and roofing; paint and formulating; formulating; gum, wood and carbon black; metal molding, casting, and finishing; coil coating; copper forming; and electrical and electronic components (EPA 1981a).

Table 7-1. Regulations and Guidelines Applicable to Chloroform

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenic classification	Group 2B[a]	IARC 1987
WHO	Drinking water guidelines	30 μg/L	WHO 1984
NATIONAL			
Regulations:			
a. Air:			
EPA OAQPS	Intent to list under Section 112 of Clean Air Act	Yes	40 CFR 61.01 EPA 1985d
	New Source Performance Standards		
	Chemicals Produced at SOCMI Facilities	Yes	40 CFR 60.489 EPA 1983b
	Chemical Affected by Standards for SOCMI Distillation Operations	Yes	40 CFR 60.667 EPA 1990e
	National Emission Standards for Hazardous Air Pollutants		
	Hazardous Air Pollutants	Yes	40 CFR 61.01 EPA 1985d
	Proposed Rule: Identification of "More Hazardous" Emission Decreases	Yes	59 FR 15504 40 CFR 63.48 EPA 1994a
	Proposed Rule: National Emission Standards for Halogenated Solvent Clearing-Applicability	Yes	58 FR 62566 40 CFR 63.460 EPA 1993a
OSHA	PEL-TWA	50 ppm	29 CFR 1910 OSHA 1974
	Permissible Exposure Limit (Ceiling)	240 mg/m^3	OSHA 1974
	Occupational Exposure to Hazardous Chemicals in Laboratories	Yes	OSHA 1974
b. Water:			
EPA	PQL	0.5 μg/L	40 CFR 264 and 270 EPA 1987a
	Effluent Guidelines and Standards		
	List of Toxic Pollutants	Yes	40 CFR 401.15 EPA 1979b
	List of Toxic Pollutants Subject to Pretreatment Standards	Yes	40 CFR 403, App. B EPA 1981a
	Definition of Total Toxic Organics (TTO) for Electroplating Point Source Category	Yes	40 CFR 413.02 EPA 1981b
	Bulk Organic Chemicals in Wastewater from Sources of Organic Chemicals, Plastics and Synthetic Fibers	Yes	40 CFR 414.70 EPA 1987e

Table 7-1. Regulations and Guidelines Applicable to Chloroform (continued)

Agency	Description	Information		References
NATIONAL (cont.)	Organic Chemicals, Plastics, and Synthetic Fibers - Effluent Limitations for Direct Discharge Point Sources Using End-of-Pipe Biological Treatment			40 CFR 414.91 EPA 1987e
	One-day maximum	46 μg/L		
	Maximum for monthly average	21 μg/L		
	Organic Chemicals, Plastics, and Synthetic Fibers - Effluent Limitations for Direct Discharge Point Sources That Do Not Use End-of-Pipe Biological Treatment			40 CFR 414.101 EPA 1987e
	One-day maximum	325 μg/L		
	Maximum for monthly average	111 μg/L		
	Priority Pollutants, Associated With Steam Electric Power Generating Sources	Yes		40 CFR 423, App. A EPA 1982b
	Proposed Rule: Effluent Limitations for Pupl, Paper, and Paperboard - Dissolving Kraft *(bleach plant effluent)*			58 FR 66078 40 CFR 430 EPA 1993d
		1-Day Max.	Monthly Avg.	
	Existing BAT New Source Pretreatment	10.1 g/kkg 10.1 g/kkg	7.06 g/kkg 7.07 g/kkg	
	Bleached paper grade kraft and soda (bleach plant effluent - existing BAT and pretreatment for existing	5.06 g/kkg	2.01 g/kkg	
	Dissolving sulfite - pretreatment for new sources	23.2 g/kkg	74.4 g/kkg	
	Proposed Rule: Monitoring Requirements for Pulp, Paper, and Paperboard Category	Yes		59 FR 12567 40 CFR 430.02 EPA 1994c
	Definition of TTO for Metal Finishing Sources	Yes		40 CFR 433.11 EPA 1983d
	Definition of TTO for Metal Molding and Casting Sources	Yes		40 CFR 464.21 EPA 1985e
	Definition of TTO for Ferrous Casting Sources			40 CFR 464.31 EPA 1985e
	Definition of TTO for Coil Coating Sources	Yes		40 CFR 465.02 EPA 1982c
EPA ODW	National Primary Drinking Water Regulations			
	Definition of Trihalomethanes (THM)	Yes		40 CFR 141.2 EPA 1975
	Maximum Contaminant Levels for THM	0.10 mg/L		40 CFR 141.12 EPA 1991f
	Method of Analysis for THM	Yes		40 CFR 141, App. C EPA 1979a

Table 7-1. Regulations and Guidelines Applicable to Chloroform (continued)

Agency	Description	Information	References
NATIONAL (cont.)	Monitoring for Inorganic and Organic Chemicals	Yes	40 CFR 141.40 EPA 1987d
	Proposed Rule: Total Trihalomethane Sampling and Analysis	Yes	58 FR 65622 40 CFR 141.30 EPA 1993c
	Proposed Rule: Maximum Contaminant Levels for Total THM	Yes	59 FR 38668 40 CFR 141.12 EPA 1994b
	Proposed Rule: Total THM Sampling, Analytical and Other Requirements	Yes	59 FR 38668 40 CFR 141.30 EPA 1994b
	Proposed Rule: Best Available Technology for Achieving Compliance with MCLs for Total THM	Yes	59 FR 38668 40 CFR 141.64 EPA 1994b
	Proposed Rule: Disinfection By-Product Compliance Monitoring for Total THM	Yes	59 FR 38668 40 CFR 141.133 EPA 1994b
EPA OW	Designation of Hazardous Substances	Yes	40 CFR 116.4 EPA 1978
	Reportable Quantities for Hazardous Substances	10 pounds	40 CFR 117.3 EPA 1986e
	National Pollutants Charge Elimination System: Permit Application Testing Requirements	Yes	40 CFR 122, App. D EPA 1983c
	Proposed Rule: Application of Part 132 Requirements to Great Lake States and Tribes - Pollutants of Initial Focus	Yes	58 FR 20802 40 CFR 132.6 EPA 1993b
	Test Procedures for the Analysis of Pollutants	Yes	40 CFR 136.3 EPA 1973
	Methods of Analysis of Municipal and Industrial Wastewater	Yes	40 CFR 136, App. A EPA 1973
c. Food:			
FDA	Substances used only as components of adhesives	Yes	21 CFR 175.105 FDA 1977
d. Other:			
EPA OERR	RQ (Ruled)	10 pounds	54 FR 155 EPA 1989c
	Threshold planning quantity	10,000 pounds	EPA 1987b
	Constituents for Solid Waste Detection Monitoring	Yes	40 CFR 258, App. I EPA 1991g
	Hazardous Constituents Subject to Regulatory Requirements	Yes	40 CFR 258, App. II EPA 1991g
	Maximum Concentration Contaminants for the Toxicity Characteristic	Yes	40 CFR 261.24 EPA 1990d

Table 7-1. Regulations and Guidelines Applicable to Chloroform (continued)

Agency	Description	Information		References
NATIONAL (cont.)	Discarded commercial chemical products, off-specification species, container residues, and spill residues	Yes		40 CFR 261.33 EPA 1990d
	Basis for Listing Hazardous Waste	Yes		40 CFR 261, App. VII EPA 1981c
	Proposed Rule: Basis Listing Hazardous Waste	Yes		59 FR 9808 40 CFR 261, App. VII EPA 1994d
	Hazardous Constituents	Yes		40 CFR 261, App. VIII EPA 1988j
	Groundwater Monitoring List for Hazardous Waste TSDF	Yes		40 CFR 264, App. IX EPA 1991d
	Health Based Limits for Exclusion of Waste-Derived Residues	$6x10^{-2}$		40 CFR 266, App. VII EPA 1991d
	Potential PICs For Determination of Exclusion of Waste-Derived Residues	Yes		40 CFR 266, App. VIII EPA 1991d
EPA	Land Disposal Restrictions			
	Identification of Waste to Be Evaluated by August 8, 1988	Yes		40 CFR 268.10 EPA 1986f
	Constituent Concentrations Which May Not be Exceeded for Land Disposal			40 CFR 268.43 EPA 1988k
	Waste Code:	Waste water	Non-waste water	
	F025	0.046 mg/L	6.2 mg/kg	
	F039, K117, U044	0.046 mg/L	5.6 mg/kg	
	Halogenated organic compounds regulated under 40 CFR 268.32	Yes		40 CFR 268, App. III EPA 1987g
	Proposed Rule: Treatment Standards for Land Disposed Waste			58 FR 48092 40 CFR 268.40 & 268.48 EPA 1993e
	Waste Code:	Waste water	Non-waste water	
	D022, K019, K029, K150, K151, universal treatment standard	0.046 mg/L	6/9 mg/kg	
	F025, K073	0.046 mg/L	6.2 mg/kg	
	F038, K117, K118, K136, U044	0.046 mg/L	5.6 mg/kg	
	K009, K010	0.1 mg/L	6.0 mg/kg	

Table 7-1. Regulations and Guidelines Applicable to Chloroform (continued)

Agency	Description	Information	References
NATIONAL (cont.)	List of Hazardous Substances and Reportable Quantities	10 pounds	40 CFR 302.4 EPA 1989d
	Proposed Rule: Reportable Quantity Adjustments - Designation of Hazardous Waste	Yes	58 FR 54836 40 CFR 302.4 EPA 1993f
	Extremely Hazardous Substances and Threshold Planning Quantities	10,000 pounds	40 CFR 355, App. A EPA 1987h
	Chemicals Subject to Toxic Chemical Release Reporting: Community Right-to-Know	Yes	40 CFR 372.65 EPA 1988l
	Chemicals Subject to the Health and Safety Data Reporting Requirements Under TSCA	Yes	40 CFR 716.120 EPA 1988m
Guidelines:			
a. Air:			
ACGIH	TLV-TWA	10 ppm (49 mg/m^3)	ACGIH 1992
	Threshold Limit Value for Occupational Exposure	49 mg/m^3	ACGIH 1994
NIOSH	STEL (60 minutes)	2 ppm (9.78 mg/m^3)	NIOSH 1990
	Recommended Exposure Limit for Occupational Exposure (STEL-60 min)	9.78 mg/m^3	NIOSH 1992
	Immediately Dangerous to Life & Health	1,000 ppm	NIOSH 1990
b. Water:			
EPA	1-d Health Advisory	4 mg/L (child)	EPA 1994e
	10-d Health Advisory (child & adult)	4 mg/L (child)	EPA 1994e
	Longer-term Health Advisory (child & adult)	0.1 mg/L (child 0.4 mg/L (adult)	EPA 1994e
	Maximum Contaminant Level		EPA 1994e
	Chloroform	0.1 mg/L	
	Total THM (community and non-transcient, non-community water systems)	0.080 mg/L	59 FR 38668 40 CFR 141.64
	Total THM (serve more than 10,000 people)	0.040 mg/L	EPA 1994b
	Maximum Contaminant Level Goal	zero	59 FR 38668 40 CFR 141.53 EPA 1994b
	q^{1*} cancer slope factor (oral exposure)	6.1×10^{-3} per mg/(kg/day)	IRIS 1996
	RfD (oral)	1.10^{-2} mg/kg/day) (UF 1,000)	
EPA ODW	Individual lifetime cancer risk 10^{-5}	60 μg/L	
NAS	Suggested No-Adverse-Response Level		
	24-hour	22 mg/L	NAS 1980
	7-day	3.2 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Chloroform (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
c. Non-specific media			
EPA	q_1^* (oral) q_1^* (inhalation)	6.1×10^{-3} (mg/kg/day)$^{-1}$ 8.1×10^{-2} (mg/kg/day)$^{-1}$ [2.3×10^{-5} (μg/m^3)$^{-1}$]	IRIS 1996
	RfD (chronic oral) Cancer classification	0.01 mg/kg/day B2[b]	
d. Other			
EPA	Cancer classification	B2	
NIOSH	Cancer classification	Yes	NIOSH 1990 NIOSH 1992
Regulations and Guidelines:			
a. Air:			
AZ	Acceptable ambient air concentrations 1 hour 24 hours 1 year	60 μg/m^3 16 μg/m^3 0.043 μg/m^3	NATICH 1992
CT	8 hours	250 μg/m^3	
FL (Ft. Lauderdale)	8 hours	0.5 mg/m^3	
FL (Pinellas Co.)	8 hours 24 hours 1 year	97.8 μg/m^3 23.5 μg/m^3 0.043 μg/m^3	
IN	8 hours Annual	48.9 μg/m^3 0.043 μg/m^3	
IN (Innap)	8 hours	1200 μg/m^3	
KS	1 year	0.0435 μg/m^3	
KS-KC	Annual	0.0435 μg/m^3	State of Kentucky 1986
LA	Annual	4.3 μg/m^3	NATICH 1992
MA	24 hours 1 year	133 μg/m^3 0.04 μg/m^3	
ME	1 year	0.043 μg/m^3	
MI	1 year	0.40 μg/m^3	
NC	1 year	0.0043 mg/m^3	
NC	1 year	0.0043 mg/m^3	
ND		BACT	
NV	8 hours	1.19 mg/m^3	
NY	1 year	167 μg/m^3	
OK	24 hours	97 μg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Chloroform (continued)

Agency	Description	Information	References
STATE (cont.)			
PA (Phil.)	1 year	120 $\mu g/m^3$	
RI	1 year	0.04 $\mu g/m^3$	
SC	24 hours	250 $\mu g/m^3$	
TX	30 minutes 1 year	98 $\mu g/m^3$ 10 $\mu g/m^3$	
VA	24 hours	490 $\mu g/m^3$	
VT	1 year	0.043 $\mu g/m^3$	
WA/SWEST	1 year	0.043 $\mu g/m^3$	
b. Water:			
	Water Quality: Human Health		FSTRAC 1990
AZ	Drinking water quality standards Domestic/ Drinking	0.49 µg/L 5.7µg/L	Sittig 1994
FL	Domestic/ Drinking	100 µg/L	
IL		1 µg/L	CELDs 1994
MA		5 µg/L	
MI	Domestic/ Drinking	5.6 µg/L	Sittig 1994
MN		57 µg/L	CELDS 1994
NJ	Domestic/ Drinking	6 µg/L	Sittig 1994
NY	Domestic/ Drinking	0.2-100µg/L	
OR	Domestic /Drinking	10 µg/L	
RI	Drinking water standard	6-100 µg/L	CELDS 1994
TN	Domestic/ Drinking	100 µg/L	Sittig 1994
TX	Domestic/ Drinking	100 µg/L	
VT	Domestic/ Drinking	6µg/L	
	Water Quality: Human Health		CELDs 1994
AZ	Domestic Water Source (DWS) Fish Consumption (FC) Full Body Contact (FBC) Partial Body Contact (PBC)	TTHM 590 µg/L 230 µg/L 1400 µg/L	
CO	MCL	0.10 mg/L	
CT	MCL	2.0 µg/L	
DC	Water Quality Criteria C D	 3,000 mg/L 0.2 mg/L	
FL	MCL	0.10 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Chloroform (continued)

Agency	Description	Information	References
STATE (cont.)			
HI	Maximum organic contaminant level: Total trihalomethane (TTHM) (TTHM = the sum of the concentration of bromodichloromethane, dibromochloromethane and chloroform)	Acute / Chronic	
	Fresh water	9,600 µg/L / ns	
	Salt water	ns / ns	
	Fish consumption	5.1	
IN	Outside of mixing zone	157 µg/L	
	Point of water intake	1.9 µg/L	
	MCL (TTHM)	0.10 mg/L	
KY	Consumption of fish	15.7 µg/L	
	MCL	0.19 µg/L	
KS	MCL (TTHM)	0.10 mg/L	
LA	Drinking water	5.30 µg/L	
	Non-drinking water	70.00 µg/L	
ME	Maximum level (TTHM)	0.10 mg/L	
NH	MCL (TTHM)	0.10 mg/L	
NM	Groundwater levels	0.1 mg/L	
NY	Groundwater effluent standard (max.)	7µg/L	
ND	MCL (TTHM)	0.10 mg/L	
NC	MCL (TTHM)	0.10 mg/L	
	Water quality standard for class GS Groundwater	0.00019 mg/L	
OG	Groundwater quality reference level (TTHM)	0.100 mg/L	
	MCL (TTHM)	0.10 mg/L	
OK	Groundwater water quailty criteria	10.0 (no units specified)	
	MCL (TTHM)	0.10 mg/L	
OH	MCL (TTHM)	0.10 mg/L	
SC	MCL (TTHM)	0.10 mg/L	
VT	Class A or B waters	0.19 mg/L	
	Class C water	15.7 mg/L	
WV	MCL (TTHM)	0.10 mg/L	
WI	Human cancer criteria: Public Water Supplier		
	Warm water sport fish communities	1.9 mg/L	
	Cold water communities	1.8 mg/L	
	Great Lakes communities	1.8 mg/L	
	Non-Public Water Supplies		
	Warm water sport fish communities	87 mg/L	
	Cold water communities	31 mg/L	
	Warm water forage and limited fish communities and limited aquatic life	380 mg/L	
	Groundwater Enforcement standard		
	Prevention action limit	6 µg/L	

Table 7-1. Regulations and Guidelines Applicable to Chloroform (continued)

Agency	Description	Information		References
STATE (cont.)				
WV	All water use categories, maximum criteria			
	B1, B2, B3 waters	15.7 μg/L		
	A	0.19 μg/L		
	Water Quality: Aquatic Life			CELDs 1994
AZ	Acute Criteria for Aquatic and Wildlife Uses	Acute	Chronic	
	Cold water fishery (A/W)	14,000 μg/L	900 μg/L	
	Warm water fishery (A/W)	14,000 μg/L	900 μg/L	
	Effluent dominated water (A/W)	14,000 μg/L	900 μg/L	
	Ephemeral (A/W)	NNS	NNS	
CO	Aquatic Life Segments			
	Acute	28,900 μg/L		
	Chronic	1,240 μg/L		
FL	MCL for mixing zone pollutants	1.57 mg/L		
LA	Acute Criteria			
	Freshwater	2,890 μg/L-acute		
		1,445 μg/L-chronic		
	Marine water	8,150 μg/L-acute		
		4,075 μg/L-chronic		
OH	Outside mixing zone: maximum	1,800 μg/L		
	Inside mixing zone: maximum	3,600 μg/L		
	Cold water mixing zone: 30-day average	79 μg/L		
	Groundwater Monitoring			CELDs
AL		Yes		
CA		Yes		
CO		Yes		
IL		Yes		
KY		Yes		
LA		Yes		
MN		Yes		
MT		Yes		
NY		Yes		
OH		Yes		
SC		Yes		
TN		Yes		
VA		Yes		
WI		Yes		
WV		Yes		

Table 7-1. Regulations and Guidelines Applicable to Chloroform (continued)

Agency	Description	Information	References
STATE (cont.)			
	Hazardous Constituents		CELDs
AL	Maxixmum Concentration of Contaminants for the Toxicity Characteristics	60 mg/L	
CA	Concentration in waste; non-RCRA solvent waste	2.0 mg/kg	
	Maximum concentration for the toxicity characteristics	6.0 mg/L	
CO	Maximum concentration for the toxicity characteristics	6.0 mg/L	
IL	Maximum concentration for the toxicity characteristics	6.0 mg/L	
KY	Maximum concentration for the toxicity characteristics	6.0 mg/L	
LA	Maximum concentration for the toxicity characteristics	6.0 mg/L	
MA	Maximum concentration for the toxicity characteristics	6.0 mg/L	
MD	Maximum concentration for the toxicity characteristics	6.0 mg/L	
ME	Maximum concentration for the toxicity characteristics	Yes	
MN	Maximum concentration for the toxicity characteristics	6.0 mg/L	
MT	Maximum concentration for the toxicity characteristics	6.0 mg/L	
ND	Maximum concentration for the toxicity characteristics	6.0 mg/L	
NH	Maximum concentration for the toxicity characteristics	Yes	
NJ	Maximum concentration for the toxicity characteristics	6.0 mg/L	
NY	Maximum concentration for the toxicity characteristics	Yes	
PA	Maximum concentration for the toxicity characteristics	6.0 mg/L	
OH	Maximum concentration for the toxicity characteristics	6.0 mg/L	
SC	Maximum concentration for the toxicity characteristics	6.0 mg/L	
TX	Maximum leachable concentration	6.0 mg/L	
VA	Maximum concentration for the toxicity characteristics	6.0 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Chloroform (continued)

Agency	Description	Information	References
STATE (cont.)			
VT	Maximum concentration for the toxicity characteristics	6.0 mg/L	
WI	Maximum concentration for the toxicity characteristics	6.0 mg/L	
WV	Maximum concentration for the toxicity characteristics	Yes	
WY	Maximum concentration for the toxicity characteristics	6.0 mg/L	

[a]Group 2B: Possible human carcinogen
[b]Group B2: Probable human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; AW = Aquatic and Wildlife; BAT = Best Available Technology Economically Achievable; CELDs = Computer-aided Environmental Legislative Database; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FR = Federal Register; FSTRAC = Federal State Toxicology and Regulatory Alliance Committee; IARC = International Agency for Research on Cancer; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute for Occupational Safety and Health; ns = No Standard Has Been Developed; NNS = No Numerical Standard; OAQPS = Office of Air Quality Planning and Standards; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OW = Office of Water; PEL = Permissible Exposure Limit; PICs = Product of Incomplete Combustion; PQL = Permissible Quantity Limit; RfD = Reference Dose; RQ = Reportable Quantity; SOCMI = Synthetic Organic Chemical Manufacturing Industry; STEL = Short-Term Exposure Limit; THM = Trihalomethanes; TLV = Threshold Limit Value; TSCA = Toxic Substance Control Act; TSDF = Treatment, Storage and Disposal Facility; TTO = Total Toxic Organics; TWA = Time-Weighted Average for 8-hour exposure; WHO=World Health Organization

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9. GLOSSARY

Acute Exposure-Exposure-- to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc})--The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF)-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL)-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory-An estimate of acceptable drinking water levels for a chemical substance based on health effects information, A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity-The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In vivo-Occurring within the living organism.

Lethal Concentration $_{(L0)}$ (LC_{LO})-The lowest concentration of a chemical in air which has been reported to have cause death in humans or animals.

Lethal Concentration $_{(50)}$ (LC_{50})- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose $_{(50)}$ (LD $_{LO}$) lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose $_{(50)}$ (LD_{50})-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time $_{(50)}$ (LT_{50})-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour shift.

9. GLOSSARY

q_1 * -The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)-The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily TLV-TWA may not be exceeded.

Target Qrgan Toxicity-This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50})-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (I) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (l-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for

establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEETS

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ]Intermediate [ ] Chronic
Key to figure: 22
Species: Mouse
MRL: 0.1 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Larson JL, Wolf DC, Morgan KT, et al. 1994c. The toxicity of 1-week exposures to inhaled chloroform in female $B6C3F_1$ mice and male F-344 rats. Fund Appl Toxicol 22:431-446.

Experimental design: The authors investigated the ability of chloroform vapors to produce toxicity and regenerative cell proliferation in female $B6C3F_1$ mice and male Fischer 344 rats. Groups of 5 animals were exposed to 0, 1, 3, 10, 30, 100, or 300 ppm chloroform via inhalation for 6 hours a day for 7 consecutive days. Actual exposure concentrations measured for mice were 0, 1.2, 3.0, 10.0, 29.5, 101, and 288 ppm and for rats were 0, 1.5, 3.1, 10.4, 29.3, 100, and 271 ppm. Necropsies were performed on day 8. Animals were administered bromodeoxyuridine (BrdU) via implanted osmotic pump for the last 3.5 days. Cell proliferation was quantitated as the percentage of cells in S-phase (labeling index = LI) measured by the immunohistochemical detection of BrdU-labeled nuclei.

Effects noted in study and corresponding doses:

Female Mice:

300 ppm: Respiratory NOAEL; proximal tubules of kidney lined by regenerating epithelium (less serious LOAEL).

100 ppm: Renal NOAEL; centrilobular hepatocyte necrosis and severe diffuse vacuolar degeneration of midzonal and periportal hepatocytes (serious LOAEL); weight loss (less serious LOAEL).

30 ppm: Body weight NOAEL

10 ppm: Mild-to-moderate vacuolar changes in centrilobular hepatocytes (less serious LOAEL).

3 ppm: Hepatic effects NOAEL

Male Rats:

300 ppm: Swelling and mild centrilobular vacuolation of hepatocytes (less serious LOAEL).

100 ppm: Hepatic effects NOAEL.

30 ppm: Increased number of S-phase nuclei for tubule cells in the renal cortex (less serious LOAEL).

10 ppm: Renal effect NOAEL; decreased body weight gain (less serious LOAEL); epithelial goblet cell hyperplasia and degeneration of Bowman's glands in olfactory mucosa (less serious LOAEL).

3 ppm: Body weight gain and respiratory NOAEL.

Dose and end point used for MRL derivation:
[X] NOAEL [ ] LOAEL: 3 ppm for hepatic effects in mice

Uncertainty factors used in MRL derivation: 30
[ ] 1 [X] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
For dosimetry adjustment, the human equivalent concentration (HEC) is calculated based on a NOAEL of 3 ppm using Equation 4-10 (EPA 1990b). This equation was used due to the observation that chloroform achieves "periodicity" within 10% of the exposure duration (see Table A-1 below). Using Equation 4-10, the calculation is:

$$NOAEL_{(HEC)} = NOAEL \times [(blood{:}air\ coeff)_{mouse}/(blood{:}air\ coeff)_{human}]$$

given that the ratio of the blood:air partition coefficients are <1. In the case of chloroform, using the blood:air partition coefficients for the mouse is 21.3 and for the human is 7.34 (Corley et al. 1990), the ratio of mouse:human partition coefficients (21.3/7.34) is >1, therefore a default value of 1 is used to derive the $NOAEL_{HEC}$:

$$NOAEL_{HEC} = 3\ ppm \times 1$$
$$NOAEL_{HEC} = 3\ ppm$$

where:

$NOAEL_{[HEC]}$ = Human Equivalent Concentration of the NOAEL (no-observed-adverse effect level)

The MRL calculation is as follows:

$$MRL = NOAEL_{[HEC]} / UF$$
$$MRL = 3\ ppm / 30$$
$$MRL = 0.1\ ppm$$

Was a conversion used from intermittent to continuous exposure?
If so, explain: No.

Other additional studies or pertinent information that lend support to this MRL:
The Larson et al. (1994c) study is accompanied by a companion study performed by Mery et al. (1994), which examined the nasal lesions much more closely than this Larson study. The purpose of the Mery et al. study was to determine nasal cavity site-specific lesions and any cell induction/ proliferation associated with varying concentrations of chloroform (0, 1, 3, 10, 30, 100, 300 ppm) inhaled by both rats and mice 6 hours a day for 7 days. Female $B6C3F^1$ mice and male Fischer 344 rats were used. Tissue abnormalities seen grossly, histopathologically, enzymatically (cytochrome P-450 levels), and in cell proliferation (BrdU labeling of cells in the S-phase) were reported for both rats and mice. The respiratory epithelium of the nasopharyngeal meatus exhibited an increase in the size of goblet cells at 100 and 300 ppm chloroform, in addition to an increase in both neutral and

acidic mucopolysaccharides. Affected epithelium was up to twice the normal thickness. New bone formation within the nasal region was prominently seen at 10 ppm and above and followed a concentration response curve. At 1 ppm, only 1 animal showed mild bone enlargement of the first endoturbinate, with no changes seen at 3 ppm. At 10 ppm, minor enlargement was present in all animals. At 30 and 100 ppm, new osseous spicules was present at the beginning of the first endoturbinate, while at 300 ppm, the width of the new bone was almost doubled compared to controls receiving no chloroform, with lesions extending to involve up to 75% of the turbinate in all of the sites studied. Enzymatically, staining for P-450-2E1 was most prominent in the control animals in the cytoplasm of olfactory epithelial sustentacular cells and in the acinar cells of Bowman's glands, and more intense in the superficial cells than in the deep cells. In general, starting at about 3 ppm, increasing the chloroform concentration tended to decrease the amount of P-450 staining. Exposure to chloroform resulted in a dramatic increase in the number of S-phase nuclei. A clear proportional concentration-related effect was observed, with the proliferative response confined to activated periosteal cells, including both osteogenic (round) and preosteogenic (spindle) cells. The proximal and central regions of the first endoturbinate had the highest increase of cell proliferation, while the distal part had only a moderate response, with this response being statistically significant from controls at concentrations of greater than 10 ppm. Decreased body weight was observed at 300 ppm only (data not provided). In mice, decreased body weight was observed at 100 and 300 ppm (data not provided). The only treatment-related histologic change observed in female mice was a slight indication of new bone growth in the proximal part of the first endoturbinate in one mouse exposed to 300 ppm chloroform. The S-phase response was observed at chloroform concentration of 10 ppm and higher.

Using the Corley PBPK model for chloroform (Corley et al. 1990) in the Scop version (courtesy of Dr. Nancy Chiu, USEPA) to simulate the mouse exposure of chloroform by inhalation. This data is presented below:

Table A-1. Corley PBPK Model for Chloroform to Simulate Mouse Exposure by Inhalation

Time (hrs):	Blood Concentration (CA) (mg/L):
0.00	0.014
0.25	0.040
0.50	0.041
0.75	0.041
1.25	0.042
1.50	0.042
1.75	0.042
2.00	0.042
2.25	0.042
2.50	0.042
3.375	0.042
4.5	0.042
5.625	0.042
6.75	0.0006

Source: Corley et al. (1990) in the Scop version (courtesy of Dr. Nancy Chiu, USEPA).

The data furnished by this model demonstrates that the arterial blood concentration (CA) of chloroform in the mouse exposed to 3 ppm of chloroform for 6 hours reached "periodicity" within 15 minutes following exposure. This data allowed the use of EPA (1990b) Equation 4-10 to derive the acute-duration inhalation MRL for chloroform exposure.

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 39
Species: Human

MRL: 0.05 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Phoon WH, Goh KT, Lee LT, et al. 1983. Toxic jaundice from occupational exposure to chloroform. Med J Malaysia 38:31-34.

Experimental design: The study describes outbreaks of toxic hepatitis in workers occupationally exposed to chloroform in two different factories. Mostly women were employed in both places.

Effects noted in study and corresponding doses: The workers in the first outbreak were exposed to concentrations up to 400 ppm chloroform in the workplace. No other chemical was involved. Blood chloroform levels in exposed workers ranged from 0.10 to 0.29 mg/100 mL. Workplace concentration levels of chloroform ranged from 14 to 50 ppm in the second outbreak. Vomiting and toxic hepatitis were noted to occur at an inhaled concentration of 14 ppm (less serious LOAEL). All affected workers were exposed to chloroform for less than six months. The patients exhibited anorexia, nausea, vomiting, and jaundice without fever. The subjects had originally been diagnosed with viral hepatitis, however the diagnosis of toxic hepatitis due to chloroform exposure was based upon epidemiological considerations.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL : 14 ppm for hepatic effects

Uncertainty factors (UF) used in MRL derivation: 100

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Modifying factor (MF) used in MRL derivation:

[ ] 1 [X] 3 [ ] 10 (for insufficient diagnostic data to determine the seriousness of hepatotoxic effects)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

No factors were used to convert to a human equivalent dose, since the data obtained from this study was obtained from human exposures to chloroform.

The MRL calculation is as follows:

MRL = LOAEL / (UF x MF)

MRL = 14 ppm / (100 x 3)

MRL = 0.05 ppm

Was a conversion used from intermittent to continuous exposure?
If so, explain: No.

Other additional studies or pertinent information that lend support to this MRL:

The study by Bomski et al. (1967) noted similar finding in a group of 68 workers occupationally exposed to chloroform for 1–4 years in a pharmaceutical plant. Inhaled chloroform concentrations ranged from 0.01 to 1 mg/L. Other solvents were reported in the air in trace amounts. Hepatomegaly was found in 25% of chloroform-exposed workers. Toxic hepatitis was found in 5.6% of the liver enlargement cases. The workers were diagnosed as having hepatosplenomegaly, enhanced serum glutamic pyruvic transaminase [SGPT] and serum glutamic oxaloacetic transaminase [SGOT] activities, and hyper-gammaglobulinemia. Hepatosteatosis (fatty liver) was detected in 20.6% of liver-enlargement cases. Chloroform-exposed workers had a higher frequency of jaundice over the years than the control group.

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ]Intermediate [X] Chronic
Key to figure: 51
Species: Human

MRL: 0.02 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Bomski H, Sobolewska A, Strakowski A. 1967. [Toxic damage of the liver by chloroform in chemical industry workers.] Int Arch F Gewerbepathologie u. Gewerbehygiene 24:127-134 (German).

Experimental design: A group of 68 workers occupationally exposed to chloroform for 1–4 years in a pharmaceutical plant were examined. Doses of inhaled chloroform ranged from 2 to 205 ppm over a 1–4-year-period. Air concentrations of chloroform ranged from 0.01 mg/L to 1 mg/L. Other solvents were reported in the air in trace amounts.

Effects noted in study and corresponding doses: A systemic LOAEL (hepatomegaly) of 2 ppm was determined from the data presented in this study. Hepatomegaly was found in 25% of chloroform exposed workers. The results were compared with a group of unexposed controls, and a group of persons who had infectious hepatitis during the last 1–4 years. Toxic hepatitis was found in 5.6% of the liver enlargement cases (the workers were diagnosed as having hepatosplenomegaly, enhanced SGPT and SGOT activities, and hyper-gammaglobulinemia). Hepatosteatosis (fatty liver) was detected in 20.6% of liver-enlargement cases. Functional tests were negative in most of the subjects; a biopsy was not performed in any case. Chloroform-exposed workers had a higher frequency of jaundice over the years than the control group. The authors speculated that a viral infection might have been promoted in the chloroform damaged liver.

Dose end point used for MRL derivation:

[ ] NOAEL [X] LOAEL: 2 ppm for hepatic effects

Uncertainty factors used in MRL derivation: 100

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

No factors were used to convert to a human equivalent dose, since the data obtained from this study was obtained from human exposures to chloroform.

The MRL calculation is as follows:

MRL = LOAEL / (UF)

MRL = 2 ppm / (100)

MRL = 0.02 ppm

Was a conversion used from intermittent to continuous exposure?
If so, explain: No.

Other additional studies or pertinent information that lend support to this MRL:

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ]Intermediate [ ] Chronic
Key to figure: 28
Species: Mouse

MRL: 0.3 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Larson JL, Wolf DC, Butterworth BE. 1994b. Induced cytotoxicity and cell proliferation in the hepatocarcinogenicity of chloroform in female $B6C3F_1$ mice: comparison of administration by gavage in corn oil vs ad libitum in drinking water. Fund Appl Toxicol 22:90-102.

Experimental design:

This study was designed to identify a relationship between the magnitude and duration of chloroform-induced histopathologic and proliferative responses for female mice dosed with chloroform in the drinking water vs those dosed in corn oil via gavage. Authors placed 0, 60, 200, 400, 900, or 1,800 ppm of chloroform in drinking water; however, due to decreased water intake, the authors' calculation of consumed chloroform was 0, 16, 26, 53, 81, or 105 mg/kg/day.

Effects noted in study and corresponding doses:

In the 400, 900, and 1,800 ppm treatment groups, the livers had tinctorial changes characterized by pale cytoplasmic eosinophilic staining of centrilobular hepatocytes compared to the periportal hepatocytes and controls. Livers from mice treated with 200 ppm (26 mg/kg/day actual intake) chloroform or less failed to showed significant histologic changes when compared to controls. Thus the dose of 26 mg/kg/day was considered the NOAEL for hepatic effects in these mice. Chloroform exposure did cause a slight dose dependent decrease in number of cells in S-phase in the kidneys, mainly in the cortex, while there was an increase in these type of cells in the outer medullary region. Decreased body weight was observed at the two highest doses. After 4 days treatment, serum clinical chemistry analyses were not different from controls in either liver alanine aminotransferase (ALT) or sorbitol dehydrogenase (SDH) at any dose.

Dose end point used for MRL derivation:

[X] NOAEL [ ] LOAEL: 26 mg/kg/day for hepatic effects in mice

Uncertainty factors used in MRL derivation: 100

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain:

Conversion of the ppm concentration of chloroform in the drinking water to a mg/kg/day dose was provided by the authors of the paper.

The MRL calculation is as follows:

MRL = NOAEL / UF

MRL = 26 mg/kg/day / 100

MRL = 0.3 mg/kg/day

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Was a conversion used from intermittent to continuous exposure?
If so, explain:

Other additional studies or pertinent information that lend support to this MRL:

Larson et al. (1995) also studied the dose response relationships for the induction of cytolethality and regenerative cell proliferation in male Fischer 344 rats given chloroform in corn oil by gavage or in the drinking water. Groups of 12 rats were administered oral doses of 0, 3, 10, 34, 90, and 180 mg/kg/day chloroform in corn oil by gavage for 4 or for 5 days a week for 3 weeks. BrdU was administered via an implanted osmotic pump to label cells in S-phase. Statistically significant decreases in body weight gains were observed in the 180 mg/kg/day dose group at 4 days and in the 90 and 180 mg/kg/day dose groups at 3 weeks. At 34 mg/kg/day, slight-to-mild centrilobular sinusoidal leukostasis was observed after 4 days of exposure. The livers of rats given 90 mg/kg/day for 4 days had a slight increase in centrilobular pallor and necrosis of hepatocytes surrounding the central vein; the remaining central and some mid-zonal hepatocytes were swollen and displayed a cytoplasmic granularity. After 3 weeks of exposure, livers of rats in the 34 or 90 mg/kg/day dose groups did not differ from controls. In the 180 mg/kg/day dose group, the livers of rats after 4 days had scattered individual cell necrosis throughout the central and midzonal regions. The cytoplasm of the centrilobular hepatocytes was pale eosinophilic and mildly vacuolated. In the 180 mg/kg/day dose group, after 3 weeks effects were similar to those seen at 4 days after exposure. Dose-dependent increases in both ALT and SDH were observed at 4 days in the 90 and 180 mg/kg/day dose groups and at 3 weeks in the 180 mg/kg/day dose group only. A dose-dependent increase in LI was seen in rat liver after 4 days of treatment with 90 and 180 mg/kg/day by gavage, but the LI remained elevated after 3 weeks of treatment only at the 180 mg/kg/day dose. At doses of 0, 60, 200, 400, 900, and 1,800 ppm for 4 days, no microscopic alterations were seen in the kidneys after 4 days of treatment. As a general observation, rats treated for 3 weeks with 200 ppm chloroform and greater had slightly increased numbers of focal areas of regenerating renal proximal tubular epithelium and cell proliferation than were

noted in controls, but no clear dose response relationship was evident. However, the overall renal LI was not increased at any dose or time point. Similarly, only mild hepatocyte vacuolation was observed in rats given 900 or 1,800 ppm in water for 4 days and in rats given 1,800 ppm in water for 3 weeks. No increase in the hepatic LI was observed at any time point. When chloroform was administered in the drinking water at doses of 0, 60, 200, 400, 900, and 1,800 ppm for 3 weeks, no microscopic alterations were seen in the kidneys after 4 days of treatment. As a general observation, rats treated for 3 weeks with 200 ppm chloroform and greater had slightly increased numbers of focal areas of regenerating renal proximal tubular epithelium and cell proliferation than were noted in controls, but no clear dose response relationship was evident. However, the overall renal LI was not increased at any dose or time point. Similarly, only mild hepatocyte vacuolation was observed in rats given 900 or 1,800 ppm in water for 4 days and in rats given 1,800 ppm in water for 3 weeks. No increase in the hepatic LI was observed at any time point. The authors noted that these data indicated more severe hepatic and renal toxicity when chloroform is administered by gavage than in the drinking water.

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 68
Species: Dog

MRL: 0.1 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Heywood R, Sortwell RJ, Noel PRB, et al. 1979. Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. J Environ Pathol Toxicol 2:835-851.

Experimental design: An intermediate oral exposure MRL of 0.1 mg/kg/day was derived using the study by Heywood et al. (1979). The study was 7.5 years in duration in which 8 male and 8 female Beagle dogs were exposed to chloroform in toothpaste capsules, with doses of 0, 15, and 30 mg/kg/day, 6 days a week for 6 weeks. Clinical chemistry parameters were monitored at 6 and 13 weeks of exposure and thereafter at intervals of 8–32 weeks.

Effects noted in study and corresponding doses: Serum glutamic pyruvic transaminase (SGPT) activity was significantly increased ($p<0.05$) in the 30 mg/kg/day group beginning at 6 weeks and at every interval thereafter. SGPT activity was not increased in the 15 mg/kg/day group until week 130. Thus, 15 mg/kg/day is the NOAEL for intermediate duration exposure.

Dose end point used for MRL derivation:

[X] NOAEL [ ] LOAEL : 15 mg/kg/day for hepatic effects

Uncertainty factors used in MRL derivation: 100

[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain:

No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Was a conversion used from intermittent to continuous exposure?
If so, explain:

(15 mg/kg/day) x 6/7 days = 12.9 mg/kg/day

The MRL calculation is as follows:

$$MRL = NOAEL_{[ADJ]} / UF$$

$$MRL = 12.9 \text{ mg/kg/day} / 100$$

$$MRL = 0.1 \text{ mg/kg/day}$$

Other additional studies or pertinent information that lend support to this MRL:

Liver effects in animals have been reported in numerous oral studies of intermediate duration. Fatty changes, necrosis, increased liver weight, and hyperplasia have been observed in rats exposed to ≥150 mg/kg/day chloroform in drinking water for 90 days (Palmer et al. 1979). An increased incidence of sporadic, mild, reversible liver changes occurred in mice exposed to chloroform in drinking water at doses of 0.3–114 mg/kg/day for 90 days, but the incidences were not significantly higher than the incidences in controls (Chu et al. 1982a). Fatty and hydropic changes, necrosis, and cirrhosis were observed in mice treated by gavage with ≥50 mg/kg/day chloroform in oil for 90 days (Bull et al. 1986; Munson et al. 1982) or at 86 mg/kg/day in drinking water for 1 year (Klaunig et al. 1986). In contrast, centrilobular fatty changes observed in mice at 64 mg/kg/day chloroform in drinking water for 90 days appeared to be reversible (Jorgenson and Rushbrook 1980), and no liver effects were found in mice treated with ≥50 mg/kg/day in aqueous vehicles (Bull et al. 1986). In addition, hepatocellular degeneration was induced in F_1 females in a 2-generation study in which mice were treated by gavage with 41 mg/kg/day chloroform in oil (Gulati et al. 1988).

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ]Intermediate [X] Chronic
Key to figure: 89
Species: Dog

MRL: 0.01 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Heywood R, Sortwell RJ, Noel PRB, et al. 1979. Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. J Environ Pathol Toxicol 2:835-851.

Experimental design: Eight male and 8 female Beagle dogs were exposed to chloroform in toothpaste capsules. Doses used were 0, 15, and 30 mg/kg/day, 6 days a week for 7.5 years. Clinical chemistry parameters were monitored at 6 and 13 weeks of exposure and thereafter at intervals of 8–32 weeks for 7.5 years.

Effects noted in study and corresponding doses: SGPT activity was significantly increased ($p<0.05$) in the 30 mg/kg/day group beginning at 6 weeks and at every interval thereafter. SGPT activity was not increased in the 15 mg/kg/day group until week 130. No treatment-related body weight changes were observed in chloroform exposed dogs. No hematological changes were found. Increased SGPT levels, and less distinct elevation of SGOT and SAP seemed to be dose-related. However, the SGPT levels tended to return to normal during the recovery period. Bromsulphalein retention test was performed during the sixth year of the study; no treatment-related abnormality was found. No organ weight changes were found in the exposed groups. No remarkable histopathological differences were observed in dogs regarding the cardiovascular system. Fatty cysts were observed in the liver in all groups; however, in females the incidence seemed to be dose-related (3 of 12, 5 of 8, 7 of 8). Fat deposition in renal glomeruli was reportedly higher in the 30 mg/kg/day chloroform group.

Dose end point used for MRL derivation:

[ ] NOAEL [X] LOAEL: 15 mg/kg/day for hepatic effects

Uncertainty factors used in MRL derivation: 1000

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Was a conversion used from intermittent to continuous exposure?
If so, explain:

(15 mg/kg/day) x 6/7 days = 12.9 mg/kg/day.

The MRL calculation is as follows:

$$MRL = LOAEL_{[ADJ]} / UF$$

$$MRL = 12.9 \text{ mg/kg/day} / 1000$$

$$MRL = 0.01 \text{ mg/kg/day}$$

Other additional studies or pertinent information that lend support to this MRL:

Numerous chronic-duration oral studies examined hepatic and renal end points as well as neurological and cancer effects. Serious effects occurred at higher doses; 15 mg/kg/day was the lowest dose used in available animals studies. A NOAEL of 2.46 mg/kg/day for liver and kidney effects (SGPT, SGOT, BUN and SAP) was found in humans who used a dentifrice containing 0.34% or a mouthwash containing 0.43% chloroform for 1–5 years (DeSalva et al. 1974).

Agency Contact (Chemical Manager): Selene Chou

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2- 1, 2-2, and 2-3) and figures (2- 1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-l

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2- 1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2- 1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects

occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3,'Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.0005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

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(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0005 ppm.

LEGEND

See Figure 2-l

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalationexposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.0005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1 *).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

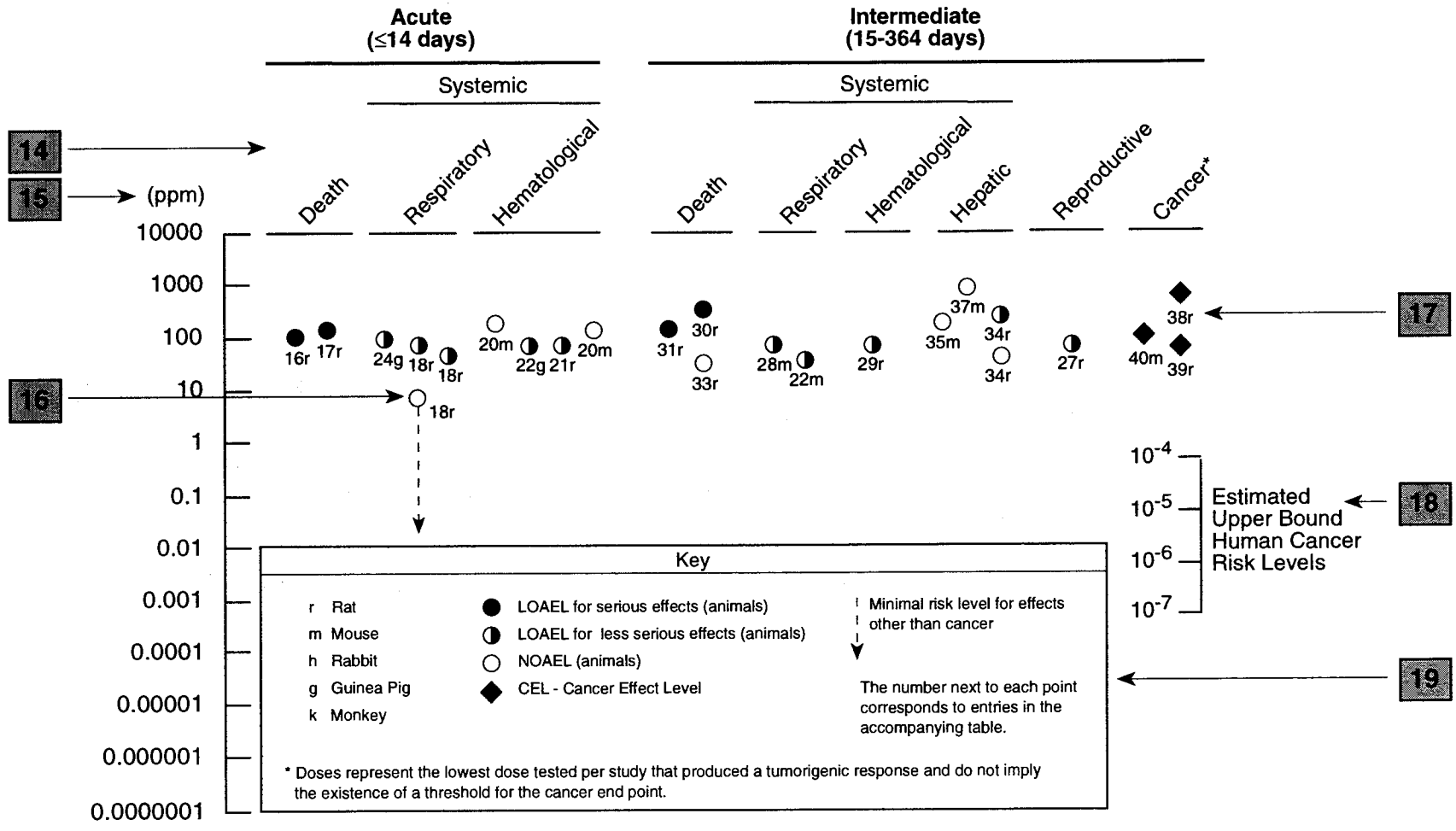
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX B

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any advers effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UT) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram

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DRAFT
TOXICOLOGICAL PROFILE FOR
CHROMIUM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2008

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UPDATE STATEMENT

A Toxicological Profile for Chromium was released in 2000. This present edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mail Stop F-32
Atlanta, Georgia 30333

Background Information

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99 499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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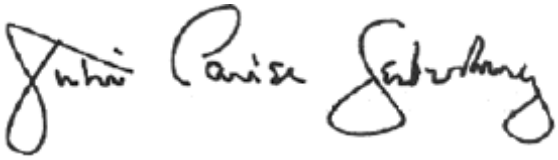

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QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for chromium. The panel consisted of the following members:

1. Dr. Detmar Beyersmann, Professor Emeritus of Biochemistry, University of Bremen, Germany,

2. John Pierce Wise, Sr., Ph.D., Director, Maine Center for Toxicology and Environmental Health, Professor of Toxicology and Molecular Epidemiology, Department of Applied Medical Sciences, University of Southern Maine, 96 Falmouth St., Portland, ME 04104-9300, and

3. Richard Sedman, Ph.D., Toxicologist, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA.

These experts collectively have knowledge of chromium's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about chromium and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Chromium has been found in at least 1,127 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which chromium is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to chromium, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS CHROMIUM?

Description	Chromium is a naturally-occurring element found in rocks, animals, plants, and soil. The three main forms of chromium are chromium(0), chromium(III), and chromium(VI). Small amounts of chromium(III) are considered to be a necessity for human health.
Uses • manufacturing • consumer products	Chromium is widely used in manufacturing processes. Chromium can be found in many consumer products such as: • wood treated with copper dichromate. • leather tanned with chromic sulfate. • stainless steel cookware.

1.2 WHAT HAPPENS TO CHROMIUM WHEN IT ENTERS THE ENVIRONMENT?

Sources	Chromium can be found in air, soil, and water after release from the manufacture, use, and disposal of chromium-based products, and during the manufacturing process.
Break down • air • water and soil	Chromium does not usually remain in the atmosphere, but is deposited into the soil and water. Chromium can change from one form to another in water and soil, depending on the conditions present.

1.3 HOW MIGHT I BE EXPOSED TO CHROMIUM?

Air exposure	You can be exposed to chromium by breathing air containing it or drinking water containing chromium. Releases of chromium into the air can occur from: • industries using or manufacturing chromium • living near a hazardous waste facility that contains chromium • cigarette smoke Rural or suburban air generally contains lower concentrations of chromium than urban air. • <10 ng/m^3 in rural areas • 0–30 ng/m^3 in urban areas • as a result of smoking, indoor air contaminated with chromium can be 10–400 times greater than outdoor air concentrations
Water and soil	Chromium is occasionally detected in groundwater, drinking water, or soil samples. Some ways to be exposed to chromium include: • drinking water containing chromium • bathing in water containing chromium
Workplace air	A large number of workers are potentially exposed to chromium. The highest potential exposure occurs in the metallurgy and tanning industries, where workers may be exposed to high air concentrations.
Food	The general population is most likely to be exposed to trace levels chromium in the food that is eaten. Low levels of chromium(III) occur naturally in a variety of foods, such as fruits, vegetables, nuts, beverages, and meats.

1.4 HOW CAN CHROMIUM ENTER AND LEAVE MY BODY?

Enter your body • inhalation	When you breathe air containing chromium, some of the chromium will enter your body through your lungs. Some forms of chromium can remain in the lungs for several years or longer.
• ingestion	A small percentage of ingested chromium will enter the body through the digestive tract.
• dermal contact	When your skin comes in contact with chromium, small amounts of chromium will enter your body.
Leave your body	Chromium(VI) is changed to chromium(III) in the body. Most of the chromium leaves the body in the urine within a week, although some may remain in cells for several years or longer.

1.5 HOW CAN CHROMIUM AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Respiratory tract	Chromium(VI) compounds are more toxic than chromium(III) compounds. The most common health problem in workers exposed to chromium involves the respiratory tract. These health effects include irritation of the lining of the nose, runny nose, and breathing problems (asthma, cough, shortness of breath, wheezing). Workers have also developed allergies to chromium compounds, which can cause breathing difficulties and skin rashes. The concentrations of chromium in air that can cause these effects may be different for different types of chromium compounds, with effects occurring at much lower concentrations for chromium(VI) compared to chromium(III) . However, the concentrations causing respiratory problems in workers are at least 60 times higher than levels normally found in the environment. Respiratory tract problems similar to those observed in workers have been seen in animals exposed to chromium in air.
Stomach and Small Intestine	The main health problems seen in animals following ingestion of chromium(VI) compounds are to the stomach and small intestine (irritation and ulcer) and the blood (anemia). Chromium(III) compounds are much less toxic and do not appear to cause these problems.
Male Reproductive System	Sperm damage and damage to the male reproductive system have also been seen in laboratory animals exposed to chromium(VI).
Cancer	The International Agency for Research on Cancer (IARC) has determined that chromium(VI) compounds are carcinogenic to humans. The National Toxicology Program 11th Report on Carcinogens classifies chromium(VI) compounds as known to be human carcinogens. In workers, inhalation of chromium(VI) has been shown to cause lung cancer. An increased in stomach tumors was observed in humans exposed to chromium(VI) in drinking water. In laboratory animals, chromium(VI) compounds have been shown to cause tumors to the stomach,intestinal tract and lung.

1.6 HOW CAN CHROMIUM AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in children	There are no studies that have looked at the effects of chromium exposure on children. It is likely that children would have the same health effects as adults. We do not know whether children would be more sensitive than adults to the effects of chromium.
Birth defects	There are no studies showing that chromium causes birth defects in humans. In animals, some studies show that exposure to high doses during pregnancy may cause miscarriage, low birth weight, and some changes in development of the skeleton and reproductive system. Birth defects in animals may be related, in part, to chromium toxicity in the mothers.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CHROMIUM?

Avoid tobacco smoke	Chromium is a component of tobacco smoke. Avoid smoking in enclosed spaces like inside the home or car in order to limit exposure to children and other family members.
Avoid older pressure treated lumber	In the past, pressure treated wood used chromated copper arsenate; however, the use of this product in residential settings was discontinued effective December 31, 2003. Avoiding older pressure treated lumber can reduce your risk of exposure to chromium. You may also have your water tested to ensure that you are not exposed to high levels of chromium.
Launder clothing from work sites	Clothing or items removed from the workplace may contain chromium if you are employed in a setting where occupational exposure is significant. Therefore, common sense hygiene and laundry practices may help avoid unnecessary exposures.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CHROMIUM?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

Detecting exposure	Since chromium is a required nutrient in the body and is normally present in food, chromium is normally present in blood, urine, and body tissues.
Measuring exposure	Higher than normal levels of chromium in blood or urine may indicate that a person has been exposed to chromium. However, increases in blood and urine chromium levels cannot be used to predict the kind of health effects that might develop from that exposure.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as “not-to-exceed” levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it.

Some regulations and recommendations for chromium include the following:

Levels in drinking water set by EPA	The EPA has determined that exposure to chromium in drinking water at concentrations of 1 mg/L for 1 day or 10 days is not expected to cause any adverse effects in a child.
Levels in bottled water set by FDA	The FDA has determined that the chromium concentration in bottled drinking water should not exceed 0.1 mg/L.
Levels in workplace air set by OSHA	OSHA set a legal limit for chromium(VI) of 0.0005 mg/m^3 chromium in air averaged over an 8-hour work day, for chromium(III) of 0.5 mg/m^3 chromium in air averaged over an 8-hour work day, and for chromium(0) of 1.0 mg/m^3 chromium in air averaged over an 8-hour work day.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfilesTM CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CHROMIUM IN THE UNITED STATES

Chromium is a naturally occurring element present in the earth's crust. Chromium is released to the environment from natural and anthropogenic sources, with the largest release occurring from industrial releases. The industries with the largest contribution to chromium release include metal processing, tannery facilities, chromate production, stainless steel welding, and ferrochrome and chrome pigment production. The estimated atmospheric concentrations of chromium in U.S. urban and nonurban areas typically contains mean total chromium concentrations ranging from 5 to 525 ng/m^3. The levels of chromium in U.S. fresh waters typically range from <1 to 30 µg/L, with a median value of 10 µg/L. Typical U.S. drinking water supplies contain total chromium levels within a range of 0.2–35 µg/L however, most supplies in the United States contain <5 µg/L of chromium. Recent monitoring data of drinking water supplies in California indicated that 86% of the sources tested had levels of chromium (reported for chromium(VI)) below 10 µg/L. U.S. soil levels of total chromium range from 1 to 2,000 mg/kg, with a mean level of 37 mg/kg. In ocean water, the mean chromium concentration is 0.3 µg/L. .

The general population is exposed to chromium by inhaling ambient air, ingesting food, and drinking water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products or soils that contain chromium. The primary route of nonoccupational workers, however, is food ingestion. Chromium content in foods varies greatly and depends on the processing and preparation. In general, most fresh foods typically contain chromium levels ranging from <10 to 1,300 µg/kg. Present-day workers in chromium-related industries can be exposed to chromium concentrations 2 orders of magnitude higher than the general population.

2.2 SUMMARY OF HEALTH EFFECTS

Chromium as an Essential Nutrient. Chromium(III) is an essential nutrient required for normal energy metabolism. The Institute of Medicine (IOM) of the National Research Council (NRC) determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 µg chromium(III)/day for adolescents and adults. IOM reported average plasma chromium concentrations of 2–3 nmol/L (equivalent to 0.10–16 µg/L) and an average urinary chromium excretion of 0.22 µg/L or 0.2 µg/day.

Currently, the biological target for the essential effects of chromium(III) is unknown. Chromodulin, also referred to as glucose tolerance factor (GTF), has been proposed as one possible candidate. The function of chromodulin, an oligopeptide complex containing with four chromic ions, has not been established; however, a possible mechanism is that chromodulin facilitates the interaction of insulin with its cellular receptor sites, although this has not been proven.

Whether chromium(III) should be considered an essential element remains controversial. Reports of chromium(III) deficiency are rare and there is no recognized disease that is attributed to chromium deficiency as there is with most other essential minerals (e.g., Wilson's disease for people with copper deficiency). Evidence of overt signs of apparent chromium deficiency in humans is limited to a few case reports. In one such case report, a woman receiving total parenteral nutrition for 3 years exhibited peripheral neuropathy, weight loss, and impaired glucose metabolism. Administration of insulin did not improve glucose tolerance. Administration of 250 μg/day chromium without exogenous insulin resulted in normal glucose tolerance of an oral load of glucose and the absence of peripheral neuropathy. Thus, direct evidence of chromium(III) deficiency in humans is lacking. In animals, severe chromium deficiency is also difficult to induce, but when it was induced hyperglycemia, decreased weight gain, elevated serum cholesterol levels, aortic plaques, corneal opacities, impaired fertility, and lethality were observed. Administration of inorganic trivalent chromium compounds or extracts of brewers' yeast resulted in decreased blood glucose levels and cholesterol levels and regression of atherosclerotic plaques. Improved insulin sensitivity also resulted in an increased incorporation of amino acids into proteins and cell transport of amino acid in rats receiving supplemental chromium. Thus, whether chromium is a true essential element or a pharmacological agent is still under debate.

Studies have shown that chromium supplementation (Brewer's yeast, extracts of brewer's yeast, synthetic chromium compounds with biological activity, chromium(III) picolinate, and inorganic trivalent chromium) in deficient and marginally deficient subjects can result in improved glucose, protein, and lipid metabolism. In general, these studies have demonstrated improved glucose tolerance to an oral glucose load in Type II diabetics (adult onset) and nondiabetic elderly subjects receiving a 4–200 μg/day chromium supplement and improved plasma lipid profiles (e.g., decreased total cholesterol, LDL-cholesterol, and serum lipids and increased in HDL-cholesterol); improvements in serum lipids and cholesterol levels may be secondary to the decreased serum glucose levels.

Chromium picolinate has been used as a dietary supplement to aid in weight loss and increase lean body mass; however, the role of chromium in the regulation of lean body mass, percentage body fat, and weight

reduction is highly controversial with negative and positive results being reported in the literature. Numerous studies have evaluated the relationship between weight loss or increases in lean body mass in active and sedentary adults and chromium picolinate supplementation, with mixed results reported. Information on adverse health effects of chromium(III) compounds, including dietary supplements, in humans and animals is reviewed below. However, based on a limited number case studies reporting adverse effects in humans ingesting high-dose chromium(III) supplements, individuals using chromium supplements are cautioned to avoid taking more than recommended doses.

Chromium Toxicokinetics. The toxicokinetics of a given chromium compound depend on the valence state of the chromium atom and the nature of its ligands. For inhaled chromium compounds of any valence state, the amount and location of deposition of inhaled chromium will be determined by factors that influence convection, diffusion, sedimentation, and interception of particles in the airways. In general, less water-soluble chromium compounds that deposit in the pulmonary region can be expected to have a longer retention time in the lung than more soluble forms. Most quantitative studies of the gastrointestinal absorption of chromium in humans have estimated the absorption fraction to be <10% of the ingested dose. In general, these studies suggest that the absorption fraction of soluble chromium compounds is higher than insoluble forms (e.g., $CrCO_3$), and is higher for soluble chromium(VI) compounds (e.g., $K_2Cr_2O_7$) than soluble chromium(III) (e.g., $CrCl_3$). Chromium(VI) is reduced in the stomach to chromium(III), which lowers the absorbed dose from ingested chromium(VI). Absorption is also affected by nutritional status; the absorption fraction is higher when dietary intakes are lower. Chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged.

Absorbed chromium distributes to nearly all tissues, with the highest concentrations found in kidney and liver. Bone is also a major depot and may contribute to long-term retention kinetics or chromium. Chromium(VI) is reduced to chromium(III) via the intermediate forms of chromium(V), chromium(IV). Reduction of chromium(VI) to chromium(III) can give rise to reactive intermediates, chromium adducts with proteins and deoxyribonucleic acid (DNA), and secondary free radicals. Chromium(VI) in blood is taken up into red blood cells, where it undergoes reduction and forms stable complexes with hemoglobin and other intracellular proteins, which are retained for a substantial fraction of the red blood cell lifetime. Absorbed chromium can be transferred to fetuses through the placenta and to infants via breast milk. Absorbed chromium is excreted predominantly in urine. Chromium has been shown to be secreted in bile of animals following parenteral (e.g., intravenous) injection of chromium(VI) or chromium (III) compounds. Chromium can also be eliminated by transfer to hair and nails.

Health Effects of Chromium. The health effects associated with exposures to chromium(VI), chromium(III) and chromium (IV) are reviewed in detail in Chapter 3. In general, chromium(VI) compounds are more toxic than chromium(III) compounds. The higher toxic potency of chromium(VI) compared to chromium(III) is complex. Chromium(VI) enters cells by facilitated uptake, whereas chromium(III) crosses cell membranes by simple diffusion; thus, cellular uptake of chromium(VI) is more effective than of chromium(III). Furthermore, in biological systems, reduction of chromium(VI) to chromium(III) results in the generation of free radicals, which can form complexes with intracellular targets. Health effects of chromium compounds can vary with route of exposure, with certain effects specific for the portal of entry. For example, respiratory effects are associated with inhalation of chromium compounds, but not with oral and dermal exposures, and gastrointestinal effects are primarily associated with oral exposure. However, as described below, effects of chromium are not limited to the portal of entry, with hematological, immunological, and reproductive systems also identified as targets for chromium. In addition to noncancer health effects, results of occupational exposure studies and chronic-duration animal studies indicate that inhalation and oral exposures to chromium(VI) compounds are associated with respiratory and gastrointestinal system cancers, respectively (see discussion under chromium(VI) below for additional information).

Chromium(VI)

The primary effects associated with exposure to chromium(VI) compounds are respiratory, gastrointestinal, immunological, hematological, reproductive, and developmental. In addition, dermal and ocular irritation may occur from direct contact. Based on available dose-response data in humans and animals, the most sensitive noncancer effects of chromium(VI) compounds are respiratory (nasal and lung irritation, altered pulmonary function), gastrointestinal (irritation, ulceration and nonneoplastic lesions of the stomach and small intestine), hematological (microcytic, hypochromic anemia), and reproductive (effects on male reproductive organs, including decreased sperm count and histopathological change to the epididymis). As reviewed below, respiratory and gastrointestinal effects appear to be portal-of-entry effects for inhalation and oral exposure, respectively. Similarly, chromium sensitization, the major immunological effect of chromium(VI), typically presents as allergic contact dermatitis resulting from dermal exposures in sensitized individuals, although respiratory effects of sensitization (asthma) may also occur. Accidental or intentional ingestion of extremely high doses of chromium(VI) compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal,

and neurological effects as part of the sequelae leading to death or in patients who survived because of medical treatment.

Respiratory Effects. The respiratory tract is the major target of inhalation exposure to chromium(VI) compounds in humans and animals. Respiratory effects have been observed in workers in the following chromium-related industries: chrome plating, chromate and dichromate production, stainless steel welding, and possibly ferrochromium production and chromite mining. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. Intermediate- and chronic-duration exposure of workers to chromium(VI) compounds has resulted in epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulceration of the nasal septum, bronchitis, pneumonoconiosis, decreased pulmonary function, and pneumonia. In some chromium-sensitive patients, inhalation of airborne chromium(VI) compounds in the workplace has resulted in asthma. Nasal irritation and mucosal atrophy and decreases in pulmonary function have occurred at occupational exposure levels ≥0.002 mg chromium(VI)/m^3 as chromium trioxide mist. Autopsies of humans who died from cardiopulmonary arrest after ingesting chromium(VI) compounds have revealed pleural effusion, pulmonary edema, bronchitis, and acute bronchopneumonia. Respiratory effects due to ingestion of nonlethal doses are not likely to occur. It is not certain whether skin contact with chromium compounds could result in respiratory effects.

Adverse effects on the respiratory system following inhalation exposure to chromium(VI) have also been observed in animals. Acute- and intermediate-duration exposure to moderate levels of chromium(VI) compounds generally caused mild irritation, accumulation of macrophages, hyperplasia, inflammation, and impaired lung function. A lowest-observed-adverse-effect level (LOAEL) of 0.025 mg chromium(VI)/m^3 as potassium dichromate particles for increased percentage of lymphocytes in bronchoalveolar lavage (BAL) fluid in rats exposes for 28 or 90 days was identified. Obstructive respiratory dyspnea at ≥0.2 mg chromium(VI)/m^3, fibrosis at ≥0.1 mg chromium(VI)/m^3, and hyperplasia at ≥0.05 mg chromium(VI)/m^3 were found in the lungs of rats exposed to sodium dichromate for 30 or 90 days. The fibrosis and hyperplasia were reversible. Increases in the levels of total protein, albumin, and activity of lactate dehydrogenase and β-glucuronidase were observed in the bronchoalveolar lavage fluid. Nasal septum perforation, hyperplasia and metaplasia of the larynx, trachea, and bronchus, and emphysema developed in mice exposed to chromium trioxide mists for 1 year. Mice exposed chronically to 4.3 mg chromium(VI)/m^3 as calcium chromate also had epithelial necrosis and hyperplasia of the bronchiolar walls.

Gastrointestinal Effects. Acute oral exposure of humans to lethal or near-lethal doses of chromium(VI) has produced adverse gastrointestinal effects, including abdominal pain, vomiting, gastrointestinal ulceration, hemorrhage and necrosis, and bloody diarrhea. Gastrointestinal effects have also been reported in association with chronic oral exposure of humans to chromium(VI). In a cross-sectional study conducted in 1965 of 155 people whose well water contained 20 mg chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and oral ulcer, diarrhea, abdominal pain, indigestion, and vomiting. Epigastric pain, irritation, and ulceration have been reported in occupational studies of chrome plating and chromate production workers. Exposures in these studies included inhalation and ingestion of chromium (e.g., mucocilliary clearance of inhaled chromium particles to the gastrointestinal tract and/or ingestion secondary to hand-to-mouth activity) and outcomes may have been influenced by other factors, such as stress and diet. Gastrointestinal effects from dermal exposures or absorption of inhaled chromium(VI) are not anticipated.

Studies in animals show that the gastrointestinal system is a primary target of intermediate- and chronic-duration oral exposure to chromium(VI). Adverse effects were observed in the gastrointestinal tract of F344/N rats and B6C3F1 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, with LOAEL values of 3.5 mg chromium(VI)/kg/day for duodenal histiocytic infiltration of the duodenum in male and female rats and of 3.1 mg chromium(VI)/kg/day for epithelial hyperplasia in mice. At a higher dose (20.9 mg chromium(VI)/kg/day), more severe effects (ulcer and epithelial hyperplasia and metaplasia of the glandular stomach) were observed in rats. Histopathological changes of the duodenum (epithelial hyperplasia and histiocytic cellular infiltrate) were also reported in a 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, a LOAEL values of 2.8 mg chromium(VI)/kg/day. After exposure for 2 years, histopathogical changes were observed in the gastrointestinal tract of rats and mice. In male and female rats exposed to 0.77 and 2.4 chromium(VI)/kg/day, respectively, histiocytic infiltration of the duodenum was observed. In mice, duodenal epithelial hyperplasia was observed in males and females at 0.38 mg chromium(VI)/kg/day and histiocytic cellular infiltration of the duodenum was observed in males at 2.4 mg chromium(VI)/kg/day and in females at 3.1 mg chromium(VI)/kg/day.

Results of intermediate-duration inhalation studies in animals yield mixed results regarding the potential for gastrointestinal effects. Although rats exposed by inhalation to $\leq$0.2 mg chromium(VI)/m^3 as sodium dichromate for $\leq$90 days did not have histopathological changes in the gastrointestinal tract, mice exposed chronically to 4.3 mg chromium(VI)/m^3 were reported to have occasional small ulcerations in the

stomach and intestinal mucosa; however, the potential of oral exposure via grooming behavior cannot be excluded.

Immunological Effects. Exposure to chromium(VI) compounds may lead to allergic sensitization in some individuals. Sensitization to chromium is produced through two types of hypersensitivity reactions: type I, an immediate onset, IgE-mediated immune mechanism, and type IV, a delayed, cell-mediated immune mechanism. Following an induction phase during which the individual becomes sensitized, subsequent exposures result in an allergic response, with symptoms typically presenting as dermatitis or asthma. Sensitization may occur from inhalation, oral, and/or dermal exposure. Estimates of the prevalence of chromium sensitivity in the general U.S. population range from 0.08 to 7%, depending upon the population evaluated. For dermal responses, the allergic response following direct skin contact with chromium compounds is characterized by eczema or dermatitis; typically, chromium-induced allergic contact dermatitis is isolated to areas at the site of contact, rarely occurring in areas remote from the point of contact. However, oral exposure to chromium(VI) has been shown to exacerbate dermatitis of sensitive individuals. The acute response phase lasts for a few days to a few weeks and is characterized by erythema, edema, and small and large blisters; the chronic phase exhibits similar clinical features, but may also include thickened, scaly, and fissured skin. Exposure to chromium compounds in chromium-related occupations appears to be the major cause of chromium contact dermatitis. Patch testing has identified chromium-sensitized workers in the printing and lithography industry, in automobile factories where assemblers handled nuts, bolts, and screws, in wet sandpapering of primer paint where workers were exposed to zinc chromate, in the cement industry, in railroad systems and diesel locomotive repair shops where antirust diesel-engine coolants and radiator fluids contained sodium chromate, in tanneries, and in the welding, plating, wood, and paper industries. Other sources of chromium that have resulted in chromium sensitivity include dichromate-containing detergents and bleach, glues, machine oils, foundry sand, match heads, boiler linings, and magnetic tapes. Exposure to low levels of chromium as found in consumer products could result in sensitization or a reaction in sensitized individuals; therefore, in hypersensitive individuals may develop rashes and erythema from contact with consumer products containing chromium. Oral doses of potassium dichromate exacerbated the dermatitis of sensitive individuals.

Several studies have estimated the exposure level required to elicit a dermal response in chromium-sensitized individuals; exposure levels of 4–25 ppm produced sensitization and elicitation of chromium-induced allergic dermatitis. However, confounding factors, such as variability in testing methods (including different chromium compounds used in challenge testing) and individual sensitivity,

complicate interpretation of results. Furthermore, the response of an individual to dermal challenge may vary over time due to changes in exposure to the sensitizing agents; if an individual is removed from exposure, circulating IgE levels may decrease, resulting in decreased sensitivity to dermal challenge. Therefore, it is anticipated that the exposure level required to elicit a dermal response in sensitized individuals will be highly variable.

Asthmatic attacks have occurred in chromium-sensitive individuals exposed by inhalation in occupational settings to chromium trioxide vapors and chromium fumes from stainless steel welding. When challenged with sodium chromate or potassium dichromate via nebulizer, chromium-sensitive patients displayed anaphylactoid reactions, characterized by dermatitis, facial angioedema and erythema, nasopharyngeal pruritus, cough, wheezing, bronchospasms, increased plasma histamine levels, urticaria, and decreased forced expiratory volume. While chromium-induced asthma might occur in some sensitized individuals exposed to elevated concentrations of chromium in air, the number of sensitized individuals is low, and the number of potentially confounding variables in the chromium industry is high.

Studies in animals also indicate that the immune system is a target for inhaled and ingested chromium(VI) compounds. Effects reported include stimulation of the humoral immune system and increased phagocytic activity of macrophages, increased proliferative responses of splenocytes to T- and B-cell mitogens and to the antigen mitomycin C and histopathological alteration (histiocytic cellular infiltration) of pancreatic lymph nodes; contact dermatitis has been elicited in guinea pigs and mice.

Hematological Effects. As discussed above (*Chromium Toxicokinetics*), chromium(VI) is distributed to and accumulated by the erythrocyte; once inside the cell, it is rapidly reduced to chromium(III) via the reactive intermediates chromium(V) and chromium(IV), and binds to hemoglobin and other ligands. The chromium-hemoglobin complex is relatively stable and remains sequestered within the cell over the life-span of the erythrocyte, with approximately 1% of chromium eluting from the erythrocyte daily. Occupational studies and other studies in humans have not consistently reported hematological effects, although microcytic, hyprochromic anemia has been reported in several recent animals studies on chromium(VI) compounds (detailed discussion follows). However, it is possible that small, exposure-related changes in hematological parameters may not have been detected in occupational exposure studies, if values were within normal clinical ranges. Hematological findings in humans exposed to lethal doses of chromium(VI) compounds are difficult to interpret in the context of multiple systemic effects observed leading up to death, including hemorrhage.

Results of acute-, intermediate-, and chronic-duration studies in animals identify the hematological system as one of the most sensitive effects of oral exposure to chromium(VI). Microcytic, hypochromic anemia, characterized by decreased mean cell volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit (Hct), and hemoglobin (Hgb), was observed in rats and mice orally exposed to chromium(VI) compounds for exposure durations ranging from 4 days to 1 year. The severity of anemia exhibited dose- and duration-dependence, with maximum effects observed after approximately 3 weeks of exposure; with increasing exposures durations (e.g., 14 weeks–1 year), anemia is less severe, presumably due to compensatory hematopoietic responses. In general, effects observed in rats were more severe than those in mice.

Acute exposure of male rats to sodium dichromate dihydrate in drinking water for 4 days, produced a slight, but statistically significant decrease (2.1%) in MCH in rats exposed to 2.7 mg chromium(VI)/ kg/day, but not at 0.7 mg chromium(VI)/kg/day. With increasing doses (≥7.4 mg chromium(VI)/kg/day), additional decreases in MCH and decreased MCV were observed. Similar effects were observed in male and female rats exposed for 5 days, with effects observed at 4.0 and 4.1 chromium(VI)/kg/day, respectively; a no-observed-adverse-effect level (NOAEL) was not established. Although the magnitude of changes to hematological parameters after acute exposure was minimal, since severe effects on hematological parameters were observed following intermediate exposure durations, with severity peaking at exposure durations of 22 days to 3 months, the minimal hematological alterations observed following acute exposure are considered to be indicative of adverse hematological effects.

More severe microcytic, hypochromic anemia occurred in rats and mice following exposure to sodium dichromate dihydrate in drinking water for 22 or 23 days. Decreased Hct, Hgb, MCV, and MCH occurred at ≥0.77 mg chromium(VI)/kg/day, with decreases exhibiting dose-dependence; effects were not observed at 0.21 mg chromium(VI)/kg/day. After exposure for 3 months to 1 year, microcytic, hypochromic anemia in rats and mice was less severe than that observed after 22 or 23 days. Hematological effects, including decreased hematocrit, hemoglobin, and erythrocyte count, have also been reported in rats exposed to chromium trivalent oxide mist for 90 days, with a LOAEL value of 0.23 mg chromium(VI)/m^3.

Reproductive Effects. Results of studies in humans and animals suggest that chromium(VI) causes adverse reproductive effects, although evidence from studies in animals is much stronger than from studies in humans. Although information regarding reproductive effects in humans is limited, the following effects have been reported: a significant increase in the number of morphologically abnormal

sperm; significant decreases on sperm count and motility; and greater incidences of complications during pregnancy and childbirth (toxicosis and postnatal hemorrhage). There no evidence of reproductive effects in humans environmentally exposed to chromium(VI).

Studies in laboratory animals show that acute- and intermediate-duration exposure to chromium(VI) produces adverse reproductive effects, with the male reproductive system exhibiting the highest sensitivity. Following a 6-day gavage administration of ≥5.2 mg chromium(VI)/kg/day as chromic acid to Wister rats, decreased sperm count, increased percentage of abnormal sperm, and morphological changes to seminiferous tubules (decreased diameter of seminiferous tubules and germ cell rearrangement) were observed (observations were made 6 weeks after completion of treatment); a NOAEL was not defined in this study. The male reproductive system was identified as a target for oral chromium(VI) exposure in intermediate-duration studies in monkeys, rats, and rabbits. Decreased sperm count and motility and histopathological changes to the epididymis (ductal obstruction, development of microcanals, depletion of germ cells, hyperplasia of Leydig cells, and Sertoli cell fibrosis) have been reported in monkeys exposed to 2.1 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 180 days. Effects on male reproductive organs and sexual behavior in rats and mice have been reported at doses of ≥2.6 mg chromium(VI)/kg/day.

In NTP studies designed to confirm or refute these findings, the reproductive effects of different concentrations of chromium(VI) as potassium dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated. Microscopic examinations of the testes and epididymis for Sertoli nuclei and preleptotene spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects at daily doses up to 32.2 mg chromium(VI)/kg/day. Similarly, exposure to sodium dichromate dihydrate in drinking water did not produce morphological changes to male reproductive organs of B6C3F1 mice exposed to 27.9 or 5.9 mg chromium(VI)/kg/day for 3 months or 2 years, respectively, or affect sperm count or motility in male B6C3F1, BALB/c, and C57BL/6N mice exposed to 8.7 mg chromium(VI)/kg/day for 3 months.

Other reproductive effects reported in rats and mice include altered weights of female reproductive organs, decreased number of follicles and ova, increased pre- and/or postimplantation losses, and increased resorptions at doses of ≥5 mg chromium(VI)/kg/day. Mixed results have been found in studies designed to assess the effects of chromium(VI) exposure on fertility. No effects on fertility were observed in mice were exposed to ≤37 mg chromium(VI)/kg/day as potassium dichromate in the diet. Decreased mating and fertility, increased preimplantation losses, and increased resorptions have been

observed in rats and mice exposed to ≥37 mg chromium(VI)/kg/day or 52 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 20 or 90 days prior to mating. Pre- and postimplantation loss and decreased litter size was also observed in mice exposed to ≥46 mg chromium(VI)/kg/day as potassium dichromate in drinking water throughout gestation. Significant decreases in the number of implantations and viable fetuses were observed when male mice exposed to 6 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 12 weeks were mated with unexposed female mice; however, sperm count was not measured and the classification of non-viable fetuses was not presented in this report. However, a similarly designed study did not find any alterations in the number of implantations or viable fetuses in unexposed female rats mated with males exposed to 42 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 12 weeks. It is not known if the species difference contributed to these conflicting results. Decreases in the number of implantations and viable fetuses and an increase in the number of animals with resorptions were also seen in females exposed for 12 weeks to 6 mg chromium(VI)/kg/day as potassium dichromate mated with unexposed males.

Developmental Effects. No studies were located regarding developmental effects in humans after exposure to chromium compounds. A number of oral exposure animal studies have shown that chromium(VI) is a developmental toxicant following premating and/or *in utero* exposure. In developmental studies in rats and mice, gestational exposure produced increased postimplantation loss, decreased number of live fetuses/litter, decreased fetal weight, internal and skeletal malformations, and delayed sexual maturation in offspring; however, these effects were observed at relatively high doses (e.g., ≥35 mg chromium(VI)/kg/day). In mated female rats administered 35.7 mg chromium(VI)/mg/day as potassium dichromate by gavage on gestational days 1–3, a decreased number of pregnancies were observed; exposure on gestational days 4–6 resulted in decreased number of viable fetuses and increased number of resorptions, but did not alter the number of pregnancies. Exposure of female rats to ≥37mg chromium(VI)/kg/day and mice to ≥52 mg chromium(VI)/kg/day to potassium dichromate(VI) in drinking water for 20 or 90 days followed by mating to unexposed males resulted in fetal mortality (postimplantation losses, resorptions, and decreased number of live fetuses), decreased growth (decreased fetal body weights and crown-rump length), reduced ossification, subdermal hemorrhagic patches, and kinky tails. Similar effects (increased resorptions, increased postimplantation losses, subdermal hemorrhages, decreased cranial ossification, tail kinking, and decreased fetal body weight and decreased crown-rump length) were observed in the offspring of mice exposed to 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation. In mice exposed to 53 mg chromium(VI)/ kg/day as potassium dichromate in drinking water during gestational days 6–14, fetal mortality,

subdermal hemorrhagic patches, and reduced ossification were observed in the offspring. Impaired development of the reproductive system (delayed vaginal opening) was observed in the offspring of mice exposed to 66 mg chromium(VI)/kg/day as potassium dichromate in the drinking water on gestation day 12 through lactation day 20.

Dermal Effects. Chromium(VI) compounds can produce effects on the skin and mucous membranes. These include irritation, burns, ulcers, and an allergic type of dermatitis. Irritation of respiratory mucosal tissues, nasal septum ulcers, and perforation are reviewed above under Respiratory Effects and allergic dermatitis is reviewed above under Respiratory Effects and Immunological Effects. Most dermal effects reported were either due to occupational intermediate-chronic exposure or acute exposure to high levels of chromium compounds. Environmental exposure to chromium compounds is not likely to result in dermal effects. Acute dermal exposure to chromium(VI) compounds can cause skin burns. Application of a salve containing potassium chromate to the skin of some individuals to treat scabies resulted in necrosis and sloughing of the skin, and some individuals even died as a result of infections of these areas. A worker whose skin came into direct contact with the chromic acid as a result of an industrial accident developed extensive skin burns.

Although skin contact with chromate salts may cause rashes, untreated ulcers or sores (also called chrome holes) on the skin can be a major problem because they can deeply penetrate the skin with prolonged exposure. For example, in an early case of a tannery worker, the penetration extended into the joint, necessitating amputation of the finger. However, chrome sores heal if exposure is discontinued, leaving a scar. Chrome sores are more often associated with occupational exposure to chromium(VI) compounds. Although chrome sores are more likely associated with direct dermal contact with solutions of chromates, exposure of the skin to airborne fumes and mists of chromium(VI) compounds may contribute to the development. Industries that have been associated with the development of chrome sores in workers include chromate and dichromate production, chrome plating, leather tanning, planographic printing, and chromite ore processing. Among the chromium(VI) compounds that workers in these industries are exposed to are chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate, and ammonium dichromate.

In addition, tonsillitis, pharyngitis, atrophy of the larynx, and irritation and ulceration of mouth structures and buccal mucosa can occur from exposure to high levels of chromium(VI) compounds. These effects were seen in workers in chrome plating plants, where excessively high concentrations of chromium trioxide fumes were present. High incidences of inflammation of oral structures, keratosis of the lips,

gingiva, and palate, gingivitis, and periodontis were also observed in chromate production workers. Oral doses of potassium dichromate exacerbated the dermatitis of chromium sensitized individuals.

Dermal effects observed in animals after direct application of potassium dichromate to their skin include inflammation, necrosis, corrosion, eschar formation, and edema in rabbits and skin ulcers in guinea pigs.

Ocular Effects. Ocular effects can occur as a result of direct contact of eyes with chromium(VI) compounds. Effects reported include corneal vesication in a man with ocular exposure to a drop or crystal of potassium dichromate and congestion of the conjunctiva, discharge, corneal scar, and burns in chromate production workers as a result of accidental splashes.

Genotoxicity. Numerous studies have evaluated the genotoxicity of chromium(VI) compounds. Results of occupational exposure studies in humans, although somewhat compromised by concomitant exposures to other potential genotoxic compounds, provide evidence of chromium(VI)-induced DNA strand breaks, chromosome aberrations, increased sister chromatid exchange, unscheduled DNA synthesis, and DNA-protein crosslinks. Although most of the older occupational exposure studies gave negative or equivocal results, more recent studies have identified chromosomal effects in exposed workers. Findings from occupational exposure studies are supported by results of *in vivo* studies in animals, *in vitro* studies in human cell lines, mammalian cells, yeast and bacteria, and studies in cell-free systems.

Cancer. Occupational exposure to chromium(VI) compounds in various industries has been associated with increased risk of respiratory system cancers, primarily bronchogenic and nasal. Among the industries investigated in retrospective mortality studies are chromate production, chromate pigment production and use, chrome plating, stainless steel welding, and ferrochromium alloy production. Numerous studies of cancer mortality among chromate production workers have been reported. Collectively, these studies provide evidence for associations between lung cancer mortality and employment in chromate production, with risks declining with improved industrial hygiene. Less consistently, nasal cancers have been observed. In chromate pigment and chrome plating workers, elevated lung cancer rates in comparison to reference populations (e.g., standard mortality ratios [SMRs]) and increased lung cancer rates in association with increased potential for chromium exposure (e.g., job type, employment duration) have been reported. Workers in the stainless steel welding and ferrochromium alloy industries are exposed to chromium(VI) compounds, as well as other chemical hazards that could contribute to cancer (e.g., nickel); however, results of studies of cancer mortality in

these populations have been mixed. Environmental exposure of humans to chromium(VI) in drinking water resulted in statistically significant increases in stomach cancer.

Chronic inhalation studies provide evidence that chromium(VI) is carcinogenic in animals. Mice exposed to 4.3 mg chromium(VI)/m^3 as calcium chromate had a 2.8-fold greater incidence of lung tumors, compared to controls. In addition, numerous animal studies using the intratracheal, intrapleural, and intrabronhical routes of exposure show that chromium(VI) produces respiratory tract tumors. However, no carcinogenic effects were observed in rats, rabbits, or guinea pigs exposed to 1.6 mg chromium(VI)/m^3 as potassium dichromate or chromium dust 4 hours/day, 5 days/week.

Exposure rats and mice to sodium dichromate dihydrate in drinking water for 2 years resulted in cancers of the gastrointestinal tract. In male and female rats, the incidences of neoplasms of the squamous epithelium of the oral mucosa and tongue were significantly increased in males (7.0 mg chromium(VI)/ kg/day) and females (5.9 mg chromium(VI)/kg/day); in mice, the incidence of neoplastic lesions of the small intestine (duodenum, jejunum, and ileum) was increased in males at 2.4 mg chromium(VI)/kg/day and females at 3.1 mg chromium(VI)/kg/day. The National Toxicology Program (NTP) concluded that results demonstrate clear evidence of carcinogenic activity in male and female F344/N rats (increased incidences of squamous cell neoplasms of the oral cavity) and in male and female B6C3F1 mice (increased incidences of neoplasms of the duodenum, jejunum, or ileum). Mice exposed to chromium(VI) as potassium chromate (9 mg chromium(VI)/kg/day) in drinking water for three generations (880 days) showed statistically significant increases in the incidence of forestomach adenoma or carcinomas of the forestomach and in the incidence of forestomach adenomas alone, compared to control; however, study authors concluded that evidence of carcinogenicity was equivocal.

NTP lists certain chromium compounds as substances that are *known to be human carcinogens*. This classification is based on sufficient evidence for a number of chromium(VI) compounds (calcium chromate, chromium trioxide, lead chromate, strontium chromate, and zinc chromate). The International Agency for Research on Cancer (IARC) classified chromium(VI) as *carcinogenic to humans (Group 1)* and metallic chromium and chromium(III) compounds as *not classifiable as to their carcinogenicity to humans (Group 3)*. EPA has classified chromium(VI) as *a known human carcinogen* by the inhalation route of exposure.

Chromium(III)

Although much less information is available on the health effects of chromium(III) compounds compared to that for chromium(VI) compounds, chromium(III) compounds appear to be less toxic than chromium(VI) compounds. Health effects associated with exposure to chromium(III) compounds have been reported in studies of occupationally exposed populations and individuals; however, interpretation of study results is complicated by concomitant exposures to chromium(VI) or other compounds that can induce adverse health effects. Similarly, interpretation of findings in case reports of exposures to dietary supplements containing high-dose chromium(III) are also complicated, since most supplements contain numerous chemicals; thus, the most reliable information on adverse health effects of chromium(III) is obtained from studies in animals. Chromium(III) picolinate, a dietary supplement, has been shown to be mutagenic in bacterial and mammalian cells *in vitro*.

The primary effects of chromium(III) compounds are on the respiratory and immunological systems. As described below, respiratory effects appear to be portal-of-entry effects for inhalation exposure. Similarly, chromium allergic dermatitis, the major immunological effect of chromium(III), is typically elicited by dermal contact in sensitized individuals; however, initial sensitization may result from inhalation, oral, or dermal exposure or from a combination of these exposure routes. Conflicting results of studies in animals have been reported in developmental and reproductive studies of chromium(III) compounds; however, results provide evidence of adverse effects on the developing and adult reproductive system. Evidence of developmental or reproductive effects of chromium(III) in humans has not been identified. Based on results of chronic-duration oral studies in animals, chromium(III) compounds (chromium acetate, chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate) do not appear to produce gastrointestinal, hematological, hepatic, renal, cardiovascular, endocrine, or musculoskeletal effects. This is in contrast to chromium(VI) compounds which produce effects in the gastrointestinal, hematological, hepatic and renal systems.

Respiratory Effects. Occupational exposure studies and case reports indicate that respiratory effects occur from exposure of humans to chromium(III) compounds; however, results of these studies are difficult to interpret since most study populations were also exposed to chromium(VI) compounds or other compounds associated with respiratory effects, and/or the studies were not adequately controlled for other confounding factors (e.g., respiratory diseases). Acute- and chronic-duration studies in animals indicate that the respiratory tract is the primary target of inhaled chromium(III). Analysis of BAL fluid from rats exposed for 5 days to 3–30 mg chromium(III)/m^3 as basic chromium sulfate (soluble) showed

alterations, including increased amounts of cell debris and lysed cells and significant decreases in nucleated cells and in the percentage of segmented neutrophils and mononuclear cells; cytoplasmic accumulation of a yellow crystalline material in mononuclear cells was observed in BAL fluid of rats exposed to 3–30 mg chromium(III)/m^3 as chromic oxide (insoluble). With longer exposure (13 weeks), histopathological changes to respiratory tissues and increased lung weights were observed in rats exposed to ≥3 mg chromium(III)/m^3chromic oxide or basic chromium sulfate. However, differences were observed in severity and location of respiratory effects produced by insoluble chromic oxide and soluble basic chromium sulfate; effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung, and respiratory lymph tissues). Differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Studies examining respiratory effects from chronic-duration inhalation exposure were not identified. Respiratory effects from oral or dermal exposure to chromium(III) compounds have not been reported.

Immunological Effects. As discussed above for chromium(VI) compounds, exposure to chromium compounds may induce allergic sensitization in some individuals. In patients with known chromium-induced allergic dermatitis, positive results have been reported using patch tests with chromium(III) compounds as the challenge agent, suggesting that allergic sensitization to chromium(III) can occur. In sensitized patients, dermal responses were elicited using a concentration of 1 mg chromium(III)/L as chromium trichloride. However, since positive responses were also observed on challenge with chromium(VI) compounds, it is unclear if individuals were sensitized to both chromium(VI) and chromium(III) or if cross-sensitivity occurs between chromium(VI) and chromium(III). Studies in animals show that chromium(III) can induce sensitization and that cross-reactivity occurs between chromium(VI) and chromium(III). Sensitization to chromium(III) was observed in guinea pigs treated with a series of intradermal injections of 0.004 mg chromium(III)/kg as chromium trichloride. In guinea pigs sensitized with chromium(III), cross-sensitivity with chromium(VI) was observed on patch test challenge.

Reproductive Effects. Adverse reproductive effects have been observed in rats and mice exposed orally to chromium(III) compounds, although conflicting results have been reported. Adverse reproductive effects have been reported following acute- and intermediate-duration exposure of animals to chromium(III) by gavage or in drinking water; effects include decreased number of pregnancies in female rats administered 33.6 mg chromium(III)/kg/day, alterations in sexual behavior, aggressive

behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats (40 mg chromium(III)/kg/day), decreased number of pregnant female Swiss mice following the mating of unexposed females to exposed males (13 mg chromium(III)/kg/day), impaired fertility in exposed female mice (5 mg chromium(III)/kg/day) mated to unexposed males, and increased testes and ovarian weights and decreased preputial gland and uterine weights in mice (5 mg chromium(III)/kg/day). Decreased spermatogenesis was observed in BALB/c mice treated with 9.1 mg chromium(III)/kg/day as chromium sulfate in drinking water for 7 weeks..

In contrast to the reproductive effects of chromium(III) chloride in drinking water, dietary exposure to chromium picolinate or chromium nicotinate has not been associated with reproductive effects. Exposure to chromium picolinate in the diet for 3 months did not produce adverse effects on reproductive tissues, as assessed by organ weights, gross and histopathological examinations, sperm count, sperm motility, duration of estrous cycle stages, and estrous cycle length at doses up to 505 and 506 mg chromium(III)/kg/day in male and female rats, respectively, or at doses up to 1,415 and 1,088 mg chromium(III)/kg/day in male and female mice. No morphological changes to reproductive organs, as assessed by histopathological examination, were observed in male and female Sprague-Dawley rats exposed to chromium nicotinate in the diet at 1.2 and 1.5 mg chromium(III)/kg/day, respectively for 2 months or 0.22 and 0.25 mg chromium(III)/kg/day, respectively, for 1 year.

In summary, conflicting results on reproductive effects of chromium(III) compounds have been reported. It is unclear if differences in results are related to experimental methods, including exposure media (drinking water versus feed), or to differences in toxicity of the specific chromium(III) compounds evaluated.

Developmental Effects. Little information is available on the potential developmental effects of chromium(III) compounds, although results of available studies are conflicting. Chromium(III) did not produce developmental effects in offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout the gestational period. Significant decreases were observed in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males and ovaries and uterus in females) of offspring of BALB/c mice exposed to 74 mg chromium(III)/kg/day as chromium(III) chloride in the drinking water on gestation day 12 through lactation day 20; however, fertility was not affected when these exposed offspring were mated with unexposed animals. The number of pregnancies was decreased in rats administered 33.6 mg chromium(III)/kg/day (only dose tested) by gavage as chromium chloride on gestational days 1–3, although when exposed on gestational days 4–6,

no effects on pregnancy rates, implantations, viable fetuses, or resorptions were observed. Thus, the available evidence does not indicate that exposure to chromium(III) consistently produces adverse developmental effects.

Cancer. No studies evaluating the carcinogenic activity of chromium(III) compounds in humans were identified. In male rats exposed to dietary chromium picolinate for 2 years, the incidence of preputial gland adenoma was significantly increased in males at 61 mg chromium(III)/kg/day, with the incidence also exceeding the historical control ranges; however, the incidence was not increased at a higher dose (313 mg chromium(III)/kg/day) and similar lesions were not observed in corresponding tissues in female rats or in male and female mice. Therefore, NTP considered the evidence of carcinogenic activity to be equivocal. The relationship of preputial gland adenoma to male reproductive function in this study was not defined.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for chromium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs—Chromium(VI)

Acute. The inhalation database for acute-duration exposure of humans to inhaled chromium(VI) compounds is limited to a few studies reporting signs of respiratory irritation (dyspnea, cough, wheezing, sneezing, rhinorrhea, choking sensation), dizziness, and headaches in individuals or small numbers of workers ($n \leq 5$) exposed to high concentrations of chromium(VI) (Lieberman 1941; Meyers 1950; Novey et al. 1983). In addition, acute inhalation exposure of individuals previously sensitized to chromium compounds has produced symptoms of asthma and signs of respiratory distress consistent with a type I allergic response (decreased forced expiratory volume, facial erythema, nasopharyngeal pruritus, blocked nasal passages, cough, and wheeze) (Leroyer et al. 1998; Olaguibel and Basomba 1989); however, the available data are not adequate to characterize the exposure-response relationship for effects of acute inhalation challenge in sensitized individuals. No other effects of acute inhalation exposure of humans to chromium(VI) have been reported.

The acute toxicity of inhaled chromium(VI) in animals has not been well investigated, and most studies are 4-hour lethality studies (American Chrome and Chemicals 1989; Gad et al. 1986). Nasal hemorrhage was observed in two of five rats after inhalation for 10 days to 1.15 mg chromium(VI)/m^3 during a 13-week exposure study (Kim et al. 2004), with no nasal effects observed at 0.49 mg chromium(VI)/m^3. However, only a small number of animals were evaluated and histopathological evaluations of the respiratory tract (or other tissues) were not conducted following the acute-duration period; thus, data are not suitable for defining NOAEL or LOAEL values for respiratory effects. Although longer duration inhalation studies show that the respiratory tract is a sensitive target of inhaled chromium(VI), the data are insufficient to determine acute-duration exposure levels that would produce respiratory tract, or other effects. In the absence of studies that could be used to identify the targets of low level exposure, an acute-duration inhalation MRL for hexavalent chromium was not derived.

Intermediate

- An inhalation MRL of 5×10^{-6} mg chromium(VI)/m^3 has been derived for intermediate (15–364 days) exposure for dissolved hexavalent chromium aerosols and mists.

The available data on inhalation exposure of humans and animals to chromium(VI) compounds indicate that dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds have different toxic potencies for producing adverse respiratory effects. Although the respiratory system is the most sensitive target for inhalation exposure to both types of chromium(VI) compounds, the

primary respiratory effects of inhaled chromic acid mists are observed in the nose (see the following discussion), while the effects of inhaled particulate chromium(VI) compounds occur throughout the respiratory tract. Since toxic potencies of these compounds appear to be different and the likelihood for environmental exposure to chromium trioxide (e.g., chromic acid mist) and other soluble chromium(VI) compound mists is less than the likelihood for environmental exposure to particulate chromium(VI) compounds, distinct intermediate-duration inhalation MRLs have been derived for dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds.

The intermediate-duration inhalation database for humans exposed to dissolved chromium(VI) aerosols and mists consists of occupational exposure studies on chromium trioxide mists (Gibb et al. 2000a, 2000b; Gomes 1972; Kleinfeld and Rosso 1965; Lindberg and Hedenstierna 1983); these studies identify the upper respiratory tract as the primary target of exposure. Upper respiratory effects include nasal irritation, ulceration, and mucosal atrophy and rhinorrhea, with LOAEL values ranging from 0.002 to 0.1 mg chromium(VI)/m^3. Other effects (e.g., non-respiratory) specific for dissolved chromium(VI) aerosols and mists in humans have not been reported. Exposure to chromium(VI) compounds (not compound-specific) can produce allergic sensitization, which may manifest as symptoms of asthma upon subsequent inhalation exposures (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989). The exposure route for the initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal exposures; however, the available data do not define the exposure-response relationship for chromium sensitization by inhalation.

Available animal studies on the effects of intermediate-duration exposure to dissolved chromium(VI) aerosols and mists identify the respiratory tract as the primary target, with LOAEL values ranging from 0.49 to 3.63 mg chromium(VI)/m^3 (Adachi 1987; Adachi et al. 1986; Kim et al. 2004). Respiratory effects reported in animals exposed to chromium(VI) trioxide include alveolar inflammation in rats (Kim et al. 2004) and nasal septal perforation and symptoms of emphysema in mice (Adachi 1987; Adachi et al. 1986). The only other effect (e.g., non-respiratory) observed in animal studies on dissolved chromium(VI) aerosols and mists were hematological effects and decreased body weight in rats exposed to chromium trioxide mist for 13 weeks. Hematological effects include decreased in hematocrit at $\geq$0.23 and 1.15 mg chromium(VI)/m^3 (but not 0.49 mg chromium(VI)/m^3) decreased hemoglobin at $\geq$0.49 mg chromium(VI)/m^3 and decreased erythrocyte count at 1.15 mg chromium(VI)/m^3 (Kim et al. 2004). In this study, body weight gain was also decreased by ~9%, with NOAEL and LOAEL values of 0.49 and 1.15 mg chromium(VI)/m^3, respectively.

Based on a comparison of LOAEL values for respiratory effects, hematological effects, and decreased body weight gain, the respiratory tract was identified as the most sensitive effect of intermediate-duration inhalation exposure to dissolved chromium(VI) aerosols and mists. The lowest LOAEL value of 0.002 mg chromium(VI)/m^3 was reported for nasal irritation, mucosal atrophy, and ulceration and decreases in spirometric parameters observed in workers exposed to chromic acid mist (Lindberg and Hedenstierna (1983); therefore, this value was selected as the basis for derivation of the intermediate-duration inhalation MRL for dissolved chromium(VI) aerosols and mists. The population evaluated by Lindberg and Hedenstierna (1983) included 85 male and 19 female chrome plating workers exposed to chromic acid and a reference group of 119 auto mechanics not exposed to chromium. Workers were assessed for nose, throat, and chest symptoms, were inspected for effects in nasal passages, and were given pulmonary function tests. The length of worker exposures to chromic acid ranged from 0.1 to 36 years, with a mean of 2.5 years, spanning both intermediate and chronic durations. Since the study population included workers exposed for an intermediate duration, data are considered appropriate for derivation of the intermediate-duration inhalation MRL. Nasal irritation ($p<0.05$), mucosal atrophy ($p<0.05$), and ulceration ($p<0.01$), and decreases in spirometric parameters (forced vital capacity, forced expired volume in 1 second, and forced mid-expiratory flow) were observed in workers occupationally exposed to ≥0.002 mg chromium(VI)/m^3 as chromic acid. Approximately 60% of the exposed subjects were smokers, but no consistent association between exposure and cigarette smoking was observed. Additional details on study methods and results are provided in Appendix A.

The LOAEL of 0.002 mg chromium(VI)/m^3 was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL ($LOAEL_{ADJ}$) of 0.0005 mg chromium(VI)/m^3. The intermediate-duration MRL of $5x10^{-6}$ was obtained by dividing the $LOAEL_{ADJ}$ (0.0005 mg chromium(VI)/m^3) by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL).

- An inhalation MRL of 0.0003 mg chromium(VI)/m^3 was derived for intermediate exposures to particulate chromium(VI) compounds.

As discussed above, available data on inhalation exposure of humans and animals to chromium(VI) compounds indicate that dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds have different toxic potencies for producing adverse respiratory effects (the primary target organ). Furthermore, since the likelihood for environmental exposure to chromium trioxide and other soluble chromium(VI) compound mists is less than the likelihood for environmental exposure to particulate chromium(VI) compounds, distinct intermediate-duration inhalation MRLs have

been derived for dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds.

Although few animal studies have reported adverse effects of intermediate-duration inhalation exposure to particulate chromium(VI) compounds (Cohen et al. 1998; Glaser et al. 1985, 1990), results of available studies conducted in rats indicate that the respiratory tract is the primary target organ. In rats exposed to inhaled sodium dichromate for 30–90 days, adverse respiratory effects included obstructive respiratory dyspnea, increased lung weights, hyperplasia of the lung, focal inflammation of the upper airway, and alterations to BAL fluid concentrations of lactate dehydrogenase, protein, and albumin, with a LOAEL value of 0.2 mg chromium(VI)/m^3 (Glaser et al. 1990). Other effects reported in the Glaser et al. (1985, 1990) studies were an increased percentage of lymphocytes in BAL fluid (LOAEL of 0.025 mg chromium(VI)/m^3), increased serum phospholipids and triglycerides (NOAEL and LOAEL values of 0.1 and 0.2 mg chromium(VI)/m^3, respectively), increased white blood cell count (LOAEL value of 0.05 mg chromium(VI)/m^3), decreased body weight gain (NOAEL and LOAEL values of 0.1 and 0.2 mg chromium(VI)/m^3), and an enhanced immune response to sheep erythrocytes (LOAEL 0.025 mg chromium(VI)/m^3); however, the toxicological significance of these finding is uncertain. Effects that may be indicative of altered immune function (altered white blood cell counts and cytokine levels in BAL fluid) were observed in rats exposed to 0.36 mg chromium(VI)/m^3 as potassium chromate or barium chromate for 2–4 weeks (Cohen et al. 1998); however, results of this study are difficult to interpret, since effects were not clearly adverse, only one exposure level was evaluated, and histopathological assessment of respiratory tissues (or other tissues) was not conducted.

Based on the available data, respiratory effects were identified as the most sensitive target of intermediate-duration exposure to particulate chromium(VI) compounds, with the study by Glaser et al. (1990) selected as the critical study. In this study, 8-week-old male Wistar rats (30 animals/group) were exposed 22 hours/day, 7 days/week to 0, 0.05, 0.1, 0.2, or 0.4 mg chromium(VI)/m^3 as sodium dichromate aerosol particulates. Detailed discussion of study methods is presented in Appendix A. No deaths or abnormal clinical signs occurred at any of the exposures. Obstructive respiratory dyspnea occurred at ≥0.2 mg chromium(VI)/m^3 after 30 and 90 days. Mean lung weight was increased in all exposure groups and was statistically increased at 0.05 mg chromium(VI)/m^3 for 30 days, and at 0.1 mg chromium(VI)/m^3 for 90 days and in the 90-day plus recovery period group. Histological examination revealed slight hyperplasia in high incidence at 0.05 mg chromium(VI)/m^3 at 30 days. Lung fibrosis occurred at 0.1 mg chromium(VI)/m^3 for 30 days, but was not seen in rats exposed for 90 days. Accumulation of macrophages was observed in all exposed rats, regardless of exposure concentration or

duration. Histology of upper airways revealed focal inflammation. Results of bronchoalveolar lavage (BAL) analysis provided further information of the irritation effect. Total protein in BAL fluid was significantly increased in all exposed groups, but declined in the recovery period. Albumin in BAL fluid increased in a dose-related manner at all concentrations in the 30-day group, but recovery started during 90-day exposure and continued during the 30-day observation period. The activities of lactate dehydrogenase and β-glucuronidase, measures of cytotoxicity, were elevated at 0.2 and 0.4 mg chromium(VI)/m^3 for 30 and 90 days, but returned to control values during the recovery period. The number of macrophages in the BAL fluid had significantly increased after 30 and 90 days, but normalized during the recovery period. The macrophages were undergoing cell division or were multinucleate and larger. This activation of macrophages was not observed in the recovered rats. Additional details on study results are presented in Appendix A.

Results of the benchmark concentration (BMC) analysis of the Glaser et al. (1990) data conducted by Malsch et al. (1994) were identified as the basis for derivation of an intermediate-duration inhalation MRL for hexavalent chromium particulate compounds. Using the 90-day exposure data (as described above), Malsch et al. (1994) developed BMCLs (defined as the 95% lower limit on the concentration corresponding to a 10% relative change in the end point compared to the control) for lung weight and BAL fluid levels of lactate dehydrogenase, protein, and albumin. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure (22 hours/day). Duration-adjusted data were then fitted to a polynomial mean response regression model by the maximum likelihood method to derive BMCLs. The lowest BMCL, 0.016 mg chromium(VI)/m^3 for alterations in lactate dehydrogenase levels in BAL fluid, was selected to derive the intermediate-duration inhalation MRL. The BMCL of 0.016 mg chromium(VI)/m^3 was converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.010 mg chromium(VI)/m^3 using the regional deposited dose ratio (RDDR) program (EPA 1994c) (see Appendix A for details).

The intermediate-duration inhalation MRL of 0.0003 mg chromium (VI)/m^3 for hexavalent chromium particulate compounds was derived by dividing the $BMCL_{HEC}$ of 0.010 mg chromium(VI)/m^3 by a composite uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Chronic

- An inhalation MRL of $5x10^{-6}$ mg chromium(VI)/m^3 has been derived for chronic (≥365 days) exposure for dissolved hexavalent chromium aerosols and mists.

The chronic-duration inhalation database for humans exposed to dissolved chromium(VI) aerosols and mists consists of occupational exposure studies on chromium trioxide mists, reporting effects to the respiratory, renal, and gastrointestinal systems (Franchini and Mutti 1988; Gibb et al. 2000a, 2000b; Hanslian et al. 1967; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975). Respiratory effects included bleeding nasal septum, nasal mucosal atrophy, nasal septal ulceration and perforation, epitaxis, rhinorrhea, and decreased lung function, with LOAEL values ranging from 0.002 to 0.414 mg chromium(VI)/m^3. Effects indicative of renal toxicity include increased retinol binding protein and tubular antigen and increased urinary β-2-microglobulin (Franchini and Mutti 1988; Lindberg and Hedenstierna 1983); LOAEL values for these effects range from 0.004 to 0.05 mg chromium(VI)/m^3. Gastrointestinal effects reported in workers include stomach pains, cramps, and ulcers, with a LOAEL value of 0.004 mg chromium(VI)/m^3 (Lucas and Kramkowski 1975). Other effects specific for dissolved chromium(VI) aerosols and mists in humans exposed for chronic exposure durations have not been reported. Exposure to chromium(VI) compounds (not compound-specific) can produce allergic sensitization, which may manifest as symptoms of asthma upon subsequent inhalation exposures (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989). The exposure route for the initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal exposures; however, the available data do not define the exposure-response relationship for chromium sensitization by inhalation. Studies in animals evaluating the effects of chronic-duration exposure to dissolved chromium(VI) aerosols and mists were not identified.

Based on a comparison of LOAEL values for respiratory, renal and gastrointestinal effects in workers, the respiratory tract was identified as the most sensitive effect of chronic-duration inhalation exposure to dissolved chromium(VI) aerosols and mists. The lowest LOAEL value of 0.002 mg chromium(VI)/m^3 was reported for nasal irritation, mucosal atrophy, and ulceration and decreases in spirometric parameters in workers occupationally exposed to chromic acid mist (Lindberg and Hedenstierna (1983); therefore, this value was selected as the basis for derivation of the chronic-duration inhalation MRL for dissolved chromium(VI) aerosols and mists. The population evaluating in this study had a mean exposure duration of 2.5 years, with a range of 0.1–23.6 years, spanning both intermediate and chronic durations. A description of study methods and results is provided above under the discussion of Intermediate-Duration Inhalation MRL for Particulate Hexavalent Chromium Compounds and in Appendix A.

The LOAEL of 0.002 mg chromium(VI)/m^3 was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL ($LOAEL_{ADJ}$) of 0.0005 mg chromium(VI)/m^3. The chronic-duration MRL of $5x10^{-6}$ was obtained by dividing the $LOAEL_{ADJ}$ (0.0005 mg chromium(VI)/m^3) by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL).

Few studies have evaluated the effects of chronic inhalation exposure to particulate hexavalent chromium compounds. In workers chronically exposed to inhaled chromium(VI) compounds at 0.0042 mg chromium(VI)/m^3, the prevalence of high urinary N-acetyl-β-glucosamidase was increased, indicating possible renal damage (Liu et al. 1998); however, since the chemical form of chromium(VI) was not reported, data from this study are not suitable as the basis for the chronic-duration inhalation MRL specific for particulate hexavalent chromium compounds. The chronic-duration database in animals consists of studies that either did not identify adverse effects of chronic inhalation exposure to particulate hexavalent chromium compounds (Glaser et al. 1986, 1988; Lee et al. 1989) or older studies that did not report sufficient experimental details (Nettesheim and Szakal 1972; Steffee and Baetjer 1965). Thus, due to inadequate data, a chronic-duration inhalation MRL for particulate hexavalent chromium compounds was not derived.

Oral MRLs—Chromium(VI)

Acute. Studies on the acute toxicity of orally-administered chromium(VI) in humans are mostly limited to case reports on ingestion of fatal doses (Clochesy 1984; Iserson et al. 1983; Kaufman et al. 1970; Loubieres et al. 1999; Saryan and Reedy 1988). At lower doses (≥0.036 mg chromium (IV)/kg as potassium dichromate), oral exposure to chromium(VI) has been shown to enhance dermatitis in individuals with known chromium sensitivity (Goitre et al. 1982; Kaaber and Veien 1977).

In animals, acute-duration studies on oral exposure to chromium(VI) compounds have shown effects on hematology and clinical chemistry (NTP 2007, 2008a), male reproductive organs (Li et al. 2001) and development (Elsaieed and Nada 2002; Junaid et al. 1996b); however, the available studies did not evaluate comprehensive toxicological end points. Decreased MCV, MCH, and reticulocyte count were observed in rats exposed to ≥0.70 mg chromium (VI)/kg/day after 4–5 days of exposure (NTP 2007, 2008a); however, the magnitude of changes was small and may not yet represent an adverse effect of chromium(VI). Significant alterations in the serum activities of liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and creatine kinase were observed at ≥4.0–4.1 mg

chromium(VI)/kg/day in rats exposed for 4–5 days (NTP 2007, 2008a). Effects on male reproductive organs, including decreased sperm count, increased percentage of abnormal sperm, and morphological change to seminiferous tubules (decreased diameter of seminiferous tubules and germ cell rearrangement) were observed in Wister rats following a 6-day gavage administration of ≥5.2 mg chromium(VI)/kg/day as chromic acid; observations were made 6 weeks after the dosing period (Li et al. 2001). A NOAEL was not defined in this study.

Developmental effects, including increased pre- and postimplantation loss, resorptions, dead fetuses/litter, and skeletal (incomplete ossification of skull bone) and visceral (renal pelvis dilatation) malformations were observed in Wister rats exposed to 8 mg chromium(VI)/kg/day (the only dose tested) as potassium chromate in drinking water (Elsaieed and Nada 2002). Other studies reported total litter loss, decreased viable fetuses and increased resorptions in rats (Bataineh et al. 2007) and increased resorptions in mice (Junaid et al. 1996b) exposed at higher doses.

Results of acute-duration studies in animals show that exposure to oral chromium(VI) compounds may cause hematological (NTP 2007, 2008a), reproductive (Li et al. 2001), and developmental effects (Elsaieed and Nada 2002; Junaid et al. 1996b). However, since the available studies did not evaluate comprehensive toxicological end points, data are inadequate for derivation of an acute-duration oral MRL for chromium(VI). Therefore, an acute-duration oral MRL for hexavalent chromium was not derived.

Intermediate

- An oral MRL of 0.005 mg chromium(VI)/kg/day has been derived for intermediate (15–364 days) exposure to hexavalent chromium compounds.

Hematological effects (microcytic, hypochromic anemia) in male rats and female mice observed after exposure for 22 days in the NTP (2008a) 2-year study were identified as the most sensitive effect of intermediate-duration oral exposure to chromium(VI) for the purpose of derivation of an intermediate-duration oral MRL for chromium(VI) compounds of 0.005 mg chromium(VI)/kg/day. The basis for this determination is as follows.

No human intermediate-duration studies on chromium(VI) were identified. Numerous animal studies examining systemic, neurological, reproductive, and developmental toxicity have reported effects following oral exposure to chromium(VI) compounds, with hematological effects (microcytic, hypochromic anemia) identified as the most sensitive. Microcytic, hypochromic anemia, characterized by

decreased MCV, MCH, Hct, and Hgb, was observed in rats and mice exposed to chromium(VI) compounds in drinking water or feed for intermediate-duration exposures ranging from 22 days to 6 months (NTP 1996a, 1996b, 1997, 2007, 2008a). The lowest reported LOAEL values for hematological effects were 0.77 mg chromium(VI)/kg/day (with a NOAEL value of 0.21 mg chromium(VI)/kg/day) for decreased Hct, Hgb, MCV, and MCH in male rats; and 0.38 mg chromium(VI)/kg/day (a NOAEL was not established) for decreased MCV and MCH in female mice exposed to sodium dichromate dihydrate in drinking water for 22 days (NTP 2008a). Slightly higher LOAEL values were observed for hematological effects in rats and mice exposed to dietary potassium dichromate for 9 weeks (NTP 1996a, 1996b, 1997).

The duration-dependence of hematological effects was evaluated in rats and mice exposed to sodium dichromate dihydrate in drinking water from 23 days up to 6 months (NTP 2007, 2008a). Results of both studies show that the severity of microcytic, hypochromic anemia was dose-dependent, with maximum effects observed after 22–23 days of exposure. For all intermediate-duration exposures (22 days to 6 months), NOAEL and LOAEL values in male rats for hematological effects were 0.21 and 0.77 mg chromium(VI)/kg/day, respectively. In female mice, microcytic, hypochromic anemia was also observed, with LOAEL values of 0.38, 1.4, and 3.1 mg chromium(VI)/kg/day at the 22-day, 3-month, and 6-month assessments, respectively, with effects less severe than those observed in rats.

Studies examining systemic toxicity in animals have reported numerous effects, including hepatotoxicity (Achaya et al. 2001; Kumar and Rana 1982, Kumar et al. 1985; NTP 1996a, 2007), gastrointestinal effects (NTP 2007), renal toxicity (Acharya et al. 2001; Diaz-Mayans et al. 1986; Kumar and Rana 1982, 1984), lymphatic and immunological effects (NTP 2007; Snyder and Valle 1991), and decreased body weight (Bataineh et al. 1997; Chowdhury and Mitra 1995; Elbetieha and Al-Hamood 1997; Kanojia et al. 1996, 1998; NTP 2007; Quinteros et al. 2007; Trivedi et al. 1989). However, LOAEL values for these effects were higher than those producing hematopoietic effects. Studies on reproductive toxicity in animals identify the male reproductive system as a target for intermediate-duration exposure to oral chromium(VI) (Aruldhas et al. 2004, 2005, 2006; Bataineh et al. 1997; Chowdhury and Mitra 1995; Subramanian et al. 2006; Yousef et al. 2006; Zahid et al. 1990), although these effects are less sensitive than hematological effects. In developmental studies in rats and mice, gestational exposure produced increased postimplantation loss, decreased number of live fetuses/litter, decreased fetal weight, internal and skeletal malformations, and delayed sexual maturation in offspring; however, these effects were observed high doses (e.g., ≥35 mg chromium(VI)/kg/day) (Al-Hamood et al. 1998; Bataineh et al. 2007; Junaid et al. 1996a; Kanojia et al. 1998; Trivedi et al. 1989).

Hematological effects (microcytic, hypochromic anemia) in male rats observed after exposure for 22 days in the NTP (2008a) 2-year study were identified as the most sensitive effect of intermediate-duration oral exposure to chromium(VI). In this study, male F344/N rats (6–7 weeks old) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study, with hematological assessments conducted at 22 days, 3 months, 6 months, and 1 year (see Appendix A for a detailed description of study methods and results). To determine the point of departure for derivation of the intermediate-duration oral MRL, available continuous-variable models in the EPA Benchmark Dose (version 1.4.1) were fit to the data for Hct, Hgb, MCV, and MCH in male rats (NTP 2008a) (detailed results of the benchmark dose analysis are provided in Appendix A). Because several hematological parameters are used to define the clinical picture of anemia, the $BMDL_{2sd}$ values for hemoglobin, MCV, and MCH (none of the models provided an adequate fit for hematocrit) were averaged resulting in a $BMDL_{2sd}$ of 0.52 mg chromium(VI)/kg/day. The intermediate-duration MRL of 0.005 mg chromium(VI)/kg/day was derived by dividing the average $BMDL_{2sd}$ by a composite uncertainty factor of 100 (10 or extrapolation from animals to humans and 10 for human variability).

Chronic

- An oral MRL of 0.001 mg chromium(VI)/kg/day has been derived for chronic (≥1 year) exposure to hexavalent chromium compounds.

Nonneoplastic lesions of the duodenum observed in mice in an chronic drinking water (NTP 2008a) was selected as the critical effect for derivation of a chronic-duration MRL for chromium(VI) compounds of 0.001 mg chromium(VI)/kg/day. The rationale for this determination is as follows.

The chronic-duration oral toxicity database in drinking water in humans consists of ecological studies of an area near a ferrochromium production plant in the Liaoning Province, China comparing cancer mortality in locations that had relatively high or low chromium concentrations in well water (Beaumont et al. 2008; Zhang and Li 1987). Evaluations of cancer mortality rates (cancers deaths per person-year in an 8-year observation period) show that the adjusted stomach cancer mortality rate was higher for the exposed population compared to the control population (Beaumont et al. 2008). However, it was not possible to estimate exposure levels based on the description of the pollution process. Thus, available human data are not adequate as the basis for the chronic-duration oral MRL.

Chronic-duration oral toxicity studies have been conducted in rats and mice (Mackenzie et al. 1958; NTP 2008a). No hematological, hepatic, or renal effects or changes in body weight were observed in study in Sprague-Dawley rats exposed to 3.6 chromium(VI)/kg/day as potassium chromate in drinking water for 1 year (Mackenzie et al. 1958). NTP (2008a) exposed groups of F344/N rats (50/sex/group) and B6C3F1 mice (50/sex/group) to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study (see Appendix A for a detailed description of all study methods and results). Results of this study identify several chromium(VI)-induced effects, including microcytic, hypochromic anemia, and nonneoplastic lesions of the liver, duodenum, mesenteric and pancreatic lymph nodes, pancreas, and salivary gland. Based on comparison of LOAEL values, the lowest LOAELs were observed for histopathological changes of the liver (chronic inflammation in female rats and histiocytic cellular infiltration in female mice), duodenum (diffuse epithelial hyperplasia in male and female mice), mesenteric lymph node (histiocytic cellular infiltration in male and female mice), and pancreas (cytoplasm cellular alteration of acinar epithelial cells in female mice), with effects occurring in all treatment groups (see Appendix A for incidence data for all nonneoplastic lesions). Therefore, all effects with LOAEL values of the lowest dose tested were considered as the possible the critical effect for derivation of the chronic-duration oral MRL.

To determine the specific end point for derivation of the chronic-duration oral MRL, all available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.4.1) were fit to the incidence data for selected end points in female rats and male and female mice exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a) (details of benchmark dose analysis are presented in Appendix A). Based on the lowest $BMDL_{10}$ value of 0.09 mg chromium(VI)/kg/day, diffuse epithelial hyperplasia of the duodenum in female mice was selected as the point of departure for derivation of the chronic-duration oral MRL. The chronic-duration MRL of 0.001 mg chromium(VI)/kg/day was derived by dividing the $BMDL_{10}$ by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The chronic-duration oral MRL based on nonneoplastic lesions of the duodenum in female mice is expected to be protective for all other adverse effects observed in the 2-year drinking water study (e.g., hematological effects and lesions of the liver, lymph nodes, pancreas and salivary gland).

Inhalation MRLs—Chromium(III)

Acute. Studies evaluating the effects of acute exposure of humans to chromium(III) compounds were not identified. Acute-duration exposure studies in rats and hamsters indicate that the respiratory tract is a

target of inhaled chromium(III) compounds (Derelanko et al. 1999; Henderson et al. 1979). Derelanko et al. (1999) evaluated effects of acute exposure to chromium(III) as chromic oxide (insoluble) or basic chromium sulfate (soluble) in rats (5 rats/sex/group) on composition of BAL fluid. After exposure of rats for 5 days (6 hours/day) to 3, 10, or 30 mg chromium(III)/m^3 as chromic oxide (insoluble), analysis of BAL fluid revealed cytoplasmic accumulation of a yellow crystalline material in mononuclear cells of all exposure groups; however, it is not clear if this observation represents an adverse effect. No other BAL parameters were affected (nucleated cell count and differential, protein, and BAL fluid activities of β-glucuronidase, lactic dehydrogenase, and glutathione reductase). In rats treated for 5 days (6 hours/day) with 3, 10, or 30 mg chromium(III)/m^3 as basic chromium sulfate (soluble), BAL fluid analysis showed significant decreases in nucleated cells at all doses in males and females and decreases in the percentage of segmented neutrophils and mononuclear cells at 30 mg chromium(III)/m^3 in males. Increased amounts of cellular debris and lysed cells were present in BAL fluid of rats treated with ≥3 mg chromium(III)/m^3 as basic chromium sulfate (incidence data were not reported). In Syrian hamsters, changes in BAL fluid and lung tissue enzyme activities were observed following exposure to inhaled chromium trichloride for 30 minutes (Henderson et al. 1979); effects included "sporadic changes" in activities of acid phosphatase and alkaline phosphatase in the BAL fluid at 25 mg chromium(III)/m^3 and increased acid phosphatase activity in lung tissue at 0.9 mg chromium(III)/m^3. In addition, histological examination of the lung revealed focal accumulations of macrophages and polymorphonuclear cells. However, it is not clear that the effects observed in this study are toxicologically significant. Thus, results of acute-duration studies in rats and hamsters show that inhaled chromium(III) compounds produce alterations in BAL fluid composition and lung tissue enzyme activities; however, data are not adequate to characterize the exposure-response relationship for respiratory effects. Therefore, an acute-duration inhalation MRL for trivalent chromium was not derived.

Intermediate. Studies evaluating the effects of intermediate-duration exposure of humans to chromium(III) compounds were not identified. In animals exposed to inhaled chromium(III) compounds for intermediate durations, the respiratory tract has been identified as the primary target organ, based on results of a 13-week study in rats exposed to chromic oxide (insoluble) or basic chromium sulfate (soluble) (Derelanko et al. 1999). In this study, which examined comprehensive toxicological end points, male and female CDF rats (15/sex/group) were exposed by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m^3 as chromic oxide or as basic chromium sulfate for 6 hours/day, 5 days/week for 13 weeks. Of the 15 rats/sex/group, 10 rats/sex/group were sacrificed after 13 weeks of exposure and 5 rats/sex/group were sacrificed after an additional 13-week recovery period (e.g., no exposure). Assessments made in this study included mortality; clinical signs of toxicity; body weight; hematology;

clinical chemistry; urinalysis; sperm morphology, count and motility; gross necropsy; microscopic examination of comprehensive tissues for all animals in the control and 30 mg chromium(III)/m^3 groups; and microscopic examination of respiratory tissues (nasal tissues, trachea, lungs, larynx, and mediastinal and mandibular lymph nodes) in all animals. Both chromic oxide and basic chromium sulfate produced adverse respiratory effects (histopathological changes to respiratory tissues and increased lung weights) in male and female rats, with no adverse effects in other tissues. However, differences between the two compounds were observed with respect to severity and location of respiratory effects; effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung, and respiratory lymph tissues). The study authors suggested that differences in the respiratory toxicity of these compounds may be related to differences in chemical-physical properties (e.g., solubility, acidity). The only other intermediate-duration inhalation study in animals was conducted in rabbits exposed to 0.6 mg chromium(III)/m^3 as chromium nitrate for 4–6 weeks (6 hours/day, 5 days/week) (Johansson et al. 1986b). Results of this study showed effects on pulmonary macrophages (altered functional and metabolic activities); however, the toxicological significance of this finding is uncertain and animals were not examined for other effects. Thus, the 13-week inhalation study by Derelanko et al. (1999) was selected as the critical study for derivation of intermediate-duration inhalation MRLs for chromium(III) compounds. Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, distinct intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds. Additional details of respiratory effects produced by chromic oxide and basic chromium sulfate are described below under derivation of intermediate-duration inhalation MRLs for insoluble trivalent chromium compounds and for soluble trivalent chromium compounds, respectively.

- An inhalation MRL of 0.005 mg chromium(III)/m^3 has been derived for intermediate (15–364 days) exposure to insoluble trivalent chromium particulate compounds.

The lung and respiratory lymphatic tissues were identified as the target tissues for inhaled insoluble trivalent chromium particulate compounds, based on observations reported in the study by Derelanko et al. (1999) (as discussed above). Similar effects were observed in male and female rats exposed to chromic oxide for 13 weeks, with histopathological changes to the respiratory lymphatic tissue occurring at ≥3 mg chromium(III)/m^3 and to the lung at ≥10 mg chromium(III)/m^3. Lymphoid hyperplasia of the mediastinal node was observed in rats of all treatment groups (severity not reported). In rats exposed to 10 and 30 mg chromium(III)/m^3, trace-to-mild chronic interstitial inflammation of the lung, characterized by inflammatory cell infiltration, was observed in alveolar septa, and hyperplasia of Type II pneumocytes

(severity not reported) were observed. Histopathological changes were isolated to the lungs and respiratory lymphatic tissues and were not observed in other tissues, including nasal tissues and the larynx.

For evaluations conducted at the end of the 13-week treatment period, a LOAEL of 3 mg chromium(III)/m^3 for hyperplasia of the mediastinal node was identified for both males and females; the severity of this effect was not reported. Following a 13-week posttreatment recovery period, trace-to-mild septal cell hyperplasia and trace-to-mild chronic interstitial inflammation of the lung were observed at ≥3 mg chromium(III)/m^3 in males and at ≥10 mg chromium(III)/m^3 in females. In addition, pigmented macrophages and black pigment in peribronchial lymphatic tissues and the mediastinal lymph node in animals from all treatment groups were also observed; this finding, although not considered adverse, indicates that the test material had not been completely cleared from the lung during the treatment-free recovery period. Thus, for evaluations conducted at the 13-week posttreatment recovery period, a minimal LOAEL (based on severity) of 3 mg chromium(III)/m^3 for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was identified.

The LOAEL of 3 mg chromium(III)/m^3 for hyperplasia of the mediastinal node in males and females (observed at the end of the 13-week treatment period) and the minimal LOAEL of 3 mg chromium(III)/m^3 for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in males (observed at the end of the 13-week recovery period) were considered as potential critical effects for derivation of the intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds. A benchmark concentration for these effects could not be determined since incidence data for lesions of the lung and respiratory lymphatic tissue were not reported; thus, a NOAEL/LOAEL approach was used. To determine the point of departure, the LOAEL value of 3 mg chromium(III)/m^3 was first adjusted for intermittent and converted to human equivalent concentrations ($LOAEL_{HEC}$) (see Appendix A for details).

Based on the lowest $LOAEL_{HEC}$ of 0.43 mg chromium(III)/m^3, trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats were selected as the critical effect. The intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds of 0.005 mg chromium(III)/m^3 was derived by dividing the minimal $LOAEL_{HEC}$ of 0.43 mg chromium(III)/m^3 by a composite uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

- An inhalation MRL of 0.0001 mg chromium(III)/m^3 has been derived for intermediate (15–364 days) exposure to soluble trivalent chromium particulate compounds.

The lung and respiratory lymphatic tissues were identified as the target tissues for inhaled soluble trivalent chromium particulate compounds, based on observations reported in the study by Derelanko et al. (1999) (as discussed above). Similar effects were observed in male and female rats exposed to inhaled basic chromium sulfate for 13 weeks, with histopathological changes to the nose, larynx, lung, and respiratory lymphatic tissues and increased relative lung weight occurring at ≥3 mg chromium(III)/m^3. Microscopic examination of the lung revealed the following changes in all treatment groups: chronic inflammation of the alveoli; alveolar spaces filled with macrophages, neutrophils, lymphocytes, and cellular debris; foci of "intense" inflammation and thickened alveolar walls; chronic interstitial inflammation with cell infiltration; hyperplasia of Type II pneumocytes; and granulomatous inflammation, characterized by infiltration of macrophages and multinucleated giant cells. Macrophage infiltration and granulomatous inflammation of the larynx, acute inflammation, and suppurative and mucoid exudates of nasal tissues and histiocytosis and hyperplasia of peribronchial lymphoid tissues and the mediastinal lymph node were also observed in all treatment groups. Thus, data for histopathological changes in various regions of the respiratory tract and increased relative lung weights were evaluated to determine the specific end point for derivation of the intermediate-duration MRL for soluble trivalent chromium particulate compounds.

Benchmark dose analysis could not be conducted for respiratory tract lesions, since incidence data were not reported by Derelanko et al. (1999); therefore, a NOAEL/LOAEL approach was used, with adjustment of the LOAEL for intermittent exposure and human equivalent concentrations (see Appendix A for details). Data for relative lung weights in males and females (presented in Appendix A) were modeled using all available continuous-variable models in the EPA Benchmark Dose program (version 1.4.1). The BMC and the 95% lower confidence limit (BMCL) calculated were estimated for doses associated with a change of 1 standard deviation from the control mean ($BMDL_{1sd}$). The $BMCL_{1sd}$ values for the best fitting models in male and female rats were adjusted for intermittent exposure and human equivalent concentrations, yielding $BMCL_{1sd, HEC}$ values of 0.17 and 0.34 mg chromium(III)/m^3 in males and females, respectively (see Appendix A for detail of benchmark dose analysis).

Based on comparison of $LOAEL_{HEC}$ values for respiratory tract lesions and $BMCL_{1sd, HEC}$ values for increased lung weight, the lowest value of 0.04 mg chromium(III)/m^3 (the $LOAEL_{HEC}$ for lesions of the larynx and nose in female rats) was selected as the point of departure. The intermediate-duration inhalation MRL for soluble trivalent chromium particulate compounds of 0.0001 mg chromium(III)/m^3

was derived by dividing the $LOAEL_{HEC}$ of 0.04 mg chromium(III)/m^3 by a composite uncertainty factor of 300 (10 for use of a LOAEL, 3 for pharmacodynamic variability between animals to humans, and 10 for human variability). It should not be concluded from comparison of the intermediate-duration MRLs for soluble particulate chromium(VI) and soluble particulate chromium(III) compounds that chromium(III) is more toxic than chromium(VI).

The respiratory tract is the major target of inhalation exposure to chromium compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. For chronic exposure of humans, the available occupational studies for exposure to chromium(III) compounds include or likely include concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors in estimating exposure levels for these effects for the purpose of deriving MRLs.

Chronic. No studies evaluating the effects of chronic-duration inhalation exposure of animals to chromium(III) compounds alone were identified. Exposure to mixtures of chromium(VI) and chromium(III) compounds (3:2 mixture of chromium(VI) trioxide and chromium(III) oxide) have resulted in adverse respiratory effects in Wistar rats, including increased lung weight and histopathological changes to lung tissues (interstitial fibrosis and thickening of the septa of the alveolar lumens; Glaser et al. 1986, 1988). However, these data not appropriate as the basis for a chronic-duration inhalation MRL for chromium(III) compounds due to concomitant exposure to chromium(VI).

Oral MRLs—Chromium(III)

No acute-, intermediate-, or chronic-duration oral MRLs were derived for chromium(III) because studies evaluating the effects of chromium(III) in humans and animals following acute, intermediate, and chronic oral exposure were inadequate for establishing the exposure concentrations associated with adverse health effects (as discussed below). The IOM has recommended an adequate intake level of 20–45 µg chromium(III) for adolescents and adults, equivalent to 0.28–0.64 µg chromium(III)/kg/day (0.0003–0.0006 mg chromium(III)/kg/day), assuming a 70-kg body weight (IOM 2001).

Little information is available on the effects of acute-duration oral exposure to chromium (III) compounds. Information on the effects of intermediate-duration oral exposure of humans is limited to case reports of renal failure (Wani et al. 2006; Wasser et al. 1997) and rhabdomyolysis (Martin and Fuller 1998) following ingestion of dietary supplements containing chromium(III). In animals, acute exposure of rats to dietary chromium(III) picolinate did not produce alterations in hematology or clinical chemistry. Following acute exposure of mated rats, an increase in total litter loss was observed in female rats (at 33.6 mg chromium(III)/kg/day) (Bataineh et al. 2007). In a study evaluating effects of chromium(III) on maturation of the reproductive system in mice (74 mg chromium(III)/kg/day), significant decreases in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males; ovaries and uterus in females) and a significant delay in timing of vaginal opening in the female offspring were observed (Al-Hamood et al. 1998). However, gestational exposure studies on chromium(III) compounds were conducted at high daily doses and do not provide sufficient information to characterize the dose-response relationship for adverse developmental effects. Thus, the data are inadequate for derivation of an acute-duration oral MRL.

Information on adverse effects of intermediate-duration oral exposure of humans to chromium(III) compounds was not identified. Results of most animal studies show no adverse effects associated with intermediate-duration oral exposure to chromium(III) compounds (chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate, and chromium potassium sulfate) (Anderson et al. 1997b; De Flora et al. 2006; Ivankovic and Preussmann 1975; NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007), even at very high daily doses. In the study conducted by NTP (2008b; Rhodes et al. 2005), daily doses of up to 506 and 1,415 mg chromium(III)/mg/day as chromium picolinate were evaluated in rats and mice, respectively, and in the Ivankovic and Preussmann (1975) study, daily doses up to 1,806 mg chromium(III)/kg/day as chromium oxide were evaluated in rats.

Adverse reproductive effects have been reported following intermediate-duration exposure of animals to chromium(III) as chromium chloride administered by gavage or in drinking water. A series of studies by the same research group evaluated reproductive effects of exposure to chromium(III) as chromium chloride in drinking water for 12 weeks (Al-Hamood et al. 1998; Bataineh et al. 1997, 2007; Elbetieha and Al-Hamood 1997). Reproductive effects observed included alterations in sexual behavior (reductions in the number of mounts, increased postejaculatory interval, and decreased rates of ejaculation), aggressive behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats (40 mg chromium(III)/kg/day; only dose tested) (Bataineh et al. (1997); decreased number of pregnant female Swiss mice following the mating of

unexposed females to exposed males (13 mg chromium(III)/kg/day) (Elbetieha and Al-Hamood 1997); impaired fertility in exposed female mice (5 mg chromium(III)/kg/day) mated to unexposed males (Elbetieha and Al-Hamood 1997); and increased testes and ovarian weights and decreased preputial gland and uterine weights in mice (5 mg chromium(III)/kg/day) (Elbetieha and Al-Hamood 1997). Results of the study by Elbetieha and Al-Hamood (1997) should be interpreted with caution due to concerns regarding experimental methods, including decreased water consumption in the higher concentration group (resulting in a potential overestimate of exposure and uncertainty regarding daily dose calculations); the study was not conducted using a standard mating protocol; sperm counts were not conducted; and the definition and classification of non-viable fetuses was not described. Decreased spermatogenesis was observed in BABL/c mice treated with 9.1 mg chromium(III)/kg/day as chromium sulfate in drinking water for 7 weeks (Zahid et al. 1990); however, sensitivity of methods used to evaluate spermatogonia in this study have been questioned by NTP (1996a). NOAEL values for reproductive effects were not identified in these studies. In studies designed to confirm or refute the findings of the Zahid et al. (1990) study, the reproductive effects of different concentrations of chromium(VI) as potassium dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated (NTP 1996a, 1996b). Groups of 24 of each species were fed potassium dichromate(VI) in their feed continuously for 9 weeks followed by an 8-week recovery period. The average daily ingestions of chromium(VI) were 1.05, 3.5, 7.5, and 32.2 mg/kg/day for male mice and were 0.35, 1.05, 2.1, and 8.4 mg/kg/day for rats (NTP 1996b). Microscopic examinations of the testes and epididymis for Sertoli nuclei and preleptotene spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects. Similarly, exposure to sodium dichromate dihydrate in drinking water did not produce morphological changes to male reproductive organs of B6C3F1 mice exposed to 27.9 or 5.9 mg chromium(VI)/kg/day for 3 months or 2 years, respectively, or affect sperm count or motility in male B6C3F1, BALB/c, and C57BL/6N mice exposed to 8.7 mg chromium(VI)/kg/day for 3 months (NTP 2007, 2008a).

In contrast to the reproductive effects of chromium chloride in drinking water, dietary exposure to chromium(III) picolinate has not been associated with reproductive effects. Exposure to chromium picolinate in the diet for 3 months did not produce adverse effects on reproductive tissues, as assessed by organ weights, gross and histopathological examinations, sperm count, sperm motility, duration of estrous cycle stages and estrous cycle length at doses up to 505 and 506 mg chromium(III)/kg/day in male and female rats, respectively, or at doses up to 1,415 and 1,088 mg chromium(III)/kg/day in male and female mice (NTP 2008b). No morphological changes to reproductive organs, as assessed by histopathological examination, were observed in male and female Sprague-Dawley rats exposed to chromium nicotinate in

the diet at 1.2 and 1.5 mg chromium(III)/kg/day, respectively for 2 months or at 0.22 and 0.25 mg chromium(III)/kg/day, respectively for 1 year (Shara et al. 2005, 2007). In summary, conflicting results on reproductive effects of chromium(III) compounds have been reported. It is unclear if differences in results are related to experimental methods, including exposure media (drinking water versus feed) or to differences in toxic potency of the specific chromium(III) compounds evaluated. Thus, available data are not sufficient define the dose-response relationship for adverse reproductive effects of chromium(III) compounds.

Little information is available on the potential developmental effects of chromium(III) compounds. No developmental effects were observed in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout the gestational period (Ivankovic and Preussmann 1975).

Results of studies in animals exposed to oral chromium(III) compounds indicate that adverse reproductive effects may occur. However, the available data are do not identify NOAEL values for effects and, therefore, are not sufficient to characterize the dose-response relationship. Thus, data are inadequate for derivation of an intermediate-duration oral MRL.

Chronic-duration studies on oral exposure of humans to chromium(III) compounds were not identified. Several animals studies show no adverse effects associated with chronic-duration oral exposure to chromium(III) compounds (chromium acetate, chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate) (Ivankovic and Preussmann 1975; Mackenzie et al. 1958; Schroeder et al. 1965; Shara et al. 2007), even at very high daily doses. Thus, in the absence of data showing adverse effects of chronic oral exposure, a chronic-duration oral MRL for chromium(III) compounds was not derived.

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of his chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of chromium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Chromium is a naturally occurring element found in animals, plants, rocks, and soil and in volcanic dust and gases. Chromium has oxidation states (or "valence states") ranging from chromium(-II) to chromium(VI). Elemental chromium (chromium(0)) does not occur naturally. Chromium compounds are stable in the trivalent state and occur in nature in this state in ores, such as ferrochromite. The hexavalent (VI) form is the second-most stable state. However, chromium(VI) rarely occurs naturally, but is usually produced from anthropogenic sources (EPA 1984a).

Trivalent chromium compounds, except for acetate, nitrate, and chromium(III) chloride-hexahydrate salts, are generally insoluble in water. Some hexavalent compounds, such as chromium trioxide (or chromic acid) and the ammonium and alkali metal (e.g., sodium, potassium) salts of chromic acid are readily soluble in water. The alkaline metal (e.g., calcium, strontium) salts of chromic acid are less soluble in water. The zinc and lead salts of chromic acid are practically insoluble in cold water. Chromium(VI) compounds are reduced to chromium(III) in the presence of oxidizable organic matter. However, in natural waters where there is a low concentration of reducing materials, chromium(VI) compounds are more stable (EPA 1984a). For more information on the physical and chemical properties of chromium, see Chapter 4.

In humans and animals, chromium(III) is an essential nutrient that plays a role in glucose, fat, and protein metabolism by potentiating the action of insulin (Anderson 1981). The biologically active form of chromium, called chromodulin, is an oligopeptide complex containing with four chromic ions (Jacquamet et al. 2003). Both humans and animals are capable of converting inactive inorganic chromium(III) compounds to physiologically active forms. The nutritional role of chromium is further discussed in Section 3.4.3. Although chromium(III) has been reported to be an essential nutrient, exposure to high

levels via inhalation, ingestion, or dermal contact may cause some adverse health effects. Most of the studies on health effects discussed below involve exposure to chromium(III) and chromium(VI) compounds. In addition, chromium(IV) was used in an inhalation study to determine permissible exposure levels for workers involved in producing magnetic tape (Lee et al. 1989).

Several factors should be considered when evaluating the toxicity of chromium compounds. The purity and grade of the reagent used in the testing is an important factor. Both industrial- and reagent-grade chromium(III) compounds can be contaminated with small amounts of chromium(VI) (Levis and Majone 1979). Thus, interpretation of occupational and animal studies that involve exposure to chromium(III) compounds is difficult when the purity of the compounds is not known. In addition, it is difficult to distinguish between the effects caused by chromium(VI) and those caused by chromium(III) since chromium(VI) is rapidly reduced to chromium(III) after penetration of biological membranes and in the gastric environment (Petrilli et al. 1986b; Samitz 1970). However, whereas chromium(VI) can readily be transported into cells, chromium(III) is much less able to cross cell membranes. The reduction of chromium(VI) to chromium(III) inside of cells may be an important mechanism for the toxicity of chromium compounds, whereas the reduction of chromium(VI) to chromium(III) outside of cells is a major mechanism of protection.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be

classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) are indicated in Tables 3-1 and 3-3 and Figures 3-1 and 3-3 for chromium(VI).

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Due to the extremely high boiling point of chromium, gaseous chromium is rarely encountered. Rather, chromium in the environment occurs as particle-bound chromium or chromium dissolved in droplets. As discussed in this section, chromium(VI) trioxide (chromic acid) and soluble chromium(VI) salt aerosols may produce different health effects than insoluble particulate compounds. For example, exposure to chromium(VI) trioxide results in marked damage to the nasal mucosa and perforation of the nasal septum, whereas exposure to insoluble(VI) compounds results in damage to the lower respiratory tract.

3.2.1.1 Death

No studies were located regarding death in humans after acute inhalation of chromium or chromium compounds. An increased risk of death from noncancer respiratory disease was reported in retrospective mortality studies of workers in a chrome plating plant (Sorahan et al. 1987) and chromate production (Davies et al. 1991; Taylor 1966) (see Section 3.2.1.2, Respiratory Effects). However, a number of methodological deficiencies in these studies prevent the establishment of a definitive cause-effect relationship. Retrospective mortality studies associating chromium exposure with cancer are discussed in Section 3.2.1.7.

Acute inhalation LC_{50} values in rats for several chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) ranged from 29 to 45 mg chromium(VI)/m^3 for females and from 33 to 82 mg chromium(VI)/m^3 for males (Gad et al. 1986). Acute inhalation LC_{50} values for chromium trioxide were 87 and 137 mg chromium(VI)/m^3 for female and male rats, respectively (American Chrome and Chemicals 1989). Female rats were more sensitive than males to the lethal effects of most chromium(VI) compounds except sodium chromate, which was equally toxic in both sexes. Signs of toxicity included respiratory distress, irritation, and body weight depression (Gad et al. 1986). The LC_{50} values for chromium(VI) are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to chromium or its compounds. Respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, dermal, ocular, and body weight effects are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1 for chromium(VI) and recorded in Table 3-2 and plotted in Figure 3-2 for chromium(III).

Respiratory Effects. The respiratory tract in humans is a major target of inhalation exposure to chromium compounds. Chromate sensitive workers acutely exposed to chromium(VI) compounds may develop asthma and other signs of respiratory distress. Five individuals who had a history of contact dermatitis to chromium were exposed via a nebulizer to an aerosol containing 0.035 mg chromium(VI)/mL as potassium dichromate. A 20% decrease in the forced expiratory volume of the lungs was observed and was accompanied by erythema of the face, nasopharyngeal pruritus, nasal blocking, coughing, and wheezing (Olaguibel and Basomba 1989).

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Fischer- 344)	4 hr				137 M (LC50) 87 F (LC50)	American Chrome and Chemicals 1989 CrO3 (VI)	
2	Rat (Fischer- 344)	4 hr				82 M (LC50) 45 F (LC50)	Gad et al. 1986 (NH4)2Cr2O7 (VI)	
3	Rat (Fischer- 344)	4 hr				35 M (LC50) 29 F (LC50)	Gad et al. 1986 K2Cr2O7 (VI)	
4	Rat (Fischer- 344)	4 hr				70 M (LC50) 31 F (LC50)	Gad et al. 1986 Na2Cr2O7.2H2O (VI)	
5	Rat (Fischer- 344)	4 hr				33 (LC50)	Gad et al. 1986 Na2CrO4 (VI)	
Systemic								
6	Rat (Sprague-Dawley)	10 d 5 d/wk 6 hr/d	Resp	0.49 M	1.15 M (nasal hemorrhage)		Kim et al. 2004 CrO3 (VI)	
INTERMEDIATE EXPOSURE								
Systemic								
7	Human	<90 d (occup)	Resp		0.025 M (irritated nasal septum)		Gibb et al. 2000a CrO3 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
8	Human	90 d- 1 yr (occup)	Resp		0.033 M perforated nasal septum		Gibb et al. 2000a CrO3 (VI)	
			Other		0.036 M perforated eardrum			
9	Human	<1 yr 5 d/wk 8 hr/d (occup)	Resp		0.1 (epitaxis rhinorrhea, nasal ulceration and perforation)		Gomes 1972 CrO3 (VI)	
10	Human	0.5-12 mo 6 mo avg 5 d/wk 8 hr/d (occup)	Resp		0.09 M (epitaxis, rhinorrhea ulceration of nasal septum)		Kleinfield and Rosso 1965 CrO3 (VI)	
11	Human	0.2-23.6 yr avg 2.5 yr 5 d/wk 8 hr/d (occup)	Resp		0.002[b] (nasal mucosa atrophy and ulceration, mild decreased lung function)		Lindberg and Hedenstierna 1983 CrO3 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
12	Rat (Wistar)	28 d 7 d/wk 22 hr/d	Resp		0.025 M (increased percentage of lymphocytes in bronchoalveolar lavage fluid)		Glaser et al. 1985 Na2Cr2O7.2H2O (VI)	
			Gastro	0.2 M				
			Hemato	0.2 M				
			Hepatic	0.2 M				
			Renal	0.2 M				
			Bd Wt	0.2 M				
13	Rat (Wistar)	90 d 7 d/wk 22 hr/d	Resp		0.025 M (increased percentage of lymphocytes in bronchial alveolar lavage fluid)		Glaser et al. 1985 Na2Cr2O7.2H2O (VI)	
			Gastro	0.2 M				
			Hemato	0.2 M				
			Hepatic	0.1 M	0.2 M (increased levels of serum phospholipids and triglycerides)			
			Renal	0.2 M				
			Bd Wt	0.2 M				

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
14	Rat (Wistar)	30 or 90 d 7 d/wk 22 hr/d	Resp		0.05 M[c] (increased lung weight, hyperplasia, macrophage infiltration, increased protein, albumin, lactate dehydrogenase in BAL fluid)		Glaser et al. 1990 Na2Cr2O7.2H2O (VI)	
			Gastro	0.4 M				
			Hemato		0.05 M (increased white blood cell count)			
			Hepatic	0.4 M				
			Renal	0.4 M				
			Bd Wt	0.1 M	0.2 M (28% decreased body weight gain)			
15	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d	Resp	0.23 M	0.49 M (inflammation and macrophage aggregation in alveolar regions of the lung)		Kim et al. 2004 CrO3 (VI)	
			Cardio	1.15 M				
			Hemato		0.23 M (decreased hematocrit)			
			Hepatic	1.15 M				
			Renal	1.15 M				
			Endocr	1.15 M				
			Bd Wt	1.15 M				

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
16	Mouse (C57BL)	12 mo 2 d/wk 120 min/d	Resp			1.81 F (emphysema, nasal septum perforation)	Adachi 1987 CrO3 (VI)	
17	Mouse (ICR)	12 mo 2 d/wk 30 min/d	Resp			3.63 F (emphysema, nasal septum perforation)	Adachi et al. 1986 CrO3 (VI)	
18	Rabbit (NS)	4-6 wk 5 d/wk 6 hr/d	Resp	0.9 M			Johansson et al. 1986b Na2CrO4 (VI)	
Immuno/ Lymphoret								
19	Rat (Fischer- 344)	2-4 wk 5 d/wk 5 hr/d			0.36 (increased neutrophils, monocytes, and decreased macrophages in BAL fluid; decreased cytokine levels)		Cohen et al. 1998 K2CrO4 (VI)	
20	Rat (Fischer- 344)	2-4 wk 5 d/wk 5 hr/d			0.36 (decreased tumor necrosis factor-alpha levels and production of superoxide anion and hydrogen peroxide and increased nitric oxide production)		Cohen et al. 1998 BaCrO4 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
21	Rat (Wistar)	28 d 7 d/wk 22 hr/d			0.025 M (increased response to sheep red blood cells, increased percentage of lymphocytes in bronchoalveolar lavage fluid)		Glaser et al. 1985 Na2Cr2O7.2H2O (VI)	
22	Rat (Wistar)	90 d 7 d/wk 22 hr/d			0.025 M (increased response to sheep RBC, increased % of lymphocytes in bronchoalveolar lavage fluid, increased % of macrophages in telophase, increased activity of macrophages)		Glaser et al. 1985 Na2Cr2O7.2H2O (VI)	
Neurological								
23	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		1.15 M			Kim et al. 2004 CrO3 (VI)	
Reproductive								
24	Rat (Wistar)	90 d 7 d/wk 22 hr/d		0.2 M			Glaser et al. 1985 Na2Cr2O7.2H2O (VI)	
25	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		1.15 M			Kim et al. 2004 CrO3 (VI)	
CHRONIC EXPOSURE								
Systemic								
26	Human	7 yr avg 5 d/wk 8 hr/d (occup)	Renal		0.05 M (increase in retinol binding protein and tubular antigen)		Franchini and Mutti 1988 CrO3 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
27	Human	>1 yr (occup)	Resp		0.025 M (bleeding nasal septum)		Gibb et al. 2000a CrO3 (VI)	
			Ocular		0.049 M			
28	Human	(occup)	Resp		0.414 (nasal septum perforation, chronic pharyngitis, atrophy of larynx)		Hanslian et al. 1967 CrO3 (VI)	
			Gastro		0.414 (chronic tonsilitis)			
29	Human	0.2-23.6 yr avg 2.5 yr 5 d/wk 8 hr/d (occup)	Resp		0.002[b] (nasal mucosa atrophy and ulceration, mild decreased lung function)		Lindberg and Hedenstierna 1983 CrO3 (VI)	
30	Human	0.1-26 yr 5.3 yr avg 5 d/wk 8 hr/d (occup)	Renal		0.004 M (increased urinary beta-2-microglobulin)		Lindberg and Vesterberg 1983b CrO3 (VI)	
31	Human	(occup)	Renal		0.0042 (increased prevalence of high N-acetyl-B-glucosamindase levels)		Liu et al. 1998 Cr(VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
32	Human	7.5 yr avg (range 3-16 yr) (occup)	Resp		0.004 M (epitaxis, rhinorrhea, nasal septum ulceration and perforation)		Lucas and Kramkowski 1975 CrO3 (VI)	
			Gastro		0.004 M (stomach pains and cramps, ulcers)			
33	Rat (Wistar)	18 mo 7 d/wk 22 hr/d	Resp	0.1 M			Glaser et al. 1986, 1988 Na2Cr2O7.2H2O (VI)	
			Hemato	0.1 M				
			Hepatic	0.1 M				
			Renal	0.1 M				
			Endocr	0.1 M				
			Bd Wt	0.1 M				
34	Rat (Wistar)	2 yr 4 d/wk 4-5 hr/d	Resp			1.6 (granulomata, giant cells, bronchopneumonia, abscesses)	Steffee and Baetjer 1965 Finely ground chromium roast (VI)	
35	Mouse (C57BL/6)	18 mo 5 d/wk 5.5 hr/d	Resp			4.3 (epithelial necrosis, hyperplasia)	Nettesheim and Szakal 1972 CaCrO4 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
36	Gn Pig (NS)	4.5 yr 4 d/wk 4-5 hr/d	Resp			1.6 (alveolar and interstitial inflammation; alveolar hyperplasia, interstitial fibrosis)	Steffee and Baetjer 1965 Mixed chromium roast K2Cr2O7, Na2CrO4 (VI)	
Immuno/ Lymphoret								
37	Human	5.8 yr (Occup)			0.001 (increased response of peripheral blood mononucleocytes to concavalin A)		Mignini et al. 2004 Cr (VI)	
Cancer								
38	Human	1 mo- 29 yr 5 d/wk 8 hr/d (occup)				0.5 M (CEL: lung cancer)	Hayes et al. 1989 PbCrO4 and ZnCrO4 (VI)	
39	Human	4-19 yr 5 d/wk 8 hr/d (occup)				0.5 (CEL: lung cancer)	Langård and Norseth 1975 PbCrO4 and ZnCrO4 (VI)	
40	Human	1-7 yr 5 d/wk 8 hr/d (occup)				0.25 (CEL: lung cancer)	Mancuso 1975 Soluble Cr(VI)	
41	Human	1 mo- 29 yr 5 d/wk 8 hr/d (occup)				0.1 M (CEL: lung cancer)	Sheffet et al. 1982 PbCrO4 and ZnCrO4 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
42	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.1 M (CEL: lung tumors)	Glaser et al. 1986, 1988 Na2Cr2O7.2H2O (VI)	
43	Mouse (C57BL/6)	18 mo 5 d/wk 5 hr/d				4.3 (CEL: alveologenic adenomas and adenocarcinomas)	Nettesheim et al. 1971 CaCrO4 (VI)	

a The number corresponds to entries in Figure 3-1.

b Used to derive an intermediate and chronic inhalation minimal risk level (MRL) of 0.000005 mg chromium(VI)/m3 for chromium (VI) trioxide and soluble chromium (VI) compounds. Exposure concentration adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL).

c Used to derive an intermediate inhalation minimal risk level (MRL) of 0.0003 mg chromium(VI)/m3 for particulate chromium (VI) compounds. Benchmark concentration of 0.016 mg chromium (VI)/m3 was divided by an uncertainty factor of 30 (3 for pharmacodynamic variability between species and 10 for human variability).

(VI) = hexavalent; avg = average; BaCrO4 = barium chromate; BAL = bronchoalveolar lavage; Bd Wt = body weight; CaCrO4 = calcium chromate; Cardio = cardiovascular; CEL = cancer effect level; Cr = chromium; CrCl3 = chromium trichloride; Cr(NO3)3SH2O = chromium nitrate; CrO2 = chromium dioxide; CrO3 = chromium trioxide; Cr2O3 = chromium oxide; Cr2(SO)3 = chromium sulfate; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; K2Cr2O7 = potassium dichromate; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = rnonth(s); Na2CrO4 = sodium chromate; Na2Cr2O7H2O = sodium dichromate dihydrate; (NH4)2Cr2O7 = ammonium dichromate; NS = not specified; NOAEL = no-observed-adverse-effect level; occup = occupational; PbCrO4 = lead chromate; RBC = red blood cell; Resp = respiratory; WBC =white blood cell; wk = week(s); x = times; yr = year(s); ZnCrO4 = zinc chromate

Figure 3-1 Levels of Significant Exposure to Chromium VI - Inhalation

Acute (≤14 days)

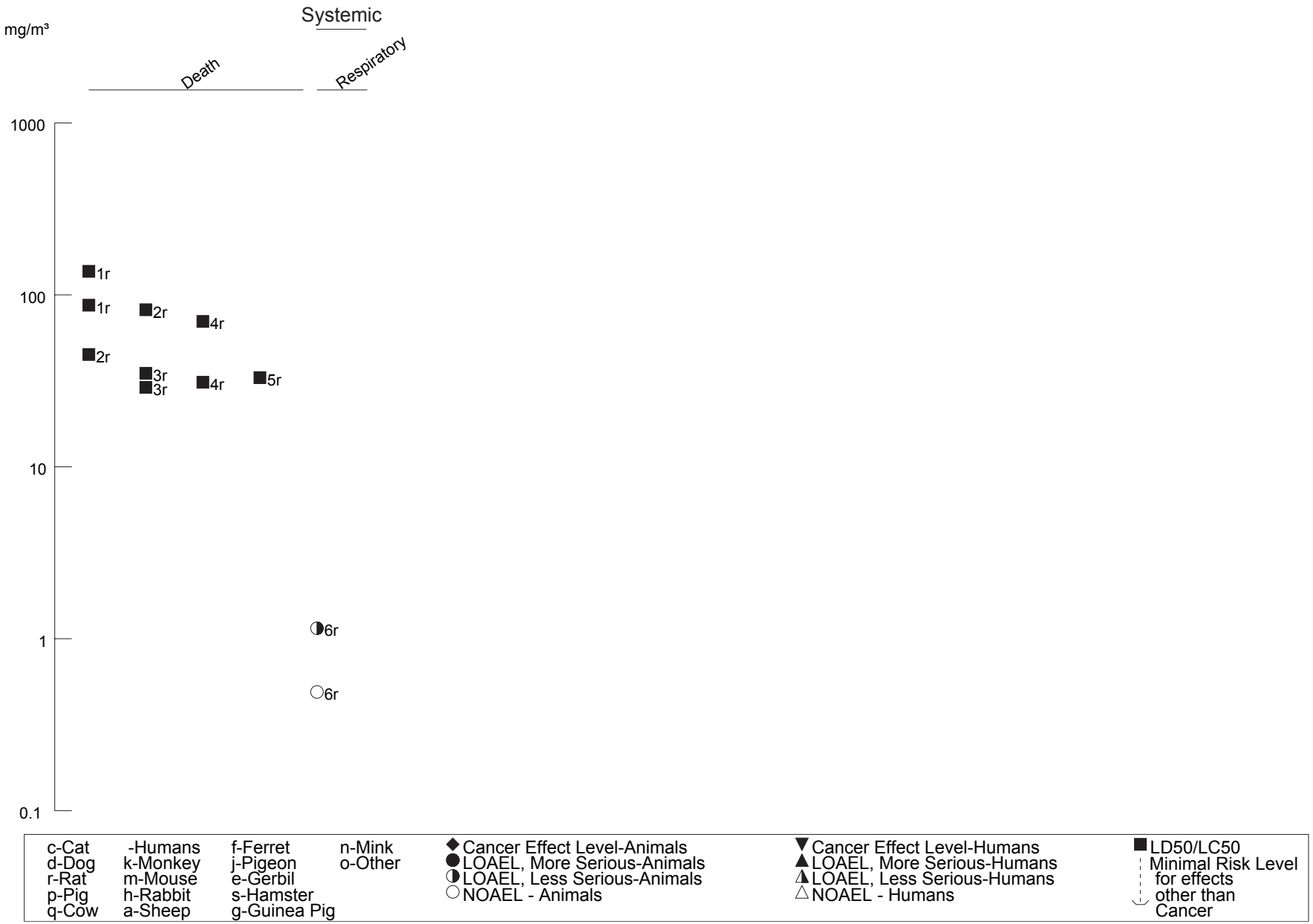


Figure 3-1 Levels of Significant Exposure to Chromium VI - Inhalation *(Continued)*

Intermediate (15-364 days)

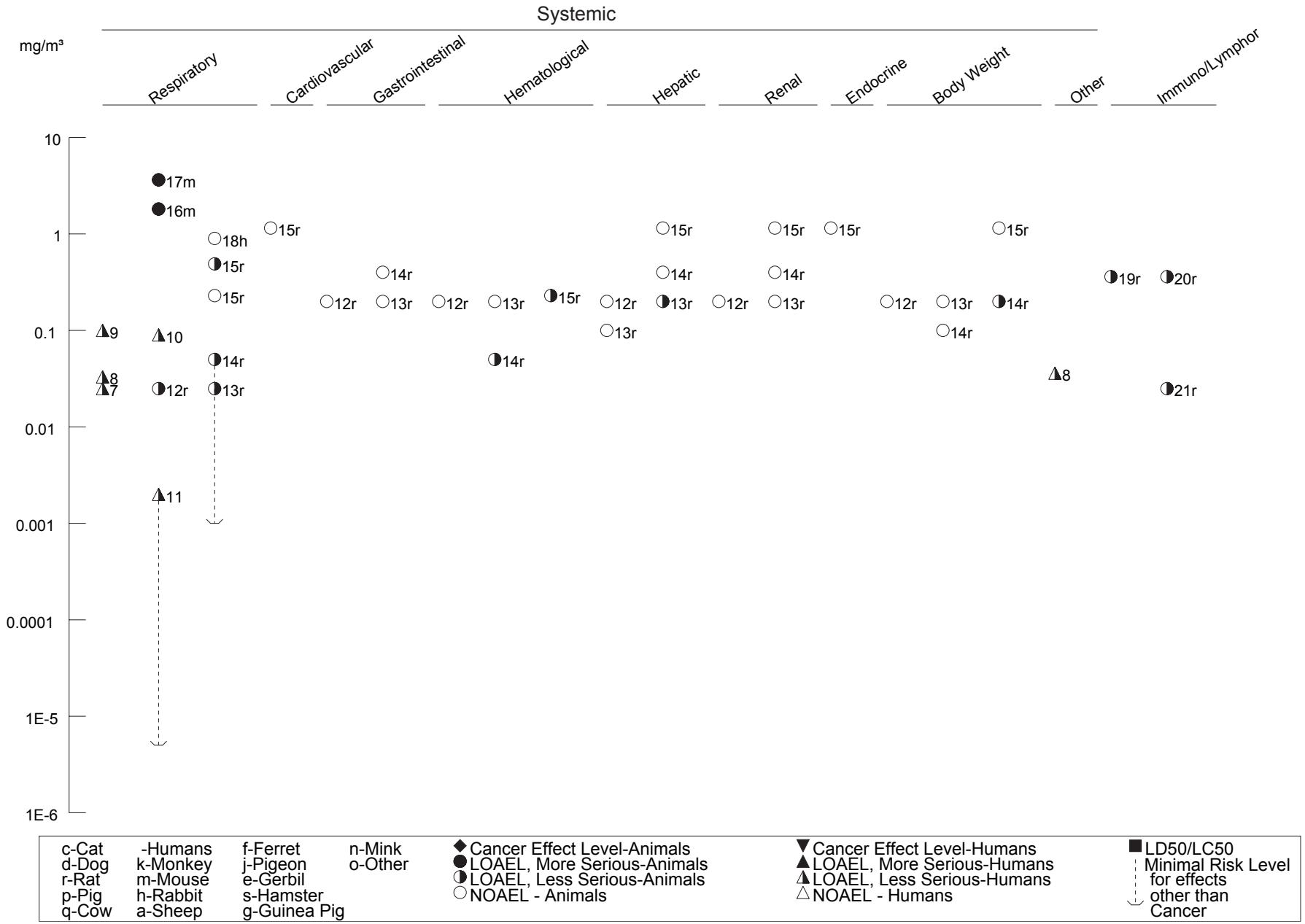


Figure 3-1 Levels of Significant Exposure to Chromium VI - Inhalation *(Continued)*

Intermediate (15-364 days)

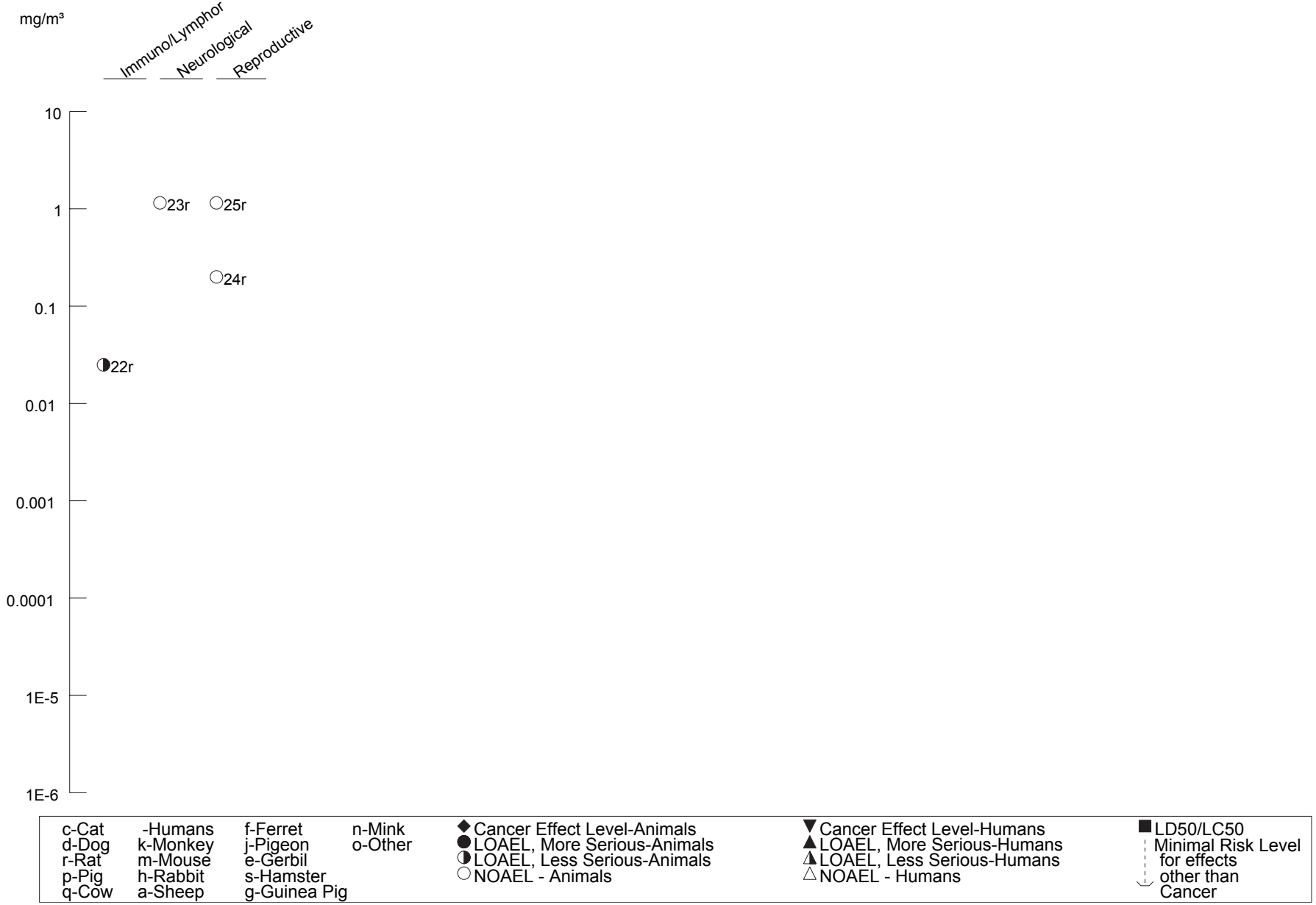
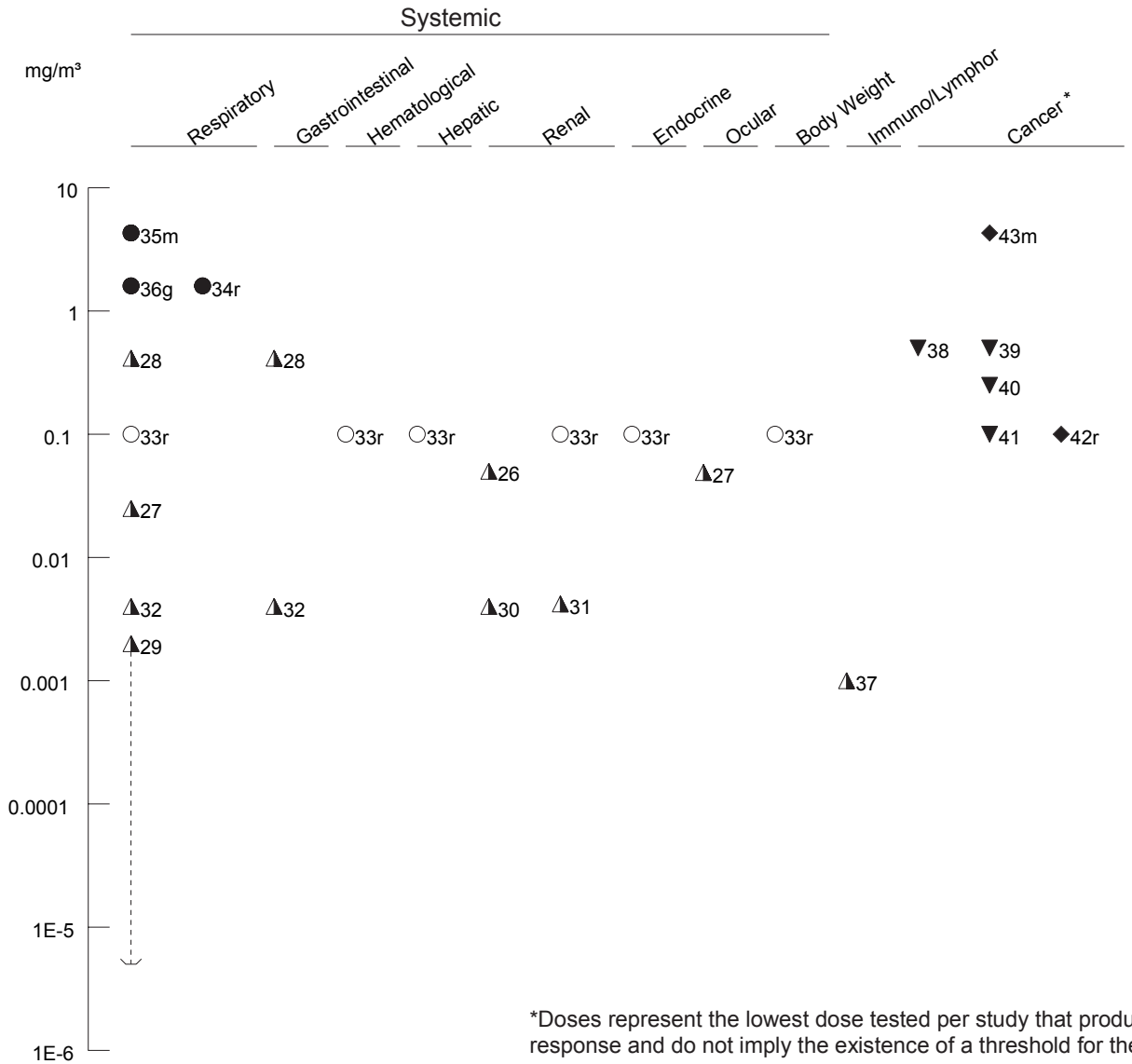


Figure 3-1 Levels of Significant Exposure to Chromium VI - Inhalation *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Table 3-2 Levels of Significant Exposure to Chromium III - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Hamster (Syrian)	30 min	Resp		0.9 (increased acid phosphatase activity in lung tissue)		Henderson et al. 1979 CrCl3 (III)	
INTERMEDIATE EXPOSURE								
Systemic								
2	Rat (CDF)	13 wk 6 hr/d 5 d/wk	Resp	3 F	3 M[b] (septal cell hyperplasia and interstitial inflammation of the lung; increased absolute and relative lung weight at 30 mg/m3)		Derelanko et al. 1999 Cr2O3 (III)	
					10 F (interstitial inflammation and hyperplasia of alveolar septa)			
			Cardio	30				
			Gastro	30				
			Hemato	30				
			Hepatic	30				
			Renal	30				
			Endocr	30				
			Ocular	30				
			Bd Wt	30				

Table 3-2 Levels of Significant Exposure to Chromium III - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
3	Rat (CDF)	13 wk 6 hr/d 5 d/wk	Resp		3[c] (inflammation of lung; nasal tissues and larynx lesions; increased lung weight)		Derelanko et al. 1999 Cr2(OH)x(SO4)yNaSO4.2H2O (III)	
			Cardio	30				
			Gastro	30				
			Hepatic	30				
			Renal	30				
			Endocr	30				
			Ocular	30				
			Bd Wt	3 M	10 M (~10% decreased in body weight)			
4	Rabbit (NS)	4-6 wk 5 d/wk 6 hr/d	Resp		0.6 M (decreased macrophage activity)		Johansson et al. 1986b Cr(NO3)39H2O(III)	
Immuno/ Lymphoret								
5	Rat (CDF)	13 wk 6 hr/d 5 d/wk			3 (hyperplasia of mediastinal lymph node)		Derelanko et al. 1999 Cr2O3 (III)	
6	Rat (CDF)	13 wk 6 hr/d 5 d/wk			3 (histiocytosis, lymphoid hyperplasia and enlargement of peribronchial and mediastinal lymph nodes)		Derelanko et al. 1999 Cr2(OH)x(SO4)yNaSO4.2H2O (III)	

Table 3-2 Levels of Significant Exposure to Chromium III - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
Neurological								
7	Rat (CDF)	13 wk 6 hr/d 5 d/wk		30			Derelanko et al. 1999 Cr2(OH)x(SO4)yNaSO4.2H2O (III)	
8	Rat (CDF)	13 wk 6 hr/d 5 d/wk		30			Derelanko et al. 1999 Cr2O3 (III)	Increased absolute and relative lung weight in males at 30 mg/m3.
Reproductive								
9	Rat (CDF)	13 wk 6 hr/d 5 d/wk		30			Derelanko et al. 1999 Cr2O3 (III)	
10	Rat (CDF)	13 wk 6 hr/d 5 d/wk		30			Derelanko et al. 1999 Cr2(OH)x(SO4)yNaSO4.2H2O (III)	
CHRONIC EXPOSURE								
Systemic								
11	Human	2-12 yr 5 d/wk 8 hr/d (occup)	Renal	0.075 M			Foa et al. 1988 Cr2O3 (III)	
12	Human	(occup)	Resp	1.99			Korallus et al. 1974a Cr2O3 and Cr2(SO4)3 (III)	

Table 3-2 Levels of Significant Exposure to Chromium III - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
			Hemato	1.99				

a The number corresponds to entries in Figure 3-2.

b Used to derive an intermediate-duration inhalation MRL of 0.005 mg chromium(III)/m3 as insoluble trivalent chromium particulate compounds. The minimal LOAEL of 3 mg chromium(III)/m3 was adjusted for intermittent exposure, converted to a human equivalent concentration (0.43 mg chromium(III)/m3), and divided by a composite uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans and 10 for human variability).

c Used to derive an intermediate-duration inhalation MRL of 0.0001 mg chromium(III)/m3 as soluble trivalent chromium particulate compounds. The LOAEL of 3 mg chromium(III)/m3 was duration-adjusted for intermittent exposure, converted to a human equivalent concentration (0.04 mg chromium(III)/m3) and divided by a composite uncertainty factor of 300 (10 for use of a LOAEL, 3 for variability between animals to humans and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Chromium III - Inhalation

Acute (≤14 days)

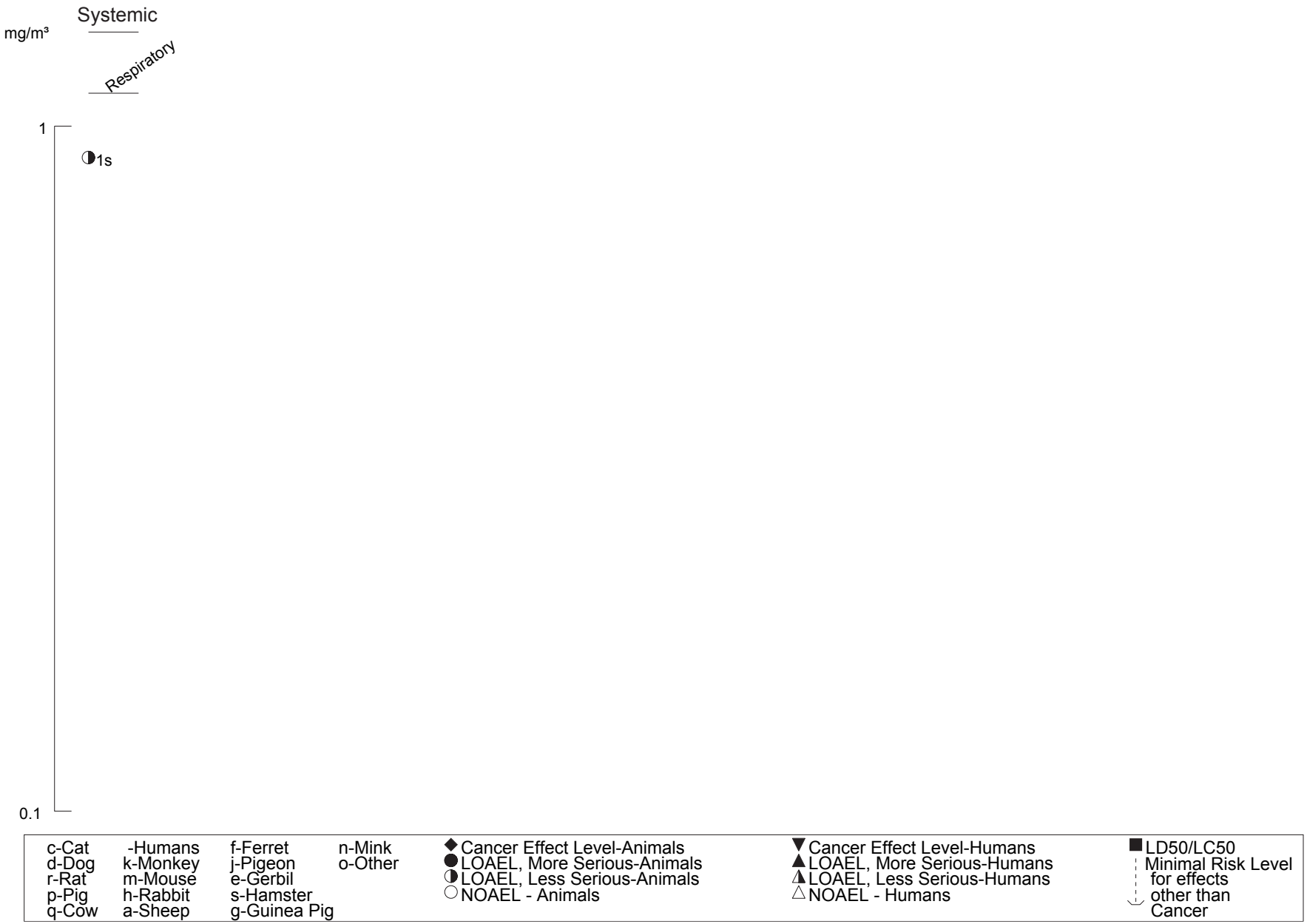


Figure 3-2 Levels of Significant Exposure to Chromium III - Inhalation *(Continued)*

Intermediate (15-364 days)

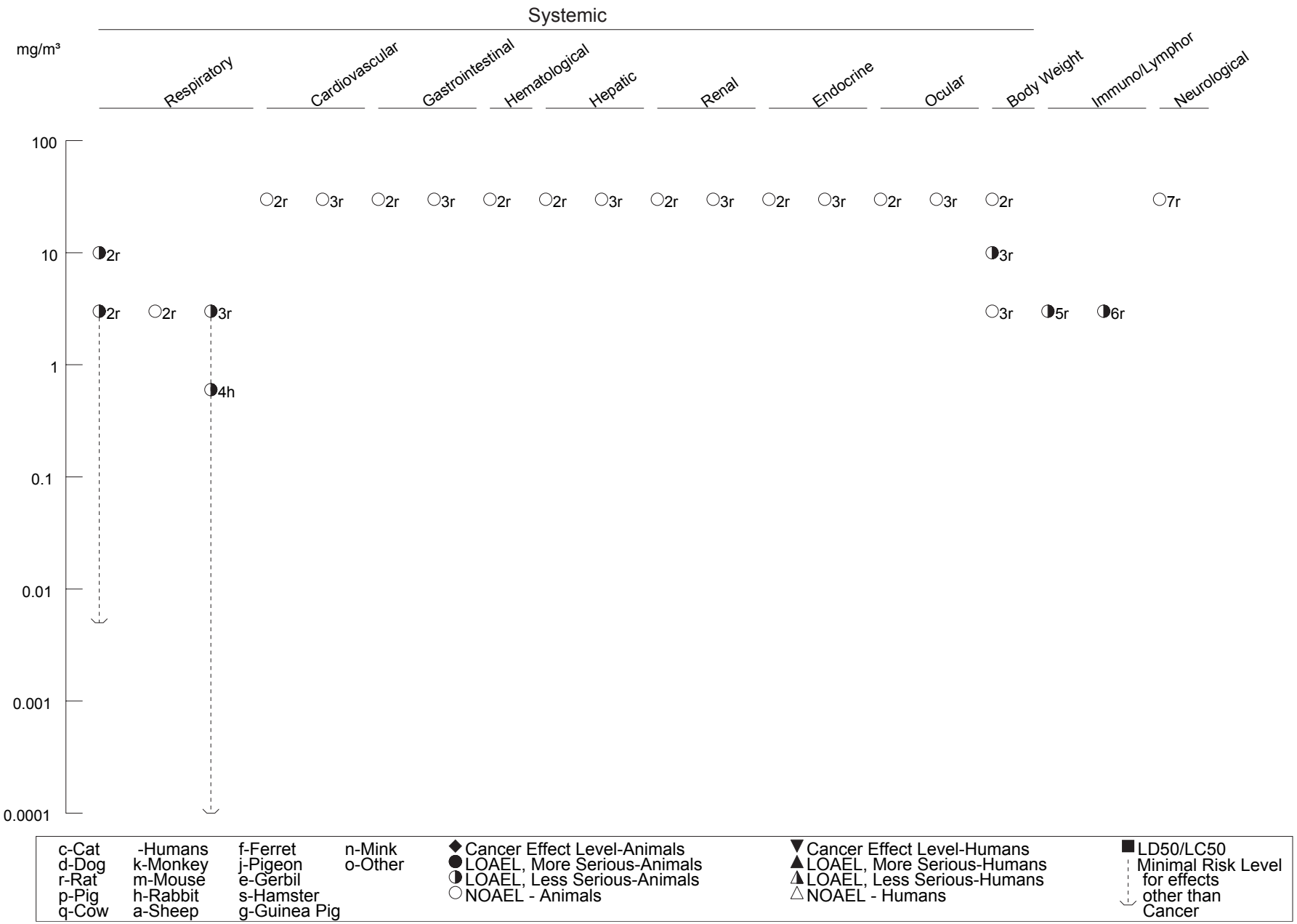


Figure 3-2 Levels of Significant Exposure to Chromium III - Inhalation *(Continued)*

Intermediate (15-364 days)

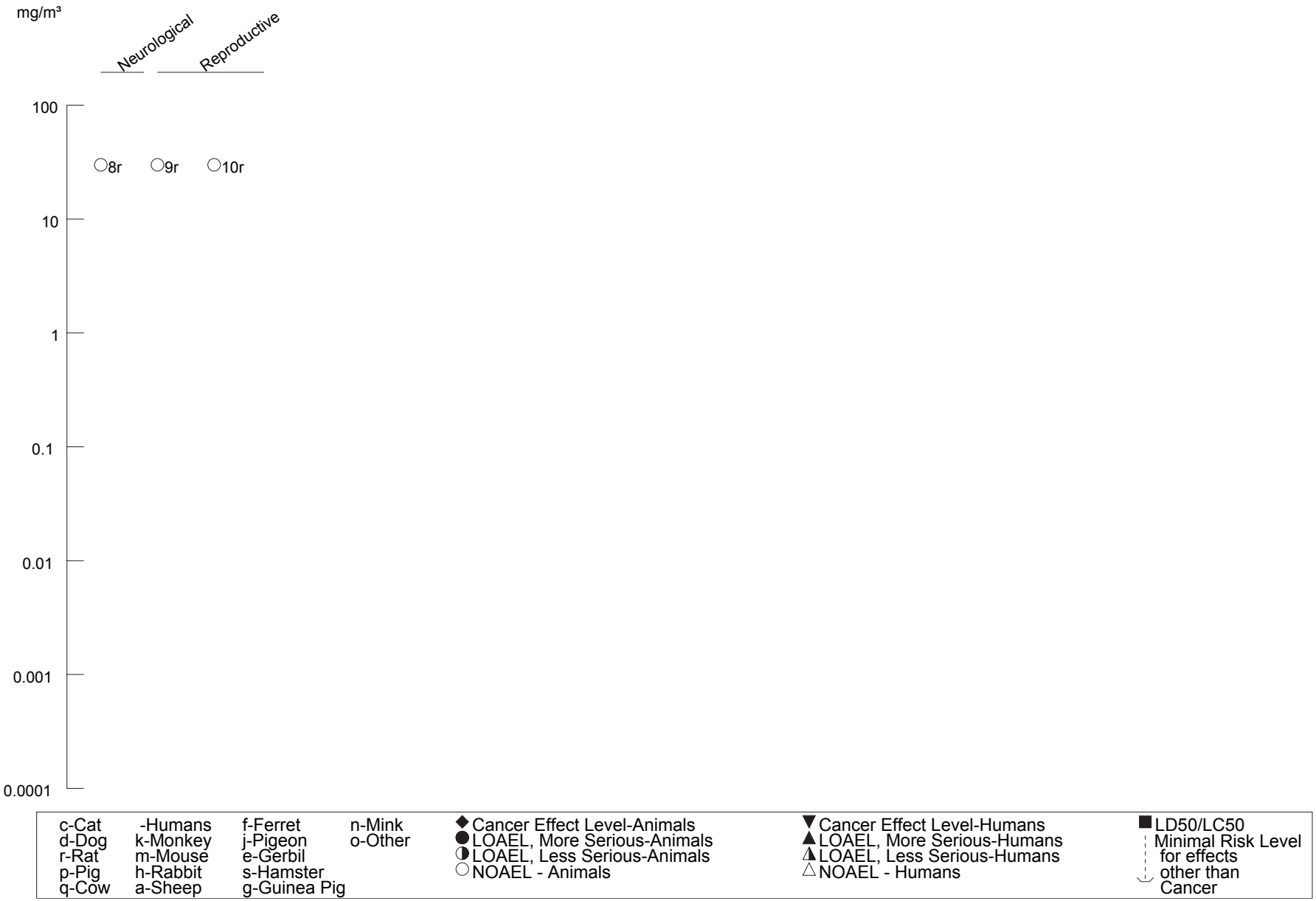
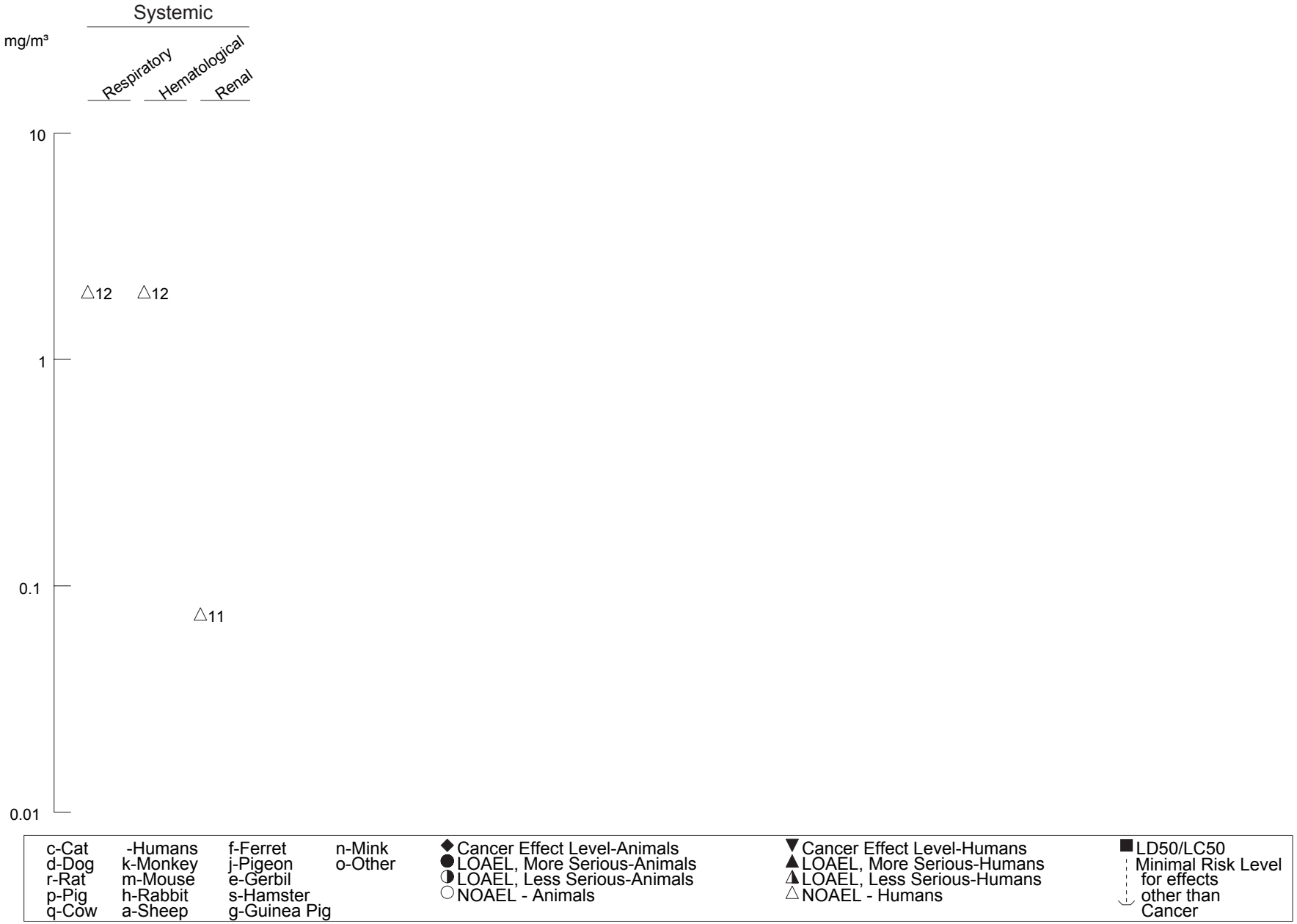


Figure 3-2 Levels of Significant Exposure to Chromium III - Inhalation *(Continued)*

Chronic (≥365 days)



Dyspnea, cough, and wheezing were reported in two cases in which the subjects inhaled "massive amounts" of chromium(VI) trioxide. Marked hyperemia of the nasal mucosa without nasal septum perforation was found in both subjects upon physical examination (Meyers 1950). In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, workers experienced symptoms of sneezing, rhinorrhea, labored breathing, and a choking sensation when they were working over the chromate tanks. All five of the subjects had thick nasal and postnasal discharge and nasal septum ulceration or perforation after 2–3 months of exposure (Lieberman 1941). Asthma developed in a man who had been well until 1 week after beginning employment as an electroplater. When challenged with an inhalation exposure to a sample of chromium(III) sulfate, he developed coughing, wheezing, and decreased forced expiratory volume. He also had a strong asthmatic reaction to nickel sulfate (Novey et al. 1983). Thus, chromium-induced asthma may occur in some sensitized individuals exposed to elevated concentrations of chromium in air, but the number of sensitized individuals is low and the number of potentially confounding variables in the chromium industry is high.

Intermediate- to chronic-duration occupational exposure to chromium(VI) may cause an increased risk of death due to noncancer respiratory disease. In a retrospective mortality study of 1,288 male and 1,401 female workers employed for at least 6 months in a chrome plating and metal engineering plant in the United Kingdom between 1946 and 1975, a statistically significant excess of death from diseases of the respiratory system (noncancer) were obtained for men (observed/expected [O/E]=72/54.8, standard mortality ratio [SMR]=131, $p<0.05$) and men and women combined (O/E=97/76.4, SMR=127, $p<0.05$), but not for women alone. Exposure was mainly to chromium trioxide, but exposure concentrations were not precisely known. The contribution of nickel exposure to the effects was found to be unimportant, while data on smoking habits were not available (Sorahan et al. 1987). Similarly, a high SMR was found for noncancer respiratory disease among 1,212 male chromate workers who were employed for at least 3 months in three chromate plants in the United States during the years 1937–1960 and followed for 24 years (O/E=19/7.843, SMR=242) (Taylor 1966). The increased risk of death from respiratory effects correlated with duration of employment in chromate production, but no information on exposure levels, smoking habits, or exposure to other chemicals was provided. The nature of the respiratory diseases was not further described in either of these reports. Chromate production workers in the United Kingdom who were first employed before 1945 had a high risk of death from chronic obstructive airways disease (O/E=41/28.66, SMR=143, $p<0.05$) (Davies et al. 1991). Exposure concentrations were not known, and reliable smoking data were not available.

Occupational exposure to chromium(VI) as chromium trioxide in the electroplating industry caused upper respiratory problems. A case history of nine men in a chrome plating facility reported seven cases of nasal septum ulceration. Signs and symptoms included rhinorrhea, nasal itching and soreness, and epistaxis. The men were exposed from 0.5 to 12 months to chromium trioxide at concentrations ranging from 0.09 to 0.73 mg chromium(VI)/m^3 (Kleinfeld and Rosso 1965). Electroplating workers in Sao Paulo, Brazil, exposed to chromium trioxide vapors while working with hot chromium trioxide solutions had frequent incidences of coughing, expectoration, nasal irritation, sneezing, rhinorrhea, and nose-bleed and developed nasal septum ulceration and perforation. The workers had been employed for <1 year, and most of the workers had been exposed to concentrations >0.1 mg chromium(VI)/m^3 (Gomes 1972). Nose and throat irritation, rhinorrhea, and nose-bleed also occurred at higher incidence in chrome platers in Singapore than in controls (Lee and Goh 1988).

Numerous studies of workers chronically exposed to chromium(VI) compounds have reported nasal septum perforation and other respiratory effects. Workers at an electroplating facility exposed to 0.0001–0.0071 mg chromium(VI)/m^3 as chromium trioxide for an average of 26.9 months complained of excessive sneezing, rhinorrhea, and epistaxis. Many of the workers had ulcerations and/or perforations of the nasal mucosa (Cohen et al. 1974). A study using only questionnaires, which were completed by 997 chrome platers and 1,117 controls, found a statistically significant increase in the incidence of chronic rhinitis, rhinitis with bronchitis, and nasal ulcers and perforations in workers exposed to chromium(VI) in the chrome plating industry in 54 plants compared to the control population (Royle 1975b). The workers had been exposed to chromium(VI) in air and in dust. The air levels were generally <0.03 mg chromium(VI)/m^3, and dust levels were generally between 0.3 and 97 mg chromium(VI)/g. The exposure levels at which effects first occurred could not be determined. A NIOSH Health Hazard Evaluation of an electroplating facility in the United States reported nasal septum perforation in 4 of 11 workers employed for an average of 7.5 years and exposed to mean concentrations of 0.004 mg chromium(VI)/m^3. Many of the workers had epistaxis, rhinitis, and nasal ulceration (Lucas and Kramkowski 1975). Nasal mucosal changes ranging from irritation to perforation of the septum were found among 77 employees of eight chromium electroplating facilities in Czechoslovakia where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m^3 (Hanslian et al. 1967). The incidence of olfactory cleft obstruction, dry nose, feelings of nasal obstruction, and nasal crusting was significantly increased in workers employed at chromium plating factories (mean employment duration of 7.9 years) in An-San, Korea compared to an unexposed control group (Kitamura et al. 2003). Air concentrations of chromium(VI) ranged from 0.005 to 0.03 mg chromium(VI)/m^3 and of chromium(III) ranged from 0.005 to 0.06 mg chromium(III)/m^3. Increased incidences of nasal septum

perforation, nasal septum ulcer, and nasal obstruction were observed in workers at chromium electroplating facilities exposed for a mean duration of 6.1 years, as compared to workers at zinc electroplating facilities (Kuo et al. 1997a). The chromium electroplating workers had 31.7 and 43.9 times greater risks of developing nasal septum ulcers or nasal perforations, respectively, than the zinc workers. A significant relationship between duration of exposure and the risk of nasal septum ulcers was also found; the chromium electroplating workers with a work duration of >9 years had a risk 30.8 times higher than those with a work duration of <2 years. Duration did not significantly affect the risk of nasal perforation. Statistically significant decreases in vital capacity, forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV_1) were also observed in the chromium workers. Alterations in lung function were also reported in a study of 44 workers at 17 chromium electroplating facilities (Bovet et al. 1977). Statistically significant decreases in forced expiratory volume in 1 second and forced expiratory flow were observed; vital capacity was not altered. Lower lung function values were found among workers with high urinary chromium levels (exposure levels were not reported), and it was determined that cigarette smoking was not a confounding variable.

A study of respiratory effects, lung function, and changes in the nasal mucosa in 43 chrome plating workers in Sweden exposed to chromium(VI) as chromium trioxide for 0.2–23.6 years (median=2.5 years) reported respiratory effects at occupational exposure levels of 0.002 mg chromium(VI)/m^3. Signs and symptoms of adverse nasal effects were observed and reported at mean exposure levels of 0.002–0.2 mg chromium(VI)/m^3. Effects noted at ≤0.002 mg chromium(VI)/m^3 included a smeary and crusty septal mucosa and atrophied mucosa. Nasal mucosal ulceration and septal perforation occurred in individuals exposed at peak levels of 0.02–0.046 mg chromium(VI)/m^3; nasal mucosal atrophy and irritation occurred in individuals exposed at peak levels of 0.0025–0.011 mg chromium(VI)/m^3; and no significant nasal effects were observed in individuals exposed at peak levels of 0.0002–0.001 mg chromium(VI)/m^3. Workers exposed to mean concentrations of 0.002–0.02 mg chromium(VI)/m^3 had slight, transient decreases in FVC, forced expired volume in 1 second (FEV_1), and forced mid-expiratory flow during the workday. Workers exposed to <0.002 mg chromium(VI)/m^3 showed no effects on lung function (Lindberg and Hedenstierna 1983). The concentrations at which minor lung function changes were observed (0.002–0.02 mg chromium(VI)/m^3) and those at which no changes were observed (<0.002 mg chromium(VI)/m^3) are similar to those for nasal effects (0.0025–0.011 mg chromium(VI)/m^3). The effects observed in this study may not have resulted from exposure levels actually measured, but may have resulted from earlier exposure under unknown conditions. Furthermore, poor personal hygiene practices resulting in transfer of chromium(VI) in chrome plating solutions from the hands to the nose could contribute to the development of nasal ulceration and

perforation (Cohen et al. 1974; Lucas and Kramkowski 1975), perhaps leading to an underestimation of airborne levels of chromium(VI) necessary to cause these effects. Despite these considerations, the study by Lindberg and Hedenstierna (1983) is useful because it indicates concentration-responses of chromium(VI) compounds that cause significant nasal and respiratory effects. The LOAEL of 0.002 mg chromium(VI)/m^3 for respiratory effects in humans was used to calculate an inhalation MRL of $5x10^{-6}$ mg chromium(VI)/m^3 for intermediate-duration exposure to chromium(VI) as chromium trioxide mists and other dissolved hexavalent chromium aerosols or mists as described in the footnotes in Table 3-1.

Occupational exposure to chromium(VI) and/or chromium(III) in other chromium-related industries has also been associated with respiratory effects. These industries include chromate and dichromate production, stainless steel welding, and possibly ferrochromium production and chromite mining.

In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were ≥0.01 mg chromium(VI)/m^3, high incidences of nasal septum perforation, septal atrophy and ulcerations, sinusitis, pharyngitis, and bronchitis were found among 65 men who worked in the production of dichromate and chromium trioxide for at least 1 year (Sassi 1956). Medical records of 2,307 male workers (all nonsmokers) employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis) (Gibb et al. 2000a). The most frequently reported clinical symptoms were irritation and ulcerated nasal septum, occurring in 68.1 and 62.9% of the cohort, respectively. For irritation of the nasal septum, the mean time of employment to first diagnosis was 89 days and the mean annual exposure level during the year of first diagnosis was 0.025 mg chromium(VI)/m^3; for nasal septal ulceration, the mean time of employment to first diagnosis was 86 days and the mean annual exposure level during the year of first diagnosis was 0.028 mg chromium(VI)/m^3. Other nasal effects had a longer time to first diagnosis. The time to first diagnosis for perforated nasal septum was 313 days, occurring in 17.3% of the cohort at a mean exposure level of 0.033 mg chromium(VI)/m^3, and for bleeding nasal septum, the time to first diagnosis was 418 days, occurring in 12.1% of the cohort at a mean exposure level of 0.025 mg chromium(VI)/m^3. In a study of 97 workers from a chromate plant exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble chromium(VI) as sodium chromate and dichromate, evaluation for respiratory effects revealed that 63% had perforations of the nasal septum, 86.6% had chemical rhinitis, 42.3% had chronic chemical pharyngitis, 10.35% had laryngitis, and 12.1% had sinus, nasal, or laryngeal polyps. The number of complaints and clinical signs increased as the exposure to

respirable chromium(VI) and chromium(III) compounds increased, but exposure levels at which effects first occurred were not clearly defined (Mancuso 1951). An extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants found that effects on the lungs consisted of bilateral hilar enlargement. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3); water-soluble hexavalent chromium compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent trivalent chromium (0–0.47 mg chromium/m^3) (PHS 1953). Challenge tests with fumes from various stainless steel welding processes indicated that the asthma observed in two stainless steel welders was probably caused by chromium or nickel, rather than by irritant gases (Keskinen et al. 1980). In a study of 54 male miners in Zimbabwe exposed to chrome ore dust, decreases in pulmonary function, as indicated by measures of FVC, FEV_1, peak expiratory flow rate (PEFR), and FEV_1%, was observed compared to an unexposed control (e.g., non-mining) population (Osim et al. 1999). Exposure levels were reported only as respirable dust, not as chromium specifically, and the mining company did not employ industrial hygiene practices to reduce exposure. In this same study, no changes in lung function were observed in a group of 46 male miners working for a company following industrial hygiene procedures (again, specific chromium exposure levels were not reported). The analysis controlled for smoking and infectious respiratory diseases. In a report of 10 cases of pneumoconiosis in underground workers in chromite mines in South Africa, radiographic analysis revealed fine nodulation and hilar shadows. Chromium in the chromite ore in South Africa was in the form of chromium(III) oxide. The cause of the pneumoconiosis was considered to be deposition of insoluble radio-opaque chromite dust in the tissues, rather than fibrosis (Sluis-Cremer and du Toit 1968). In a case report of a death of a sandblaster in a ferrochromium department of an iron works, the cause of death was silicosis, but autopsy also revealed diffuse enlargement of alveolar septae and chemical interstitial and alveolar chronic pneumonia, which were attributed to inhalation of chromium(III) oxide (Letterer 1939). In an industrial hygiene survey of 60 ferrochromium workers exposed to chromium(III) and chromium(VI) (0.02–0.19 mg total chromium/m^3) conducted in 1975, appreciably higher incidences of subjective symptoms of coughing, wheezing, and dyspnea were reported compared with controls. These workers had been employed at the plant for at least 15 years. The control group consisted of workers employed at the same plant for <5 years. Statistically significant decreased mean FVC ($p<0.01$) and FEV_1 ($p<0.05$) were found in the ferrochromium workers compared with controls. Two of the ferrochromium workers had nasal septum perforations, which were attributed to previous exposure to hexavalent chromium. A major limitation of this study is that the control group was significantly younger than the study cohort. In addition, the weekly amount of tobacco smoked by the control group was slightly greater than that

smoked by the study groups, and the controls began smoking 5 years earlier than the study groups. Therefore, the increase in subjective respiratory symptoms and decreased pulmonary function parameters cannot unequivocally be attributed to chromium exposure (Langård 1980). However, no increase in the prevalence of respiratory illness was found in a study of 128 workers from two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b) or in 106 workers at a factory that produced these chromium(III) compounds where workroom levels were ≤1.99 mg chromium(III)/m^3 (Korallus et al. 1974a). Similar results were reported in a cross-sectional study that was conducted to determine whether occupational exposure to trivalent chromium or hexavalent chromium caused respiratory diseases, decreases in pulmonary function, or signs of pneumoconiosis in stainless steel production workers (Huvinen et al. 1996). The median personal exposure levels were 0.0005 μg/m^3 for chromium(VI) and 0.022 μg/m^3 for chromium(III); the 221 workers were employed for >8 years with an average potential exposure of 18 years. Spirometry measurements were taken and chest radiographic examinations were conducted. There were no significant differences in the odds ratios between the exposed workers and the 95 workers in the control group. The deficits in lung function shown in both populations could be explained by age and smoking habits. In a follow-up study of these workers (Huvinen et al. 2002a), no adverse respiratory effects were observed (as assessed by spirometry, chest x-ray ,and self-reported symptoms) in workers in the chromium(VI) group (n=104) compared to controls (n=81). Workers exposed to chromium(III) in the sintering and crushing departments (n=68) reported an increase in respiratory symptoms (phlegm production, shortness of breath on exertion) compared to control, but no differences in spirometry or chest x-ray. Workers exposed to chromium(III) as chromite ore (n=31) had lower lung function tests, although smoking was a confounding factor. In addition to chromium, workers were also exposed to nickel and molybdenum. In a study of stainless steel workers (all nonsmokers) exposed for a minimum of 14 years to chromium(VI) (n=29), chromium(III) (n=14), or chromite(III) ore (n=5), no increase was observed in the incidence of nasal diseases or nasal symptoms in exposed chromium-exposed workers compared to a control population of 39 workers (Huvinen et al. 2002b). However, although an exposure-related increase in the incidence of clinical signs of nasal irritation was not observed, anterior rhinoscopy revealed a slight increase in the incidence of inflammatory changes in the nasal mucosa of workers exposed to chromium(VI) (risk ratio=2.4) or chromium(III) (risk ratio=2.3), compared to control. The mean exposure level for the chromium(VI) group was 0.5 μg Cr(VI)/m^3, for the chromium(III) group was 248 μg total Cr/m^3 (concentration of chromium(III) not reported) and for the chromite ore group was 22 μg Cr(III)/m^3.

The respiratory system in animals is also a primary target for acute- and intermediate-duration inhalation exposure to chromium(VI) and chromium(III). Rats exposed to sodium dichromate for 28 or 90 days had

increased lung weight but no histopathological abnormalities at concentrations ≤0.2mg chromium(VI)/m^3. The percentage of lymphocytes was increased in the bronchoalveolar lavage fluid at ≥0.025 mg/m^3. A decrease in macrophage activity was observed in the 0.2 mg chromium(VI)/m^3 group exposed for 90 days. Clearance of iron oxide from the lungs decreased in rats exposed to 0.2 mg chromium(VI)/m^3 for 42 days prior to and 49 days after challenge with iron oxide particles when compared to controls. The decreased clearance of iron oxide correlated with the decrease in macrophage activity (Glaser et al. 1985). In a similar but more extensive study, obstructive respiratory dyspnea was observed in rats exposed to sodium dichromate at ≥0.2 mg chromium(VI)/m^3 for 30 or 90 days, and mean lung weight was increased at ≥0.05 mg chromium(VI)/m^3. Slight hyperplasia was observed at high incidence in rats at ≥0.05 mg chromium(VI)/m^3. Lung fibrosis occurred at low incidence in the rats exposed to ≥0.1 mg chromium(VI)/m^3 for 30 days, but not in the 0.05 mg/m^3 or the control groups. The incidence of both these lesions declined after longer exposure, indicating repair. Accumulation of macrophages and inflammation occurred at ≥0.05 mg chromium(VI)/m^3 regardless of duration. Results of bronchoalveolar lavage (BAL) analysis provided further evidence of an irritation effect that was reversible (Glaser et al. 1990). The data from the Glaser et al. (1990) study was used to develop benchmark concentrations (BMCs) (Malsch et al. 1994). The BMC of 0.016 mg chromium(VI)/m^3 for alterations in lactate dehydrogenase levels in BAL fluid was used to calculate an inhalation MRL of 0.0003 mg chromium(VI)/m^3 for intermediate-duration exposure to chromium(VI) as particulate hexavalent compounds as described in the footnote of Table 3-1.

Male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m^3 as chromium trioxide mist developed nasal hemorrhage after 10 days (lasting for 4 weeks) during a 90-day inhalation study (Kim et al. 2004). "Peculiar sounds" during respiration were noted starting after 1 week of exposure and resolving by week 8 in rats exposed to ≥0.23 mg chromium(VI)/m^3; however, no additional information on this observation was reported. After 90 days, histopathological changes to respiratory tissue included macrophage aggregation and foamy cells, and inflammation of alveolar regions; however, no abnormalities were observed in nasal tissue at 0.49 mg chromium(VI)/m^3 (incidence data were not reported). Mice exposed to chromium trioxide mist at concentrations of 1.81 and 3.63 mg chromium(VI)/m^3 intermittently for ≤12 months developed perforations in the nasal septum, hyperplastic and metaplastic changes in the larynx, trachea, and bronchus, and emphysema (Adachi 1987; Adachi et al. 1986).

The respiratory effects of chromium(III) compounds were investigated in male and female CDF rats exposed to insoluble chromic oxide or soluble basic chromium sulfate by nose-only inhalation at 3, 10, or

30 mg chromium(III)/m^3 for 6 hours/day, 5 days/week for 13 weeks (Derelanko et al. 1999). After 5 days of exposure, BAL was conducted on a subgroup of animals. In rats treated with chromic oxide, a yellow crystalline material was observed in the cytoplasm of mononuclear cells of all exposure groups; however, it is not clear if this observation represents an adverse effect. No other BAL parameters were affected (nucleated cell count and differential, protein and BAL fluid activities of β-glucuronidase, lactic dehydrogenase, and glutathione reductase). In rats treated with basic chromium sulfate, BAL fluid analysis showed significant decreases in nucleated cells at all doses in males and females and decreases in the percentage of segmented neutrophils and mononuclear cells at 30 mg chromium(III)/m^3 in males. Increased amounts of cell debris and lysed cells were present in all basic chromium sulfate groups (incidence data were not reported). In rats exposed to chromic oxide for 13 weeks, absolute and relative lung weights were increased by 12 and 13%, respectively, in males exposed to 30 mg chromium(III)/m^3 as chromic oxide; no change was observed in females. Histopatholgical examination of respiratory tissues showed pigmented macrophages containing a dense black substance, presumably the test substance, throughout the terminal bronchioles and alveolar spaces in rats from all treatment groups; this finding is consistent with normal physiological clearance mechanisms for particulates deposited in the lung and is not considered to be adverse. At concentrations of 10 and 30 mg chromium(III)/m^3, trace to mild chronic interstitial inflammation, characterized by inflammatory cell infiltrates, and septal cell hyperplasia was observed. No lesions were observed in the nasal cavity. Following a 13-week recovery period, microscopic examination of respiratory tissues of rats treated with chromic oxide showed pigmented macrophages and black pigment in peribronchial tissues and the mediastinal lymph node in all treatment groups and septal cell hyperplasia and chronic interstitial inflammation of the lung, both trace-to-mild in severity, in males of all treatment groups and in females exposed to 10 and 30 mg chromium(III)/m^3. In rats treated with basic chromium sulfate, a dose-related increase in absolute and relative lungs weights was observed in all treatment groups. Histopathological examination of respiratory tract tissues revealed chronic inflammation of the lung (characterized by cell infiltration and debris in alveolar spaces and intense inflammation) and alveolar wall hyperplasia in all treatment groups. In addition, inflammation and suppurative and mucoid exudates of nasal tissues and granulomatous inflammation of the larynx were observed in all treatment groups. Incidence data for histopathological findings were not reported. Following the 13-week recovery period for rats treated with basic chromium sulfate, enlargement of the mediastinal lymph node was observed on gross necropsy in all treatment groups. Microscopic examination of respiratory tissues showed changes to the lung (chronic alveolar inflammation, interstitial inflammation, septal cell hyperplasia, and granulomatous inflammation) in all treatment groups, larynx (granulomatous inflammation) in the 10 and 30 mg chromium(III)/m^3 groups, nasal tissues (trace suppurative exudates) in one to two animals in each groups, and mediastinal lymph

node (histiocytosis and hyperplasia) in all treatment groups chromium(III)/m^3 groups. Results of this study demonstrate differences in the respiratory effects of inhaled chromium oxide and inhaled basic chromium sulfate. Effects of soluble basic chromium sulfate were more severe and were observed throughout the respiratory tract, while effects of chromic oxide were more mild and limited to the lung; these observations may be related to differences in chemical-physical properties of the test compounds. Data from the Derelanko et al. (1999) study was used as the basis for intermediate-duration inhalation MRLs for chromium(III) compounds. Since soluble and insoluble chromium(III) compounds exhibited different effects in the respiratory tract, distinct intermediate-duration MRLs were derived for insoluble and soluble trivalent chromium particulates. For insoluble chromium(III) compounds (chromic oxide), the minimal LOAEL of 3 mg chromium(III)/m^3 was used to calculate an intermediate-duration inhalation MRL of 0.005 mg chromium(III)/m^3 for exposure to trivalent chromium particulates as described in the footnote of Table 3-2. For soluble chromium(III) (basic chromium sulfate) compounds, the LOAEL of 3 mg chromium(III)/m^3 was used to calculate an intermediate-duration inhalation MRL of 0.0001 mg chromium(III)/m^3 for exposure to trivalent chromium particulates as described in the footnote of Table 3-2.

Pulmonary fluid from hamsters exposed to 0.9 or 25 mg chromium(III)/m^3 as chromium trichloride for 30 minutes revealed sporadic changes in activities of acid phosphatase and alkaline phosphatase in the lavage fluid at 25 mg chromium(III)/m^3. In the lung tissue, a 75% increase in the acid phosphatase activity was found at 0.9 mg chromium(III)/m^3 and in the β-glucuronidase activity at an unspecified concentration. Histological examination revealed alterations representing mild nonspecific irritation but no morphological damage (Henderson et al. 1979). In rabbits exposed to 0.6 mg chromium(III)/m^3 as chromium nitrate intermittently for 4–6 weeks, changes in the lungs were confined to nodular accumulations of macrophages in the lungs. Macrophage morphology demonstrated black inclusions and large lysosomes. These changes represent normal physiological responses of the macrophages to the chromium particle. Phagocytosis and the reduction of nitroblue tetrazolium to formazan was impaired by chromium(III), indicating a decrease in the functional and metabolic activity of the macrophage (Johansson et al. 1986a, 1986b).

Chronic exposure to chromium(VI) compounds and mixtures of chromium(VI) and chromium(III) compounds have also resulted in adverse respiratory effects in animals. Experiments in which rats were exposed to either chromium(VI) alone as sodium dichromate or a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months showed similar loading of macrophages and increases in lung weight. However, histopathology of rats exposed to 0.1 mg/m^3 of chromium(III) and chromium(VI)

together revealed interstitial fibrosis and thickening of the septa of the alveolar lumens due to the large accumulation of chromium in the lungs, whereas histopathology of the lungs was normal in rats exposed only to chromium(VI) (Glaser et al. 1986, 1988). Mice exposed to 4.3 mg chromium(VI)/m^3 as calcium chromate dust intermittently for 18 months had epithelialization of alveoli. Histopathology revealed epithelial necrosis and marked hyperplasia of the large and medium bronchi, with numerous openings in the bronchiolar walls (Nettesheim and Szakal 1972). Significantly increased incidences of pulmonary lesions (lung abscesses, bronchopneumonia, giant cells, and granulomata) were found in rats exposed chronically to a finely ground, mixed chromium roast material that resulted in airborne concentrations of 1.6–2.1 mg chromium(VI)/m^3 compared with controls. In the same study, guinea pigs exposed chronically to the chromium roast material along with mists of potassium dichromate or sodium chromate solutions that also resulted in 1.6–2.1 mg chromium(VI)/m^3 had significantly increased incidences of alveolar and interstitial inflammation, alveolar hyperplasia, and interstitial fibrosis, compared with controls. Similarly, rabbits were also exposed and also had pulmonary lesions similar to those seen in the rats and guinea pigs, but the number of rabbits was too small for meaningful statistical analysis (Steffee and Baetjer 1965).

In the only study of chromium(IV) exposure, all rats treated with 0.31 or 15.5 mg chromium(IV)/m^3 as chromium dioxide dust for 2 years had discolored mediastinal lymph nodes and lungs, and dust laden macrophages. Lung weight was increased at 12 and 24 months in the 15.5 mg chromium(IV)/m^3 group (Lee et al. 1989). The increased lung weight and macrophage effects probably represent the increased lung burden of chromium dioxide dust and normal physiological responses of macrophages to dust.

Cardiovascular Effects. Information regarding cardiovascular effects in humans after inhalation exposure to chromium and its compounds is limited. In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were $\geq$0.01 mg chromium(VI)/m^3, electrocardiograms were recorded for 22 of the 65 workers who worked in the production of dichromate and chromium trioxide for at least 1 year. No abnormalities were found (Sassi 1956). An extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants found no association between heart disease or effects on blood pressure and exposure to chromates. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent trivalent chromium (0–0.47 mg chromium/m^3) (PHS 1953). No excess deaths were observed from cardiovascular diseases and ischemic heart disease in a

cohort of 4,227 stainless steel production workers from 1968 to 1984 when compared to expected deaths based on national rates and matched for age, sex, and calendar time (Moulin et al. 1993). No measurements of exposure were provided. In a cohort of 3,408 individuals who had worked in four facilities that produced chromium compounds from chromite ore in northern New Jersey sometime between 1937 and 1971, where the exposure durations of workers ranged from <1 to >20 years, and no increases in atherosclerotic heart disease were evident (Rosenman and Stanbury 1996). The proportionate mortality ratios for white and black men were 97 (confidence limits 88–107) and 90 (confidence limits 72–111), respectively.

Cardiovascular function was studied in 230 middle-aged workers involved in potassium dichromate production who had clinical manifestations of chromium poisoning (96 with respiratory effects and 134 with gastrointestinal disorders) and in a control group of 70 healthy workers of similar age. Both groups with clinical manifestations had changes in the bioelectric and mechanical activity of the myocardium as determined by electrocardiography, kinetocardiography, rheocardiography, and ballistocardiography. These changes were more pronounced in the workers with respiratory disorders due to chromium exposure than in the workers with chromium-induced gastrointestinal effects. The changes in the myocardium could be secondary to pulmonary effects and/or to a direct effect on the blood vessels and myocardium (Kleiner et al. 1970).

For intermediate-duration exposures, no histopathological changes to the heart were observed in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m^3 as chromium trioxide (Kim et al. 2004) or in male and female CDF rats exposed to 30 mg chromium(III)/m^3 as chromic oxide or basic chromium sulfate for 3 months, (Derelanko et al. 1999). No histopathological lesions were found in the hearts of rats exposed chronically to chromium dioxide at 15.5 mg chromium(IV)/m^3 (Lee et al. 1989). Additional information regarding cardiovascular effects in animals after exposure to chromium or chromium compounds was not located.

Gastrointestinal Effects. Gastrointestinal effects have been associated with occupational exposure of humans to chromium compounds. In a report of two cases of acute exposure to "massive amounts" of chromium trioxide fumes, the patients complained of abdominal or substernal pain, but further characterization was not provided (Meyers 1950).

In a NIOSH Health Hazard Evaluation of an electroplating facility in the United States, 5 of 11 workers reported symptoms of stomach pain, 2 of duodenal ulcer, 1 of gastritis, 1 of stomach cramps, and 1 of

frequent indigestion. The workers were employed for an average of 7.5 years and were exposed to mean concentrations of 0.004 mg chromium(VI)/m^3 (Lucas and Kramkowski 1975). These workers were not compared to a control group. An otolaryngological examination of 77 employees of eight chromium electroplating facilities in Czechoslovakia, where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m^3, revealed 12 cases of chronic tonsillitis, 5 cases of chronic pharyngitis, and 32 cases of atrophy of the left larynx (Hanslian et al. 1967). In a study of 97 workers from a chromate plant exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble chromium(VI) as sodium chromate and dichromate, gastrointestinal radiography revealed that 10 of the workers had ulcer formation, and of these, 6 had hypertrophic gastritis. Nearly all of the workers breathed through the mouth while at work and swallowed the chromate dust, thereby directly exposing the gastrointestinal mucosa. Only two cases of gastrointestinal ulcer were found in 41 control individuals, who had the same racial, social, and economic characteristics as the chromium-exposed group (Mancuso 1951). In a survey of a facility engaged in chromate production in Italy where exposure concentrations were ≥0.01 mg chromium(VI)/m^3, 15.4% of the 65 workers who worked in the production of dichromate and chromium trioxide for at least 1 year had duodenal ulcers and 9.2% had colitis. The ulcers were considered to be due to exposure to chromium (Sassi 1956). Gastric mucosa irritation leading to duodenal ulcer was found in 21 of 90 workers engaged in the production of chromium salts. Symptoms of gastrointestinal pathology appeared about 3–5 years after the workers' initial contact (Sterekhova et al. 1978). Most of these studies reporting gastrointestinal effects did not compare the workers with appropriate controls. Although the gastrointestinal irritation and ulceration due to exposure to chromium(VI) in air could be due to a direct action of chromium(VI) on the gastrointestinal mucosa from swallowing chromium as a result of mouth breathing (or transfer via hand-to-mouth activity), other factors, such as stress and diet, can also cause gastrointestinal effects. While occupational exposure to chromium(VI) may result in gastrointestinal effects, a lower than expected incidence of death from diseases of the digestive tract was found among a cohort of 2,101 employees who had worked for at least 90 days during the years 1945–1959 in a chromium production plant in Baltimore, Maryland, and were followed until 1977. The rate (O/E=23/36.16, SMR=64) is based on comparison with mortality rates for Baltimore (Hayes et al. 1979). In contrast to findings with chromium(VI) compounds, no indication was found that exposure to chromium(III) resulted in stomach disorders in workers employed in two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b).

Information regarding gastrointestinal effects in animals after inhalation exposure to chromium or its compounds is limited. For intermediate-duration exposures, no histopathological changes to gastrointestinal tissues in male and female CDF rats exposed to 30 mg chromium(III)/m^3 as chromic

oxide or basic chromium sulfate for 3 months, (Derelanko et al. 1999). Histological examination of the stomachs of rats exposed to sodium dichromate dihydrate at ≤0.2 mg chromium(VI)/m^3 for 28 or 90 days revealed no abnormalities (Glaser et al. 1985). In mice exposed intermittently to 4.3 mg chromium(VI)/m^3 as calcium chromate for 18 months, small ulcerations in the stomach and intestinal mucosa were reported to occur occasionally, but the incidence in the treated mice or controls and other details regarding these lesions were not reported (Nettesheim et al. 1971). No treatment-related histopathological lesions were found in the stomach, large intestine, duodenum, jejunum, or ileum of rats chronically exposed to chromium dioxide at 15.5 mg chromium(IV)/m^3 (Lee et al. 1989).

Hematological Effects. Hematological evaluations of workers occupationally exposed to chromium compounds have yielded equivocal results. Ninety-seven workers from a chromate plant were exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble sodium chromate and dichromate. Hematological evaluations revealed leukocytosis in 14.4% or leukopenia in 19.6% of the workers. The leukocytosis appeared to be related primarily to monocytosis and eosinophilia, but controls had slight increases in monocytes and occasional increases in eosinophils without leukocytosis. Decreases in hemoglobin concentrations and slight increases in bleeding time were also observed (Mancuso 1951). Whether these hematological findings were significantly different from those seen in controls was not stated, but the effects were attributed to chromium exposure. In a survey of a facility engaged in chromate production in Italy where exposure concentrations were ≥0.01 mg chromium(VI)/m^3, hematological evaluation of workers who worked in the production of dichromate and chromium trioxide for at least 1 year were unremarkable or inconclusive (Sassi 1956). In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, hematological evaluations revealed no effects on red blood cell counts, hemoglobin, hematocrit, or white blood cell counts. The sedimentation rate of red cells was higher than that of controls, but the difference was not statistically significant. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m^3) (PHS 1953). Likewise, no effects on red blood cell counts, white blood cell counts, hemoglobin levels, or sedimentation rate were found in a case control study of 17 male manual metal arc stainless steel welders from six industries with mean occupational durations of 20 years (Littorin et al. 1984). The relationship between serum and urine chromium levels and blood hemoglobin was examined in workers exposed to chromium(III) at a tannery plant in Leon, Mexico (Kornhauser et al. 2002). Groups of workers were classified as unexposed (control; n=11), moderately

exposed (n=14) or highly exposed (n=11) based on job type; exposure levels were not reported. Blood chromium levels of 0.13, 0.25, and 0.39 μg/L and urine chromium levels of 1.35, 1.43, and 1.71 μg/L were observed in the control, moderate, and high exposure groups, respectively; statistically significant differences were observed between the control group and both chromium groups for blood chromium and between the control and the high exposure groups for urine chromium. An inverse relationship was observed between urine chromium and blood hemoglobin (r=-0.530), serum chromium and urine iron (r=-0.375) and the chromium/iron ratio in urine and hemoglobin (r=-0.669; <0.05). Results indicate a potential effect of chromium(III) exposure on hemoglobin; however, due to small group size, definitive conclusions cannot be made. No hematological disorders were found among 106 workers in a chromium(III) producing plant where workroom levels were ≤1.99 mg chromium(III)/m^3 as chromium(III) oxide and chromium(III) sulfate (Korallus et al. 1974a).

Results from hematological evaluations in rats yielded conflicting results. Hematological effects were observed in male Sprague-Dawley rats exposed to chromium trioxide mist for 90 days; changes included significant decreases in hematocrit (at 0.23 and 1.15, but not 0.49 mg chromium(VI)/m^3), hemoglobin (at 0.49 and 1.15 mg chromium(VI)/m^3) and erythrocyte count (at 1.15 mg chromium(VI)/m^3) (Kim et al. 2004). Hematological evaluations of rats exposed to sodium dichromate at 0.025–0.2 mg chromium(VI)/m^3 for 28 or 90 days or 0.1 mg chromium(VI)/m^3 for 18 months were unremarkable (Glaser et al. 1985, 1986, 1988). However, increased white blood cell counts were found in rats exposed to ≥0.1 mg chromium(VI)/m^3 as sodium dichromate for 30 days and at ≥0.05 mg chromium(VI)/m^3 for 90 days. The white blood cell counts were not increased 30 days postexposure (Glaser et al. 1990). Rats exposed to 0.1 mg chromium/m^3 as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months had increased red and white blood cell counts, hemoglobin content, and hematocrit (Glaser et al. 1986, 1988).

No changes in hematological parameters were observed in rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years (Lee et al. 1989).

In male and female CDF rats exposed to insoluble chromic oxide or soluble basic chromium sulfate by nose-only inhalation at 3, 10, or 30 mg chromium(III)/m^3 for 6 hours/day, 5 days/week for 13 weeks, no adverse effects on hematological parameters were observed (Derelanko et al. 1999).

Musculoskeletal Effects. No musculoskeletal effects have been reported in either humans or animals after inhalation exposure to chromium.

Hepatic Effects. Chromium(VI) has been reported to cause severe liver effects in four of five workers exposed to chromium trioxide in the chrome plating industry. Derangement of the cells in the liver, necrosis, lymphocytic and histiocytic infiltration, and increases in Kupffer cells were reported. Abnormalities in tests for hepatic dysfunction included increases in sulfobromophthalein retention, gamma globulin, icterus, cephalin cholesterol flocculation, and thymol turbidity (Pascale et al. 1952). In a cohort of 4,227 workers involved in production of stainless steel from 1968 to 1984, excess deaths were observed from cirrhosis of the liver compared to expected deaths (O/E=55/31.6) based on national rates and matched for age, sex, and calendar time having an SMR of 174 with confidence limits of 131–226 (Moulin et al. 1993). No measurements of exposure were provided. Based on limited information, however, the production of chromium compounds does not appear to be associated with liver effects. As part of a mortality and morbidity study of workers engaged in the manufacture of chromium(VI) compounds (84%) and chromium(III) compounds (16%) derived from chromium(VI) in Japan, 94 workers who had been exposed for 1–28 years were given a complete series of liver function tests 3 years after exposure ended. All values were within normal limits (Satoh et al. 1981). In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were ≥0.01 mg chromium(VI)/m^3, 15 of 65 men who worked in the production of dichromate and chromium trioxide for at least 1 year had hepatobiliary disorders. When the workers were given liver function tests, slight impairment was found in a few cases. These disorders could have been due to a variety of factors, especially heavy alcohol use (Sassi 1956). No indication was found that exposure to chromium(III) resulted in liver disorders in workers employed in two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b).

The hepatic effects observed in animals after inhalation exposure to chromium or its compounds were minimal and not considered to be adverse. Rats exposed to as much as 0.4 mg chromium(VI)/m^3 as sodium dichromate for ≤90 days did not have increased serum levels of alanine aminotransferase or alkaline phosphatase, cholesterol, creatinine, urea, or bilirubin (Glaser et al. 1990). Triglycerides and phospholipids were increased only in the 0.2 mg chromium(VI)/m^3 group exposed for 90 days (Glaser et al. 1985). No histopathological changes to the liver were observed in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m^3 as chromium trioxide (Kim et al. 2004) or in male and female CDF rats exposed to 30 mg chromium(III)/m^3 as chromic oxide or basic chromium sulfate for 3 months, (Derelanko et al. 1999). Chronic exposure of rats to 0.1 mg chromium(VI)/m^3 as sodium dichromate, to 0.1 mg total chromium/m^3 as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide, or to

15.5 mg chromium(IV)/m^3 as chromium dioxide did not cause adverse hepatic effects as assessed by histological examination and liver function tests (Glaser et al. 1986, 1988; Lee et al. 1989).

Renal Effects. No increases in genital/urinary disease were evident in a cohort of 3,408 workers from four former facilities that produced chromium compounds from chromite ore in northern New Jersey sometime between 1937 and 1971. The proportionate mortality ratios for white and black men were 71 (40–117) and 47 (15–111), respectively. Exposure durations ranged from <1 to >20 years (Rosenman and Stanbury 1996).

Renal function has been studied in workers engaged in chromate and dichromate production, in chrome platers, in stainless steel welders, in workers employed in ferrochromium production, in boilermakers, and in workers in an alloy steel plant. Workers exposed to chromium(VI) compounds in a chromate production plant were found to have higher levels of a brush border protein antigen and retinol binding protein in the urine compared with controls (Mutti et al. 1985a). A similar study was conducted in 43 male workers in the chromate and dichromate production industry, where occupational exposures were between 0.05 and 1.0 mg chromium(VI)/m^3 as chromium trioxide, and mean employment duration was 7 years. Workers with >15 μg chromium/g creatinine in the urine had increased levels of retinol binding protein and tubular antigens in the urine (Franchini and Mutti 1988). These investigators believe that the presence of low molecular weight proteins like retinol binding protein or antigens in the urine are believed to be early indicators of kidney damage. In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, analysis of the urine revealed a higher frequency of white blood cell and red blood cell casts than is usually found in an industrial population (statistical significance not reported). Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m^3) (PHS 1953).

Some studies of renal function in chromate production workers found negative or equivocal results. In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were ≥0.01 mg chromium(VI)/m^3, results of periodic urinalyses of workers who worked in the production of dichromate and chromium trioxide for at least 1 year were generally unremarkable, with the exception of one case of occasional albuminuria and a few cases of slight urobilinuria (Sassi 1956). As part of a mortality and morbidity study of workers engaged in the manufacture of chromium(VI) compounds

(84%) and chromium(III) compounds (16%) derived from chromium(VI) in Japan, 94 workers who had been exposed for 1–28 years were given a complete series of kidney function tests (not further characterized) 3 years after exposure ended. All values were within normal limits (Satoh et al. 1981).

Studies of renal function in chrome platers, whose exposure is mainly to chromium(VI) compounds, have also yielded equivocal results. A positive dose-response for elevated urinary levels of β_2-microglobulin was found in chrome platers who were exposed to 0.004 mg chromium(VI)/m^3, measured by personal air samplers, for a mean of 5.3 years. However, since no increase in β_2-microglobulin levels was found in ex-chrome platers who had worked for at least 1 year in an old chrome plating plant from 1940 to 1968, this effect may be reversible (Lindberg and Vesterberg 1983b). Liu et al. (1998) similarly found significantly higher urinary β_2-microglobulin and N-acetyl-β-glucosaminidase levels in hard-chrome electroplaters exposed to 0.0042 mg chromium/m^3 for a mean of 5.8 years, as compared to aluminum anode-oxidation workers. The prevalence of elevated levels (higher than reference values) was significantly increased for N-acetyl-β-glucosaminidase, but not for β_2-microglobulin. In another study, comparison of results of renal function tests between chrome platers and construction workers revealed that the chrome platers had significantly ($p<0.001$) increased levels of urinary chromium and increased clearance of chromium, but decreased ($p<0.05$) levels of retinol binding protein. However, no differences were found for blood urea nitrogen, serum and urinary β_2-microglobulin, serum immunoglobulin, total protein in the urine, urinary albumin, N-acetyl-β-D-glucosamidase, β-galactosidase, or lysozyme (Verschoor et al. 1988).

Studies of renal function in stainless steel welders, whose exposure is mainly to chromium(VI) compounds, were negative. Stainless steel welders had significantly increased ($p<0.001$) levels of urinary chromium, increased clearance of chromium, and increased serum creatinine compared with controls, but no differences were found in the levels of retinol binding protein, β_2-microglobulin, or other indices of kidney damage (Verschoor et al. 1988). Similar negative results were found in another group of stainless steel welders (Littorin et al. 1984).

Occupational exposure to chromium(III) or chromium(0) does not appear to be associated with renal effects. No renal impairment based on urinary albumin, retinol binding protein, and renal tubular antigens was found in 236 workers employed in the ferrochromium production industry where ferrochromite is reduced with coke, bauxite, and quartzite. The mean airborne concentration of chromium in various sample locations was 0.075 mg chromium(III)/m^3; chromium(VI) was below the detection limit of 0.001 mg chromium(VI)/m^3 at all locations (Foa et al. 1988). Workers employed in an alloy steel plant

with a mean exposure of 7 years to metallic chromium at 0.61 mg chromium(0)/m^3 and to other metals had normal urinary levels of total protein and β_2-microglobulin, enzyme activities of alanine-aminopeptidase, N-acetyl-β-D-glucosaminidase, gammaglutamyl-transpeptidase, and β-galactosidase (Triebig et al. 1987). In boilermakers exposed to chromium(0), no increase in urinary levels of chromium, and no differences in the levels of retinol binding protein, β_2-microglobulin, or other indices of renal toxicity were found (Verschoor et al. 1988).

In a group of 30 men and 25 women who were lifetime residents of an area in northern New Jersey contaminated with chromium landfill, signs of preclinical renal damage were assessed by examining the urinary levels of four proteins, intestinal alkaline phosphatase, tissue nonspecific alkaline phosphatase, N-acetyl-β-D-glucosaminidase, and microalbumin (Wedeen et al. 1996). The mean urinary chromium concentrations were 0.2±0.1 μg/g creatinine for the women and 0.3 μg/g creatinine for the men. None of the four proteins exceeded normal urinary levels in either men or women. The authors concluded that long-term environmental exposure to chromium dust did not lead to tubular proteinurea or signs of preclinical renal damage.

Exposure of rats to sodium dichromate at ≤0.4 mg chromium(VI)/m^3 for ≤90 days did not cause abnormalities, as indicated by histopathological examination of the kidneys. Serum levels of creatinine and urea and urine levels of protein were also normal (Glaser et al. 1985, 1990). No changes in urinalysis parameters or histopathological changes to the kidneys were observed in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m^3 as chromium trioxide (Kim et al. 2004) and no histopathological lesions were observed in the kidneys of male and female CDF rats exposed to 30 mg chromium(III)/m^3 as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999). Furthermore, no renal effects were observed in rats exposed to 0.1 mg chromium/m^3 as sodium dichromate (chromium(VI)) or as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months, based on histological examination of the kidneys, urinalysis, and blood chemistry (Glaser et al. 1986, 1988). Rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years showed no histological evidence of kidney damage or impairment of kidney function, as measured by routine urinalysis. Serum levels of blood urea nitrogen, creatinine, and bilirubin were also normal (Lee et al. 1989).

Endocrine Effects. Increased serum amylase activity (a marker for pancreatic function) was observed in a group of 50 chrome plating workers in Bangalore, India, compared to 50 workers with no history of chromium(VI) exposure. Employment duration of exposed workers ranged from 15 to 20 years; exposure levels were not reported (Kalahasthi et al. 2007). Serum amylase activity in exposed workers was

significantly correlated to urine chromium ($r=0.289$; $p<0.05$). No studies were located regarding endocrine effects in humans following inhalation exposure to chromium(III) compounds.

For intermediate-duration exposures, no histopathological changes to the endocrine tissues were observed in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m^3 as chromium trioxide (Kim et al. 2004) or in male and female CDF rats exposed to 30 mg chromium(III)/m^3 as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999). Male rats exposed 22 hours/day for 18 months to 0.1 mg chromium(VI)/m^3 as sodium dichromate or exposed to a mixture of chromium(VI) and chromium(III) (0.06 mg chromium(VI)/m^3 plus 0.04 mg chromium(III)/m^3) as chromium(VI) trioxide and chromium(III) oxide did not result in any histopathological changes in adrenal glands (Glaser et al. 1986, 1988). Rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years showed no histopathological abnormalities in adrenals, pancreas, and thyroid glands (Lee et al. 1989).

Dermal Effects. Acute systemic and dermal allergic reactions have been observed in chromium-sensitive individuals exposed to chromium via inhalation as described in Sections 3.2.3.2 and 3.2.3.3.

No studies were located regarding systemic dermal effects in animals after inhalation exposure to chromium(VI) or chromium(III) compounds.

Ocular Effects. Effects on the eyes due to direct contact of the eyes with airborne mists, dusts, or aerosols or chromium compounds are described in Section 3.2.3.2. Medical records of 2,307 male workers (all nonsmokers) employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis) (Gibb et al. 2000a). Conjunctivitis was reported on 20.0% of the study population, at a mean exposure level of 0.025 mg Cr(VI)/m^3 and a mean time-to-onset of 604 days.

Opthalmoscopic examination did not reveal any changes in male and female CDF rats exposed to 30 mg chromium(III)/m^3 as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999).

Histopathologic examination of rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years revealed normal morphology of the ocular tissue (Lee et al. 1989).

Body Weight Effects. In a report of a case of acute exposure to "massive amounts" of chromium trioxide fumes, the patient became anorexic and lost 20–25 pounds during a 3-month period following exposure (Meyers 1950).

In rats exposed to an aerosol of sodium dichromate for 30 or 90 days or for 90 days followed by an additional 30 days of nonexposure, body weight gain was significantly decreased at 0.2 and 0.4 mg chromium(VI)/m^3 for 30 days ($p<0.001$), at 0.4 mg chromium(VI)/m^3 for 90 days ($p<0.05$), and at 0.2 ($p<0.01$) and 0.4 mg chromium(VI)/m^3 ($p<0.05$) in the recovery group (Glaser et al. 1990). There was no effect on body weight gain in rats exposed for 28 days to 0.2 mg/m^3 (Glaser et al. 1985) or for ≤18 months to 0.1 mg chromium(VI)/m^3 as sodium dichromate (Glaser et al. 1986, 1988, 1990) or 0.1 mg chromium(III and VI)/m^3 as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months (Glaser et al. 1986, 1988). Body weight was significantly decreased in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m^3 as chromium trioxide mist for 90 days (Kim et al. 2004) and in male, but not female, rats exposed to 10 mg chromium(III)/m^3 as chromic oxide for 13 weeks (Derelanko et al. 1999). However, exposure of male and female rats to 30 mg chromium(III)/m^3 as basic chromium sulfate for 13 weeks did not produce body weight changes (Derelanko et al. 1999). Similarly, there was no effect on body weight gain in rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years (Lee et al. 1989).

3.2.1.3 Immunological and Lymphoreticular Effects

Sensitization of workers, resulting in respiratory and dermal effects, has been reported in numerous occupational exposure studies. Although the route of exposure for initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal routes, information on the exposure levels producing sensitization by the inhaled route was not identified. Additional information on contact dermatitis in sensitized workers is provided in Section 3.2.3.3 (Dermal Exposure, Immunological and Lymphoreticular Effects).

Acute reactions have been observed in chromium sensitive individuals exposed to chromium via inhalation as noted in several individual case reports. A 29-year-old welder exposed to chromium vapors from chromium trioxide baths and to chromium and nickel fumes from steel welding for 10 years complained of frequent skin eruptions, dyspnea, and chest tightness. Chromium sensitivity in the individual was measured by a sequence of exposures, via nebulizer, to chromium(VI) as sodium chromate. Exposure to 0.029 mg chromium(VI)/mL as sodium chromate caused an anaphylactoid

reaction, characterized by dermatitis, facial angioedema, bronchospasms accompanied by a tripling of plasma histamine levels, and urticaria (Moller et al. 1986). Similar anaphylactoid reactions were observed in five individuals who had a history of contact dermatitis to chromium, after exposure, via nebulizer, to an aerosol containing 0.035 mg chromium(VI)/mL as potassium dichromate. Exposure resulted in decreased forced expiratory volume, facial erythema, nasopharyngeal pruritus, nasal blocking, cough, and wheezing (Olaguibel and Basomba 1989). Challenge tests with fumes from various stainless steel welding processes indicated that the asthma observed in two stainless steel welders was probably caused by chromium or nickel, rather than by irritant gases produced by the welding process (Keskinen et al. 1980). A 28-year-old construction worker developed work-related symptoms of asthma, which worsened during periods when he was working with (and sawing) corrugated fiber cement containing chromium. A skin patch test to chromium was negative. Asthmatic responses were elicited upon inhalation challenge with fiber cement dust or nebulized potassium chromate (Leroyer et al. 1998). A 40-year-old woman exposed to chromium and nickel in a metalworks company developed occupational asthma and tested positive to skin prick tests and bronchial challenge tests with potassium dichromate (Cruz et al. 2006). In four male workers (two electroplating workers, one welder, and one cement worker) with work-related symptoms of asthma, two tested positive to skin prick tests with potassium dichromate and nickel sulfate and all tested positive to bronchial challenge tests with potassium dichromate and nickel sulfate (Fernandez-Nieto et al. 2006). Chromium-induced asthma may occur in some sensitized individuals exposed to elevated concentrations of chromium in air, but the number of sensitized individuals is low and the number of potentially confounding variables in the chromium industry is high.

Concentrations of some lymphocyte subpopulations (CD4+ helper-inducer, CD5--CD19+ B, CD3--CD25+ activated B, and CD3--HLA-DR+ activated B and natural killer lymphocytes) were significantly reduced (about 30–50%) in a group of 15 men occupationally exposed to dust containing several compounds (including hexavalent chromium as lead chromate) in a plastics factory. Worker blood lead and urine chromium levels were significantly higher than those of 15 controls not known to be occupationally exposed to toxic agents. Serum chromium concentrations and serum immunoglobulins IgA, IgG, and IgM were not significantly different between the two groups (Boscolo et al. 1997). The immunological effects of chromium were evaluated in a small group tannery workers (n=20) in Italy, compared to a matched group of unexposed controls (n=24) (Mignini et al. 2004). Exposure of individual workers was not reported, but monitoring of 20 factories with participating workers reported TWA concentrations of 0.09–0.10 mg total chromium/m^3 and 0.001–0.002 mg chromium(VI)/m^3. The mean time of employment of the exposed group was 5.8 years. Urine chromium excretion was significantly

increased in workers, although no increased in plasma chromium was observed, compared to controls. In workers, proliferative response of peripheral blood mononucleocytes (PBMC) in response to concavalin A was increased approximately 24% compared to controls; no difference between workers and controls were observed for the percent distribution of lymphocyte subsets (e.g., T lymphocytes, T helper lymphocytes, T cytotoxic lymphocytes, B lymphocytes, and natural killer cells).

Immunological effects of exposure to chromic acid were evaluated in 46 electroplating workers in Taiwan (Kuo and Wu 2002). The entire group was employed for an average of 6.1 years. Workers were divided into low (n=19), moderate (n=17), and high (n=10) subgroups based on mean urine chromium excretion of <1.13, 1.14–6.40, and >6.40 μg chromium/g creatinine, respectively. Airborne chromium was measured by personal samplers for all study participants for the duration of one 8-hour shift (data not reported); however, no information was reported on individual or group exposures over the time of employment. A negative correlation was observed between urine chromium and B cell percentage and a positive correlation was observed between urine chromium and blood IL-8 concentration. The study authors report that smoking was an important factor for lymphocyte subsets; thus, interpretation of these results is limited by confounding factors.

An animal study was designed to examine the immunotoxic effects of soluble and insoluble hexavalent chromium agents released during welding (Cohen et al. 1998). Rats exposed to atmospheres containing soluble potassium chromate at 0.36 mg chromium(VI)/m^3 for 5 hours/day, 5 days/week for 2 or 4 weeks had significantly increased levels of neutrophils and monocytes and decreased alveolar macrophages in bronchoalveolar lavage than air-exposed controls. Significantly increased levels of total recoverable cells were noted at 2 (but not 4) weeks of exposure. In contrast, no alterations in the types of cells recovered from the bronchoalveolar lavage fluid were observed in rats exposed to 0.36 mg chromium(VI)/m^3 as insoluble barium chromate, as compared to controls. However, the cell types recovered did differ from those recovered from rats exposed to soluble chromium. Changes seen in pulmonary macrophage functionality varied between the soluble and insoluble chromium(VI) exposure groups. The production of interleukin (IL)-1 and tumor necrosis factor (TNF)-α cytokines were reduced in the potassium chromate exposed rats; only TNF-α was decreased in the barium chromate rats. IL-6 levels were not significantly altered in either group. Barium chromate affected zymosan-inducible reactive oxygen intermediate formation and nitric oxide production to a greater degree than soluble chromium(VI). Insoluble chromium(VI) reduced the production of superoxide anion, hydrogen perodise, and nitric oxide; soluble chromium(VI) only reduced nitric oxide production.

Rats exposed to 0.025–0.2 mg chromium(VI)/m^3 as sodium dichromate for 28 or 90 days had increased spleen weights at ≥0.05 mg chromium(VI)/m^3 and increased response to sheep red blood cells at ≥0.025 mg chromium(VI)/m^3. In the 90-day study, serum immunoglobulin content was increased in the 0.05 and 0.1 mg chromium(VI)/m^3 groups but not in the 0.2 mg chromium(VI)/m^3 group. There was an increase in mitogen-stimulated T-cell response in the group exposed for 90 days to 0.2 mg chromium(VI)/m^3. Bronchial alveolar lavage fluid had an increased percentage of lymphocytes in the groups exposed to 0.025 and 0.05 mg chromium(VI)/m^3 and an increased percentage of granulocytes in the groups exposed to 0.05 mg chromium(VI)/m^3 for 28 days. The phagocytic activity of macrophages was increased in the 0.05 mg chromium(VI)/m^3 group. A higher number of macrophages in telophase was observed in the 0.025 and 0.05 mg chromium(VI)/m^3 groups. Bronchial alveolar lavage fluid from rats exposed for 90 days had an increased percentage of lymphocytes in the 0.025, 0.05, and 0.2 mg chromium(VI)/m^3 groups and an increased percentage of granulocytes and number of macrophages in the 0.05 mg chromium(VI)/m^3 groups. The phagocytic activity of the macrophages was increased in the 0.025 mg and 0.05 mg chromium(VI)/m^3 groups and decreased in the 0.2 mg chromium(VI)/m^3 group. A greater number of macrophages in telophase and an increase in their diameter were observed in the 0.025, 0.05, and 0.2 mg chromium(VI)/m^3 groups (Glaser et al. 1985).

Low-level exposure to sodium dichromate seems to stimulate the humoral immune system (as indicated by the significant increase in total immunoglobin levels); exposure to 0.2 mg chromium(VI)/m^3 ceases to stimulate the humoral immune system (significant decreases in total immunoglobin levels) but still may have effects on the T lymphocytes. The depression in macrophage cell count and phagocytic activities correlated with a 4-fold lower rate of lung clearance for inhaled iron oxide in the 0.2 mg chromium(VI)/m^3 group (Glaser et al. 1985).

Intermediate-duration exposure of rats to inhaled chromium(III) compounds produces histopathological alterations to respiratory lymph nodes and tissues. In male and female CDF rats, exposure to 3, 10, and 30 mg chromium(III)/m^3 as soluble basic chromium sulfate for 13 weeks resulted in histiocytic cellular infiltration and hyperplasia of peribronchial lymphoid tissue and mediastinal lymph nodes; lymph node enlargement was also observed on necropsy (Derelanko et al. 1999). Following a 13-week recovery period, enlargement, histiocytosis, and hyperplasia of the mediastinal lymph node was observed in rats exposed to 3, 10, and 30 chromium(III)/m^3 as basic chromium sulfate. Hyperplasia of the mediastinal lymph node was observed in male and female CDF rats exposed to chromium oxide at concentrations of 3, 10, and 30 mg chromium(III)/m^3 for 13 weeks (Derelanko et al. 1999). Following a 13-week recovery

period, black pigment (trace-to-mild) in peribronchial lymphoid tissue and mediastinal lymph nodes was found in all treatment groups.

The LOAELs for immunological effects in rats are recorded in Table 3-1 and plotted in Figure 3-1 for chromium(VI) and recorded in Table 3-2 and plotted in Figure 3-2 for chromium(III).

3.2.1.4 Neurological Effects

In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, workers experienced symptoms of dizziness, headache, and weakness when they were working over the chromate tanks (Lieberman 1941). Such poor working conditions are unlikely to still occur in the United States because improvements in industrial hygiene have been made over the years. Results of olfactory perceptions tests conducted in workers employed at chromium plating factories in An-San Korea (mean employment duration of 7.9 years) indicate that olfactory recognition thresholds were significantly higher in exposed workers compared to controls (Kitamura et al. 2003). Air concentrations of chromium(VI) ranged from 0.005 to 0.03 mg chromium(VI)/m^3 and of chromium(III) ranged from 0.005 to 0.06 mg chromium(III)/m^3. Although the cause of this change was not determined, the study authors suggest that chromium may directly affect the olfactory nerve.

No increases in vascular lesions in the central nervous system were evident in a cohort of 3,408 workers from four former facilities that produced chromium compounds from chromite ore in northern New Jersey (Rosenman and Stanbury 1996). The proportionate mortality ratios for white and black men were 78 (61–98) and 68 (44–101), respectively. The subjects were known to have worked in the four facilities sometime between 1937 and 1971 when the last facility closed. Exposure durations ranged from <1 to >20 years.

No information was located regarding neurological effects in humans or animals after inhalation exposure to chromium(III) compounds or in animals after inhalation exposure to chromium(VI) compounds. No histopathological lesions were found in the brain of male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m^3 as chromium trioxide for 3 months or in male and female CDF rats exposed to 30 mg chromium(III)/m^3 as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999; Kim et al. 2004) or in the brain, spinal cord, or nerve tissues of rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years (Lee et al. 1989). No neurological or behavioral tests were conducted in these studies.

3.2.1.5 Reproductive Effects

Information regarding reproductive effects in humans after inhalation to chromium compounds is limited. Semen quality was evaluated in 61 workers in a chromium sulfate manufacturing plant in India (Kumar et al. 2005). Employment duration and chromium exposure levels were not reported. The study included a control group of 15 unexposed workers. Chromium blood levels in the exposed group were significantly increased compared to the control group. Although no effect was observed on semen volume, liquefaction time, or pH or on sperm viability, count, motility, or concentration, a significant increase was observed in the number of morphologically abnormal sperm in exposed workers. In the exposed group, 53% of subjects had less than 30% normal sperm; in the control group, only 10% of subject had <30% normal sperm. A significant positive correlation ($r=0.301$; $p=0.016$) was observed between blood chromium and the percentage of abnormal sperm in exposed workers. Sperm count and motility were significantly decreased by 47 and 15%, respectively in a group of 21 workers employed at a chrome plating plant in Henan, China, compared to age-matched, unexposed controls (Li et al. 2001). Serum follicle stimulating hormone (FSH) concentration was significantly increased by 204% and semen lactate dehydrogenase activity was significantly decreased by 30% in exposed compared to control workers, although no effect on serum luteinizing hormone (LH) concentration was observed. Serum chromium levels were 11% higher in the exposed workers compared to control; however, the increase was not statistically significant. Duration of employment for all study participants ranged from 1 to 15 years; no information on exposure levels or demographics of the exposed and control groups were reported.

The effect of chromium(VI) on the course of pregnancy and childbirth was studied in women employees at a dichromate manufacturing facility in Russia. Complications during pregnancy and childbirth (not further described) were reported in 20 of 26 exposed women who had high levels of chromium in blood and urine, compared with 6 of 20 women in the control group. Toxicosis (not further described) was reported in 12 exposed women and 4 controls. Postnatal hemorrhage occurred in four exposed and two control women (Shmitova 1980). Similar results were reported in a more extensive study of 407 women who worked at a factory producing chromium compounds (not otherwise specified) compared with 323 controls. The frequency of birth complications was 71.4% in a subgroup of highly exposed women, 77.4% in a subgroup of women with a lower level of exposure, and 44.2% in controls. Toxicosis in the first half of pregnancy occurred in 35.1% of the high exposure group, 33.3% of the low exposure group, and 13.6% of the controls. The frequency of postnatal hemorrhage was 19.0% for the high exposure group and 5.2% in controls (Shmitova 1978). Because these studies were generally of poor quality and

the results were poorly reported, no conclusions can be made regarding the potential for chromium to produce reproductive effects in humans.

The occurrence of spontaneous abortion among 2,520 pregnancies of spouses of 1,715 married Danish metal workers exposed to hexavalent chromium from 1977 through 1987 were examined (Hjollund et al. 1995). Occupational histories were collected from questionnaires and information on spontaneous abortion, live births, and induced abortion was obtained from national medical registers. The number of spontaneous abortions was not increased for pregnant women whose spouses worked in the stainless steel welding industry when compared to controls (odds ratio 0.78, 95% confidence interval [CI] 0.55–1.1). The authors believed that the risk estimate was robust enough that factors such as maternal age and parity and smoking and alcohol consumptions were not confounders. There was no association found in spontaneous abortions in women whose husbands were in the cohort subpopulations who were mild steel welders and metal-arc stainless steel welders, which would lead to higher exposures to welding fumes (workplace chromium exposures not provided). This more recent study does not corroborate earlier findings (Bonde et al. 1992) that showed that wives of stainless steel welders were at higher risk of spontaneous abortions. The current study was based on abortions recorded in a hospital register, while the earlier study was based on self-reporting data. The latter study probably included more early abortions and was biased because the job exposure of male metal workers is apparently modified by the outcome of their partners' first pregnancy.

Histopathological examination of the testes of rats exposed to 0.2 mg chromium(VI)/m^3 as sodium dichromate for 28 or 90 days (Glaser et al. 1985), to 0.1 mg chromium(VI)/m^3 as sodium dichromate for 18 months, or to 0.1 mg chromium/m^3 as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months (Glaser et al. 1986, 1988) revealed no abnormalities. For intermediate-duration exposures to chromium(III) compounds, no histopathological changes to the reproductive tissues in male and female CDF rats exposed to 30 mg chromium(III)/m^3 as chromic oxide or basic chromium sulfate for 3 months; treatment also had no effect on sperm count, motility, or morphology (Derelanko et al. 1999). No histopathological lesions were observed in the prostate, seminal vesicle, testes, or epididymis of male rats or in the uterus, mammary gland, or ovaries of female rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years (Lee et al. 1989).

The NOAELs for reproductive effects in rats are recorded in Table 3-1 and plotted in Figure 3-1 for chromium(VI) and recorded in Table 3-2 and plotted in Figure 3-2 for chromium(III).

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to chromium or its compounds.

3.2.1.7 Cancer

Occupational exposure to chromium(VI) compounds in various industries has been associated with increased risk of respiratory system cancers, primarily bronchogenic and nasal. Among the industries investigated in retrospective mortality studies are chromate production, chromate pigment production and use, chrome plating, stainless steel welding, ferrochromium alloy production, and leather tanning. Compilations and discussion of many of these studies can be found in reviews of the subject (Goldbohm et al. 2006; IARC 1990; Steenland et al. 1996). Studies of chromium workers have varied considerably in strength of design for determining cancer risks related to chromium exposure. The strongest designs have provided estimates of chromium(VI) (or exposure to other chromium species) for individual members of the cohorts, enabling application of dose-response analysis to estimate the contribution of chromium exposure to cancer risk. Studies that do not provide estimates of chromium exposure have relied on surrogate dose metrics (e.g., length of employment at job titles associated with chromium exposure) for exploring attribution of cancer risk to chromium exposure. However, these surrogate measures are often strongly correlated with exposures to other work place hazards, making conclusions regarding possible associations with chromium exposures more uncertain. Chromium dose-response relationships have been reported for chromate production workers, but not for other categories of chromium workers. In studies of chromate production workers, increased risk of respiratory tract cancers have been found in association with increased cumulative exposure to chromium(VI) and several estimates of excess lifetime risk attributed to chromium exposure have been reported. Studies of chrome platers, who were exposed to chromium(VI) and other carcinogenic chemicals, including nickel, have found significant elevations in lung cancer risk in association with surrogate indicators of chromium exposure, such as duration of employment at jobs in which exposure to chromium occurred; however, estimates of risk attributable to specifically to chromium exposure have not been reported. Results of studies in stainless steel welders exposed to chromium(VI) and other chemicals, and in ferrochromium alloy workers, who were exposed mainly to chromium(0) and chromium(III), but also to some chromium(VI), have been mixed and are inconclusive with respect to work-associated elevations in cancer rates. Studies in leather tanners, who are exposed to chromium(III), have not found elevated cancer rates.

Chromate Production. Numerous studies of cancer mortality among chromate production workers have been reported (Alderson et al. 1981; Bidstrup and Case 1956; Buckell and Harvey 1951; Crump et al. 2003; Davies et al. 1991; Enterline 1974; Gibb et al. 2000b; Korallus et al. 1982; Mancuso 1997a; Ohsaki et al. 1978; Park and Stayner 2006; Park et al. 2004; Pastides et al. 1994; PHS 1953; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1994; Taylor 1966). Collectively, these studies provide evidence for associations between lung cancer mortality and employment in chromate production, with risks declining with improved industrial hygiene. Less consistently, nasal cancers have been observed (Alderson et al. 1981; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1994). Evidence for associations between exposure to chromium and cancer is strongest for lung cancer mortality, which has been corroborated and quantified in numerous studies. A meta-analysis of 49 epidemiology studies based on 84 papers of cancer outcomes, primarily among chromium workers, found SMRs ranging from 112 to 279 for lung cancer, with and overall SMR of 141 (95% CI 135–147; Cole and Rodu 2005). When limited to high-quality studies controlled for smoking, the overall SMR for lung cancer was 112 (95% CI 104–119). SMRs for other forms of cancer from studies that controlled for confounders were not elevated. Several studies have attempted to derive dose-response relationships for this association (Crump et al. 2003; Gibb et al. 2000b; Mancuso 1997a; Park and Stayner 2006; Park et al. 2004). These studies are particularly important because they have included individual exposure estimates to chromium for each member of the cohort based on work place monitoring; dose-response modeling to ascertain the contribution of changing exposures to chromium to risk (in workers who were also exposed to other work-place hazards that could have contributed to cancer risk); and evaluation of the impacts of potential co-variables and confounders (e.g., age, birth cohort, and smoking) on chromium-associated risk.

Gibb et al. (2000b) examined lung cancer mortality in a cohort of chromate production workers (n=2,357, males) in Baltimore, Maryland, who were first hired during the period 1950–1974, with mortality followed through 1992. This cohort was the subject of numerous earlier studies, which found significantly increased lung cancer mortality (i.e., standard mortality ratios) among workers at the plant (Baetjer 1950b; Braver et al. 1985; Hayes et al. 1979; Hill and Ferguson 1979). In the Gibb et al. (2000b) study, cumulative exposures to chromium(VI) or chromium(III) (mg/m^3-year) were reconstructed for each member of the cohort from historical workplace air monitoring data and job title records (Gibb et al. 2000b). Lung cancer for the entire group had a relative risk of 1.80 (95% CI 1.49–2.14). Relative risk of lung cancer mortality (adjusted for smoking) increased by a factor to 1.38 (95% CI 1.20–1.63) in association with a 10-fold increase in cumulative exposure to chromium(VI). The analogous relative risk for cumulative exposure to chromium(III) was 1.32 (95% CI 1.15–1.51). Exposures to chromium(III) and chromium(VI) were highly correlated; therefore, discrimination of risks associated with either were

problematic. However, in a combined model that included cumulative exposure to both chromium species, relative risk for chromium(VI) exposure remained significant (1.66, p=0.045), whereas relative risk for chromium(III) was negative (-0.17, p=0.4). This outcome suggests that exposure to chromium(VI), rather than chromium(III), was the dominant (if not sole) contributor to lung cancer risk (after adjustments for smoking). Park et al. (2004) reanalyzed the data for the Baltimore, Maryland cohort using a variety of dose-response models. In the preferred model (linear with cumulative chromium exposure and log-linear for age, smoking, race), cancer rate ratio for a 45-year cumulative exposure to 1 mg/m^3-year of chromium(VI) was estimated to be 2.44 (95% CI 1.54–3.83). This corresponded to an excess lifetime risk unit risk (i.e., additional lifetime risk from occupational exposure to 1 μg CrO_3/m^3 or 0.52 μg Cr(VI)/m^3) of 0.003 (95% CI 0.001–0.006) or to 100 μg chromium(VI)/m^3 of 0.255 (95% CI 0.109–0.416). Subsequent analyses conducted by Park and Stayner (2006) attempted to estimate possible thresholds for increasing lung cancer risk. This analysis was able to exclude possible thresholds in excess of 16 μg/m^3 chromium(VI) or 0.4 mg/m^3-year cumulative exposure to chromium(VI).

Several studies have examined cancer mortality in a cohort of chromate production workers in Painesville, Ohio, and have found increased lung cancer mortality (e.g., SMRs) among workers at the plant (Crump et al. 2003; Luippold et al. 2003; Mancuso 1997a; Mancuso and Hueper 1951). Mancuso (1997a) reconstructed cumulative exposure histories of individual members of the cohort (n=332), hired during the period 1931–1937 and followed through 1993. The exposure estimations were based on historical workplace air monitoring data for soluble and insoluble chromium and job title records. Age-adjusted death rates from lung cancer were estimated for cumulative exposure strata, and increased with increasing cumulative exposure to total chromium, insoluble chromium, and soluble chromium (a dose response model was not reported). The highest rates were observed in soluble chromium strata >4 mg/m^3-years (2,848 per 100,000). Death rates were not adjusted for smoking, which would have been a major contributor to lung cancer death rates in the cohort. Although the study discriminated exposures to soluble and insoluble chromium, these classifications are not adequate surrogates for exposures to trivalent or hexavalent chromium (Kimbrough et al. 1999; Mundt and Dell 1997); therefore, the study cannot attribute risk specifically to either species. More recent studies of this cohort have attempted to reconstruct individual exposure histories to chromium(VI), based on species-specific air monitoring data, and have attempted to quantify the potential contribution of smoking to lung cancer risk (Crump et al. 2003; Luippold et al. 2003). These studies included workers (n=482) hired after 1940 and followed through 1997. Increasing lung cancer risk was significantly associated with increasing cumulative exposure to chromium(VI). Relative risk for lung cancer mortality was estimated to be 0.794 per mg/m^3-year (90% CI 0.518–1.120). The analogous additive risk was 0.00161 per mg/m^3-year per person year

(90% CI 0.00107–0.00225). These estimates correspond to unit risks (i.e., additional lifetime risk from occupational exposure to 1 μg/m^3) of 0.00205 (90% CI 0.00134–0.00291), based on the relative risk Poison model, and 0.00216 (90% CI 0.00143–0.00302), based on the additional risk Poison model. Risk estimates were not appreciably sensitive to birth cohort or to smoking designation (for the 41% of the cohort that could be classified). The latter outcome suggests that smoking did not have a substantial effect on chromium(VI) associated lung cancer risk (i.e., smoking and chromium appeared to contribute independently to cancer risk).

A meta-analysis of the Crump et al. (2003); Gibb et al. (2000b), and Mancuso (1997a) studies has also been reported (Goldbohm et al. 2006). Excess lifetime risk of lung cancers was estimated from a life table analysis (using Dutch population vital statistics) and estimates of relative risk from each study, or in the case of Mancuso (1997a), estimated in the meta-analysis (approximately 0.0015 per mg/m^3-year). Estimates of excess lifetime risks (deaths attributed to a 40-year occupational exposure to chromium(VI) at 1 μg/m^3, for survival up to age 80 years) were 0.0025, 0.0048, and 0.0133, based on Crump et al. (2003), Mancuso et al. (1997a), and Gibb et al. (2000b), respectively.

In conclusion, despite limitations of some studies, occupational exposure to chromium(VI) in the chromate production industry is associated with increased risk of respiratory cancer. Estimates of excess lifetime occupational risks range from 0.002 to 0.005 per μg/m^3 of chromium(VI). Changes in production process and industrial hygiene appear to have reduced overall risk over the past 30–40 years.

Chromate Pigments Production and Use. Studies of workers engaged in the production of chromate pigments provide evidence for increased risk of lung cancer associated with employment in work areas where exposure to chromium compounds occurred. However, the contribution of chromium exposure to cancer risk in these cohorts remains uncertain for several reasons: (1) members of the cohorts experienced exposures to a variety of chemicals that may have contributed to cancer (e.g., nickel); (2) exposures of the individual cohort members to chromium were not quantified or subjected to exposure-response analysis; and (3) dose metrics used in dose-response analysis were measures of employment duration, which are highly correlated with exposures to chemical hazards other than chromium. Nevertheless, these studies have found elevated lung cancer rates in chromium pigment workers in comparison to reference populations (e.g., SMRs) and, in some studies, increased lung cancer rates in association with increased potential (e.g., job type, employment duration) for exposure to chromium (Dalager et al. 1980; Davies 1979, 1984; Franchini et al. 1983; Frentzel-Beyme 1983;

Haguenoer et al. 1981; Hayes et al. 1989; Langård and Norseth 1975; Langård and Vigander 1983; Sheffet et al. 1982).

Chrome Plating. Studies of chrome platers provide evidence for increased risk of lung cancer associated with employment in work areas where exposure to chromium compounds occurred. However, the contribution of chromium exposure to cancer risk in these cohorts remains uncertain for several reasons: members of the cohorts experienced exposures to a variety of chemicals that may have contributed to cancer (e.g., nickel, sulfuric acid); (2) exposures of the individual cohort members to chromium were not quantified or subjected to exposure-response analysis; and (3) dose metrics used in dose-response analysis were measures of employment duration, which are highly correlated with exposures to chemical hazards other than chromium. Nevertheless, these studies have founds elevated lung cancer rates in chrome bath workers in comparison to reference populations (e.g., standard mortality ratios) who were exposed primarily to soluble chromium(VI) (e.g., chromic acid mists) and, in some studies, increased lung cancer rates in association with increased potential (e.g., job type, employment duration) for exposure to chromium (Dalager et al. 1980; Guillemin and Berode 1978; Hanslian et al. 1967; Okubo and Tsuchiya 1977, 1979; Royle 1975a; Silverstein et al. 1981; Sorahan et al. 1987, 1998; Takahashi and Okubo 1990).

Sorahan et al. (1998) examined lung cancer risks in a cohort of nickel/chrome platters (n=1,762, hired during the period 1946–1975 with mortality follow-up through 1995). The same cohort was studied by Royle (1975a). Significant excess risks of lung cancer were observed among males and females working in the chrome bath area for <1 year (SMR=172; 95% CI 112–277; $p<0.05$) or >5 years (SMR=320; 95% CI 128–658; $p<0.001$), females working in the chrome bath area for <1 year (SMR=245; 95% CI 118–451; $p<0.5$), males starting chrome work in the period of 1951–1955 (SMR=210; 95% CI 132–317; $p<0.01$), and in male chrome workers 10–19 years after first chrome work (SMR=203; 95% CI 121–321; $p<0.01$). A significant ($p<0.01$) positive trend for lung cancer mortality and duration of exposure was found for the male chrome bath workers, but not for the female workers. Lung cancer mortality risks were also examined using an internal standard approach, in which mortality in chrome workers was compared to mortality in workers without chromium exposure. After adjusting for sex, age, calendar period, year of starting chrome work, period from first chrome work, and employment status, a significant positive trend ($p<0.05$) between duration of chrome bath work and lung cancer mortality risk was found.

Stainless Steel Welding. Workers in the stainless steel welding industry are exposed to chromium(VI) compounds, as well as other chemical hazards that could contribute to cancer (e.g., nickel); however, results of studies of cancer mortality in these populations have been mixed. Some studies have found

increased cancer mortality rates among workers; however, examinations of possible associations with exposures to chromium have not been reported. A study of 1,221 stainless steel welders in the former Federal Republic of Germany found no increased risk of lung cancer or any other specific type of malignancy compared with 1,694 workers involved with mechanical processing (not exposed to airborne welding fumes) or with the general population of the former Federal Republic of Germany (Becker et al. 1985). A follow-up study (Becker 1999) which extended the observation period to 1995, found similar results for lung (includes bronchus and trachea) cancer (SMR=121.5, 95% CI 80.7–175.6). An excess risk of pleura mesothelioma was observed (SMR=1,179.9; 95% CI=473.1–2430.5); however, this was attributed to asbestos exposure. A study of 234 workers from eight companies in Sweden, who had welded stainless steel for at least 5 years during the period of 1950–1965 and followed until 1984, found five deaths from pulmonary tumors, compared with two expected (SMR=249), based on the national rates for Sweden. The excess was not statistically significant. However, when the incidence of lung cancer in the stainless steel welders was compared with an internal reference group, a significant difference was found after stratification for age. The average concentration of chromium(VI) in workroom air from stainless steel welding, determined in 1975, was reported as 0.11 mg/m^3 (Sjogren et al. 1987). The cohort in this study was small, and stainless welders were also exposed to nickel fumes. Smoking was probably not a confounding factor in the comparisons with the internal reference group.

In a study of the mortality patterns in a cohort of 4,227 workers involved in the production of stainless steel from 1968 to 1984, information was collected from individual job histories, and smoking habits were obtained from interviews with workers still active during the data collection (Moulin et al. 1993). The observed number of deaths was compared to expected deaths based on national rates and matched for age, sex, and calendar time. No significant excess risk of lung cancer was noted among workers employed in melting and casting stainless steel (SMR=104). However, there was a significant excess among stainless steel foundry workers (SMR=229). The SMR increased for workers with length of employment over 30 years to 334 (119–705). No measurements of exposure were provided.

Ferrochromium Production. Workers in the ferrochromium alloy industry are exposed to chromium(III) and chromium(VI) compounds, as well as other chemical hazards that could contribute to cancer; however, results of studies of cancer mortality in these populations have been mixed. No significant increase in the incidence of lung cancer was found among 1,876 employees who worked in a ferrochromium plant in Sweden for at least 1 year from 1930 to 1975 compared with the expected rates for the county in which the factory was located. The workers had been exposed mainly to metallic chromium and chromium(III), but chromium(VI) was also present. The estimated levels ranged from 0 to

2.5 mg chromium(0) and chromium(III)/m^3 and from 0 to 0.25 mg chromium(VI)/m^3 (Axelsson et al. 1980). An excess of lung cancer was found in a study of 325 male workers employed for >1 year in a ferrochromium producing factory in Norway between 1928 and 1977 (Langård et al. 1980), and whose employment began before 1960 (SMR=850, p=0.026); however, in a follow-up of this cohort (n=379, hired before 1965 and followed through 1985), the SMR for lung cancer was not significant (SMR=154; Langård et al. 1990). Workroom monitoring in 1975 indicated that the ferrochromium furnace operators worked in an atmosphere with 0.04–0.29 mg total chromium/m^3, with 11–33% of the total chromium as chromium(VI) (Langård et al. 1980).

An ecological study examined the distribution of lung cancer cases in Dolný Kubin in the Slovak Republic where ferrochromium production facility was located. Cases were stratified into three groups (males): ferrochomium workers (n=59), workers (n=106) thought not to have been exposed to chromium, and residents (n=409) who were not thought to have had appreciable exposure to chromium. Lung cancer rates were higher in the chromium workers (320 per 1,000 per year, 95% CI 318–323) compared to workers (112, 95% CI 109–113) and residents (79, 95% CI 76–80) who were not thought to have been exposed to chromium (relative risk=4.04 for chromium workers compared to residents). Mean work shift air concentrations in the smelter were 0.03–0.19 mg/m^3 for total chromium and 0.018–0.03 mg/m^3 for chromium(VI). Theses estimates were not adjusted for smoking or other potential co-variables that might have contributed to cancer rates in the chromium workers.

Leather Tanning. Studies of workers in tanneries, where exposure is mainly to chromium(III), in the United States (0.002–0.054 mg total chromium/m^3) (Stern et al. 1987), the United Kingdom (no concentration specified) (Pippard et al. 1985), and the Federal Republic of Germany (no concentration specified) (Korallus et al. 1974a) reported no association between exposure to chromium(III) and excess risk of cancer.

Environmental Exposure. In addition to the occupational studies, a retrospective environmental epidemiology study was conducted of 810 lung cancer deaths in residents of a county in Sweden where two ferrochromium alloy industries are located. No indication was found that residence near these industries is associated with an increased risk of lung cancer (Axelsson and Rylander 1980).

A retrospective mortality study conducted on a population that resided in a polluted area near an alloy plant that smelted chromium in the People's Republic of China found increased incidences of lung and stomach cancer. The alloy plant began smelting chromium in 1961 and began regular production in 1965,

at which time sewage containing chromium(VI) dramatically increased. The population was followed from 1970 to 1978. The size of the population was not reported. The adjusted mortality rates of the exposed population ranged from 71.89 to 92.66 per 100,000, compared with 65.4 per 100,000 in the general population of the district. The adjusted mortality rates for lung cancer ranged from 13.17 to 21.39 per 100,000 compared with 11.21 per 100,000 in the general population. The adjusted mortality rates for stomach cancer ranged from 27.67 to 55.17 per 100,000 and were reported to be higher than the average rate for the whole district (control rates not reported). The higher cancer rates were found for those who lived closer to the dump site (Zhang and Li 1987). Attempts to abate the pollution from chromium(VI) introduced in 1967 also resulted in additional pollution from sulfate and chloride compounds. It was not possible to estimate exposure levels based on the description of the pollution process. Exposure of this population was mainly due to chromium(VI) in drinking water, although air exposure cannot be ruled out.

The studies in workers exposed to chromium compounds clearly indicate that occupational exposure to chromium(VI) is associated with an increased risk of respiratory cancer. Using data from the Mancuso (1975) study and a dose-response model that is linear at low doses, EPA (1984a) derived a unit risk estimate of $1.2x10^{-2}$ for exposure to air containing 1 μg chromium(VI)/m^3 (or potency of $1.2x10^{-2}$ [μg/m^3]$^{-1}$) (IRIS 2008).

Chronic inhalation studies provide evidence that chromium(VI) is carcinogenic in animals. Mice exposed to 4.3 mg chromium(VI)/m^3 as calcium chromate had a 2.8-fold greater incidence of lung tumors, compared to controls (Nettesheim et al. 1971). Lung tumors were observed in 3/19 rats exposed to 0.1 mg chromium(VI)/m^3 as sodium dichromate for 18 months, followed by 12 months of observation. The tumors included two adenomas and one adenocarcinoma. No lung tumors were observed in 37 controls or the rats exposed to ≤0.05 mg chromium(VI)/m^3 (Glaser et al. 1986, 1988). The increased incidence of lung tumors in the treated rats was significant by the Fisher Exact Test (p=0.03) performed by Syracuse Research Corporation.

Several chronic animal studies reported no carcinogenic effects in rats, rabbits, or guinea pigs exposed to ≈1.6 mg chromium(VI)/m^3 as potassium dichromate or chromium dust 4 hours/day, 5 days/week (Baetjer et al. 1959b; Steffee and Baetjer 1965).

Rats exposed to ≤15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years had no statistically significant increased incidence of tumors (Lee et al. 1989).

The Cancer Effect Levels (CELs) are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2 Oral Exposure

3.2.2.1 Death

Cases of accidental or intentional ingestion of chromium that have resulted in death have been reported in the past and continue to be reported even in more recent literature. In many cases, the amount of ingested chromium was unknown, but the case reports provide information on the sequelae leading to death. For example, a 22-month-old boy died 18.5 hours after ingesting an unknown amount of a sodium dichromate solution despite gastric lavage, continual attempts to resuscitate him from cardiopulmonary arrest, and other treatments at a hospital. Autopsy revealed generalized edema, pulmonary edema, severe bronchitis, acute bronchopneumonia, early hypoxic changes in the myocardium, liver congestion, and necrosis of the liver, renal tubules, and gastrointestinal tract (Ellis et al. 1982). Another case report of a 1-year-old girl who died after ingesting an unknown amount of ammonium dichromate reported severe dehydration, caustic burns in the mouth and pharynx, blood in the vomitus, diarrhea, irregular respiration, and labored breathing. The ultimate cause of death was shock and hemorrhage into the small intestine (Reichelderfer 1968).

Several reports were available in which the amount of ingested chromium (VI) compound could be estimated. A 17-year-old male died after ingesting 29 mg chromium(VI)/kg as potassium dichromate in a suicide. Despite attempts to save his life, he died 14 hours after ingestion from respiratory distress with severe hemorrhages. Caustic burns in the stomach and duodenum and gastrointestinal hemorrhage were also found (Clochesy 1984; Iserson et al. 1983). A 35-year-old female died after ingesting approximately 25 g chromium(VI) (357 mg chromium(VI)/kg assuming 70 kg body weight) as chromic acid in a suicide (Loubieres et al. 1999). The patient died of multiple organ failure. Terminal laboratory analysis and autopsy revealed metabolic acidosis, gastrointestinal hemorrhage and necrosis, fatty degeneration of the liver, and acute renal failure and necrosis.

A few reports have described death of humans after ingesting lower doses of chromium(VI). In one case, a 14-year-old boy died 8 days after admission to the hospital following ingestion of 7.5 mg chromium(VI)/kg as potassium dichromate from his chemistry set. Death was preceded by gastro-intestinal ulceration and severe liver and kidney damage (Kaufman et al. 1970). In another case, a

44-year-old man died of severe gastrointestinal hemorrhage 1 month after ingesting 4.1 mg chromium(VI)/kg as chromic acid (Saryan and Reedy 1988).

Acute oral LD_{50} values in rats exposed to chromium(III) or chromium(VI) compounds varied with the compound and the sex of the rat. LD_{50} values for chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) range from 13 to 19 mg chromium(VI)/kg in female rats and from 21 to 28 mg chromium(VI)/kg in male rats (Gad et al. 1986). LD_{50} values of 108 (female rats) and 249 (male rats) mg chromium(VI)/kg for calcium chromate were reported by Vernot et al. (1977). The LD_{50} values for chromium trioxide were 25 and 29 mg chromium(VI)/kg for female and male rats, respectively (American Chrome and Chemicals 1989). An LD_{50} of 811 mg chromium(VI)/kg as strontium chromate was reported for male rats (Shubochkin and Pokhodzie 1980). Twenty percent mortality was observed when female Swiss Albino mice were exposed to potassium dichromate(VI) in drinking water at a dose of 169 mg chromium(VI)/kg/day (Junaid et al. 1996a). Similar exposure to a dose level of 89 mg chromium(VI)/kg/day resulted in 15% mortality among female rats of the Druckrey strain (Kanojia et al. 1998). The disparity between this dose and the LD_{50} identified in the Gad et al. (1986) study may be due to the route of administration, drinking water versus gavage. Chromium(III) compounds are less toxic than chromium(VI) compounds, with LD_{50} values in rats of 2,365 mg chromium(III)/kg as chromium acetate (Smyth et al. 1969) and 183 and 200 mg chromium(III)/kg as chromium nitrate in female and male rats, respectively (Vernot et al. 1977). The lower toxicity of chromium(III) acetate compared with chromium(III) nitrate may be related to solubility; chromium(III) acetate is less soluble in water than is chromium(III) nitrate. Signs of toxicity included hypoactivity, lacrimation, mydriasis, diarrhea, and change in body weight. Treatment with the chromium(III) dietary supplement chromium nicotinate of male and female rats resulted in no mortality at doses up to >621.6 mg/kg/day (Shara et al. 2005). The LD_{50} values for chromium(VI) or chromium(III) compounds indicate that female rats are slightly more sensitive to the toxic effects of chromium(VI) or chromium(III) than male rats. LD_{50} values in rats are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

Intermediate and chronic exposure of rats and mice to chromium(III) or chromium(VI) compounds did not decrease survival. Survival was not affected in rats and mice exposed to chromium(VI) as sodium dichromate dihydrate in drinking water at doses up to 20.9 and 27.9 mg chromium(VI)/kg/day, respectively, for 3 months (NTP 2007) or at doses up to 7.0 and 8.7 mg chromium(VI)/kg/day,

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Human	once (IN)				29 M (death)	Clochesy 1984; Iserson et al. 1983 K2Cr2O7 (VI)	17-year-old, 60 kg boy ingested 5 g potassium dichromate [1,750 mg Cr(VI)]; dose = 29 mg Cr(VI)/kg.
2	Human	once (IN)				7.5 M (death)	Kaufman et al. 1970 K2Cr2O7 (VI)	14-year-old boy ingested 1.5 g potassium dichromate [0.53 mg Cr(VI)]. Assuming 70 kg body weight, dose = 7.5 mg Cr(VI)/kg.
3	Human	once (IN)				357 F (death)	Loubieres et al. 1999 CrO3 (VI)	35-year-old woman ingested chromic acid solution containing 25 g Cr(VI). Assuming 70 kg body weight, dose = 357 mg Cr(VI)/kg.
4	Human	once (IN)				4.1 M	Saryan and Reedy 1988 CrO3 (VI)	44-year-old man ingested ~2.8g Cr(VI) as chromium trioxide; ~4.1 mg Cr(VI)/kg body weight.
5	Rat (Fischer- 344)	once (G)				29 M (LD50) 25 F (LD50)	American Chrome and Chemicals 1989 CrO3 (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
6	Rat (Fischer- 344)	once (GW)				21 M (LD50) 14 F (LD50)	Gad et al. 1986 Na2Cr2O7.2H2O (VI)	
7	Rat (Fischer- 344)	once (GW)				26 M (LD50) 17 F (LD50)	Gad et al. 1986 K2Cr2O7 (VI)	
8	Rat (Fischer- 344)	once (GW)				22 M (LD50) 19 F (LD50)	Gad et al. 1986 (NH4)2Cr2O7 (VI)	
9	Rat (Fischer- 344)	once (GW)				28 M (LD50) 13 F (LD50)	Gad et al. 1986 Na2CrO4 (VI)	
10	Rat Druckrey	2 wk (W)				89 F (15% mortality)	Kanojia et al. 1998 K2Cr2O7 (VI)	
11	Rat (NS)	once (G)				811 M (LD50)	Shubochkin and Pokhodzie 1980 SrCrO4 (VI)	
12	Rat (Sprague-Dawley)	once (G)				249 M (LD50) 108 F (LD50)	Vernot et al. 1977 CaCrO4 (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
13	Human	once (IN)	Resp			29 M (congested lungs, pleural effusions)	Clochesy 1984; Iserson et al. 1983 K2Cr2O7 (VI)	17-year-old, 60 kg boy ingested 5 g potassium dichromate [1,750 mg Cr(VI)]; dose = 29 mg Cr(VI)/kg.
			Cardio			29 M (hemorrhage, cardiac arrest)		
			Gastro			29 M (hemorrhage)		
			Hemato			29 M (inhibited coagulation)		
			Renal			29 M (necrosis swelling of renal tubules)		
14	Human	once (IN)	Dermal		0.04 M (enhancement of dermatitis)		Goitre et al. 1982 K2Cr2O7 (VI)	
15	Human	once (C)	Dermal		0.036 (dermatitis)		Kaaber and Veien 1977 K2Cr2O7 (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Human	once (IN)	Gastro		7.5 M (abdominal pain and vomiting)		Kaufman et al. 1970 K2Cr2O7 (VI)	14-year-old boy ingested 1.5 g potassium dichromate [0.53 mg Cr(VI)]. Assuming 70 kg body weight, dose = 7.5 mg Cr(VI)/kg.
			Hepatic			7.5 M (necrosis)		
17	Human	once (IN)	Gastro			357 F (intestinal hemorrhage and necrosis)	Loubieres et al. 1999 CrO3 (VI)	35-year-old woman ingested chromic acid solution containing 25 g Cr(VI). Assuming 70 kg body weight, dose = 357 mg Cr(VI)/kg.
			Hepatic			357 F (fatty degeneration)		
			Renal			357 F (acute renal failure and renal necrosis)		
			Metab			357 F (metabolic acidosis)		
18	Human	once (IN)	Gastro			4.1 M (gastrointestinal hemorrhage)	Saryan and Reedy 1988 CrO3 (VI)	44-year-old man ingested ~2.8g Cr(VI) as chromium trioxide; ~4.1 mg Cr(VI)/kg body weight.
			Renal			4.1 M (acute tubular necrosis)		

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
19	Rat (Fischer- 344)	5 d (W)	Hemato		4 M (decreased mean cell volume, mean cell hemoglobin, and reticulocyte count)		NTP 2007 Na2Cr2O7.2H2O (VI)	
			Musc/skel	15.9 M 8.2 F	31.8 M (serum creatine kinase activity increased by 31%)			
					16.4 F (serum creatine kinase activity increased by 45%)			
			Hepatic		4 M (serum ALT activity increased by 15%)			
20	Rat (Fischer- 344)	4 d (W)	Hemato	0.7 M	2.8 M (decreased mean cell hemoglobin)		NTP 2008a Na2Cr2O7.2H2O (VI)	
			Renal	19.3 M				
21	Rat (NS)	once (G)	Gastro			130 (hemorrhage)	Samitz 1970 K2Cr2O7 (VI)	
22	Mouse (Swiss albino)	9 d Gd 6-14 (W)	Bd Wt	53.2 F	101.1 F (8.2% decrease in gestational weight gain)	152.4 F (24.3% decrease in gestational weight gain)	Junaid et al. 1996b K2Cr2O7 (VI)	
Immuno/ Lymphoret								
23	Human	once (IN)			0.04 M (enhancement of chromium dermatitis)		Goitre et al. 1982 K2Cr2O7 (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
24	Human	once (C)			0.036 (dermatitis)		Kaaber and Veien 1977 K2Cr2O7 (VI)	
Neurological								
25	Human	once (IN)				7.5 M (cerebral edema)	Kaufman et al. 1970 K2Cr2O7 (VI)	14-year-old boy ingested 1.5 g potassium dichromate [0.53 mg Cr(VI)]. Assuming 70 kg body weight, dose = 7.5 mg Cr(VI)/kg.
Reproductive								
26	Rat (NS)	3 d Gd 1-3 (G)				35.7 F (preimplanation loss)	Bataineh et al. 2007 K2Cr2O7 (VI)	
27	Rat (NS)	3 d Gd 4-6 (G)				35.7 F (decreased number of viable fetuses; increased resorptions)	Bataineh et al. 2007 K2Cr2O7 (VI)	
28	Rat (Wistar)	6 d (G)				5.2 M (sperm count decreased by 76%, percentage of abnormal sperm increased by 143% and histopathological changes to seminiferous tubules)	Li et al. 2001 CrO3 (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
29	Rat (Wistar)	Gd 6-15 (W)				8 F (increased pre- and post-implantation loss, resorptions, dead fetuses/litter, skeletal and visceral malformations)	Elsaieed and Nada 2002 K2CrO4 (VI)	
30	Mouse (Swiss albino)	9 d Gd 6-14 (W)				53.2 F (increase in resorptions)	Junaid et al. 1996b K2Cr2O7 (VI)	
INTERMEDIATE EXPOSURE								
Death								
31	Mouse (Swiss albino)	20 d (W)				169 F (3/15 died)	Junaid et al. 1996a K2Cr2O7 (VI)	
Systemic								
32	Rat (Wistar)	22 wk (W)	Hepatic			1.3 M (increased serum ALT and AST and histopathological changes, including degeneration, vacuolization, increased sinusoidal space and necrosis)	Acharya et al. 2001 K2Cr2O2 (VI)	
			Renal		1.3 M (histopathological changes, including vacuolization in glomeruli, degeneration of basement membrane of Bowman's capsule and renal tubular epithelial degeneration)			

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
33	Rat (Sprague-Dawley)	12 wk (W)	Bd Wt		42 M (19% lower final body weight)		Bataineh et al. 1997 K2Cr2O7 (VI)	
34	Rat Charles Foster	90 d 1 x/d (G)	Bd Wt	20 M		40 M (57% decreased body weight)	Chowdhury and Mitra 1995 Na2Cr2O7 (VI)	
35	Rat (Wistar)	28 d (W)	Renal	10 M		100 M (proteinuria, oliguria)	Diaz-Mayans et al. 1986 Na2CrO4 (VI)	
36	Rat Swiss albino	20 d (W)	Bd Wt	37	70 (14% reduced maternal body weight gain)	87 (21% reduced maternal body weight gain)	Kanojia et al. 1996 K2Cr2O7 (VI)	
37	Rat Druckrey	3 mo (W)	Bd Wt	45	89 (18% reduced maternal body weight gain)	124 (24% reduced maternal body weight gain)	Kanojia et al. 1998 K2Cr2O7 (VI)	
38	Rat (albino)	20 d 7 d/wk (G)	Hepatic		13.5 M (lipid accumulation)		Kumar and Rana 1982 K2CrO4 (VI)	
			Renal		13.5 M (lipid accumulation)			

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
39	Rat (white)	20 d 7 d/wk (G)	Renal		13.5 M (inhibition of membrane enzymes; alkaline phosphatase, acid phosphatase, lipase)		Kumar and Rana 1984 K2CrO4 (VI)	
40	Rat (albino)	20 d 7 d/wk (G)	Hepatic		13.5 M (changes in liver enzyme activities; inhibition of acid phosphatase; enhancement of lipase)		Kumar et al. 1985 K2CrO4 (VI)	
41	Rat (Sprague-Dawley)	9 wk (F)	Hemato	2.1 M	8.4 M		NTP 1996b K2Cr2O7 (VI)	
				2.5 F	9.8 F (decreased mean corpuscular volume)			
			Hepatic	9.8				
			Renal	9.8				
			Bd Wt	9.8				

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
42	Rat (Fischer- 344)	14 wk (W)	Resp	20.9				NTP 2007 Na2Cr2O7.2H2O (VI)	
			Cardio	20.9					
			Gastro	1.7	3.5	(duodenal histiocytic cellular infiltration)			
			Hemato		1.7	(microcytic, hypochromic anemia)			
			Musc/skel	3.5	5.9	(serum creatine kinase activity increased by 31% in males and 45% in females)			
			Hepatic		1.7	(serum ALT activity increased by 14% in males 30% in females, serum SDH activity increased by 77% in males and 359% in females)			
			Renal	20.9					
			Endocr	20.9					
			Ocular	20.9					
			Bd Wt	5.9 M	11.2 M	(11% decrease in body weight)			

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
43	Rat (Fischer- 344)	23 d (W)	Hemato		1.7 M (decreased hematocrit, mean cell volume, mean hemoglobin concentration, reticulocyte)		NTP 2007 Na2Cr2O7.2H2O (VI)	
					1.7 F (decreased hemoglibin and mean cell volume)			
44	Rat (Fischer- 344)	6 mo (W)	Hemato	0.21 M	0.77 M (microcytic, hypochromic anemia)		NTP 2008a Na2Cr2O7.2H2O (VI)	
45	Rat (Fischer- 344)	22 d (W)	Hemato	0.21 M	0.77 M[b] (microcytic, hypochromic anemia)		NTP 2008a Na2Cr2O7.2H2O (VI)	
46	Rat (Wistar)	30 d (W)	Endocr		73 M (59% decrease in serum prolactin)		Quinteros et al. 2007 K2Cr2O7 (VI)	
			Bd Wt		73 M (11.6% in body wieght)			

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
47	Rat (Wistar)	10 wk (W)	Hepatic			3.7 M (serum ALT activity increased by 253%, histopathological changes including focal necrosis and degeneration with changes in vascularization)	Rafael et al. 2007 Cr (VI)	
			Metab		3.7 M (65% increase in serum glucose)			
48	Mouse BDF1	210 d (W)	Bd Wt	1.4 F	14 F (13.5% decrease in body weight gain)		De Flora et al. 2006 Na2Cr2O7.2H2O (VI)	
49	Mouse (BALB/c)	9 wk (F)	Hemato	7.4 M 12 F	32.2 M 48 F (decreased mean corpuscular volume)		NTP 1996a K2Cr2O7 (VI)	
			Hepatic	1.1 M 1.8 F	3.5 M 5.6 F (cytoplasmic vacuolization of hepatocytes)			
			Renal	48				
			Bd Wt	48				

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
50	Mouse (BALB/c)	85 d + pnd 1-74 (F1) + pnd 1-21(F2) (F)	Gastro	36.7 F			NTP 1997 K2Cr2O7 (VI)	
			Hemato		7.8 F (decreased mean corpuscular volume in F1)			
			Hepatic	36.7 F				
			Renal	36.7 F				
			Bd Wt	36.7 F				

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
51	Mouse (B6C3F1)	14 wk (W)	Resp	27.9			NTP 2007 Na2Cr2O7.2H2O (VI)	
			Cardio	27.9				
			Gastro		3.1 (epithelial hyperplasia of duodenum)			
			Hemato		3.1 M (decreased mean cell volume)			
					3.1 F (decreased mean cell hemoglobin)			
			Hepatic	27.9				
			Renal	27.9				
			Endocr	27.9				
			Ocular	27.9				
			Bd Wt	3.1 F	3.1 M (6% decrease in body weight)			
					5.2 F (8% decrease in body weight)			
52	Mouse (B6C3F1)	22 d (W)	Hemato		0.38 F (microcytic, hypochromic anemia and increased lymphocytes)		NTP 2008a Na2Cr2O7.2H2O (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
53	Mouse (B6C3F1)	6 mo (W)	Hemato	0.38 F	1.4 F (decreased mean cell volume)		NTP 2008a Na2Cr2O7.2H2O (VI)	
54	Mouse (albino)	19 d (W)	Bd Wt	46 F	98 F (decreased maternal weight gain)		Trivedi et al. 1989 K2Cr2O7 (VI)	
55	Rabbit (New Zealand)	daily 10 wk (G)	Bd Wt	3.6 M			Yousef et al. 2006 K2Cr2O7 (VI)	
Immuno/ Lymphoret								
56	Rat (Fischer- 344)	14 wk (W)		11.2 F	1.7 M (histiocytic cellular infilratration of pancreatic lymph nodes)		NTP 2007 Na2Cr2O7.2H2O (VI)	
					20.9 F (histiocytic cellular infiltration of pancreatic lymph nodes)			
57	Rat (Fischer- 344)	3-10 wk (W)			16 (increased proliferation of T- and B- lymphocytes in response to mitogens and antigens)		Snyder and Valle 1991 K2CrO4 (VI)	
58	Mouse (B6C3F1)	14 wk (W)			3.1 (histiocytic infiltrate of mesenteric lymph nodes)		NTP 2007 Na2Cr2O7.2H2O (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
59	Rat (Wistar)	28 d (W)		10 M	100 M (decreased motor activity)		Diaz-Mayans et al. 1986 Na2CrO4 (VI)	
60	Rat (Fischer- 344)	14 wk (W)		20.9			NTP 2007 Na2Cr2O7.2H2O (VI)	
61	Mouse (B6C3F1)	14 wk (W)		27.9			NTP 2007 Na2Cr2O7.2H2O (VI)	
Reproductive								
62	Monkey macaca	180 d (W)				2.1 M (histopathological changes to epididymides, including ductal obstruction and development of microcanals)	Aruldhas et al. 2004 K2Cr2O7 (VI)	
63	Monkey macaca	180 d (W)				2.1 M (decreased testes weight, histopathological changes including depletion of germ cells, hyperplasia of Leydig cells, disrupted spermatogenesis, Sertoli cell fibrosis, alterations of sperm morpholologgy)	Aruldhas et al. 2005 K2Cr2O7 (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
64	Monkey macaca	180 d (W)				2.1 M (histopathological changes to basal cells and principal cells of epididymis)	Aruldhas et al. 2006 K2Cr2O7 (VI)	
65	Monkey macaca	180 d (W)		1.1 M		2.1 M (sperm count and motility decreased by 25%)	Subramanian et al. 2006 K2Cr2O7 (VI)	
66	Rat (Sprague-Dawley)	12 wk (W)			42 (altered sexual behavior, decreased absolute testes, seminal vesicles, and preputial gland weights)		Bataineh et al. 1997 K2Cr2O7 (VI)	
67	Rat (Charles Foster)	90 d 1 x/d (G)			20 M (decreased testicular protein, 3 beta-hydroxy steroid dehydrogenase and serum testosterone)	40 M (28% decreased testicular weight; decreased testicular protein, DNA, RNA, seminiferous tubular diameter; decreased Leydig cells, pachytene cells, spermatocytes, spermatids, and testosterone levels)	Chowdhury and Mitra 1995 Na2Cr2O7 (VI)	
68	Rat Swiss albino	20 d (W)				37 (increased resorptions)	Kanojia et al. 1996 K2Cr2O7 (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
69	Rat Druckrey	3 mo (W)				45 (decreased fertility, increased pre- and post-implantation loss)	Kanojia et al. 1998 K2Cr2O7 (VI)	
70	Rat (Sprague-Dawley)	9 wk (F)		8.4 M 9.8 F			NTP 1996b K2Cr2O7 (VI)	
71	Rat (Fischer- 344)	14 wk (W)		20.9			NTP 2007 Na2Cr2O7.2H2O (VI)	
72	Mouse (Swiss albino)	20 d (W)			52 F (decreased placental weight)	98 F (preimplantation loss, increased resorptions)	Junaid et al. 1996a K2Cr2O7 (VI)	
73	Mouse Swiss albino	20 d (W)			60 F (decreased number of follicles at different stages of maturation)	120 F (decreased number of ova/mouse)	Murthy et al. 1996 K2Cr2O7 (VI)	
74	Mouse (BALB/c)	9 wk (F)		32.2 M 48 F			NTP 1996a K2Cr2O7 (VI)	
75	Mouse (BALB/c)	85 d + pnd 1-74 (F1) + pnd 1-21(F2) (F)		36.7 F			NTP 1997 K2Cr2O7 (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
76	Mouse (B6C3F1)	14 wk (W)		27.9			NTP 2007 Na2Cr2O7.2H2O (VI)	
77	Mouse (B6C3F1)	14 wk (W)		8.7 M			NTP 2007 Na2Cr2O7.2H2O (VI)	
78	Mouse (albino)	Gd 1-19 19 d (W)				46 F (increase in fetal resorption and post implantation loss)	Trivedi et al. 1989 K2Cr2O7 (VI)	
79	Mouse (BALB/c)	7 wk 7 d/wk (F)				15.2 M (decreased spermatogenesis)	Zahid et al. 1990 K2Cr2O7 (VI)	
80	Rabbit (New Zealand)	daily 10 wk (G)				2.6 M (plasma testosterone decreased by 20.8%, sperm count decreased by 18%, % dead sperm increased by 23.9%, total mobile sperm decreased by 34.3%)	Yousef et al. 2006 K2Cr2O7 (VI)	
Developmental								
81	Rat Swiss albino	20 d (W)				37 (increased post-implantation loss and decreased number of live fetuses)	Kanojia et al. 1996 K2Cr2O7 (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
82	Rat Druckrey	3 mo (W)				45 (reduced fetal caudal ossification, increased post-implantation loss, reduced fetal weight, subhemorrhagic patches)	Kanojia et al. 1998 K2Cr2O7 (VI)	
83	Mouse (BALB/c)	Gd 12- Ld 20 (W)			66 F (delayed time of vaginal opening and impaired fertility in female offspring)		Al-Hamood et al. 1998 K2Cr2O7 (VI)	
84	Mouse BDF1	Gd 0-18 (W)		4.8 F			De Flora et al. 2006 Na2Cr2O7.2H2O (VI)	
85	Mouse BDF1	Gd 0-18 (W)		2.4 F			De Flora et al. 2006 K2Cr2O7 (VI)	
86	Mouse (Swiss albino)	20 d (W)				52 F (reduced caudal ossification in fetuses; decreased fetal weight; post-implantation loss)	Junaid et al. 1996a K2Cr2O7 (VI)	
87	Mouse (albino)	Gd 1-19 19 d (W)				46 (increased resorptions, reduced ossification, gross anomalies)	Trivedi et al. 1989 K2Cr2O7 (VI)	
CHRONIC EXPOSURE								
Death								
88	Rat (Fischer- 344)	2 yr (W)		7 F			NTP 2008a Na2Cr2O7.2H2O (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
89	Mouse (B6C3F1)	2 yr (W)		8.7 F			NTP 2008a Na2Cr2O7.2H2O (VI)	
Systemic								
90	Human	NS (environ)	Gastro		0.57 (oral ulcer, diarrhea, abdominal pain, indigestion, vomiting)		Zhang and Li 1987 (VI)	Exposed to well water containing 20 mg Cr(VI)/L; assuming 70 kg body weight and drinking water consumption of 2 L/day, dose = 0.57 mg Cr(VI)/kg/day.
			Hemato		0.57 (leukocytosis, immature neutrophils)			
91	Rat (Sprague-Dawley)	1 yr (W)	Hemato	3.6			MacKenzie et al. 1958 K2CrO4 (VI)	
			Hepatic	3.6				
			Renal	3.6				
			Bd Wt	3.6				
92	Rat (Fischer- 344)	12 mo (W)	Hemato	0.21 M	0.77 M (decreased mean cell hemoglobin)		NTP 2008a Na2Cr2O7.2H2O (VI)	
			Musc/skel	0.94 M	2.4 M (creatine kinase activity increased by 64%)			
			Hepatic	0.21 M	0.77 M (serum ALT increased by 156%)			

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
93	Rat (Fischer- 344)	2 yr (W)	Resp	7 F			NTP 2008a Na2Cr2O7.2H2O (VI)	
			Cardio	7 F				
			Gastro	0.21 M 0.94 F	0.77 M (histiocytic cellular infiltration of duodenum) 2.4 F (histiocytic cellular infiltrate of duodenum)			
			Hepatic	0.21 M	0.77 M (basophilic foci of liver) 0.24 F (chronic inflammation)			
			Renal	7 F				
			Endocr	7 F				
			Ocular	7 F				
			Bd Wt	2.1 M	5.9 M (12% decrease in body weight)			
94	Mouse (B6C3F1)	1 yr (W)	Hemato	1.4 F	3.1 F (increased RBC count, decreased mean cell volume and mean cell hemoglobin)		NTP 2008a Na2Cr2O7.2H2O (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
95	Mouse (B6C3F1)	2 yr (W)	Resp	8.7 F			NTP 2008a Na2Cr2O7.2H2O (VI)	
			Cardio	8.7 F				
			Gastro		0.38[c] (epithelial hyperplasia of duodenum in males and female and cytoplasmic alteration of pancreas in females)			
			Hepatic	2.4 M	5.9 M (clear cell and eosinophilic foci)			
					0.38 F (histiocytic cellular infiltration)			
			Renal	8.7 F				
			Endocr	8.7 F				
			Ocular	8.7 F				
Immuno/ Lymphoret								
96	Rat (Fischer- 344)	2 yr (W)		0.21 M 0.94 F	0.77 M (histiocytic cellular infiltration and hemorrhage of mesenteric nodes)		NTP 2008a Na2Cr2O7.2H2O (VI)	
					2.4 F (histiocytic cellular infiltration of mesenteric and pancreatic nodes)			

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
97	Mouse (B6C3F1)	2 yr (W)			0.38 (histiocytic cellular infiltration of mesenteric lymph nodes)		NTP 2008a Na2Cr2O7.2H2O (VI)	
Neurological								
98	Rat (Fischer- 344)	2 yr (W)		7 F			NTP 2008a Na2Cr2O7.2H2O (VI)	
99	Mouse (B6C3F1)	2 yr (W)		8.7 F			NTP 2008a Na2Cr2O7.2H2O (VI)	
Reproductive								
100	Rat (Fischer- 344)	2 yr (W)		6.6 M 7 F			NTP 2008a Na2Cr2O7.2H2O (VI)	
101	Mouse (B6C3F1)	2 yr (W)		5.9 M 8.7 F			NTP 2008a Na2Cr2O7.2H2O (VI)	

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Cancer								
102	Human	(environ)				0.57 (CEL: lung and stomach cancer)	Zhang and Li 1987 Cr (VI)	Exposed to well water containing 20 mg Cr(VI)/L; assuming 70 kg body weight and drinking water consumption of 2 L/day, dose = 0.57 mg Cr(VI)/kg/day.
103	Rat (Fischer- 344)	2 yr (W)				5.9 M (CEL: neoplasm of squamous epithelium of mouth and tongue) 7 F (CEL: neoplasm of squamous cell epithelium of mouth and tongue)	NTP 2008a Na2Cr2O7.2H2O (VI)	
104	Mouse (B6C3F1)	2 yr (W)				3.1 M (CEL: neoplastic lesions of small intestine) 2.4 M (CEL: neoplastic lesions of small intestine)	NTP 2008a Na2Cr2O7.2H2O (VI)	

a The number corresponds to entries in Figure 3-3.

b Used to derive an intermediate-duration oral MRL of 0.005 mg chromium(VI)/kg/day for chromium(VI) compounds. The benchmark dose of 0.52 mg/kg/day (average of the benchmark doses derived for MCV, MCH, and Hgb) was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

c Used to derive a chronic-duration oral MRL of 0.001 mg chromium(VI)/kg/day for chromium(VI) compounds. Benchmark dose of 0.09 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

(VI) = hexavalent; avg = average; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; environ = environmental; (F) = feed; F = female; F1 = first generation; F2 = second generation; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; (IN) = ingestion; Ld = lactational day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; (occup) = occupational; pnd = post natal day; Resp = respiratory; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; (W) = drinking water; wk = week(s); x = times; yr = year(s)

Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral

Acute (≤14 days)

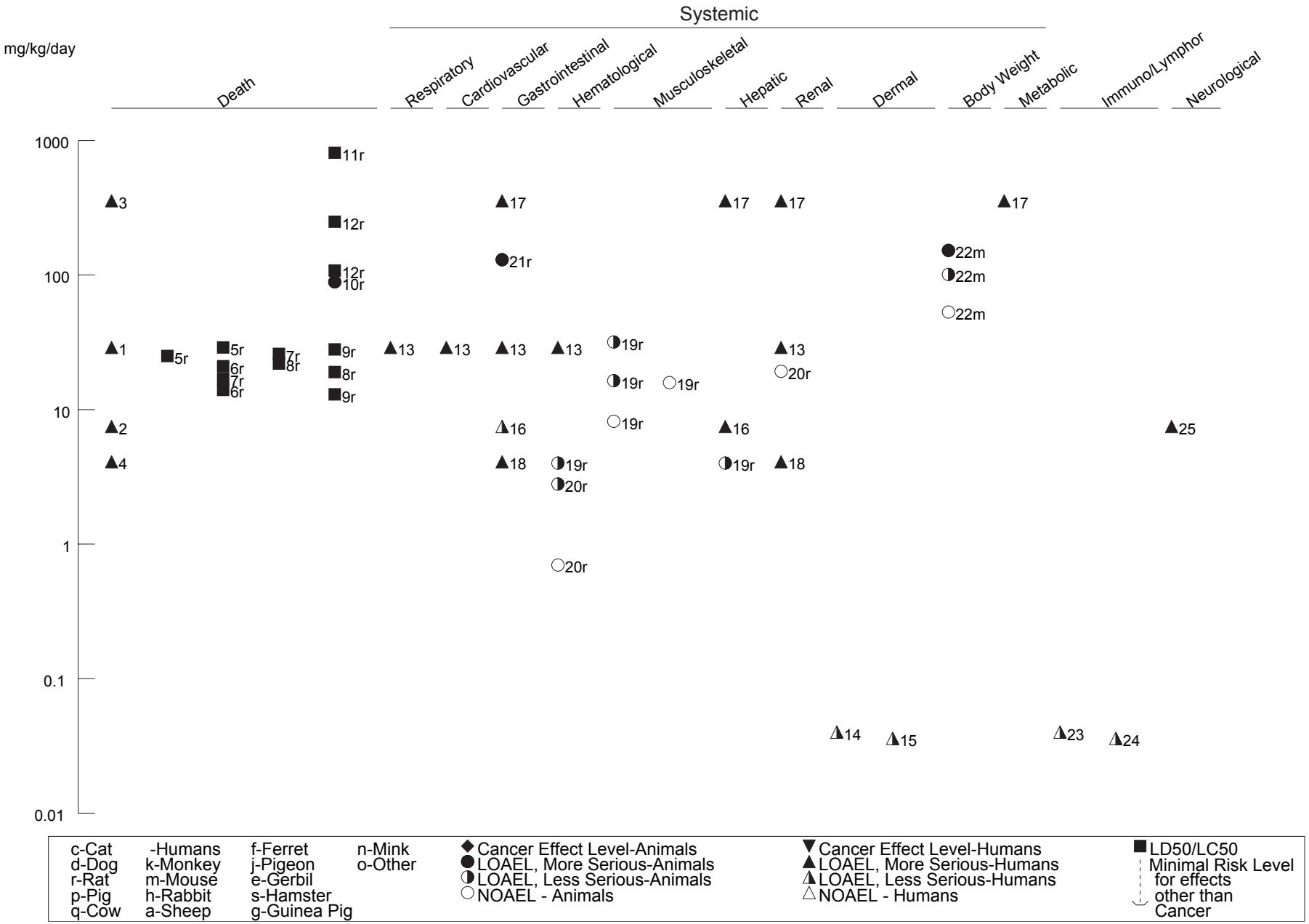


Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral *(Continued)*

Acute (≤14 days)

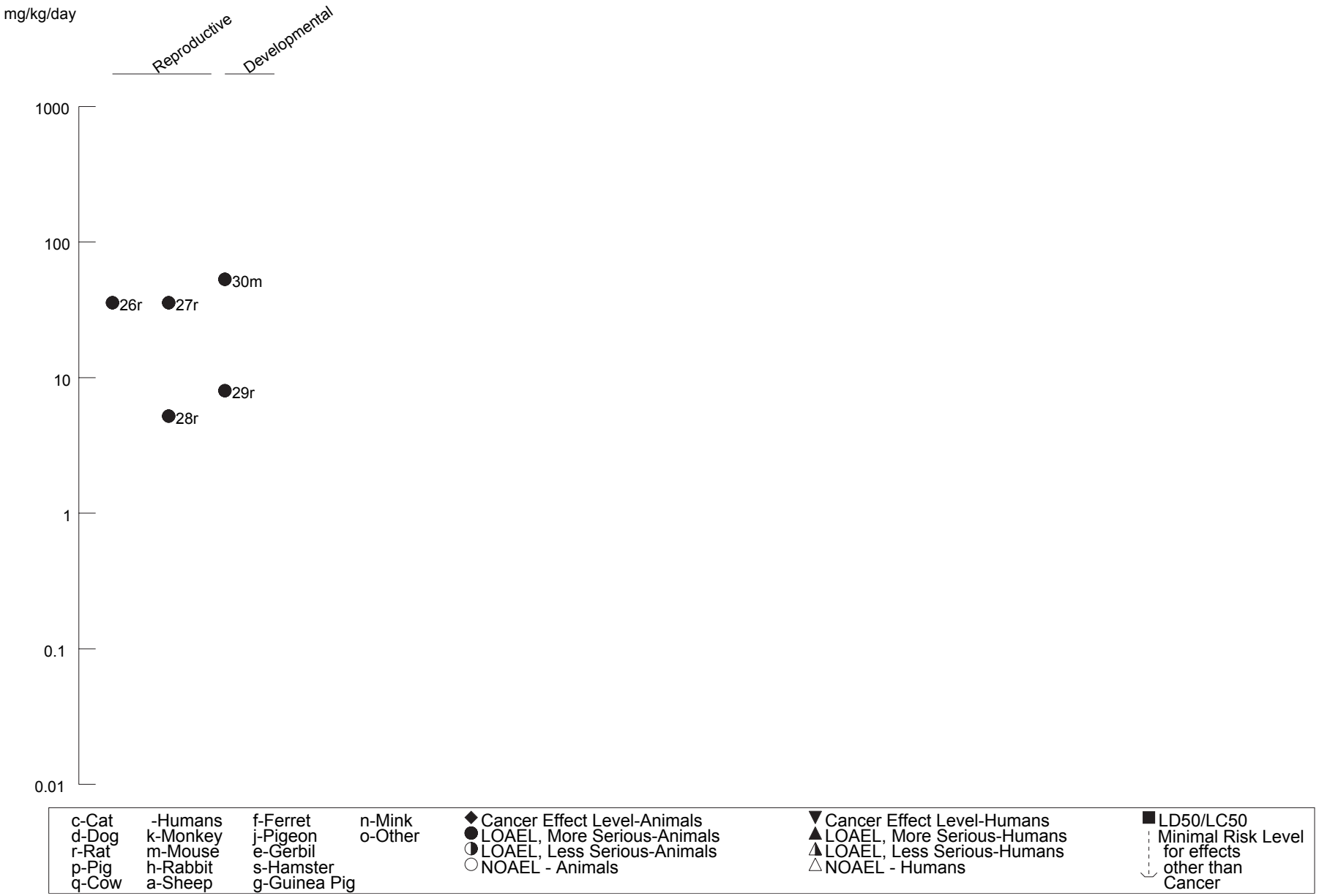


Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral *(Continued)*

Intermediate (15-364 days)

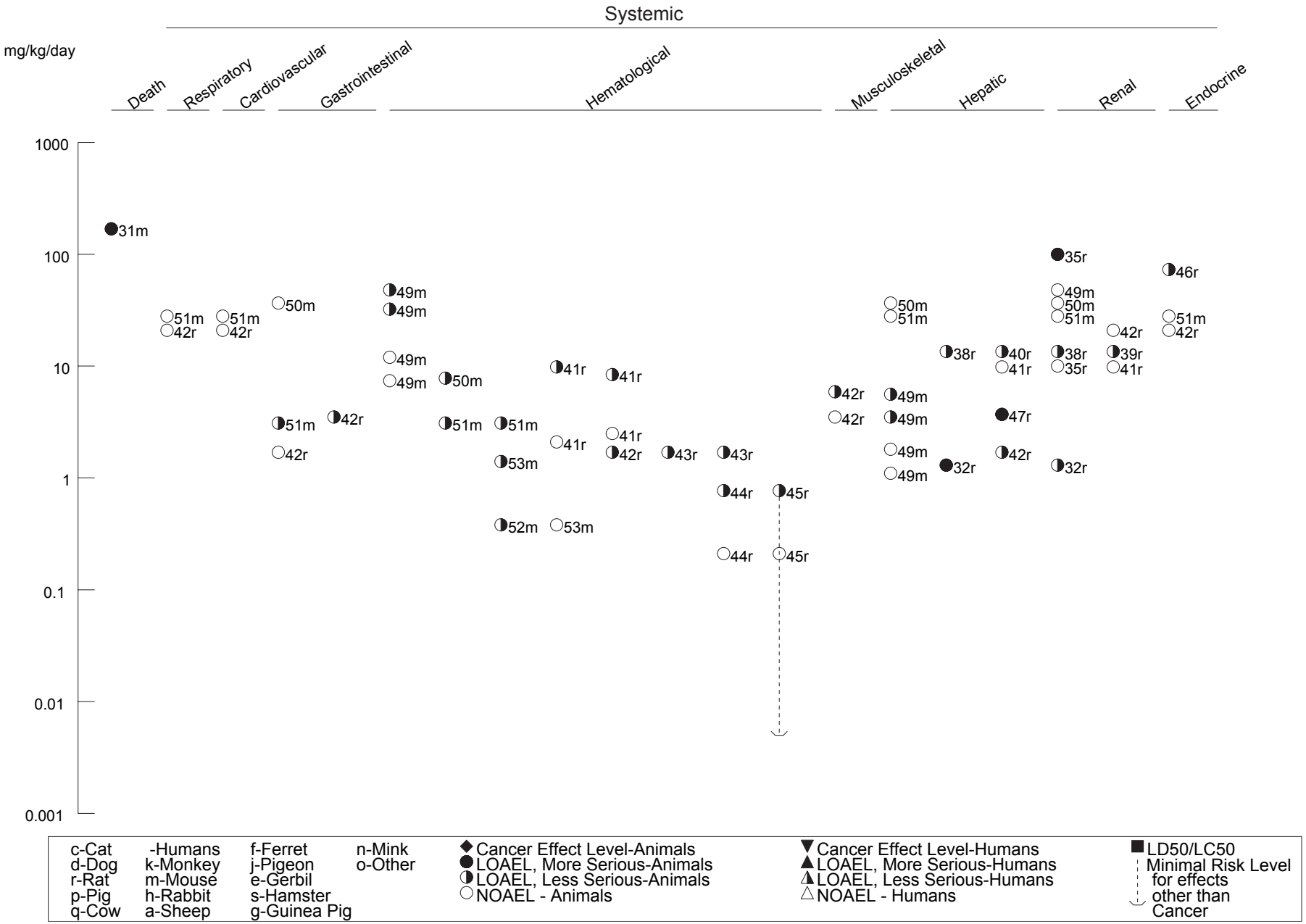


Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral *(Continued)*

Intermediate (15-364 days)

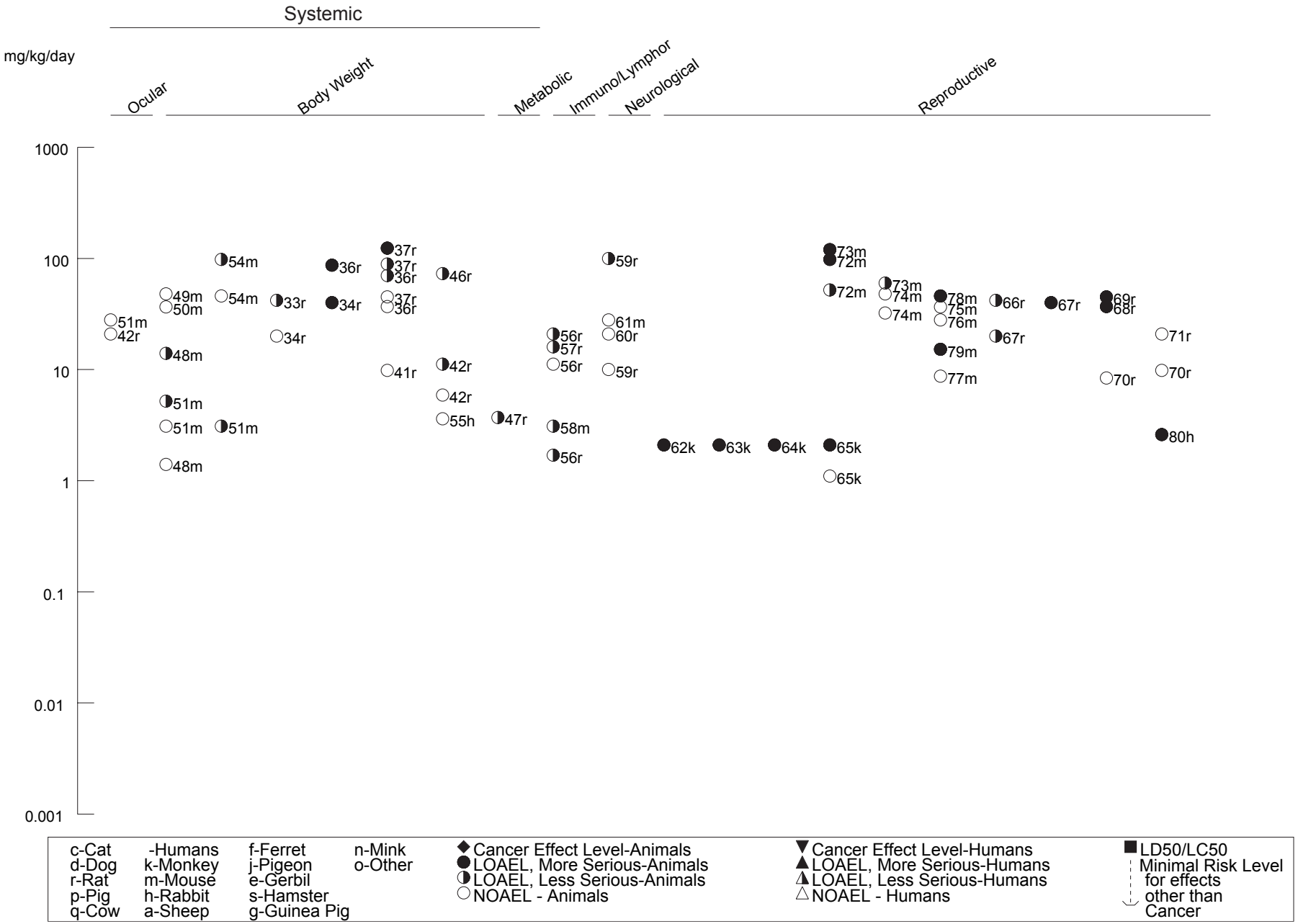


Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral *(Continued)*

Intermediate (15-364 days)

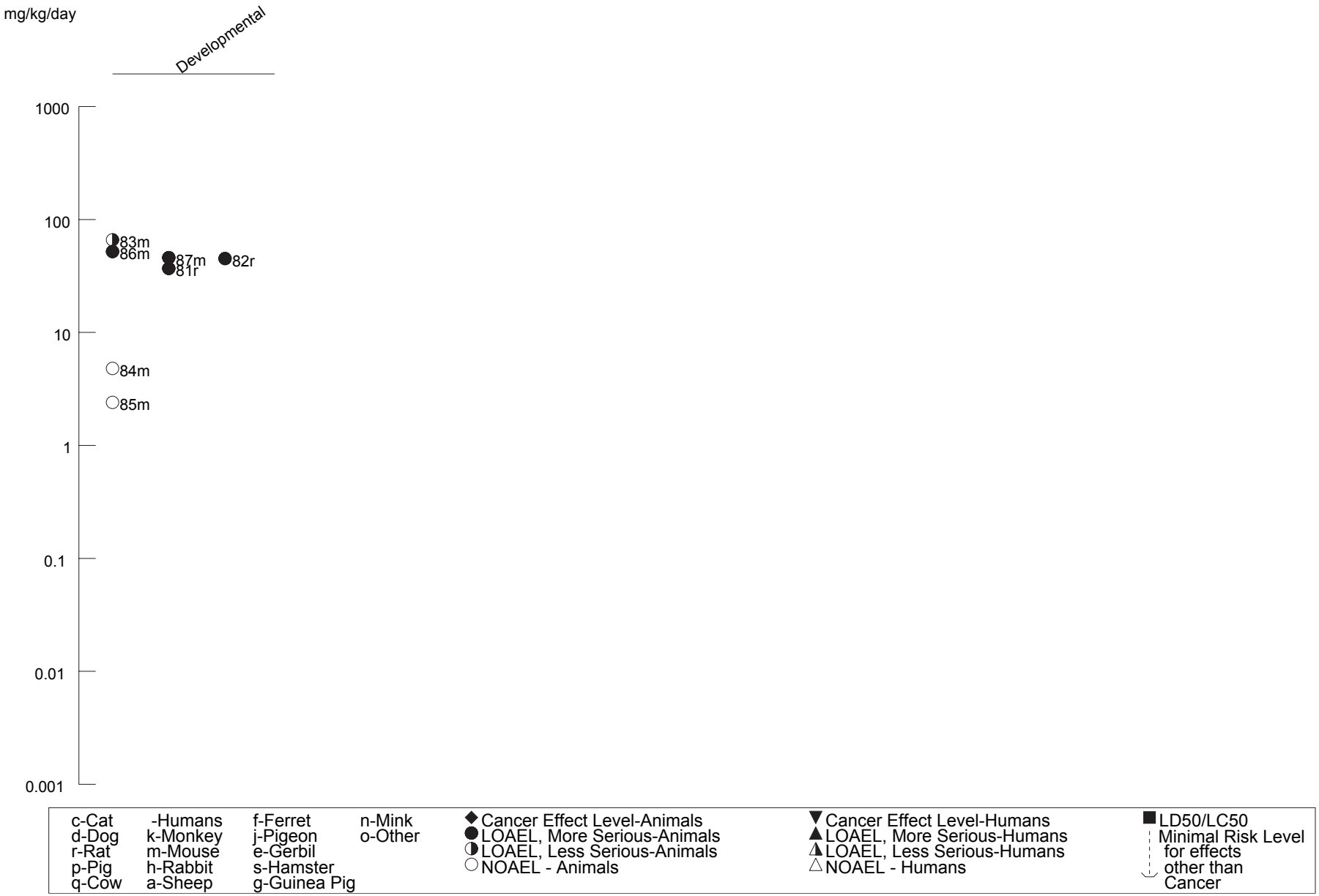


Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral *(Continued)*

Chronic (≥365 days)

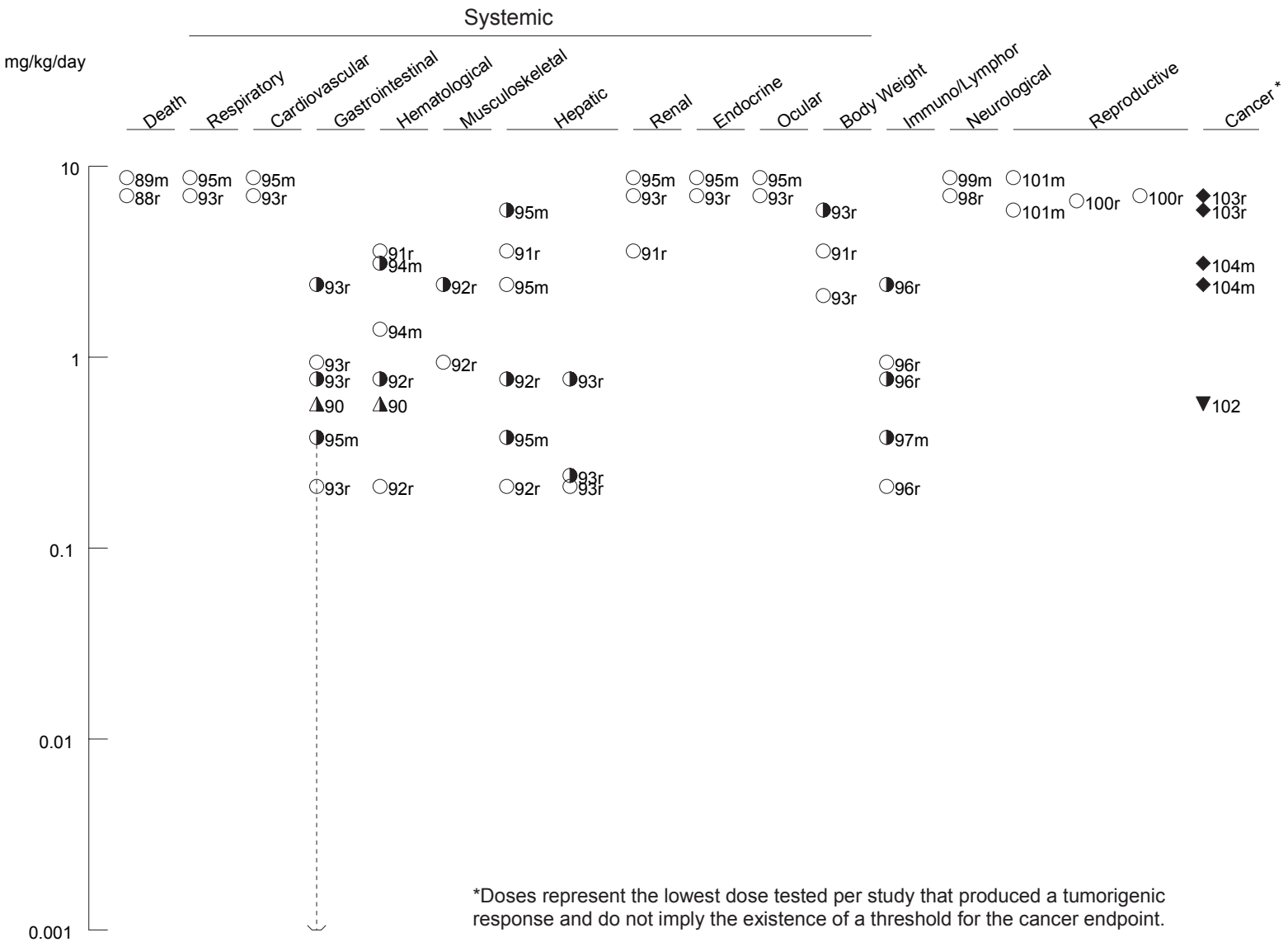


Table 3-4 Levels of Significant Exposure to Chromium III - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (NS)	once (GW)				2365 (LD50)	Smyth et al. 1969 Cr(CH3COO)3H2O (III)	
2	Rat (Sprague-Dawley)	once (G)				200 M (LD50) 183 F (LD50)	Vernot et al. 1977 Cr(NO3)3.9H2O (III)	
Systemic								
3	Rat (Fischer- 344)	3 d (F)	Hemato	506 F			NTP 2008 Cr picolinate (III)	
Reproductive								
4	Rat (NS)	3 d Gd 1-3 (G)				33.6 F (decreased number of pregnancies)	Bataineh et al. 2007 CrCl3 (III)	
5	Rat (NS)	3 d Gd 4-6 (G)		33.6 F			Bataineh et al. 2007 CrCl3 (III)	
INTERMEDIATE EXPOSURE								
Systemic								
6	Rat (Sprague-Dawley)	daily 20 wk (F)	Hepatic	9			Anderson et al. 1997b CrCl3 (III)	
			Renal	9				
			Bd Wt	9				

Table 3-4 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
7	Rat (Sprague-Dawley)	daily 20 wk (F)	Hepatic	9			Anderson et al. 1997b Cr picolinate (III)	
			Renal	9				
			Bd Wt	9				
8	Rat (Sprague-Dawley)	12 wk (W)	Bd Wt			40 (24% lower final body weight)	Bataineh et al. 1997 CrCl3 (III)	
9	Rat (BD)	90 d 5 d/wk (F)	Resp	1806			Ivankovic and Preussmann 1975 Cr2O3 (III)	
			Cardio	1806				
			Gastro	1806				
			Hemato	1806				
			Hepatic	1806				
			Renal	1806				

Table 3-4 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
10	Rat (Fischer- 344)	14 wk (F)	Resp	506 F			NTP 2008 Cr picolinate (III)	
			Cardio	506 F				
			Gastro	506 F				
			Hemato	506 F				
			Hepatic	506 F				
			Renal	506 F				
			Endocr	506 F				
			Ocular	506 F				
			Bd Wt	506 F				
11	Rat (Sprague-Dawley)	90 d (F)	Resp	1.5 F			Shara et al. 2005 Cr nicotinate (III)	
			Cardio	1.5 F				
			Gastro	1.5 F				
			Hemato	1.5 F				
			Hepatic	1.5 F				
			Renal	1.5 F				
			Endocr	1.5 F				
			Bd Wt	1.5 F				

Table 3-4 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
12	Rat (Sprague-Dawley)	38 wk (F)	Resp	0.25 F			Shara et al. 2007 Cr nicotinate (III)	
			Cardio	0.25 F				
			Gastro	0.25 F				
			Hemato	0.25 F				
			Hepatic	0.25 F				
			Renal	0.25 F				
			Endocr	0.25 F				
13	Mouse BDF1	210 d (W)	Bd Wt	165 M 140 F			De Flora et al. 2006 CrK(SO4)2 (III)	
14	Mouse (Swiss)	12 wk (W)	Bd Wt	14 F	5 M (14% decrease in body weight gain)		Elbetieha and Al-Hamood 1997 CrCl3 (III)	

Table 3-4 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
15	Mouse (B6C3F1)	14 wk (F)	Resp	1415 M			NTP 2008 Cr picolinate (III)	
			Cardio	1415 M				
			Gastro	1415 M				
			Hemato	1415 M				
			Hepatic	1415 M				
			Renal	1415 M				
			Endocr	1415 M				
			Ocular	1415 M				
			Bd Wt	1415 M				
Immuno/ Lymphoret								
16	Rat (Fischer- 344)	14 wk (F)		506 F			NTP 2008 Cr picolinate (III)	
17	Rat (Sprague-Dawley)	90 d (F)		1.5 F			Shara et al. 2005 Cr nicotinate (III)	
18	Rat (Sprague-Dawley)	38 wk (F)		0.25 F			Shara et al. 2007 Cr nicotinate (III)	
19	Mouse (B6C3F1)	14 wk (F)		1415 M			NTP 2008 Cr picolinate (III)	
Neurological								
20	Rat	90 d 5 d/wk (F)		1806			Ivankovic and Preussmann 1975 Cr III	

Table 3-4 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Rat (Fischer- 344)	14 wk (F)		506 F			NTP 2008 Cr picolinate (III)	
22	Rat (Fischer- 344)	14 wk ad lib (F)		506 F			NTP 2008 Cr picolinate (III)	
23	Rat (Sprague-Dawley)	90 d (F)		1.5 F			Shara et al. 2005 Cr nicotinate (III)	
24	Rat (Sprague-Dawley)	38 wk (F)		0.25 F			Shara et al. 2007 Cr nicotinate (III)	
25	Mouse (B6C3F1)	14 wk ad lib (F)		1415 M			NTP 2008 Cr picolinate (III)	
Reproductive								
26	Rat (Sprague-Dawley)	12 wk (W)			40 (altered sexual behavior, decreased absolute testes, seminal vesicles, and preputial gland weights)		Bataineh et al. 1997 CrCl3 (III)	
27	Rat (Fischer- 344)	14 wk (F)		506 F			NTP 2008 Cr picolinate (III)	
28	Rat (Sprague-Dawley)	90 d (F)		1.5 F			Shara et al. 2005 Cr nicotinate (III)	

Table 3-4 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Rat (Sprague-Dawley)	38 wk (F)		0.25 F			Shara et al. 2007 Cr nicotinate (III)	
30	Mouse (Swiss)	12 wk (W)			5 M (increased testes and decreased preputial gland weights)	5 F (decreased number of implantations and viable fetuses; increased ovarian and decreased uterine weights)	Elbetieha and Al-Hamood 1997 CrCl3 (III)	
31	Mouse (B6C3F1)	14 wk (F)		1415 M			NTP 2008 Cr picolinate (III)	
32	Mouse (BALB/c)	7 wk 7 d/wk (F)				9.1 M (decreased spermatogenesis)	Zahid et al. 1990 Cr2(SO4)3 (III)	
Developmental								
33	Rat (BD)	90 d 5 d/wk (F)		1806			Ivankovic and Preussmann 1975 Cr2O3 (III)	
34	Mouse (BALB/c)	Gd 12- Ld 20 (W)			74 (reduced ovary and testis weights in offspring and impaired fertility in female offspring)		Al-Hamood et al. 1998 CrCl3 (III)	

Table 3-4 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
35	Rat (BD)	2 yr 5 d/wk (F)	Resp	2040			Ivankovic and Preussmann 1975 Cr2O3 (III)	
			Cardio	2040				
			Gastro	2040				
			Hepatic	2040				
			Renal	2040				
36	Rat (Sprague-Dawley)	1 yr (W)	Hemato	3.6			MacKenzie et al. 1958 CrCl3 (III)	
			Hepatic	3.6				
			Renal	3.6				
			Bd Wt	3.6				
37	Rat (Fischer- 344)	2 yr (F)	Resp	313 F			NTP 2008 Cr picolinate (III)	
			Cardio	313 F				
			Gastro	313 F				
			Hepatic	313 F				
			Renal	313 F				
			Endocr	313 F				
			Ocular	313 F				
			Bd Wt	313 F				

Table 3-4 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
38	Rat (Long- Evans)	2-3 yr 7 d/wk (W)	Cardio	0.46			Schroeder et al. 1965 Cr(CH3COO)3 (III)	
			Hepatic	0.46				
			Renal	0.46				
			Bd Wt	0.46				
39	Rat (Sprague-Dawley)	52 wk (F)	Resp	0.25 F			Shara et al. 2007 Cr nicotinate (III)	
			Cardio	0.25 F				
			Gastro	0.25 F				
			Hemato	0.25 F				
			Hepatic	0.25 F				
			Renal	0.25 F				
			Endocr	0.25 F				
			Bd Wt		0.22 M (14.9% decrease in body weight)			
					0.25 F (9.6% decrease in body weight)			

Table 3-4 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
40	Mouse (B6C3F1)	2 yr (F)	Resp	781 M			NTP 2008 Cr picolinate (III)	
			Cardio	781 M				
			Gastro	781 M				
			Hepatic	781 M				
			Renal	781 M				
			Endocr	781 M				
			Ocular	781 M				
			Bd Wt	781 M				
Immuno/ Lymphoret								
41	Rat (Fischer- 344)	2 yr (F)		313 F			NTP 2008 Cr picolinate (III)	
42	Rat (Sprague-Dawley)	52 wk (F)		0.25 F			Shara et al. 2007 Cr nicotinate (III)	
43	Mouse (B6C3F1)	2 yr (F)		781 M			NTP 2008 Cr picolinate (III)	
Neurological								
44	Rat	2 yr 5 d/wk (F)		2040			Ivankovic and Preussmann 1975 Cr III	
45	Rat (Fischer- 344)	2 yr (F)		313 F			NTP 2008 Cr picolinate (III)	

Table 3-4 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
46	Rat (Sprague-Dawley)	52 wk (F)		0.25 F			Shara et al. 2007 Cr nicotinate (III)	
47	Mouse (B6C3F1)	2 yr (F)		781 M			NTP 2008 Cr picolinate (III)	
Reproductive								
48	Rat (Fischer- 344)	2 yr (F)		313 F			NTP 2008 Cr picolinate (III)	
49	Rat (Sprague-Dawley)	52 wk (F)		0.25 F			Shara et al. 2007 Cr nicotinate (III)	
50	Mouse (B6C3F1)	2 yr (F)		781 M			NTP 2008 Cr picolinate (III)	
Cancer								
51	Rat (Fischer- 344)	2 yr (F)				55 M (equivocal evidence for prepubital gland adenoma)	NTP 2008 Cr picolinate (III)	

a The number corresponds to entries in Figure 3-4.

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn Pig = guinea pig; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; ppd = post-parturition day; ppm = parts per million; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-4 Levels of Significant Exposure to Chromium III - Oral

Acute (≤14 days)

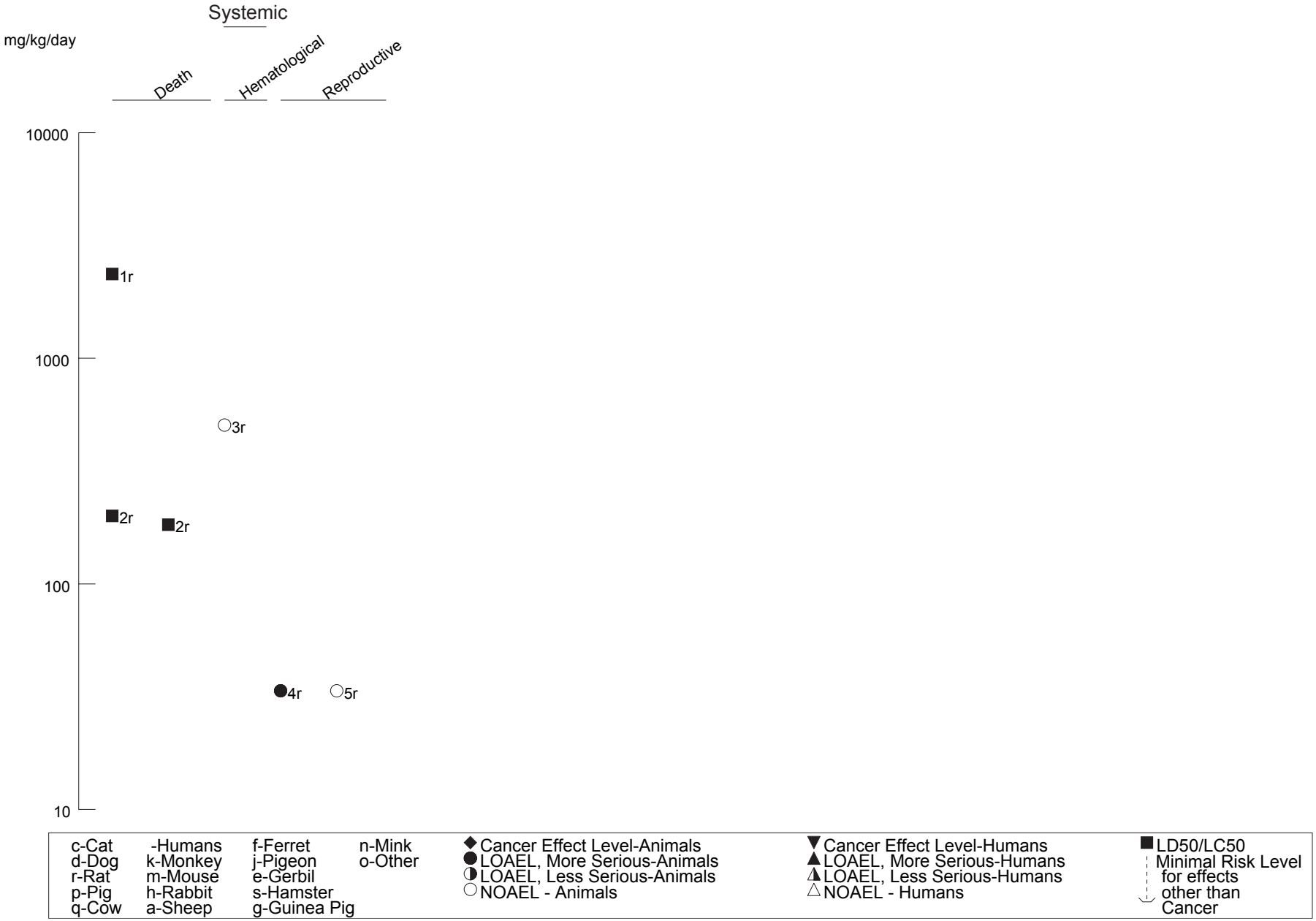


Figure 3-4 Levels of Significant Exposure to Chromium III - Oral *(Continued)*

Intermediate (15-364 days)

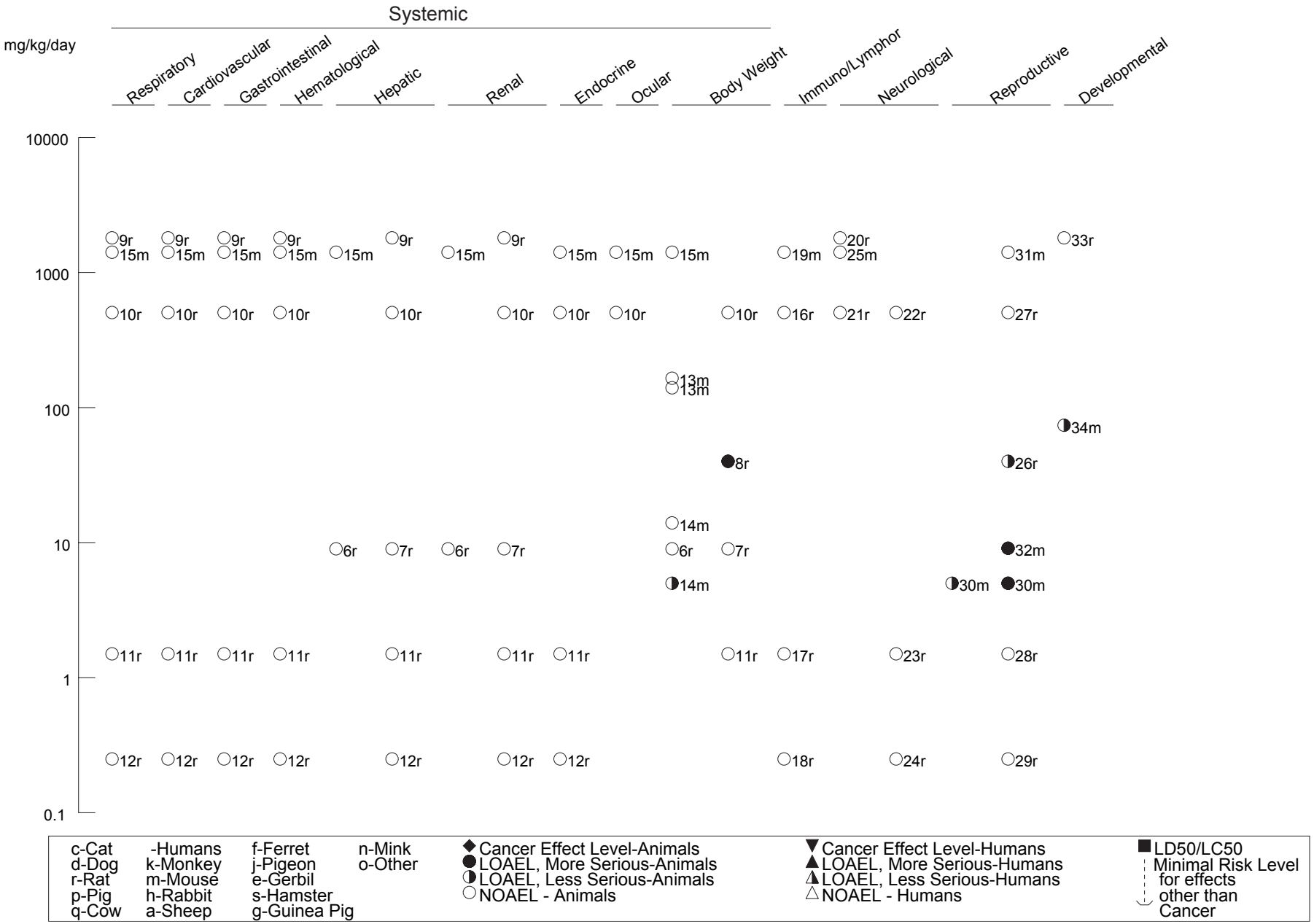
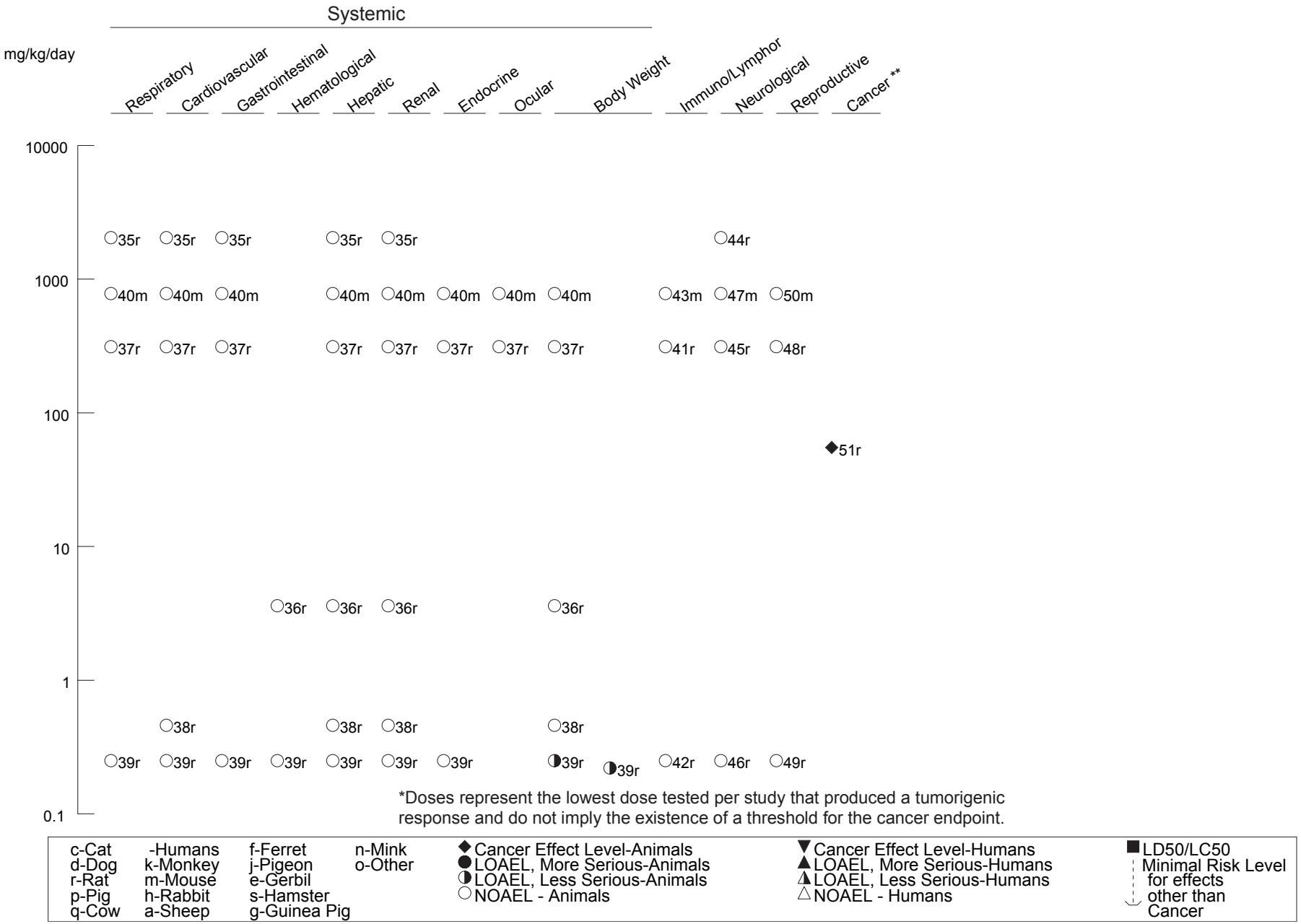


Figure 3-4 Levels of Significant Exposure to Chromium III - Oral *(Continued)*

Chronic (≥365 days)



respectively, for 2 years (NTP 2008a). Mortality was not increased in rats fed 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975) or in rats and mice fed up to 313 and 781 mg chromium(III)/kg/day, respectively, as chromium picolinate in the diet for 2 years (NTP 2008b).

3.2.2.2 Systemic Effects

The systemic effects of oral exposure to chromium(III) and chromium(VI) compounds are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

Respiratory Effects. Case reports of humans who died after ingesting chromium(VI) compounds have described respiratory effects as part of the sequelae leading to death. A 22-month-old boy who ingested an unknown amount of sodium dichromate died of cardiopulmonary arrest. Autopsy revealed pleural effusion, pulmonary edema, severe bronchitis, and acute bronchopneumonia (Ellis et al. 1982). Autopsy of a 17-year-old male who committed suicide by ingesting 29 mg chromium(VI)/kg as potassium dichromate revealed congested lungs with blood-tinged bilateral pleural effusions (Clochesy 1984; Iserson et al. 1983). Respiratory effects were not reported at nonlethal doses. No information was identified on respiratory effects in humans after oral exposure to chromium(III) compounds.

No studies were identified regarding respiratory function in animals after oral exposure to chromium(VI) or chromium(III) compounds. The histopathology of lung and nasal tissue has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydrate) and chromium(III) (as chromium nicotinate, chromium oxide and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (Ivankovic and Preussmann 1975; NTP 2007, 2008a, 2008b; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,806 and 2,040 mg chromium(III)/kg/day, respectively, as chromium oxide in the diet 5 days/week (Ivankovic and Preussmann 1975).

Cardiovascular Effects. Case reports of humans who died after ingesting chromium(VI) compounds have described cardiovascular effects as part of the sequelae leading to death. A 22-month-old boy who

ingested an unknown amount of sodium dichromate died of cardiopulmonary arrest. Autopsy revealed early hypoxic changes in the myocardium (Ellis et al. 1982). In another case, cardiac output, heart rate, and blood pressure dropped progressively during treatment in the hospital of a 17-year-old male who had ingested 29 mg chromium(VI)/kg as potassium dichromate. He died of cardiac arrest. Autopsy revealed hemorrhages in the anterior papillary muscle of the left ventricle (Clochesy 1984; Iserson et al. 1983). Cardiovascular effects have not been reported at nonlethal doses. No information was identified on cardiovascular effects in humans after oral exposure to chromium(III) compounds.

No studies were located regarding effects on cardiovascular function in animals after oral exposure to chromium(VI) compounds. Histopathological examination of the heart has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydrate and sodium acetate) and chromium(III) (as chromium nicotinate, chromium oxide and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (Ivankovic and Preussmann 1975; NTP 2007, 2008a, 2008b; Schroeder et al. 1965; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,806 and 2,040 mg chromium(III)/kg/day, respectively, as chromium oxide in the diet 5 days/week (Ivankovic and Preussmann 1975). None of these studies assessed cardiovascular end points such as blood pressure or electrocardiograms.

Gastrointestinal Effects. Cases of gastrointestinal effects in humans after oral exposure to chromium(VI) compounds have been reported. In one study, a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate experienced abdominal pain and vomiting before death. Autopsy revealed gastrointestinal ulceration (Kaufman et al. 1970). In another study, a 44-year-old man died of gastrointestinal hemorrhage after ingesting 4.1 mg chromium(VI)/kg as chromic acid solution (Saryan and Reedy 1988). Gastrointestinal hemorrhage and extensive necrosis of all digestive mucous membranes were also observed on autopsy of a 35-year-old woman who died following ingestion of 357 mg chromium(VI)/kg as chromic acid (Loubieres et al. 1999). Gastrointestinal burns and hemorrhage have also been described as contributing to the cause of death of infants who ingested unknown amounts of sodium dichromate (Ellis et al. 1982) or ammonium dichromate (Reichelderfer 1968) and a 17-year-old male who ingested ~29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983).

Some chromium(VI) compounds, such as potassium dichromate and chromium trioxide, are caustic and irritating to mucosal tissue. A 25-year-old woman who drank a solution containing potassium dichromate experienced abdominal pain and vomited (Goldman and Karotkin 1935). Two people who ate oatmeal contaminated with potassium dichromate became suddenly ill with severe abdominal pain and vomiting, followed by diarrhea (Partington 1950). Acute gastritis developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis, which saved his life (Fristedt et al. 1965). Nausea, hemetemesis, and bloody diarrhea were reported in a 24-year-old woman who ingested ammonium dichromate in a suicide attempt (Hasan 2007).

Ingestion of chromium compounds as a result of exposure at the workplace has occasionally produced gastrointestinal effects. In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, in addition to symptoms of labored breathing, dizziness, headache, and weakness from breathing the fumes during work, workers experienced nausea and vomiting upon eating on the premises (Lieberman 1941). Gastrointestinal effects were also reported in an epidemiology study of 97 workers in a chromate plant exposed to dust containing both chromium(III) and chromium(VI) compounds. Blocked nasal passages, as a result of working in the dust laden atmosphere, forced the individuals to breathe through their mouths, thereby probably ingesting some of the chromium dust. A 10.3% incidence of gastric ulcer formation and a 6.1% incidence of hypertrophic gastritis was reported. Epigastric and substernal pain were also reported in the chromate production workers (Mancuso 1951). Gastric mucosa irritation resulting in duodenal ulcer, possibly as a result of mouth breathing, has also been reported in other studies of chromate production workers (Sassi 1956; Sterekhova et al. 1978). Subjective symptoms of stomach pain, duodenal ulcers, gastritis, stomach cramps, and indigestion were reported by workers exposed to a mean concentration of 0.004 mg chromium(VI)/m^3 in an electroplating facility where zinc, cadmium, nickel, tin, and chromium plating were carried out (Lucas and Kramkowski 1975). An otolaryngological examination of 77 employees of eight chromium electroplating facilities in Czechoslovakia, where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m^3, revealed 12 cases of chronic tonsillitis, 5 cases of chronic pharyngitis, and 32 cases of atrophic changes in the left larynx (Hanslian et al. 1967). These effects were probably also due to exposure via mouth breathing.

In a cross-sectional study conducted in 1965 of 155 villagers whose well water contained chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and oral ulcer, diarrhea, abdominal

pain, indigestion, and vomiting. The alloy plant began chromium smelting in 1961 and began regular production in 1965. Similar results were found in two similar studies in other villages, but further details were not provided (Zhang and Li 1987). The highest concentration of chromium(VI) detected during sampling was 20 mg chromium(VI)/L, equivalent to a dose of 0.57 mg chromium(VI)/kg/day based on a default reference water consumption rate and body weight value of 2 L/day and 70 kg, respectively (note that these values may not be appropriate for the Chinese study population). However, exposure estimates for this population are uncertain and it is likely that exposure levels in many cases were to concentrations less than 20 mg chromium(VI)/L. At least some residents obtained drinking water from alternative sources (Sedman et al. 2006) and exposure may have been self-limiting due to lack of palatability of water (Beaumont et al. 2008). Thus, exposure levels associated with adverse effects are not well characterized.

No information was identified on gastrointestinal effects in humans after oral exposure to chromium(III) compounds.

Oral exposure of animals to chromium(VI), but not chromium(III), compounds results in irritation and histopathological changes to tissues of the gastrointestinal tract. Gastrointestinal hemorrhage was observed in rats given a lethal gavage dose of potassium dichromate (130 mg chromium(VI)/kg) (Samitz 1970). Histopathological changes were observed in rats and mice exposed to chromium(VI) as sodium dichromate dihydrate in drinking water for 3 months (NTP 2007) or 2 years (NTP 2008a). Following exposure for 3 months, duodenal histiocytic infiltration of the duodenum was observed in male and female F344/N rats exposed at ≥3.5 mg chromium(VI)/kg/day. At the highest daily dose (20.9 mg chromium(VI)/kg/day), ulcer and epithelial hyperplasia and metaplasia of the glandular stomach were observed. Epithelial hyperplasia and histiocytic cellular infiltration of the duodenum was observed at ≥3.1 and ≥5.2 mg chromium(VI)/kg/day, respectively, in male and female B6C3F1 mice. Similar nonneoplastic lesions of the duodenum were also reported in the 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice, with epithelial hyperplasia at ≥2.8 mg chromium(VI)/kg/day in B6C3F1 and BALB/c strains and ≥5.2 in the C57BL/6 strain, and histiocytic cellular infiltration at ≥2.8 mg chromium(VI)/kg/day in B6C3F1 and C57BL/6 strains and ≥5.2 mg chromium(VI)/kg/day in the BALB/c strain. After exposure for 2 years, duodenal histiocytic infiltration was observed in male and female rats exposed at 0.77 and 2.4 chromium(VI)/kg/day, respectively; in mice, duodenal epithelial hyperplasia was observed at 0.38 mg chromium(VI)/kg/day for 2 years and histiocytic cellular infiltration of the duodenum was also observed in males at 2.4 mg chromium(VI)/kg/day and females at 3.1 mg chromium(VI)/kg/day. In the 2-year study (NTP 2008a), neoplasms of the squamous epithelium of the

oral mucosa and tongue were observed in rats and of the small intestine (duodenum, jejunum and ileum) were observed in mice; these findings are discussed in Section 3.2.2.7 (Oral Exposure, Cancer). In female mice exposed to 0.38 mg chromium(VI)/kg/day and male mice exposed to 2.4 mg chromium(VI)/kg/day for 2 years, cytoplasmic alteration of the pancreas (depletion of cytoplasm zymogen granules) was observed; NTP stated that the biological significance of this finding was uncertain (NTP 2008a). In contrast to the findings in the NTP 3-month and 2-year drinking water studies of sodium dichromate dihydrate (NTP 2007, 2008a), no histopathological changes to the gastrointestinal tract were observed in BALB/c mice exposed to dietary potassium dichromate at doses up to 36.7 chromium(VI)/kg/day in a multigeneration continuous breeding study (NTP 1997). Differences in results of these studies could be attributed to difference in the exposure media (water versus feed). Data from the 2-year drinking water study on sodium dichromate dihydrate in mice (NTP 2008a) were used to used to develop the chronic-duration oral MRL for chromium(VI) compounds. The $BMDL_{10}$ value of 0.09 mg chromium(VI)/kg/day for diffuse epithelial hyperplasia of the duodenum in female mice was used to calculate an oral MRL of 0.001 mg chromium(VI)/kg/day for chronic-duration exposure to chromium(VI) a compounds as described in the footnote of Table 3-3.

No histopathological changes to the stomach or small intestine were observed in mice and rats exposed to oral chromium(III) (as chromium nicotinate, chromium oxide, and chromium picolinate) for 3 months or 2 years (Ivankovic and Preussmann 1975; NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007). The highest doses of chromium(III) tested were 1,415 mg chromium(III)/kg/day as chromium picolinate in the diet for 3 months (NTP 2008b; Rhodes et al. 2005) and 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975).

Hematological Effects. Cases of hematological effects have been reported in humans after the ingestion of lethal or sublethal doses of chromium(VI) compounds. In a case of an 18-year-old woman who ingested a few grams of potassium dichromate, decreased hemoglobin content and hematocrit, and increased total white blood cell counts, reticulocyte counts, and plasma hemoglobin were found 4 days after ingestion. These effects were indicative of intravascular hemolysis (Sharma et al. 1978). A 25-year-old woman who drank a solution containing potassium dichromate had a clinically significant increase in leukocytes due to a rise in polymorphonuclear cells (Goldman and Karotkin 1935). In another study, a 44-year-old man had decreased hemoglobin levels 9 days after ingestion of 4.1 mg chromium(VI)/kg as chromic acid solution that probably resulted from gastrointestinal hemorrhage (Saryan and Reedy 1988). Inhibition of blood coagulation was described in a case of a 17-year-old male who died after ingesting ~29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983). Anemia

following severe hemorrhaging developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis, which saved his life (Fristedt et al. 1965).

In a cross-sectional study conducted in 1965 of 155 villagers whose well water contained 20 mg chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and leukocytosis and immature neutrophils. The alloy plant began chromium smelting in 1961 and began regular production in 1965. Similar results were found in two similar studies in other villages, but further details were not provided (Zhang and Li 1987). The highest concentration of chromium(VI) detected during sampling was 20 mg chromium(VI)/L, equivalent to a dose of 0.57 mg chromium(VI)/kg/day. However, exposure estimates for this population are uncertain and it is likely that exposure levels in many cases were to concentrations <20 mg chromium(VI)/L. At least some residents obtained drinking water from alternative sources (Sedman et al. 2006) and exposure may have been self-limiting due to lack of palatability of water at higher concentrations (Beaumont et al. 2008). Thus, exposure levels associated with adverse effects are not well characterized.

No reliable information was identified on hematological effects in humans of oral exposure to chromium(III) compounds.

Microcytic, hypochromic anemia, characterized by decreased mean cell volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit (Hct), and hemoglobin (Hgb), was observed in F344/N rats and B6C3F1 mice exposed to chromium(III) compounds in drinking water for exposure durations ranging from 4 days to 1 year (NTP 2007, 2008a). Severity was dose-dependent. Maximum effects were observed after approximately 3 weeks of exposure; with increasing exposures durations (e.g., 14 weeks to 1 year), effects were less pronounced, presumably due to compensatory hematopoietic responses. In general, effects were more severe in rats than mice. Following acute exposure of male rats to sodium dichromate dihydrate in drinking water for 4 days, a slight, but statistically significant decrease (2.1%) in MCH was observed at 2.7 mg chromium(VI)/kg/day, but not at 0.7 mg chromium(VI)/kg/day. With increasing doses (7.4 mg chromium(VI)/kg/day and greater), additional decreases in MCH and decreased MCV were observed (NTP 2008a). Similar effects were observed in male and female rats exposed for 5 days, with effects observed at 4.0 and 4.1 chromium(VI)/kg/day, respectively (NTP 2007); a NOAEL was not established.

More severe microcytic, hypochromic anemia occurred in rats and mice following exposure to sodium dichromate dihydrate in drinking water for 22 or 23 days (NTP 2007, 2008a). Decreased Hct (6.1%), Hgb (8.4%), MCV (7.7%), and MCH (10.6%) occurred in male rats exposed for 22 days to 0.77 mg chromium(VI)/kg/day, with decreases exhibiting dose-dependence; effects were not observed at 0.21 mg chromium(VI)/kg/day (NTP 2008a). Similar hematological effects were observed in male and female rats exposed to 1.7 mg chromium(VI)/kg/day for 23 days (NTP 2007). In female mice exposed to 22 days, slight, but significant decreases in MCV (2.0%) and MCH (1.2%) were observed at 0.38 mg chromium(VI)/kg/day, with more severe effects at higher doses (NTP 2008a). After exposure for 3 months to 1 year, microcytic, hypochromic anemia in rats and mice was less severe than that observed after 22 or 23 days (NTP 2007, 2008a). For example in male rats exposed for 22 days, decreases in Hct (6.1%), Hgb (8.4%), MCV (7.7%), and MCH (10.6%) were observed at 0.77 mg chromium(VI)/kg/day, whereas after exposure to 0.77 mg chromium(VI)/kg/day for 1 year, decreased MCH (2.4%), but not MCV, Hct ,or Hgb, were observed (NTP 2008a). Similar decreases in severity was also observed in female rats and in male and female mice exposed for 1 year compared to 22 days (NTP 2008a). In contrast, routine hematological examination revealed no changes in Sprague-Dawley rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year (MacKenzie et al. 1958); however, data on hematological parameters or statistical analyses were not presented in the report. Data from the 22-day evaluation in the 2-year NTP (2008a) drinking water study on sodium dichromate dihydrate in rats were used to used to develop the intermediate-duration oral MRL for chromium(VI) compounds. Because several hematological parameters are used to define the clinical picture of anemia, the intermediate-duration oral MRL was based on the average $BMDL_{2sd}$ value (e.g., the average of $BMDL_{2sd}$ values for Hgb, MCV, and MCH; BMD models did not provide adequate fit for hematocrit) of 0.52 mg chromium(VI)/kg/day, as described in the footnote of Table 3-3.

In feeding studies of potassium dichromate in Sprague-Dawley rats and BALB/c mice, slight microcytic hyprochromic anemia, characterized by slightly reduced MCV and MCH values was observed (NTP 1996a, 1996b, 1997). In rats and mice fed potassium dichromate for 9 weeks, MCV and MCH values, were decreased at the highest concentration only, which was equivalent to 8.4 and 9.8 mg chromium(VI)/ kg/day in male and female rats, respectively (NTP 1996b), and 32.2 and 48 mg chromium(VI)/kg/day in male and female mice, respectively (NTP 1996a). These effects did not occur at lower dietary concentrations equivalent to ≤2.1 or ≤2.45 mg chromium(VI)/kg/day for male and female rats, respectively, or to ≤7.35 or ≤12 mg chromium(VI)/day for male and female mice, respectively. In a multigeneration study of mice given potassium dichromate in the diet, F_1 males had decreased MCVs at dietary concentrations equivalent to 16 and 36.7 mg chromium(VI)/kg/day and decreased MCH values at

36.7 mg chromium(VI)/kg/day (NTP 1997). F_1 females had dose-related decreased MCV at concentrations equivalent to ≥7.8 mg chromium(VI)/kg/day. Since 7.8 mg chromium(VI)/kg/day was the lowest dose in the study, a no effect level was not identified. Compared to results of the drinking water studies on sodium dichromate dihydrate (NTP 2007, 2008a), hematological effects observed in the dietary studies on potassium dichromate (NTP 1996a, 1996b, 1997) occurred at higher daily doses. Differences may be related to differences in the exposure media (feed versus drinking water).

No hematological effects were observed in animals after oral exposure to chromium(III) compounds for exposure durations ranging from acute to chronic. Exposure of F344/N rats to chromium picolinate in the diet for 3 days at doses up to 506 mg chromium(III)/kg/day did not produce hematological effects (NTP 2008b). For intermediate duration exposure, no hematological effects were observed in rats exposed to chromic oxide in the diet at doses up to 1,806 chromium(III)/kg/day for 3 months (Ivankovic and Preussmann 1975), in rats and mice exposed to chromium picolinate in the diet at 506 and 1,415 mg chromium(III)/kg/day, respectively, for 3 months (NTP 2008b), or in rats chromium nicotinate in the diet at 1.5 or 0.25 mg chromium(III)/kg/day for 3 months or 38 weeks, respectively (Shara et al. 2005). For chronic exposure durations, no hematological abnormalities were found in rats exposed to 3.6 mg chromium(III)/kg/day as chromium trichloride in the drinking water for 1 year (MacKenzie et al. 1958), or in rats exposed to 0.25 mg chromium(III)/kg/day as chromium nicotinate for 2 years (Shara et al. 2007).

Musculoskeletal Effects. No information regarding musculoskeletal effects in humans exposed to oral chromium (VI) compounds was identified. The development of rhabdomyolysis was reported in a 24-year-old woman who ingested a dietary supplements containing chromium(III) picolinate (Martin and Fuller 1998). Over a 48-hour period, the patient ingested 1,200 μg of chromium(III) picolinate, equivalent to148.8 μg of chromium(III) or 2.2 μg of chromium(III)/kg body weight (based on a reported body weight of 67 kg) over a 48-hour period. Upon evaluation 4 days after initially ingesting the dietary supplement, she reported muscle pain on palpation and had muscular hypertrophy and elevated serum creatine kinase, although no myoglobin was detected in urine. In addition to chromium(III) picolinate, the dietary supplements contained numerous other substances.

Increases in serum creatine kinase (CK) activity were observed in F344/N rats following acute and intermediate exposure to sodium dichromate dihydrate in drinking water (NTP 2007). After exposure for 5 days, serum CK activity was increased in males by 31% at 31.8 mg chromium(VI)/kg/day and in females by 46% at 16.4 chromium(VI)/kg/day; after exposure for 13 weeks, serum CK activity was

increased by 70% and 50% in males and females, respectively, at 5.9 mg chromium(VI)/kg/day. Since serum CK activity increased with dose, NTP (2007) suggested that findings were consistent with muscle injury. After exposure of rats for 12 months to 2.4 mg chromium(VI)/kg/day as sodium dichromate dihydrate in drinking water, serum CK activity was increased by 64% (NTP 2008a). No information regarding muscoskeletal effects in animals exposed to oral chromium(III) compounds was identified.

Hepatic Effects. Effects on the liver have been described in case reports of humans who had ingested chromium(VI) compounds. Liver damage, evidenced by the development of jaundice, increased bilirubin, and increased serum lactic dehydrogenase, was described in a case of a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L (Fristedt et al. 1965). In a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate, high levels of the liver enzymes, glutamic-oxaloacetic transaminase (aspartate aminotransferase) and glutamic-pyruvic transaminase (alanine aminotransferase), were found in the serum 24 hours after ingestion. Upon postmortem examination, the liver had marked necrosis (Kaufman et al. 1970). Fatty degeneration of the liver was observed on autopsy of a 35-year-old female who died after ingesting approximately 257 mg chromium(VI)/kg (assuming a70-kg body weight) as chromic acid in a suicide (Loubieres et al. 1999).

Effects on the liver of rats and mice exposed to oral chromium(VI) compounds for acute, intermediate and chronic durations have been detected by biochemical and histochemical techniques. In male and female F344/N rats exposed to 4.0 and 4.1 mg chromium(VI)/kg/day, respectively, as disodium dichromate in drinking water for 5 days, serum alanine aminotransferase (ALT) activity was increased by 15 and 30%, respectively (NTP 2007). After 14 weeks of exposure, serum ALT activity was increased by 14% in male rats and by 30% in female rats and serum sorbital dehydrogenase (SDH) activity was increased by 77% in male rats and 359% in female rats at 1.7 mg chromium(VI)/kg/day (NTP 2007). In females, morphological changes to the liver included cellular histiocyte infiltration and chronic focal inflammation at doses of 3.5 and 20.9 mg chromium(VI)/kg/day, respectively; no morphological changes were observed in male rats, indicating that female rats may be more sensitive than males. However, similar exposure to B6C3F1 mice to 27.9 mg chromium(VI)/kg/day for 14 weeks produced no effects on serum liver enzymes or hepatic morphology (NTP 2007). Increased serum ALT and aspartate aminotransferase (AST) activities and hepatic morphological changes (vacuolization, increased sinusoidal space, and necrosis) were observed in rats exposed to 1.3 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 22 weeks (Acharya et al. 2001). Increased serum ALT (253%) and histopathological changes (focal necrosis and degeneration with changes in vascularization) were reported

in Wistar rats exposed to chromium(VI) (compound not specified) in drinking water for 10 weeks (Rafael et al. 2007). Rats treated by gavage with 13.5 mg chromium(VI)/kg/day as potassium chromate for 20 days had increased accumulations of lipids (Kumar and Rana 1982) and changes and relocalization of liver enzymes (alkaline phosphatase, acid phosphatase, glucose-6-phosphatase, cholinesterase, and lipase) (Kumar et al. 1985), as determined by histochemical means. In another study, no treatment-related histological changes in liver cells were observed in groups of Sprague-Dawley rats containing 24 males and 48 females that were exposed to chromium(VI) as potassium dichromate in the diet for 9 weeks followed by a recovery period of 8 weeks (NTP 1996b). Average daily ingestion of chromium(VI) for males was 1, 3, 6, and 24 mg/kg/day and 1, 3, 7, and 28 mg/kg/day for females. Although no indication of hepatic effects was found in mice exposed to ≤36.7 mg/kg/day in a multigeneration feeding study (NTP 1997), some indication of liver toxicity was found in a 9-week feeding study in BALB/c mice exposed to 1.1, 3.5, 7.4, and 32 mg chromium(VI)/kg/day for males and 1.8, 5.6, 12, and 48 mg chromium(VI)/kg/day for females (NTP 1996a). Hepatocyte cytoplasmic vacuolization occurred in 1/6 males at 3.5 mg/kg/day, 2/5 males at 7.4 mg/kg/day, and 2/6 males at 32 mg/kg/day, and in 1/12 control females, 0/12 females at 1.8 mg/kg/day, 3/12 females at 5.6 mg/kg/day, 2/12 females at 12 mg/kg/day, and 4/12 females at 48 mg/kg/day. The vacuoles were small, clear, and well demarcated, which is suggestive of lipid accumulation. The small number of animals and lack of a clear dose-response preclude a definitive conclusion as to whether this effect was toxicologically significant. For chronic exposure durations, adverse liver effects have been observed in F344/N rats and B6C3F1 mice exposed to chromium(VI) as sodium chromate dihydrate in drinking water (NTP 2008a). In male rats exposed for 1 year to 0.77 mg chromium(VI)/kg/day, serum ALT activity was increased by 156%. After exposure for 2 years, histopathological examination of the liver showed the following morphological changes, with females of both species appearing more sensitive than males: chronic inflammation (2.1 chromium(VI)/kg/day), histiocytic cellular infiltration (5.9 chromium(VI)/kg/day) and basophilic foci (0.77 chromium(VI)/kg/day) in male rats; chronic inflammation (0.24 mg chromium(VI)/kg/day), histiocytic cellular infiltration (0.94 mg chromium(VI)/kg/day) and fatty change (0.94 mg chromium(VI)/kg/day) in female rats; clear cell and eosinophilic foci in male mice (5.9 mg chromium(VI)/kg/day); and histiocytic cellular infiltration (0.38 mg chromium(VI)/kg/day) and chronic inflammation (3.1 mg chromium(VI)/kg/day) in female mice (NTP 2008a). No morphological changes, however, were detected in the livers of rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year (MacKenzie et al. 1958).

No evidence of liver damage has been observed in rats and mice treated with oral chromium(III) compounds for intermediate and chronic exposure durations, based on histopathological examination of

the liver. For intermediate-duration exposures, no morphological changes were observed in rats exposed to 1,806 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 90 days (Ivankovic and Preussmann 1975), rats exposed to 9 mg chromium(III)/kg/day as chromium chloride or chromium picolinate in the diet for 20 weeks (Anderson et al. 1997b), rats exposed to 506 mg chromium(III)/kg/day and mice exposed to 1,415 mg chromium(III)/kg/day as chromium picolinate in the diet for 14 weeks (NTP 2008b; Rhodes et al. 2005), or rats exposed to chromium nicotinate in the diet at 1.5 mg chromium(III)/kg/day for 14 weeks or 0.25 mg chromium(III)/kg/day as chromium nicotinate for 38 weeks (Shara et al. 2005, 2007). For chronic-duration exposures, histological examination revealed no morphological changes in the livers of rats exposed to chromium oxide in the diet 5 days/week at 2,040 mg chromium(III)/kg/day for 2 years (Ivankovic and Preussmann 1975), rats exposed to 3.6 mg chromium(III)/kg/day as chromium trichloride in the drinking water for 1 year (MacKenzie et al. 1958), of rats exposed to 513 mg chromium(III)/kg/day and mice exposed to 781 mg chromium(III)/kg/day as chromium picolinate in the diet for 2 years (NTP 2008b), rats exposed to 0.25 mg chromium(III)/kg/day as chromium nicotinate in the diet for 2 years (Shara et al. 2005, 2007), or rats exposed to 0.46 mg chromium(III)/kg/day as chromium acetate in the drinking water for 2–3 years (Schroeder et al. 1965).

Renal Effects. Case studies were located regarding renal effects in humans after oral exposure to chromium(VI) compounds. Acute renal failure, characterized by proteinuria, and hematuria, and followed by anuria, developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis (Fristedt et al. 1965). Necrosis of renal tubules was found upon autopsy of a 22-month-old boy who died after ingesting an unknown amount of sodium dichromate (Ellis et al. 1982) and of a 17-year-old boy who died after ingesting 29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983). A fatal ingestion of 4.1 mg chromium(VI)/kg as a chromic acid solution in a 44-year-old man resulted in acute tubular necrosis and renal failure (Saryan and Reedy 1988). A 14-year-old boy who ingested 7.5 mg chromium(VI)/kg as potassium dichromate died from renal failure 8 days after he was admitted to the hospital. Upon postmortem examination, the kidneys were pale, enlarged, and necrotic with tubular necrosis and edema (Kaufman et al. 1970). Acute renal failure and necrosis also observed on autopsy of a 35-year-old woman who died following ingestion of 357 mg chromium(VI)/kg as chromic acid (Loubieres et al. 1999). Another case study of an 18-year-old woman who ingested a few grams of potassium dichromate reported proteinuria, oliguria, and destruction of the tubular epithelium of the kidneys. She regained renal function following dialysis (Sharma et al. 1978). Proteinuria and oliguria were also observed after ingestion of potassium dichromate by a 25-year-old woman (Goldman and Karotkin 1935).

Acute renal failure was reported in a 24-year-old man who ingested the an unknown quantity of a dietary supplement (Arsenal X®) containing chromium picolinate daily for 2 weeks (Wani et al. 2006). Serum creatinine was elevated approximately 3 times above the normal range, blood urea nitrogen was elevated slightly above normal range, urinalysis was positive for protein, and renal biopsy showed acute tubular necrosis. The patient developed severe impairment of renal function that required hemodialysis. Renal function improved within 4 weeks of discontinuation of treatment with the supplement. Chemical analysis of the dietary supplement was not conducted and the patient's plasma chromium levels were not obtained. Adverse renal effects were reported in a 49-year-old woman who ingested 600 µg of chromium(III) picolinate (equivalent to 74.4 µg chromium(III)/day or 1.1 µg chromium(III)/kg/day, assuming a body weight of 70 kg) daily for 6 weeks (Wasser et al. 1997). The patient was evaluated approximately 5 months after initiating the 6-week treatment. Serum creatinine levels were approximately 6 times above the normal range, blood urea nitrogen was approximately 4 times above the normal range, and trace amounts of blood were found in the urine. Renal biopsy showed severe chronic active interstitial nephritis. After 2 months of treatment with prednisone, serum creatinine levels were approximately 4 times above the normal range (other values were not reported) Chemical analysis of the dietary supplement was not conducted and the patient's plasma chromium levels were not obtained.

Renal effects have been observed in animals following oral exposure to chromium(VI), but not chromium(III), compounds. Effects on the kidneys of rats exposed to potassium chromate have been detected by biochemical and histochemical techniques. Rats treated by gavage with 13.5 mg chromium(VI)/kg/day for 20 days had increased accumulation of lipids and accumulated triglycerides and phospholipids in different regions of the kidney than controls (Kumar and Rana 1982). Similar treatment of rats also resulted in inhibition of membrane and lysosomal enzymes (alkaline phosphatase, acid phosphatase, glucose-6-phosphatase, and lipase) in the kidneys (Kumar and Rana 1984). Histopathological changes to the kidneys, including vacuolization in glomeruli, degeneration of basement membrane of Bowman's capsule, and renal tubular epithelial degeneration, were observed in Wistar rats exposed to 1.3 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 22 weeks (Acharya et al. 2001). Oliguria and proteinuria were observed in Wistar rats exposed to 100 mg chromium(VI)/kg/day as sodium chromate in drinking water for 28 days (Diaz-Mayans et al. 1986). However, histological examination revealed no morphological changes in the kidneys of rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in drinking water for 1 year (MacKenzie et al. 1958). Results of studies in rats and mice conducted by NTP (1996a, 1996b, 1997, 2007, 2008a) also show no histopathological changes in kidneys following intermediate-or chronic-duration exposure to

chromium(VI) compounds in the diet or drinking water. The respective highest doses of chromium(VI) tested for intermediate and chronic exposure durations were 48 mg chromium(VI)/kg/day in mice exposed to dietary potassium dichromate for 9 weeks (NTP 1996a) and 8.7 chromium(VI)/kg/day, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a).

Exposure of mice and rats to chromium(III) compounds (chromium acetate, chromium nicotinate, chromium oxide, chromium picolinate, and chromium trichloride) in food or drinking water for up to 2 years did not result in renal damage, based on histopathological examination of kidneys (Anderson et al. 1997b; Ivankovic and Preussmann 1975; MacKenzie et al. 1958; NTP 2008b; Schroeder et al. 1965; Shara et al. 2005, 2007). The respective highest doses of chromium(III) tested for intermediate and chronic exposure durations were 1,806 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 3 months and 2,040 mg chromium(III)/kg/day chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975). Renal function was not assessed in these studies.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to chromium(VI) or (III) compounds. Serum prolactin levels were decreased by 59% in male Wistar rats exposed to 74 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 30 days (Quinteros et al. 2007). Histopathological examination of the endocrine tissues (including adrenal gland, parathyroid, and thyroid) has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydrate) and chromium(III) (as chromium nicotinate and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (NTP 2007, 2008a, 2008b; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,415 and 781 mg chromium(III)/kg/day, respectively, as chromium picolinate in the diet for 3 months and 2 years, respectively (NTP 2008b; Rhodes et al. 2005). Endocrine function was not assessed in these studies.

Dermal Effects. Administration of 0.04 mg chromium(VI)/kg as potassium dichromate in an oral tolerance test exacerbated the dermatitis of a building worker who had a 20-year history of chromium contact dermatitis. A double dose led to dyshidrotic lesions (vesicular eruptions) on the hands (Goitre et al. 1982). Dermatitis in 11 of 31 chromium-sensitive individuals worsened after ingestion of 0.036 mg chromium(VI)/kg as potassium dichromate (Kaaber and Veien 1977). The sensitizing exposures were not

discussed or quantified. No information regarding dermal effects of oral exposure of humans to chromium(III) compounds was identified.

No studies were located regarding noncancer dermal effects in animals after oral exposure to chromium(VI) or chromium(III) compounds. The effect of oral exposure to chromium(VI) compounds on increased susceptibility of hairless mice to ultraviolet light-induced skin cancer is discussed in Section 3.2.2.7 (Oral Exposure, Cancer).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to chromium(VI) or chromium(III) compounds. Histopathologic examination of rats and mice exposed to sodium dichromate dihydrate in drinking water at 20.9 and 27.9 mg chromium(IV)/kg/day, respectively, for 3 months or at 7.0 and 8.7 mg chromium(IV)/kg/day, respectively, for 2 years revealed normal morphology of the ocular tissue (NTP 2007, 2008a). Similar negative findings were observed in rats and mice exposed to chromium(III) as dietary chromium picolinate at 506 and 1415 mg chromium(III)/kg/day, respectively, for 3 months or at 313 and 781 mg chromium(III)/kg/day, respectively, for 2 years (NTP 2008b).

Body Weight Effects. Studies reporting body weight effects in humans exposed to chromium(VI) were not identified. The potential beneficial effect of dietary supplementation with chromium(III) (as chromium picolinate or other chromium(III) compounds) to aid in weight loss and increase lean body mass has been reported. Although the role of chromium(III) in the regulation of lean body mass, percentage body fat, and weight reduction is highly controversial with negative and positive results being reported in the literature, studies assessing these effects were not designed to evaluate weight loss as a toxicological end point (Anderson 1998b). Thus, body weight effects associated with dietary supplementation with chromium(III) compounds is not considered adverse (see Section 2.2 for additional information).

Significant decreases in body weight have been reported in several intermediate-duration oral chromium(VI) studies in animals (Bataineh et al. 1997; Chowdhury and Mitra 1995; De Flora et al. 2006; Elbetieha and Al-Hamood 1997; NTP 1996a, 1996b, 2007; Quinteros et al. 2007; Yousef et al. 2006). However, it should be noted that high concentrations of chromium in drinking water decrease palatability of water, resulting in decreased water consumption; thus, decreased body weight may, in part, be due to decreased water consumption, in addition to other causes. In male rats exposed to 73 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 30 days, body weight was decreased

by 11.6% (Quinteros et al. 2007). A 19% decrease in body weight gain was observed male rats exposed to 42 mg chromium(VI)/kg/day (Bataineh et al. 1997) and a 10% decrease was reported in male mice exposed to 6 mg chromium(VI)/kg/day (Elbetieha and Al-Hamood 1997) as potassium dichromate in drinking water for 12 weeks. Note that daily doses in the study by Elbetieha and Al-Hamood (1997) may be overestimated, due to decreased water consumption in the higher concentration group (decrease was not quantified by study authors). Final body weight was decreased in rats and mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks (NTP 2007). In rats, body weight was decreased in males by 11% at 11.2 mg chromium(VI)/kg/day and in females by 6% at 20.9 mg chromium(VI)/kg/day; in mice, body weight was decreased by 6% in males at 3.1 mg chromium(VI)/kg/day and by 8% in females at 5.2 mg chromium(VI)/kg/day. Decreases in body weight were also observed in male mice (9.3%) and female (13.5%) mice exposed to 165 and 14 mg chromium(VI)/kg/day as sodium dichromate dihydrate in drinking water for 210 days (De Flora et al. 2006). Gavage administration of 40 or 60 mg chromium(VI)/kg/day as sodium dichromate for 90 days resulted in 57 and 59% decreases in body weight gain, respectively (Chowdhury and Mitra 1995). In contrast, no changes in body weight gain were seen in rats or mice exposed to 9.8 or 48 mg chromium(VI)/kg/day, respectively, as potassium dichromate in the diet for 9 weeks (NTP 1996a, 1996b) or in rabbits administered 3.6 mg chromium(VI)/kg/day by gavage as potassium dichromate (Yousef et al. 2006). No alterations in body weight gain were observed in rats chronically exposed (1 year) to 3.6 mg chromium(VI)/kg/day as potassium chromate in drinking water (Mackenzie et al. 1958). In contrast, final body weight was decreased by 12% decrease male rats at 5.9 mg chromium(VI)/kg/day and by 11% in female rats at 7.0 mg chromium(VI)/kg/day as sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a).

Several studies have examined the effect of exposure to potassium dichromate in drinking water on maternal body weight gain. An acute exposure (9 days) resulted in 8 and 24% decreases in body weight gain in pregnant mice exposed to 101 or 152 mg chromium(VI)/kg/day, respectively (Junaid et al. 1996b). Similarly, a decrease in maternal body weight gain was observed in pregnant mice exposed to 98 mg chromium(VI)/kg/day as potassium dichromate for 19 days (Trivedi et al. 1989). Reduced maternal body weight gains of 8, 14, and 21% were observed in rats exposed to 37, 70, or 87 mg chromium(VI)/kg/day for 20 days prior to mating (Kanojia et al. 1996). Similar decreases in body weight gain (18 and 24%) were observed in rats exposed to 89 or 124 mg chromium(VI)/kg/day, respectively, for 3 months prior to mating (Kanojia et al. 1998). However, no alterations in maternal body weight gain were observed in a continuous breeding study in which rats were exposed to 36.7 mg chromium(VI)/kg/day as potassium dichromate in the diet (NTP 1997).

Conflicting results have been reported for alterations in body weight in rats and mice exposed to oral chromium(III) compounds for intermediate and chronic exposure durations. Dietary exposure to 9 mg chromium(III)/kg/day as chromium chloride or chromium picolinate for 20 weeks (Anderson et al. 1997b) or 3.6 mg chromium(III)/kg/day as chromium chloride (Mackenzie et al. 1958) did not result in significant alterations in body weight gain. No alterations on body weight were observed in rats or mice exposed to dietary chromium picolinate for 14 weeks at doses up to 506 and 1,415 mg chromium(III)/kg/day, respectively (NTP 2008b; Rhodes et al. 2005) or in male and female mice exposed to chromic potassium sulfate in drinking water for 210 days at doses of 165 and 140 mg chromium(III)/kg/day, respectively (De Flora et al. 2006). No change in body weight was observed in male and female rats exposed to dietary chromium nicotinate for 90 days at 1.5 and 1.2 mg chromium(III)/kg/day, respectively (Shara et al. 2005); however, body weight was decreased by 8.1% in males at 0.22 mg chromium(III)/kg/day and by 11.4% in females at 0.25 mg chromium(III)/kg/day following exposure to dietary chromium nicotinate for 38 weeks (Shara et al. 2007). Exposure to chromium chloride in drinking water resulted in 14 and 24% decreases in body weight gain in rats exposed to 40 mg chromium(III)/kg/day for 12 weeks (Bataineh et al. 1997) and male mice exposed to 5 mg chromium(III)/kg/day for 12 weeks (Elbetieha and Al-Hamood 1997), respectively. Note that daily doses in the study by Elbetieha and Al-Hamood (1997) may be overestimated, due to decreased water consumption in the higher concentration group (decrease was not quantified by study authors). No alterations in body weight gain were observed in rats or mice exposed to 0.46 or 0.48 mg chromium(III)/kg/day, respectively, as chromium acetate for a lifetime (Schroeder et al. 1964, 1965), or in mice and rats exposed to dietary chromium picolinate for 2 years at doses up to 313 and 781 mg chromium(III)/kg/day, respectively (NTP 2008b). However, exposure to dietary chromium nicotinate for 2 years resulted in a 14.9% decrease in male rats at 0.22 mg chromium(III)/kg/day and a 9.6% decrease in female rats at 0.25 mg chromium(III)/kg/day (Shara et al. 2007).

Metabolic Effects. Metabolic acidosis was observed in a 35-year-old female died after ingesting approximately 257 mg chromium(VI)/kg (assuming a 70-kg body weight) as chromic acid in a suicide (Loubieres et al. 1999). No information on adverse metabolic effects of chromium(III) compounds in humans was identified. Serum glucose was elevated by 65% in male Wistar rats exposed to 3.7 mg chromium(VI)/kg/day (compound not specified) in drinking water for 10 weeks (Rafael et al. 2007). No changes in serum glucose were reported in rats and mice exposed to sodium dichromate dihydrate in drinking water for 3 months at doses up to 27.9 mg chromium(VI)/kg/day or for 2 years at doses up to 8.7 mg chromium(VI)/kg/day (NTP 2007, 2008a); however, data on serum glucose were not presented in

the study reports. No information on adverse metabolic effects of chromium(III) compounds in animals was identified.

3.2.2.3 Immunological and Lymphoreticular Effects

The only reported effect of orally exposed humans on the immune system was the exacerbation of chromium dermatitis in chromium-sensitive individuals, as noted for dermal effects in Section 3.2.2.2. Sensitization of workers, resulting in respiratory and dermal effects, has been reported in numerous occupational exposure studies. Although the route of exposure for initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal routes, information on the exposure levels producing sensitization by the oral route was not identified. Additional information on contact dermatitis in sensitized workers is provided in Section 3.2.3.3 (Dermal Exposure, Immunological and Lymphoreticular Effects).

Oral exposure of animals to chromium(VI), but not chromium (III), compounds resulted in functional and histopathological changes to the immune system (NTP 2007, 2008a; Snyder and Valle 1991). Splenocytes prepared from rats given potassium chromate in drinking water at 16 mg chromium(VI)/kg/day for 3 weeks showed an elevated proliferative response of T-and B-lymphocytes to the mitogens, concanavalin A and liposaccharide, compared with splenocytes from control rats. A 5-fold enhancement of the proliferative response to mitomycin C was also seen when splenocytes from rats exposed for 10 weeks were incubated with splenocytes from nonexposed rats and additional chromium (0.1 mg chromium(VI)/L) was added to the incubation compared to the system without added chromium. It was suggested that these increased proliferative responses represent chromium-induced sensitization (Snyder and Valle 1991). Microscopic changes to lymphatic tissues, including histiocytic cellular infiltration of mesenteric and/or pancreatic nodes, were observed in rats and mice exposed to sodium dichromate dihydrate in drinking water for 3 months or 2 years (NTP 2007, 2008a). Following 3 months of exposure, histiocytic cellular infiltration was observed in male and female rats at 1.7 and 20.9 mg chromium(VI)/kg/day, respectively, and in mice at 3.1 mg chromium(VI)/kg/day (NTP 2007). After 2 years of exposure, histiocytic cellular infiltration and hemorrhage of mesenteric lymph nodes were observed in male rats at 0.77 mg chromium(VI)/kg/day (NTP 2008a). Histiocytic cellular infiltration of lymph nodes, but not hemorrhage, was observed at 2.4 mg chromium(VI)/kg/day in female rats and at 0.38 mg chromium(VI)/kg/day in mice (NTP 2008a). No abnormal histopathological changes were observed in lymphatic tissues of rats and mice exposed to oral chromium(III) (as chromium nicotinate and chromium picolinate) for 3 months or 2 years (NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007).

These highest doses of chromium(III) tested for intermediate and chronic exposure durations were 1,415 mg chromium(III)/kg/day as chromium picolinate in feed for 3 months and 781 mg chromium(III)/kg/day as chromium picolinate in feed for 2 years. The NOAEL and LOAEL values are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

3.2.2.4 Neurological Effects

The only information regarding neurological effects in humans after oral exposure to chromium(VI) is the report of an enlarged brain and cerebral edema upon autopsy of a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate. These effects may be the result of accompanying renal failure (Kaufman et al. 1970). No information was identified on neurological effects in humans after oral exposure to chromium(III) compounds.

A decrease in motor activity and balance was reported in rats given 98 mg chromium(VI)/kg/day as sodium chromate in drinking water for 28 days (Diaz-Mayans et al. 1986). No additional studies were identified evaluating neurological function in laboratory animals following oral exposure to chromium(VI) or chromium(III) compounds. Histopathological examination of the brain and nervous system tissues has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydate) and chromium(III) (as chromium nicotinate, chromium oxide, and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (Ivankovic and Preussmann 1975; NTP 2007, 2008a, 2008b; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,806 and 2,040 mg chromium(III)/kg/day, respectively, as chromium oxide in the diet 5 days/week (Ivankovic and Preussmann 1975). None of theses studies conducted more sensitive neurological, neurochemical, or neurobehavioral tests.

The NOAEL and LOAEL values are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to chromium(VI) or chromium(III) compounds.

A number of studies have reported reproductive effects in animals orally exposed to chromium(VI). Functional and morphological effects on male reproductive organs have been reported in monkeys, rats, mice, and rabbits. In a series of studies in male bonnet monkeys (*Macaca radiate*) (Aruldhas et al. 2004, 2005, 2006; Subramanian et al. 2006), decreased testes weight, histopathological changes of the epididymis, disrupted spermatogenesis, and decreased sperm count and motility were observed following exposure to 2.1, 4.1, and 8.3 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 180 days. Histopathological changes, characterized by ductal obstruction and development of microcanals, germ cell depletion, hyperplasia of Leydig cells, and Sertoli cell fibrosis, increased in severity with dose. Sperm count and motility were significantly decreased, with effects exhibiting duration- and dose-dependence (Subramanian et al. 2006). After exposure for 2 months, significant decreases in sperm count (by 13%) and motility (by 12%) were observed only in monkeys treated with 8.3 mg chromium(VI)/kg/day, whereas after 6 months, dose-dependent decreases in sperm count and motility were observed at doses of ≥2.1 mg chromium(VI)/kg/day. No effects on sperm count or motility were observed in monkeys treated with 1.1 chromium(VI)/kg/day, although histopathological assessment of male reproductive tissues was not conducted in this dose group.

Exposure of male Wistar rats to 5.2 and 10.4 mg chromium(VI)/kg/day administered as chromic acid by gavage for 6 days produced decreased sperm count and histopathological changes to the testes (Li et al. 2001). Similar effects occurred at both doses, with sperm count decreased by 75.5 and 79.6% at 5.2 and 10.4 mg chromium(VI)/kg/day, respectively, and the “level of abnormal sperm" was increased 2.4-fold and 2.8-fold at 5.2 and 10.4 mg chromium(VI)/kg/day, respectively. Histopathological assessment of testes showed decreased diameter of seminiferous tubules and germ cell rearrangement within the tubules. In contrast, exposure of F344/N male rats to chromium(VI) as sodium dichromate dihydrate in drinking water at doses up to 20.9 or mg chromium(VI)/kg/day for 3 months or 5.9 mg chromium(VI)/kg/day for 2 years did not produce histopathological changes to male reproductive tissues (NTP 2007, 2008a).

Male reproductive effects were observed in groups of 10 mature male Charles Foster strain rats administered 20, 40, and 60 mg chromium(VI)/kg/day as sodium dichromate(VI) by gavage for 90 days (Chowdhury and Mitra 1995). Testis weight, population of Leydig cells, seminiferous tubular diameter,

testicular protein, DNA, and RNA were all significantly reduced at 40 and 60 mg chromium(VI)/kg/day. The number of spermatogonia was not affected by treatment; however, resting spermatocytes (high dose), pachytene spermatocytes (high dose, intermediate dose) and stage-7 spermatid (high and intermediate doses) counts were significantly reduced and were treatment related. Testicular activity of succinic dehydrogenase was significantly lowered in the two high-dose groups, testicular cholesterol concen trations were elevated in the highest-dosed group, and both serum testosterone and testicular levels of 3β-Δ^5-hydroxysteroid dehydrogenase were significantly lowered. The authors also determined that the total testicular levels of ascorbic acid in the two higher-dosing groups was about twice that of the control values whereas, in the highest-treated group the total ascorbic acid levels were about half those of controls. At the low dose (20 mg/kg/day), testicular protein, 3β-Δ^5-hydroxysteroid dehydrogenase, and serum testosterone were decreased. The authors indicated that chromium enhanced levels of the vitamin, but at the highest dose, testicular levels became exhausted, thus decreasing the ability of the cells to reduce chromium(VI).

Significant alterations in sexual behavior and aggressive behavior were observed in male Sprague-Dawley rats exposed to 42 mg chromium(VI)/kg/day as potassium dichromate in the drinking water for 12 weeks (Bataineh et al. 1997). The alterations in sexual behavior included decreased number of mounts, lower percentage of ejaculating males, and increased ejaculatory latency and postejaculatory interval. The adverse effects on aggressive behavior included significant decreases in the number of lateralizations, boxing bouts, and fights with the stud male and ventral presenting. No significant alterations in fertility were observed when the exposed males were mated with unexposed females.

Reduced sperm count and degeneration of the outer cellular layer of the seminiferous tubules were observed in BALB/c mice exposed for 7 weeks to 15.2 mg chromium(VI)/kg/day as potassium dichromate in the diet (Zahid et al. 1990). Morphologically altered sperm occurred in mice given diets providing 28 mg chromium(VI)/kg/day as potassium dichromate. No effect was found on testis or epididymis weight, and reproduction function was not assessed. In contrast, an increase in testes weight was observed in Swiss mice exposed in drinking water to 6 mg chromium(VI)/kg/day as potassium dichromate for 12 weeks. At the next highest dose (14 mg chromium(VI)/kg/day), decreases in seminal vesicle and preputial gland weights were observed, although no information of sperm count was reported (Elbetieha and Al-Hamood 1997). At the higher exposure level, mice consumed less water (data on water consumption were not included in the study report); thus, the daily chromium(VI) dose may be overestimated for this exposure group. In studies designed to confirm or refute the findings of the Zahid et al. (1990) study, the reproductive effects of different concentrations of chromium(VI) as potassium

dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated (NTP 1996a, 1996b). Groups of 24 of each species were fed potassium dichromate(VI) in their feed continuously for 9 weeks followed by an 8-week recovery period. For mice, the average daily ingestions of chromium(VI) were 1.05, 3.5, 7.5, and 32.2 mg/kg/day for males and for rats were 0.35, 1.05, 2.1, and 8.4 mg/kg/day (NTP 1996b). Microscopic examinations of the testes and epididymis for Sertoli nuclei and preleptotene spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects. Similarly, exposure to sodium dichromate dihydrate in drinking water did not produce morphological changes to male reproductive organs of B6C3F1 mice exposed to 27.9 or 5.9 mg chromium(VI)/kg/day for 3 months or 2 years, respectively, or affect sperm count or motility in male B6C3F1, BALB/c and C57BL/6N mice exposed to 8.7 mg chromium(VI)/kg/day for 3 months (NTP 2007, 2008a).

Reduced sperm count and plasma testosterone were observed in male New Zealand rabbits administered 3.6 mg chromium(VI)/kg/day as potassium dichromate for 10 weeks by gavage (Yousef et al. 2006). Sperm count was decreased by 18%, total sperm output was decreased by 25.9%, total number of mobile sperm was decreased by 34.3%, and number of dead sperm increased by 23.9%. In addition, relative weight of testes and epididymis were decreased by 22.2% and plasma testosterone was decreased by 20.8%.

Effects of chromium(VI) on the female reproductive system have been reported in rats and mice. Murthy et al. (1996) reported a number of reproductive effects in female Swiss albino mice exposed to potassium dichromate in drinking water for 20 days. The observed effects included a significant reduction in the number of follicles at different stages of maturation at ≥60 mg chromium(VI)/kg/day, reduction in the number of ova/mice at ≥120 mg chromium(VI)/kg/day, significant increase in estrus cycle duration at 180 mg chromium(VI)/kg/day, and histological alterations in the ovaries (e.g., proliferated, dilated, and congested blood vessels, pyknotic nuclei in follicular cells, and atretic follicles) at ≥120 mg chromium(VI)/kg/day. The severity of the reproductive effects appeared to be dose-related. In an ancillary study, electron microscopy of selected ovarian tissues revealed ultrastructural changes (disintegrated cell membranes of two-layered follicular cells and altered villiform cristae of mitochondria and decreased lipid droplets in interstitial cells) in mice exposed to 1.2 mg chromium(VI)/kg/day for 90 days; the toxicological significance of these alterations is not known. The study authors suggest that the effects observed in the interstitial cells may be due to a reduction in lipid synthesizing ability, which could lead to decreased steroid hormone production. An increase in relative ovarian weight was observed in female Swiss mice exposed for 12 weeks to 14 mg chromium(VI)/kg/day as potassium dichromate (Elbetieha and Al-Hamood 1997) , although the calculated daily dose may be overestimated, due to

decreased water consumption in the higher concentration group (decrease was not quantified by study authors). In contrast, microscopic examinations of the ovaries showed no treatment-related effects in female BALB/c mice and Sprague-Dawley rats fed up to 9.8 and 48 mg chromium(VI)/kg/day, respectively, as potassium dichromate(VI) in the diet continuously for 9 weeks followed by an 8-week recovery period (NTP 1996b). Similarly, exposure of female F344/N rats and B6C3F1 mice to sodium dichromate dihydrate in drinking water at doses up to 20.9 and 27.9 mg chromium(VI)/kg/day, respectively, for 3 months or at doses up to 7.0 and 8.6 mg chromium(VI)/kg/day, respectively, for 2 years did not produce histopathological changes to the ovaries (NTP 2007, 2008a).

Several studies have reported increases in preimplantation losses and resorptions in rats and mice exposed to chromium(VI). However, for studies evaluating high concentration of chromium, it is possible that effects may, in part, be secondary to maternal toxicity. In addition, high concentration of chromium in food and water decrease palatability and can result in decreased food and drinking water consumption. Exposure of pregnant mice to 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation resulted in increased preimplantation and postimplantation loss, and decreased litter size. Maternal body weight gain decreased at doses ≥98 mg chromium(VI)/kg/day (Trivedi et al. 1989). In female Swiss albino mice exposed for 20 days prior to mating to potassium dichromate in drinking water at concentrations that resulted in doses of 0, 52, 98, or 169 mg chromium(VI)/kg/day and then mated, the number of corpora lutea was decreased at 169 mg/kg/day, preimplantation loss and resorptions were increased at ≥98 mg/kg/day, and placental weights were decreased at ≥57 mg/kg/day (Junaid et al. 1996a). Increases in the number of resorptions were also found in female Swiss albino rats exposed to 37, 70, or 87 mg chromium(VI)/kg/day (as potassium dichromate in the drinking water) for 20 days prior to mating (Kanojia et al. 1996). Additional reproductive effects observed at 70 or 87 mg chromium(VI)/kg/day include decreased number of corpora lutea, decreased number of implantations, and increased number of preimplanation losses. A treatment-related increase in the length of estrus cycle was significantly different from controls only in the 87 mg chromium(VI)/kg/day group. Decreased mating, decreased fertility, and increased pre- and postimplantation loss were observed in female Druckrey rats receiving doses of 45, 89, and 124 mg chromium(VI)/kg/day (as potassium dichromate in the drinking water) for 3 months prior to mating; the 89 and 124 mg chromium(VI)/kg/day groups exhibited increased resorptions as well (Kanojia et al. 1998). A decrease in fertility (decreased number of implantations and viable fetuses) was observed in male and female Swiss mice that were exposed to 6 mg chromium(VI)/kg/day as potassium dichromate for 12 weeks and then were mated with unexposed males and females; however, the classification of non-viable fetuses was not presented in this report (Elbetieha and Al-

Hamood 1997). An increase in the number of mice with resorptions was also observed in the exposed females.

No reproductive effects were observed in a multigeneration reproductive assessment by continuous breeding study of BALB/c mice were fed a diet containing potassium dichromate(VI). Males and females were exposed to chromium for 7 days and then 20 pairs (F_0) in each dose group were allowed to continuously mate for 85 days (NTP 1997). The mean doses of chromium(VI) in F_0 animals were 6.8, 13.5, and 30.0 mg/kg/day. Litters produced during the 85-day mating period were examined at postnatal day 1. There were no treatment related changes in average litters/pair, number of live and dead pups per litter, sex ratios, pup weights, or changes in gestational time. There were no dose related gross pathological organ differences observed for both F_0 males and females, nor any differences in organ to body weight ratios. At the highest dose the F_0 females had lower mean body weights than control animals by about 7%. There were no effects on sperm number or motility, nor were there any increases in abnormal sperm morphology. Histopathological examination of livers and kidneys from F_0 males and females showed no changes that were treatment related. F_1 litters produced after 85 days were reared by the dam until weaning on postnatal day 21 then separated and allowed to mature for about 74 days. At that time, 20 pairs were allowed to mate and produce F_2 progeny. Mean exposures to chromium(VI) to F_1 animals were determined to be 7.8, 16.0, and 36.7 mg/kg/day. F_2 litters were reared by the dam until weaning on postnatal day 21 before being sacrificed. There were no differences in F_2 average litters/pair, number of live and dead pups per litter, sex ratios, pup weights, or changes in gestational time between exposed groups and controls. There were no dose-related gross pathological organ differences observed for both F_1 males and females, nor any differences in organ to body weight ratios. No histological lesions were observed in liver and kidney cells that were dose related, nor did chromium(VI) have any effects on estrous cycling.

Studies on the reproductive effects of chromium(III) yield conflicting results. Exposure to chromium(III) as chromium oxide did not cause reproductive effects in rats. Male and female rats fed 1,806 mg chromium(III)/kg/day as chromium oxide 5 days/week for 60 days before gestation and throughout the gestational period were observed to have normal fertility, gestational length, and litter size (Ivankovic and Preussmann 1975). A study by Bataineh et al. (1997) found significant alterations in sexual behavior (reductions in the number of mounts, increased postejaculatory interval, and decreased rates of ejaculation), aggressive behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats exposed to 40 mg chromium(III)/ kg/day as chromium chloride in the drinking water for 12 weeks. Male fertility indices (assessed by

impregnation, number of implantations, and number of viable fetuses) did not appear to be adversely affected by exposure to chromium chloride, although the untreated females mated to treated males exhibited an increase in the total number of resorptions (Bataineh et al. 1997). In contrast, a decrease in the number of pregnant females was observed following the mating of unexposed females to male Swiss mice exposed to 13 mg chromium(III)/kg/day as chromium chloride (Elbetieha and Al-Hamood 1997). Impaired fertility (decreased number of implantations and viable fetuses) was also observed in females exposed to 5 mg chromium(III)/kg/day mated to unexposed males; however, no information on sperm count was reported and the definition and classification of viable fetuses were not provided (Elbetieha and Al-Hamood 1997). This study also found increased testes and ovarian weights and decreased preputial gland and uterine weights at 5 mg chromium(III)/kg/day. At lower concentrations of chromium chloride (9 mg chromium(III)/kg/day in the diet for 20 weeks), no alterations in testes or epididymis weights were observed in rats (Anderson et al. 1997b). A similar exposure to chromium(III) picolinate also did not result in testes or epididymis weight alterations (Anderson et al. 1997b). This study did not assess reproductive function. Mice exposed for 7 weeks to 9.1 mg chromium(III)/kg/day as chromium sulfate in the diet had reduced sperm count and degeneration of the outer cellular layer of the seminiferous tubules. Morphologically altered sperm occurred in BALB/c mice given diets providing 42.4 mg chromium(III)/kg/day as chromium sulfate (Zahid et al. 1990).

Exposure of rats and mice to high doses of chromium(III) compounds (chromium nicotinate and chromium picolinate) in the diet for 3 months or 2 years did not produce histopathological changes to male or female reproductive organs (NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007). In the 3-month studies on chromium picolinate, doses up to 505 and 506 mg chromium(III)/kg/day were evaluated in male and female F344/N rats, respectively, and doses up to 1,415 and 1,088 mg chromium(III)/kg/day were evaluated in male and female B6C3F1 mice, respectively; in the 2-year studies, doses up to 286 and 313 mg chromium(III)/kg/day were evaluated in male and female rats, respectively and doses up to 781 and 726 mg chromium(III)/kg/day, were evaluated in male and female mice, respectively (NTP 2008b; Rhodes et al. 2005). In addition, the 3-month study in rats and mice did not find any treatment-related effects on sperm count and motility or on estrous cycle (percentage of time spent in various estrous cycle stages or estrous cycle length, based on evaluation of vaginal cytology (NTP 2008b; Rhodes et al. 2005). Although the 3-month and 2-year studies on chromium nicotinate did not reveal any morphological changes to reproductive tissues of male and female Sprague-Dawley rats, only low doses were evaluated (up to 1.5 mg chromium(III)/kg/day for 3 months and up to 0.25 mg chromium(III)/kg/day for 2 years) (Shara et al. 2005, 2007).

As discussed in greater detail in Section 3.2.2.6, the reproductive system is also a target in the developing organism. Delayed vaginal opening and decreased relative weights of the uterus, ovaries, testis, seminal vesicle, and preputial glands were observed in mouse offspring exposed to potassium dichromate or chromium(III) chloride on gestational day 12 through lactation day 20 (Al-Hamood et al. 1998). Impaired fertility was observed in the chromium(III) chloride-exposed female offspring when they were mated with unexposed males (Al-Hamood et al. 1998); no effect on fertility was observed in the male offspring.

The highest NOAEL value and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to chromium or its compounds.

Several animal studies provide evidence that chromium(VI) is a developmental toxicant in rats and mice. A series of studies (Junaid et al. 1996a; Kanojia et al. 1996, 1998) were conducted to assess whether pre-mating exposure to potassium dichromate would result in developmental effects. In the first study, groups of 15 female Swiss albino mice were exposed to 0, 52, 98, or 169 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 20 days (Junaid et al. 1996a) and then mated with untreated males. At 52 mg chromium(VI)/kg/day, there was a 17.5% postimplantation loss over controls and a 30% decrease in fetal weight. At 98 mg/kg/day, there were decreases in the number of implantation sites, number of live fetuses, and fetal weight. There were also increases in the number of resorptions and number of pre- and postimplantation losses. At 169 mg chromium(VI)/kg/day, there was 100% preimplantation loss. The fetuses in the 98 mg/kg/day group had higher numbers of subdermal hemorrhagic patches and kinky short tails and decreased fetal body weight and crown rump length. Although there were no major skeletal abnormalities in any other treated animals, there was a significant reduction in ossification at 52 mg chromium(VI)/kg/day (53% compared to 12% for controls) and significant reduction in ossification in caudal, parietal and interparietal bones of fetuses at 98 mg chromium(VI)/kg/day. There were no significant soft tissue deformities in any of the treated fetuses. Although dosing occurred prior to mating, internal chromium levels remaining in females after mating may have been toxic to the conceptus that caused adverse developmental effects.

In the second study, female Swiss albino rats were exposed to potassium dichromate concentrations in the drinking water resulting in doses of 37, 70, or 87 mg chromium(VI)/kg/day for 20 days prior to mating (Kanojia et al. 1996). Lower gestational weight gain, increased postimplantation loss, and decreased number of live fetuses were observed in all treatment groups, relative to controls. Increased incidences of reduced fetal ossification in fetal caudal bones were reported at the 70 and 87 mg chromium(VI)/kg/day dose levels; additionally, the 87 mg chromium(VI)/kg/day dose group of fetuses exhibited increased incidences of reduced ossification in parietal and interparietal bones, as well as significant incidences of subdermal hemorrhagic thoracic and abdominal patches (42%), kinky tails (42%), and short tails (53%), relative to 0% in controls. No treatment-related gross visceral abnormalities were seen.

In the third study, groups of 10 female Druckrey rats were exposed to potassium dichromate in the drinking water for 3 months pre-mating at concentrations yielding dose levels of 45, 89, or 124 mg chromium(VI)/kg/day (Kanojia et al. 1998). Reduced maternal gestational weight gain, increased pre- and postimplantation loss, reduced fetal weight, fetal subdermal hemorrhagic thoracic and abdominal patches, increased chromium levels in maternal blood, placenta, and fetuses, and increased incidences of reduced ossification in fetal caudal bones were observed in all treatment groups. In addition, the 89 and 124 mg chromium(VI)/kg/day dose groups exhibited increased resorptions, reduced numbers of corpora lutea and fetuses per litter, reduced implantations, reduced placental weight, increased incidences of reduced ossification in fetal parietal and interparietal bones, and reduced fetal crown-rump length. No treatment-related gross visceral abnormalities were seen. A decreased number of pregnancies were observed in mated female rats administered 35.7 mg chromium(VI)/mg/day as potassium dichromate by gavage on gestational days 1–3; exposure on gestational days 4–6 decreased the number of viable fetuses and increased the number of resorptions, but did not alter the number of pregnancies (Bataineh et al. 2007).

Exposure of pregnant mice to 57 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation resulted in embryo lethal effects (i.e., increased resorptions and increased post-implantation loss), gross abnormalities (i.e., subdermal hemorrhage, decreased cranial ossification, tail kinking), decreased crown-rump length, and decreased fetal weight. The incidence and severity of abnormalities increased at higher doses. Maternal toxicity, evidenced by decreased body weight gain, occurred at doses ≥120 mg chromium(VI)/kg/day. No implantations were observed in the dams given 234 mg chromium(VI)/kg/day (Trivedi et al. 1989).

Groups of 10 female Swiss albino mice received chromium(VI) as potassium dichromate in drinking water during organogenesis on days 6–14 at levels that provided 0, 53.2, 101.1, and 152.4 mg chromium(VI)/kg/day (Junaid et al. 1996b). No notable changes in behavior or clinical signs were observed in control or treated animals. Reduction of gestational weight gains of 8.2 and 30% were observed for the animals in the intermediate- and high-dose groups. The number of dead fetuses was higher in the high-dose group and fetal weight was lower in both intermediate- and high-dose groups (high dose=1.06 g, intermediate dose=1.14 g) as compared to the control value of 1.3 g. The number of resorption sites was 0.31 for controls, 1.00 for the low dose, 1.70 for the intermediate dose, and 2.30 for the high dose, demonstrating a dose-response relationship. The studies also showed that there was a significantly greater incidence of postimplantation loss in the two highest-dose groups of 21 and 34.60% as compared to control value of 4.32%. No significant gross structural abnormalities in any of the treated dosed groups were observed except for drooping of the wrist (carpal flexure) and subdermal hemorrhagic patches on the thoracic and abdominal regions in 16% in the offspring of the high-dose group. Significant reduced ossification in nasal frontal, parietal, interparietal, caudal, and tarsal bones were observed only in the 152.4 mg chromium(VI)/kg/day-treated animals.

Impaired development of the reproductive system was observed in the offspring of female BALB/c mice exposed to 66 mg chromium(VI)/kg/day as potassium chromate in the drinking water on gestation day 12 through lactation day 20 (Al-Hamood et al. 1998). A significant delay in vaginal opening was observed. Significant decreases in the numbers of pregnant animals, of implantations, and of viable fetuses were also observed when the female offspring were mated at age 60 days with unexposed males. No developmental effects were observed in the male offspring. In pregnant rats exposed to 8 mg chromium(VI)/kg/day as potassium chromate in drinking water on gestational days 6 through 15, pre- and postimplanation losses and the number of resorbed and dead fetuses per litter were increased compared to controls (Elsaieed and Nada 2002). Fetal weight was significantly decreased by 67% and the number of visceral (renal pelvis dilatation) and skeletal (incomplete ossification of skull bone) anomalies per litter were significantly increased. No effects on fetal body weight or the number of fetuses per litter were observed in mice exposed to 4.8 mg chromium(VI)/kg/day as sodium dichromium dihydrate or 2.4 mg chromium(VI)/kg/day as potassium dichromate in drinking water on gestational days 0 through 18; however, no additional assessments on fetal development were conducted in this study (De Flora et al. 2006).

Three studies examined the developmental toxicity of chromium(III) following oral maternal exposure. In the first study, no developmental effects were observed in offspring of rats fed 1,806 mg

chromium(III)/kg/day as chromium oxide 5 days/week for 60 days before mating and throughout gestation (Ivankovic and Preussmann 1975). In contrast, reproductive effects have been observed in the offspring of mice exposed to chromium(III) chloride. Significant decreases in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males; ovaries and uterus in females) were observed in the offspring of BALB/c mice exposed to 74 mg chromium(III)/kg/day as chromium(III) chloride in the drinking water on gestation day 12 through lactation day 20 (Al-Hamood et al. 1998). A significant delay in timing of vaginal opening was also noted in the female offspring. At age 60 days, the male and female offspring were mated with unexposed animals. No significant alterations in fertility (number of pregnant animals, number of implantations, number of viable fetuses, and total number of resorptions) were observed in the exposed males. A significant decrease in the number of pregnant females (62.5 versus 100% in controls) was observed among the female offspring mated with untreated males. The conflicting results between the Ivankovic and Preussmann (1975) study and the Al-Hamood et al. (1998) study may be a reflection on the developmental end points examined or the differences in the species tested. In rats administered 33.6 mg chromium(III)/kg/day (only dose tested) by gavage as chromium chloride on gestational days 1–3, a decreased number of pregnancies were observed; however, when exposed on gestational days 4–6, no effects on pregnancy rates, implantations, viable fetuses, or resorptions were observed (Bataineh et al. 2007).

The NOAEL and LOAEL values for developmental effects in each species are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

3.2.2.7 Cancer

Studies of associations between environmental exposures to chromium and cancer outcomes in humans are limited to several ecological studies (Beaumont et al. 2008; Fryzek et al. 2001; Zhang and Li 1987). These types of studies investigate possible associations between rates of selected diseases (e.g., cancer deaths) within a geographic population and some measure of average exposure to chromium (e.g., drinking water chromium concentrations or location with respect to potential sources of exposure). Actual exposures to individuals are not determined and therefore, exposure misclassification bias often contributes to uncertainty regarding associations between outcomes and exposure. Findings from ecological studies are mixed and do not strongly support associations between cancer mortality and exposures to chromium. One study did find significantly higher stomach cancer death rates in areas where well water chromium levels had been elevated (Beaumont et al. 2008).

An ecological study of an area near a ferrochromium production plant in the Liaoning Province, China compared cancer mortality in locations that had relatively high or low chromium concentrations in well water (Beaumont et al. 2008; Zhang and Li 1987). The most recent study of the area estimated cancer mortality rates (cancers deaths per person-year in an 8-year observation period) based on mortality records for the period 1970–1978 (Beaumont et al. 2008). The province was divided into nine areas, four of which were designated as no (or low) chromium (groundwater concentration <0.001 mg Cr/L) and five which were designated as high chromium. The main sources of chromium in well water were from discharges from the plant to surface water and groundwater, which began operating in 1961. Chromium levels in well water from samples collected in the contaminated areas in 1965 (by this time, full-scale production was occurring) ranged from 0.6 to 20 mg/L with 15% of wells having concentrations >2 mg/L. Total number of cancer deaths were 80 (of 98,458 person-years) in the high chromium areas and 182 (of 252,277 person-years) in the comparison areas. Age-adjusted cancer mortality rate ratios (rate in high regions/rate in low regions) were 1.82 (95% CI 1.11–2.91) for stomach cancer, 1.15 (95% CI 0.62–2.05) for lung cancer, 0.86 (95% CI 0.53–1.36) for other cancers, and 1.13 (95% CI 0.86–1.46) for all cancer.

An ecological study of areas in Kings County and San Bernardino County, California compared cancer mortality in locations near natural gas compressor plants with areas not located near the plants (Fryzek et al. 2001). Hexavalent chromium compounds had been used as additives in cooling tower water at the gas plants during the period 1950 to approximately 1980. Mortality records for zip codes for the cities of Kettleman City (in Kings County), and Hinkely and Topock (in San Bernadino County), in which natural gas compressor plants were located, were compared to records from zip codes in Kings County and San Bernadino County, other than those encompassing these three cities.. The study included mortality records for the period 1989–1998, during which time 2,226,214 deaths were recorded. Age-adjusted cancer mortality rate ratios (rate in areas near the plant/rate in comparison areas) were 1.03 (95% CI 0.90–1.17) for lung cancer death, 0.93 (95% CI 0.87–1.00) for all cancer deaths, and 0.98 (95% CI 0.95–1.02) for all deaths.

An ecological study compared levels of chromium (and other chemicals) in drinking water in 453 Nebraska communities with death rates in these areas (Bednar and Kies 1991). Data on chromium in drinking water were obtained for the year period 1986–1987, and mortality data was obtained for the year 1986. Mean chromium concentration in drinking water was 0.002 mg/L (range <0.001–0.01). Linear correlation (Pearson) between chromium levels and death from chronic lung disease was -0.101 (p=0.03).

Chronic exposure to chromium(VI) as sodium dichromate in drinking water resulted in increased incidence of neoplasms of the digestive tract in mice and rats (NTP 2008a). Groups of 50 male and 50 female F344/N rats were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate for 2 years. NTP (2008a) calculated 2-year mean daily doses of 0, 0.6, 2.2, 6, or 17 mg sodium dichromate dihydrate/kg/day (equivalent to 0, 0.21, 0.77, 2.1 or 5.9 mg chromium(VI)/kg/day) in male rats and, 0, 0.7, 2.7, 7, or 20 mg sodium dichromate dihydrate/kg/day (equivalent to 0, 0.24, 0.94, 2.4, and 7.0 mg chromium(VI)/kg/day) in female rats. Incidences of squamous epithelial neoplasms of the oral mucosa and tongue were elevated in rats exposed to sodium dichromate compared to controls, with significant increased mortality-adjusted incidence in males at the 5.9 mg chromium(VI)/kg/day dose (15.7 versus 0% in controls, $p=0.007$), and in females at the 7.0 mg chromium(VI)/kg/day (23.9 versus 2.2% in controls, $p<0.001$). In both male and female rats, there was a significant dose trend for digestive tract neoplasms ($p<0.001$). Groups of 50 male B6C3F1 mice were exposed to 0, 14.3, 28.6, 85.7, or 257.4 mg sodium dichromate dihydrate/L, and 50 female B6C3F1 mice were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. NTP (2008a) calculated 2-year mean daily doses of sodium dichromate dihydrate in male mice of 1.1, 2.6, 7 or 17 mg/kg/day (equivalent to 0, 0.38, 0.91, 2.4 and 5.9 mg chromium(VI)/kg/day); and in female mice of 0, 1.1, 3.9, 9, or 25 mg/kg/day (equivalent to 0, 0.38, 1.4, 3.1, or 8.7 mg chromium(VI)/kg/day). Incidences of neoplasms of the of the small intestine (duodenum, jejunum, or ileum) were elevated in mice exposed to sodium dichromate compared to controls, with significant increased mortality-adjusted incidence in males at the 2.4 (15.1 versus 2.2% in controls, $p=0.032$) or 5.9 mg chromium(VI)/kg/day dose (43.8 versus 2.2% in controls, $p=0.001$), and in females at the 3.1 (36.3 versus 2,2% in controls) or 8.7 mg chromium(VI)/kg/day (45.9 versus 2.2% in controls, $p<0.001$). In both male and female mice, there was a significant dose trend for digestive tract neoplasms ($p<0.001$). NTP (2008a) concluded that the results of these studies provided clear evidence of carcinogenic activity of sodium dichromate dihydrate in male and female F344/N rats based on increased incidences of squamous cell neoplasms of the oral cavity; and clear evidence of carcinogenic activity of in male and female B6C3F1 mice based on increased incidences of neoplasms of the small intestine (duodenum, jejunum, or ileum).

The carcinogenicity of chromium(VI) was evaluated in mice exposed potassium chromate in drinking water at 9 mg chromium(VI)/kg/day for three generations (880 days) (Borneff et al. 1968). In treated mice, 2 of 66 females developed forestomach carcinoma and 9 of 66 females and 1 of 35 males developed forestomach papilloma. The vehicle controls also developed forestomach papilloma (2 of 79 females, 3 of 47 males) but no carcinoma. The incidence of forestomach tumors in the treated mice was not significantly higher than controls. Although study authors concluded that evidence of carcinogenicity

was equivocal, statistical analysis of these data (performed by Syracuse Research Corporation) using Fischer's exact test shows statistically significant increases in the incidence of adenoma or carcinomas (forestomach) (p=0.0067) and in the incidence of adenomas (forestomach) alone (p=0.027), compared to control. In this same study, coexposure to both potassium chromate and 3,4-benzpyrene in a similar protocol showed that potassium chromate did not potentiate the carcinogenicity of 3,4-benzpyrene (Borneff et al. 1968). Exposure of female hairless mice to ultraviolet light in combination with chromium(VI) as potassium chromate in drinking water at concentrations of 2.5 or 5.0 mg potassium chromate(VI)/L (approximately 0.18, or 0.35 mg chromium(VI)/kg/day) for 182 days, or in the diet at concentrations of 0, 2.5, or 5.0 mg potassium chromate(VI)/kg food (approximately 0.13, or 0.26 mg chromium(VI)/kg/day) for 26 weeks, produced an increased incidence of skin tumors compared to animals exposed to UV light alone or chromium(VI) alone (Davidson et al. 2004; Uddin et al. 2007). Exposure to chromium(VI) alone did not result in neoplasms.

Chronic exposure to chromium(III) as chromium picolinate dihydrate in the diet resulted in increased incidence of neoplasms of the preputial gland in male rats; however, no increased neoplasms were observed in female rats, or in male or female mice (NTP 2008b). Groups of 50 male and 50 female F344/N rats were fed a diet containing 0, 2,000, 10,000, or 50,000 ppm chromium picolinate monohydrate for 2 years. NTP (2008b) calculated 2-year mean daily doses of chromium picolinate monohydrate of 0, 90, 460, and 2,400 mg/kg/day (equivalent to 0, 11, 55, or 286 mg chromium(III)/kg/day) in male rats and 0, 100, 510, and 2,630 mg/kg/day (equivalent to 0, 12, 61, or 313 mg chromium(III)/kg/day) in female rats. Mortality-adjusted incidence of adenoma of the preputial gland of male rats was significantly elevated in rats that received 55 mg chromium(III)/kg/day (14.9 versus 2.2% in controls, p=0.031), but not in rats exposed to lower dose or the higher dose (286 mg chromium(III)/kg/day), and there was no significant dose trend for the neoplasm. Incidences of neoplasms were not significantly different from controls in females, including neoplasms of the clitoral gland. Groups of 50 male and 50 female F6C3F1 mice were fed a diet containing 0, 2,000, 10,000, or 50,000 ppm chromium picolinate monohydrate for 2 years. NTP (2008b) calculated 2-year mean daily doses of chromium picolinate monohydrate of 0, 250, 1,200, and 6,565 mg/kg/day (equivalent to 0, 30, 143, 2.1, or 781 mg chromium(III)/kg/day) in male mice and 100, 510, and 2,630 mg/kg/day (equivalent to 0, 29, 143, or 726 mg chromium(III)/kg/day) in female mice. No neoplasms or lesions were attributed to exposure to chromium picolinate monohydrate in male or female mice. NTP (2008b) concluded that evidence for carcinogenicity of chromium picolinate in male rats was equivocal and that the study provided no evidence of carcinogencity in mice.

No evidence of carcinogenicity was observed in male or female rats fed diets containing chromium oxide at 2,040 mg chromium(III)/kg/day 5 days/week for 2 years. Moreover, no evidence of carcinogenicity was found in the offspring of these rats after 600 days of observation (Ivankovic and Preussmann 1975).

The Cancer Effect Levels (CELs) for chromium(VI) are recorded in Table 3-3 and plotted in Figure 3-3.

3.2.3 Dermal Exposure

Some chromium(VI) compounds, such as chromium trioxide (chromic acid), potassium dichromate, potassium chromate, sodium dichromate, and sodium chromate, are very caustic and can cause burns upon dermal contact. These burns can facilitate the absorption of the compound and lead to systemic toxicity.

3.2.3.1 Death

A 49-year-old man with an inoperable carcinoma of the face was treated with chromic acid crystals. Severe nephritis occurred following the treatment with the chromium(VI) compounds. Death occurred 4 weeks after exposure (Major 1922). Twelve individuals died as a result of infection to necrotic areas of the skin that were caused by application of a salve made up with potassium chromate used to treat scabies. Renal failure was observed. Autopsies revealed fatty degeneration of the heart, hyperemia and necrosis of kidney tubules, and hyperemia of the gastric mucosa (Brieger 1920).

Single-dose dermal LD_{50} values in New Zealand rabbits exposed to chromium(VI) as sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate were determined by Gad et al. (1986). LD_{50} values ranged from 361 to 553 mg chromium(VI)/kg for females and from 336 to 763 mg chromium(VI)/kg for males. Signs of toxicity included dermal necrosis, eschar formation, dermal edema and erythema, diarrhea, and hypoactivity. The dermal LD_{50} value for chromium trioxide was 30 mg chromium(VI)/kg for combined sexes (American Chrome and Chemicals 1989). In male and female Sprague-Dawley rats, no mortalities were observed following a single dermal application of 621.6 mg chromium(III)/kg as chromium nicotinate (Shara et al. 2005).

The LD_{50} values are recorded in Table 3-5 for chromium(VI) and Table 3-6 for chromium(III).

Table 3-5 Levels of Significant Exposure to Chromium VI - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
ACUTE EXPOSURE								
Death								
Rabbit (Fischer- 344)	24 hr					30 mg/kg (LD50)	American Chrome and Chemicals 1989 CrO3 (VI)	
Rabbit (New Zealand)	once					763 M mg/kg (LD50)	Gad et al. 1986 (NH4)2Cr2O7 (VI)	
						549 F mg/kg (LD50)		
Rabbit (New Zealand)	once					403 M mg/kg (LD50)	Gad et al. 1986 K2Cr2O7 (VI)	
						490 F mg/kg (LD50)		
Rabbit (New Zealand)	once					336 M mg/kg (LD50)	Gad et al. 1986 Na2Cr2O72H2O (VI)	
						361 F mg/kg (LD50)		
Rabbit (New Zealand)	2 d					426 M mg/kg (LD50)	Gad et al. 1986 Na2CrO4 (VI)	
						553 F mg/kg (LD50)		

Table 3-5 Levels of Significant Exposure to Chromium VI - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Systemic							
Rat (NS)	once	Hepatic		0.175 Percent (%) (altered carbohydrate metabolism)		Merkur'eva et al. 1982 K2Cr2O7 (VI)	
		Dermal		0.175 Percent (%) (dermatitis)			
Gn Pig (albino)	once	Dermal			1.9 M mg/kg (skin corrosion)	Samitz 1970 K2Cr2O7 (VI)	
Gn Pig (NS)	3 d 1 x/d	Dermal		0.35 mg/kg (skin ulcers)		Samitz and Epstein 1962 K2Cr2O7 (VI)	
Rabbit (NS)	5 min or 24 hr	Ocular	0.1 M ml			Fujii et al. 1976 Na2CrO4 and Na2Cr2O7 (VI)	
Rabbit (New Zealand)	4 hr	Dermal		55 mg/kg (necrosis, erythema, edema)		Gad et al. 1986 (NH4)2Cr2O7 (VI)	
Rabbit (New Zealand)	4 hr	Dermal		47 M mg/kg (erythema, edema, necrosis)		Gad et al. 1986 K2Cr2O7 (VI)	
Rabbit (New Zealand)	4 hr	Dermal		47 M mg/kg (necrosis, erythema, edema)		Gad et al. 1986 Na2Cr2O7 (VI)	

Table 3-5 Levels of Significant Exposure to Chromium VI - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Rabbit (New Zealand)	4 hr	Dermal		42 M mg/kg (erythema, edema)		Gad et al. 1986 Na2CrO4 (VI)	
Immuno/ Lymphoret							
Human	once			0.175 Percent (%) (positive patch test)		Engebrigsten 1952 K2Cr2O7 (VI)	
Human	48 hr			0.001 Percent (%) (increased skin thicknes and blood flow)		Eun and Marks 1990 K2Cr2O7 (VI)	
Human	48 hr (NS)			1 B mg/L (positive patch test)		Hansen et al. 2003 K2Cr2O7 (VI)	
Human	48 hr			0.18 Percent (%) (positive patch test)		Hansen et al. 2006b K2Cr2O7 (VI)	
Human	48 hr			0.26 M Percent (%) (erythema)		Levin et al. 1959 CrO3 (VI)	
Human	once		0.0013 µg/mm2	0.0026 µg/mm2 (positive patch test)		Mali et al. 1966 K2Cr2O7 (VI)	
Human	once			0.018 µg/cm² (positive patch test)		Nethercott et al. 1994 K2Cr2O7 (VI)	

Table 3-5 Levels of Significant Exposure to Chromium VI - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Human	2 d			0.175 Percent (%) (positive patch test)		Newhouse 1963 K2Cr2O7 (VI)	
Human	48 hr			0.175 Percent (%) (chromium allergy)		Peltonen and Fraki 1983 K2Cr2O7 (VI)	
Human	once			0.09 mg (erythema)		Samitz and Shrager 1966 K2Cr2O7 (VI)	
Human	once			0.09 Percent (%) (positive patch test)		Wahba and Cohen 1979 K2Cr2O7 (VI)	
Human	once			0.09 Percent (%) (positive patch test)		Winston and Walsh 1951 Na2Cr2O7 (VI)	
Gn Pig (albino)	once			0.009 mg/kg (contact sensitivity)		Gross et al. 1968 K2Cr2O7 (VI)	
Gn Pig (NS)	once			0.04 F mg/kg (erythematic reaction)		Jansen and Berrens 1968 K2Cr2O7 (VI)	

Table 3-5 Levels of Significant Exposure to Chromium VI - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE							
Immuno/ Lymphoret							
Mouse (BALB/c or ICR)	18 d			0.35 Percent (%) (contact sensitivity)		Mor et al. 1988 K2Cr2O7 (VI)	
CHRONIC EXPOSURE							
Systemic							
Human	>1 yr (occup)	Dermal		0.03 M mg/m³ (ulcerated skin)		Gibb et al. 2000a CrO3 (VI)	
				0.029 M mg/m³ (dermatitis)			
				0.027 M mg/m³ (burn)			
				0.025 M mg/m³ (irritated skin)			
Human	7.5 yr avg (range 3-16 yr) (occup)	Resp		0.004 M mg/m³ (nasal septum ulceratior and perforation)		Lucas and Kramkowski 1975 CrO3 (VI)	
		Gastro		0.004 M mg/m³ (possible gastritis, ulcers			
		Dermal		0.005 M mg/m³ (chrome holes)			

avg = average; d = day(s); F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; x = times; yr = year(s)

Table 3-6 Levels of Significant Exposure to Chromium III - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
ACUTE EXPOSURE							
Systemic							
Gn Pig (NS)	3 d 1 x/d	Dermal	1 mg/kg			Samitz and Epstein 1962 Cr2(SO4)3 (III)	
Immuno/ Lymphoret							
Human	48 hr			0.37 Percent (%) (positive patch test)		Fregert and Rorsman 1964 CrCl3.6H2O (III)	
Human	48 hr (NS)			6 mg/L (positive patch test)		Hansen et al. 2003 CrCl3.6H2O (III)	
Human	48 hr			3.7 Percent (%) (positive patch test)		Hansen et al. 2006b CrCl3 (III)	
Human	once			0.16 µg/mm2 (positive patch test)		Mali et al. 1966 CrCl3 (III)	
Human	once		33 µg/cm²			Nethercott et al. 1994 CrCl3 (III)	
Human	once			0.33 mg (erythema)		Samitz and Shrager 1966 Cr2(SO4)3 (III)	
Human	once			0.08 mg (erythema)		Samitz and Shrager 1966 CrCl3 (III)	

Table 3-6 Levels of Significant Exposure to Chromium III - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Gn Pig (albino)	once			0.004 mg/kg (erythematic reaction)		Gross et al. 1968 CrCl3 (III)	
Gn Pig (NS)	once			0.03 F mg/kg (erythematic reaction)		Jansen and Berrens 1968 Cr2(SO4)3 (III)	

d = day(s); F = female; Gn Pig = guinea pig; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; x = times

3.2.3.2 Systemic Effects

Several reports of health effects in individuals treated with potassium dichromate are discussed below (Brieger 1920; Major 1922; Smith 1931). The results of these studies should be interpreted cautiously because pre-existing conditions may have contributed to the observed effects. The highest NOAEL value and all reliable LOAEL values for dermal effects in each species and duration category are recorded in Table 3-5 for chromium(VI) and Table 3-6 for chromium(III).

Respiratory Effects. Occupational exposure to chromium compounds results in direct contact of mucocutaneous tissue, such as nasal and pharyngeal epithelium, due to inhalation of airborne dust and mists of these compounds. Such exposures have led to nose and throat irritation and nasal septum perforation. Because exposure is to airborne chromium, studies noting these effects are described in Section 3.2.1.2.

A case report of a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment where he had worked for a few months noted that he also had breathing difficulties. However, because he also had many previous attacks of hay fever and asthma, it was not possible to distinguish whether his breathing difficulties were caused by or exacerbated by dermal exposure to ammonium dichromate (Smith 1931).

No studies were located regarding respiratory effects in animals after dermal exposure to chromium or its compounds.

Cardiovascular Effects. Information regarding cardiovascular effects in humans after dermal exposure to chromium or its compounds is limited. Weak, thready, and markedly dicrotic pulse developed ≈1.5 hours after a salve made up with potassium chromate to treat scabies was applied to skin of an unspecified number of individuals. Some of the people died as a result of infection to the exposed area, and autopsy revealed degeneration of the heart (Brieger 1920).

No studies were located regarding cardiovascular effects in animals after dermal exposure to chromium or its compounds.

Gastrointestinal Effects. Vomiting occurred soon after application of a salve made up of potassium chromate to the skin of an unspecified number of individuals for the treatment of scabies. Some of these

individuals died as a result of infection of the exposed area, and autopsy revealed hyperemia of the gastric mucosa (Brieger 1920).

Diarrhea was reported in New Zealand rabbits exposed to lethal concentrations of chromium(VI) compounds (Gad et al. 1986).

Hematological Effects. Severe leukocytosis, with notable increases in immature polymorphonuclear cells, myelocytes, and myeloblasts and nucleated red cells and Howell-Jolly bodies, indicative of hemolytic anemia were observed in individuals after application of a salve that contained potassium chromate to treat scabies (Brieger 1920). Leukocytosis was also described in a case report of a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment, where he had worked for a few months (Smith 1931). It should be noted that the man had a history of asthma.

No studies were located regarding hematological effects in animals after dermal exposure to chromium compounds.

Musculoskeletal Effects. Information regarding musculoskeletal effects in humans after dermal exposure to chromium or its compounds is limited to a case report. A man was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment, where he had worked for a few months. He also had tenderness and edema of the muscles of the extremities (Smith 1931).

No studies were located regarding musculoskeletal effects in animals after dermal exposure to chromium or its compounds.

Hepatic Effects. No reliable studies were located regarding hepatic effects in humans after dermal exposure to chromium compounds.

Information regarding liver effects in animals after dermal exposure to chromium or its compounds is limited. A single application of 0.5% potassium dichromate (0.175% chromium(VI)) to the shaved skin of rats resulted in increased levels of serotonin in the liver, decreased activities of acetylcholinesterase and cholinesterase in the plasma and erythrocytes, increased levels of acetylcholine in the blood, and increased glycoprotein hexose in the serum. These effects may indicate alterations in carbohydrate

metabolism (Merkur'eva et al. 1982). Application of 50 mg chromium/kg/day (specific chemical or valence state not reported) for 30 days to clipped skin under occluded conditions to female guinea pigs produced small increases in enzyme activities in liver tissue, specifically asparatate aminotransferase (17%), alanine aminotransferase (2%), acid phosphatase (16%), and gamma glutamyl transpeptidase (54%), compared to untreated controls (Mathur 2005). Microscopic evaluation of the liver showed "shrunken" hepatocytes and thickening of the walls of hepatic arteries.

Renal Effects. Acute nephritis with albuminuria and oliguria, polyuria, and nitrogen retention were observed in individuals after application of a salve that contained potassium chromate. These effects disappeared in individuals who survived. Autopsy of people who died revealed hyperemia and tubular necrosis (Brieger 1920). Acute nephritis with polyuria and proteinuria were also described in a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment where he had worked for a few months (Smith 1931). A 49-year-old man with an inoperable carcinoma of the face was treated with chromic acid crystals. Severe nephritis occurred after treatment with the chromium(VI) compound. Urinalysis revealed marked protein in the urine. Death resulted 4 weeks after exposure. A postmortem examination of the kidneys revealed extensive destruction of the tubular epithelium (Major 1922).

Application of 50 mg chromium/kg/day (specific chemical or valence state not reported) for 30 days to clipped skin under occluded conditions to female guinea pigs produced increases in enzyme activities in renal tissue, specifically asparatate aminotransferase (8%), alanine aminotransferase (96%), and acid phosphatase (4%), compared to untreated controls (Mathur 2005). Microscopic evaluation of the kidney showed lobularization of the glomerular tuft and congestion of capillaries. No additional information on renal effects of dermal exposure to chromium(VI) or chromium(III) compounds was identified.

Dermal Effects. Occupational exposure to airborne chromium compounds has been associated with effects on the nasal septum, such as ulceration and perforation. These studies are discussed in Section 3.2.1.2 on Respiratory Effects. Dermal exposure to chromium compounds can cause contact allergic dermatitis in sensitive individuals, which is discussed in Section 3.2.3.3. Skin burns, blisters, and skin ulcers, also known as chrome holes or chrome sores, are more likely associated with direct dermal contact with solutions of chromium compounds, but exposure of the skin to airborne fumes and mists of chromium compounds may contribute to these effects.

Acute dermal exposure of humans to chromium(VI) compounds causes skin burns. Necrosis and sloughing of the skin occurred in individuals at the site of application of a salve containing potassium chromate. Twelve of 31 people died as a result of infection of these areas (Brieger 1920). In another case, a man who slipped at work and plunged his arm into a vat of chromic acid had extensive burns and necrosis on his arm (Cason 1959).

Longer-term occupational exposure to chromium compounds in most chromium-related industries can cause deep penetrating holes or ulcers on the skin. A man who had worked for a few months in a planographic printing establishment, where he handled and washed sheets of zinc that had been treated with a solution of ammonium dichromate, had skin ulceration on both hands (Smith 1931).

In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, 50% of the chromate workers had skin ulcers or scars. In addition, inflammation of oral structures, keratosis of the lips, gingiva, and palate, gingivitis, and periodontis due to exposure of these mucocutaneous tissues to airborne chromium were observed in higher incidence in the chromate workers than in controls. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3 air); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m^3 air) (PHS 1953). Among 258 electroplating workers exposed to chromium trioxide fumes at 0.1 mg chromium(VI)/m^3 for <1 year, 5% developed dental lesions, consisting of yellowing and wearing down of the teeth (Gomes 1972).

Chronic exposure of chrome chemical production workers produced dermal symptoms, including irritated and ulcerated skin, dermatitis, and burns (Gibb et al. 2000a). Medical records of 2,307 male workers (all nonsmokers) employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis). Ulcerated skin occurred in 31.6% of workers, at a mean exposure of 0.029 mg Cr(VI)/m^3 and a mean time to first diagnosis of 373 days. Ulcerated skin was significantly associated with chromium(VI) exposure ($p=0.004$), with a relative risk of 1.11. Burns were observed in 31.4% of workers, with a mean exposure and time to onset of 0.027 mg/m^3 and 409 days, respectively. Dermatitis was observed in 18.5% of workers, with a mean exposure and time to onset of 0.029 mg/m^3 and 624 days,

respectively. Irritated skin was observed in 15.1% of workers, with a mean exposure and time to onset of 0.025 mg/m^3 and 719 days, respectively.

Irritation and ulceration of the buccal cavity, as well as chrome holes on the skin, were also observed in workers in a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes (Lieberman 1941). Electroplaters in Czechoslovakia exposed to an average of 0.414 mg chromium(VI)/m^3 above the plating baths also had high incidences of buccal cavity changes, including chronic tonsillitis, pharyngitis, and papilloma (Hanslian et al. 1967). In a study of 303 electroplating workers in Brazil, whose jobs involve working with cold chromium trioxide solutions, >50% had ulcerous scars on the hands, arms, and feet. Air monitoring revealed that most workers were exposed to ≥0.1 mg chromium(VI)/m^3, but even those exposed to <0.1 mg chromium(VI)/m^3 developed lesions (Gomes 1972). Chrome holes were also noted at high incidence in chrome platers in Singapore, while controls had no skin ulcers (Lee and Goh 1988). The incidence of skin ulcers was significantly increased in a group of 997 chrome platers compared with 1,117 controls. The workers had been exposed to chromium(VI) in air and in dust. The air levels were generally <0.3 mg chromium(VI)/m^3, and dust levels were generally between 0.3 and 97 mg chromium(VI)/g (Royle 1975b). In a NIOSH Health Hazard Evaluation of an electroplating facility in the United States, seven workers reported past history of skin sores, and nine had scars characteristic of healed chrome sores. The workers had been employed for an average of 7.5 years and were exposed to a mean concentration of 0.004 mg chromium(VI)/m^3 in air. In addition, spot tests showed widespread contamination of almost all workroom surfaces and hands (Lucas and Kramkowski 1975).

An early report of cases of chrome ulcers in leather tanners noted that the only workmen in tanneries who suffered chrome holes were those who handled dichromate salts. In one of these cases, the penetration extended into the joint, requiring amputation of the finger (Da Costa et al. 1916). In a medical survey of a chemical plant that processed chromite ore, 198 of 285 workers had chrome ulcers or scars on the hands and arms. These workers had been exposed to one or more chromium(VI) compounds in the form of chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate, and ammonium dichromate (Edmundson 1951).

Similar dermal effects have been observed in animals. Dermal application of chromium(VI) compounds to the clipped, nonabraded skin of rabbits at 42–55 mg/kg resulted in skin inflammation, edema, and necrosis. Skin corrosion and eschar formation occurred at lethal doses (see Section 3.2.3.1) (Gad et al. 1986). Application of 0.01 or 0.05 mL of 0.34 molar solution of potassium dichromate (0.35 mg

chromium(VI) or 1.9 mg chromium(VI)/kg) to the abraded skin of guinea pigs resulted in skin ulcers (Samitz 1970; Samitz and Epstein 1962). Similar application of 0.01 mL of a 1 molar solution of chromium sulfate (1 mg chromium(III)/kg) however, did not cause skin ulcers in guinea pigs (Samitz and Epstein 1962). In a primary dermal irritation test, application of 88 mg chromium(III) as chromium nicotinate in corn oil to clipped skin of male and female New Zealand albino rabbits produced very slight erythema after 1 hour after application, with no signs of dermal irritation 48 hours after application (Shara et al. 2005).

Dermal sensitization due to hypersensitivity to chromium is discussed in Section 3.2.3.3.

Ocular Effects. Medical records of 2,307 male workers (all nonsmokers) employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis) (Gibb et al. 2000a). Conjunctivitis was reported on 20.0% of the study population, at a mean exposure level of 0.025 mg Cr(VI)/m^3 and a mean time-to-onset of 604 days.

Direct contact of the eyes with chromium compounds also causes ocular effects. Corneal vesication was described in a worker who accidentally got a crystal of potassium dichromate or a drop of a potassium dichromate solution in his eye (Thomson 1903). In an extensive study of chromate workers in seven U.S. chromate production plants, eyes were examined because accidental splashes of chromium compounds into the eye had been observed in these plants. Congestion of the conjunctiva was found in 38.7% of the 897 workers, discharge in 3.2%, corneal scaring in 2.3%, any abnormal finding in 40.8%, and burning in 17.0%, compared with respective frequencies of 25.8, 1.3, 2.6, 29.0, and 22.6% in 155 nonchromate workers. Only the incidences of congestion of the conjunctiva and any abnormal findings were significantly higher in the exposed workers than in the controls (PHS 1953).

Instillation of 0.1 mL of a 1,000 mg chromium(VI)/L solution of sodium dichromate and sodium chromate (pH 7.4) was not irritating or corrosive to the eyes of rabbits (Fujii et al. 1976). Histological examination of the eyes of rats exposed to chromium dioxide (15.5 mg chromium(IV)/m^3) in air revealed no lesions (Lee et al. 1989). In a primary eye irritation test, direct conjunctival instillation of 5.2 mg chromium(III) as chromium nicotinate in water to male and female New Zealand albino rabbits produced

conjunctivitis within 1 hour of application, although no corneal opacity or iritis was observed (Shara et al. 2005).

3.2.3.3 Immunological and Lymphoreticular Effects

In addition to the irritating and ulcerating effects, direct skin contact with chromium compounds elicits an allergic response, characterized by eczema or dermatitis, in sensitized individuals. Chromium-induced allergic contact dermatitis is typically isolated to areas at the site of contact, rarely occurring in areas remote to the point of contact (Winder and Carmody 2002). Following an induction phase during which the patient becomes sensitized, subsequent dermal exposure results in an allergic response. The acute response phase lasts for a few days to a few weeks and is characterized by erythema, edema, and small and large blisters; the chronic phase exhibits similar clinical features, but may also include thickened, scaly, and fissured skin (Winder and Carmody 2002). Evaluation by light and electron microscopy of skin biopsies of individuals with active dermatitis due to chromium shows increased intracellular edema of lower epidermal keratinocytes, formation of vacuoles in cells of the lower epidermis and dendritic, spindle-shaped cells in the upper dermis (Shah and Palmer 2002).

Studies using dermal patch testing as a technique to diagnose chromium sensitivity show that challenge with small amounts of chromium(VI) or chromium(III) can induce a response in sensitized individuals. A series of studies conducted by Hansen et al. (2003, 2006a, 2006b) show that patients with chromium-induced dermatitis associated with exposure to leather products responded to both low-dose and high-dose chromium(VI) and chromium(III) challenge using skin patch tests. In a group of 18 patients previously diagnosed with chromium sensitivity, the concentration of chromium(VI) as potassium dichromate required to elicit a positive response on skin patch challenge was 6 mg chromium(VI)/L and 1 mg chromium(III)/L as chromium trichloride (Hansen et al. 2003). Using higher doses in 2,211 patients with suspected contact dermatitis, 71 (3.2%) tested positive to 0.5% potassium dichromate (0.18% chromium(VI)) on skin patch challenge; of these 71 chromium(VI)-positive patients, 31 also produce a positive result when challenged with 13% chromium trichloride (3.7% chromium(III)) (Hansen et al. 2006b). The positive response to both chromium(VI) and chromium(III) challenge may indicate that exposure to both compounds may induced sensitivity or that there is cross-sensitivity between chromium(VI) and chromium(III) compounds on challenge. Similar results have been reported with high-dose chromium(III), showing that patch testing of chromium(VI)-sensitive patients with chromium(III) compounds can elicit an allergic reaction (Fregert and Rorsman 1964, 1966; Mali et al. 1966).

A study was performed on 54 volunteers who with chromium-induced allergic contact dermatitis to determine a dose-response relationship and to determine a minimum-elicitation threshold concentration (MET) that produces an allergic response in sensitive individuals (Nethercott et al. 1994). Patch testing was performed on the subjects in which the concentration of potassium chromate(VI) was varied up to 4.4 μg chromium/cm^2. Two percent (1/54) had a MET of 0.018. About 10% were sensitized at 0.089 μg/cm^2 and all were sensitized at 4.4 μg/cm^2. Comparable studies were performed with chromium(III) chloride, however, only 1 showed a positive response at 33 μg chromium/cm^2, and upon retesting was negative. Based on these findings the authors concluded that soil concentrations of chromium(VI) and chromium(III) of 450 and 165,000 ppm, respectively, should not pose a hazard of allergic contact dermatitis to 99.99% of people who might be exposed to chromium through soil-skin contact.

Numerous studies have investigated the cause of dermatitis in patients and in workers in a variety of occupations and industries and have determined that chromium compounds are the sensitizing agents. In these studies, patch tests were conducted with chromium(VI) or chromium(III) compounds using various concentrations. In one study using 812 healthy volunteers, patch testing with a 0.5% solution of potassium dichromate chromium(VI) revealed chromium sensitivity in 14 of the volunteers (1.7% of the test population). Of the 14 positive reactions, 10 occurred in a group of 110 offset printers, lithographers, and printing plant cleaners with concurrent exposure to chromium (Peltonen and Fraki 1983). Subjects with a sensitivity to chromium and challenged with a 0.001% solution potassium dichromate had increased skin thickness and blood flow (Eun and Marks 1990). Studies conducted on chromium(VI) sensitive printers and lithographers indicate that chromium(VI) compounds elicit reactions more frequently than do chromium(III) compounds (Levin et al. 1959; Mali et al. 1966; Samitz and Shrager 1966). The authors attributed this to a greater degree of permeation of the hexavalent form than the trivalent form through the skin (see Section 3.4.1.3).

In a study of skin disease among workers at an automobile factory, 230 workers with skin disease and 66 controls were patch tested with potassium dichromate (0.175% chromium(VI)). Sensitivity to potassium dichromate was seen in 24% of the patients and 1% of the controls. Most of the sensitive patients were assemblers who handled nuts, bolts, screws, and washers, which were found to have chromate on the surfaces as a result of a chromate dip used in the engine assembly process. Discontinuation of use of the chromate dip resulted in a significant decrease in the prevalence of dermatitis 6 months later (Newhouse 1963). Among 300–400 men directly exposed to cement dust, 8 had clinical symptoms of cement eczema. All eight tested positive with potassium dichromate, while only

four tested positive with cement (Engebrigtsen 1952). Patch testing of employees of the Baltimore and Ohio Railroad system with a variety of chemicals revealed that in 32 of 98 cases of dermatitis, the antirust diesel-engine coolant compound, which contained sodium chromate, was the etiological agent (Kaplan and Zeligman 1962). Among 200 employees who worked in a diesel locomotive repair shop, 6 cases of chromate dermatitis were diagnosed by positive patch tests to samples of radiator fluid and to 0.25% sodium dichromate (0.09% chromium(VI)). The radiator fluid to which the workers were occupationally exposed contained 66% sodium dichromate (Winston and Walsh 1951). A search for the source of chromium exposure in workers who developed contact dermatitis in wet sandpapering of primer paint on automobiles revealed that the paint contained zinc chromate (Engel and Calnan 1963).

In a study of 1,752 patients considered to have occupational dermatoses, contact dermatitis was the main diagnosis in 1,496 patients (92% women, 83% men). The allergic type, as opposed to the irritant type, was more prevalent in men (73%) than in women (51%). Positive patch tests to chromium (not otherwise specified) occurred in 8% of the women and 29% of the men. Among 280 chromium-sensitized men, 50% were employed in building and concrete work, 17% in metal work, and 12% in tanneries. In the 42 chromium-sensitized women, 20% were in cement work, 19% in metal work, 28% in cleaning, and 15% in laboratory work (Fregert 1975). A survey study of 335 construction workers (including tile setters, painters, construction and cement workers, and wood processors) with occupational dermatitis showed that 152 workers (approximately 45%) were sensitized to chromium based on positive to patch test to potassium dichromate (Bock et al. 2003).

Chromate sensitivity has also been reported in women who frequently used dichromate-containing detergent and bleach (Basketter et al. 2001; Wahba and Cohen 1979).

Other industries and sources of chromium that have resulted in chromium sensitivity include welding, printing, glues, wood ash, foundry sand, match heads, machine oils, timber preservative, boiler linings, making of television screens, magnetic tapes, tire fitting, chrome plating, wood and paper industry, leather tanning, cement working, and milk testing (Burrows 1983; Chen et al. 2008; Gass and Todd 2007; Lockman 2002; Wong et al. 1998).

Animals can also be sensitized to chromium compounds. Contact sensitivity was induced in mice by rubbing a solution of 1% potassium dichromate (0.35% chromium(VI)) ≈50 times on the shaved abdomens. Challenge with potassium dichromate on the ear resulted in significant induction of

sensitivity, measured by ear thickness and histologically observed infiltration of nucleophilic leukocytes (Mor et al. 1988).

Guinea pigs can be sensitized to chromium(VI) and chromium(III) compounds by a series of intradermal injections of 0.009 mg chromium(VI)/kg as potassium dichromate or of 0.004 mg chromium(III)/kg as chromium trichloride. Regardless of the compound used to sensitize the guinea pigs, subsequent patch testing with chromium(VI) or chromium(III) yielded the same erythmatic reaction. The response, however, was greater when chromium(VI) was used as the sensitizer (Gross et al. 1968). Similarly, the same erythmatic response to chromium(VI) and chromium(III) compounds was noted in guinea pigs sensitized to 0.04 mg chromium(VI)/kg as potassium dichromate or 0.03 mg chromium(III)/kg as chromium sulfate (Jansen and Berrens 1968).

Results of skin testing to demonstrate or diagnose chromium sensitization are recorded in Table 3-5 for chromium(VI) and Table 3-6 for chromium(III).

No studies were located regarding the following health effects in humans or animals after dermal exposure to chromium compounds:

3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to chromium compounds.

3.3 GENOTOXICITY

In vivo studies of chromium compounds are summarized in Table 3-7. *In vitro* studies on the genotoxicity of chromium(VI) and chromium(III) compounds are summarized in Tables 3-8 and 3-9, respectively. Chromium(VI) compounds rapidly (within seconds to minutes) enter cells by facilitated diffusion, while chromium(III) compounds enter much more slowly (within days) by simple diffusion; therefore, chromium(VI) compounds are of greater concern with regard to health effects. Available genotoxicity studies on occupationally exposed humans typically evaluate effects in blood cells since blood is easily accessible, whereas evaluation of effects in cells from cancer target tissues (e.g., lung,

Table 3-7. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Drosophila melanogaster	Gene mutation	+	Gava et al. 1989b; Rasmuson 1985; Rodriguez-Arnaiz and Martinez 1986; Zimmering et al. 1985	(VI)	Potassium dichromate, sodium dichromate, chromium trioxide, calcium chromate
D. melanogaster	Gene mutation	+	Olvera et al. 1993	(VI)	Chromium trioxide
D. melanogaster	Gene mutation	+	Kaya et al. 2002	(VI)	Potassium dichromate
D. melanogaster	Gene mutation	+	Amrani et al. 1999	(VI)	Potassium chromate, potassium dichromate
D. melanogaster	Gene mutation	–	Amrani et al. 1999	(III)	Chromium chloride
Human lymphocytes	Chromosomal aberrations	+	Koshi et al. 1984; Sarto et al. 1982	(VI)	Stainless steel, welding fumes, chromium trioxide
Human lymphocytes	Chromosomal aberrations	–	Hamamy et al. 1987	(III)	Chrome alum (primarily chromium sulfate)
Human lymphocytes	Chromosomal aberrations	–	Husgafvel-Pursiainen et al. 1982	(VI)	Stainless steel, welding fumes
Human lymphocytes	Sister chromatid exchanges	+	Koshi et al. 1984; Lai et al. 1998; Sarto et al. 1982; Stella et al. 1982	(VI)	Chromium plating, stainless steel, welding fumes, chromium trioxide
Human lymphocytes	DNA strand breaks, hydroxylation of deoxyquanosine	–	Gao et al. 1994	(VI)	Production of bichromate
Human lymphocytes	Sister chromatid exchanges	–	Nagaya et al. 1991	(VI)	Chromium plating
Human lymphocytes	Sister chromatid exchanges, DNA strand breaks	+	Werfel et al. 1998	(VI)	Welding fumes
Human lymphocytes	Sister chromatid exchanges	–	Nagaya 1986	(VI)	Chromium plating

Table 3-7. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Human peripheral lymphocytes	Micronuclei	+	Vaglenov et al. 1999	(VI)	Chromium electroplating
Human peripheral lymphocytes	Micronuclei	+	Benova et al. 2002	(VI)	Chromium plating
Human buccal mucosa	Micronuclei	+	Benova et al. 2002	(VI)	Chromium plating
Human peripheral lymphocytes	Chromosome aberrations, sister chromatid exchanges	–	Benova et al. 2002	(VI)	Chromium plating
Human peripheral lymphocytes	DNA strand breaks	+	Gambelunghe et al. 2003	(VI)	Chromium plating
Human buccal mucosa	Chromosome aberrations, sister chromatid exchanges	–	Benova et al. 2002	(VI)	Chromium plating
Human whole blood cells	Sister chromatid exchanges	+	Wu et al. 2001	(VI)	Chromium electroplating
Human peripheral lymphocytes	Micronuclei, DNA-protein crosslinks	+	Medeiros et al. 2003a	(III)	Tanners
Human peripheral lymphocytes	Micronuclei	–	Medeiros et al. 2003a	(VI)	Welders
Human peripheral lymphocytes	DNA-protein crosslinks	+	Medeiros et al. 2003a	(VI)	Welders
New polychromatic erythrocytes	Micronuclei	+	LeCurieux et al. 1992	(VI)	Potassium chromate
Rat lung (intratracheal exposure)	DNA alterations	+	Izzotti et al. 1998	(VI)	Sodium dichromate
Rat liver (intratracheal exposure)	DNA alterations	–	Izzotti et al. 1998	(VI)	Sodium dichromate
Rat liver (oral exposure)	DNA-protein crosslinks	+	Coogan et al. 1991a	(VI)	Potassium chromate
Rat liver and kidney nuclei (intraperitoneal exposure)	DNA crosslinks, DNA-protein crosslinks, DNA strain breaks	–	Cupo and Wetterhahn 1985	(III)	Chromium oxide
Rat liver, kidney, and lung nuclei (intraperitoneal exposure)	DNA-protein crosslinks	+	Tsapalos et al. 1983b	(VI)	Sodium dichromate
Rat hepatocytes (oral exposure)	Unscheduled DNA synthesis	–	Mirsalis et al. 1996	(VI)	Potassium chromate
Rat (F344/N) bone marrow cells (oral exposure)	Micronuclei	–	NTP 2008b	(III)	Chromium picolinate

Table 3-7. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Rat (Sprague-Dawley) hepatic	DNA fragmentation	–	Shara et al. 2005	(III)	Niacin-bound chromium
Mouse erythrocytes (oral exposure)	Micronuclei	–	Shindo et al. 1989	(VI)	Potassium chromate
Mouse ($B_6C_3F_1$, BALB/c) erythrocytes (oral exposure)	Micronuclei	–	NTP 2007	(VI)	Sodium dichromate dihydrate
Mouse (am3-C57BL/6) erythrocytes (oral exposure)	Micronuclei	+	NTP 2007	(VI)	Sodium dichromate dihydrate
Mouse $B_6C_3F_1$ (oral exposure)	Micronuclei	–	NTP 2008b	(III)	Chromium picolinate monohydrate
Mouse ($B_6C_3F_1$) erythrocytes (oral exposure)	Micronuclei	–	NTP 2008b	(III)	Chromium picolinate monohydrate
Mouse (transplacental exposure)	DNA deletions	+	Kirpnick-Sobol et al. 2006	(III)	Chromium (III) chloride salt
Mouse (transplacental exposure)	DNA deletions	+	Kirpnick-Sobol et al. 2006	(VI)	Potassium dichromate
Mouse (BDF1) bone marrow cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (BDF1) peripheral blood cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (BDF1) bone marrow cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (BDF1) peripheral blood cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (BDF1) peripheral blood cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(III)	Chromic potassium sulfate dodecahydrate
Mouse (BDF1) bone marrow cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(III)	Chromic potassium sulfate dodecahydrate
Mouse (BDF1) bone marrow cells (gavage exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate

Table 3-7. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Mouse (BDF1) bone marrow cells (intraperitoneal exposure)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) bone marrow—dams (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) bone marrow—dams (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) bone marrow—dams (intraperitoneal exposure)	Micronuclei	+	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) bone marrow—dams (intraperitoneal exposure)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal liver cells (transplacental exposure from drinking water)	Micronuclei	–	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) fetal liver cells (transplacental exposure from drinking water)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from drinking water)	Micronuclei	–	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from drinking water)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal liver cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) fetal liver cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate

Table 3-7. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse leukocytes	DNA damage	+	Devi et al. 2001	(VI)	Potassium dichromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	–	Shindo et al. 1989	(VI)	Potassium chromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	+	Itoh and Shimada 1997; Wild 1978	(VI)	Potassium chromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	–	Itoh and Shimada 1996	(III)	Chromium chloride
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	+	Itoh and Shimada 1996	(VI)	Potassium chromate
Mouse peripheral lymphocytes	DNA damage	+	Wang et al. 2006	(VI)	Potassium chromate
Mouse bone marrow cells (oral exposure)	Micronuclei	–	Mirsalis et al. 1996	(VI)	Potassium chromate
Mouse bone marrow cells (gavage)	Chromosomal aberrations	+	Sarkar et al. 1993	(VI)	Chromium trioxide
Mouse bone marrow (intraperitoneal exposed)	Cell mutation	+	Itoh and Shimada 1998	(VI)	Potassium dichromate
Mouse hepatocytes (intraperitoneal exposed)	Cell mutation	+	Itoh and Shimada 1997, 1998	(VI)	Potassium dichromate
Mouse bone marrow (intraperitoneal exposed)	Micronuclei	+	Chorvatovičová et al. 1993; Wrońska-Nofer et al. 1999	(VI)	Potassium dichromate
Mouse (intraperitoneal exposure)	Dominant lethality	+	Paschin et al. 1982	(VI)	Potassium dichromate
Mouse liver and kidney cells (intraperitoneal exposure)	Single strand breaks	+	Ueno et al. 2001	(VI)	Potassium dichromate
Mouse spleen, lung, and brain cells (intraperitoneal exposure)	Single strand breaks	–	Ueno et al. 2001	(VI)	Potassium dichromate

– = negative results; + = positive results; (0) = 0 valence; (III) = trivalent; (VI) = hexavalent; DNA = deoxyribonucleic acid;

Table 3-8. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Subcellular targets:					
Escherichia coli DNA	DNA-protein crosslinks	No data	–	Fornance et al. 1981	Potassium chromate
Nuclei of mouse L1210 leukemia cells	DNA fragmentation	No data	–	Fornance et al. 1981	Potassium chromate
Double-standed M13mp2 bacteriophage DNA transferred to *E. coli*	Forward mutations	No data	+	Snow and Xu 1989	Potassium chromate
Puc 19 plasmid DNA	Gene mutation	No data	+	Kortenkamp et al. 1996b	Potassium chromate
Papilloma virus	Gene mutation	No data	+	Kowalski et al. 1996	Potassium chromate
PSV2neo-based plasmid DNA	DNA polymerase arrest	+	–	Bridgewater et al. 1994b, 1998	Sodium dichromate
Prokaryotic organisms:					
Bacillus subtilis	Recombinations	No data	+	Kanematsu et al. 1980; Nakamuro et al. 1975	Potassium chromate, potassium dichromate
E. coli PQ37, PQ35	Induction of SOS response	–	+	Olivier and Marzin 1987	Potassium chromate, potassium dichromate
E. coli AB1157, GC2375, UA4202, PQ30	Induction of SOS response	No data	+	Llagostera et al. 1986	Chromium chromate, potassium dichromate, chromium trioxide
E. coli Wp2, Hs30R, B/rWP2	Reverse mutations	No data	+	Kanematsu et al. 1980; Nakamuro et al. 1978; Venitt and Levy 1974	Potassium dichromate, potassium chromate, sodium chromate

Table 3-8. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
E. coli, WP2/pKM101, WP2 uvrA/pKM101	Reverse mutations	No data	+	Watanabe et al. 1998a	Chromium trioxide, sodium dichromate
E. coli, WP2 uvrA/pKM101	Reverse mutations	+	+	NTP 2007	Sodium dichromate dihydrate
Salmonella typhimurium TA100, TA98	Reverse mutations	+	+	NTP 2007	Sodium dichromate dihydrate
S. typhimurium TA100	Base pair substitutions	No data	+	DeFlora 1978	Sodium dichromate
S. typhimurium TA100	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA102	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA92	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA1535	Base pair substitutions	No data	–	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA97	Frame shift mutations	No data	+	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA1537, TA1538	Frame shift mutations	No data	–	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA1978	Frame shift mutations	No data	±	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA1535	Base pair substitutions	–	±	Nakamura et al. 1987	Potassium dichromate
S. typhimurium TA100	Base pair substitutions	+	+	Venier et al. 1982	Potassium dichromate
S. typhimurium TA1538	Frame shift mutations	–	–	Venier et al. 1982	Potassium dichromate
S. typhimurium TA98	Frame shift mutations	–	±	Venier et al. 1982	Potassium dichromate
S. typhimurium TA97a, TA98	Frame shift mutations	+	+	Tagliari et al. 2004	Potassium dichromate
S. typhimurium TA100, TA102	Base pair substitutions	+	+	Tagliari et al. 2004	Potassium dichromate

Table 3-8. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
S. typhimurium TA100	Base pair substitutions	–	–	DeFlora 1981	Sodium dichromate, potassium chromate, calcium chromate, ammonium chromate, chromium trioxide
S. typhimurium TA1535	Base pair substitutions	No data	+	DeFlora 1981	Sodium dichromate, potassium chromate, calcium chromate, ammonium chromate, chromium trioxide
S. typhimurium TA100, TA1535	Base pair substitutions	No data	+	Haworth et al. 1983	Calcium chromate
S. typhimurium TA98, TA1537	Frame shift mutations	No data	+	Haworth et al. 1983	Calcium chromate
S. typhimurium TA100, TA1535	Base pair substitutions	No data	–	Kanematsu et al. 1980	Potassium dichromate
S. typhimurium TA100, TA1537, TA1538	Frame shift mutations	No data	–	Kanematsu et al. 1980	Potassium dichromate
S. typhimurium TA 1535 pSK1002	Mutations	+	+	Yamamoto et al. 2002	Potassium dichromate
S. typhimurium TA102, TA2638	Reverse mutations	No data	+	Watanabe et al. 1998a	Chromium trioxide, sodium dichromate
Eukaryotic organisms:					
Yeasts:					
Saccharomyces cerevisiae D7	Mitotic gene conversions	No data	+	Fukunaga et al. 1982; Singh 1983	Chromium trioxide
S. cerrevisiae D7	Reverse mutations	No data	+	Singh 1983	Potassium dichromate
S. cerrevisiae D7	Mitotic cross-over	No data	+	Fukunaga et al. 1982	Chromium trioxide
S. cerrevisiae	DNA deletions	No data	+	Kirpnick-Sobol et al. 2006	Potassium dichromate

Table 3-8. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Schizosacharomyces pombe	Mitotic gene conversion	No data	+	Bonatti et al. 1976	Potassium dichromate
S. pombe	Forward mutations	No data	+	Bonatti et al. 1976	Potassium dichromate
Chickens:					
Chick embryos	DNA damage cross links, strand breaks, DNA-protein crosslinks	No data	+	Tsapakos et al. 1983a	Sodium chromate
Mammalian cells:					
Human embryonic lung fibroblasts (IMR-90)	DNA-protein crosslinks, DNA fragmentation	No data	+	Fornance et al. 1981	Potassium chromate
Human bronchial epithelial cells	DNA fragmentation	No data	+	Fornance et al. 1981	Potassium chromate
Human lymphocytes	Single strand breaks	No data	+	Depault et al. 2006	Potassium chromate
Human lymphocytes	DNA damage	No data	+	Blasiak and Kowalik 2000	Potassium dichromate
Human dermal fibroblasts (GM03440 cells)	DNA double-strand breaks	No data	+	Ha et al, 2003, 2004	Sodium chromate
Human bronchial fibroblasts (WTHBF-6 cells)	chromosome aberrations	No data	+	Holmes et al. 2006	Sodium chromate
Human bronchial fibroblasts (WTHBF-6 cells)	Disruption of mitosis	No data	+	Wise et al. 2006a	Sodium chromate
Human bronchial epithelial cells (BEP2D cells)	chromosome aberrations	No data	+	Wise et al. 2006b	Sodium chromate
Human lung fibroblasts	DNA polymerase arrest, DNA-DNA crosslinks	No data	+	Xu et al. 1996	Sodium chromate
Chinese hamster lung DON cells	Sister chromatid exchange, chromosomal aberrations	No data	+	Koshi 1979, Koshi and Iwaski 1983	chromium trioxide, zinc bromate, calcium chromate, potassium chromate
Chinese hamster ovary cells	Chromosomal aberrations, DNA fragmentation	No data	+	Blankenship et al. 1997	sodium chromate

Table 3-8. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Mouse L1210 leukemia cells	DNA fragmentation, DNA-protein crosslinks	No data	+	Fornace et al. 1981	Potassium chromate
Mouse embryo fibroblast cells	Chromosomal aberrations	No data	+	Sugiyama et al. 1986a	Calcium chromate
Mouse A18BcR cells	Unscheduled DNA synthesis	No data	+	Raffetto et al. 1977	Potassium dichromate
Mouse primary fetal cells	Transformations, chromosomal aberrations	No data	+	Raffetto et al. 1977	Potassium dichromate
Human gastric mucosa	DNA damage	No data	+	Trzeciak et al. 2000	Potassium dichromate
Human peripheral blood lymphocytes	DNA damage	No data	+	Trzeciak et al. 2000	Potassium dichromate
Human fibroblasts	Double strand breaks	No data	+	Ha et al. 2004	Sodium chromate
Human primary bronchial fibroblasts	Chromosomal aberrations	No data	+	Wise et al. 2002, 2004	Sodium chromate
Chinese hamster ovary cells	Chromosomal damage	No data	+	Seoane and Dulout 1999	Potassium dichromate
Mouse mammary FM3A carcinoma cells	Chromosomal aberrations	No data	+	Umeda and Nishmura 1979	Potassium dichromate, potassium chromate, chromium trioxide
Rat liver epithelial cells	Transformations	No data	+	Briggs and Briggs 1988	Potassium chromate

– = negative results; + = positive results; ± = weakly positive results; (VI) = hexavalent; DNA = deoxyribonucleic acid

Table 3-9. Genotoxicity of Chromium(III) *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Subcellular targets:					
Escherichia coli DNA	DNA-protein crosslinks	No data	+	Fornace et al. 1981	Chromium trichloride
Nuclei of mouse L1210 leukemia cells	DNA fragmentation	No data	+	Fornace et al. 1981	Chromium trichloride
Single-stranded M13mp2 bacteriophange DNA	Replication assay: increased nucleotide incorporation	No data	+	Snow 1991; Snow and Xu 1989	Chromium trichloride
Double-stranded M13mp2 bacteriophage DNA transferred to *E. coli*	Forward mutations	No data	+	Snow 1991; Snow and Xu 1989	Chromium trichloride
pSV2neoTS DNA	DNA polymerase arrest	No data	+	Bridgewater et al. 1994b	Chromium trichloride
Prokaryotic organisms:					
Bacillus subtilis	Recombinations	No data	–	Kanematsu et al. 1980	Chromium sulfate, chromium potassium sulfate
B. subtilis	Recombinations	No data	–	Matsui 1980; Nakamuro et al. 1978; Nishioka 1975	Chromium trichloride
B. subtilis	Recombinations	No data	±	Nakamuro et al. 1978	Chromium nitrate
B. subtilis	Recombinations	No data	±	Nakamuro et al. 1978	Chromium acetate
E. coli	Gene mutations	No data	+	Sugden et al. 1990	cis-Dichlorobis (2,2'-bipyridyl) chromium(III)
E. coli WP2 *uvrA*/pKM101	Gene mutations	–	–	NTP 2008b	Chromium picolinate monohydrate
E. coli AB1157, GC275, VA4202, PQ30	Induction of SOS response	No data	–	Llagostera et al. 1986	Chromium trichloride, chromium nitrate, chromium acetate
E. coli PQ37, PQ35	Induction of SOS response	–	–	Olivier and Marzin 1987	Chromium trichloride hexahydrate
E. coli PQ37	Induction of SOS response	–	–	Venier et al. 1989	Chromium trichloride, chromium nitrate

Table 3-9. Genotoxicity of Chromium(III) *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
E. coli PQ37	Induction of SOS response	–	±	Venier et al. 1989	Chromium acetate
Salmonella typhimurium TA100, TA1535	Reverse mutationsBase pair substitutions	–	–	De Flora 1981;Petrilli and De Flora 1978b	Chromium trichloride hexahydrate, chromium nitrite, monohydrate, chromium potassium sulfate, chromium acetate, neochromium, chromium alum, chromite
TA98, TA1537, TA1538	Frame shift mutations	–	–		
S. typhimurium TA102	Base pair substitutions	–	–	Bennicelli et al. 1983	Chromium nitrate
S. typhimurium TA100, TA1535	Base pair substitutions	–	–	Venier et al. 1982	Chromium chloride hexahydrate, chromium nitrate monohydrate
TA98, TA1538	Frame shift mutations	–	–		
S. typhimurium TA100, TA98	Reverse mutations	–	–	NTP 2008b	Chromium picolinate monohydrate
S. typhimurium TA102, TA104, TA100, TA1535, TA97, TA98	Reverse mutations	–	–	NTP 2008b	Chromium picolinate
S. typhimurium TA92, TA98, TA100	Reverse mutations	No data	+	Warren et al. 1981	Chromium complexes with 2,2'-bipyridine and 1,10-phenanthroline
S. typhimurium TA98, TA100, TA1535, TA1537	Reverse mutations	–	–	Whittaker et al. 2005	Chromium picolinate
S. typhimurium TA98, TA100, TA1535, TA1537	Reverse mutations	–	–	Whittaker et al. 2005	Chromium chloride
S. typhimurium TA1535, TA97a, TA98, TA100, TA102	Reverse mutations	–	–	Shara et al. 2005	Niacin-bound chromium
S. typhimurium TA 1535 pSK1002	Mutations	–	–	Yamamoto et al. 2002	Chromium nitrate

Table 3-9. Genotoxicity of Chromium(III) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Eukaryotic organisms:					
Yeasts:					
Saccharomyces cerevisiae	Reverse mutations, mitotic gene conversions	No data	+	Bronzetti et al. 1986	Chromium trichloride
S. cerrevisiae	DNA deletions	No data	+	Kirpnick-Sobol et al. 2006	Cromium (III) chloride salt
Chickens:					
Chick embryos	DNA damage (crosslinks, strand breaks)	No data	–	Tsapakos et al. 1983a	Chromium nitrate
Mammalian cells:					
Human lymphocytes	DNA damage	No data	+	Blasiak and Kowalik 2000	Chromium chloride
Human skin fibroblasts	Unscheduled DNA synthesis	No data	–	Whiting et al. 1979	Chromium trichloride
Human skin fibroblasts	DNA fragmentation	No data	–	Whiting et al. 1979	Chromium trichloride
Human leukocytes	Chromosomal aberrations	No data	±	Nakamuro et al. 1978	Chromium trichloride, chromium nitrate, chromium acetate
Human lymphocytes	Chromosomal aberrations	No data	±	Stella et al. 1982	Chromium trichloride hexahydrate
Human lymphocytes	Chromosomal aberrations	No data	–	Sarto et al. 1980	Chromium trichloride
Human lymphocytes	Sister chromatid exchange	No data	–	Stella et al. 1982	Chromium trichloride hexahydrate
Chinese hamster V79 cells	Chromosomal aberrations	No data	–	Newbold et al. 1979	Chromium acetate
Syrian hamster embryonal cells	Chromosomal aberrations	No data	–	Tsuda and Kato 1977	Chromium trichloride hexachloride, chromium sulfate tetrahydrate
Chinese hamster lung DON cells	Chromosomal aberrations	No data	–	Ohno et al. 1982	Chromium trichloride hexahydrate, chromium sulfate tetrahydrate

Table 3-9. Genotoxicity of Chromium(III) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Chinese hamster ovary cells	aberrations		±	Levis and Majone 1979	Chromium trichloride hexachloride, chromium nitrate monohydrate, chromium potassium sulfate, chromium acetate
Chinese hamster ovary cells	Sister chromatid exchange	No data	–	Levis and Majone 1979; MacRae et al. 1979; Venier et al. 1982	Chromium trichloride hexachloride, chromium nitrate, monohydrate, chromium potassium sulfate, chromium acetate
Chinese hamster ovary cells (*hprt* locus)	Mutations	No data	+	Coryell and Stearns 2006; Stearns et al. 2002	Chromium trispicolinate
Mouse L5178Y+/- lymphoma	Mutations	–	–	Shara et al. 2005	Niacin-bound chromium
Mouse L5178Y lymphoma	Mutations	+	+	Whittaker et al. 2005	Chromium picolinate
Mouse L5178Y lymphoma	Mutations	–	±	Whittaker et al. 2005	Chromium chloride
Mouse leukemia cells	Chromosomal aberrations	No data	–	Fornace et al. 1981	Chromium trichloride
Mouse mammary carcinoma	Chromosomal aberrations	No data	–	Umeda and Nishimura 1979	Chromium sulfate
Fm3A cells:					
Mouse fetal cells	Chromosomal aberrations	No data	±	Raffetto et al. 1977	Chromium trichloride
Mouse fetal cells	Morphological transformations	No data	+	Raffetto et al. 1977	Chromium trichloride
Mouse A18BcR cells	Unscheduled DNA synthesis	No data	–	Raffetto et al. 1977	Chromium trichloride

– = negative results; + = positive results; ± = weakly positive results; (III) = trivalent; DNA = deoxyribonucleic acid

gastrointestinal tract) are not easily obtained for analysis. However, negative genotoxicity results in tissues that are not cancer targets (e.g., blood) should not be extrapolated to cancer target tissues.

Occupational exposure studies have yielded mixed results on the genotoxic potential of chromium compounds. Studies involving workers exposed to chromium(VI) in stainless steel welding and electroplating (Husgafvel-Pursiainen et al. 1982; Littorin et al. 1983; Nagaya 1986; Nagaya et al. 1991), and to chromium(III) in tanneries (Hamamy et al. 1987) did not report increases in the number of chromosomal aberrations or sister chromatid exchanges in peripheral lymphocytes of these workers. No elevations in DNA strand breaks or hydroxylation of deoxyguanosine were detected in lymphocytes of workers exposed to chromium(VI) involved in the production of bichromate (Gao et al. 1994), while DNA strand breaks were reported in the peripheral lymphocytes of 19 chromium platers (Gambelunghe et al. 2003). In contrast, other studies involving electroplaters and stainless steel welders reported higher levels of chromosomal aberrations or sister chromatid exchanges in workers exposed to chromium(VI) compared to controls (Deng et al. 1988; Koshi et al. 1984; Lai et al. 1998; Sarto et al. 1982; Stella et al. 1982; Werfel et al. 1998).

Urine samples from six workers working in chromium plating factories were tested for the induction of unscheduled DNA synthesis (UDS) in pleural mesothelial cells (Pilliere et al. 1992). The mean chromium concentration in the urine samples was 11.7±8.8 μg/L. The urine from five of the workers showed a significant elevated in UDS over control subjects who were nonsmokers, with a trend toward increasing amounts of urine being tested. However, there was no correlation between UDS and chromium concentrations in urine.

An epidemiology study of stainless steel welders, with mean exposure levels of 0.055 mg chromium(VI)/m^3 or 0.081 mg chromium (total)/m^3, did not report increases in the number of sister chromatid exchanges in the lymphocytes of exposed workers. The welders were also exposed to nickel and molybdenum from the welding rods (Littorin et al. 1983). A similar study was conducted to detect genotoxic effects of chromium(VI) on workers in electroplating factories. Of the 24 workers examined, none showed significant differences in sister chromatid exchange frequency (Nagaya 1986). Similarly, no correlation was found between excretion of chromium in the urine and the frequency of sister chromatid exchanges in 12 male chromium platers whose mean urinary chromium level was 17.9 μg/g creatinine (Nagaya et al. 1991). In chrome platers (n=15) in low (0.0075 mg Cr(VI)/m^3) and high (0.0249 mg Cr(VI)/m^3) exposure groups, no significant differences in the frequency of sister chromatid exchanges and chromosomal aberrations in peripheral lymphocytes and buccal mucosa cells were observed

compared to controls (0.0004 mg Cr(VI)/m^3; n=15) (Benova et al. 2002). No increase in chromosomal aberrations was observed in 17 tannery workers exposed primarily to chromium(III) as compared with 13 controls (Hamamy et al. 1987). However, parallel measurements in these tannery workers showed that the average chromium levels in plasma (0.115 μg/L) and urine (0.14 μg/100 L) did not differ from the nonexposed workers. In addition, stainless steel welders occupationally exposed to chromium(VI) for a mean of 21 years did not have any increase in chromosomal aberrations or sister chromatid exchanges compared to a control group. No actual exposure levels were provided (Husgafvel-Pursiainen et al. 1982). Yet, other studies involving electroplaters and welders report a higher incidence of chromosomal aberrations or sister chromatid exchanges in lymphocytes of workers than in controls. In one study, a causal relationship between chromium exposure and the observed effects could not be established because the exposure was confounded by co-exposure to nickel and manganese (Elias et al. 1989a). In another study, although chromium workers were found to have higher rates of sister chromatid exchanges than workers exposed to nickel-chromium or controls (after adjusting for potential confounding factors), the differences were not significantly correlated to chromium concentrations in blood or urine (Lai et al. 1998). The frequency of sister chromatid exchanges was also higher in the blood of 35 chromium platers in Taiwan when compared to controls (Wu et al. 2001). The frequency of sister chromatid exchanges in the lymphocytes of 12 workers exposed to chromium(VI) as chromic acid fumes in a chrome plating industry was significantly increased (Stella et al. 1982). Significantly increased incidences of chromosomal aberrations in peripheral lymphocytes were found in workers exposed to chromium(VI) as chromium trioxide in two of four electroplating plants. Of the two plants where the increases were significant, one was a "bright" plating plant, where exposure involved nickel as well as chromium, and one was a "hard" plating plant, where exposure involved only chromium. However, the increase in chromosomal aberrations correlated poorly with urinary chromium levels, and only the increase in the "bright" platers showed a significant correlation with duration of exposure. A significantly increased incidence of sister chromatid exchanges was found in "hard" platers compared with controls (sister chromatid exchange was not evaluated in "bright" platers), and smoking appeared to enhance the increase (7 of 8 smokers and 7 of 11 nonsmokers had incidences significantly higher than controls). Moreover, the increased incidence of sister chromatid exchange showed a positive correlation with urinary chromium levels (Sarto et al. 1982). Repeated cytogenetic analysis of peripheral lymphocytes for 3 years revealed an increased frequency of chromosomal aberrations and sister chromatid exchanges in a group of stainless steel welders compared to controls. The workers were exposed to unreported chromium(VI) concentrations for a mean of 12.1 years, but exposure to ultraviolet rays and small amounts of manganese, nickel, iron, and magnesium could not be ruled out (Koshi et al. 1984). Compared to 39 controls, significantly elevated sister chromatid exchange values in lymphocytes and significantly higher rates of

DNA single-strand breakages were found in a group of 39 welders exposed to unreported chromium(VI) and nickel concentrations (Werfel et al. 1998). Only one study was located regarding the average levels of exposure for electroplating workers: workers exposed to an average level of 0.008 mg chromium(VI)/m^3 had increases in chromosomal aberrations and sister chromatid exchanges. However, high levels of nickel as well as chromium were found in hair and stool samples when compared to controls (Deng et al. 1988). Increased frequencies of micronuclei were reported in the peripheral lymphocytes and buccal mucosa cells in two studies of chromium electroplating workers in Bulgaria (Benova et al. 2002; Vaglenov et al. 1999). In chrome platers (n=15), significant increases in micronuclei in peripheral lymphocytes and buccal mucosa cells were observed in low (0.0075 mg Cr(VI)/m^3) and high (0.0249 mg Cr(VI)/m^3) exposure groups compared to controls (0.0004 mg Cr(VI)/m^3; n=15) (Benova et al. 2002). Increased micronuclei frequency and DNA-protein crosslinks were observed in the peripheral lymphocytes of tanners primarily exposed to chromium(III) compounds, while welders, who are primarily exposed to chromium(VI) compounds had evidence of DNA-protein crosslinks, but not increased micronuclei frequency in peripheral lymphocytes (Medeiros et al. 2003a). No elevated levels of DNA strand breaks or hydroxylation of deoxyguanosine in lymphocytes were found in 10 workers occupationally exposed in the production of bichromate when compared with 10 nonoccupationally-exposed workers at the same facility Gao et al. (1994). From general background monitoring levels of chromium(VI), exposures were estimated to be between 0.001 and 0.055 mg/m^3. In contrast, DNA strand breaks were reported in the peripheral lymphocytes of 19 chromium platers with a mean postshift urinary concentration of 7.31 μg/g creatinine when compared to non-exposed control subjects (Gambelunghe et al. 2003).

Chromium(VI) and chromium(III) have been shown to be genotoxic in human cell lines. S phase-dependent DNA double-strand breaks were observed in cultured human dermal fibroblasts exposed to sodium chromate (chromium(VI)) (Ha et al. 2003, 2004). Sodium chromate also induced concentration-dependent chromosome damage in cultured human bronchial fibroblasts and bronchial epithelial cells (Holmes et al. 2006; Wise et al. 2006b). Exposure of cultured human bronchial fibroblasts to sodium chromate produced disruption of mitosis, most likely through spindle assembly checkpoint bypass (Wise et al. 2006a). Weakly positive responses were observed for chromium(III) (Nakamuro et al. 1978; Stella et al. 1982). However, it should be noted that in positive studies, the genotoxic potency of chromium(III) compounds was several orders lower than that of chromium(VI) compounds tested in the same systems. Positive results for increased micronuclei and DNA damage were also observed in lymphocytes exposed to chromium(III) chloride (Blasiak and Kowalik 2000). Positive results of chromium(III) in intact cells could be due to contamination of the test compounds with traces of chromium(VI) (De Flora et al. 1990;

IARC 1990), nonspecific effects at very high doses, experimental conditions that would increase the penetration of chromium(III) into cells (e.g., detergents), or a technical artifact formed during the extraction procedures (De Flora et al. 1990). In one case, chromium(III) compounds showed genotoxicity that was linked to redox cycling of a chromium-DNA complex (Sugden et al. 1990). Although chromium(III) compounds are less toxic than chromium(VI) compounds because of its relative inability to cross cell membranes, chromium(III) causes more DNA damage and mutations when it is formed by intracellular reduction from chromium(VI) or it is reacted with DNA in subcellular systems (Bridgewater et al. 1994a, 1994b, 1998; Fornace et al. 1981; Snow 1991; Snow and Xu 1989).

Thus, results of studies in occupationally exposed humans and in human cell lines indicate that chromium(VI) and chromium(III) are genotoxic; however, studies in humans were limited in several aspects. Generally, the levels of exposure to chromium(VI) were not known and co-exposure to other potentially active compounds (namely ultraviolet rays and other potentially genotoxic metals) occurred in several studies. Some negative results (Hamamy et al. 1987) were probably due to low exposure, because the chromium levels in plasma and urine of exposed and unexposed workers did not differ. Furthermore, some of the studies (Deng et al. 1988; Hamamy et al. 1987; Stella et al. 1982) used groups that were too small (<20 individuals) to have the statistical power to reliably assess the cytogenetic changes in workers. Although most older occupational exposure studies gave negative or equivocal results, most recent studies have identified chromosomal effects in exposed workers (Benova et al. 2002; Gambelunghe et al. 2003; Wu et al. 2001). Furthermore, results of studies in human cell lines provide evidence of the genotoxic activity of chromium compounds. Thus, the available studies support that chromium compounds, particularly chromium(VI), have carcinogenic potential because interactions with DNA have been linked with the mechanism of carcinogenicity. No studies were located regarding genotoxic effects in humans after oral exposure to chromium or its compounds.

Numerous studies have evaluated the genotoxicity of chromium compounds in animals by several exposure routes, including oral, inhalation, and parenteral routes. No increased incidence of micronuclei in polychromatic erythrocytes was observed in mice given single gavage doses of potassium chromate at ≤86 mg chromium(VI)/kg (Shindo et al. 1989) or in mice exposed to potassium chromate via drinking water at 1–20 ppm for 48 hours or to bolus doses up to 4 μg/kg for 2 days (Mirsalis et al. 1996). Similarly, no UDS in hepatocytes was found in rats. However, an increase in DNA-protein crosslinking was found in the livers of rats exposed to potassium chromate in the drinking water at ≥6 mg chromium(VI)/kg/day for 3 or 6 weeks (Coogan et al. 1991a).

The clastogenic effects of male Swiss albino mice fed chromium(VI) trioxide (20 mg/kg body weight) by gavage were studied; after 24 hours, bone marrow cells were isolated and 500 metaphase plates were scored for chromosomal aberrations (Sarkar et al. 1993). The treated cells showed a significant increase in aberrations per cell over controls by 4.4-fold. When animals were treated simultaneously with chlorophyllin (1.5 mg/kg), a sodium-copper derivative of chlorophyll and an antioxidant, numbers of aberrations were reduced to nearly background levels.

An increase in DNA-protein crosslinking was found in the livers of rats that had been exposed to potassium chromate in the drinking water at ≥6 mg chromium(VI)/kg/day for 3 or 6 weeks (Coogan et al. 1991a). Bone marrow cells from male mice fed chromium(VI) trioxide at 20 mg chromium(VI)/kg by gavage had a 4.4-fold increase in chromosomal aberration over controls (Sarkar et al. 1993). Significant DNA alterations were seen in the lung, but not the liver, of rats exposed to chromium (VI) by intratrachael instillation of sodium dichromate (Izzotti et al. 1998). DNA damage was also reported in leukocytes and peripheral lymphocytes of mice orally exposed to chromium(VI) as potassium chromate (Devi et al. 2001; Wang et al. 2006), and transplacental exposure of potassium dichromate resulted in DNA deletions the retinal pigment epithelium of mice (Kirpnick-Sobol et al. 2006). Intraperitoneal exposure to chromium(VI) as potassium dichromate caused single strand breaks in mouse liver and kidney cells, but did not in spleen, lung, or brain cells (Ueno et al. 2001). Micronucleated polychromatic erythrocytes were found in mice following intraperitoneal exposure to chromium(VI) as potassium dichromate (Chorvatovičová et al. 1993; De Flora et al. 2006; Itoh and Shimada 1996, 1997; Wild 1978; Wroñska-Nofer et al. 1999), though one study reported negative results following intraperitoneal exposure to potassium chromate (Shindo et al. 1989). In contrast, oral exposure of mice to chromium(VI), as potassium dichromate or sodium dichromate dihydrate, did not induce micronuclei in bone marrow or in peripheral blood cells (De Flora et al. 2006; Mirsalis et al. 1996; NTP 2008a). Similar to chromium(VI) compounds, oral exposure of chromium(III) compounds also did not induce micronuclei in mouse erythrocytes (NTP 2008b), bone marrow cells (De Flora et al. 2006; NTP 2008b), or in peripheral blood cells (De Flora et al. 2006). Transplacental exposure to fetuses from dams exposed to chromium(VI) as either sodium dichromate dihydrate or potassium dichromate through drinking water did not result in micronuclei in fetal liver or peripheral blood cells (De Flora et al. 2006), while transplacental exposure to fetuses from dams exposed by intraperitoneal injection to these same chromium(VI) compounds did result in micronuclei in both fetal liver and peripheral blood cells (De Flora et al. 2006).

No unscheduled DNA synthesis was found in rat hepatocytes after the rats were exposed to potassium chromate in drinking water (Mirsalis et al. 1996). The contrasting results may relate to route-specific

differences in absorption or metabolic fate of chromate *in vivo*. Furthermore, intraperitoneal exposure to chromium(VI) as potassium dichromate induced dominant lethality in mice (Paschin et al. 1982) and a significant increase in mutant frequency within mouse hepatocytes (Itoh and Shimada 1997, 1998) and bone marrow cells (Itoh and Shimada 1998). Intraperitoneal injection in rats with sodium dichromate chromium(VI)) resulted in DNA crosslinks in liver, kidney, and lung nuclei (Tsapakos et al. 1983b), while similar injection in rats with chromium(III) trichloride did not cause DNA interstrand crosslinks, DNA-protein crosslinks, or DNA strand breaks in liver and kidney nuclei (Cupo and Wetterhahn 1985). Oral exposure to niacin-bound chromium(III) did not cause DNA fragmentation in rats after 90 days of dietary exposure at doses >621.6 mg Cr(III)/kg/day (Shara et al. 2005). In addition, studies in *Drosophila melanogaster* showed an induction of gene mutations after exposure to chromium(VI) (Amrani et al. 1999; Gava et al. 1989a; Kaya et al. 2002; Rasmuson 1985; Rodriguez-Arnaiz and Martinez 1986; Olvera et al. 1993; Zimmering et al. 1985), but not after exposure to chromium(III) (Amrani et al. 1999).

The vast majority of studies reported genotoxic effects of chromium(VI) in mammalian cells *in vitro* (Blasiak and Kowalik 2000; Briggs and Briggs 1988; Depault et al. 2006; DiPaolo and Casto 1979; Douglas et al. 1980; Elias et al. 1989b; Fornace et al. 1981; Gomez-Arroyo et al. 1981; Ha et al. 2004; Koshi 1979; Koshi and Iwasaki 1983; Kowalski et al. 1996; Levis and Majone 1979; MacRae et al. 1979; Majone and Levis 1979; Montaldi et al. 1987; Nakamuro et al. 1978; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarto et al. 1980; Seoane and Dulout 1999; Stella et al. 1982; Sugiyama et al. 1986a; Trzeciak et al. 2000; Tsuda and Kato 1977; Umeda and Nishimura 1979; Venier et al. 1982; Whiting et al. 1979; Wise et al. 2002, 2003; Yang et al. 1992). Chromium(VI) also induced DNA damage (DNA interstrand crosslinks, DNA strand breaks, DNA-protein crosslinks) in cultured chick embryo hepatocytes (Tsapakos et al. 1983a). In contrast, mostly negative results were reported for chromium(III) in mammalian cells (Fornace et al. 1981; Levis and Majone 1979; MacRae et al. 1979; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarto et al. 1980; Shara et al. 2005; Stella et al. 1982; Tsuda and Kato 1977; Umeda and Nishimura 1979; Venier et al. 1982; Whiting et al. 1979) and chick embryo hepatocytes (Tsapakos et al. 1983a). Positive results were obtained in Chinese hamster ovary cells (Coryell and Stearns 2006; Levis and Majone 1979; Stearns et al. 2002), mouse fetal cells (Raffetto et al. 1977), and mouse lymphoma cells (Whittaker et al. 2005). Chromium(III) picolinate caused chromosome damage (Stearns et al. 1995b) and mutations in cultured mammalian cells (Stearns et al. 2002).

Chromium(VI) was genotoxic in *Saccharomyces cerevisiae* (Fukunaga et al. 1982; Kirpnick-Sobol et al. 2006; Singh 1983) and *Schizosaccharomyces pombe* (Bonatti et al. 1976). Two studies demonstrated the genotoxicity of chromium(III) in *S. cerevisiae* (Bronzetti et al. 1986; Kirpnick-Sobol et al. 2006).

In vitro studies indicated that soluble chromium(VI) compounds are mutagenic in *Salmonella typhimurium* reverse mutation assays (Bennicelli et al. 1983; De Flora 1978, 1981; Haworth et al. 1983; Nakamura et al. 1987; NTP 2007a; Venier et al. 1982; Watanabe et al. 1998a; Yamamoto et al. 2002), and in a *Salmonella* microsuspension bioassay (Tagliari et al. 2004). Only one study reported negative results with chromium(VI) in all tested strains (Kanematsu et al. 1980). In contrast, studies with chromium(III) did not report the induction of reverse mutations in *S. typhimurium* (Bennicelli et al. 1983; De Flora 1981; NTP 2008b; Petrilli and De Flora 1978b; Shara et al. 2005; Venier et al. 1982; Whittaker et al. 2005; Yamamoto et al. 2002). After preincubation with mammalian microsomes, the mutagenicity of chromium(VI) compounds was reduced or abolished due to concentrations of the reductant glutathione, cysteine, or NADPH capable of converting chromium(VI) to chromium(III) compounds (Bennicelli et al. 1983; De Flora 1978,1981). Chromium(VI) compounds caused gene mutations in *Bacillus subtilis* (Kanematsu et al. 1980; Nakamuro et al. 1978; Nishioka 1975) and *Escherichia coli* (Kanematsu et al. 1980; Kortenkamp et al. 1996b; Llagostera et al. 1986; Nakamuro et al. 1978; NTP 2007; Olivier and Marzin 1987; Venitt and Levy 1974; Watanabe et al. 1998a). Negative or weakly positive results were reported in *B. subtilis* with chromium(III) (Kanematsu et al. 1980; Matsui 1980; Nakamuro et al. 1978; Nishioka 1975) and mostly negative results were reported in *E. coli* (Llagostera et al. 1986; NTP 2008b; Olivier and Marzin 1987; Venier et al. 1989). However, hydrophobic ligands such as 2,2´-bipyridine, 1,10-phenanthroline, or picolinic acid form complexes with chromium(III), which are able to penetrate cell membranes and to cause genotoxicity. Complexes of chromium(III) with 2,2´-bipyridine or 1,10-phenanthroline were mutagenic in *S. typhimurium* (Warren et al. 1981). Chromium(III) picolinate was not mutagenic in *S. typhimurium* or *E. coli* (NTP 2008b).

A chromium(IV) ester was synthesized with 2,4-dimethyl-pentane-2,4-diol to examined its ability to cause DNA double strand breaks (Luo et al. 1996). Calf thymus DNA was reacted with the chromium(IV) complex (1.3 mg/mL) in the presence of 2 mM hydrogen peroxide for 6 days at pH 6.8. The results showed that the complex in the presence of hydrogen peroxide significantly damaged DNA by causing double strand breaks. Neither chromium(IV) or hydrogen peroxide alone damaged DNA. The kinetics of the reaction of chromium(IV) with hydrogen peroxide showed the formation of proportional amounts of hydroxyl radical with chromium(V). Use of a free radical scavenger prevented DNA strand breaks. Other studies have shown that chromium(IV) is a better Fenton reagent than chromium(V) for

reducing hydrogen peroxide, and thus, chromium(IV)-type damage by generating hydroxyl radicals may also be a contributor of *in vivo* genotoxicity.

In conclusion, chromium(VI) compounds were positive in the majority of tests reported, and their genotoxicity was related to the solubility and, therefore, to the bioavailability to the targets. Results of occupational exposure studies in humans, although somewhat compromised by concomitant exposures to other potential genotoxic compounds, provide evidence of chromium(VI)-induced DNA strand breaks, chromosome aberrations, increased sister chromatid exchange, unscheduled DNA synthesis, and DNA-protein crosslinks. Findings from occupational exposure studies are supported by results of *in vivo* studies in animals, *in vitro* studies in mammalian cells, yeast and bacteria, and studies in cell-free systems. Compared to chromium(VI), chromium(III) was more genotoxic in subcellular targets, but lost this ability in cellular systems. The reduction of chromium(VI) in the cells to chromium(III) and its subsequent genotoxicity may be greatly responsible for the final genotoxic effects (Beyersmann and Koster 1987; Zhitkovich et al. 2005). Reduction of chromium(VI) can also result in the formation of chromium(V), which is highly reactive and capable of interaction with DNA (Jennette 1982; Norseth 1986).

3.4 TOXICOKINETICS

The toxicokinetics of a given chromium compound depend on the valence state of the chromium atom and the nature of its ligands. Naturally occurring chromium compounds are generally in the trivalent state (chromium(III)), while hexavalent chromium compounds (chromium(VI)) are produced industrially by the oxidation of chromium(III) compounds.

The amount and location of deposition of inhaled chromium will be determined by factors that influence convection, diffusion, sedimentation, and interception of particles in the airways. These factors include air flow velocities, which are affected by breathing rate and tidal volume; airway geometry; and aerosol particle size (ICRP 1994). In general, deposition in the thoracic and pulmonary regions of the respiratory tract increase (as a fraction of the total deposited dose) as particle sizes decrease. Larger particles (e.g., >10 μm in diameter) deposit in the extrathoracic region. Chromium that deposits in the respiratory tract are subject to three general clearance processes: (1) mucociliary transport to the gastrointestinal tract for the ciliated airways (i.e. trachea, bronchi, and proximal bronchioles); (2) phagocytosis by lung macrophages and cellular transport to thoracic lymph nodes; or (3) absorption and transfer by blood and/or lymph to other tissues. The above processes apply to all forms of deposited chromium, although

the relative contributions of each pathway and rates associated with each pathway may vary with the physical characteristics (e.g., particle size), chemical form (degree of water solubility), and chemotactic properties of the chromium particles. In general, less water-soluble chromium compounds that deposit in the pulmonary region can be expected to have a longer retention time in the lung than more soluble forms. In addition, lung concentrations of chromium increase with increasing age.

Most quantitative studies of the gastrointestinal absorption of chromium in humans have estimated the absorption fraction to be <10% of the ingested dose. In general, these studies suggest that the absorption fraction of soluble chromium compounds is higher than insoluble forms (e.g., $CrCO_3$), and is higher for soluble chromium(VI) compounds (e.g., $K_2Cr_2O_7$) than soluble chromium(III) (e.g., $CrCl_3$). Chromium(VI) is reduced in the stomach to chromium(III), which lowers the absorbed dose from ingested chromium(VI). Absorption is also affected by the nutritional status of chromium(III); the absorption fraction is higher when dietary intakes are lower. Peak plasma concentrations of chromium occur within 2 hours following an oral dose of soluble chromium, suggesting that absorption occurred. Chromium absorption occurs in the upper small intestine.

Chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Few quantitative estimates of dermal absorption in humans have been reported. A 3-hour immersion in a warm aqueous bath of 22 mg Cr(VI)/L (as $K_2Cr_2O_7$) resulted in absorption (based on urine measurements) of approximately $3.3x10^{-5}$–$4.1x10^{-4}$ μg Cr/cm^2-hour (Corbett et al. 1997).

Absorbed chromium distributes to nearly all tissues, with the highest concentrations found in kidney and liver. Bone is also a major depot and may contribute to long-term retention kinetics or chromium. Chromium(VI) is unstable in the body and is reduced to chromium(V), chromium(IV), and ultimately to chromium(III) by many substances including ascorbate and glutathione. Reduction of chromium(VI) to chromium(III) can give rise to reactive intermediates, chromium adducts with proteins and DNA, and secondary free radicals. Chromium(VI) in blood is taken up into red blood cells, where it undergoes reduction and forms complexes with hemoglobin and other intracellular proteins that are sufficiently stable to retain chromium for a substantial fraction of the red blood cell lifetime. Absorbed chromium can be transferred to fetuses through the placenta and to infants via breast milk. Absorbed chromium is excreted predominantly in urine. Studies in animals have shown that chromium can be secreted in bile following parenteral (e.g., intravenous) injection of chromium(VI) or chromium (III) compounds. Chromium can also be eliminated by transfer to hair and nails. Chromium absorbed following ingestion of chromium(VI) (as $K_2Cr_2O_7$) appears to have a slower elimination rate ($t_{1/2}$ approximately 40 hours)

than when chromium is absorbed following ingestion of soluble chromium(III) (as $CrCl_3$; $t_{1/2}$ approximately 10 hours).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

The absorption of inhaled chromium compounds depends on a number of factors, including physical and chemical properties of the particles (oxidation state, size, solubility) and the activity of alveolar macrophages.

The identification of chromium in urine, serum and tissues of humans occupationally exposed to soluble chromium(III) or chromium(VI) compounds in air indicates that chromium can be absorbed from the lungs (Cavalleri and Minoia 1985; Gylseth et al. 1977; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Tossavainen et al. 1980). In most cases, chromium(VI) compounds are more readily absorbed from the lungs than chromium(III) compounds, due in part to differences in the capacity to penetrate biological membranes. Nevertheless, workers exposed to chromium(III) lignosulfonate dust at 0.005–0.23 mg chromium(III)/m^3 had clearly detectable concentrations of chromium in the urine at the end of their shifts. Based on a one-compartment kinetic model, the biological half-life of chromium(III) from the lignosulfonate dust was 4–10 hours, which is the same order of magnitude as the half-life for chromium(VI) compounds (Kiilunen et al. 1983).

Rats exposed to 2.1 mg chromium(VI)/m^3 as zinc chromate 6 hours/day achieved steady-state concentrations in the blood after ~4 days of exposure (Langård et al. 1978). Rats exposed for a single inhalation of chromium(VI) trioxide mist from electroplating at a concentration of 3.18 mg chromium(VI)/m^3 for 30 minutes rapidly absorbed chromium from the lungs. The content of chromium in the lungs declined from 13.0 mg immediately after exposure to 1.1 mg at 4 weeks in a triphasic pattern with an overall half-life of 5 days (Adachi et al. 1981). Based on a study in rats exposed to chromium(VI) as potassium dichromate or to chromium(III) as chromium trichloride, the pulmonary clearance of both valence states was dependent on particle size, and chromium(VI) was more rapidly and extensively transported to the bloodstream than chromium(III). The rats had been exposed to 7.3–15.9 mg chromium(VI)/m^3 as potassium dichromate for 2–6 hours or to 8 or 10.7 mg chromium(III)/m^3 as chromium trichloride for 6 or 2 hours, respectively. Chromium(VI) particles of 1.5 or 1.6 μm had a two-compartment pulmonary clearance curve with half-lives of 31.5 hours for the first phase and 737 hours for the second phase. Chromium(VI) particles of 2 μm had a single component curve with a half-life

between 151 and 175 hours. Following exposure to chromium(VI), the ratio of blood chromium/lung chromium was 1.44 at 0.5 hours, 0.81 at 18 hours, 0.85 at 48 hours, and 0.96 at 168 hours after exposure. Chromium(III) particles of 1.5–1.8 μm had a single component pulmonary clearance curve with a half-life of 164 hours. Following exposure to chromium(III), the ratio of blood chromium/lung chromium was 0.39 at 0.5 hours, 0.24 at 18 hours, 0.22 at 48 hours, and 0.26 at 168 hours after exposure. Therefore, the amount of chromium(VI) transferred to the blood from the lungs was always at least 3 times greater than the amount of chromium(III) transferred (Suzuki et al. 1984). Other studies reporting absorption from the lungs are intratracheal injection studies (Baetjer et al. 1959b; Bragt and van Dura 1983; Visek et al. 1953; Wiegand et al. 1984, 1987). These studies indicate that 53–85% of chromium(VI) compounds (particle size <5 μm) are cleared from the lungs by absorption into the bloodstream or by mucociliary clearance in the pharynx; the rest remain in the lungs. Absorption by the bloodstream and mucociliary clearance was only 5–30% for chromium(III) compounds.

The kinetics of three chromium(VI) compounds, sodium chromate, zinc chromate, and lead chromate, were compared in rats in relation to their solubility. The rats received intratracheal injections of the ^{51}chromium-labeled compounds (0.38 mg chromium(VI)/kg as sodium chromate, 0.36 mg chromium(VI)/kg as zinc chromate, or 0.21 mg chromium(VI)/kg as lead chromate). Peak blood levels of ^{51}chromium were reached after 30 minutes for sodium chromate (0.35 μg chromium/mL), and 24 hours for zinc chromate (0.60 μg chromium/mL) and lead chromate (0.007 μg chromium/mL). At 30 minutes after administration, the lungs contained 36, 25, and 81% of the respective dose of the sodium, zinc, and lead chromate. On day 6, >80% of the dose of all three compounds had been cleared from the lungs, during which time, the disappearance from lungs followed linear first-order kinetics. The residual amounts left in the lungs on day 50 or 51 were 3.0, 3.9, and 13.9%, respectively. The results indicate that zinc chromate, which is ~1,000 times less soluble than sodium chromate, is more slowly absorbed from the lungs, but peak blood levels are higher than sodium chromate. Lead chromate was more poorly and slowly absorbed, as indicated by very low levels in blood and other tissues, and greater retention in the lungs (Bragt and van Dura 1983).

The fate of lead chromate(VI), chromium(VI) trioxide, chromium(III) oxide and chromium(III) sulfate were examined when solutions or suspensions of these chemicals were slowly infused into the tracheal lobe bronchus of sheep via bronchoscopic catheterization (Perrault et al. 1995). At 2, 3, 5, and 30 days, the samples of bronchoalveolar lavage were taken, and on day 31, the animals were sacrificed and lung specimens were examined for chromium particulates. There was no difference in lung particle concentrations among the four different compounds. The values ranged from $0.14x10^5$ to

$1.02x10^5$ particles/g dry tissue compared to control values of $0.03x10^5$. The alveolar clearance of slightly soluble chromium(III) oxide and chromium(III) sulfate was calculated to be 11 and 80 days, respectively. The insoluble lead chromate particles appeared to break up, forming isometric particles of lead chromate as well as lead-containing particulates that may have retarded clearance. Retention of chromium particulates from exposure to soluble chromium trioxide may have resulted in the formation of a less-soluble hydroxyl complex and/or chemical interaction between chromium and protein that prolongs the retention of the metal. Analyses of the particulates in lavage samples indicate that these diameters increase with time for lead chromate, decrease with time for chromium sulfate and chromium trioxide, and are unchanged for chromium(III) oxide. The authors state that their findings indicate that slightly soluble chromium(III) oxide and chromium sulfate that are chemically stable can be cleared from lungs at different rates, depending on the nature and morphology of the compound.

Amounts of total chromium were measured in lymphocytes, blood, and urine after intratracheal administration of either sodium dichromate(VI) or chromium(III) acetate hydroxide (a water-soluble chromium(III) compound) to male Wistar rats (Gao et al. 1993). The total amount of chromium administered was 0.44 mg chromium/kg body weight for each compound. The highest concentrations in tissues and urine occurred at 6 hours after treatment, the first time point examined. Mean chromium concentrations (n=4 rats per time point) from treatment with chromium(III) were 56.3 μg/L in whole blood, 96 μg/L in plasma, 0.44 $\mu g/10^{10}$ in lymphocytes, and 4,535.6 μg/g creatinine in urine. For treatment with chromium(VI) the levels were 233.2 μg/L for whole blood, 138 μg/L for plasma, 2.87 $\mu g/10^{10}$ for lymphocytes, and 2,947.9 μg/g creatinine in urine. The levels in lymphocytes in the chromium(III) treated animals were no different than in untreated animals. However, for chromium(VI) the lymphocyte levels were about 6-fold higher than control values. After 72 hours, the chromium levels were significantly reduced. These results suggest that absorbed chromium(III) compounds may be excreted more rapidly than absorbed chromium(VI) compounds because of a poorer ability to enter cells.

3.4.1.2 Oral Exposure

Chromium(III) is an essential nutrient required for normal energy metabolism. The Institute of Medicine (IOM 2001) of the NAS determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 μg chromium(III)/day for adolescents and adults (IOM 2001). Currently, the biological target for the essential effects of chromium(III) is unknown. Chromodulin, also referred to as glucose tolerance factor (GTF), has been proposed as one possible candidate (Jacquamet et al. 2003). The function of chromodulin, an oligopeptide complex containing with four chromic ions, has not been

established; however, a possible mechanism is that chromodulin facilitates the interaction of insulin with its cellular receptor sites, although this has not been proven (Anderson 1998a, 2003; IOM 2001). Chromium(III) picolinate is a common form of chromium(III) nutritional supplementation.

Trivalent chromium is very poorly absorbed from the gastrointestinal tract. Typically, ≤1% of an orally administered dose of trivalent chromium has been recovered in the urine of experimental animals of humans (Aitio et al. 1984; Anderson et al. 1983; Doisy et al. 1971; Donaldson and Barreras 1966; Gargas et al. 1994; Garcia et al. 2001; Kerger et al. 1996a) or experimental animals (Donaldson and Barreras 1966; Febel et al. 2001). Oral absorption of trivalent chromium complexed with an organic ligand is similarly low and not higher than inorganic forms **(**Anderson et al. 1996; Gonzalez-Vergara et al. 1981). Bypassing the stomach by infusing trivalent chromium into the duodenum or jejunum resulted in at most 1–2% of the dose being absorbed in humans (Donaldson and Barreras 1966), or 1% (Febel et al. 2001) to 4% in the rat (Donaldson and Barreras 1966).

Approximately 0.5–2.0% of dietary chromium(III) is absorbed via the gastrointestinal tract of humans (Anderson 1986; Anderson et al. 1983) as inferred from urinary excretion measurements. The absorption fraction is dependent on the dietary intake. At low levels of dietary intake (10 μg), ~2.0% of the chromium was absorbed. When intake was increased by supplementation to ≥40 μg, the absorption decreased to ~0.5% (Anderson 1986; Anderson et al. 1983). Net absorption of chromium(III) by a group of 23 elderly subjects who received an average of 24.5 μg/day (0.00035 mg chromium(III)/kg/day) from their normal diets was calculated to be 0.6 μg chromium(III)/day, based on an excretion of 0.4 μg chromium/day in the urine and 23.9 μg chromium/day in the feces, with a net retention of 0.2 μg/day. Thus, about 2.4% was absorbed. The retention was considered adequate for their requirements (Bunker et al. 1984).

The absorption fraction of soluble chromium(III), as chromium picolinate, is greater than $CrCl_3$ (DiSilvestro and Dy 2007; Gargas et al. 1994). Following ingestion of 400 μg chromium(III)/day as chromium picolinate (in a capsule) for 3 consecutive days, mean absorption fraction in eight healthy adults was 2.8% (±1.4 % standard deviation [SD]; Gargas et al. 1994). Based on urinary excretion following oral administration of a single dose (200 μg chromium(III)) of four different chromium(III) supplements to healthy women (n=24; cross-over design), the absorption of chromium picolinate was higher than that of chromium chloride, chromium polynicotinate, and chromium nicotinate-glucinate; estimates of oral absorption were not reported (DiSilvestro and Dy 2007). Urinary excretion of chromium following administration of chromium picolinate was approximately 16-fold higher than that following

administration of chromium chloride and approximately 2-fold greater than that following administration of the two nicotinate complexes.

Association of chromium with chelating agents, which may be naturally present in feed, can alter the bioavailability from food. In rats that were given ^{51}Cr-chromium(III) trichloride mixed with chelating agents, either oxalate or phytate, phytate significantly ($p<0.05$) decreased the levels of radioactivity in blood, whole body, and urine achieved with chromium(III) trichloride alone (Chen et al. 1973). Oxalate, however, greatly increased the levels in blood, whole body, and urine. The oxalate served as a strong ligand to protect against the tendency of chromium(III) to form insoluble macromolecular chromium oxides at physiological pH. Fasted rats absorbed significantly more ^{51}chromium than did nonfasted rats, indicating that the presence of food in the gastrointestinal tract slows the absorption of chromium. Results of an *in vitro* experiment in this study indicated that the midsection had greater uptake than the duodenum or ileum and that oxalate significantly ($p<0.05$) increased, while phytate significantly ($p<0.05$) decreased the transport of chromium(III) across all three sections, paralleling the *in vivo* results. Ethylenediamine tetraacetic acid (EDTA) and citrate were also tested in the *in vitro* system, but were found to have no effect on chromium(III) intestinal transport; therefore, these chelating agents were not tested *in vivo* (Chen et al. 1973).

The absorption fraction of soluble chromium(VI) is higher than that of soluble chromium(III) (Anderson et al. 1983; Donaldson and Barreras 1966; Kerger et al. 1996a). Average absorption fractions, determined from cumulative urinary excretion in 8 healthy adults who ingested 5 mg chromium (in 10 mg Cr/L drinking water) as $CrCl_3$ or $K_2Cr_2O_7$ were 0.13% (±0.04, standard error [SE]) and 6.9% (±3.7, SE), respectively. Chromium(VI) can be reduced to chromium(III) when placed in an ascorbic acid solution (Kerger et al. 1996a). When $K_2Cr_2O_7$ was ingested in orange juice (where it was reduced and may have formed complexes with constituents of the juice), the mean absorption fraction was 0.60% (±0.11, SE; Kerger et al. 1996a). Plasma concentrations generally peaked around 90 minutes following exposure for all three chromium mixtures tested. Based on measurements of urinary excretion of chromium in 15 female and 27 male subjects who ingested 200 µg chromium(III) as $CrCl_3$, the absorption fraction was estimated to be approximately 0.4% (Anderson et al. 1983). The absorption fraction of chromium(VI) (as sodium chromate) was substantially higher when administered directly into the duodenum (approximately 10%) compared to when it is ingested (approximately 1.2%), whereas the absorption fraction for $CrCl_3$ was similar when administered into the small intestine (0.5%; Donaldson and Barreras 1966). These results are consistent with studies that have shown that gastric juice can reduce chromium(VI) to chromium(III) (De Flora et al. 1987a).

The absorption of chromium(VI) and chromium(III) was measured in four male and two female volunteers (ages ranging from 25 to 39 years) treated orally with potassium chromate (chromium(VI)) or chromic oxide (chromium(III)) in capsules at doses of 0.005 and 1.0 mg/kg/day, respectively (Finley et al. 1996b). Subjects were exposed to each compound for 3 days. Based on urinary excretion data, the mean absorption of potassium chromate was 3.4% (range 0.69–11.9%). No statistically significant increase in urinary chromium was observed during chromic oxide dosing, indicating that little, if any, was absorbed. In a follow-up study by the same group (Finley et al. 1997), five male volunteers ingested a liter, in three volumes of 333 mL, of deionized water containing chromium(VI) concentrations ranging from 0.1 to 10.0 mg/L (approximately 0.001–0.1 mg chromium(VI)/kg/day) for 3 days. A dose-related increase in urinary chromium was seen in all subjects and the percent of the dose excreted ranged from <2 to 8%. Dose-related increases in plasma and erythrocyte chromium levels were also observed.

In a repeated dose study, three healthy adults ingested chromium(VI) (as $K_2Cr_2O_7$) in water at 5 mg chromium/day for 3 consecutive days (Kerger et al. 1997). Three divided doses were taken at approximately 6-hour intervals over a 5–15-minute period. After at least 2 days without dosing, the 3-day exposure regimen was repeated at 10 mg chromium/day. Estimated doses based on body weight were 0.05 and 0.1 mg/kg/day, respectively. Bioavailability based on 4-day urinary excretion was 1.7% (range 0.5–2.7%) at 0.05 mg chromium(VI)/kg/day and 3.4% (range 0.8–8.0%) at 0.1 mg chromium(VI)/kg/day. Absorption of 0.05 mg chromium(VI)/kg appeared to be somewhat lower when given as three divided doses rather than when given as a single bolus dose (1.7 versus 5.7%).

Uptake of potassium dichromate was determined in a man who was given 0.8 mg of chromium(VI) in drinking water 5 times each day for 17 days (Paustenbach et al. 1996). Steady-state concentrations of chromium in blood were attained after 7 days. Red blood cell and plasma levels returned to background levels within a few days after exposure was stopped. The data are consistent with a bioavailability of 2% and a plasma elimination half-life of 36 hours.

Studies with ^{51}chromium in animals indicate that chromium and its compounds are also poorly absorbed from the gastrointestinal tract after oral exposure. When radioactive sodium chromate (chromium(VI)) was given orally to rats, the amount of chromium in the feces was greater than that found when sodium chromate was injected directly into the jejunum. Since chromium(III) is absorbed less readily than chromium(VI) by the gastrointestinal tract, these results are consistent with evidence that the gastric environment has a capacity to reduce chromium(VI) to chromium(III). Furthermore, the administration

of radioactive chromium(III) or chromium(VI) compounds directly into the jejunum decreased the amount of chromium recovery in the feces indicating that the jejunum is the absorption site for chromium (Donaldson and Barreras 1966). Absorption of either valence state was ≤1.4% of the administered oral dose in rats (Sayato et al. 1980) and hamsters (Henderson et al. 1979). Based on distribution (see Section 3.3.2.2) and excretion (see Section 3.3.4.2) studies in rats administered chromium by gavage for 2–14 days from various sources, that is, from sodium chromate (chromium(VI)), from calcium chromate (chromium(VI)), or from soil contaminated with chromium (30% chromium(VI) and 70% chromium(III)), the low gastrointestinal absorption of chromium from any source was confirmed. Chromium appeared to be better absorbed from the soil than from chromate salts, but <50% of the administered chromium could be accounted for in these studies, partly because not all tissues were examined for chromium content and excretion was not followed to completion (Witmer et al. 1989, 1991). Adult and immature rats given chromium(III) chloride absorbed 0.1 and 1.2% of the oral dose, respectively (Sullivan et al. 1984). This suggests that immature rats may be more susceptible to potential toxic effects of chromium(III) compounds.

Treatment of rats by gavage with a nonencapsulated lead chromate pigment or with a silica-encapsulated lead chromate pigment resulted in no measurable blood levels of chromium (detection limit=10 μg/L) after 2 or 4 weeks of treatment or after a 2-week recovery period. However, kidney levels of chromium were significantly higher in the rats that received the nonencapsulated pigment than in the rats that received the encapsulated pigment, indicating that silica encapsulation reduces the gastrointestinal bioavailability of chromium from lead chromate pigments (Clapp et al. 1991).

The issue of whether or not chromium(VI) absorption occurs only when or principally when the reducing capacity of the gastrointestinal tract is exhausted is a factor to consider in evaluating and interpreting oral dosing bioassays in animals and human epidemiology studies of health outcomes related to ingestion exposures to chromium. Potentially, tumor responses could be enhanced if the reducing capacities of saliva and stomach fluid were exhausted. This is more likely to occur at the relatively high doses of chromium(VI) administered in animal bioassays than at doses experienced by humans from environmental exposures. However, results of experimental studies of chromium absorption in humans have not found evidence for an effect of limited of reducing capacity on absorption of chromium. The range of doses of chromium administered to humans in these different studies was considerable and demonstrated oral bioavailability at all doses. Donaldson and Barreras (1996) administered 20 ng of radiolabeled chromium(VI), Kerger et al. (1996a) administered 5 mg of chromium(VI), Finley et al. (1996b) administered 0.005 mg/kg-day of chromium(VI) for 3 days, and Finley et al. (1997) administered

0.1, 0.5, 1.0, 5.0 or 10 mg/day of chromium(VI) for 4 days. In the Finley et al. (1997) study, the percent of the administered dose of chromium(VI) recovered in the urine did not increase with dose. The results of these studies do not indicate that oral absorption of administered chromium(VI) only begins to occur when the reducing capacity of the stomach is exhausted, and are consistent with estimates of gastrointestinal reducing capacity (De Flora 2000; Proctor et al. 2002).

3.4.1.3 Dermal Exposure

Both chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Systemic toxicity has been observed in humans following dermal exposure to chromium compounds, indicating significant cutaneous absorption (see Section 3.2.3). Fourteen days after a salve containing potassium chromate was applied to the skin of an individual to treat scabies, appreciable amounts of chromium were found in the blood, urine, feces, and stomach contents (Brieger 1920) (see Section 3.4.2.3). It should be noted that the preexisting condition of scabies or the necrosis caused by the potassium chromate (see Section 3.2.3) could have facilitated dermal absorption of potassium chromate. Potassium dichromate (chromium(VI)), but not chromium(III) sulfate, penetrated the excised intact epidermis of humans (Mali et al. 1963). Dermal absorption by humans of chromium(III) sulfate in aqueous solution was negligible, with slightly larger amounts of chromium(III) nitrate in aqueous solution absorbed. The absorption of chromium(III) chloride was similar to potassium dichromate(VI) (Samitz and Shrager 1966). Chromium(III) from a concentrated chromium sulfate solution at pH 3 penetrated cadaverous human skin at a rate of $5x10^{-11}$ cm/sec, compared with a rate for chromium(VI) (source unspecified) of $5x10^{-7}$ cm/second (Spruit and van Neer 1966). In contrast, both chromium(VI) from sodium chromate and chromium(III) from chromium trichloride penetrated excised human mammary skin at similar rates, but the rate was generally slightly faster for chromium(VI). Absolute rates of absorption in nmol chromium/hour/cm^2 increased with increasing concentration of both chromium(VI) and chromium(III) (Wahlberg 1970). The average rate of systemic uptake of chromium in four volunteers submersed up to the shoulders in a tub of chlorinated water containing a 22 mg chromium(VI)/L solution of potassium dichromate for 3 hours was measured to be $1.5x10^{-4}$ μg/cm^2-hour based on urinary excretion of total chromium (Corbett et al. 1997).

The influence of solvent on the cutaneous penetration of potassium dichromate by humans has been studied. The test solutions of potassium dichromate in petrolatum or in water were applied as occluded circular patches of filter paper to the skin. Results with dichromate in water revealed that chromium(VI) penetrated beyond the dermis and penetration reached steady state with resorption by the lymph and

blood vessels by 5 hours. About 10 times more chromium penetrated when potassium dichromate was applied in petrolatum than when applied in water. About 5 times more chromium penetrated when potassium dichromate was applied than when a chromium trichloride glycine complex was applied (Liden and Lundberg 1979). The rates of absorption of solutions of sodium chromate from the occluded forearm skin of volunteers increased with increasing concentration. The rates were 1.1 μg chromium(VI)/ cm^2/hour for a 0.01 M solution, 6.4 μg chromium(VI)/cm^2/hour for a 0.1 M solution, and 10 μg chromium(VI)/cm^2/hour for a 0.2 M solution (Baranowska-Dutkiewicz 1981).

Chromium and its compounds are also absorbed dermally by animals. The dermal absorption of sodium chromate (chromium(VI)) by guinea pigs was somewhat higher than that of chromium(III) trichloride, but the difference was not significant. At higher concentrations (0.261–0.398 M), absorption of sodium chromate was statistically higher than that of chromium trichloride. The peak rates of absorption were 690–725 and 315–330 nmol/hour/cm^2 for sodium chromate at 0.261–0.398 M and chromium trichloride at 0.239–0.261 M, respectively. Percutaneous absorption of sodium chromate was higher at pH≥6.5 compared with pH≤5.6 (Wahlberg and Skog 1965).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Examination of tissues from Japanese chrome platers and chromate refining workers at autopsy revealed higher chromium levels in the hilar lymph node, lung, spleen, liver, kidney, and heart, compared to normal healthy males (Teraoka 1981). Analysis of the chromium concentrations in organs and tissues at autopsy of a man who died of lung cancer 10 years after his retirement from working in a chromate producing plant for 30 years revealed measurable levels in the brain, pharyngeal wall, lung, liver, aorta, kidney, abdominal rectal muscle, suprarenal gland, sternal bone marrow, and abdominal skin. The levels were significantly higher than in five controls with no occupational exposure to chromium. The man had been exposed mainly to chromium(VI), with lesser exposure to chromium(III) as the chromite ore (Hyodo et al. 1980). The levels of chromium were higher in the lungs, but not in the liver or kidneys, of autopsy specimens from 21 smeltery and refinery workers in North Sweden compared with that for a control group of 8 individuals. The amount of enrichment in the lungs decreased as the number of elapsed years between retirement and death increased (Brune et al. 1980). Tissues from three individuals having lung cancer who were industrially exposed to chromium were examined by Mancuso (1997b). One was employed for 15 years as a welder, a second worked for 10.2 years, and a third for 31.8 years in ore milling and preparations and boiler operations. The three cumulative chromium exposures for the three

workers were 3.45, 4.59, and 11.38 mg/m^3 years, respectively. Tissues from the first worker were analyzed 3.5 years after last exposure, the second worker 18 years after, and the third worker 0.6 years after last exposure. All tissues from the three workers had elevated levels of chromium with the possible exception of neural tissues. Levels were orders of magnitude higher in lungs than other tissues. The highest lung level reported was 456 mg/10 g tissue in the first worker, 178 in the second worker, and 1,920 for the third worker. There were significant chromium levels in the tissue of the second worker even though he had not been exposed to chromium for 18 years. Chromium concentrations in lung tissues from autopsy samples were 5 times higher in subjects who originated from the Ruhr and Dortmund regions of Germany, where emissions of chromium are high, than in subjects from Munster and vicinity. The lung concentrations of chromium increased with increasing age. Men had twice as high concentrations of chromium in the lungs than did women, which may reflect the greater potential for occupational exposure by men, the higher vital capacity of men, and possibly a greater history of smoking (Kollmeier et al. 1990).

Chromium may be transferred to fetuses through the placenta and to infants via breast milk. Analysis of chromium levels in women employees of a dichromate manufacturing facility in Russia during and after pregnancy revealed that the exposed women had significantly higher levels of chromium in blood and urine during pregnancy, in umbilical cord blood, placentae, and breast milk at child birth, and in fetuses aborted at 12 weeks than did nonexposed controls (Shmitova 1980). The reliability of this study is suspect because the levels of chromium reported in the blood and urine of the control women were much higher than usual background levels of chromium in these biological fluids (see Section 6.5), perhaps due to problems with analytical methods. Measurement of the chromium content in 255 samples from 45 lactating American women revealed that most samples contained <0.4 μg/L, and the mean value was 0.3 μg/L (Casey and Hambidge 1984). While these probably represent background levels in women whose main exposure to chromium is via the diet, the findings indicate that chromium may be transferred to infants via breast milk.

The distribution of radioactivity in rats given ^{51}chromium as sodium dichromate intratracheally was followed for 40 days by autoradiography and scintillation counting. Three days after the administration of 0.01 mg chromium(VI)/m^3 as radioactive sodium dichromate, the tissue distribution based on the relative concentrations in the tissue was lung > kidney > gastrointestinal tract > erythrocytes > liver > serum > testis > skin. Twenty-five days after dosing, the tissue distribution was lung > kidney > erythrocytes > testis > liver > serum > skin > gastrointestinal tract. Kidney, erythrocytes, and testis maintained their chromium levels for a period of 10–15 days before decreasing (Weber 1983). The

distribution of chromium(VI) compared with chromium(III) was investigated in guinea pigs after intratracheal instillation of potassium dichromate or chromium trichloride. At 24 hours after instillation, 11% of the original dose of chromium from potassium dichromate remained in the lungs, 8% in the erythrocytes, 1% in plasma, 3% in the kidney, and 4% in the liver. The muscle, skin, and adrenal glands contained only a trace. All tissue concentrations of chromium declined to low or nondetectable levels in 140 days with the exception of the lungs and spleen. After chromium trichloride instillation, 69% of the dose remained in the lungs at 20 minutes, while only 4% was found in the blood and other tissues, with the remaining 27% cleared from the lungs and swallowed. The only tissue that contained a significant amount of chromium 2 days after instillation of chromium trichloride was the spleen. After 30 and 60 days, 30 and 12%, respectively, of the chromium(III) was retained in the lungs, while only 2.6 and 1.6%, respectively, of the chromium(VI) dose was retained in the lung (Baetjer et al. 1959a).

3.4.2.2 Oral Exposure

Autopsy studies in the United States indicate that chromium concentrations in the body are highest in kidney, liver, lung, aorta, heart, pancreas, and spleen at birth and tend to decrease with age. The levels in liver and kidney declined after the second decade of life. The aorta, heart, and spleen levels declined rapidly between the first 45 days of life and 10 years, with low levels persisting throughout life. The level in the lung declined early, but increased again from mid life to old age (Schroeder et al. 1962).

The distribution of chromium in human body tissue after acute oral exposure was determined in the case of a 14-year-old boy who ingested 7.5 mg chromium(VI)/kg as potassium dichromate. Despite extensive treatment by dialysis and the use of the chelating agent British antilewisite, the boy died 8 days after admission to the hospital. Upon autopsy, the chromium concentrations were as follows: liver, 2.94 mg/100 cc (normal, 0.016 mg/100 cc); kidneys, 0.64 and 0.82 mg/100 cc (normal, 0.06 mg/100 cc); and brain, 0.06 mg/100 cc (normal, 0.002 mg/100 cc) (Kaufman et al. 1970). Although these data were obtained after extensive treatment to rid the body of excess chromium, the levels of chromium remaining after the treatment clearly demonstrate that these tissues absorbed at least these concentrations after an acute, lethal ingestion of a chromium(VI) compound.

Chromium may be transferred to infants via breast milk as indicated by breast milk levels of chromium in women exposed occupationally (Shmitova 1980) or via normal levels in the diet (Casey and Hambidge 1984). It has been demonstrated that in healthy women, the levels of chromium measured in breast milk are independent of serum chromium levels, urinary chromium excretion, or dietary intake of chromium

(Anderson et al. 1993, Mohamedshah et al. 1998), but others (Engelhardt et al. 1990) have disputed this observation.

The tissue distribution of chromium was studied in rats administered chromium from a variety of sources. In one experiment, sodium chromate in water was administered by gavage for 7 days at 0, 1.2, 2.3, or 5.8 mg chromium(VI)/kg/day. Very little chromium (generally <0.5 μg/organ) was found in the organs analyzed (liver, spleen, lung, kidney, and blood) after administration of the two lower doses. The levels were generally comparable to those in controls. After 5.8 mg/kg/day, the largest amount of chromium (expressed as μg chromium/whole organ) was found in the liver (≈22 μg), followed by the kidney (≈7.5 μg), lung (≈4.5 μg), blood (≈2 μg), and spleen (≈1 μg). The total amount of chromium in these tissues represented only 1.7% of the final dose of 5.8 mg/kg/day, but not all organs were analyzed. In the next experiment, rats were exposed by gavage to 7 mg chromium/kg/day for 7 days from various sources: (1) sodium chromate; (2) calcium chromate; (3) soil containing chromium (30% chromium(VI), 70% chromium(III)); or (4) a mixture of calcium chromate and the contaminated soil. The highest levels of chromium were found in liver, spleen, kidney, lung, blood, brain, and testes after dosing with sodium chromate, but the relative levels in these tissues after the other treatments followed no consistent pattern. Rats gavaged for 14 days with 13.9 mg chromium/kg/day from the four different sources had higher levels of chromium in the tissues after they were dosed with the contaminated soil or the mixture of calcium chromate and the contaminated soil than with either of the chromate salts alone. Thus, the relative organ distribution of chromium depends on the source of chromium (Witmer et al. 1989, 1991). Components in soil may affect the oxidation state and the binding of chromium to soil components, and pH of the soil may also affect the bioavailability from soil.

The chromium content in major organs (heart, lung, kidney, liver, spleen, testes) of mice receiving drinking water that provided doses of 4.8, 6.1, or 12.3 mg chromium(III)/kg/day as chromium trichloride or 4.4, 5.0, or 14.2 mg chromium(VI)/kg/day as potassium dichromate was determined after 1 year of exposure. Chromium was detected only in the liver in the chromium(III)-treated mice. Mice treated with chromium(VI) compounds had accumulation in all of the above organs, with the highest levels reported in the liver and spleen. Liver accumulation of chromium was 40–90 times higher in the chromium(VI)-treated group than in the chromium(III)-treated group (Maruyama 1982). Chromium levels in tissue (bone, kidney liver, spleen) were 9 times higher in rats given chromium(VI) as potassium chromate in drinking water for 1 year than in rats given the same concentration of chromium(III) as chromium trichloride (MacKenzie et al. 1958). In rats exposed to potassium chromate in the drinking water for 3 or 6 weeks, a general trend of increasing chromium concentration with time of exposure was apparent in the

liver and kidneys, but only the kidneys showed a difference in the concentration after exposure to 100 and 200 ppm. Blood concentrations were almost saturated by 3 weeks with little further accumulation by 6 weeks. No chromium was detected in the lungs after drinking water exposure (Coogan et al. 1991a). After acute oral dosing with radiolabeled chromium trichloride (1 μCi for immature rats, 10 μCi for adults), adult and neonatal rats accumulated higher levels of chromium in the kidneys than in the liver. At 7 days after dosing, the liver and kidney contained 0.05 and 0.12% of the dose, respectively, in the neonates and 0.002 and 0.003% of the dose, respectively, in the adult rats. The carcass contained 0.95% of the dose in the neonates and 0.07% of the dose in adult rats. The lungs contained 0.0088% of the dose in neonates and 0.0003% of the dose in adult rats. No chromium(III) was detected in the skeleton or muscle. Approximately 35 and 0.2% of the administered dose of chromium(III) at day 7 was retained in the gut of neonates and adults, respectively (Sullivan et al. 1984).

The distribution of potassium chromate(VI) was compared in male Fisher rats and C57BL/6J mice exposed either by drinking water (8 mg chromium(VI)/kg/day for 4 and 8 weeks) or by intraperitoneal injection (0.3 and 0.8 mg chromium(VI)/kg/day for 4 or 14 days) (Kargacin et al. 1993). The concentrations of chromium (μg/g wet tissue) after drinking water exposures for 8 weeks in mice were: liver 13.83, kidney 4.72, spleen 10.09, femur 12.55, lung 1.08, heart 1.02, muscle 0.60, and blood 0.42. These concentrations were not markedly different than for 4-week exposures. For rats, the concentrations were: liver 3.59, kidney 9.49, spleen 4.38, femur 1.78, lung 0.67, heart 1.05, muscle 0.17, and blood 0.58. These results demonstrate that considerable species differences exist between mice and rats and need to be factored into any toxicological extrapolations across species even if the routes of administration are the same. In the drinking water experiments, blood levels in rats and mice were comparable, but in intraperitoneal injection experiments, rats' levels were about 8-fold higher than mice after 4 days of exposure. This difference appeared to be due to increased sequestering by rat red blood cells, since accumulation in white blood cells was lower in rats than mice. The higher incidence of red cell binding was also associated with greater binding of chromium to rat hemoglobin.

The feeding of five male Wistar rats at 0.49 mg chromium(III)/kg/day as chromium(III) chloride for 10 weeks resulted in increased chromium levels in liver, kidney, spleen, hair, heart, and red blood cells (Aguilar et al. 1997). Increases were highest in kidney (0.33 μg/g wet tissue in controls versus 0.83 μg/g in treated animals) and erythrocytes (1.44 μg/g wet tissue in controls versus 3.16 μg/g in treated animals).

The higher tissue levels of chromium after administration of chromium(VI) than after administration of chromium(III) (MacKenzie et al. 1958; Maruyama 1982; Witmer et al. 1989, 1991) reflect the greater

tendency of chromium(VI) to traverse plasma membranes and bind to intracellular proteins in the various tissues, which may explain the greater degree of toxicity associated with chromium(VI). In an experiment to determine the distribution of chromium in red and white blood cells, rats were exposed orally to 0.0031 mg/kg of ^{51}chromium(VI) as sodium chromate. The ^{51}chromium content of the fractionated blood cells was determined either 24 hours or 7 days after exposure. After 24 hours, the white blood cells contained much more ^{51}chromium (≈250 pg chromium/billion cells) than did the red blood cells (≈30 pg chromium/billion cells). After 7 days, the ^{51}chromium content of the white blood cells was reduced only 2.5-fold, while that of the red blood cells was reduced 10-fold. Thus, white blood cells preferentially accumulated chromium(VI) and retained the chromium longer than did the red blood cells. As discussed in Section 3.4.2.4, a small amount of chromium(III) entered red blood cells of rats after intravenous injection of ^{51}chromium trichloride, but no ^{51}chromium was detectable in white blood cells (Coogan et al. 1991b).

Twelve pregnant female albino rats (Druckrey strain) and 13 Swiss albino mice were exposed to 500 ppm potassium dichromate(VI) in their drinking water during pregnancy up to 1 day before delivery (Saxena et al. 1990a). The chromium(VI) daily intake was calculated to be 11.9 mg chromium(VI)/day for the rats and 3.6 mg chromium(VI)/day for mice which were considered to be maximal nontoxic doses for both species. In rats, concentrations of chromium were 0.067, 0.219, and 0.142 μg/g fresh weight in maternal blood, placenta, and fetuses, respectively, and 0.064, 0.304, and 0.366 μg/g fresh weight in mice, respectively. In treated rats, chromium levels were 3.2-fold higher in maternal blood, 3-fold higher in placenta, and 3.1-fold higher in fetal tissue when compared to control values. In treated mice, chromium levels were 2.5-fold higher in maternal blood, 3.2-fold higher in placenta, and 9.6-fold higher in fetuses when compared to control values. In treated mice, there was a significant elevation in chromium levels in placental and fetal tissues over maternal blood levels, and a significant increase in chromium levels in fetal tissue over placental concentrations when compared to controls. These differences were not observed in rats, indicating that the distribution patterns in mice and rats are different.

A study of transplacental transfer of chromium(III) in different forms indicated that placental transport varies with the chemical form. Male and female rats were fed either a commercial diet that contained 500 ppb chromium or a 30% Torula yeast diet that contained <100 ppb chromium. They were also given drinking water with or without 2 ppm chromium(III) added as chromium acetate monohydrate. The rats were mated and immediately after delivery, the neonates were analyzed for chromium content. The neonates whose dams were fed the commercial diet contained almost twice as much chromium as those whose dams were fed the chromium-deficient yeast diet. Addition of chromium(III) acetate to the

drinking water of the yeast-fed rats (2 ppm) did not increase the levels of chromium in the neonates. Administration of chromium(III) trichloride intravenously or by gavage before mating, during mating, or during gestation resulted in no or only a small amount of chromium in the neonates. Administration of chromium(III) in the form of GTF from Brewer's yeast by gavage during gestation resulted in chromium levels in the litters that were 20–50% of the dams' levels. The results indicate that fetal chromium is derived from specific chromium complexes in the diet (e.g., GTF) (Mertz et al. 1969).

3.4.2.3 Dermal Exposure

The findings of toxic effects in the heart, stomach, blood, muscles, and kidneys of humans who were dermally exposed to chromium compounds is suggestive of distribution to these organs (see Section 3.2.3.2). Fourteen days after a salve containing potassium chromate(VI) was applied to the skin of an individual to treat scabies, appreciable amounts of chromium were found in the blood (2–5 mg/100 mL), urine (8 mg/L), feces (0.61 mg/100 g), and stomach contents (0.63 mg/100 mL) (Brieger 1920). The preexisting condition of scabies or the necrosis caused by the potassium chromate could have facilitated its absorption. A transient increase in the levels of total chromium in erythrocytes and plasma was observed in subjects immersed in a tank of chlorinated water containing potassium dichromate(VI) (Corbett et al. 1997).

Chromium compounds are absorbed after dermal administration by guinea pigs. Measurement of ^{51}chromium in the organs and body fluids revealed distribution, due to dermal absorption of chromium(III) and chromium(VI) compounds, to the blood, spleen, bone marrow, lymph glands, urine, and kidneys. Absorption was greater for chromium(VI) than for chromium(III) (see Section 3.4.1.3) (Wahlberg and Skog 1965).

3.4.2.4 Other Routes of Exposure

The distribution of chromium(III) in humans was analyzed using a whole-body scintillation scanner, whole-body counter, and plasma counting. Six individuals given an intravenous injection of ^{51}chromium(III) as chromium trichloride had >50% of the blood plasma chromium(III) distributed to various body organs within hours of administration. The liver and spleen contained the highest levels. After 3 months, the liver contained half of the total body burden of chromium. The study results indicated a three-compartment model for whole-body accumulation and clearance of chromium(III). The half-lives were 0.5–12 hours for the fast component, 1–14 days for the medium component, and 3–12 months for the slow component (Lim et al. 1983).

An *in vitro* study in human blood showed that chromium(VI) was rapidly cleared from the plasma (Corbett et al. 1998). The reduction capacity appears to be concentration dependent and is overwhelmed at spike concentrations between 2,000 and 10,000 µg/L. High chromium(VI) concentrations (10,000 µg/L spike concentration) resulted in an accumulation of chromium(VI) in the erythrocytes and a lower plasma:erythrocyte ratio of total chromium. This study also found that the plasma reduction capacity was enhanced by a recent meal.

Both human and rat white blood cells accumulated more ^{51}chromium per cell than red blood cells after *in vitro* exposure of whole blood to ^{51}chromium(VI). The uptake of chromium by rat blood cells was also measured after intravenous exposure to ^{51}chromium(VI) as sodium chromate. After intravenous exposure, the white blood cells contained significantly more ^{51}chromium (≈30 pg chromium/billion cells) than the red blood cells (≈4 pg chromium/billion cells), and the amount of ^{51}chromium in the cells was the same after 24 hours as it was after 1 hour. The amount of ^{51}chromium in the white blood cells, but not in the red blood cells, decreased by approximately 1.7-fold after 7 days. When rats were injected intravenously with 20 ng of radiolabeled sodium chromate (chromium(VI)) or radiolabeled chromium trichloride (chromium(III)), the amount of chromium was ≈2 pg/billion red blood cells but not detectable in white blood cells after injection of chromium(III) chloride. The amount of chromium was ≈5 pg/billion red blood cells and ≈60 pg/billion white blood cells after injection of sodium chromate (Coogan et al. 1991b).

The distribution pattern in rats treated with sodium chromite (chromium(III)) by intravenous injection revealed that most of the chromium was concentrated in the reticuloendothelial system, which, together with the liver, accumulated 90% of the dose. The accumulation in the reticuloendothelial system was thought to result from colloid formation by chromite at physiological pH. Organs with detectable chromium levels 42 days postinjection were: spleen > liver > bone marrow > tibia > epiphysis > lung > kidney. Chromium trichloride given to rats by intravenous injection also concentrated in the liver, spleen, and bone marrow (Visek et al. 1953). In rats administered chromium(III) nitrate intraperitoneally for 30 or 60 days, the highest levels of chromium were found in the liver, followed by the kidneys, testes, and brain. The levels increased with increased doses but not linearly. The levels in the kidneys, but not the other organs, increased significantly with duration (Tandon et al. 1979).

Whole-body analysis of mice given a single intraperitoneal injection of 3.25 mg chromium(III)/kg as chromium trichloride showed that chromium trichloride was released very slowly over 21 days: 87% was

retained 3 days after treatment, 73% after 7 days treatment, and 45% after 21 days. In contrast, mice given a single intraperitoneal injection of 3.23 chromium(VI)/kg as potassium dichromate retained only 31% of the chromium(VI) dose at 3 days, 16% at 7 days and 7.5% at 21 days. Mice injected weekly with chromium(III) compounds at 17% of the LD_{50} retained 6 times the amount of chromium as mice injected with chromium(VI) compounds at 17% of the LD_{50}. The retention of chromium(III) was attributed to its ability to form coordination complexes with tissue components such a proteins and amino acids (Bryson and Goodall 1983).

In rats injected intraperitoneally with 2 mg chromium(VI)/kg/day as potassium chromate 6 days/week for 45 days, the mean levels of chromium (μg chromium/g wet weight) were 25.68 in the liver, 40.61 in the kidney, 7.56 in the heart, and 4.18 in the brain (Behari and Tandon 1980).

In rats injected subcutaneously with 5.25 mg chromium(VI)/kg as potassium dichromate, most of the chromium in the tissues analyzed was found in the red blood cells with a peak level (63 μg chromium/g) achieved 24 hours after dosing. White blood cells were not analyzed for chromium content. Whole plasma contained 2.7–35 μg/mL and the plasma ultrafiltrate contained 0.15–0.79 μg/mL. Tissue distribution 48 hours after dosing was as follows: 221.2 μg/g in renal cortex, 110.0 μg/g in liver, 103.0 μg/g in spleen, 86.8 μg/g in lung, 58.9 μg/g in renal medulla, and 8.8 μg/g in bone, compared with 2.28–5.98 μg/g in any tissues in controls. When rats were given repeated subcutaneous injections of 1.05 mg chromium(VI)/kg/day, every other day for 2, 4, 8, 10, or 12 weeks, most of the chromium was again found in the red blood cells. However, while red blood cell levels rose progressively during treatment, levels as high as those seen after a single dose were never achieved, even when the total dose exceeded the dose in the single injection experiment 10-fold. The tissue levels of chromium determined 48 hours after the last dose in the rats injected for 12 weeks were of the same order of magnitude as those seen after a single injection. These results suggest little tendency of soluble chromium(VI) compounds to accumulate in tissues with repeated exposure (Mutti et al. 1979).

In an *in vitro* study, whole blood samples were spiked with water-soluble chromium(VI) or chromium(III) compounds. The results showed a greater level of chromium inside erythrocytes after treatment with chromium(VI) compounds, compared to chromium(III) compounds. The investigators reported that only chromium(VI) compounds are taken up by erythrocytes and, presumably after reduction to chromium(III), form complexes with intracellular proteins that could not be eliminated (Lewalter et al. 1985).

The distribution of radioactivity was compared in mouse dams and fetuses following the intravenous injection of the dams with ^{51}Chromium labelled-sodium dichromate(VI) or ^{51}chromium labelled-chromium(III) trichloride. In the maternal tissues, the highest levels of radioactivity from both treatments were achieved in the renal cortex, but the concentration of radioactivity in the tissues of dams given the hexavalent form was much higher than that of the dams given the trivalent form. The patterns of distribution of radioactivity in other tissues were identical regardless of administered valence state, with the skeleton, liver, kidneys, and ovaries accumulating the highest levels and the brain and muscle accumulating the lowest levels. The serum concentration of radioactivity after treatment with chromium(III) was 3 times higher than that after treatment with chromium(VI). Radioactivity after treatment with both valence forms crossed the placenta, but the radioactivity from the hexavalent form crossed more readily. For chromium(VI), ≈12% of the maternal serum concentration of radioactivity was found in the fetuses when the dams were administered sodium dichromate in mid-gestation (days 12–15). When the dams were injected in late gestation (days 16–18), ≈19% of the radioactivity in maternal serum was found in the fetuses. For chromium(III), the fetal concentration of radioactivity was only ≈0.4% of the maternal serum concentration when the dams were injected with radiolabeled chromium trichloride in mid-gestation and 0.8% of the maternal serum radioactivity concentration when injected in late gestation. Radioactivity from both treatments accumulated in fetal skeletons in calcified areas and in the yolk sac placenta (Danielsson et al. 1982). Danielsson et al. (1982) noted that the radioactivity after administration of chromium(VI) may represent chromium(III) after reduction in the tissues. Chromium(III) also crossed the placenta of mice injected intraperitoneally with chromium trichloride (Iijima et al. 1983). While the results indicate that both chromium(VI) and chromium(III) may pose developmental hazards, they cannot be used to indicate that exposure of pregnant animals to chromium(III) by inhalation or oral routes would result in significant placental transfer because chromium(III) compounds are not well absorbed by these routes (see Section 3.4.1).

Tissue distribution in rats and mice after 14 days of intraperitoneal injection of 0.8 mg chromium(VI)/day as potassium chromate were: liver 6.00 μg/g wet weight in rats and 8.89 in mice, kidney 24.14 and 11.77, spleen 15.26 and 6.92, femur 6.53 and 6.30, lung 3.99 and 2.89, heart 3.13 and 1.75, muscle 1.10 and 0.51, and blood 4.52 and 1.56. (Kargacin et al. 1993). Kidney and blood chromium concentrations were 2- and 4-fold higher, respectively, in rats compared to mice. Red blood cell concentrations were 3-fold higher in rats than mice and hemoglobin binding of chromium was twice as high in rats. By contrast, after oral exposure levels, in blood for rats and mice were similar. The authors ascribed this to faster entry into the blood after intraperitoneal injection and thus a greater likelihood that chromium(VI) could be sequestered in rat erythrocytes by reduction.

3.4.3 Metabolism

Chromium(III) compounds are essential to normal glucose, protein, and fat metabolism. In addition, chromium(III) is capable of forming complexes with nucleic acids and proteins. Chromium(III) may also participate in intracellular reduction and oxidation reactions. Chromium(VI) is unstable inside the body and is ultimately reduced to chromium(III) *in vivo* by a variety of reducing agents. Chromium(V) and chromium(IV) are transient intermediates in this process.

Currently, the biological target for the essential effects of chromium(III) is unknown. Chromodulin, also referred to as GTF, has been proposed as one possible candidate (Jacquamet et al. 2003). The function of chromodulin, an oligopeptide complex containing with four chromic ions, has not been established; however, a possible mechanism is that chromodulin facilitates the interaction of insulin with its cellular receptor sites, although this has not been proven (Anderson 1998a, 2003; IOM 2001).

In vivo and *in vitro* experiments in rats indicated that, in the lungs, chromium(VI) can be reduced to chromium(III) by ascorbate. The reduction of chromium(VI) by ascorbate results in a shorter residence time of chromium in the lungs and constitutes the first defense against oxidizing reagents in the lungs. When ascorbate is depleted from the lungs, chromium(VI) can also be reduced by glutathione. The level of ascorbic acid in the adult human lung has been estimated as approximately 7 mg/100 g wet tissue (Hornig 1975). The reduction of chromium(VI) by glutathione is slower and results in greater residence time of chromium in the lungs, compared to reduction by ascorbate (Suzuki and Fukuda 1990). Other studies reported the reduction of chromium(VI) to chromium(III) by epithelial lining fluid (ELF) obtained from the lungs of 15 individuals by bronchial lavage. The average reduction accounted for 0.6 µg chromium(VI)/mg of ELF protein. In addition, cell extracts made from pulmonary alveolar macrophages derived from five healthy male volunteers were able to reduce an average of 4.8 µg chromium(VI)/10^6 cells or 14.4 µg chromium(VI)/mg protein (Petrilli et al. 1986b). Metabolism of the chromium(VI) to chromium(III) by these cell fractions significantly reduced the mutagenic potency of the chromium when tested in the Ames reversion assay. Postmitochondrial (S12) preparations of human lung cells (peripheral lung parenchyma and bronchial preparations) were also able to reduce chromium(VI) to chromium(III) (De Flora et al. 1984). Moreover, large individual differences were observed (De Flora et al. 1984, 1987b), and extracts from pulmonary alveolar macrophages of smokers reduced significantly more chromium(VI) to chromium(III) than extracts from cells of nonsmokers. Because chromium(III) does not readily enter cells, these data suggest that reduction of chromium(VI) by the ELF may constitute the first

line of defense against toxicity of inhaled chromium compounds. Furthermore, uptake and reduction of chromium compounds by the pulmonary alveolar macrophages may constitute a second line of defense against pulmonary toxicity of chromium(VI) compounds. Microsomal reduction of chromium(VI) occurs in the lungs mainly as it does in the liver, as discussed below.

The first defense against chromium(VI) after oral exposure is the reduction of chromium(VI) to chromium(III) in the gastric environment where gastric juice (De Flora et al. 1987a) and ascorbate (Samitz 1970) play important roles. Studies using low-frequency electron paramagnetic resonance (EPR) spectrometry have shown that chromium(VI) is reduced to chromium(V) *in vivo* (Liu et al. 1994, 1995, 1997a, 1997b; Ueno et al. 1995b). *In vitro*, low concentrations of ascorbate favor the formation of chromium(V), whereas higher concentrations of ascorbate favor the formation of the reduced oxidation state, chromium(III) (Liu et al. 1995). EPR spectrometric monitoring also showed that chromium(VI) was rapidly reduced to chromium(V) on the skin of rats, with a 3-fold greater response when the stratum corneum was removed (Liu et al. 1997a). Thus, dermal effects from direct skin contact with chromium(VI) compounds may be mediated by rapid reduction to chromium(V). In whole blood and plasma, increasing ascorbate levels led to an increased oxidation of chromium(VI) to chromium(III) (Capellmann and Bolt 1992).

For humans, the overall chromium(VI)-reducing/sequestering capacities were estimated to be 0.7–2.1 mg/day for saliva, 8.3–12.5 mg/day for gastric juice, 11–24 mg for intestinal bacteria eliminated daily with feces, 3,300 mg/hour for liver, 234 mg/hour for males and 187 mg/hour for females for whole blood, 128 mg/hour for males and 93 mg/hour for females for red blood cells, 0.1–1.8 mg/hour for ELF, 136 mg/hour for pulmonary alveolar macrophages, and 260 mg/hour for peripheral lung parenchyma. Although these *ex vivo* data provide important information in the conversion of chromium(VI) to reduced states, the values may over- or underestimate the *in vivo* reducing capabilities (De Flora et al. 1997).

Reduction of chromium(VI) in the red blood cell occurs by the action of glutathione. Since the red blood cell membrane is permeable to chromium(VI) but not chromium(III), the chromium(III) formed by reduction of chromium(VI) by glutathione is essentially trapped within the erythrocyte for the life-span of the cell (Paustenbach et al. 2003), with approximately 1% of chromium eluting from the erythrocyte daily (ICSH 1980). Eventually, the diffusion of chromium(VI), the reduction to chromium(III), and complexing to nucleic acids and proteins within the cell will cause the concentration equilibrium to change so that more chromium(VI) is diffused through the membrane. Thus, there is a physiological drag so that increased diffusion results in greater chromium concentrations in the cell (Aaseth et al. 1982). It

appears that the rate of uptake of chromium(VI) by red blood cells may not exceed the rate at which they reduce chromium(VI) to chromium(III) (Corbett et al. 1998). *In vitro* incubation of red blood cells with an excess of sodium chromate(VI) (10 mM) decreased glutathione levels to 10% of the original amount (Wiegand et al. 1984). The above concepts are applicable to the uptake and reduction of chromium(VI) in other cell types.

The effect of glutathione-depleting agents on the amounts of cellular chromium(III) and chromium(V) was determined in Chinese hamster V-79 cells treated with sodium chromate (Sugiyama and Tsuzuki 1994). Buthionine sulfoximine at 25 μM reduced glutatione levels to about 1% of control values, and increased chromium(V) levels by about 67%. The total chromium uptake was decreased by about 20% and chromium(III) levels were decreased by 20%. Diethylmaleate (1 mM) decreased glutathione levels to <1%, decreased chromium(V) levels by 27% and chromium(III) levels by 31%. However, the cellular uptake of total chromium was decreased to nearly 46%. The authors explained that the reason that the diethylmaleate inhibited the reduction of chromium(VI) to both chromium(III) and chromium(V) was not due to the decreased uptake, but involved the inhibition of the chromate-reducing enzymes in the cell.

In addition to the reduction of chromium(VI) by ascorbate or glutathione, *in vitro* studies have demonstrated reduction of chromium(VI) by microsomal enzymes. Hepatic microsomal proteins from male Sprague-Dawley rats pretreated with chromium(VI) reduced chromium(VI) to chromium(III). The rate of reduction varied both with the concentration of microsomal protein and the concentration of nicotinamide adenine dinucleotide phosphate (NADPH). In the absence of NADPH, microsomes did not reduce significant amounts of chromium(VI) over the 24-hour observation period. Therefore, the reduction of chromium(VI) in rat hepatic microsomes is NADPH-dependent (Gruber and Jennette 1978). Another study followed the kinetics of chromium(VI) reduction in hepatic microsomes from rats (Garcia and Jennette 1981). Induction of cytochrome P448 enzymes had no effect on the kinetics of the reaction, while induction of cytochrome P450 and NADPH-cytochrome P450 reductase resulted in a decrease in the apparent chromate-enzyme dissociation constant, and an increase in the apparent second-order rate constant, and no change in the apparent turnover number. Inhibition of NADPH-cytochrome P450 reductase and NADH-cytochrome b_5 reductase inhibited the rate of microsomal reduction of chromium(VI), as did the addition of specific inhibitors of cytochrome P450. The results demonstrate the involvement of cytochrome P450, NADPH-dependent-cytochrome P450 reductase, and to a lesser extent cytochrome b_5 and NADH-dependent-cytochrome b_5 reductase, in the reduction of chromate by rat hepatic microsomes. The conversion of chromium(VI) to chromium(III) in rats can occur by electron transfer through cytochrome P450 and cytochrome b_5. Both oxygen and carbon monoxide were found to

inhibit the *in vitro* cytochrome P450 and cytochrome b_5-dependent reduction of chromium(VI) (Mikalsen et al. 1989). The assertion that cytochrome P450 is involved in the reduction of chromium(VI) to chromium(III) has been further strengthened by Petrilli et al. (1985), who demonstrated that inducers of cytochrome P450 can increase the conversion of chromium(VI) to chromium(III) in S-9 mixtures prepared from the liver and lungs of exposed rats. Furthermore, it was observed that chromium(VI) can induce pulmonary cytochrome P450 and thus its own reduction in the lungs (Petrilli et al. 1985). Chromium(VI) apparently can alter the P450 activity in isolated rat microsomes. Witmer et al. (1994) demonstrated that hepatic microsomes from male rats treated with chromium(VI) resulted in a significant decrease in hydroxylation of testosterone at the 6β, 16α, and 2α positions, indicating a decrease in the activity of P4503A1 and 3A2. In lung microsomes, an increased hydroxylation was observed at the 16α and 16β positions, indicating an increase in P450IIB1 activity. However, hepatic microsomes from treated females showed a 4-to5-fold increase in hydroxylation activity of testosterone at the 6β position, which demonstrated that the metabolic effects of chromium differ between males and females.

Two studies have examined possible species differences in the ability of microsomes to reduce chromium(VI) (Myers and Myers 1998; Pratt and Myers 1993). Chromium(VI) reduction was enzymatic and NADPH-dependent, and the rates were proportional to the amount of microsome added. In humans, the K_m for chromium(VI) was 1–3 orders of magnitude lower than K_m values in rats, although the V_{max} was similar. This suggests that the human liver has a much greater capacity to reduce chromium(VI) than the rat liver. Also contrary to the rodent data, oxygen and cytochrome P450 inhibitors (carbon monoxide, piperonyl butoxide, metyrapone, and aminopyrine) did not inhibit chromium(VI) reduction. These differences indicate that, in humans, cytochrome P450 does not play a significant role in the reduction process, but that other microsomal flavoproteins are responsible for reducing chromium(VI). Inhibition of flavoproteins by $TlCl_3$ decreased chromium(VI) reduction by 96–100%, while inhibition of cytochrome c reductase (P450 reductase) by bromo-4'-nitroacetophenone resulted in an 80–85% inhibition of chromium(VI) reduction. Combined, these observations implicate P450 reductase, working independently of cytochrome P450, as a major contributor in the reduction of chromium(VI) in human microsomes. These findings suggest that metabolism of chromium(VI) in rodent systems may not readily be extrapolated to humans.

Microsomal reduction of chromium(VI) can also result in the formation of chromium(V), which involves a one-electron transfer from the microsomal electron-transport cytochrome P450 system in rats. The chromium(V) complexes are characterized as labile and reactive. These chromium(V) intermediates persist for 1 hour *in vitro*, making them likely to interact with deoxyribonucleic acid (DNA), which may

eventually lead to cancer (Jennette 1982). Because chromium(V) complexes are labile and reactive, detection of chromium(V) after *in vivo* exposure to chromium(VI) was difficult in the past. More recently, Liu et al. (1994) have demonstrated that chromium(V) is formed *in vivo* by using low-frequency electron paramagnetic resonance (EPR) spectroscopy on whole mice. In mice injected with sodium dichromate(VI) intravenously into the tail vein, maximum levels of chromium(V) were detected within 10 minutes and declined slowly with a life-time of about 37 minutes. The time to reach peak *in vivo* levels of chromium(V) decreased, in a linear manner as the administered dose levels of sodium dichromate decreased. The relative tissue distributions of chromium(V) indicated that most was found in the liver and much lesser amounts in blood. None was detected in kidney, spleen, heart, or lung. When the mice were pretreated with metal ion chelators, the intensity of the EPR signal decreased demonstrating that the formation of chromium(V) was inhibited. Reactions of chromium(VI) with glutathione produced two chromium(V) complexes and a glutathione thiyl radical. Reactions of chromium(VI) with DNA in the presence of glutathione produced chromium-DNA adducts. The level of chromium-DNA adduct formation correlated with chromium(V) formation. The reaction of chromium(VI) with hydrogen peroxide produced hydroxyl radicals. Reactions of chromium(VI) with DNA in the presence of high concentrations of hydrogen peroxide (millimolar compared to 10^{-7}–10^{-9} M inside cells) produced significant DNA strand breakage and the 8-hydroxy guanosine adduct, which correlated with hydroxyl radical production (Aiyar et al. 1989, 1991). Very little chromium(V) was generated by this pathway. It was postulated that the reaction of chromium(VI) with hydrogen peroxide produces tetraperoxochromium(V) species that act as a catalyst in a Fenton-type reaction producing hydroxyl radicals in which chromium(V) is continuously being recycled back to chromium(VI). The regeneration of chromium(VI) through interactions with chromium(V) and hydrogen peroxide is consistent with the findings of Molyneux and Davies (1995) (see Section 3.5.2). As discussed above, chromium(VI) is ultimately reduced to chromium(III) within the cell. Chromium(III) can form stable complexes with DNA and protein (De Flora and Wetterhahn 1989), which is discussed further in Section 3.5.2.

The mechanism for clearance of chromium(VI) once reduced inside the liver cell may involve a chromium(III)-glutathione complex. The glutathione complex would be soluble through the cell membrane and capable of entering the bile (Norseth et al. 1982). The complexing of chromium(III) to other ligands has been shown to make them more permeable to the cell membrane (Warren et al. 1981).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Normal urinary levels of chromium in humans have been reported to range from 0.22 to 1.8 μg/L (0.00024–0.0018 mg/L) with a median level of 0.4 μg/L (0.0004 mg/L) (IOM 2001; Iyengar and Woittiez 1988). Humans exposed to 0.05–1.7 mg chromium(III)/m^3 as chromium sulfate and 0.01–0.1 mg chromium(VI)/m^3 as potassium dichromate (8-hour TWA) had urinary excretion levels of 0.0247–0.037 mg chromium(III)/L. Workers exposed mainly to chromium(VI) compounds had higher urinary chromium levels than workers exposed primarily to chromium(III) compounds. An analysis of the urine did not detect the hexavalent form of chromium, indicating that chromium(VI) was rapidly reduced before excretion (Cavalleri and Minoia 1985; Minoia and Cavalleri 1988). Chromium(III) compounds were excreted rapidly in the urine of workers, following inhalation exposure to chromium(III) as chromium lignosulfonate. Workers exposed to 0.005–0.23 mg chromium(III)/m^3 had urine concentrations of 0.011–0.017 mg chromium(III)/L. The half-time for urinary excretion of chromium was short, 4–10 hours, based on an open, one-compartment kinetic model (Kiilunen et al. 1983). Tannery workers had higher urinary chromium(III) concentrations in postshift urine samples taken Friday afternoon and in preshift urine samples taken Monday, compared to controls. These workers also had hair concentrations of chromium that correlated with urinary levels. Analysis of workroom air revealed no detectable chromium(VI) and 0.0017 mg chromium(III)/m^3 (time-weighted average) (Randall and Gibson 1987). Elimination of chromium(III) from hair, serum, and urine has been studied in a group of 5 men who had ceased working in a leather tannery 9 months earlier (Simpson and Gibson 1992). Compared to levels recorded during employment, the mean level of chromium in hair was reduced from 28.5 to 2.9 μmol/g; serum levels were reduced from 9.4 to 3.8 nmol/L. These levels are comparable to those in the general population. Urine levels were unchanged (13.8 nmol/L while working and 14.4 nmol/L 9 months later); the authors stated that this was probably caused by consumption of beer (a source of chromium) the night before sampling. Data from autopsy studies indicate that chromium can be retained in the lung for decades following cessation of occupational exposures (Brune et al. 1980; Hyodo et al. 1980; Mancuso 1997b).

Peak urinary chromium concentrations were observed at 6 hours (the first time point examined) in rats exposed intratracheally to 0.44 mg/kg chromium(III) as chromium acetate hydroxide or chromium(VI) as sodium dichromate (Gao et al. 1993). Chromium urinary concentrations decreased rapidly, falling from 4,535 μg chromium/g creatinine at 6 hours to 148 μg chromium/g at 72 hours for the chromium acetate

hydroxide and from 2,947 μg chromium/g creatinine at 6 hours to 339 μg chromium/g at 72 hours for sodium dichromate.

Elimination of chromium was very slow in rats exposed to 2.1 mg chromium(VI)/m^3 as zinc chromate 6 hours/day for 4 days. Urinary levels of chromium remained almost constant for 4 days after exposure and then decreased, indicating that chromium bound inside the erythrocyte is released slowly (Langård et al. 1978).

3.4.4.2 Oral Exposure

Given the low absorption of chromium compounds by the oral route, the major pathway of excretion after oral exposure is through the feces.

An acute, oral dose of radioactive chromium(III) as chromium chloride or chromium(VI) as sodium chromate was administered to humans after which feces and urine were collected for 24 hours and 6 days, respectively, and analyzed for chromium. The amount of chromium in the 6-day fecal collection was 99.6 and 89.4% of the dose for chromium(III) and chromium(VI) compounds, respectively. The amount of chromium in the 24-hour urine collection was 0.5 and 2.1% of the dose for chromium(III) and chromium(VI) compounds, respectively (Donaldson and Barreras 1966). In subjects drinking 0.001–0.1 mg chromium(VI)/kg/day as potassium chromate in water for 3 days, <2–8% of the dose was excreted in the urine (Finley et al. 1997). The percentage of the dose excreted appeared to increase with increasing dose.

Urinary excretion rates have been measured in humans after oral exposure to several chromium compounds (Finley et al. 1996b). A group of four male and two female volunteers ingested capsules containing chromium(III) picolinate at a dose of 200 μg/day for 7 days, to ensure that chromium deficiency was not a confounding factor. They then ingested 0.005 mg/kg/day chromium(VI) as potassium chromate (3 days), and 1.0 mg/kg/day chromium(III) as chromic oxide (3 days), with 3 days without dosing between the potassium chromate and chromic oxide doses. Urinary excretion rates of chromium were significantly elevated compared to postdosing control levels after seven daily doses of chromium(III) picolinate (2.4±0.8 versus 0.75±0.53 μg/day). The excretion rate increased sharply on the first of 3 days of potassium chromate dosing (11±17 μg/day) and remained steady over the next 2 days (13–14 μg/day). Excretion rates fell to 2.5±0.72 during 2 days without dosing and continued to fall during the 3 days of chromic oxide dosing, reaching rates similar to those seen postdosing. Mean pooled

urinary concentrations during the dosing periods were 2.4 μg chromium/g creatinine from exposure to chromium(VI) and 0.4 μg chromium/g creatinine from exposure to chromium(III) as compared to 0.23 μg chromium/g creatinine during the postdosing time periods. The lower urinary excretion of chromium(III) after exposure to chromic oxide reflects the poorer absorption of inorganic chromium(III) compounds compared to inorganic chromium(VI) compounds.

The half-life for chromium urinary excretion after administration in drinking water as potassium dichromate has been estimated in humans (Kerger et al. 1997). Ingestion of 0.05 mg chromium(VI)/kg resulted in an extended time course of excretion. Approximately 76–82% of the 14-day total amount of chromium in the urine was excreted within the first 4 days (mean peak concentration 209 μg chromium/g creatinine; range 29–585 μg chromium/g creatinine). The average urinary excretion half-life for four of the volunteers was 39 hours at this dose. All subjects had returned to background concentrations (0.5–2.0 μg chromium/g creatinine) by 14 days postdosing. About 87% of the total amount of chromium in the urine measured over 8 days was excreted during the first 4 days for one volunteer ingesting 0.03 mg chromium(VI)/kg (peak 97 μg chromium/g creatinine on day of ingestion). Urinary chromium concentrations had returned to an average of 2.5 μg chromium/g creatinine within 7 days postdosing, the last time point measured. Urinary excretion half-life in this volunteer was 37 hours. Similar time courses of excretion were observed when volunteers took the same doses as daily doses over 3-day periods. An earlier study by this group (Kerger et al. 1996a) examined urinary excretion half-lives following a bolus dose of 10 ppm (approximately 0.06 mg chromium/kg) chromium(III) chloride, potassium dichromate reduced with orange juice (presumably, the juice reduced the potassium dichromate to chromium(III)-organic complexes and chromium(III) ions), or potassium dichromate. The calculated urinary excretion half-lives for the three chromium solutions were 10.3, 15, and 39.3 hours, respectively. The potassium dichromate half-life is consistent with the results from the Kerger et al. (1997) study. If, in these studies, all of the absorbed chromium(VI) was rapidly and completely converted to chromium(III), there should be no difference in urinary half-life. The difference in excretion half-lives following dosing with chromium(III) and chromium(VI) appears to reflect incomplete reduction of absorbed chromium(VI) to chromium(III) as well as longer retention of chromium(VI) in tissues. The prolonged half-life following dosing with chromium(VI) appears to be a composite of the half-lives the chromium(VI) and chromium(III) derived from the reduction of chromium(VI) in the blood. Given that most is converted to chromium(III), the half-life for the sequestered chromium is quite long (much longer than 40 hours) and reflects the half-life of chromium observed in the red blood cells. Pretreatment of chromium(VI) with orange juice apparently did not convert all chromium(VI) to chromium(III), as indicated by a half-life of 15 hours.

The urinary excretion kinetics of chromium have also been examined in eight adults that were administered chromium(III) at 400 μg/day as chromium(III) picolinate for 3 consecutive days (Gargas et al. 1994). The mean time to peak urinary concentration was 7.18±2.11 hours (range 2.9–13.0 hours), the mean peak concentration being 7.92±4.24 μg chromium/g creatinine (range 3.58–19.13 μg/g creatinine). Excretion diminished rapidly after the peak, but did not appear to return to background in most of the volunteers before the next daily dose.

Pharmacokinetic models were used to predict the retention and excretion of ingested chromium(III) picolinate (Stearns et al. 1995a). A single dose of 5.01 mg (assuming 2.8% or 140 μg of the chromium(III) picolinate is absorbed) resulted in 11 μg (7.9%) retained after 1 year. The model predicted that about 1.4 μg would still be present in body tissues 10 years after dosing, and continuous dosing over a 1-year period would result in 6.2 mg of chromium(III) picolinate being retained, requiring about 20 years to reduce the retained level to 0.046 mg. These projected retention estimates may be 2–4-fold lower than results obtained from actual clinical findings. The authors caution that accumulative daily intake of chromium(III) may result in tissue concentrations that could be genotoxic.

Daily urinary excretion levels of chromium were nearly identical in men and women (averages of 0.17 and 0.20 μg/L, respectively; 0.18 μg/L combined) who ate normal dietary levels of chromium (≈60 μg chromium(III)/day). When the subjects' normal diets were supplemented with 200 μg chromium(III)/day as chromium trichloride to provide intakes of ≈260 μg chromium(III)/day, urinary excretion of chromium rose proportionately to an average of 0.98 μg/L combined. Thus a 5-fold increase in oral intake resulted in about a five-fold increase in excretion, indicating absorption was proportional to the dose regardless of whether the source was food or supplement (Anderson et al. 1983). A group of 23 elderly subjects who received an average of 24.5 μg/day (0.00035 mg chromium(III)/kg/day) from their normal diets excreted 0.4 μg chromium/day in the urine (1.6%) and 23.9 μg chromium/day in the feces (97.6%), with a net retention of 0.2 μg/day (0.8%). Based on the 1980 daily requirement for absorbable chromium of 1 μg/day by the National Academy of Science Food and Nutrition Board, the retention was considered adequate for their requirements (Bunker et al. 1984).

An estimate of the half-life of elimination from plasma has been reported in humans. Uptake of potassium dichromate was determined in a man who was given 0.8 mg of chromium(VI) in drinking water 5 times each day for 17 days (Paustenbach et al. 1996). Steady-state concentrations of chromium in blood were attained after 7 days and a plasma elimination half-life of 36 hours was estimated.

Measurement of the chromium content in 255 milk samples from 45 lactating American women revealed that most samples contained <0.4 μg/L with a mean value of 0.3 μg/L (Casey and Hambidge 1984). Another study (Anderson et al. 1993) measured chromium levels in the breast milk of 17 women 60 days postpartum, and reported mean levels of ~0.2 μg/L. Lactation, therefore, represents a route of excretion of chromium and a potential route of exposure to the nursing infant. However, the precise relationship between maternal chromium levels and levels in breast milk is unclear, if such a relationship exists at all (Anderson et al. 1993; Engelhardt et al. 1990; Mohamedshah et al. 1998).

Chromium can be excreted in hair and fingernails. Mean trace levels of chromium detected in the hair of individuals from the general population of several countries were as follows: United States, 0.23 ppm; Canada, 0.35 ppm; Poland, 0.27 ppm; Japan, 0.23 ppm; and India, 1.02 ppm (Takagi et al. 1986). Mean levels of chromium in the fingernails of these populations were: United States, 0.52 ppm; Canada, 0.82 ppm; Poland, 0.52 ppm; Japan, 1.4 ppm; and India, 1.3 ppm (Takagi et al. 1988).

Rats given 18 mg chromium(VI)/kg as potassium dichromate by gavage excreted about 25 μg chromium in the first 24 hours after dosing and ≈10 μg chromium in each of the next 24-hour periods (Banner et al. 1986).

In rats and hamsters fed chromium compounds, fecal excretion of chromium varied slightly from 97 to 99% of the administered dose. Urinary excretion of chromium varied from 0.6 to 1.4% of the dose administered as either chromium(III) or chromium(VI) compounds (Donaldson and Barreras 1966; Henderson et al. 1979; Sayato et al. 1980). The urinary and fecal excretion over 2-day periods in rats treated for 8 days by gavage with 13.92 mg chromium/kg/day in corn oil was higher when soil containing 70% chromium(III) and 30% chromium(VI) was the source of chromium than when chromium(VI) as calcium chromate was the source (see Section 3.4.2.2). Total urinary and fecal excretion of chromium on days 1 and 2 of dosing were 1.8 and 19%, respectively, of the dose from soil and <0.5 and 1.8%, respectively, of the dose from calcium chromate. Total urinary and fecal excretion of chromium on days 7 and 8 of dosing were higher than on days 1 and 2. For contaminated soil, urinary excretion was 1.12% and fecal excretion was 40.6% of the dose. For calcium chromate, urinary excretion was 0.21% and fecal excretion was 12.35% of the dose (Witmer et al. 1991). Whether the higher excretion of chromium after dosing with soil than with the chromate salt represents greater bioavailability from soil could not be determined because about 50% of the administered dose could not be accounted for from the excretion and distribution data (see Section 3.4.2.2). Excretion of chromium(III) in dogs was approximately equal

to the clearance of creatinine, indicating little tubular absorption or reabsorption of chromium in the kidneys (Donaldson et al. 1984).

3.4.4.3 Dermal Exposure

Information regarding the excretion of chromium in humans after dermal exposure to chromium or its compounds is limited. Fourteen days after application of a salve containing potassium chromate(VI), which resulted in skin necrosis and sloughing at the application site, chromium was found at 8 mg/L in the urine and 0.61 mg/100 g in the feces of one individual (Brieger 1920). A slight increase (over background levels) in urinary chromium levels was observed in four subjects submersed in a tub of chlorinated water containing 22 mg chromium(VI)/L as potassium dichromate(VI) for 3 hours (Corbett et al. 1997). For three of the four subjects, the increase in urinary chromium excretion was <1 μg/day over the 5-day collection period.

^{51}Chromium was detected in the urine of guinea pigs after radiolabeled sodium chromate(VI) or chromium(III) trichloride solutions were placed over skin depots that were monitored by scintillation counting to determine the dermal absorption (Wahlberg and Skog 1965).

3.4.4.4 Other Routes of Exposure

Elevated levels of chromium in blood, serum, urine, and other tissues and organs have been observed in patients with cobalt-chromium knee and hip arthroplasts (Michel et al. 1987; Sunderman et al. 1989). Whether corrosion or wear of the implant can release chromium (or other metal components) into the systemic circulation depends on the nature of the device. In one study, the mean postoperative blood and urine levels of chromium of nine patients with total hip replacements made from a cast cobalt-chromium-molybdenum alloy were 3.9 and 6.2 μg/L, respectively, compared with preoperative blood and urine levels of 1.4 and 0.4 μg/L, respectively. High blood and urinary levels of chromium persisted when measured at intervals over a year or more after surgery. These data suggest significant wear or corrosion of the metal components. No significant difference was found for patients with hip replacements made from the alloy and articulated with polyethylene (Coleman et al. 1973). Similarly, serum and urinary levels of chromium in patients with implants made from a porous coated cobalt chromium alloy with polyethylene components (to prevent metal-to-metal contact) were not significantly different from patients with implants made without chromium (Sunderman et al. 1989).

A number of factors have been shown to alter the rate of excretion of chromium in humans. Intravenous injection of calcium EDTA resulted in a rapid increase in the urinary excretion of chromium in metal workers (Sata et al. 1998). Both acute and chronic exercises have been shown to increase chromium excretion in the urine, though the increased excretion did not appear to be accompanied with decreased levels of total native chromium (Rubin et al. 1998). An increased rate of chromium excretion has been reported in women in the first 26 weeks of pregnancy (Morris et al. 1995b). Chromium supplementation did not appear to alter the rate of excretion into breast milk in postpartum women (Mohamedshah et al. 1998).

The urinary excretion of chromium after a single or during repeated subcutaneous injections of potassium dichromate was followed in rats. Following a single dose of 5.35 mg chromium(VI)/kg, chromium was excreted rapidly in two phases and was essentially complete at 48 hours. The filtered chromium load rose considerably during the first few hours after dosing and exceeded the tubular reabsorption rate. This increase was followed by a decrease that paralleled the urinary excretion of chromium. During repeated injections with 1.05 mg chromium(VI)/kg/day, every other day for 12 weeks, urinary excretion and diffusible chromium renal clearance rose at relatively high parallel rates, and reached plateaus at 10 ng/min for urinary excretion and 550 µL/minute for renal clearance. The filtered load increased slightly. Since high levels of chromium were found in the renal cortex (see Section 3.4.2.4), the tubular reabsorption appeared to be limited by the accumulation of chromium in the tubular epithelium (Mutti et al. 1979).

Rats given a subcutaneous injection of potassium dichromate (chromium(VI)) and chromium nitrate (chromium(III)) excreted 36% of the chromium(VI) dose in urine and 13.9% in the feces within 7 days; 8 and 24.2% of the chromium(III) was excreted in the urine and feces within the same time period, respectively (Yamaguchi et al. 1983). Within 4 days after an intravenous dose of ^{51}chromium as chromium(III) chloride at 3 mg/kg chromium, rats excreted 5.23% of the dose in the feces and 16.3% in the urine (Gregus and Klaassen 1986).

In rats treated by intravenous injection with ^{51}chromium-labeled sodium chromate (chromium(VI)) or chromium(III) trichloride at 0.0003 or 0.345 mg chromium/kg, the bile contained 2–2.5% of the dose following chromium(VI) exposure; however, after chromium(III) exposure the concentration in the bile was ≈50 times lower (Manzo et al. 1983). Similarly, 3.5–8.4% of chromium(VI) compounds was excreted in the bile as chromium(III), compared to 0.1–0.5% of chromium(III) compounds, after intravenous injection in rats (Cikrt and Bencko 1979; Norseth et al. 1982). Administration of

diethylmaleate, which depletes glutathione, resulted in only chromium(VI) in the bile after injection of sodium chromate.

Two hours after dosing rats intravenously with potassium dichromate at 0.45–4.5 mg chromium(VI)/kg, 1.4–2.2% of the chromium was recovered in the bile. Less than 1% of the total measurable chromium in the bile was identified as chromium(VI) compounds (Cavalleri et al. 1985).

Male Swiss mice exposed to 52 mg chromium(III)/kg as chromium chloride by single intraperitoneal injection or subcutaneous injection had plasma clearance half-times of 41.2 and 30.6 hours, respectively. In each case, blood levels reached control levels by 6–10 days (Sipowicz et al. 1997).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of

toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

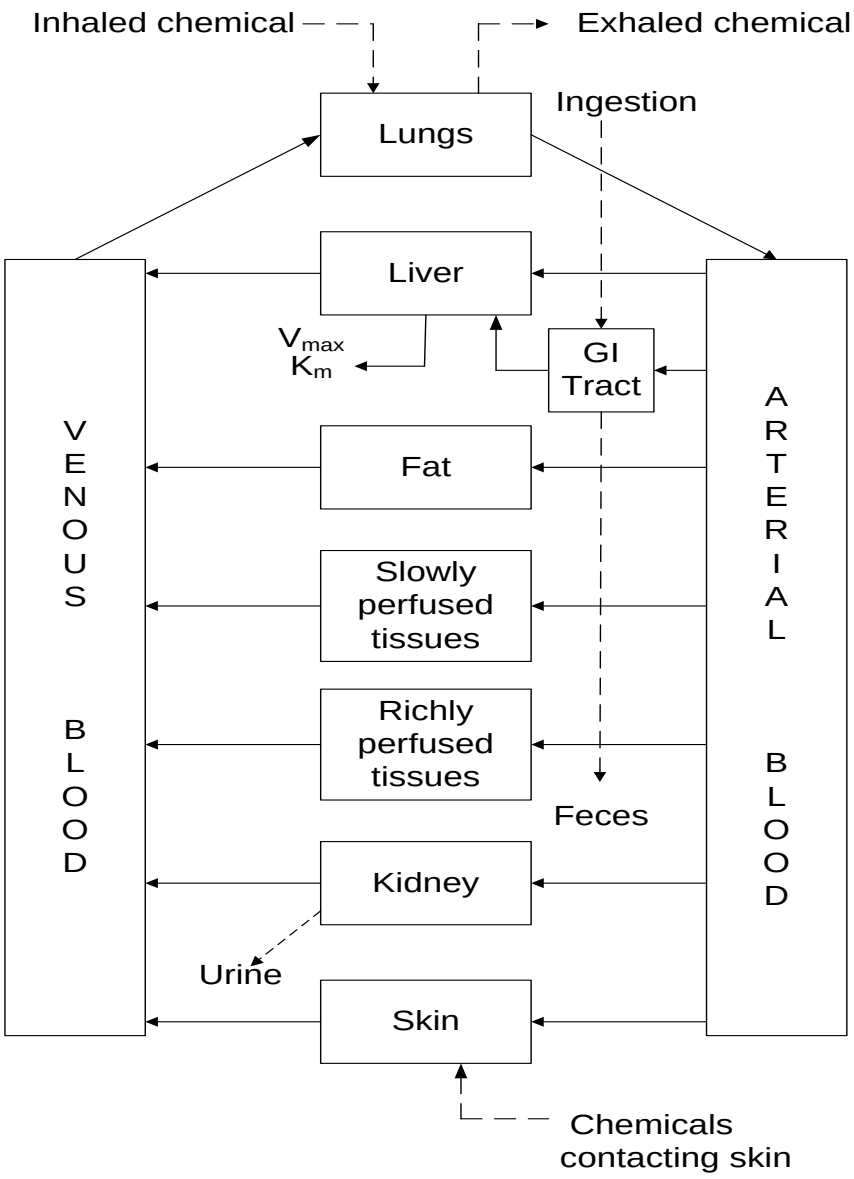
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

PBPK models for chromium are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations. Two PBPK models for chromium have been reported that simulated developed by O'Flaherty absorption, distribution, metabolism, elimination, and excretion of chromium(III) and chromium(VI) compounds in the rat (O'Flaherty 1993c, 1996) and human (O'Flaherty et al. 2001).

3.4.5.1 O'Flaherty Model (1993a, 1996, 2001)

The structure of the O'Flaherty model is depicted in Figure 3-6. Values for chromium parameters in the rat and human model are presented in Table 3-10. The model includes compartments representing bone, kidney, liver, gastrointestinal tract, plasma, poorly-perfused tissues (e.g., muscle, skin), red blood cells, respiratory tract, and well-perfused tissues (e.g., brain, heart, lung, viscera). Chromium(VI) is assumed to

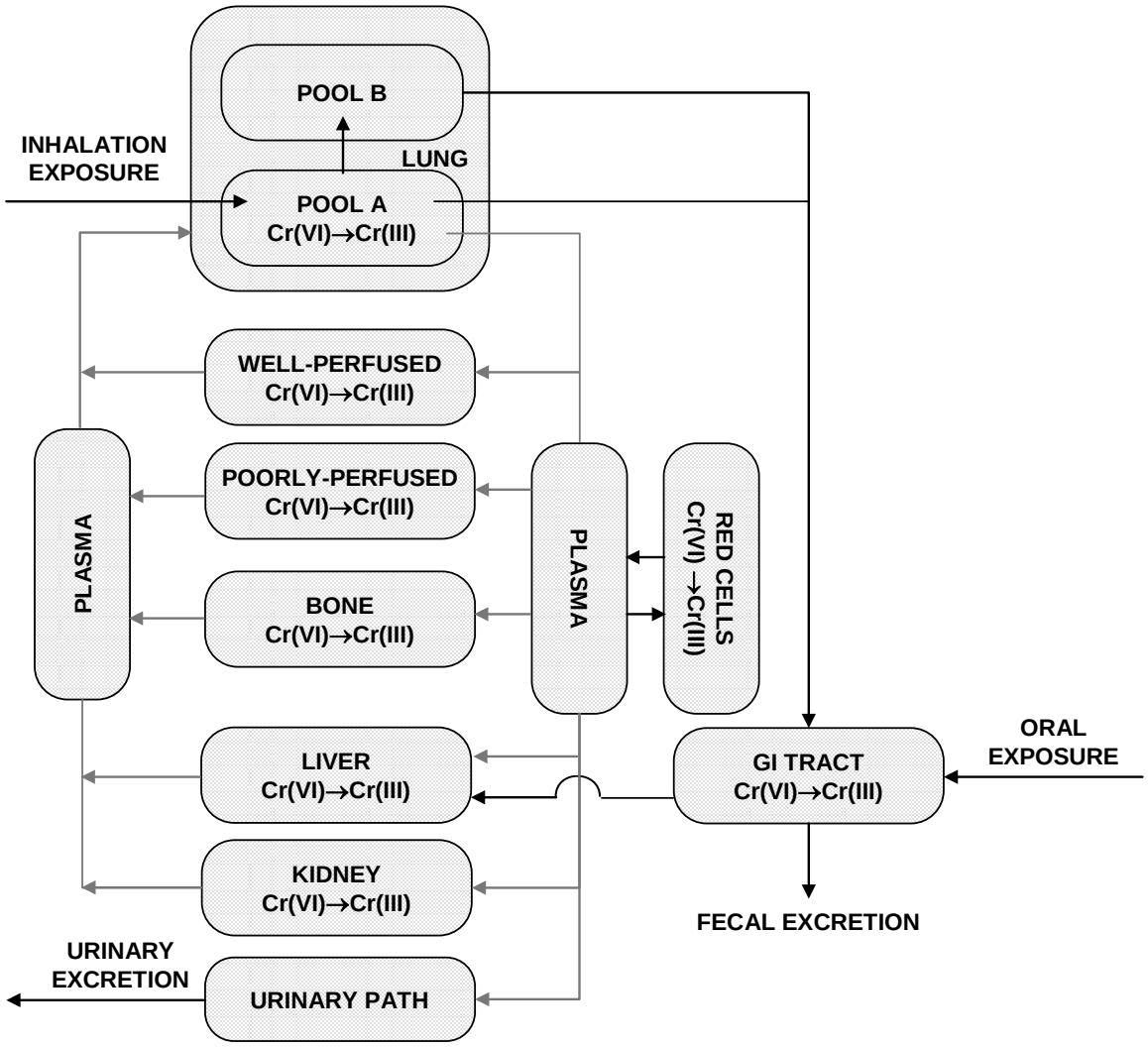
Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

Figure 3-6. A Physiologically Based Model of Chromium Kinetics in the Rat



Source: O'Flaherty et al. 1996

Table 3-10. Chemical-specific Parameters in the Rat and Human Chromium Models

	Rat		Human		
Parameter[a]	Cr(IIII)	Cr(VI)	Cr(IIII)	Cr(VI)	Definition
Absorption					
KGI	0.01	0.04	0.25	2.5	First-order rate constant for absorption from the gastrointestinal tract (Da^{-1})
KLU	0.2	2.0	NA	NA	First-order rate constant for absorption from the bioavailable lung pool (pool A) (Da^{-1})
KMUCOA	0.8	0.8	NA	NA	First-order rate constant for mucociliary clearance from pool A to the gastrointestinal tract (Da^{-1})
KMUCOB	0.025	0.025	NA	NA	First-order rate constant for mucociliary clearance from the nonbioavailable lung pool (pool B) to the gastrointestinal tract (Da^{-1})
KLUAB	1.2	1.2	NA	NA	First-order rate constant for transfer from pool A to pool B (Da^{-1})
FRLUNG	NA	NA	0.3	0.3	Fraction of inhaled chromium absorbed to blood
FRTRGI	NA	NA	0.7	0.7	Fraction of inhaled chromium transferred to gastrointestinal tract.
Distribution					
CR	5.0	15.0	NA[b]	NA[b]	Relative clearance of chromium into mineralizing bone (liters of blood plasma cleared per liter of new bone formed)
KINRBC	0.0003	1.5	12.0	NA	Clearance from plasma to red cell (L/Da)
KDIN	0.007	1.5	3.0	30.0	Clearance from plasma to kidney (L/Da)
LDIN	0.0001	1.5	3.0	30.0	Clearance from plasma to liver (L/Da)
WDIN	0.0001	1.5	3.0	30.0	Clearance from plasma to other well-perfused tissues (L/Da)
PDIN	0.0001	0.01	3.0	30.0	Clearance from plasma to poorly-perfused tissues (L/Da)
BDIN	0.0001	0.01	NA[b]	NA[b]	Clearance from plasma to bone (L/Da)
CR	NA	NA	5.0	15.0	Fraction deposition from blood to forming bone
KOUTRBC	0.0003	10.0	12.0	NA	Clearance from red cell to plasma (L/Da)
KDOUT	0.001	10.0	3.0	30.0	Clearance from kidney to plasma (L/Da)
LDOUT	0.0003	10.0	3.0	30.0	Clearance from liver to plasma (L/Da)
WDOUT	0.001	10.0	3.0	30.0	Clearance from other well-perfused tissues to plasma (L/Da)
PDOUT	0.003	10.0	3.0	30.0	Clearance from poorly perfused tissues to plasma (L/Da)
BDOUT	0.003	10.0	NA[b]	NA[b]	Clearance from bone to plasma (L/Da)
Excretion					
KFX	1.5	1.5	14.0	14.0	First-order rate constant for loss of chromium from intestinal tract contents to the feces (Da^{-1})
QEC	0.065	0.065	NA[c]	NA[c]	Excretion clearance from the plasma (urinary clearance) (L/kg/Da)

Table 3-10. Chemical-specific Parameters in the Rat and Human Chromium Models

	Rat		Human		
Parameter[a]	Cr(IIII)	Cr(VI)	Cr(IIII)	Cr(VI)	Definition
CLEAR[b]	NA	NA	12.0	12.0	Parameter in expression for clearance from blood plasma to urine (L/day)
MAX[b]	NA	NA	0.008	0.008	Parameter in expression for clearance from blood plasma to urine (mg/day)
KM[b]	NA	NA	0.0008	0.0008	Parameter in expression for clearance from blood plasma to urine (mg/L)
FB	0.0	0.0	NA	NA	Fraction of body burden secreted in the bile
FI	0.0	0.0	NA	NA	Fraction of body burden excreted via the gastrointestinal tract
Reduction					
KREDRC	NA	0.7	NA	7.0	First-order rate constant for reduction of Cr(VI) to Cr(III) in the red cell (Da^{-1})
KREDBP	NA	NA	NA	0.2	First-order rate constant for reduction of Cr(VI) to Cr(III) in blood plasma (Da^{-1})
KREDKL	NA	NA	NA	500.0	First-order rate constant for reduction of Cr(VI) to Cr(III) in kidney (Da^{-1})
KREDGI	NA	10.0	NA	100.0	First-order rate constant for reduction of Cr(VI) to Cr(III) in gastrointestinal tract contents (Da^{-1})
KRED	NA	0.5	NA	5.0	First-order rate constant for reduction of Cr(VI) to Cr(III) in all other tissues and in lung contents (Da^{-1})
Lag time for excretion of urine					
FRHOLD	0.7	0.7	NA	NA	Fraction of urinary chromium not excreted immediately; that is, temporarily held in pool
KHOLD	0.05	0.05	NA	NA	First-order rate constant for excretion from the retained urine pool (Da^{-1})
FR	0.10	0.10	NA	NA	Fraction of chromium in retained urine that is associated with the kidney

[a]Parameter names are those for human model in cases where the reported rat and human parameter names were not identical.

[b]Exchanges between blood plasma and cortical and trabecular bone are simulated as functions of bone formation and resorption rates.

[c] $QE = CLEAR - \frac{MAX}{KM + CBP}$, where QE is clearance from blood plasma to urine (L/day) and CBP is plasma concentration of chromium (mg/L).

NA = not applicable

Sources: O'Flaherty 1996 (rat parameters); O'Flaherty et al. 2001 (human parameters)

be reduced to chromium(III) in all tissues, and in the gastrointestinal and respiratory tract. Reduction is represented as a first-order rate, with distinct rates for the red cell and gastrointestinal tract, and a single value representing all other tissues.

Absorption of chromium from the gastrointestinal tract is simulated as the sum of competing first-order processes; transfer to the liver (absorption) and transfer of unabsorbed chromium to feces. Parameter values for these two processes result in absorption of approximately 1–2% of an oral dose.

The respiratory tract is represented with two subcompartments to distinguish a bioavailable chromium (pool A) from a nonbioavailable chromium (pool B). Inhaled chromium first deposits in pool A from where it can be transferred to blood (i.e., absorption), transferred to the gastrointestinal tract (i.e., mucocilliary clearance), or transferred to pool B. Chromium in pool B is cleared to the gastrointestinal tract. Transfers within and out of the respiratory tract are represented with first-order rate constants.

Transfers of chromium between plasma and soft tissues are represented with clearance terms (i.e., L/day), where clearance is given by the first-order rate constant (k_e) for transfer and tissue volume (V, clearance=k_e x V). Distinct plasma-to-tissue and tissue-to-plasma clearance values are assigned to chromium(III) and chromium(VI), with faster clearances assumed for chromium(VI), by a factor of 3,000–10,000, compared to chromium(III). In the rat model, transfers of chromium between plasma and bone are represented with clearance constants; however, this is expanded in the human model to represent chromium uptake into bone as a function of bone formation rate, and return of chromium to plasma from bone as a function of bone resorption rate (see also O'Flaherty 1993c, 1995 for further information on the bone growth and reabsorption model).

Absorbed chromium is excreted in urine. Although a biliary secretion pathway was included in the model, flux through the pathway was subsequently set to zero, based on optimizations of the model against observations. This parameterization is equivalent to assuming that either chromium is not secreted in bile, or if it is secreted into bile, it is essentially completely (and rapidly) absorbed. Urinary excretion of chromium is represented as clearance from plasma. In the rat model, plasma-to-urine clearance was assigned a constant value. In the human model, urinary clearance is represented as a variable fraction of the glomerular filtration rate, with the fraction increasing with increasing plasma concentration (e.g., 0.7% of GFR at a concentration of 0.0001 mg/L; 40% of GFR at 0.01 mg/L).

Validation of the model. Optimization of parameter values and evaluation of the rat model are described in O'Flaherty (1996). Initial values for the rat model were established based on data reported in various intravenous, oral, or intratracheal rat studies (Bragt and van Dura 1983; Cavalleri et al. 1985; Cikrt and Bencko 1979; Edel and Sabbioni 1985; MacKenzie et al. 1959; Mertz et al. 1969; Thompson and Hollis 1958; Weber 1983). Parameter values were optimized against data on kinetics of tissue levels and chromium excretion measured in rats that received intratracheal doses of ^{51}Cr(VI) or ^{51}Cr(III) (Bragt and van Dura 1983; Edel and Sabbioni 1985; Weber 1983). The optimized rat model was evaluated by comparing predictions of blood ^{51}Cr kinetics to observations made in rats exposed 6 hours/day for 4 days to dusts of zinc [^{51}Cr]chromate (76% respirable, Langård et al. 1978). Predicted blood concentrations during exposure and postexposure kinetics agreed with observations. The model was also evaluated against data from a drinking water study in which rats were exposed to drinking water concentrations of $K_2Cr(VI)O_4$ ranging from 0.45 to 25 mg/L, or to $Cr(III)Cl_3$ at a concentration of 25 mg/L for a period of 1 year (MacKenzie et al. 1958). This was not a completely independent evaluation of the model since data from this study were used to set parameters for fractional uptake of chromium into bone. Ranges for predicted:observed ratios for terminal tissue levels in rats exposed to 0.45–25 mg chromium(VI)/L were 1.2–5 for liver, 0.3–1.2 for kidney, and 0.2–1.5 for bone (femur). The ratio for rats exposed to 25 mg chromium(III)/L were 15 for liver, 0.9 for kidney, and 2 for bone.

Optimization and evaluation of the human model is described in O'Flaherty et al. (2001). The model was optimized with data on plasma and red blood cell chromium concentrations, and urinary chromium excretion in adult subjects who ingested a single dose of chromium(III) as $CrCl_3$ or chromium(VI) as $K_2Cr_2O_7$ (Finley et al. 1997; Kerger et al. 1996a, see Section 3.4.1.2 for description of these studies). The model was evaluated against data on plasma chromium concentration kinetics and urinary excretion of chromium in a single adult subject who ingested 4 mg chromium(VI)/day as $K_2Cr_2O_7$ for 17 days (Paustenbach et al. 1996; see Section 3.4.1.2), with the only adjusted parameter being the absorption rate constant. Although the model was optimized based on data from single dose studies, it reproduced the observed steady-state plasma chromium concentration, time to steady state, and elimination kinetics following cessation of the 17-day exposure.

Risk assessment. The model accounts for most of the major features of chromium(VI) and chromium(III) absorption and kinetics, and reduction chromium(VI) to chromium(III), uptake into and retention in red blood cells, and uptake and retention in bone. The human model associated bone chromium kinetics with bone formation and resorption and provides a structure for simulating age-dependent kinetics attributable to changes in bone turnover (e.g., growth, pregnancy, senescence).

Bioavailability of chromium from environmental sources is mostly unknown, except for a few chemically defined salts.

Target tissues. The rat and human models include parameters for predicting levels of chromium(III) and chromium(VI) in plasma, red blood cells, kidney, liver, bone, gastrointestinal tract, and respiratory tract. However, the rat model was calibrated against data on the above tissues, only for single dose intratracheal or intravenous exposures. Evaluations of predictions for repeated-dose exposures have been limited to blood concentration kinetics in an acute repeated dose inhalation exposure; and for terminal bone, kidney, and liver chromium levels in a 1-year drinking water study. The human model has been calibrated against data on plasma and red blood cell chromium concentrations and urinary chromium excretion following single oral doses administered to humans. Evaluation of predictions of repeated-dose outcomes have been limited to plasma and urine chromium kinetics, based on a study of a single subject exposure to chromium(VI) in drinking water for 17 days.

Species extrapolation. Evaluation of the robustness of extrapolation of the rat or human models to other species has not been reported.

Interroute extrapolation. The rat and human models include parameters for simulating inhalation and ingestion of chromium. The rat model was calibrated against data from single-dose intratracheal or intravenous exposures, and was evaluated against repeated-dose studies of inhaled and ingested chromium. The human model was calibrated and evaluated with data from ingestion studies; evaluation of the robustness of the model for predicting chromium kinetics following exposures to other routes has not been reported.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

The absorption of inhaled chromium compounds depends on a number of factors, including physical and chemical properties of the particles (oxidation state, size, solubility) and the activity of alveolar macrophages. Chromium has been identified in the tissues of occupationally-exposed humans, suggesting that chromium can be absorbed from the lungs (Cavalleri and Minoia 1985; Gylseth et al. 1977; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Tossavainen et al. 1980). Animal studies have also demonstrated increased amounts of chromium in the blood following inhalation or intratracheal instillation exposures (Baetjer et al. 1959b; Bragt and van

Dura 1983; Langård et al. 1978; Visek et al. 1953; Wiegand et al. 1984, 1987). Chromium(VI) is more rapidly absorbed into the bloodstream than is chromium(III) (Gao et al. 1993; Suzuki et al. 1984). Chromium that is not absorbed in the lungs may be cleared via mucociliary clearance and enter the gastrointestinal tract.

Chromium is poorly absorbed from the gastrointestinal tract; the primary site of chromium absorption appears to be the jejunum (Donaldson and Barreras 1966). The bioavailability of chromium compounds seems to be most dependent on the oxidation state of the chromium atom. However, other factors, including formulation of the chromium, can influence the extent of absorption. Inorganic chromium(III) is very poorly absorbed, with only 0.5–2.8% of dietary chromium absorbed via the gastrointestinal tract of humans (Anderson 1986; Anderson et al. 1983; Donaldson and Barreras 1966; Gargas et al. 1994; Kerger et al. 1996a; Kuykendall et al. 1996). Human studies demonstrate that chromium(VI) is effectively reduced to chromium(III) by gastric juices (De Flora et al. 1987a) and in general, chromium(VI) is better absorbed than chromium(III) following oral exposure in humans (Donaldson and Barreras 1966; Finley et al. 1996b; Kerger et al. 1996a; Kuykendall et al. 1996). Absorption efficiencies ranging from 1.7 to 6.9% have been estimated in humans (Finley et al. 1996a; Kerger et al. 1996a, 1997; Kuykendall et al. 1996). Ingestion of chromium with a meal appears to increase the absorption efficiency (Chen et al. 1973).

Both chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Following dermal exposure, chromium has been detected in the blood, feces, and urine of exposed humans (Brieger 1920), though in this study, the skin was damaged, which likely facilitated absorption. An average rate of systemic uptake of chromium(VI) in humans submersed in chlorinated water containing potassium dichromate(VI) for 3 hours was 1.5×10^{-4} μg/cm^2-hour (Corbett et al. 1997). Chromium(VI) appears to penetrate the skin faster than chromium(III) (Mali et al. 1963; Spruit and van Neer 1966; Wahlberg 1970), though many other factors may be involved, including solvent (Liden and Lundberg 1979) and concentration (Baranowska-Dutkiewicz 1981).

Absorbed chromium is carried throughout the body in the blood, eventually being distributed to all tissues. Greatest concentrations of chromium are found in the blood, liver, lung, spleen, kidney, and heart (Kaufman et al. 1970; Schroeder et al. 1962; Teraoka 1981). Because insoluble chromium is not completely cleared or absorbed following inhalation exposure, greater levels of chromium are often found in lung tissues following inhalation of chromium compounds than following other methods of exposure. Tissue levels appeared to be higher after exposure to chromium(VI) than to chromium(III). This may be due to the greater ability of chromium(VI) to cross cell membranes and may also be a function of

administration of doses high enough to overwhelm the chromium(VI) reduction mechanisms. De Flora et al. (1997) have demonstrated that liver, erythrocytes, whole blood, lung epithelial fluid, alveolar macrophages, and peripheral parenchyma cells all have the ability to reduce chromium(VI) to chromium(III). Chromium has been detected in breast milk (Casey and Hambidge 1984; Shmitova 1980), but the relationship between chromium exposure, dietary or otherwise, and breast milk chromium levels is inconclusive (Anderson et al. 1993; Engelhardt et al. 1990; Mohamedshah et al. 1998).

Systemic chromium(III) does not appear to be stored for extended periods of time within the tissues of the body. However, the prolonged half-life of chromium(VI) compared to chromium(III) in humans (Kerger et al. 1997) and animals indicate that a portion of the absorbed chromium(VI) dose that is not converted to chromium(III) is being sequestered inside cells. Single- and multiple-exposure studies in humans have shown a one-compartment clearance half-time in humans on the order of 36 hours (Kerger et al. 1997; Paustenbach et al. 1996) following oral exposure. This half-time is sufficiently long to allow for accumulation of chromium following regular repeated exposure. Following inhalation exposure, insoluble chromium that is not cleared from the lungs may remain for a considerable time. In the blood, chromium(VI) is taken up by erythrocytes and reduced to chromium(III) which forms complexes with hemoglobin and other intracellular macromolecules; these complexes are retained within the erythrocyte for the life-span of the cell (Paustenbach et al. 2003).

Inhaled chromium can be eliminated from the lungs by absorption into the bloodstream, by mucociliary clearance, and by lymphatic system clearance (Bragt and van Dura 1983; Perrault et al. 1995; Visek et al. 1953; Wiegand et al. 1984, 1987). The primary routes of elimination of absorbed chromium is urine and feces. It can also be eliminated in hair and fingernails (Randall and Gibson 1989; Stearns et al. 1995a; Takagi et al. 1986). Chromium, once reduced to chromium(III) in the liver, is then conjugated with glutathione and enters bile where it is excreted in the feces (Norseth et al. 1982). Because chromium is poorly absorbed following oral exposure, a large percentage of the amount ingested is excreted in the feces. The half-time of urinary excretion of chromium is short, 4–10 hours for inhalation exposure (Kiilunen et al. 1983), 10 hours for oral exposure to chromium(III) (Kerger et al. 1996a), and 40 hours for oral exposure to chromium(VI) (Kerger et al. 1996a, 1997). Following dermal exposure, chromium that is not absorbed into the bloodstream will remain on the skin until it is eliminated, usually by washing or other physical processes. Absorbed chromium is primarily eliminated in the urine.

3.5.2 Mechanisms of Toxicity

The toxic potency of chromium is dependent on the oxidation state of the chromium atom, with chromium(VI) more potent than chromium(III). The mechanisms of chromium toxicity and carcinogenicity are very complex. They are mediated partly through reactive intermediates during intracellular reduction of chromium(VI) to chromium(III) and oxidative reactions, and partly mediated by chromium(III) which is the final product of intracellar chromium(VI) reduction and forms deleterious complexes with critical target macromolecules (Chen and Shi 2002; Costa 2003; Costa and Klein 2006a; Ding and Shi 2002; Jeejeebhoy 1999; Levina and Lay 2005; Liu and Shi 2001; O'Brien et al. 2003; Paustenbach et al. 2003; Shrivastava et al. 2002; Zhitkovich 2005). Chromium(III) may form complexes with peptides, proteins, and DNA, resulting in DNA-protein crosslinks, DNA strand breaks, and alterations in cellular signaling pathways, which may contribute to toxicity and carcinogenicity of chromium compounds.

The greater toxic potency of chromium(VI) relative to chromium(III) most likely is related to two factors: (1) the higher redox potential of chromium(VI) (Levina and Lay 2005; Reddy and Chinthamreddy 1999); and (2) the greater ability of chromium(VI) to enter cells (Costa 2003). Differences in molecular structure contribute the greater cellular uptake of chromium(VI) compared to chromium(III) (Costa 2003; Costa and Klein 2006a). At physiological pH, chromium(VI) exists as the tetrahedral chromate anion, resembling the forms of other natural anions (e.g., sulfate and phosphate) which are permeable across nonselective membrane channels. Chromium(III), however, forms octahedral complexes and cannot easily enter through these channels. Therefore, the lower toxicity to chromium(III) may be due in part to lack of penetration through cell membranes. It follows that extracellular reduction of chromium(VI) to chromium(III) may result in a decreased penetration of chromium into cells, and therefore, a decreased toxicity.

The higher redox potential of chromium(VI) contributes to the higher toxic potency of chromium(VI) relative to chromium(III) (Levina and Lay 2005), because once it is taken into cells, chromium(VI) is rapidly reduced to chromium(III), with chromium(V) and chromium(IV) as intermediates. These reactions commonly involve intracellular species, such as ascorbate, glutathione, or amino acids (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Hojo and Satomi 1991; Kim and Yurkow 1996; Lin et al. 1992; Liu et al. 1997b; Mao et al. 1995; Wiegand et al. 1984; Zhitkovich et al. 1996). Chromium(VI), chromium(V), and chromium(IV) have all been shown to be involved in Fenton-like oxidative cycling, generating oxygen radical species (Aiyar et al. 1991; Chen et al. 1997; Liu et al. 1997b;

Luo et al. 1996; Mao et al. 1995; Molyneux and Davies 1995; Tsou et al. 1996). It is believed that the formation of these radicals may be responsible for many of the deleterious effects of chromium on cells, including lipid peroxidation (Bagchi et al. 2002a; Hojo et al. 1999, 2000) and alterations in cellular communication, signaling pathways and cytoskeleton (Chen et al. 1997; Gao et al. 2002; Gunaratnam and Grant 2002, 2004; Kim and Yurkow 1996; Mikalsen 1990; O'Hara et al. 2007; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Ye et al. 1995). Cellular damage from exposure to many chromium compounds can be blocked by radical scavengers, further strengthening the hypothesis that oxygen radicals play a key role in chromium toxicity (Hojo et al. 2000; Luo et al. 1996; Tsou et al. 1996; Ueno et al. 1995a).

The products of metabolic reduction of chromium(VI) (free radicals and chromium(IV) and (V)) and the newly generated chromium(III) are thought to be in part responsible for the carcinogenic effects seen in human and animal studies. The interaction of free radicals, chromium(V), chromium(IV), and chromium(III) with DNA can result in structural DNA damage, functional damage, and other cellular effects (Levina and Lay 2005; Singh et al. 1998a). The types of chromium-induced structural damage include DNA strand breaks (Aiyar et al. 1991; Bagchi et al. 2002a; Bryant et al. 2006; Casadevall et al. 1999; Ha et al. 2004; Kuykendall et al. 1996; Manning et al. 1992; Messer et al. 2006; Pattison et al. 2001; Ueno et al. 1995a), DNA-protein crosslinks (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Costa et al. 1996, 1997; Kuykendall et al. 1996; Lin et al. 1992; Manning et al. 1992; Mattagajasingh and Misra 1996; Miller et al. 1991; O'Brien et al. 2005; Quievryn et al. 2001; Zhitkovich et al. 1996), DNA-DNA interstrand crosslinks (Xu et al. 1996), chromium-DNA adducts, and chromosomal aberrations (Blankenship et al. 1997; Sugiyama et al. 1986a; Umeda and Nishimura 1979; Wise et al. 1993). Functional damage includes DNA polymerase arrest (Bridgewater et al. 1994a, 1994b, 1998), RNA polymerase arrest, mutagenesis, and altered gene expression. However, DNA double strand breaks may not be due to free radical formation, but due to the formation of chromium-DNA ternary adducts, which lead to repair errors and collapsed replication forks (Ha et al. 2004). Double strand breaks can also lead to alterations in cellular communication and effects on signaling pathways and cytoskeleton. In addition, results of recent studies in human lung cells suggest that chromosome instability is an important mechansism in the development of lung cancers; specifically, chromium-induced chromosome instability appears to be mediated through centrosome and spindle assembly checkpoint bypass (Holmes et al. 2006; Wise et al. 2006a).

Location of particle deposition in the lung and extracellular dissolution of chromium(VI) compounds (e.g., solubility) are also important considerations regarding the mechansim of chromium(VI)-induced

carcinogenesis. In chromate workers, analysis of bronchial tissues shows higher chromium concentrations in areas of bronchial bifurcation compared to other areas in the bronchi (Ishikawa et al. 1994a). Also, autopsy results show that some precancerous bronchial lesions originated at bronchial bifurcations (Ishikawa et al. 1994b). Solubility of chromium(VI) compounds may also play a role in carcinogenic potency, with extracellular dissolution of the chromium compound critical to activity (Wise et al. 2004). This hypothesis is supported by *in vitro* data suggesting that extracellular chromium ions are the proximate clastogen in Chinese hamster ovary cells (Wise et al. 2004).

Chromium(III) can also interact with DNA to form adducts/complexes and DNA-protein crosslinks that interfere with DNA replication and transcription, and can promote the expression of regulatory genes such as nuclear factor-κβ, or may inhibit regulatory genes such as GRP78 (Chen et al. 1997; Kim and Yurkow 1996; Manning et al. 1992; Mikalsen 1990; O'Hara et al. 2003; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Ye et al. 1995). Disruption of these pathways by other compounds has been implicated in carcinogenesis. The structural and functional damage can lead to growth arrest (Xu et al. 1996) and apoptosis (Carlisle et al. 2000; Singh et al. 1999). Numerous studies show that chromium can induce apoptosis (Asatiani et al. 2004; Bagchi et al. 2001; Carlisle et al. 2000; Flores and Perez 1999; Gambelunghe et al. 2006; Gunaratnam and Grant 2002, 2004; He et al. 2007; Manygoats et al. 2002; Petit et al. 2004; Russo et al. 2005; Vasant et al. 2003); although the mechanism by which chromium induces apoptosis is not fully understood, it is believed to involve oxidative stress and activation of the p-53 protein (Pulido and Parrish 2003; Singh et al. 1998a).

3.5.3 Animal-to-Human Extrapolations

Species-related differences in chromium pharmacokinetics have been demonstrated, both between rodent species and between rodents and humans. However, studies directly examining species differences have been limited. Human microsomal chromium(VI) reduction is different from the P450-mediated microsomal reduction in rodents; specifically, the human system is much less oxygen-sensitive, has a much greater affinity for chromate, and is apparently mediated by flavoproteins (Myers and Myers 1998; Pratt and Myers 1993). Tissue distributions of chromium were found to be different between rats and mice after administration of bolus amounts of chromium(VI). Rat erythrocytes had a greater capacity to sequester chromium(VI) and reduce it to chromium(III) than mouse erythrocytes (Coogan et al. 1991b; Kargacin et al. 1993), thus demonstrating that both physiologic and metabolic differences can exist among species.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Based on results of *in vivo* and *in vitro* studies, chromium(VI) may alter function of the hypothalamic-pituitary axis function. Serum prolactin levels were decreased by 59% in male Wistar rats exposed to 74 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 30 days. Incubation of cultured rats anterior pituitary cells with 0.1–10 μM chromium(VI) as potassium dichromate decreased prolactin secretion and cell viability (Quinteros et al. 2007). No additional assessments of hypothalamic-

pituitary axis function were conduced in this study. Serum testosterone levels were decreased by 20.8% in male New Zealand rabbits administered 3.6 mg chromium(VI)/kg/day as potassium dichromate for 10 weeks by gavage (Yousef et al. 2006); however, since function of the hypothalamic-pituitary-gonadal axis was not assessed, it is unclear if this effect reflects endocrine disruption.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and

sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990b; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Chromium(III) is an essential nutrient required for maintaining normal glucose metabolism. The IOM of the NAS determined an adequate intake of 0.2 μg chromium/day for infants aged 0–6 months; 5.5 μg chromium/day for infants aged 7–12 months; 11 μg chromium/day for children aged 1–3 years; 15 μg chromium/day for children aged 4–8 years; 25 μg chromium/day for boys aged 9–13 years; 21 μg chromium/day for girls aged 9–13 years; 35 μg chromium/day for boys aged 14–18 years; and 24 μg chromium/day for girls aged 14–18 years (IOM 2001).

There is a limited amount of information available on the toxicity of chromium in children. Most of the available data come from several case reports of children ingesting lethal concentrations of chromium(VI). A variety of systemic effects were observed in a 22-month-old who accidentally ingested an unknown amount of sodium dichromate (Ellis et al. 1982), a 1-year-old who ingested an unknown amount of ammonium dichromate (Reichelderfer 1968), a 17-year-old who intentionally ingested 29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983), and a 14-year-old who ingested 7.5 mg chromium(VI)/kg as potassium dichromate (Kaufman et al. 1970). The effects included pleural effusion, bronchopneumonia, hypoxic changes in the myocardium, decreased blood pressure and cardiac output, abdominal pain and vomiting, gastrointestinal burns and hemorrhage, and liver and kidney necrosis. An enlarged brain and cerebral edema were also observed in the 14-year-old (Kaufman et al.

1970). These effects are similar to effects observed in adults who have ingested lethal doses and are part of the sequelae leading to death.

A number of additional health effects have been observed in adults exposed to chromium (primarily chromium(VI)) at work. The primary targets appear to be the respiratory tract, gastrointestinal tract, hematological system, liver, and kidneys; an increased cancer risk has also been observed. Dermal contact in chromium sensitized individuals can lead to an allergic type dermatitis. In the absence of data to the contrary, it is likely that these organs/systems will also be sensitive targets in children. There is insufficient information to determine whether the susceptibility of children would differ from that of adults.

Although there are no human studies that examined developmental end points, animal studies have consistently shown that chromium, particularly chromium(VI), is a developmental toxicant. A number of developmental effects have been reported in oral studies involving maternal exposure to ≥46 mg chromium(VI)/kg/day as potassium dichromate (Al-Hamood et al. 1998; Junaid et al. 1996b; Trivedi et al. 1989). The observed effects included increases in postimplantation losses, gross abnormalities (e.g., subdermal hemorrhage, decreased ossification, kinky tail), and impaired development of the reproductive system (e.g., impaired fertility in female offspring). Similar developmental effects (e.g., post implantation losses, subdermal hemorrhage, decreased ossification) have also been observed in the offspring of rats and mice exposed to ≥37 mg chromium(VI)/kg/day for 20 or 90 days prior to mating (Junaid et al. 1996a; Kanojia et al. 1996, 1998). Conflicting results have been found for chromium(III). No developmental effects were reported in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout gestation (Ivankovic and Preussmann 1975). However, impaired development of the reproductive system (decreased reproductive tissue weight and impaired fertility) were observed in the offspring of mice exposed to 74 mg chromium(III)/kg/day as chromium chloride (Al-Hamood et al. 1998). Developmental effects have also been observed following intraperitoneal administration of chromium(III) chloride (Iijima et al. 1983; Matsumoto et al. 1976).

Chromium may be transferred to fetuses through the placenta and to infants via breast milk. Elevated levels of chromium have been reported in umbilical cord blood, placentae, and breast milk of women working in a dichromate(VI) manufacturing facility (Shmitova 1980). As noted elsewhere in the profile, the reliability of this study is suspect because the levels of chromium in the blood and urine of the control women were much higher than background levels. Measurement of the chromium content in 255 samples from 45 lactating American women revealed that most samples contained <0.4 μg/L, and the mean value

was 0.3 µg/L (Casey and Hambidge 1984). While these probably represent background levels in women whose main exposure to chromium is via the diet, the findings indicate that chromium may be transferred to infants via breast milk. These findings in humans are supported by animal data. Studies in rats and mice have shown that chromium(VI) and chromium(III) crosses the placenta and enters into fetal tissue. Elevated levels of chromium have been observed in the placenta and fetal tissue of rats and mice exposed to potassium dichromate(VI) in drinking water during pregnancy (Saxena et al. 1990a). The levels of chromium in the placenta were 3-and 3.2-fold higher in the exposed rats and mice, respectively, than in controls and fetal tissue chromium levels were 3.1-and 9.6-fold higher, respectively; the difference over control was only statistically significant in the mice. Another study (Danielsson et al. 1982) also found elevated fetal tissue levels of chromium. The chromium levels in the fetal tissues were 12–19% of maternal blood levels following maternal intravenous injections of sodium dichromate(VI) on gestational days 12–15 or 16–18 and 0.4–0.8% following maternal intravenous injections of chromium(III) trichloride on gestational days 12–15 or 16–18. A study of transplacental transfer of chromium(III) in different forms indicated that placental transport varies with the chemical form (Mertz et al. 1969). Higher levels of chromium were found in the neonates of rats fed chromium in a commercial diet as compared to neonates of rats fed a chromium-deficient diet and given drinking water containing chromium acetate monohydrate. Similarly chromium levels were significantly elevated in the offspring of rats administered chromium in the form of chromodulin from Brewer's yeast by gavage than in the offspring of rats administered chromium trichloride intravenously or by gavage.

There is very little information available in which to assess whether the pharmacokinetic properties of chromium would be different in children. Sullivan et al. (1984) found that gastrointestinal absorption of radiolabeled chromium chloride, administered by gavage, was 10 times higher in 2-day-old rats as compared to levels absorbed in adult rats. A similar pattern of distribution in the body was found in the immature and mature rats.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment

of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to chromium are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by chromium are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Chromium

As an essential nutrient, chromium is normally present in blood and urine. Chromium in body fluids (e.g., blood and urine) is the exposure biomarker of choice. Mean dietary chromium intake in the general U.S. population was estimated as 0.505 μg/kg/day (equivalent to 35.35 μg/day, assuming a body weight of 70 kg), with a range of 0.293–0.867 μg/kg/day (Moschandreas et al. 2002); however, only a small amount of dietary chromium is absorbed (≤3%). The IOM of the NAS (IOM 2001) determined an

adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 μg chromium(III)/day for adolescents and adults. Daily dietary intake levels have been shown to correlate with total excretion of chromium in the urine and feces (Bunker et al. 1984). The IOM (2001) reported average plasma chromium concentrations of 2–3 nmol/L (equivalent to 0.10–16 μg/L) and an average urinary chromium excretion of 0.22 μg/L or 0.2 μg/day; endogenous chromium concentrations also have been reported as 0.01–0.17 μg/L (median 0.06 μg/L) in serum (Sunderman et al. 1989), 0.24–1.8 μg/L (median 0.4 μg/L) in urine (Iyengar and Woittiez 1988), and 0.234 mg/kg in hair (Takagi et al. 1986). However, normal chromium levels in human fluid and tissues should be interpreted with caution. The low sensitivity of the most commonly used detection methods and the ubiquitous presence of chromium in laboratories make detection of low levels of chromium in blood and urine difficult.

Exposure to chromium may result in increased chromium concentrations in blood (whole blood, serum, and erythrocytes), urine, expired air, hair, and nails; of these, elevations of chromium in blood and urine are considered the most reliable indicators of exposure (Barceloux 1999; Caglieri et al. 2006). Urinary elimination half-times for absorbed chromium(III) range from 10–40 hours (Kerger et al. 1996a). Assuming an elimination half-time of 40 hours, steady state, plasma concentration, and urinary excretion rate of chromium would reach 95% of steady state levels in approximately 7 days (Paustenbach et al. 1996). Once steady state is achieved, the daily amount of chromium excreted in urine will reflect the daily amount absorbed. With cessation of exposure levels of chromium in plasma and urine will reach 5% of steady state within 7 days. The relatively rapid elimination kinetics of absorbed chromium(III) has implications for the use of plasma and urine as biomarkers of exposure to chromium. Plasma and urinary chromium concentrations will largely reflect relatively recent exposure (i.e., exposures that occurred several weeks prior to the sample may not be detected from plasma or urinary chromium measurements). During relatively constant or repetitive exposures that achieve a steady state in plasma, daily urinary chromium excretion measured on a single day can be expected to be highly correlated with chromium intake. This correlation will weaken with greater intermittency in the exposure, with greater dependence on the time of sampling with respect to the most recent exposure. The above general principles apply to exposures to absorbed chromium(III) compounds; however, absorbed chromium(VI) has a longer retention time in blood. Chromium(VI) that enters blood is taken up by red blood cells, reduced to chromium(III), and, in the process, form adducts with red blood cell hemoglobin and other proteins. These complexes are sufficiently stable to remain in the red blood cells for a substantial fraction of the lifespan of the red blood cell. Therefore, following absorption of chromium(VI) in to blood, the elimination half-time of chromium in blood will be substantially longer than that in plasma. The elimination half-time of injected chromium(VI) (e.g., sodium chromate-51, used in the clinical assessment

of red blood cell volume) is approximately 25–35 days (Dever et al. 1989). Based on a half-time of 30 days in red blood cells, with cessation of exposure to and absorption of chromium(IV), levels of chromium in red blood cells will reach 5% of a previous steady state level within 130 days.

Although chromium also accumulates in white blood cells, erythrocyte chromium has been shown to be a more sensitive measure of chromium exposure (Coogan et al. 1991b; Lukanova et al. 1996). An increase in plasma levels of chromium may reflect both recent exposure and exposure that occurred during the past few months (e.g., chromium that is sequestered within erythrocytes for the lifespan of the cell), whereas elevated urine chromium primarily reflects exposure over the past 1–2 days (Barceloux 1999). Distinct measurements of chromium in plasma and whole blood (reflecting intracellular distribution to erythrocytes) also be useful in distinguishing exposures to chromium(VI) compounds versus chromium(III) compounds; increased plasma levels of chromium may indicate exposure to both chromium(VI) and chromium(III), whereas increased chromium in erythrocytes indicates exposure to chromium(VI), since chromium(III) is not taken up by erythrocytes. For example, evaluation of postshift whole blood, serum, erythrocytes, and urine in groups of dichromate production workers exposed mainly to chromium(VI) or chromium(III) showed relationships between exposure type (e.g., chromium(VI) or chromium(III)) and chromium in blood and urine (Minoia and Cavalleri 1988). In 22 workers exposed primarily to chromium(VI) (0.008–0.212 mg chromium(VI)/m^3, 0.010–0.10 mg chromium(III)/m^3), the mean postwork-shift urinary chromium level was 31.5 μg total chromium/L; chromium(VI) was not detected in the urine samples (detection limit=0.05 μg chromium(VI)/L) due to *in vivo* reduction of chromium(VI) to chromium(III). Concentrations of total chromium in serum, erythrocytes, and whole blood were 2.2, 8.9 and 6.9 μg/L, respectively; compared with control levels of 1.1, 1.0, and 1.4 μg/L, respectively. In 15 workers exposed primarily to chromium(III) (0.046–1.689 mg chromium(III)/m^3, 0.002–0.023 mg chromium(VI)/m^3), the mean postwork-shift urinary chromium level was 24.7 μg total chromium/L and concentrations of total chromium in serum, erythrocytes, and whole blood were 3.1 μg/L, 1.4, and 1.8, respectively. The level of chromium in serum of the workers exposed mainly to chromium(III) was significantly ($p<0.001$) higher than that measured in workers exposed mainly to chromium(VI) or in controls. The level of chromium in erythrocytes of the workers exposed mainly to chromium(III) was significantly ($p<0.001$) less than that in workers exposed mainly to chromium(VI). The finding of higher levels of chromium in serum and lower levels of chromium in erythrocytes of workers exposed mainly to chromium(III) than in workers exposed mainly to chromium(VI) reflects the relative inability of chromium(III) to enter erythrocytes.

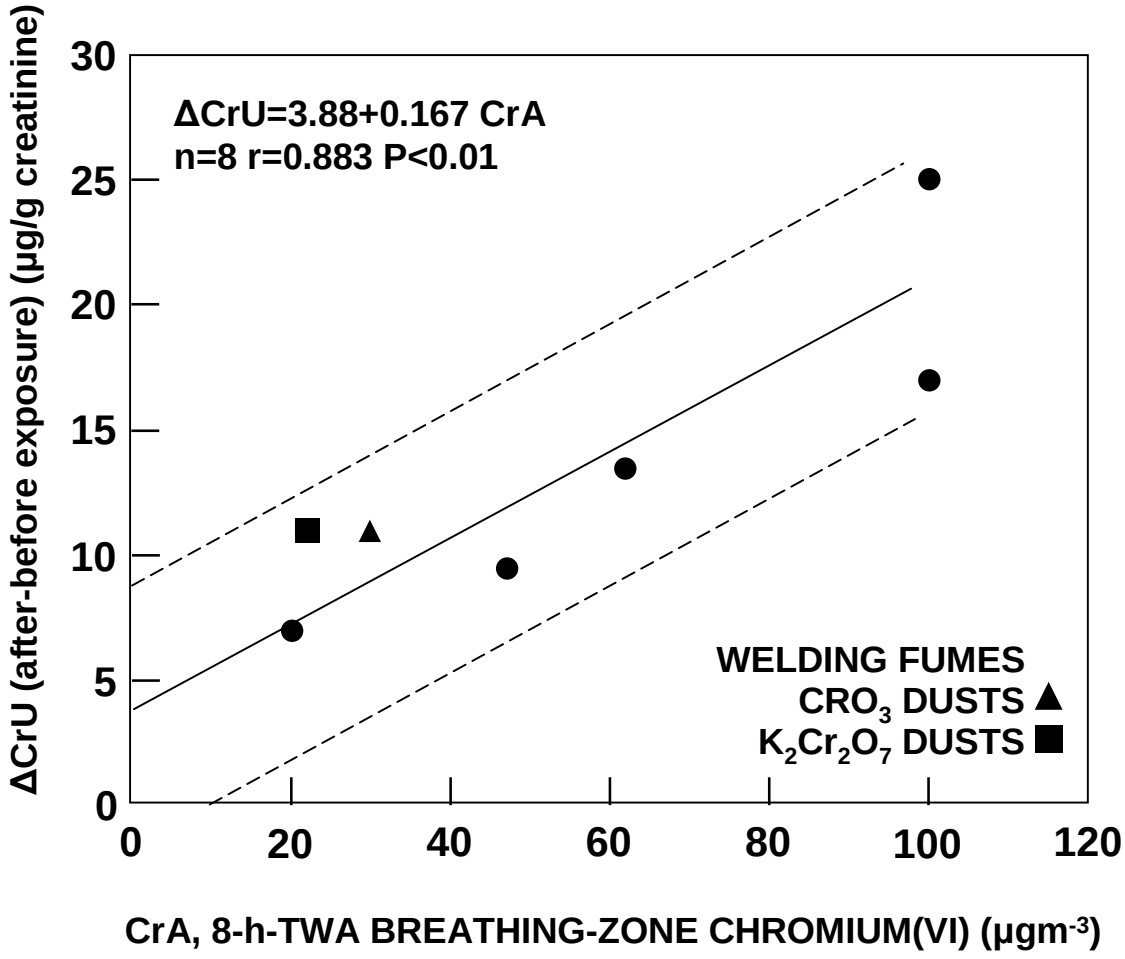
Although exposure to chromium may produce increases in chromium levels in both blood and urine chromium levels, the relationship between blood and urinary chromium levels may vary. Entry of chromium(VI) into the red blood cells probably reflects a competition between plasma reduction to chromium(III) and red blood cells uptake of chromium(VI) and not the result or consequence of the exhaustion of plasma reducing ability. When hexavalent chromium is incubated with washed isolated erythrocytes, almost all of the entire dose is taken up by the cells. Chromium(VI) is then reduced inside the cells to trivalent chromium, essentially trapping it inside the erythrocyte. In contrast, little chromium(III) appears to be taken up by erythrocytes *in vitro* incubations (Aaseth et al. 1982; Bentley 1977; Donaldson and Barreras 1966; Gray and Sterling, 1950). When chromium(VI) is incubated with whole blood or erythrocytes plus plasma, only a fraction (depending on conditions) of the chromium(VI) is taken up by the erythrocytes (Coogan et al. 1991b; Corbett et al. 1998; Lewalter et al. 1985; Wiegand et al. 1985), most likely due to the reduction of a portion of chromium(VI) to chromium(III) outside of the erythrocyte (Capellmann and Bolt 1992; Korallus et al. 1984; Richelmi et al. 1984). Thus, chromium(III) is then largely excluded from the erythrocyte. However, Korallus (1986a, 1986b) has proposed that the relationship between blood and urinary chromium levels may vary, possibly due to variability in plasma reduction capacity. *In vitro* experiments indicate that when chromium(VI) plasma levels exceed the plasma reduction capacity (PRC), chromium(VI) enters erythrocytes, is reduced, and binds to hemoglobin. The bond persists for the lifetime of the erythrocytes (120 days); therefore, a single determination of chromium in erythrocytes allows a longitudinal evaluation of exposure for an extended period in the past. Low chromium concentrations in erythrocytes indicate that the amount of chromium(VI) uptake did not exceed the PRC. Limited evidence suggests that the capacity of human plasma to reduce chromium(VI) compounds to chromium(III) compounds varies, with slow and fast reducers recognized (Korallus 1986a, 1986b). It is not clear what is responsible for individual differences in the PRC, although difference in magnitude of PRC appears to correlate with the levels of ascorbic acid in plasma.

The relationship between serum and urine chromium levels to occupational exposure levels has been investigated in numerous studies, with results showing correlations between exposure levels and chromium levels in blood and urine (Gylseth et al. 1977; Iarmarcovai et al. 2005; Kilburn et al. 1990; Lewalter et al. 1985; Lindberg and Vesterberg 1983a; McAughey et al. 1988; Medeiros et al. 2003a; Minoia and Cavalleri 1988; Muttamara and Leong 2004; Mutti et al. 1985b; Randall and Gibson 1987, 1989; Saner et al. 1984; Sathwara et al. 2007; Simpson and Gibson 1992; Sjogren et al. 1983; Stridsklev et al. 2004; Takagi et al. 1986; Tola et al. 1977; Wiegand et al. 1988). In workers exposed to chromium(VI) as chromium trioxide in the chrome plating industry, a significant correlation (r=0.71) was

observed found between exposure levels and postshift urinary chromium; for a TWA exposure of 0.002 mg chromium(VI)/m^3, the mean urinary chromium level was 5.2 μg/L (excluding workers with obvious skin contamination) (Lindberg and Vesterberg 1983a). Significant correlations were observed between chromium concentrations in air (measured by personal sampling devices; 8-hour TWA) and levels of chromium in blood (r=0.99) and urine (r=0.89) in workers at a chromium alloy facility (Muttamara and Leong 2004). In areas of low exposure, the air concentration of chromium (type not specified) was 5.75 μg/m^3; in workers in this area, mean chromium concentrations in blood and urine (duration of sample collection was not reported) were 0.925 and 0.095 μg/dL, respectively. In areas of high exposure, the air concentration of chromium was 7.25 μg/m^3, in workers in this area, mean chromium concentrations in blood and urine were 3.64 and 0.34 μg/dL, respectively. An increase in urinary chromium of 12.2 μg/g creatinine above preexposure values or a total concentration of 29.8 μg/g creatinine (end-of-shift values) corresponded to an air concentration of 50 μg chromium(VI)/m^3 from welding fumes (Mutti et al. 1985b). Examination of end-of-shift chromium levels indicated a correlation between urinary chromium levels and exposure to soluble chromium(VI) compounds, but not to insoluble chromates or chromium(III) compounds (Minoia and Cavalleri 1988; Mutti et al. 1985b). The relationship between workroom air concentrations of water soluble chromium(VI) compounds and daily increases in urinary chromium (preexposure values subtracted from end-of-shift values) are shown in Figure 3-7. Serum and urine concentrations of chromium were significantly elevated in a group of 73 tannery workers, with exposure primarily to chromium(III) compounds, compared to a group of 52 control subjects, at the end of the workweek on Friday and before exposure began on Monday (Randall and Gibson 1987). Serum and urine chromium levels correlated with work area of the tannery, with the highest concentrations in workers handling wet hides in the chrome tanning and wringing departments. The time-weighted average level of total chromium in tannery air was 1.7 μg/m^3 and did not vary significantly among the various tanneries involved in the study or among the various work areas of each tannery, with chromium(VI) levels in tannery air were below the detection limit of (0.1 μg/m^3).

Urinary and blood chromium have also been used as a biomarker for environmental exposure (Bukowski et al. 1991; Chang et al. 2006; Fagliano et al. 1997). However, interpretation of results may be limited by several factors, including that exposure must be sufficient such that urinary and blood concentrations are higher than the range of background concentrations and analytical limit of detection, high inter- and intrapersonal variability, and that different chemical forms have different bioavailabilities (Paustenbach et al. 1997; Finley et al. 1996b; Gargas et al. 1994; Kerger et al. 1997). Furthermore, the short half-life of chromium (e.g., at least 90% of absorbed chromium is eliminated within 24 hours) make it difficult to assess exposure incidents. Low-level, intermittent exposure, such as would occur with environmental

Figure 3-7. Relationship Between Water Soluble Chromium(VI) CrA and Daily Increase in Urinary Chromium Levels (CrU) (Pre-exposure Values were Subtracted from End-of-Shift Values)



Source: Mutti et al. 1985b

exposures to soil, dust, and residential drinking water, may not be detected with urinary monitoring; however, it is more likely that urinary monitoring would detect higher-level continuous exposure or daily inhalation exposure to chromium(VI). Paustenbach et al. (1997) note that chromium intakes would have to exceed 2 μg/day in order to distinguish the exposure from background. Large interpersonal variability (as high as a factor of 10) and intrapersonal variability (as high as a factor of 3) can result in highly variable erroneous conclusions regarding significant differences among populations.

3.8.2 Biomarkers Used to Characterize Effects Caused by Chromium

Chromium has been shown to produce effects to several systems, including the respiratory, gastrointestinal, hematological, and immunological systems (see Section 3.2); however, many of these effects are not specific for chromium. Although effects to these physiological systems can be assessed with blood and respiratory function tests and by physical examination, these assessments would not serve as biomarkers specific for effects of chromium as impairment of these systems can result from a variety of other causes, including chemical toxicity, nutritional insufficiencies, and disease.

Occupational exposure to chromium and its compounds has caused respiratory effects, such as pneumonitis, impaired pulmonary function, nasal septum perforations, irritation of the mucosa, inflammation, and cancer. In addition, chromium can be irritating and corrosive to the skin. Chromium exposure may cause asthma attacks and dermatitis in sensitive individuals. Workers with urinary levels of chromium >15 μg/g creatinine had increased retinol binding protein and tubular antigens in the urine. The workroom levels ranged from 0.05 to 1.0 mg chromium(VI)/m^3 as chromium trioxide (Franchini and Mutti 1988). The urine of chromium(VI) exposed workers in a chromate production plant contained higher levels of a brush border protein and of retinol-binding protein in the urine than did nonexposed controls (Mutti et al. 1985a). In a study of currently exposed chrome platers, ex-chrome platers, and referent groups of nonexposed workers, the urinary levels of β_2-microglobulin were significantly higher ($p=0.045$), and elevated levels occurred more often in the presently exposed groups compared with its age-matched control group. The levels of β_2-microglobulin in the urine of the ex-chrome platers, however, were not different than those of its age-matched control group (Lindberg and Vesterberg 1983b). Another study of hard chrome electroplaters found a higher prevalence of workers with elevated N-acetyl-β-glucosamindase levels (Liu et al. 1998). Although this study also found higher levels of β_2-microglobulins in the chrome plater, the prevalence of elevated values was not significantly increased. The presence of low molecular weight proteins, such as retinol binding protein, antigens, or

$ß_2$-microglobulin in the urine is believed to be an early indication of kidney dysfunction. The lack of a significant difference in the ex-chrome platers compared with the control group suggests that the chromium-induced kidney damage may be reversible. Cell culture and cell free studies discussed in Section 3.5.2 demonstrated that chromium forms protein-DNA crosslinks and adducts with DNA, and that these end points may be potentially useful biological markers, indicating the possibility of genotoxic effects or cancer in humans exposed to chromium. However, no increases in protein-DNA crosslinks were observed in white cells from volunteers who were exposed to chromium(VI) in drinking water (Kuykendall et al. 1996).

The possibility of using an immune-function assay as a potential biomarker for humans exposed to chromium has been examined (Snyder et al. 1996). Isolated mononuclear cells from 46 individuals who lived and/or worked in areas in northern New Jersey at sites contaminated by chromium processing were stimulated by pokeweed mitogen. Rates of stimulated cell growth and production of interleukin 6 (IL-6) were measured and compared to a control population of people who lived/worked in uncontaminated areas. There was no significant increase in mitogen stimulation between people from contaminated areas and controls, but there was a significant (36%) decrease in the levels of IL-6 in monocytes in the chromium exposed group. IL-6 is an important cytokine that is involved in the T-cell helper pathway of antibody production. The significance of the lower levels may lead to decreased levels of antibody production.

The effects of chromium(III) chloride, sodium chromate(VI), and potassium chromate(VI) on proliferation of mononuclear leukocytes obtained from chromium sensitive individuals (confirmed with positive patch tests) was compared to nonsensitive controls (confirmed by negative patch tests) (Räsänen et al. 1991). Isolated cells were exposed to 25–50 µg/mL culture medium of chromium(III) chloride and to 0.025 to 0.1 µg/mL culture medium chromium(VI) salts, which gave optimum responses and cell growth ratios of treated/nontreated cells from eight sensitive individuals ranging from 1.56 to 13.22, average=5.8 (chromium(III)), from 2.24 to 11.43, average 5.4 sodium chromate, and from 1.82 to 9.48, average 5.4potassiium dichromate. The nonsensitive individuals' ratios were consistently lower with ranges from 0.90 to 2.28 and average ratios of 1.14, 1.30, and 1.56, respectively. The authors felt that this *in vitro* methodology could be used diagnostically to assess chromium-sensitive individuals.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (Agency for Toxic Substances and Disease Registry 1990c) and for information on biomarkers for neurological effects see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

Potassium dichromate (10 mg/kg) administered by subcutaneous injection potentiated the effects of the nephrotoxins, mercuric chloride, citrinin, and hexachloro-1,3-butadiene, in rats. Effects on renal function included changes in urine volume, osmolality, electrolyte and glucose excretion, and a reduction in renal cortical slice organic ion transport. Chromium(VI) compounds potentiated the effect of mercuric chloride on organic acid uptake but not organic base uptake by renal cortical slices (Baggett 1986; Haberman et al. 1987). A similar experiment with another nephrotoxin, maleic acid, demonstrated the potentiating effect of potassium dichromate (10 mg/kg administered subcutaneously) (Christenson et al. 1989). Christenson et al. (1989) suggested that the combination of potassium dichromate with maleic acid might enhance damage to the brush border of the renal proximal tubules or that damage to the luminal cells by potassium dichromate might allow maleic acid to more easily enter the cells.

Concomitant exposure of female Sprague-Dawley rats to chromium(VI) potassium dichromate and ethanol in drinking water for 22 weeks indicates that ethanol may enhance the hepatic effects of chromium(VI) (Acharya et al. 2001). Serum enzyme activity of ALT in rats treated with 10% ethanol and 25 mg chromium(VI)/L (3.8 mg chromium(VI)/kg/day) was significantly increased compared to treatment of rats with ethanol or chromium(VI) alone. However, the toxicological significance of this finding is uncertain, since serum ALT activities of rats treated with ethanol and chromium(VI) were increased by only 18% compared to treatment of rats with chromium(VI) alone.

Interactions between selenium in the diet and ammonium dichromate in the drinking water were investigated in a study using rats. During the experiment, one rat died and the other rats had atrophy of the central liver lobe when given selenium alone. Dietary selenium and ammonium chromate in combination caused hepatic necrosis, resulting in the death of four rats (Moxon and DuBois 1939). Although the rats were not fed chromium alone, other studies indicate that the liver is a target for chromium exposure (see Section 3.2). The mechanism for the interaction was not discussed.

Exposure of female hairless mice to ultraviolet light in combination with chromium(VI) as potassium chromate in drinking water at concentrations of 2.5 or 5.0 mg potassium chromate(VI)/L (approximately 0.18 or 0.35 mg chromium(VI)/kg/day) for 182 days, or in the diet at concentrations of 0, 2.5, or 5.0 mg potassium chromate(VI)/kg food (approximately 0.13 or 0.26 mg chromium(VI)/kg/day) for 26 weeks, produced an increased incidence of skin tumors compared to animals exposed to UV light alone or

chromium(VI) alone (Davidson et al. 2004; Uddin et al. 2007). Exposure to chromium(VI) alone did not result in neoplasms. The chromium-induced enhancement of UV light-induced skin tumors did not appear to be mediated through oxidative damage, since concomitant treatment with vitamin E or selenomethionine did not decrease the chromium effect.

Concomitant inhalation exposure to ozone and chromium(VI) may alter pulmonary clearance mechanisms in the deep lung (Cohen et al. 2003). Compared to rats treated with insoluble chromium(VI) as calcium chromate (0.34–0.36 mg chromium(VI)/m^3) alone for up to 48 weeks, concomitant exposure to ozone (0.59 mg/m^3) resulted in decreased particle uptake and altered postphagocytic/endocytic processing of chromium particles by alveolar macrophages. However, since toxicity was not assessed in this study, it is not known if ozone-induced alteration in alveolar macrophage function would result in increased toxicity of chromium(VI).

A number of studies indicate an increase in the mutagenic effects of chromium(VI) compounds in combination with other chemicals. Synergism has been observed between chromium(VI) and 9-aminoacridine, nitrilotriacetic acid, and azide (Bronzetti and Galli 1989; Gava et al. 1989a; LaVelle 1986a, 1986b; Montaldi et al. 1987), but the mechanisms are not clearly understood. Potassium dichromate potentiated mutations produced by sodium azide in *S. typhimurium* or by 9-aminoacridine in *S. typhimurium* and *E. coli*. Although the data were insufficient for speculation on the specific biochemical mechanism, it was suggested that the potentiation involved a specific effect of potassium dichromate on the interaction of 9-aminoacridine or sodium azide with DNA or on subsequent DNA replication and/or repair (LaVelle 1986a, 1986b). Nitrilotriacetic acid, which appears to have no genotoxic potential itself, increased the frequencies of sister chromatid exchanges in Chinese hamster ovary cells and of micronuclei and chromosomal aberrations in cultured human lymphocytes that were seen with lead chromate alone. However, nitrilotriacetic acid had no effect on the dose-related induction of sister chromatid exchanges in Chinese hamster ovary cells that was seen with potassium chromate alone. It was suggested that nitrilotriacetic acid increased the solubility of the originally insoluble lead chromate, leading to increased uptake of the metal cation by the cells and subsequent increased genotoxicity (Montaldi et al. 1987). Nitrilotriacetic acid increased the frequency of point mutations in *S. cerevisiae* observed with a low concentration of sodium chromate, but decreased the frequency with a 5-fold higher concentration of sodium chromate. It was suggested that at the low concentration of sodium chromate, nitrilotriacetic acid affected the uptake of chromium(VI), favoring reduction to chromium(III) ions, which formed a complex with nitrilotriacetic acid that can cross the membrane and interact with DNA. At the high dose of sodium chromate, nitrilotriacetic acid may have affected the mechanism of

recombination repair of DNA breaks induced by chromate oxidizing activity (Bronzetti and Galli 1989). Nitrilotriacetic acid also increased the mutagenicity of potassium dichromate in *S. typhimurium* and *D. melanogaster*, presumably by favoring the reduction of chromium(VI) to chromium(III) (Gava et al. 1989a). Thus, it is possible that other hazardous substances at hazardous waste sites may be more dangerous due to the presence of chromium(VI).

Ascorbic acid has been shown to have a protective effect in rats administered lethal dermal doses of potassium dichromate (25 mg chromium(VI)/rat), and in preventing ulcerations of the skin (Samitz 1970). The nephrotoxicity due to subcutaneous injections of potassium chromate in rats was prevented by intramuscular administration of ascorbic acid (Powers et al. 1986). This occurred mainly through the reduction of chromium(VI) to the less toxic chromium(III) state. In cultured human bronchial cells, co-exposure to ascorbic acid and sodium chromate blocked chromate-induced clastenogenicity by preventing uptake of chromium(VI) ions by cells (Wise et al. 2004). Vitamin E protected against, while vitamin B_2 enhanced, the cytotoxicity and DNA strand breaks induced by sodium chromate in Chinese hamster cells *in vitro*. Vitamin E may exert its protective effect by scavenging radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991) (see Section 3.11.3). N-Acetylcysteine, the glutathione precursor, was reported to be effective in increasing the urinary excretion of chromium in rats (Nadig 1994).

Studies have examined the effects of interactions between chromium and arsenic on blood cholesterol and glucose levels and changes in organ weight in rats (Aguilar et al. 1997). Groups of five male Wistar rats were given food containing 5 μg/g of either arsenic(V) oxide, chromium(III) chloride, or a combination of both chemicals for 10 weeks. Organ weight to body weight ratios of liver, spleen, lung, kidney, and heart were similar to control values for the three exposed groups. Arsenic alone increased the cholesterol blood level from 47.27(±6.85 SD) mg/dL in the control group to 96.83(±6.11 SD). The combination of arsenic and chromium reduced the blood cholesterol level to 46.69(±6.11 SD) mg/dL. Neither chemical alone or in combination affected blood glucose levels. In most tissues, the combination of chemicals reduced the chromium level appreciably below control values. Supplemental chromium increased arsenic levels in liver, kidney, spleen, heart, and red blood cells, and reduced levels of arsenic in lung and hair tissues. Chromium did not appear to alter concentrations of arsenic in the liver.

A study examining the chromium(VI) reduction in microsomes noted that the level of iron in the test system markedly influenced the V_{max} of chromium(VI) reduction, suggesting that coexposure to

chromium(VI) and agents that increase intracellular iron might lead to increased risk for chromium(VI) toxicity (Myers and Myers 1998).

The effects of chromium(III) chloride and sodium chromate(VI) on the hepatotoxicity of carbon tetrachloride exposure to mouse hepatocytes were examined by Tezuka et al. (1995). Primary cultures of mouse hepatocytes were pretreated with 10 or 100 μM chromium for 24 hours followed by exposure to 1–5 mM carbon tetrachloride for up to 1 hour. Chromium(VI) pretreatment significantly reduced the cell toxicity as well as lipid peroxidation caused by carbon tetrachloride. Chromium(III) pretreatment did not have any effect on cell toxicity. About 50% of chromium(VI) was taken up and reduced in the cells by 90% to chromium(III) within 10 minutes. The initial uptake rate of chromium(III) into cells was greater than 500-fold less than chromium(VI), and only about 5% was absorbed. The protection against carbon tetrachloride damage by chromium(VI) was attributed to its rapid uptake and conversion to chromium(III), and it was determined that chromium(III) acts as a radical scavenger for the free radicals generated by carbon tetrachloride within the cell. Furthermore, chromium(VI) pretreatment reduced the activity of NADPH cytochrome c reductase, which metabolizes carbon tetrachloride to reactive species. In a previous study (Tezuka et al. 1991), the same group found that pretreating mice and rats with chromium(III) also protected against hepatic toxicity.

In order to examine the speciation of chromium in lemonade, Kool Aid, tea, dripped coffee, percolated coffee, and orange juice, potassium chromate(VI) was added to each of the beverages at a chromium concentration of 10 mg/L (Kerger et al. 1996b). After 15 minutes, the concentrations of chromium(VI) were determined to be <0.4 mg/L for orange juice, <0.3 mg/L for coffee and tea, 2 mg/L for Kool Aid, and 0.3 mg/L for lemonade. After 3–5 hours, essentially no residual chromium(VI) remained. At higher concentrations (50 mg/L chromium(VI)), >99, 40, and 84% of the chromium(VI) was reduced after 3–5 hours in orange juice, lemonade, and coffee, respectively (not tested at the higher concentration in Kool Aid and tea). The reducing capacities were not correlated with total organic carbon or pH. The reducing capacities of the beverages were attributed in part to ascorbic acid in lemonade and orange juice and to tannins in tea and coffee.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to chromium than will most persons exposed to the same level of chromium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke).

These parameters result in reduced detoxification or excretion of chromium, or compromised function of organs affected by chromium. Populations who are at greater risk due to their unusually high exposure to chromium are discussed in Section 6.7, Populations with Potentially High Exposures.

Acute inhalation LC_{50} and oral and dermal LD_{50} studies suggest that female animals are more sensitive to the lethal effects of chromium(VI) compounds (see Sections 3.2.1.1, 3.2.2.1, and 3.2.3.1). Whether human females are more sensitive than males to toxic effects of chromium or its compounds is not known. Other information identifying possible susceptible populations was not located. The primary and most sensitive effects of exposure to chromium compounds to the respiratory, gastrointestinal, hematological, and immunological systems; thus, individuals with preexisting conditions of these systems may be at increased risk of exposure to chromium compounds. Due to the sensitizing effects of chromium, some individuals who are sensitive to chromium may develop asthma as an anaphylactic response to inhaled chromium. Also, there is limited evidence in some individuals have less ability than others to reduce chromium(VI) in the bloodstream and are more likely to be affected by the adverse effects of chromium exposure (Korallus 1986a, 1986b). The ability to reduce chromium(VI) in the bloodstream may be related to the ascorbic levels in the plasma. However, the metabolic reduction of chromium(VI) may result in bioactivation and/or detoxification.

Since chronic inhalation of cigarette smoke may result in squamous metaplasia in the respiratory mucosa, the risk of lung cancer due to inhalation of carcinogenic chromium compounds may be exacerbated in individuals who smoke cigarettes or are excessively exposed to passive smoke (Albert 1991).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chromium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to chromium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to chromium:

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Chromium. In: Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: W.B. Sanders Company, 794-795.

Leikin JB, Paloucek FP, eds. 2002. In: Leikin and Paloucek's poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 372-379.

Schonwald S. 2004. Chromium. In: Dart RC, ed. Medical toxicology. 3rd ed. Philadelphia, PA: Lippicott Williams & Wilkins, 1415-1417.

3.11.1 Reducing Peak Absorption Following Exposure

General recommendations for reducing absorption of chromium following acute inhalation exposure have included moving the patient to fresh air, monitoring for respiratory distress, and administering humidified supplemental oxygen with assisted ventilation if required (Haddad et al. 1998; Schonwald 2004). If pulmonary effects such as bronchoconstriction are present, treatment with oxygen and bronchodilator drugs may be administered (Haddad et al. 1998). The absorption of inhaled chromium compounds depends on such factors as oxidation state, particle size, and solubility. Chromium(VI) passes through the alveolar lining of the lungs to the bloodstream more readily than does chromium(III) (see Section 3.4.1.1), and more soluble compounds are absorbed more readily than those that are less soluble (Bragt and van Dura 1983). Although chromium(VI) is more readily absorbed from the lungs than chromium(III), various components of the respiratory system can reduce chromium(VI) to chromium(III), which is far less capable of crossing cell membranes than chromium(VI), thereby reducing the bioavailability of chromium to target cells other than the lung (De Flora and Wetterhahn 1989). Epithelial lining fluid (ELF) is capable of reducing chromium(VI) (Petrilli et al. 1986b) and may represent the first line of defense against inhaled chromium(VI). Ascorbic acid (vitamin C) and glutathione, both of which were found to reduce chromium(VI) to chromium(III) in cell-free bronchoalveolar lavage fluid or soluble fractions of rat lungs *in vitro*, appear to be involved in this activity of ELF (Suzuki and Fukuda 1990). Uptake and reduction of chromium(VI) by pulmonary alveolar macrophages, catalyzed by NADH- or NADPH-dependent cytosolic enzyme activities, may lead to virtually irreversible sequestration and efficient removal by mucociliary action (De Flora and Wetterhahn 1989; De Flora et al. 1984, 1987b). Reduction of chromium(VI) within pulmonary alveolar macrophage homogenates was stimulated in rats by the administration of the glutathione precursor, N-acetylcysteine (De Flora and Wetterhahn 1989). As mentioned above, the reduction of chromium(VI) to chromium(III) by these various processes within the lungs serves as a natural defense mechanism by decreasing the amount of chromium absorbed and enhancing mucociliary clearance of chromium(III). However, reduction of chromium(VI) to chromium(III) generates reactive intermediates, which may produce adverse effects. Theoretically, further clearance from the lungs might be achieved by the administration of expectorants, but the efficacy of such a procedure has not been tested.

Chromium(III) is also poorly absorbed by the gastrointestinal tract, and chromium(VI) is reduced to chromium(III) in the gastric environment, limiting the bioavailability of chromium(VI) (De Flora et al. 1987a; Donaldson and Barreras 1966). Thus, the oral toxicity of chromium metal is low. However, chromium(VI) compounds are highly corrosive to the gastrointestinal tract and can lead to hepatic, renal, hematological, and neurological effects (Clochesy 1984; Coogan et al. 1991a; Diaz-Mayans et al. 1986; Iserson et al. 1983; Kaufman et al. 1970; Kumar and Rana 1982, 1984; Samitz 1970; Saryan and Reedy 1988). The reduction of chromium(VI) to chromium(III) in the stomach is greatly enhanced at low pH and shortly after meals due to increased gastric juice secretion (De Flora et al. 1987a). Therefore, administration of food might help decrease the gastrointestinal absorption of chromium. The enhanced reduction of chromium(VI) at low pH suggests that, theoretically, oral administration of bicarbonates and antacids should be avoided. Oral administration of ascorbic acid to further reduce chromium(VI) to chromium(III) might further decrease bioavailability (Haddad et al. 1998; Schonwald 2004), although this has not been proven (Leikin and Paloucek 2002; Schonwald 2004). Other recommendations for reducing gastrointestinal absorption of chromium include diluting with water or saline followed by gastric lavage (Schonwald 2004). Inducing emesis with syrup of ipecac is not recommended because of the possibility of irritation or burns to the esophagus (Nadig 1994; Schonwald 2004).

In cases of dermal exposure, the skin should be thoroughly washed to prevent chromium absorption by the skin (Haddad et al. 1998; Leikin and Paloucek 2002; Schonwald 2004). As chromium(VI), but not chromium(III), is readily absorbed by the skin, ascorbic acid in the washing solution could reduce chromium(VI) to chromium(III), thus decreasing absorption. Application of the calcium disodium salt of ethylenediamine tetraacetic acid (EDTA), which acts as a chelating agent, has also been recommended after washing with water and application of ascorbic acid (Nadig 1994), especially in cases where the skin has been cut or abraded (Burrows 1983). Ascorbic acid was found to protect chromium-sensitive workers who handled chromates in the lithographing and printing industries from dermatitis. The ascorbic acid (10% solution) was kept near the work areas, and the workers soaked their hands and forearms as soon as possible after handling the chromate mixtures. In addition, ascorbic acid prevented ulcerations of the skin in rats treated with potassium dichromate dermally (Samitz 1970). An antichrome powder consisting of a mixture of 40% sodium metabisulfite, 20% ammonium chloride, 20% tartaric acid, and 20% sucrose as a 10% aqueous solution was effective in reducing the healing time of chrome sores on the skin of guinea pigs to which potassium dichromate had been applied (Samitz and Epstein 1962). Thorough irrigation with water has been recommended if the eyes have been exposed (Haddad et al. 1998; Schonwald 2004).

Both the cytotoxic effects of chromium(III) chloride, chromium(III) nitrate, sodium chromate(VI), sodium dichromate(VI), potassium dichromate(VI), and chromium(V) potassium sulfate dodecahydrate and the ability of ascorbic acid, glutathione 4-acetamido-4'-isothiocyanato-2,2-stibenedisolphonic acid (SITS) to prevent chromium toxicity in transformed human keratinocytes were examined (Little et al. 1996). This cell line was used because histopathological studies have shown that dichromate compounds have caused keratinocyte necrosis. Cells were exposed to the chromium salts for 24 hours, and the viability of the cultures was examined for their ability to take up neutral red dye and release lactate dehydrogenase into the media. None of the chromium(III) or chromium(V) salts seemed toxic to the cells at concentrations up to about 100 μM. The chromium(VI) salts showed toxicity at about 8 μM, and there was little cell survival at 100 μM. The dose-response curves were similar for all chromium(VI) salts tested. Similar experiments were conducted with normal human keratinocytes obtained from abdominoplasties or breast reductions from six donors and treated with sodium dichromate. The toxicity to normal cells overall seemed to be less than in the transformed line. Ascorbic acid at 500 μM completely inhibited the cell toxicity caused by chromium(VI), whereas glutathione and SITS were less effective. Ascorbate probably protected cells by reducing chromium(VI) and chelation of the reduced complex. Glutathione may have formed complexes with the chromium(VI), which eventually led to chromium(III), whereas SITS may have inhibited the cellular uptake of the chromate by altering the non-specific membrane anion carrier. The authors conclude that these available drugs provide protection against cytotoxicity to keratinocytes involved in dermatitis and may be useful to prevent toxic reactions to metals contacting the skin.

The effect of decreasing the concentration of water-soluble chromium in cement from about 10 to 2 ppm on the incidences of chromium-induced dermatitis was examined among construction workers in Finland (Roto et al. 1996). After 1987, when the decrease occurred, allergic dermatitis caused by chromium in the industry was reduced by 33% from previous levels, whereas irritant contact dermatitis remained unchanged.

3.11.2 Reducing Body Burden

Once chromium has been absorbed, it can be widely distributed throughout the body (see Section 3.4.2). Forced diuresis with careful monitoring of fluid and electrolyte status has been suggested, but not proven, to increase the elimination of chromates (Haddad et al. 1998). In a case report of a fatality after ingestion of potassium chromate, hemodialysis and charcoal hemoperfusion did not significantly remove chromium from whole blood and had little effect on the management of chromium toxicity (Iserson et al. 1983).

However, hemodialysis was effective in saving the life of an electroplater who accidentally swallowed plating fluid containing chromium trioxide (Fristedt et al. 1965). Because chromium may be sequestered in erythrocytes, exchange transfusion has been used as a way to decrease the body burden in serious acute poisoning (Kelly et al. 1982).

Both chromium(VI) and chromium(III) can be transported in the blood. Chromium(III) tends to bind to plasma proteins and is excreted in the urine. Chromium(VI) may be poorly reduced to chromium(III) in plasma, but this reduction can be enhanced by the intravenous administration of ascorbic acid (Korallus et al. 1984). However, reactions of chromium(VI) with sulfhydryl compounds or ascorbate may have mixed effects on toxicity, since such reactions yield reactive chromium intermediates, reactive oxygen species, and free cysteinyl and carbon radical species, which may be more damaging than chromium(VI) itself (Reynolds and Zhitkovich 2007; Shi et al. 1994; Stearns et al. 1994). Generally, treatments for reducing body burden of chromium are chelation therapies similar to those used to reduce body burdens of other metals, although the use of ascorbic acid is specific for chromium. Use of hemodialysis and N-acetylcysteine has been suggested to enhance elimination (Haddad et al. 1998; Leikin and Paloucek 2002; Schonwald 2004), however, this has not been proven. N-acetylcysteine, the glutathione precursor, was reported to be more effective than EDTA or dimercaptosuccinic acid in increasing the urinary excretion of chromium in rats (Banner et al. 1986; Nadig 1994); however, chelation with agents available in human clinical medicine, such as British Anti Lewisite (dimercaprol) and EDTA, has been shown to be generally ineffective in increasing the elimination of chromium (Ellis et al. 1982). However, calcium EDTA, administered intravenously, resulted in a rapid increase in the urinary excretion of chromium in metal workers (Sata et al. 1998). Other polyaminocarboxylic acid chelating agents may be effective in removing chromium from organs. In rats injected with potassium chromate, subsequent treatment with various polyaminocarboxylic acid chelating agents resulted in significant removal of chromium from the liver, kidney, heart, or brain, depending on the agent. Ethylenediamine N,N'-diacetic acid (EDDA) removed significant amounts of chromium from the liver and heart. Ethylenediamine N,N'-di (O-hydroxyphenyl acetic acid (EDDHA) removed significant amounts of chromium from the kidney, heart, and brain. N-(2-hydroxyethyl)ethylenediamine triacetic acid (HEDTA) removed significant amounts of chromium from the liver and kidney. Hexamethylene 1,6-diamino N,N,N',N'-tetraacetic acid (HDTA) removed significant amounts of chromium from the liver, kidney, and brain. Triethylene tetramine N,N,N',N',N'',N''-hexaacetic acid (TTHA) removed significant amounts of chromium from the liver. Ethyleneglycol-bis-(2-aminoethyl) tetraacetic acid (EGATA) did not remove significant amounts of chromium from any of the organs. The relative ability of the polyaminocarboxylic acids to remove chromium from organs may be related to the number of amino or carboxyl groups as complexing centers

or by the presence of hydroxyl groups (Behari and Tandon 1980). The use of these agents in humans has not been tested. Chromium(VI), but not chromium(III), can readily cross cell membranes. Chromium(VI) readily enters erythrocytes, where it is reduced to chromium(III) by glutathione, and chromium(III) is essentially trapped within erythrocytes, where it binds to proteins, primarily hemoglobin. This may explain the fact that chromium shows little toxicity at sites distant from administration sites (De Flora and Wetterhahn 1989). The chromium(III) trapped within the erythrocytes would be released upon natural destruction of the erythrocyte and excreted in the urine.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The reduction of chromium(VI) to chromium(III) inside of cells may be an important mechanism for the toxicity of chromium, whereas reduction of chromium(VI) outside of cells may be a major mechanism of protection. After entering target cells, chromium(VI) itself and/or the metabolically reduced valence states exert toxic effects, as discussed in detail below (De Flora and Wetterhahn 1989). Administration of a reducing agent (such as ascorbate) early enough after exposure to reduce chromium(VI) to chromium(III) in extracellular fluids before chromium(VI) penetrates cells may reduce toxicity; however, increased intracellular ascorbate may enhance toxicity. For example, in animal studies, ascorbic acid has been shown to protect against lethality of dermal potassium dichromate (Samitz 1970) and prevent nephrotoxicity of subcutaneously administered potassium chromate (Powers et al. 1986). However, increased intracellular ascorbate concentrations has been shown to enhance chromium(VI) toxicity in cultured human fibroblasts (Reynolds and Zhitkovich 2007). Therefore, agents that enhance reduction of chromium(VI) to chromium(III) may have mixed effects on toxicity. The effect of ascorbate or other reducing agents on chromium toxicity in humans has not been established.

Once chromium enters the cell, ligand displacement and/or redox reactions of chromium(VI) with enzymes, proteins, and other molecules leads to reduction to chromium(V), chromium(IV), and chromium(III), with the generation of active oxygen species and radicals. The resulting toxicity depends on the nature of the cellular component that reacts with chromium(VI) and on the nature of the reactive species formed from the reaction. Chromium(VI) can be reduced metabolically by a number of cellular components under physiological conditions. Reduction by glutathione or cysteine can lead to generation of all valence states (particularly chromium(V)) and radicals. For example, *in vitro* reaction of chromium(VI) with glutathione led to the formation of glutathione thiyl radicals and chromium(V) complexes (Aiyar et al. 1991). Chromium(V)-glutathione complexes have been shown to form DNA adducts. Reduction by ascorbate leads to chromium(III), but chromium(V) has been generated by the

reaction of chromium(VI) with riboflavin (vitamin B_2) and ribose derivatives (De Flora and Wetterhahn 1989). Reaction of chromium(VI) with hydrogen peroxide has led to the formation of chromium(V) complexes and hydroxyl radicals (Aiyar et al. 1991). Other important intracellular reduction reactions of chromium(VI) involve enzyme-catalyzed and NADPH-dependent mechanisms. Microsomal reduction of chromium(VI) by cytochrome P450 to chromium(III) may involve the transient formation of chromium(V) (De Flora and Wetterhahn 1989). Chromium(III), the final stable product of chromium(VI) reduction, can form chromium-DNA adducts and mediate crosslinking of DNA strands and DNA protein (De Flora and Wetterhahn 1989; Manning et al. 1992; Xu et al. 1996). Thus, the metabolic reduction of chromium(VI) may represent bioactivation and/or detoxification. If a bioactivation process, intracellular reduction of chromium(VI) would lead to the ultimate toxic species. Conversely, if chromium(VI) is the toxic agent, then effects would be elicited only if the amount of chromium(VI) entering target cells saturates the reducing mechanisms.

Differences in the intracellular metabolic pathways that result in the reduction of chromium(VI) will affect the nature of the reactive intermediates. For example, chelating ligands, such as glutathione and sugars, stabilize chromium(V) as an oxidation state, increasing its lifetime in the cell and ability to reach DNA in the nucleus. Cytochrome P450-dependent reduction of chromium(VI) to chromium(V) and chromium(IV), with generation of reactive radicals, which takes place in the endoplastic reticulum, could occur in close enough proximity to the nuclear membrane and nonenzymatic reduction within the nucleus could occur in close enough proximity to chromatin for the transient intermediates to exert their effects, such as DNA strand breaks and radical-DNA adducts. As noted above, chromium(III) can form chromium-DNA adducts and mediate crosslinking of DNA strands and DNA protein (De Flora and Wetterhahn 1989).

The role of glutathione in chromium-induced renal toxicity was investigated by Hojo and Satomi (1991). Male ddY mice (6 animals per dose group) were administered potassium dichromate(VI) (0.6 mmol chromium/kg), potassium tetraperoxochromate(V) (1.0 mmol/kg), green chromium(V)-glutathione complex (1.0 mmol/kg), and chromium nitrate (III) (0.6 mmol/kg); animals were sacrificed 24 hours after chromium injection and changes in kidney weight and function were assessed. Chromium(VI) resulted in a 10.7%±2.7 decrease in body weight, a 2-fold increase in serum urea nitrogen, a decrease in kidney nonprotein sulfhydryl contents (3.3±0.1 versus control values of 3.7±0.1) and a decrease of kidney-glutathione reductase activity from a control value of 17.4±1.5 to 14.1±1.3 U/g. Potassium tetraperoxochromate(V) treatment resulted in 50% of the animals dying. Body weights and kidney-glutathione reductase activity were much lower than for animals treated with chromium(VI), and serum

urea levels were 102.9±17.7 mg/dL, which is about twice that observed in animals treated with chromium(VI). The chromium(V) glutathione complex was much less toxic and showed values that were similar or close to control values. Pretreatment with 10 mmol/kg glutathione methyl ester in the chromium(VI)-treated animals appeared to reduce the body weight loss and caused the serum urea levels to be normal. Butathione sulfoximine (an inhibitor of glutathione synthesis) greatly enhanced the levels of serum urea, loss of glutathione reductase activity and decrease in kidney nonprotein sulfhydryl groups. Butathione sulfoximine pretreatment resulted in one of the six animals dying. Animals treated with chromium(III) experienced weight loss, but other parameters were not markedly changed from control values. Pretreatment with butathione sulfoximine in animals treated with chromium(III) only caused a decrease in kidney nonprotein sulfhydryl groups. The authors indicated that with excess levels of glutathione, chromium(VI) is more readily reduced to chromium(III), whereas at lower levels of glutathione the reduction process is slower, resulting in slower reduction of the more toxic intermediate chromium(V). Also, at higher concentrations of glutathione, chromium(V)-glutathione complexes may form which may prevent chromium(V) from reacting at target sites that elicit toxic responses.

As discussed above, reactive intermediates formed during intracellular reduction of chromium(VI) to chromium(III) may interact with hydrogen peroxide, generating hydroxyl radicals, which can induce cell damage. Several animal and *in vitro* studies have assessed the effects of anti-oxidant agents on chromium-induced oxidative cell injury. Administration of folic acid, a free radical scavenger, to rabbits reduced potassium dichromate-induced increases in the concentration of free radical in liver, testes, brain, kidney, and lung and in serum liver enzyme activities of AST and ALT (El-Demerdash et al. 2006). Vitamin E, an antioxidant, has been shown to reduce potassium dichromate-induced renal toxicity and hepatotoxicity in rats (Appenroth et al. 2001; Arreola-Mendoza et al. 2006; Rao et al. 2006). Vitamin B_6, which may have anti-oxidant potential due to its role as a co-factor in the synthesis of cysteine, reduced oxidative stress in the liver of rats exposed to potassium dichromate (Anand 2005). *In vitro* studies indicated that vitamin E protected against, while vitamin B_2 enhanced, the cytotoxicity and DNA single-strand breaks induced by sodium chromate in Chinese hamster cells. Formation of DNA-protein crosslinks by chromium(VI) in cell culture was prevented by addition of ascorbic acid (Capellmann et al. 1995), and ascorbic acid protected cells against chromosomal breakage and apoptosis. Vitamin E also protected cells against chromosomal breaks (Blankenship et al. 1997) and decreased chromium(III)-induced oxidative damage to calf thymus DNA *in vitro*, as indicated by decreased formation of 8-hydroxydeoxyguanosine (Qi et al. 2000). Vitamin E may exert its protective effect by scavenging radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991). Selenium (as sodium selenate), an essential trace element, has been shown to reduce the genotoxicity of chromium

dichromate in human lymphocytes *in vitro* as assessed by the Comet assay, although sodium selenite and selenous acid enhanced chromium-induced DNA damage; sodium selenate also decreased chromium-induced genotoxicity in *S. typhmuirium* (strain TA102), as assessed by the Ames assay (Cemeli et al. 2003). Other vitamins or essential elements might also be effective in mitigating the effects of chromium by modulating the metabolic processes. The use of vitamins and essential elements for reducing the toxicity of chromium has not been studied in humans.

Thyroxine was found to ameliorate acute renal failure induced in rats by potassium dichromate, possibly by stimulating gluconeogenesis and Na-K ATPase activity in the renal cortex, influencing protein synthesis, and promoting glucose and amino acid uptake by epithelial cells. These events would be expected to aid in the repair and regeneration of the damaged tubular epithelial cells (Siegel et al. 1984). The use of thyroxine has not been tested in humans.

Todralazine, an antihypertensive drug, was found to markedly reduce the mutagenic activity of potassium dichromate (VI) in the bacterial tester strain TA100 and in the *B. subtilis* rec assay (Gasiorowski et al. 1997). Spectroanalysis indicated that chromium(VI) was reduced to chromium(III) by todralazine and that todralazine formed a complex with the chromium(III) ions. The reduction and complexing of chromium may have prevented chromium from crossing the membrane and may have prevented harmful interactions with DNA. Another study by this group found that complexing copper(II) chromate(VI) to organic ligands (e.g., 2-(2'-pyridyl)imidazole, 2,2'-bipyridyl, 1,10-phenanthroline) resulted in a decrease in the mutagenicity of chromium(VI) as assessed by the Ames and *B. subtilis* rec assays (Gasiorowski et al. 1998).

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chromium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chromium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would

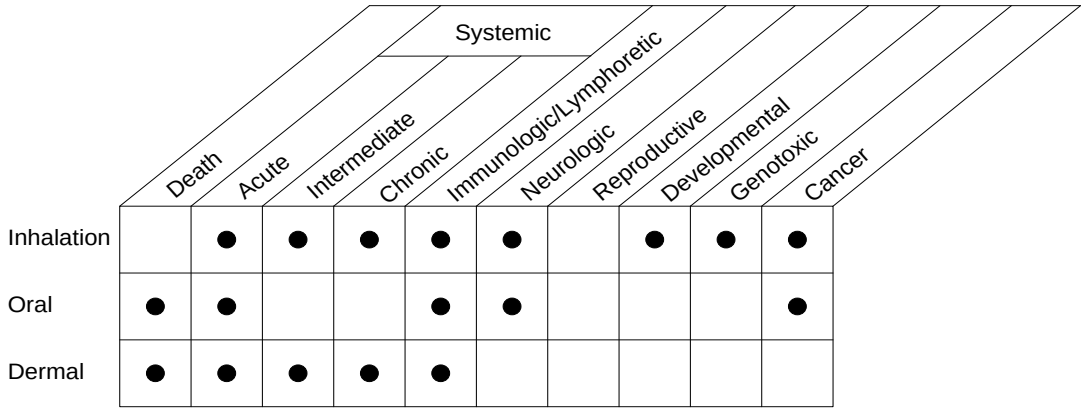
reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Chromium

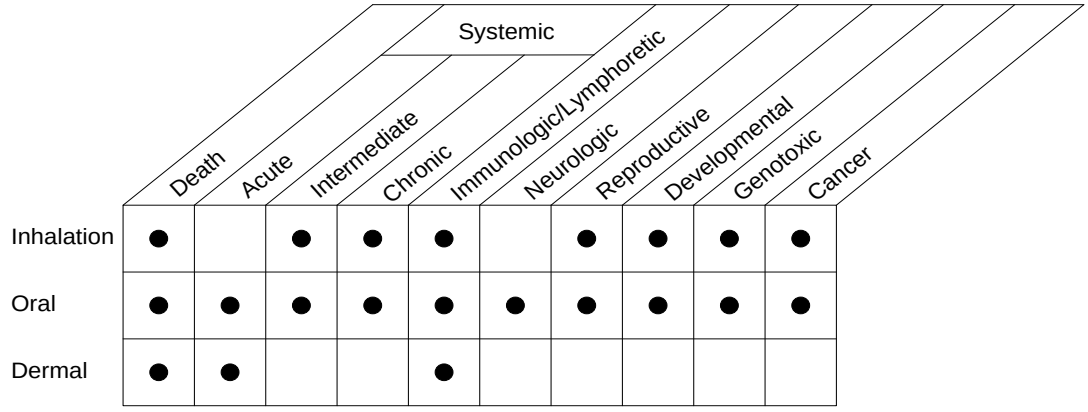
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chromium are summarized in Figures 3-8 and 3-9. The purpose of these figures is to illustrate the existing information concerning the health effects of chromium. Each dot in the figures indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

A major source of oral exposure of humans to chromium is via the diet including chromium-rich diet supplements. Chromium(III) at low levels is essential to nutrition, and studies of chromium deficiency have been conducted. Information regarding health effects of exposure to chromium(VI) or chromium(III) in humans comes mainly from case reports of acute accidental or intentional ingestion, acute accidental dermal exposure, and from occupational case reports and epidemiology studies, which primarily involve inhalation and dermal exposure. In occupational studies, it is often difficult to separate exposure to chromium(VI) from chromium(III). Case reports have shown that ingestion and dermal contact with chromium(VI) can cause death. These reports have also described the serious systemic and neurological sequelae of exposure leading to death. Occupational exposures to chromium(VI) and/or chromium(III) are associated with respiratory and nasal, cardiovascular, gastrointestinal, hematological, hepatic, renal, and dermal effects. Immunological effects in humans exposed by inhalation and dermal contact consist of sensitization resulting in asthma and contact dermatitis, which can be exacerbated by oral exposure. Limited information was available regarding reproductive effects of occupational exposure to chromium(VI). Limited information was found on neurological behavioral effects. Information is also available regarding genotoxic effects in workers exposed to chromium(VI) and cancer in workers exposed to chromium(VI) and/or chromium(III).

Figure 3-8. Existing Information on Health Effects of Chromium(VI)



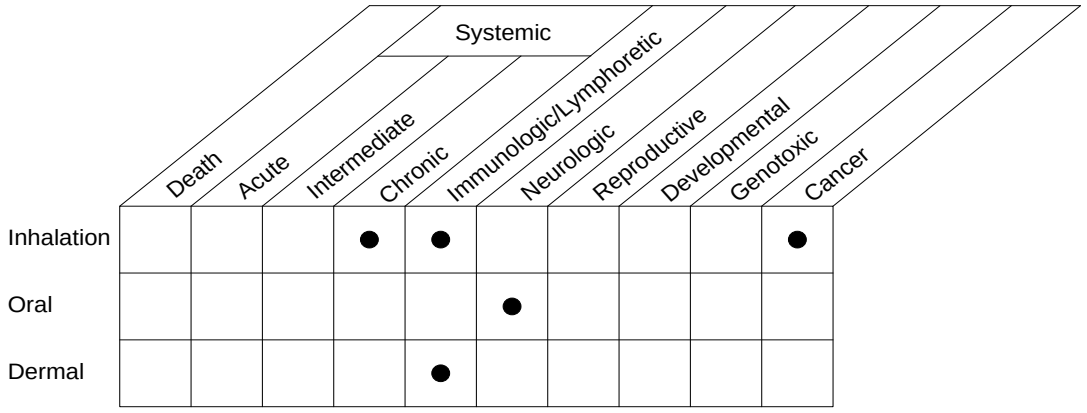
Human



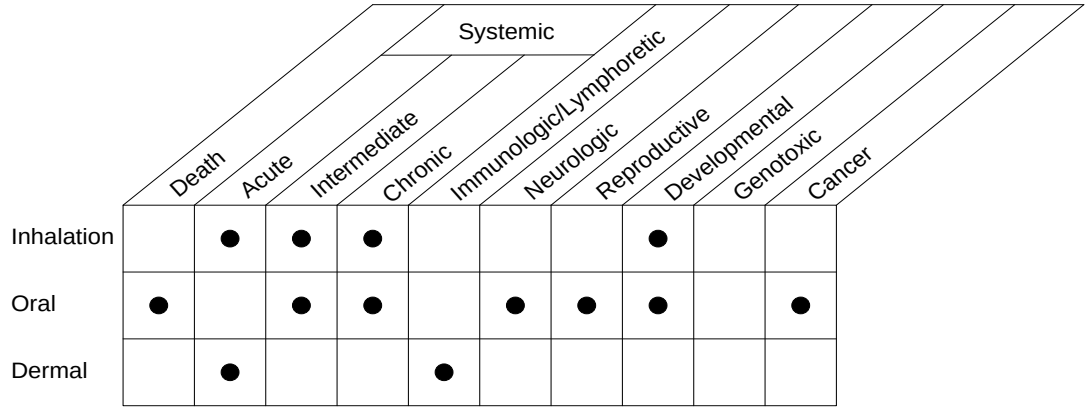
Animal

● Existing Studies

Figure 3-9. Existing Information on Health Effects of Chromium(III)



Human



Animal

● Existing Studies

Information regarding the levels of exposure to chromium(VI) compounds that cause death in animals is available for the inhalation, oral, and dermal routes. Information regarding respiratory effects of acute inhalation exposure of animals to chromium(VI) was available. Acute oral studies have evaluated effects of chromium(VI) on hematology and clinical chemistry. Acute dermal exposure of animals to chromium(VI) can cause irritation, edema, necrosis, and chrome sores. Information on systemic effects of chromium(VI) in animals is available for intermediate- and chronic-duration exposure by the inhalation route. Information regarding effects of oral exposure is available for intermediate and chronic durations. The immunological effects of chromium(VI) in animals have been studied after inhalation and dermal exposure. An inhalation study reported no developmental or reproductive effects of chromium(VI). The reproductive and developmental effects of oral chromium(VI) have been evaluated following oral exposure, showing adverse effects, particularly to the male reproductive system. Information regarding the genotoxicity and carcinogenicity of chromium(VI) is available for both the inhalation and oral routes.

Information regarding levels of chromium(III) compounds that result in death is available only for the oral route. Systemic effects of acute-duration exposure to chromium(III) are limited to the respiratory system- and intermediate-duration inhalation exposure to chromium(III) are limited to the respiratory system. Information on systemic effects of chronic inhalation exposure to chromium(III) is limited to a study that used a mixture of chromium(VI) and chromium(III). Studies of intermediate- and chronic duration oral exposure to chromium(III) failed to find any systemic, neurological, developmental, reproductive, or carcinogenic effects. The immunological and genotoxic effects of chromium(III) in animals have not been tested by the oral route. Information regarding effects of dermal exposure of animals to chromium(III) is limited to a study of skin ulceration after acute exposure and dermal sensitization tests. One report of chronic renal failure after ingestion of over-the-counter chromium picolinate at 0.6 mg/day was found in literature (Wasser et al. 1997).

In addition to the information on chromium(VI) and chromium(III), limited information is available regarding health effects of chromium(0) and chromium(IV). Briefly, the available information on chromium(0) consists of studies that examined workers at an alloy steel plant (Triebig et al. 1987) and boilermakers (Verschoor et al. 1988) for possible renal effects. Information on chromium(IV) consists of a 2-year inhalation study of chromium dioxide in rats that found no effects upon hematological, clinical chemistry, and urinalysis parameters and no histopathological effects on respiratory, cardiovascular, gastrointestinal, hepatic, renal, dermal/ocular, neurological, and reproductive organs (Lee et al. 1989).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Acute inhalation exposure of humans to chromium(VI) as occurs in occupational settings can result in respiratory irritation (dyspnea, cough, wheezing, sneezing, rhinorrhea, choking sensation), dizziness, and headache at high concentrations, and can trigger asthmatic attacks in sensitized individuals (Lieberman 1941; Meyers 1950; Novey et al. 1983; Olaguibel and Basomba 1989). High airborne levels of chromium(VI) can also cause gastrointestinal irritation (Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950). Information on toxic effects in humans after oral exposure to chromium(VI) is limited to case reports of humans who ingested lethal or near lethal doses. Serious respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, and neurological effects have been described as sequelae leading to death (Clochesy 1984; Iserson et al. 1983; Kaufman et al. 1970; Saryan and Reedy 1988). Acute dermal exposure can cause skin burns and can also have similar sequelae that lead to death (Brieger 1920; Major 1922). No information regarding systemic effects of acute inhalation exposure of animals to chromium(VI) was located. Information regarding effects of acute oral exposure of animals to chromium(VI) include a report of gastrointestinal hemorrhage in rats given a lethal dose of potassium dichromate (Samitz 1970), evaluations of hematology and clinical chemistry parameters in rats and mice exposed for 4–5 days (NTP 2007, 2008a) and increased resorptions in mice given potassium dichromate during gestation (Junaid et al. 1996b). Information regarding effects of acute dermal exposure of animals to chromium(VI) is limited to studies of dermal irritation and sensitization (Gad et al. 1986; Merkur'eva et al. 1982; Samitz 1970; Samitz and Epstein 1962). The information in humans indicates that many organs can be targets of acute exposure to chromium(VI) if exposure levels are high enough. Studies in animals show that hematological effects occur following acute oral exposure and may be the earliest indication of more severe adverse effects observed following longer duration exposures. No information was located regarding systemic effects in humans after acute exposure to chromium(III) compounds by any route. Acute inhalation studies of chromium trichloride in hamsters (Henderson et al. 1979) and chromic oxide and basic chromium sulfate in rats (Derelanko et al. 1999) indicated that the respiratory system is also a target of chromium(III) exposure. Acute dermal studies show that chromium(III) can be a sensitizer, and that dermal challenge of sensitized individuals with chromium(III) compounds can elicit a response (Hansen et al. 2003; Samitz and Epstein 1962). LD_{50} values for chromium(VI) and chromium(III) compounds indicate that chromium(III) is less toxic than chromium(VI) (Shubochkin and Pokhodzie 1980; Smyth et al. 1969; Vernot et al. 1977).

Additional studies involving acute exposure to both chromium(VI) and chromium(III) compounds by all routes would be helpful, especially if they evaluated comprehensive toxicological end points and

exposure-response relationships. Studies defining the possible synergistic effects of chromium with other nephrotoxins, such as mercury and cadmium, which may be stored together at toxic waste sites, would also be useful. There are populations surrounding hazardous waste sites that might be exposed to the substance for short periods; therefore, this information is important.

Intermediate-Duration Exposure. There are no studies regarding systemic effects in humans after oral exposure of intermediate duration to either chromium(VI) or chromium(III). Intermediate-duration exposure to primarily chromium(VI) in occupational studies caused nasal and respiratory effects (Bovet et al. 1977; Davies et al. 1991; Gomes 1972; Kleinfeld and Rosso 1965; Lee and Goh 1988; Sorahan et al. 1987; Taylor 1966). Intermediate-duration exposure in occupational settings involving dermal exposure also can cause chrome ulcers or holes in the skin (Gomes 1972; Lee and Goh 1988; Lieberman 1941; PHS 1953; Smith 1931). An MRL of $5x10^{-6}$ mg chromium(VI)/m^3 has been determined for upper respiratory effects in humans after intermediate-duration inhalation exposure to chromium(VI) as chromium(VI) trioxide mist and other hexavalent chromium mists and dissolved aerosols, based on the study by Lindberg and Hedenstierna (1983).

The respiratory tract and the immune system are targets in animals exposed to chromium(VI) and chromium(III) via inhalation for intermediate durations (Adachi 1987; Adachi et al. 1986; Glaser et al. 1985, 1990; Johansson et al. 1986a, 1986b), with LOAEL values identified for respiratory and immune effects after inhalation (Glaser et al. 1985, 1990). An MRL of 0.0003 mg chromium(VI)/m^3 has been determined for lower respiratory effects in humans after intermediate-duration inhalation exposure to chromium(VI) as particulate hexavalent compounds based on the study in rats by Glaser et al. (1990). An intermediate-duration study on chromium(III) compounds in rats identified respiratory system as the target for inhaled insoluble chromic oxide and soluble basic chromium sulfate (Derelanko et al. 1999). Based on differences in respiratory effects of these two compounds, distinct intermediate-duration MRLs were derived for insoluble and soluble trivalent chromium compounds. The minimal LOAEL of 3 mg chromium(III)/m^3 for septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats exposed to chromic oxide was used to derive the intermediate-duration inhalation MRL of 0.005 mg chromium(III)/m^3 for insoluble trivalent chromium compounds. The LOAEL of 3 mg chromium(III)/m^3 for lesions of the larynx (granulomatous inflammation) and nose (inflammation) in female rats exposed to basic chromium sulfate was used to derive the intermediate-duration inhalation MRL of 0.0001 mg chromium(III)/m^3 for soluble trivalent chromium compounds.

The gastrointestinal and hematological systems were identified as the primary targets of intermediate-duration oral exposure of rats and mice exposed to chromium(VI) in drinking water (NTP 2007, 2008a). An intermediate-duration oral MRL of 0.005 mg chromium(VI)/kg/day has been determined for hematological effects (e.g., microcytic, hypochromic anemia) in rats after intermediate-duration oral exposure to chromium(VI) as sodium dichromate dihydrate in drinking water in a study by NTP (2008a). In addition, developmental and reproductive studies identify chromium(VI) as a reproductive and developmental toxicant in monkey, rats, and mice after oral exposure (Al-Hamood et al. 1998; Aruldhas et al. 2004, 2005, 2006; Bataineh et al. 1997; Chowdhury and Mitra 1995; Junaid et al. 1996b; Kanojia et al. 1996, 1998; Subramanian et al. 2006; Trivedi et al. 1989; Yousef et al. 2006; Zahid et al. 1990). Oral studies of intermediate-duration in rats and mice reported no effects of chromium(III) in any system (Ivankovic and Preussmann 1975; NTP 2008b; Shara et al. 2005). Adverse reproductive effects were observed following oral exposure to chromium(III), although NOAEL values were not established. No dermal studies of intermediate duration in animals were located. The toxicity of intermediate-duration exposure to chromium compounds is relatively well characterized for the oral and inhalation routes. Dermal studies would be useful to determine possible target organs other than the skin. There are populations surrounding hazardous waste sites that might be exposed to the substance for similar durations.

Chronic-Duration Exposure and Cancer. The respiratory system (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gibb et al. 2000a; Keskinen et al. 1980; Kleinfeld and Rosso 1965; Kuo et al. 1997a; Letterer 1939; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Olaguibel and Basomba 1989; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al. 1987; Taylor 1966) and the skin (Gomes 1972; Hanslian et al. 1967; Lee and Goh 1988; Lieberman 1941; PHS 1953; Royle 1975b) are the primary target organs for occupational exposure to chromium and its compounds. An MRL of $5x10^{-6}$ mg chromium(VI)/m^3 has been determined for upper respiratory effects in humans after chronic-duration inhalation exposure to chromium(VI) as chromium(VI) trioxide mist and other hexavalent chromium mists and dissolved aerosols, based on the study by Lindberg and Hedenstierna (1983). There are more data regarding the effects of chronic inhalation exposure in humans and animals than there are regarding the effects of oral exposure. Studies of populations residing in areas contaminated with chromium(VI) in China have found such effects as oral ulcer, diarrhea, abdominal pain, indigestion, vomiting, constipation, nose and eye irritation, headache, fatigue, dizziness, and leukocytosis (Zhang and Li 1987). Chronic inhalation studies with rats, mice, guinea pigs, and rabbits also identify the respiratory system as the main target of chromium(VI) and chromium(III) exposure (Glaser et al. 1986, 1988; Nettesheim and Szakal 1972; Steffee and Baetjer

1965). Chronic oral exposure studies in rats and mice exposed to chromium(VI) in drinking water identify the hematological and gastrointestinal systems as the primary targets of chronic oral exposure (NTP 2008a), with gastrointestinal effects more sensitive than hematological effects. A chronic-duration oral MRL of 0.001 mg chromium(VI)/kg/day based on gastrointestinal effects (diffuse epithelial hyperplasia of the duodenum) was derived for hexavalent chromium compounds. Chronic oral exposure to chromium(III) compounds did not result in any target organ toxicity in animals (Ivankovic and Preussmann 1975; MacKenzie et al. 1958; NTP 2008b; Schroeder et al. 1965; Shara et al. 2007); thus, no chronic-duration MRL was derived for chromium(III) compounds since target organs have not been identified and no NOAEL for reproductive effects of oral exposures has been adequately characterized. As noted above, the skin is a sensitive target of toxicity in workers exposed to airborne chromium (the effects resulted from direct dermal contact with chromium). No chronic dermal studies in animals were located. Because water and soil sources can be contaminated near hazardous waste sites, more information regarding chronic oral or dermal exposure would be useful.

Cancer. Occupational and environmental epidemiological studies indicate a correlation between long-term exposure to chromium(VI) compounds and lung cancer (Alderson et al. 1981; Baetjer 1950b; Bidstrup 1951; Bidstrup and Case 1956; Braver et al. 1985; Cole and Rodu 2005; Crump et al. 2003; Dalager et al. 1980; Davies 1979, 1984; Davies et al. 1991; EEH 1976, 1983; Enterline 1974; Franchini et al. 1983; Frentzel-Beyme 1983; Gibb et al. 2000b; Goldbohm et al. 2006; Haguenoer et al. 1981; Hayes et al. 1979, 1989; Korallus et al. 1982; Langård and Norseth 1975; Langård and Vigander 1983; Langård et al. 1980; Machle and Gregorius 1948; Mancuso 1975, 1997a; Mancuso and Hueper 1951; Ohsaki et al. 1978; Park and Stayner 2006; Park et al. 2004; Pastides et al. 1994; PHS 1953; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1981; Sheffet et al. 1982; Silverstein et al. 1981; Sjogren et al. 1987; Sorahan et al. 1987; Taylor 1966; Zhang and Li 1987). Occupational studies generally consider inhalation exposures, while environmental studies involve exposure by inhalation, ingestion, and dermal contact. Additional studies on populations exposed to chromium in drinking water would be useful to determine if a causal relationship with cancer exists. A unit risk for cancer from inhalation exposure to chromium(VI) compounds has been derived (IRIS 2008) from an occupational study (Mancuso 1975). Chronic inhalation of chromium(VI) compounds was carcinogenic in rats (Glaser et al. 1986) and mice (Nettesheim et al. 1971), and the 2-year carcinogenicity study on oral chromium(VI) provided clear evidence of oral cancers in rats and gastrointestinal cancers in mice (NTP 2008a). Cancer studies by parenteral route support the conclusions that chromium(VI) is carcinogenic (Furst et al. 1976; Hueper 1955, 1958; Hueper and Payne 1959, 1962; Laskin et al. 1970; Levy et al. 1986; Roe and Carter 1969; Steinhoff et al. 1986). For chromium(III) compounds, evidence for carcinogenesis (preputial adenomas in

male rats) in the NTP (2008b) 2-year bioassay was equivocal. The available human and animal data are sufficient for determining that chromium(VI) is carcinogenic following inhalation and oral exposure. However, additional animal studies are needed to adequately assess the carcinogenic potential of chromium(III) following inhalation and oral exposure.

Genotoxicity. Several studies evaluating chromosomal aberrations, sister chromatid exchange, micronuclei, DNA strand breaks and DNA-protein crosslinks in workers exposed to chromium(VI) have been conducted, some reporting positive results (Benova et al. 2002; Deng et al. 1988; Gambelunghe et al. 2003; Koshi et al. 1984; Lai et al. 1998; Medeiros et al. 2003a; Sarto et al. 1982; Stella et al. 1982; Vaglenov et al. 1999; Werfel et al. 1998; Wu et al. 2001) and some reporting negative results (Benova et al. 2002; Gao et al. 1994; Hamamy et al. 1987; Husgafvel-Pursiainen et al. 1982; Littorin et al. 1983; Medeiros et al. 2003a; Nagaya 1986; Nagaya et al. 1991). However, most of these studies are limited by factors such as lack of exposure data, co-exposure to other potentially genotoxic agents, and too few workers for meaningful statistical analysis. Mostly positive results have been found in rodents and *D. melanogaster* exposed to chromium(VI) compounds *in vivo* (De Flora et al. 2006; Gava et al. 1989a; Itoh and Shimada 1993; Kaya et al. 2002; Kirpnick-Sobol et al. 2006; Mirsalis et al. 1996; NTP 2007; Olvera et al. 1993; Paschin et al. 1982; Rasmuson 1985; Rodriguez-Arnaiz and Martinez 1986; Sarkar et al. 1993; Shindo et al. 1989; Tsapakos et al. 1983b; Ueno et al. 2001; Wang et al. 2006; Wild 1978; Zimmering et al. 1985). Numerous *in vitro* genotoxicity studies have been conducted in bacteria (Bennicelli et al. 1983; De Flora 1978, 1981; Haworth et al. 1983; Kanematsu et al. 1980; Kortenkamp et al. 1996b; Llagostera et al. 1986; Nakamuro et al. 1978; Nishioka 1975; NTP 2007; Olivier and Marzin 1987; Tagliari et al. 2004; Venier et al. 1982; Venitt and Levy 1974; Watanabe et al. 1998a; Yamamoto et al. 2002), yeast (Bonatti et al. 1976; Fukunaga et al. 1982; Kirpnick-Sobol et al. 2006; Singh 1983), cultured animal cell systems (Briggs and Briggs 1988; DiPaolo and Casto 1979; Douglas et al. 1980; Elias et al. 1989b; Fornace et al. 1981; Kowalski et al. 1996; Levis and Majone 1979; MacRae et al. 1979; Montaldi et al. 1987; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Seoane and Dulout 1999; Sugiyama et al. 1986a; Tsuda and Kato 1977; Ueno et al. 1995a; Umeda and Nishimura 1979; Venier et al. 1982; Wise et al. 1993; Yang et al. 1992), and human cell systems (Blasiak and Kowalik 2000; Depault et al. 2006; Douglas et al. 1980; Fornace et al. 1981; Gomez-Arroyo et al. 1981; Ha et al. 2004, 2004; Holmes et al. 2006; MacRae et al. 1979; Montaldi et al. 1987; Nakamuro et al. 1978; Sarto et al. 1980; Stella et al. 1982; Sugiyama et al. 1986a; Trzeciak et al. 2000; Whiting et al. 1979; Wise et al. 2002, 2004, 2006a, 2006b), mostly with positive results. The vast majority of studies, therefore, clearly indicated that chromium(VI) compounds are genotoxic.

Genotoxicity data are also available for chromium(III) compounds. A study in tannery workers, who were exposed mainly to chromium(III), reported negative results for chromosomal aberrations and sister chromatid exchange (Hamamy et al. 1987), while positive results for micronuclei and DNA-protein crosslinks were reported in another study on tannery workers (Medeiros et al. 2003a). Chromium trichloride, chromium picolinate, and niacin-bound chromium(III) also did not cause DNA damage, or increased frequencies of micronuclei in rats exposed *in vivo* (Cupo and Wetterhahn 1985; De Flora et al. 2006; NTP 2008b; Shara et al. 2005). Transplacental exposure to chromium(III) chloride salt resulted in DNA deletions (Kirpnick-Sobol et al. 2006). Mostly negative results have been found in *in vitro* genotoxicity studies of chromium(III) compounds in bacteria (Bennicelli et al. 1983; De Flora 1981; Kanematsu et al. 1980; Llagostera et al. 1986; Matsui 1980; Nishioka 1975; NTP 2008b; Olivier and Marzin 1987; Petrilli and De Flora 1978b; Shara et al. 2005; Venier et al. 1982, 1989; Yamamoto et al. 2002), and mammalian cell systems (Fornace et al. 1981; Itoh and Shimada 1996; Le Curieux et al. 1992; Levis and Majone 1979; MacRae et al. 1979; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarkar et al. 1993; Sarto et al. 1980; Shara et al. 2005; Stella et al. 1982; Tsuda and Kato 1977; Ueno et al. 1995a; Umeda and Nishimura 1979; Whiting et al. 1979; Wise et al. 1993; Yang et al. 1992). Chromium(III) did not increase the number of micronuclei in polychromatic erythrocytes in mice (Itoh and Shimada 1996). Several studies have found weakly positive or positive results in Chinese hamster ovary cells (Coryell and Stearns 2006; Levis and Majone 1979; Stearns et al. 2002), mouse fetal cells (Raffetto et al. 1977), mouse lymphoma cells (Whittaker et al. 2005), and human cell lines (Blasiak and Kowalik 2000; Nakamuro et al. 1978; Stella et al. 1982).

Chromium(III) compounds are less genotoxic than chromium(VI) compounds in intact cell systems because of the relative inability of chromium(III) to cross cell membranes; however, chromium(III) is more genotoxic than chromium(VI) when tested *in vitro* in subcellular targets (Kowalski et al. 1996; Snow 1991; Snow and Xu 1989). The reduction of chromium(VI) to chromium(III) as the ultimate genotoxicant within cells may account for the genotoxicity of chromium(VI) (Beyersmann and Koster 1987). However, in intact cells, chromium(III) appears less genotoxic than chromium(VI) due to decreased cellular permeability to chromium(III).

Additional studies in workers with known levels of chromium exposure that control for confounding factors would be useful for defining levels at which chromosomal aberrations occur in humans exposed to chromium(VI) in the workplace. Also, better dose-response relationships would be useful for the various genotoxic and regulatory effects observed with chromium to better determine which end points are the most sensitive and dominant at exposures near environmental levels.

Reproductive Toxicity. No reliable information was located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to chromium or its compounds. Studies in women exposed occupationally also show that chromium can be transferred to fetuses through the placenta (Shmitova 1980). Inhalation studies would be useful for determining the reproductive toxicity of inhaled chromium and compounds and for establishing exposure-response relationships. Adverse effects on the male reproductive system (included decreased spermatogenesis and histopathological alterations to the epididymis) were observed in monkeys exposed to chromium(VI) in drinking water for 180 days (Aruldhas et al. 2004, 2005, 2006; Subramanian et al. 2006). Effects on spermatogenesis were reported in male rats given chromium(VI) by gavage for 90 days (Chowdhury and Mitra 1995) and in rabbits exposed to chromium(VI) in drinking water for 10 weeks (Yousef et al. 2006). In male mice, oral exposure of intermediate duration to chromium(VI) or chromium(III) was reported to result in decreased spermatogenesis and cellular degeneration of the outer layer of seminiferous tubules (Zahid et al. 1990); alterations in testicular, seminal vesicle, and preputial gland weights and decreased fertility were observed in mice following intermediate-duration exposure to chromium(VI) or chromium(III) (Elbetieha and Al-Hamood 1997). However, results of the study by Elbetieha and Al-Hamood 1997 should be interpreted with caution due to concern regarding experimental methods (see discussion in Section 2.3, Minimal Risk Levels). But other studies found no reproductive effects in male or female mice (NTP 1996a, 1996b, 1997, 2007, 2008a) exposed to chromium(VI) or chromium(III) (NTP 2008b; Shara et al. 2005, 2007). Alterations in sexual behavior and aggressive behavior toward other males were observed in male rats exposed to chromium(VI) or chromium(III) (Bataineh et al. 1997). Female mice or rats exposed orally to chromium(VI) compounds prior to mating (Junaid et al. 1996a; Kanojia et al. 1996, 1998) or female mice exposed during gestation (Junaid et al. 1996b; Trivedi et al. 1989) had increased fetal resorptions and decreased litter size. Alterations in ovarian and uterine weights and impaired fertility were observed in female mice that were exposed to chromium(III) or chromium(VI) and then were mated with unexposed mice (Elbetieha and Al-Hamood 1997) ; however, these results should be interpreted with caution due to concern regarding experimental methods (see discussion in Section 2.3, Minimal Risk Levels). Reductions in numbers of follicles and ova/mouse were seen following oral chromium(III) exposure (Murthy et al. 1996). Impaired development of the reproductive system was observed in the female offspring of mice exposed to potassium dichromate(VI) or chromium(III) chloride (Al-Hamood et al. 1998). A decrease in the number of pregnancies was observed in female rats administered 33.6 mg chromium(III)/kg/day as chromium chloride (by gavage) on gestational days 1–3; the same treatment on gestational days 4–6 did not alter the number of pregnancies (Bataineh et al. 2007). Distribution studies in pregnant rats given chromium(VI) or chromium(III) orally (Mertz et al. 1969) or intravenously

(Danielsson et al. 1982) and in pregnant mice given chromium(III) intraperitoneally (Iijima et al. 1983) indicated that chromium can cross the placenta after administration of either valence state. The available data on reproductive effects of chromium and its compounds are inadequate for establishing dose relationships; thus, further studies to establish the LOAEL and NOAEL values would be valuable. No dermal toxicity studies examining reproductive end points were identified; dermal studies would be useful for assessing the reproductive toxicity of chromium and compounds following dermal contact and for establishing exposure-response relationships.

Developmental Toxicity. No reliable information was located regarding developmental toxicity in humans after inhalation, oral, or dermal exposure or in animals after dermal exposure to chromium or its compounds. A study in women exposed occupationally reported that chromium can be transferred to fetuses through the placenta (Shmitova 1980), but the poor quality and reporting of this study preclude its use for drawing conclusions regarding potential developmental effects of chromium in humans. In female rats and mice, oral exposure of acute or intermediate duration to chromium(VI) compounds resulted in fetal toxicity (Elsaieed and Nada 2002; Junaid et al. 1996a, 1996b; Kanojia et al. 1996, 1998; Trivedi et al. 1989), but a NOAEL for these effects was not identified. Impaired development of the reproductive system was observed in the female offspring of mice exposed to potassium dichromate(VI) or chromium(III) chloride (Al-Hamood et al. 1998). Distribution studies in rat dams given chromium(VI) or chromium(III) intravenously (Danielsson et al. 1982) or orally (Mertz et al. 1969) and in mouse dams given chromium(III) intraperitoneally (Iijima et al. 1983) indicated that chromium can cross the placenta after administration of either valence state. No developmental effects were observed in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout the gestational period (Ivankovic and Preussmann 1975). No pharmacokinetic studies have been conducted regarding the distribution of chromium or its compounds to the fetus after inhalation or dermal exposure of the dams. Further oral developmental studies of chromium(VI) and chromium(III) in mice and other species would be useful to determine a NOAEL. These studies should include examination of developmental/neural end points. Developmental studies using inhalation exposure would be useful to determine if developmental effects are route specific. Data from oral, inhalation and dermal studies would be useful for determining dose-response relationships.

Immunotoxicity. In humans, allergic sensitization, characterized by asthma attacks and dermatitis, has been reported after occupational inhalation or occupational dermal exposure (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989) or dermal exposure (Burrows 1983; Engel and Calnan 1963; Engebrigtsen 1952; Eun and Marks 1990; Fregert 1975; Hansen et al. 2003;

Kaplan and Zeligman 1962; Levin et al. 1959; Nethercott et al. 1994; Newhouse 1963; Peltonen and Fraki 1983; Samitz and Shrager 1966; Wahba and Cohen 1979; Winder and Carmody 2002; Winston and Walsh 1951) to chromium compounds. Two occupational studies suggest that chromium exposure affects the leukocyte populations in the blood of workers (Boscolo et al. 1997; Mancuso 1951). Delayed anaphylactoid reaction was observed in one case (Moller et al. 1986). Dermatitis was exacerbated in sensitized individuals by oral exposure to chromium(VI) (Goitre et al. 1982; Kaaber and Veien 1977).

In rats, nonspecific disease resistance mechanisms of the lung are inhibited by inhalation exposure to chromium and its compounds (Glaser et al. 1985). Inhalation exposure of intermediate duration alters immunoglobulin levels, lymphocyte responses to antigen and lectin, and spleen weight in rats (Glaser et al. 1985), as well as alteres numbers of total recoverable cells, neutrophils, and monocytes, and percentages of pulmonary macrophages in bronchopulmonary lavage (Cohen et al. 1998). Intermediate-duration oral exposure of rats to chromium(VI) increased the proliferative response of T- and B-lymphocytes to mitogens and antigens (Snyder and Valle 1991).

There are sufficient data to determine that chromium or its compounds affect the immune system. More sensitive tests of the immune function after inhalation, oral, or dermal exposure to chromium or its compounds would be useful to determine the threshold levels for effects in humans. Studies evaluating exposure levels required to produce sensitization and elicitation of allergic responses would also provide additional information regarding threshold levels. Additional studies that explore changes in cytokine levels (Snyder et al. 1996) caused by chromium exposure should prove helpful since they may provide mechanistic information as to how chromium may affect immune function.

Neurotoxicity. Exposure of humans to high levels of airborne chromium(VI) in occupational and environmental settings produced symptoms of dizziness, headache, and weakness (Lieberman 1941). Cerebral edema was found in a case of fatal poisoning by ingestion (Kaufman et al. 1970). No studies were located describing neurotoxic effects in animals after inhalation and dermal exposure to chromium or its compounds. A 28-day drinking water study in rats reported decreased motor activity and ponderal balance, although a complete battery of neurological function tests was not conducted (Diaz-Mayans et al. 1986). Some distribution studies have detected chromium in the brain (Behari and Tandon 1980; Danielsson et al. 1982; Kaufman et al. 1970; Tandon et al. 1979). More recently, patients with 8–25-fold higher chromium blood levels that resulted from parenteral feeding did not have increased signs of somatopsychic responses (Lovrincevic et al. 1996). However, the number of patients studied was small and they were suffering from serious clinical diseases.

Since the central nervous system may be a target organ for exposure to chromium or its compounds, additional inhalation, oral, and dermal studies would be useful to corroborate the limited data and would provide useful information for populations near hazardous waste sites. More information on people (adults, children) environmentally exposed to chromium would be useful to assess its potential to effect neuro/behavioral end points.

Epidemiological and Human Dosimetry Studies. Most epidemiology studies use cohorts of occupationally exposed individuals and provide consistent data indicating that inhaled chromium can be carcinogenic (Alderson et al. 1981; Baetjer 1950b; Bidstrup 1951; Bidstrup and Case 1956; Braver et al. 1985; Cole and Rodu 2005; Crump et al. 2003; Cruz et al. 2006; Dalager et al. 1980; Davies 1979, 1984; Davies et al. 1991; EEH 1976, 1983; Enterline 1974; Fernandez-Nieto et al. 2006; Franchini et al. 1983; Frentzel-Beyme 1983; Gibb et al. 2000b; Goldbohm et al. 2006; Haguenoer et al. 1981; Hayes et al. 1979, 1989; Korallus et al. 1982; Langård and Norseth 1975; Langård and Vigander 1983; Langård et al. 1980; Machle and Gregorius 1948; Mancuso 1975, 1997a; Mancuso and Hueper 1951; Ohsaki et al. 1978; Park and Stayner 2006; Park et al. 2004;Pastides et al. 1994; PHS 1953; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1981; Sheffet et al. 1982; Silverstein et al. 1981; Sjogren et al. 1987; Sorahan et al. 1987; Taylor 1966) and can cause other toxic effects such as respiratory irritation, nasal septum perforation, and chrome sores on the skin (due to dermal exposure) (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gibb et al. 2000a; Gomes 1972; Hanslian et al. 1967; Keskinen et al. 1980; Kitamura et al. 2003; Kleinfeld and Rosso 1965; Lee and Goh 1988; Lieberman 1941; Letterer 1939; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Olaguibel and Basomba 1989; Osim et al. 1999; PHS 1953; Royle 1975b; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al. 1987; Taylor 1966). Results of epidemiological data are consistent with results of studies in experimental animals showing that the lung is the target organ for inhaled chromium(VI). Epidemiology studies in the chromate production industry and in chrome pigment manufacture and chrome plating have consistently shown an association with increased risk of lung cancer, but studies in other industries, such as stainless steel welding, electroplating, and ferrochromium production, have yielded inconclusive results. Exposure to chromium(VI) in these industries is associated with these effects, but the case for chromium(III) is less clear. Further studies in these industries may lead to more conclusive results. Measurements of chromium in urine and blood are useful for monitoring occupational exposure to chromium compounds. However, chromium(III) is an essential nutrient, and levels in biological fluids might be enough to mask low level exposures. One environmental epidemiology study suggested that residence near a ferrochromium plant did not pose a risk of cancer (Axelsson and Rylander 1980), but an environmental

study (which included oral exposure due to contaiminated well water) in China found that residence near an alloy plant that smelted chromium was associated with increased incidences of lung and stomach cancer (Zhang and Li 1987).

Mechanisms of Action. Numerous studies have investigated the mechanisms of celluar toxicity and genotoxicity. Toxicity appears to be related partly through reactive intermediates during intracellular reduction of chromium(VI) and oxidative reactions, and partly mediated by chromium(III), which is the final product of intracellar chromium(VI) reduction and forms deleterious complexes with critical target macromolecules (Chen and Shi 2002; Costa 2003; Costa and Klein 2006a; Ding and Shi 2002; Jeejeebhoy 1999; Levina and Lay 2005; Liu and Shi 2001; O'Brien et al. 2003; Paustenbach et al. 2003; Shrivastava et al. 2002; Zhitkovich 2005). The products of metabolic reduction of chromium(VI) (free radicals and chromium(V) and (IV)) and the newly generated chromium(III) are thought to be, in part, primarily responsible for the genotoxic effects that lead to carcinogeniticty seen in human and animal studies. The types of chromium-induced structural damage include DNA strand breaks (Aiyar et al. 1991; Bagchi et al. 2002a; Bryant et al. 2006; Casadevall et al. 1999; Ha et al. 2004; Kuykendall et al. 1996; Manning et al. 1992; Messer et al. 2006; Pattison et al. 2001; Ueno et al. 1995a), DNA-protein crosslinks (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Costa et al. 1996, 1997; Kuykendall et al. 1996; Lin et al. 1992; Manning et al. 1992; Mattagajasingh and Misra 1996; Miller et al. 1991; O'Brien et al. 2005; Quievryn et al. 2001; Zhitkovich et al. 1996), DNA-DNA interstrand crosslinks (Xu et al. 1996), chromium-DNA adducts, and chromosomal aberrations (Blankenship et al. 1997; Sugiyama et al. 1986a; Umeda and Nishimura 1979; Wise et al. 1993). Results of other studies suggest that geneotoxicity of chromium is due to the formation of chromium-DNA ternary adducts, which lead to repair errors, collapsed replication forks, alterations in cellular communication, and effects on signaling pathways and cytoskelton (Ha et al. 2004), and centrosome and spindle assembly checkpoint bypass leading to chromosome instability (Holmes et al. 2006; Wise et al. 2006a). Studies on mechanisms of action of chromium are actively ongoing in the current and future literature (see Section 3.12.3, Ongoing Studies).

Biomarkers of Exposure and Effect.

Exposure. There are studies correlating chromium in urine (Gylseth et al. 1977; Iarmarcovai et al. 2005; Kilburn et al. 1990; Lindberg and Vesterberg 1983a; Lukanova et al. 1996; Medeiros et al. 2003a; McAughey et al. 1988; Minoia and Cavalleri 1988; Muttamara and Leong 2004; Mutti et al. 1985b; Sjogren et al. 1983; Stridsklev et al. 2004; Tola et al. 1977), blood (Iarmarcovai et al. 2005; Kilburn et al. 1990; Medeiros et al. 2003a; McAughey et al. 1988; Minoia and Cavalleri 1988; Muttamara and Leong

2004; Randall and Gibson 1987; Stridsklev et al. 2004; Sathwara et al. 2007), hair (Randall and Gibson 1989; Saner et al. 1984; Takagi et al. 1986), and erythrocytes (Lukanova et al. 1996; Minoia and Cavalleri 1988) to occupational exposure levels. All current methods of biological monitoring are useful primarily for occupational exposure scenarios. Since chromium is an essential element, levels of chromium compounds have to be relatively high in humans before they signify an increase due to exposure. Hair has been useful in determining chronic occupational exposure to chromium in high concentrations (Randall and Gibson 1989); the usefulness of this method for detecting prior exposures is limited to a timespan of months (Simpson and Gibson 1992). Erythrocytes (with a half-life of 120 days) can be used to monitor intermediate exposures, and blood or urine can be used to determine acute exposures (Korallus 1986a, 1986b). Occupational exposure to chromium can cause chromosomal aberrations (Koshi et al. 1984; Sarto et al. 1982; Stella et al. 1982). Therefore, chromosomal abnormalities may be useful for monitoring chromium exposure; however, other chemicals are capable of causing these effects. Chromium(VI) compounds are able to bind to macromolecules in the body and can form DNA-protein crosslinks (Coogan et al. 1991b). However, no increase in these crosslinks was observed in leukocytes from volunteers over a 240-minute time period after ingestion of chromium(VI) as potassium chromate (Kuykendall et al. 1996). The identification of chromium-protein/peptide complexes specific for chromium(VI) exposure and small enough to be excreted in the urine may be useful for biomonitoring in detecting low level exposure to populations near hazardous waste sites. As discussed in Section 3.8.1, there are a number of limitations to using urinary monitoring to assess environmental exposure to chromium (Paustenbach et al. 1997). However, urinary monitoring has the advantage of easy sample collection and is noninvasive. Mathematical models have been used to identify “excess” urinary chromium in a population exposed to low levels of chromium (Fagliano et al. 1997). Further refinement of these models as more data are collected from unexposed and exposed populations will also be useful in detecting low level exposures.

Effect. Chromosomal aberrations have been observed in workers exposed by inhalation to chromium compounds (Koshi et al. 1984; Sarto et al. 1982; Stella et al. 1982). Moreover, chromium(VI) compounds can bind to macromolecules that are excreted in the urine (Coogan et al. 1991b). The use of these techniques to detect chromosomal aberrations and chromium-macromolecular complexes would be useful in identifying populations near hazardous waste sites that would be at higher risk. In addition, the finding of increased retinol binding protein, $ß_2$-microglobulin, and brush border proteins in the urine of workers exposed to chromium may serve as an early indication of kidney damage (Franchini and Mutti 1988; Lindberg and Vesterberg 1983b; Liu et al. 1998; Mutti et al. 1985b). Additional screening for low molecular weight proteins in occupationally exposed individuals will help to determine if these proteins

can be used as reliable indicators of renal damage due to chromium exposure. Snyder et al. (1996) found no difference in mitogenic stimulation of mononuclear cells isolated from people environmentally/ occupationally exposed to chromium as compared to nonexposed individuals. However, monocytes in the exposed population had a 36% lower level of the cytokine IL-6 that is involved in antibody production. As discussed in Section 3.3, chromium induces many types of DNA lesions such as chromium-DNA complexes, DNA adducts, and DNA-protein crosslinks that are potential markers of genotoxic or cancer effects due to chromium exposure. However, only one study has attempted to utilize such end points and reported that volunteers exposed to chromium in drinking water showed no increase in protein-DNA crosslinking in blood cells (Kuykendall et al. 1996). However, further studies may show that other types of lesions induced by chromium may be more sensitive. Räsänen et al. (1991) developed an *in vitro* method to assess chromium sensitivity by measuring mononuclear leukocyte proliferation in response to chromium(III) chloride, sodium chromate(VI), and potassium chromate(VI). Additional studies would be useful to validate this method.

Absorption, Distribution, Metabolism, and Excretion. The pharmacokinetics database is substantial for human and animal exposure to chromium compounds. Chromium and its compounds can be absorbed after oral (Anderson 1981, 1986; Anderson et al. 1983; Bunker et al. 1984; DiSilvestro and Dy 2007; Donaldson and Barreras 1966; Finley et al. 1996b; Gargas et al. 1994; Kerger et al. 1997; Kuykendall et al. 1996; Paustenbach et al. 1996), inhalation (Adachi et al. 1981; Cavalleri and Minoia 1985; Gylseth et al. 1977; Langård et al. 1978; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Suzuki et al. 1984; Tossavainen et al. 1980), and dermal (Baranowska-Dutkiewicz 1981; Brieger 1920; Corbett et al. 1997; Liden and Lundberg 1979; Mali et al. 1963; Samitz and Shrager 1966; Spruit and van Neer 1966; Wahlberg 1970; Wahlberg and Skog 1965) exposure. For the general population, oral exposure via the diet to chromium(III) is the most significant route. Occupational exposure usually involves inhalation and dermal routes. Pharmacokinetic data are generally consistent with regard to absorption, distribution, and excretion among species. Chromium(VI) compounds are absorbed more readily through cell membranes than are chromium(III) compounds (MacKenzie et al. 1958; Maruyama 1982; Witmer et al. 1989, 1991). Absorption is greater through the lungs than through the gastrointestinal tract (Baetjer et al. 1959b; Bragt and van Dura 1983; Kuykendall et al. 1996; Visek et al. 1953; Wiegand et al. 1984, 1987).

Examination of tissues taken at autopsy from occupationally and environmentally exposed people indicate widespread distribution of chromium (Brune et al. 1980; Hyodo et al. 1980; Kollmeier et al. 1990; Mancuso 1997b; Schroeder et al. 1962; Teraoka 1981). Widespread distribution of chromium has also

been found in animals after oral exposure (Kargacin et al. 1993; Witmer et al. 1989, 1991). The distribution of chromium in animals after intratracheal, parenteral, or dermal exposure is greatest in the lungs, liver, kidneys, blood, spleen, testes, and brain (Baetjer et al. 1959a; Behari and Tandon 1980; Bryson and Goodall 1983; Coogan et al. 1991b; Lim et al. 1983; Mutti et al. 1979; Tandon et al. 1979; Visek et al. 1953; Wahlberg and Skog 1965; Weber 1983). Oral exposure studies indicate that higher levels of chromium(VI) compounds are absorbed than are levels of chromium(III) compounds. Studies in humans occupationally and environmentally exposed to chromium(VI) (Casey and Hambidge 1984; Shmitova 1980) and in animals exposed to chromium(VI) or chromium(III) demonstrate the ability for chromium to cross the placenta (Mertz et al. 1969; Saxena et al. 1990a). Chromium(VI) crosses more readily than chromium(III).

There are no data to indicate that the route of exposure influences the metabolism of chromium. Regardless of the route of exposure, chromium(VI) inside the body is reduced to chromium(III) by ascorbic acid, glutathione, or by the NADPH-dependent cytochrome P450 system (Aaseth et al. 1982; Chen and Shi 2002; Costa 2003; Costa and Klein 2006a; De Flora et al. 1984, 1997; Ding and Shi 2002; Garcia and Jennette 1981; Gruber and Jennette 1978; Jeejeebhoy 1999; Levina and Lay 2005; Liu and Shi 2001; Liu et al. 1995; Mikalsen et al. 1989; O'Brien et al. 2003; Paustenbach et al. 2003; Petrilli et al. 1985, 1986a; Samitz 1970; Shrivastava et al. 2002; Suzuki and Fukuda 1990; Wiegand et al. 1984; Zhitkovich 2005).

Analysis of the urine of workers occupationally exposed to chromium(VI) indicates that chromium is excreted in the trivalent form, which is consistent with *in vivo* reduction of chromium(VI) to chromium(III) (Cavalleri and Minoia 1985; Minoia and Cavalleri 1988). Oral studies in humans and animals indicate that most of the chromium(VI) or chromium(III) ingested is excreted in the feces (Bunker et al. 1984; Donaldson and Barreras 1966; Donaldson et al. 1984; Henderson et al. 1979; Sayato et al. 1980), consistent with the poor gastrointestinal absorption of chromium. After dermal exposure of humans and animals, chromium can be found in the urine and feces (Brieger 1920; Wahlberg and Skog 1965). Chromium has been detected in hair and fingernails of the general population of several countries (Takagi et al. 1986, 1988) and in the breast milk of nursing mothers (Casey and Hambidge 1984), indicating these media as routes of excretion. Data regarding excretion after exposure of animals to chromium(VI) or chromium(III) by other routes indicated that excretion occurs rapidly, and primarily via the kidneys, once chromium(VI) is reduced (Gregus and Klaassen 1986; Yamaguchi et al. 1983). Thus, absorption, distribution, and excretion of chromium have been studied extensively. Additional studies

examining the enzymatic reduction of chromium(VI) compounds in rodents and humans would be of value in determining the potential biological impact of the reported differences in those pathways.

Comparative Toxicokinetics. Toxicokinetic data in humans, dogs, rats, mice, rabbits, and hamsters generally correlate well among species (see references above). However, exposures to chromium(VI) resulted in different organ distribution patterns between rats and mice (Kargacin et al. 1993), and the chromium levels in mouse fetal tissues were elevated over maternal blood levels, whereas in rats, these differences were not found (Saxena et al. 1990a). In addition, comparisons of human and rat hepatic microsomal ability to reduce chromium(VI) indicated differences in microsomal complexes involved (Myers and Myers 1998; Pratt and Myers 1993). Therefore, additional comparison studies among species would be useful to determine variations in the absorption, distribution, metabolism, and excretion of chromium. A PBPK model (O'Flaherty 1996; O'Flaherty et al. 2001) that has been partially validated has been developed based on rats. As described previously, the model is quite sophisticated, but additional physiological and kinetic parameters from both humans and other animal species are needed in order for the model to be employed for extrapolation across species and for use in risk assessment. Furthermore, additional metabolic data are needed with regard to insoluble chromium and its elimination and solubilization, particularly in lung tissue.

Methods for Reducing Toxic Effects. Methods for reducing the absorption of chromium from the lungs consist primarily of administering ascorbic acid or N-acetylcysteine, which enhance the reduction of chromium(VI) to chromium(III) (De Flora and Wetterhahn 1989; Suzuki and Fukuda 1990). Chromium(III) passes the alveolar lining into the bloodstream less readily than chromium(VI) and is cleared by mucociliary clearance. A study might be conducted to determine whether administration of expectorants would enhance clearance from the lungs. Oral administration of ascorbic acid to further reduce chromium(VI) to chromium(III) might further decrease bioavailability (Haddad et al. 1998; Kuykendall et al. 1996; Schonwald 2004), although this has not been proven (Leikin and Paloucek 2002; Schonwald 2004). After dermal exposure, thorough washing and ascorbic acid therapy to enhance the reduction of chromium(VI) to chromium(III) (Schonwald 2004), followed by chelation with EDTA (Nadig 1994), would greatly reduce dermal absorption. Administration of ascorbic acid has also been used to enhance the reduction of chromium(VI) to chromium(III) in plasma (Korallus et al. 1984), which would reduce the body burden of chromium because chromium(III) would bind to plasma protein and be excreted in the urine. Studies could be conducted to determine if other reducing agents would be more effective than ascorbic acid. Once inside the cell, chromium(VI) can enter many reactions resulting in reduction to various oxidation states with the generation of reactive oxygen species and radicals, all of

which may be more or less toxic than chromium(III) (De Flora and Wetterhahn 1989). Gasiorowski et al. (1997, 1998) showed that stabilizing chromium in the hexavalent oxidation state, via complexing to a ligand, decreased the mutagenicity of chromium(VI). Methods could be developed to interfere with these various reactions, but such methods may be counterproductive because they might shift one reaction to another with undesirable consequences. *In vitro* studies have indicated that vitamin E, ascorbic acid, and glutatione protected against cellular damage, including chromosomal breakage, DNA-protein crosslinks, and apoptosis (cell death) (Blankenship et al. 1997; Little et al. 1996; Sugiyama 1991; Wise et al. 1993, 2004), while vitamin B_2 enhanced the cytotoxicity and DNA single-strand breaks induced by chromium(VI) (Sugiyama 1991). Vitamin E may have scavenged radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991). Other vitamins might also be effective in mitigating chromium's effects; thus, studies on the effect of vitamins on chromium toxicity may provide additional information on the potential to reduce toxic effects. Although the administration of thyroxine has been shown to ameliorate potassium dichromate-induced acute renal failure in rats (Siegel et al. 1984), its use in humans has not been tested. Further studies are needed to assess the safety of administering thyroxine to mitigate chromium toxicity.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

A limited amount of information is available on the toxicity of chromium in children; most of the available data come from children ingesting lethal doses of chromium(VI) (Clochesy 1984; Ellis et al. 1982; Iserson et al. 1983; Kaufman et al. 1970; Reichelderfer 1968). Studies that examine sensitive end points such as respiratory effects following inhalation exposure, or gastrointestinal, hematological, liver and kidney effects in young animals would be useful for assessing whether children will be unusually susceptible to chromium toxicity. The available animal data suggest that chromium is a developmental toxicant. As discussed in Section 3.2.2.6, the observed developmental effects include postimplantation losses, gross abnormalities, and impaired reproductive development in the offspring (Al-Hamood et al. 1998; Junaid et al. 1996a, 1996b; Kanojia et al. 1996, 1998; Trivedi et al. 1989). Data needs relating to development are discussed in detail in the Developmental Toxicity subsection above. There are some data in humans and animals that provide evidence that chromium can cross the placenta and be transferred to an infant via breast milk (Casey and Hambidge 1984; Danielsson et al. 1982; Mertz et al. 1969; Saxena et al. 1990a; Shmitova 1980). There are no data on whether chromium is stored in maternal tissues and whether these stores can be mobilized during pregnancy or lactation.

An age-related difference in the extent of gastrointestinal absorption of chromium(III) was reported in one study (Sullivan et al. 1984); it is not known if a similar relationship would exist for chromium(VI). No other information is available that evaluated potential differences between adults and children. Toxicokinetic studies examining how aging can influence the absorption, distribution, and excretion of chromium, particularly chromium(VI) would be useful in assessing children's susceptibility to chromium toxicity. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children. There is very little available information on methods for reducing chromium toxic effects or body burdens; it is likely that research in adults would also be applicable to children.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies pertaining to chromium toxicity have been identified and are shown in Table 3-11.

Table 3-11. Ongoing Studies on Chromium

Investigator	Study Topic	Institution	Sponsor
Avery S	Role of oxidative mechanisms in the toxicity of metals	University of Nottingham	National Institute of General Medical Sciences
Cohen M	Properties of metals may govern toxicities in the lungs	New York University School of Medicine	National Institute of General Medical Sciences
Myers C	Human lung chromium toxicity: Role of cytochrome b5	Medical College of Wisconsin	National Institute of Environmental Health Sciences
Patierno S	Chromium genotoxicity: Response and repair mechanisms	George Washington University	National Institute of Environmental Health Sciences
Stearns D	Uptake and mutagenicity of moderately soluble hexavalent chromium	Northern Arizona University	National Institute of Environmental Health Sciences
Sugden K	Oxidative DNA lesion formation from chromate exposure	University of Montana	National Institute of Environmental Health Sciences
Zhitkovich A	Biological dosimetry of hexavalent chromium	Brown University	National Institute of Environmental Health Sciences
Zhitkovich A	Genotoxicity of chromium compounds	Brown University	National Institute of Environmental Health Sciences
Zhitkovich A	Sensitivity mechanisms in chromium toxicity	Brown University	National Institute of Environmental Health Sciences

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of chromium is located in Table 4-1.

The synonyms, trade name, chemical formula, and identification numbers of chromium and selected salts are reported in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of chromium is located in Table 4-2.

Chromium is a metallic element with oxidation states ranging from chromium(-II) to chromium(+VI). The important valence states of chromium are II, III, and VI. Elemental chromium, chromium(0), does not occur naturally. The divalent state (II or chromous) is relatively unstable and is readily oxidized to the trivalent (III or chromic) state. Chromium compounds are stable in the trivalent state and occur in nature in this state in ores, such as ferrochromite ($FeCr_2O_4$). The hexavalent (VI or chromate) is the second most stable state. However, hexavalent chromium rarely occurs naturally, but is produced from anthropogenic sources (Alimonti et al. 2000; Barceloux 1999; EPA 1984a; Johnson et al. 2006; Shanker et al. 2005). Chromium in the hexavalent state occurs naturally in the rare mineral crocoite ($PbCrO_4$) (Hurlbut 1971; Papp and Lipin 2001).

The solubility of chromium compounds varies, depending primarily on the oxidation state. Trivalent chromium compounds, with the exception of acetate, hexahydrate of chloride, and nitrate salts, are generally insoluble in water (Table 4-2). The zinc and lead salts of chromic acid are practically insoluble in cold water (Table 4-2). The alkaline metal salts (e.g., calcium, strontium) of chromic acid are less soluble in water. Some hexavalent compounds, such as chromium(VI) oxide (or chromic acid), and the ammonium and alkali metal salts (e.g., sodium and potassium) of chromic acid are readily soluble in water. The hexavalent chromium compounds are reduced to the trivalent form in the presence of oxidizable organic matter. However, in natural waters where there is a low concentration of reducing materials, hexavalent chromium compounds are more stable (EPA 1984a; Loyaux-Lawniczak et al. 2001).

Table 4-1. Chemical Identity of Chromium and Compounds

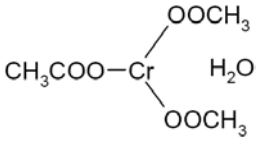
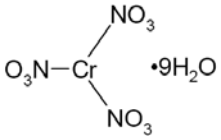
Characteristic	Information		
Chemical name	Chromium(0)	Chromium(III) acetate, monohydrate	Chromium(III) nitrate, nonahydrate
Synonym(s)	Chrome; Chrom (German); Chrome (French)	Acetic acid, chromium salt, hydrate; chromic acetate, hydrate	Nitric acid, chromium (III) salt, nonahydrate; chromium nitrate, nonahydrate
Registered trade name(s)	Chrome	No data	No data
Chemical formula	Cr	$Cr(CH_3COO)_3•H_2O$	$Cr(NO_3)_3•9H_2O$
Chemical structure	Cr		
Identification numbers:			
CAS registry	7440-47-3	25013-82-5	7789-02-8
NIOSH RTECS	GB420000	AG3053333	GB6300000
EPA hazardous waste	D007	No data	No data
OHM/TADS	7216647	No data	No data
DOT/UN/NA/IMDG shipping	Not assigned	No data	No data
HSDB	910	No data	No data
NCI	Not assigned	No data	No data

Table 4-1. Chemical Identity of Chromium and Compounds

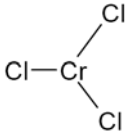
Characteristic	Information		
Chemical name	Chromium(III) chloride	Chromium(III) chloride, hexahydrate	Ferrochromite (Chromium[III])
Synonym(s)	Chromium trichloride	Hexaaquachromium (III) chloride	Chromite
Registered trade name(s)	C177295	No data	No data
Chemical formula	CrCl3	Cr(Cl)3•6H20	FeCr2O4
Chemical structure		Cr[Cl2(H2O)4]Cl•2H2O	FeOCr2O3
Identification numbers:			
CAS registry	10025-73-7	10060-12-5	1308-31-2
NIOSH RTECS	GB5425000	GB5450000	GB4000000
EPA hazardous waste	No data	No data	D007
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	No data	No data	2963
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Chromium and Compounds

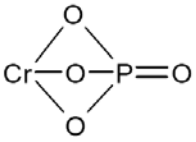
Characteristic	Information		
Chemical name	Chromium(III) oxide	Chromium(III) phosphate	Chromium(III) sulfate
Synonym(s)	Chromium sesquioxide; dichromium trioxide	Chromumorthophosphate; phosphoric acid, chromium (III) salt	Sulfuric acid, chromium (III) salt
Registered trade name(s)	No data	Amaudon's Green	Chromitan B
Chemical formula	Cr_2O_3	$CrPO_4$	$Cr_2(SO_4)_3$
Chemical structure	O=Cr—O—Cr=O		SO_4=Cr–SO_4–Cr=SO_4
Identification numbers:			
CAS registry	1308-38-9	7789-04-0	10101-53-8
NIOSH RTECS	GB6475000	GB6840000	GB7200000
EPA hazardous waste	D007	No data	D0007
OHM/TADS	Not assigned	No data	7800052
DOT/UN/NA/IMDG shipping	Not assigned	No data	Not assigned
HSDB	1619	No data	2543
NCI	Not assigned	No data	Not assigned

Table 4-1. Chemical Identity of Chromium and Compounds

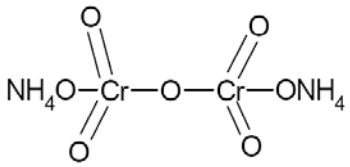
Characteristic	Information		
Chemical name	Sodium chromite (Chromium[III])	Chromium(IV) oxide	Ammonium dichromate (Chromium[VI])
Synonym(s)	No data	Chromium dioxide	Chromic acid, diamonium salt
Registered trade name(s)	No data	No data	No data
Chemical formula	$NaCrO_2$	CrO_2	$(NH_4)_2Cr_2O_7$
Chemical structure	NaO–Cr=O	O=Cr=O	
Identification numbers:			
CAS registry	12314-42-0	12018-01-8	7789-09-5
NIOSH RTECS	No data	GB6400000	HX7650000
EPA hazardous waste	No data	D007	Not assigned
OHM/TADS	No data	No data	7217321
DOT/UN/NA/IMDG shipping	No data	No data	UN1439; IM05.1
HSDB	No data	1620	481
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Chromium and Compounds

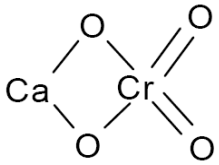
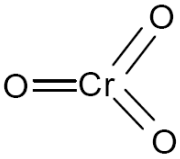
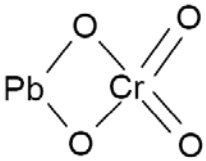
Characteristic	Information		
Chemical name	Calcium chromate (Chromium[VI])	Chromium(VI) trioxide	Lead chromate (Chromium[VI])
Synonym(s)	Chromic acid, calcium salt	Chromic acid, chromium anhydride	Chromic acid, lead salt
Registered trade name(s)	Calcium Chrome Yellow	No data	Chrome Yellow G
Chemical formula	$CaCrO_4$	CrO_3	$PbCrO_4$
Chemical structure			
Identification numbers:			
CAS registry	13765-19-0	1333-82-0	7758-97-6
NIOSH RTECS	GB2750000	GB6650000	GB2975000
EPA hazardous waste	U032; D007	D007	D007; D008
OHM/TADS	7800051	Not assigned	Not assigned
DOT/UN/NA/IMDG shipping	NA9096	YB1463/UNI5.1; IM05.1	Not assigned
HSDB	248	518; NA1463	1650
NCI	Not assigned	UN1463	Not assigned

Table 4-1. Chemical Identity of Chromium and Compounds

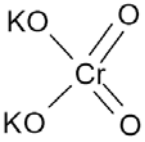
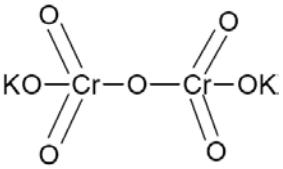
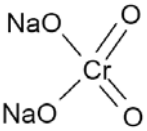
Characteristic	Information		
Chemical name	Potassium chromate (Chromium[VI])	Potassium dichromate (Chromium[VI])	Sodium chromate (Chromium[VI])
Synonym(s)	Chromic acid, dipotassium salt	Chromic acid, dipotassium salt	Chromic acid, disodium salt
Registered trade name(s)	No data	No data	Caswell No. 757
Chemical formula	K2CrO4	$K_2Cr_2O_7$	Na_2CrO_4
Chemical structure			
Identification numbers:			
CAS registry	7789-00-6	7778-50-9	7775-11-3
NIOSH RTECS	GB2940000	HX7680000	GB2955000
EPA hazardous waste	No data	No data	D007
OHM/TADS	7217277	7217278	7216891
DOT/UN/NA/IMDG shipping	NA9142	NA1479; IM09.0	No data
HSDB	1249	1238	2962
NCI	Not assigned	Not assigned	Not assigned

Table 4-1. Chemical Identity of Chromium and Compounds

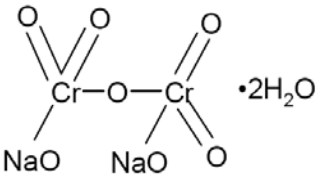
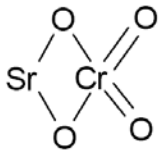
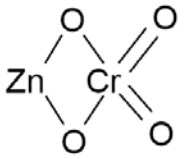
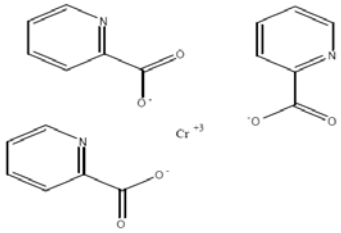
Characteristic	Information	
Chemical name	Sodium dichromate, dihydrate (Chromium[VI])	Strontium chromate (Chromium[VI])
Synonym(s)	Chromic acid, disodium salt; dihydrate	Chromic acid, strontium salt
Registered trade name(s)	No data	No data
Chemical formula	$NaCr_2O_7•2H_20$	$SrCrO_4$
Chemical structure		
Identification numbers:		
CAS registry	7789-12-0	7789-06-2
NIOSH RTECS	HX7750000	GB3240000
EPA hazardous waste	No data	D007
OHM/TADS	No data	780058
DOT/UN/NA/IMDG shipping	No data	NA9149
HSDB	No data	2546
NCI	No data	Not assigned

Table 4-1. Chemical Identity of Chromium and Compounds

Characteristic	Information	
Chemical name	Zinc chromate (Chromium[VI])	Chromium(III) picolinate
Synonym(s)	Chromic acid, zinc salt	CrPic; Chromium 2-pyridinecarboxylate; Chromium; tris(picolinato)-; Picolinic acid; chromium salt
Registered trade name(s)	CI Pigment Yellow	No data
Chemical formula	$ZnCrO_4$	$C_{18}H_{12}CrN_3O_6$
Chemical structure		
Identification numbers:		
CAS registry	13530-65-9	14639-25-9
NIOSH RTECS	GB3290000	No data
EPA hazardous waste	D007	No data
OHM/TADS	7217401	No data
DOT/UN/NA/IMDG shipping	Not assigned	No data
HSDB	6188	No data
NCI	Not assigned	No data

Sources: HSDB 2008; NIOSH 2005

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Chromium	Chromium(III) acetate, monohydrate	Chromium(III) nitrate, nonahydrate	Chromium(III) chloride
Molecular weight	51.996	229.13	400.15	158.35
Color	Steel-gray	Gray-green or bluish-green	Purple or violet	Violet or purple
Physical state	Solid	Solid	Solid	Solid
Melting point	1,90±10 °C	No data	60 °C	≈1,150 °C
Boiling point	2,642 °C	No data	Decomposes at 100 °C	Decomposes at 1,300 °C
Density at 20 °C	7.14 (28 °C)[a]	No data	No data	2.87 (25 °C)[a]
Odor	odorless	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	Insoluble	Soluble	Soluble	Slightly soluble in hot water
Organic solvents	Insoluble in common organic solvents	45.4 g/L in methanol (15 ^{o}C); 2 g/L in acetone (15 ^{o}C)	Soluble in ethanol and acetone	Insoluble in cold water, acetone, methanol, and ether
Partition coefficients:				
Log K_{ow}	Not applicable	Not applicable	Not applicable	Not applicable
Log K_{oc}	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	1 mmHg (1,616 °C)	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Chromium(III) chloride, hexahydrate	Ferrochromite (Chromium[III])	Chromium(III) oxide	Chromium(III) phosphate
Molecular weight	266.45	223.84	151.99	146.97
Color	Violet	Brown-black	Green	Gray-brown to black[d]
Physical state	Solid	Solid	Solid	Solid
Melting point	83 °C	No data	2,435 °C	>1,800 °C
Boiling point	No data	No data	3,000 °C	No data
Density at 20 °C	1.76[b]	4.97 (20 °C)	5.22 (25 °C)[b]	2.94 (32.5 °C)[a,c]
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	58.5 g/100 cc at 25 °C	Insoluble	Insoluble	Insoluble[c]
Organic solvents	Soluble in ethanol	No data	Insoluble in ethanol	Insoluble in alcohol, acetone
Partition coefficients:				
Log K_{ow}	No data	Not applicable	Not applicable	Not applicable
Log K_{oc}	No data	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data	No data
Henry's law constant at 25 °C	No data	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Chromium(III) sulfate	Sodium chromite (Chromium[III])	Chromium(IV) oxide	Ammonium dichromate (Chromium[IV])
Molecular weight	392.18	106.98	83.99	252.07
Color	Violet, red, peach	No data	Brown-black	Orange
Physical state	Solid	No data	Solid	Solid
Melting point	No data	No data	Decomposes at 300 °C	Decomposes at 180 °C
Boiling point	No data	No data	Not applicable	Not applicable
Density at 20 °C	3.012	No data	No data	2.15 (25 °C)[a]
Odor	No data	No data	No data	odorless
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	Insoluble	No data	Insoluble	In water (wt/wt): 15.5% (0 ^{o}C); 26.67% (20 ^{o}C); 36.99% (40 ^{o}C); 46.14% (60 ^{o}C); 54.20% (80 ^{o}C)
Organic solvents	soluble in alcohols	No data	No data	Soluble in alcohols, insoluble in acetone
Partition coefficients:				
Log K_{ow}	Not applicable	Not applicable	Not applicable	Not applicable
Log K_{oc}	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Calcium chromate (Chromium[VI])	Chromium(VI) trioxide	Lead chromate (Chromium[VI])	Potassium chromate (Chromium[VI])
Molecular weight	156.07	99.99	323.19	194.19
Color	Yellow	Red	Yellow	Yellow
Physical state	Solid	Solid	Solid	Solid
Melting point	No data	197 °C	844 °C	975 °C
Boiling point	No data	Decomposes	Decomposes	No data
Density at 20 °C	2.89[b]	2.70 (25 °C)	6.12 (15 °C)	2.732 (18 °C)
Odor	No data	Odorless	No data	Odorless
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	2.23 g/100 mL	61.7 g/100 cc at 0 °C	5.8 μg/100 mL	62.9 g/100 at 20 °C
Organic solvents	No data	Soluble in ethanol, ethyl ether, sulfuric and nitric acids Soluble 61.7 g/100 cc water (0 °C) 67.45 g/100 cc water (100 °C) 167.299 lb/100 lb water (70 °F) Soluble in acetic acid and acetone	Soluble 0.2 mg/l water Insoluble in acetic acid; soluble in dilute nitric acid and in solution of fixed alkali hydroxides Soluble in acid, insoluble in ammonia	62.9 G/100 cc water (20 °C) 79.2 g/100 cc water (100 °C) Insoluble in alcohol
Partition coefficients:				
Log K_{ow}	Not applicable	Not applicable	Not applicable	Not applicable
Log K_{oc}	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data	0
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Potassium dichromate (Chromium[VI])	Sodium chromate (Chromium[VI])	Sodium dichromate, dihydrate (Chromium[VI])
Molecular weight	294.18	161.97	298.00
Color	Red	Yellow	Red
Physical state	Solid	Solid	Solid
Melting point	398 °C	792 °C	356.7 °C
Boiling point	Decomposes at 500 °C	No data	Decomposes at 400 °C
Density at 20 °C	2.676 (25 °C)	2.710–2.736[b]	2.52 (13 °C)
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 20 °C	4.9 g/100 cc at 0 °C	87.3 g/100 cc at 30 °C	230 g/100 cc at 0 °C
Organic solvents	Insoluble in ethanol and acetone	Soluble in methanol	Insoluble in ethanol
Partition coefficients:			
Log K_{ow}	Not applicable	Not applicable	Not applicable
Log K_{oc}	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Strontium chromate (Chromium[VI])	Zinc chromate (Chromium[VI])	Chromium(III) picolinate
Molecular weight	203.61	181.97	418.3[c]
Color	Yellow	Lemon-yellow	Ruby red[d]
Physical state	Solid	Solid	Crystal[d]
Melting point	No data	No data	No data
Boiling point	No data	No data	No data
Density at 20 °C	3.895 (15 °C)	3.40[b]	No data
Odor	No data	Odorless	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 20 °C	0.12 g/100 cc at 15 °C	Insoluble	1 ppm at 25 °C[d]
Organic solvents	Soluble in acetyl acetone	Insoluble in acetone	>6 g/L (DMSO)[d]
Partition coefficients:			
Log K_{ow}	Not applicable	Not applicable	1.753[e]
Log K_{oc}	Not applicable	Not applicable	No data
Vapor pressure at 20 °C	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

[a]Temperature at which the densities were measured has been given only when such data are available
[b]Temperature at which density was measured was not specified.
[c]O'Neil et al. 2006
[d]Broadhurst et al. 1997
[e]Chakov et al. 1999

DMSO=dimethylsulfoxide

In humans, chromium(III) is an essential nutrient that may play a role in glucose, fat, and protein metabolism possibly by potentiating the action of insulin. However, there is some emerging controversy whether chromium(III) is essential and more work has been suggested to elucidate its mechanism of action. Chromium picolinate, a trivalent form of chromium complexed with picolinic acid, is used as a dietary supplement, because it is claimed to speed metabolism and may have anti-diabetic effects (Broadhurst et al. 1997). However, there still remains controversy over the use of chromium(III) in diabetes, and several researchers claim no demonstrated effects of chromium(III) on diabetes or insulin resistance (Althuis et al. 2002). Currently, the mechanism of transport and absorption of chromium picolinate has not been determined, although spectroscopic analysis has shown that chromium picolinate is a very stable complex in the body and its absorption properties may be due to its ability to cross membranes (Chakov et al. 1999).

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Tables 5-1 and 5-2 list the facilities in each state that manufacture or process chromium, the intended use, and the range of maximum amounts of chromium that are stored on site. There are currently 3,567 facilities that produce or process chromium in the United States. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI) (TRI06 2008). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

Chromium metal is commercially produced in the United States by the reduction of chromite ore with carbon, aluminum, or silicon, and subsequent purification. Sodium chromate and dichromate are produced by roasting chromite ore with soda ash. Most other chromium compounds are produced from sodium chromate and dichromate (Hartford 1979; Papp and Lipin 2001; Westbrook 1979). For example, basic chromic sulfate ($Cr(OH)SO_4$), commonly used in tanning, is commercially produced by the reduction of sodium dichromate with organic compounds (e.g., molasses) in the presence of sulfuric acid or by the reduction of dichromate with sulfur dioxide. Lead chromate, commonly used as a pigment, is produced by the reaction of sodium chromate with lead nitrate or by reaction of lead monoxide with chromic acid solution (IARC 1990).

The major manufacturers of chromium compounds in 2007 are summarized in Table 5-3 (SRI 2007). Tables 5-1 and 5-2 report the number of facilities in each state that manufacture and process chromium, the intended use of the products, and the range of maximum amounts of chromium products that are stored on site. The data reported in Tables 5-1 and 5-2 are derived from TRI of EPA (TRI06 2008). The TRI data should be used with caution since only certain types of facilities were required to report. Hence, this is not an exhaustive list.

5.2 IMPORT/EXPORT

Chromite ore and foundry sand; chromium chemicals, ferroalloys, and metal; and stainless steel represent the bulk of the market for chromium. In 2006, the United States produced chromium ferroalloys, metal, chemicals, and stainless steel. The United States is a major producer of the end products of chromium,

Table 5-1. Facilities that Produce, Process, or Use Chromium

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	2	10,000	999,999	12
AL	94	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	52	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	56	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	174	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	48	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
CT	72	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DE	12	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
FL	45	0	499,999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14
GA	88	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	1	10,000	99,999	8
IA	82	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
ID	14	0	999,999	1, 3, 5, 8, 9, 10, 12, 13
IL	138	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	157	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	47	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	98	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	70	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
MA	66	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MD	48	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ME	16	0	9,999,999	1, 2, 3, 8, 12
MI	162	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	74	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	67	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	34	0	499,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12
MT	12	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 14
NC	79	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	14	1,000	999,999	1, 2, 3, 5, 7, 8, 9, 12, 13
NE	35	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NH	21	0	49,999,999	3, 6, 7, 8, 9, 11, 12
NJ	99	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	17	100	999,999	2, 3, 6, 7, 8, 9, 10, 11, 12
NV	41	100	999,999	1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	118	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	229	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	83	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	68	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PA	238	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-1. Facilities that Produce, Process, or Use Chromium

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PR	11	0	99,999,999	1, 2, 3, 5, 8, 9, 11, 12
RI	18	0	999,999	1, 2, 3, 6, 7, 8, 9, 11, 12
SC	97	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	15	100	999,999	1, 5, 7, 8, 9, 11, 12, 13, 14
TN	101	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	189	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	54	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	61	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VT	14	100	999,999	2, 3, 4, 6, 8, 9, 11
WA	64	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	123	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	40	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
WY	9	0	99,999	1, 8, 9, 11, 12, 13

aPost office state abbreviations used
bAmounts on site reported by facilities in each state
cActivities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI06 2008 (Data are from 2006)

Table 5-2. Facilities that Produce, Process, or Use Chromium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	12	10,000	9,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 13, 14
AL	125	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	73	0	99,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
AZ	79	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	185	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	31	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
CT	58	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DE	29	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
FL	71	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	119	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	9	1,000	999,999	7, 8, 10, 11
IA	62	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	23	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IL	219	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	191	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	64	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	107	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	75	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MA	67	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MD	70	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ME	27	100	499,999,999	1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MI	196	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	71	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	91	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	69	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	17	100	999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
NC	119	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	14	1,000	999,999	1, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14
NE	37	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NH	16	0	99,999	1, 4, 5, 7, 8, 9, 10, 11
NJ	121	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	32	100	10,000,000,000	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
NV	40	100	499,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	140	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	303	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	59	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	59	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
PA	272	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Chromium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PR	22	0	9,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 13, 14
RI	20	0	999,999	2, 3, 4, 7, 8, 9, 12
SC	103	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	11	100	99,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 13
TN	118	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	279	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	62	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	73	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VT	8	100	99,999	2, 3, 7, 8, 10, 11
WA	72	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	127	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	74	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
WY	20	0	9,999,999	1, 2, 3, 4, 5, 7, 9, 11, 12, 13, 14

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI06 2008 (Data are from 2006)

Table 5-3. Major Manufacturers of Chromium Compounds in 2007

Chemical	Manufacturer	Location
Chromic anhydride	Johnson Matthey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
Chromic hydrate	Elementis Chromium LP	Corpus Christi, Texas
Chromic sulfate	Blue Grass Chemical Specialties, LLC	New Albany, Indiana
	Elementis LTP L.P.	Amarillo, Texas
		Dakota City, Nebraska
		Milwaukee, Wisconsin
	Johnson Mathey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
Chromium(III) acetate	Blue Grass Chemical Specialties, LLC	New Albany, Indiana
	McGean-Rohco, Inc.; McGean Speciality Chemical Division	Cleveland, Ohio
	The Shepherd Chemical Company	Cincinnati, Ohio
Chromium(III) acetylacetonate	MacKenzie Company	Bush, Louisiana
	The Shepherd Chemical Company	Cincinnati, Ohio
Chromium boride	CERAC, Inc.	Milwaukee, Wisconsin
	Johnson Mathey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
Chromium carbonyl	Strem Chemicals Incorporated	Newburyport, Massachusetts
	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium(III) chloride	Blue Grass Chemical Specialties, LLC	New Albany, Indiana
	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium diboride	Johnson Matthey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
Chromium difluoride	Atotech USA, Inc.	Rock Hill, South Carolina
Chromium 2-ethylhexanoate	OM Group, Inc.	Franklin, Pennsylvania
	The Shepherd Chemical Company	Cincinnati, Ohio
Chromium fluoride	Atotech USA	Rock Hill, South Carolina
Chromium hexacarbonyl	Strem Chemicals Incorporated	Newburyport, Massachusetts
Chromium hydroxide	Elementis Chromium LP	Corpus Christi, Texas
Chromium(III) hydroxide	Elementis Chromium LP	Corpus Christi, Texas
Chromium hydroxyl diacetate	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium hydroxyl dichloride	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium napthenate	OM Group, Inc.	Franklin, Pennsylvania
Chromium nitrate	Blue Grass Chemical Specialties, LLC	New Albany, Indiana
	McGean-Rohco Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
	The Shepherd Chemical Company	Cincinnati, Ohio
Chromium ocetenoate	OM Group, Inc.	Franklin, Pennsylvania
	The Shepherd Chemical Company	Cincinnati, Ohio
Chromium octoate	OM Group, Inc.	Franklin, Pennsylvania
	The Shepherd Chemical Company	Cincinnati, Ohio
Chromium oxide	Elementis Chromium LP	Corpus Christi, Texas

Table 5-3. Major Manufacturers of Chromium Compounds in 2007

Chemical	Manufacturer	Location
Chromium potassium sulfate	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium-silicon monoxide	CERAC, Inc.	Milwaukee, Wisconsin
Chromium(III) sulfate	Blue Grass Chemical Specialties, LLC	New Albany, Indiana
	Elementis LTP L.P.	Amarillo, Texas
		Dakota City, Nebraska
		Milwaukee, Wisconsin
	Johnson Mathey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
Chromotropic acid, disodium salt	Johnson-Mathhey, Inc.; Alfa Aesar	Ward Hill, Massachusetts

Source: SRI 2007

which include chromium chemicals, metal, and stainless steel, but until recently, the United States had not mined chromium (Stokinger 1981; USGS 2008b). Oregon Resources Corporation (ORC), a subsidiary of Industrial Minerals Corporation (Australia), extracted bulk samples of chromite ore at its surface mine in Coos County, Oregon. ORC developed its material beneficiation process to recover chromite, garnet, and zircon minerals with production expected to start in 2008 (IMC 2007). Although chromium is currently mined in Oregon, the United States receives the majority of chromium ores from other countries. From 2003 to 2006, chromium contained in chromite ore and chromium ferroalloys and metal were imported from South Africa (34%), Kazakhstan (18%), Russia (7%), Zimbabwe (6%), and other (35%) (USGS 2008b).

U.S. imports and exports are summarized in Table 5-4 (USGS 2008a).

5.3 USE

The metallurgical, refractory, and chemical industries are the fundamental users of chromium. In the metallurgical industry, chromium is used to produce stainless steels, alloy cast irons, nonferrous alloys, and other miscellaneous materials. In 1988, the U.S. chemical and metallurgical industries accounted for 83.9% and the refractory industry for 16.1% of the total domestic consumption of chromite (USDI 1988a). The stainless steel industry is the leading consumer of chromium materials. A significant amount of chromium is imported and exported in stainless steel mill products and scrap, with ferrochromiums as the main components used by the metallurgical industry. Typical weight percent of chromium in stainless steel and chromium alloys ranges from 11.5 to 30%. In the refractory industry, chromium is a component in chrome and chrome-magnesite, magnesite-chrome bricks, and granular chrome-bearing and granular chromite, which are used as linings for high temperature industrial furnaces. In the chemical industry, both chromium(III) and chromium(VI) are used primarily in pigments. Other uses include chromium(VI) in metal finishing, chromium(III) in leather tanning, and chromium(VI) in wood preservatives. Table 5-5 lists the approximate distribution of use for chromium chemicals in the major applications in the United States and Western world in 1996 with a comparison to use in the United States for 1951 (Barnhart 1997). Smaller amounts of chromium are used as catalysts and in miscellaneous applications, such as drilling muds, chemical manufacturing, textiles, toners for copying machines, magnetic tapes, and dietary supplements (Carlton 2003; CMR 1988a, 1988b; Davis and Vincent 1997; EPA 1984a; IARC 1990; Papp and Lipin 2001; Radivojevic and Cooper 2008; USDI 1988a). Chromium alloys are also used in metal joint prostheses (Sunderman et al. 1989). Chromium picolinate, a trivalent form of chromium complexed with picolinic acid, is used as a dietary supplement,

Table 5-4. U.S. Chromium Imports and Exports

Year	Imports (thousands of metric tons gross weight)	Exports (in thousands of metric tons gross weight)
2003	441	188
2004	489	171
2005	503	220
2006	520	212
2007	510	210

Source: USGS 2008a

Table 5-5. Historical Use of Chromium in the United States and Western World

Use	1996 Western world	1996 United States	1951 United States
Wood preservation	15%	52%	2%
Leather tanning	40%	13%	20%
Metals finishing	17%	13%	25%
Pigments	15%	12%	35%
Refractory	3%	3%	1%
Other	10%	7%	17%

Souce: Barnhart 1997

with the claim that it reduces symptoms of type II diabetes and hypoglycemia (Broadhurst et al. 1997), although a recent meta-review concludes that the results are still inconclusive (Althuis et al. 2002).

5.4 DISPOSAL

Information regarding the disposal of finished products and wastes produced during the manufacturing of consumable items that contain chromium is limited. In 1987, 25% of the chromium demand in the United States was supplied by recycled stainless steel scrap. Although a large portion of the chromium wastes from plating operations is also recovered, large amounts of chromium-containing waste waters from plating, finishing, and textile industries are discharged into surface waters. A substantial amount of chromium enters sewage treatment plants from industrial and residential sources (Klein et al. 1974; TRI06 2008). Presently, slag from roasting/leaching of chromite ore is one of the materials excluded from regulation under the Resource Conservation and Recovery Act by the 1980 Bevill Amendment. However, emission control dust or sludge from ferrochromium and ferrochromium-silicon production is listed as hazardous waste by EPA (1988b). Land filling appears to be the most important method for the disposal of chromium wastes generated by chemical industries. Of the total chromium released in the environment by chemical industries, approximately 82.3% is released on land. An equally large amount of chromium waste is transferred off-site (see Section 5.2). It is anticipated that most of this off-site waste will be disposed of in landfills after proper treatment. It is important to convert chromium wastes into forms of chromium that have low mobilities in soils and low availabilities to plants and animals before land disposal. Chromium(III) oxide is one such form. Chromium in chemical industry wastes occurs predominantly in the hexavalent form. The treatment of chromium(VI) waste often involves reduction to chromium(III) and precipitation as the hydrous oxide with lime or caustic soda. Chromium(III) waste can also be converted into hydrous oxide or may be incinerated to form the oxide before land disposal. There is not much known about the disposal method of waste refractory materials used as lining for metallurgical furnaces or the disposal practices for the finished products containing chromium, such as chromium-containing pigments (Fishbein 1981; Komori et al. 1990a; NRCC 1976; Polprasert and Charnpratheep 1989; Westbrook 1979).

Chromium is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995). Disposal of wastes containing chromium is controlled by a number of federal regulations (see Chapter 8).

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6. POTENTIAL FOR HUMAN EXPOSURE

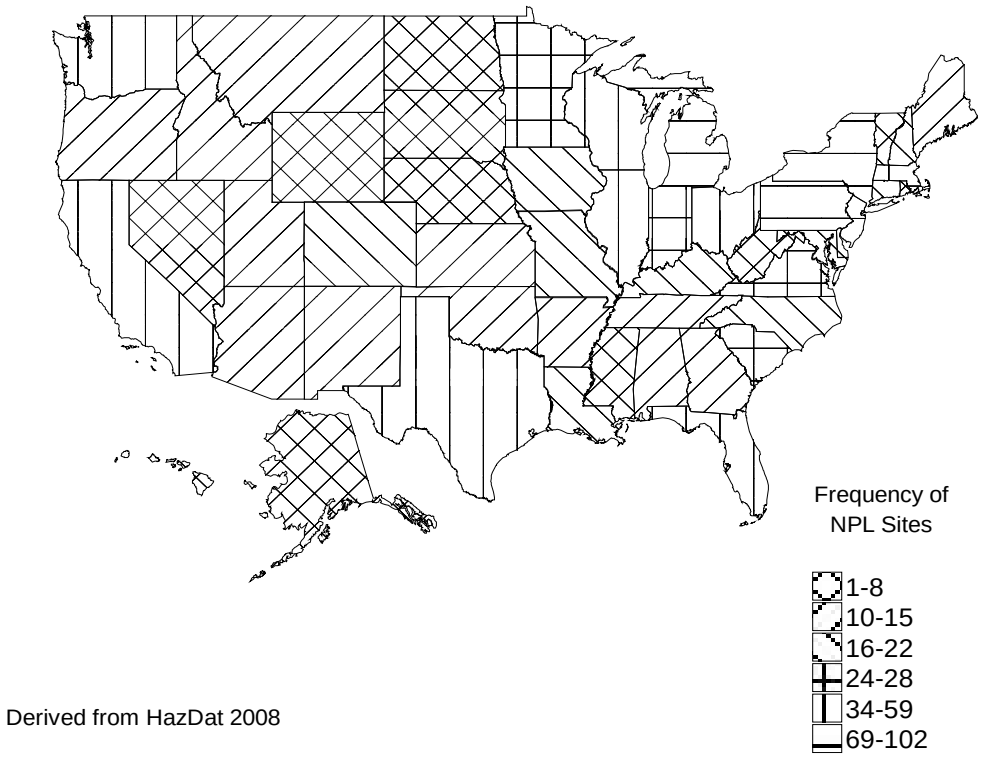
6.1 OVERVIEW

Chromium has been identified in at least 1,127 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). However, the number of sites evaluated for chromium is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 1,117 are located within the United States and 10 are located in the Commonwealth of Puerto Rico (not shown).

Human exposure to chromium occurs from both natural and anthropogenic sources. Chromium is present in the Earth's crust, with the main natural source of exposure being continental dust present in the environment (Barnhart 1997; Fishbein 1981; Pellerin and Booker 2000). Chromium is released into the environment in larger amounts as a result of human activities, which account for 60–70% of the total emissions of atmospheric chromium (Alimonti et al. 2000; Barceloux 1999; Seigneur and Constantinous 1995). This is indicated by the value of the enrichment factor (the enrichment factor relates the amount of chromium relative to an aluminum standard) of 3.5–8.1 (Dasch and Wolff 1989; Milford and Davidson 1985). Elements with enrichment factors >1 are assumed to have originated from anthropogenic sources (Schroeder et al. 1987). Of the estimated 2,700–2,900 tons of chromium emitted to the atmosphere annually from anthropogenic sources in the United States, approximately one-third is in the hexavalent form (EPA 1990b; Johnson et al. 2006). Industrial releases to the air, water, and soil are also potential sources of chromium exposure, and account for the majority of the anthropogenic releases (Johnson et al. 2006). The electroplating, leather tanning, and textile industries release large amounts of chromium to surface waters (Avudainayagam et al. 2003; Fishbein 1981; Johnson et al. 2006). Disposal of chromium-containing commercial products and coal ash from electric utilities and other industries are major sources of chromium releases into the soil (Barceloux 1999; Nriagu and Pacyna 1988). Solid waste and slag produced during chromate manufacturing processes when disposed of improperly in landfills can be potential sources of chromium exposure as well (Barceloux 1999; Kimbrough et al. 1999).

Chromium is primarily removed from the atmosphere by fallout and precipitation. The residence time of chromium in the atmosphere has not been directly measured, but by using copper as a model, it is expected to be <10 days (Nriagu 1979). The arithmetic mean concentrations of total chromium in the ambient air in United States, urban, suburban, and rural areas monitored during 1977–1984 ranged from

Figure 6-1. Frequency of NPL Sites with Chromium Contamination



5 to 525 ng/m^3, with the vast majority of samples <100 ng/m^3 (EPA 1984a, 1990b). Ambient air in the United States usually contains very little chromium; at most measuring stations, the concentration was <300 ng/m^3 and median levels were <20 ng/m^3 As a result of smoking, indoor air contaminated with chromium can be 10–400 times greater than outdoor air concentrations (WHO 2003).

Chromium in the aquatic phase occurs in the soluble state or as suspended solids adsorbed onto clayish materials, organics, or iron oxides. Most of the soluble chromium is present as chromium(VI) or as soluble chromium(III) complexes and generally accounts for a small percentage of the total. Soluble chromium(VI) may persist in some bodies of water, but will eventually be reduced to chromium(III) by organic matter or other reducing agents in water (Cary 1982; EPA 1984a; Lide 1998). The residence times of chromium (total) in lake water range from 4.6 to 18 years, with the majority of the chromium in lakes and rivers ultimately deposited in the sediments (Schmidt and Andren 1984). In the United States, chromium concentrations are up to 84 µg/L in surface water and 0.2–1 µg/L in rainwater (WHO 2003). Most drinking water supplies in the United States contain <5µg/L of chromium (WHO 2003). In ocean water, the mean chromium concentration is 0.3 µg/L (Cary 1982). In the United States, the groundwater concentration of chromium is generally low, with measurements in the range of 2–10 µg/L in shallow groundwater; levels as high as 50 µg/L have been reported in some supplies (WHO 2003).

Total chromium concentrations in U.S. soils range from 1 to 2,000 mg/kg, with a mean of 37.0 mg/kg (USGS 1984). Chromium(III) in soil is mostly present as insoluble carbonate and oxide of chromium(III); therefore, it will not be mobile in soil. The solubility of chromium(III) in soil and its mobility may increase due to the formation of soluble complexes with organic matter in soil, with a lower soil pH potentially facilitating complexation (Avudainayagam et al. 2003). Chromium has a low mobility for translocation from roots to the aboveground parts of plants (Calder 1988; Cary 1982; EPA 1984a, 1985a; King 1988; Stackhouse and Benson 1989).

A common area for exposure to chromium is from food sources. The typical chromium levels in most foods range from <10 to 1300 µg/kg, with the highest concentrations being found in meat, fish, fruits, and vegetables (WHO 2003). The general population is exposed to chromium by inhaling air, drinking water, or eating food or food supplements that contain chromium. However, the primary source of exposure for non-occupational workers to chromium comes from food sources, although drinking water can be a source of exposure when the levels are >25 µg/L (WHO 2003).

Dermal exposure to chromium may also occur during the use of consumer products that contain chromium, such as wood treated with copper dichromate or chromated copper arsenate and leather tanned with chromic sulfate. In addition, people who reside in the vicinity of chromium waste disposal sites and chromium manufacturing and processing plants have a greater probability of elevated chromium exposure (Pellerin and Booker 2000).

Exposure to chromium for occupational groups can be two orders of magnitude higher than the exposure to the general population (Hemminki and Vainio 1984). Occupational exposure to chromium occurs mainly from chromate production, stainless steel production and welding, chrome plating, production of ferrochrome alloys, chrome pigment production and user industries, and from working in tanning industries (Pellerin and Booker 2000; Stern 1982)

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 337,330 pounds of chromium to the atmosphere from 938 domestic manufacturing and processing facilities in 2006, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). Estimated releases of 490,546 pounds of chromium compounds to the atmosphere from 1,521 domestic manufacturing and processing facilities in

2006, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). These releases are summarized in Tables 6-1 and 6-2.

Total chromium has been identified in air samples at 48 of 1,699 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

Continental dust flux is the main natural source of chromium in the atmosphere; volcanic dust and gas flux are minor natural sources of chromium in the atmosphere (Fishbein 1981). Chromium is released into the atmosphere mainly by anthropogenic stationary point sources, including industrial, commercial, and residential fuel combustion, *via* the combustion of natural gas, oil, and coal (Kimbrough et al. 1999; Pacyn and Pacyn 2001; Seigneur and Constantinous 1995). Other important anthropogenic stationary point sources of chromium emission to the atmosphere are metal industries, such as chrome plating and steel production (EPA 1990b; Johnson et al. 2006; Pacyn and Pacyn 2001). Approximately one-third of the atmospheric releases of chromium are believed to be in the hexavalent form, chromium(VI) (Johnson et al. 2006). Other potentially small sources of atmospheric chromium emission are cement-producing plants (cement contains chromium), the wearing down of asbestos brake linings that contain chromium, incineration of municipal refuse and sewage sludge, and emission from chromium-based automotive catalytic converters. Emissions from cooling towers that previously used chromate chemicals as rust inhibitors are also atmospheric sources of chromium (EPA 1984b, 1990b; Fishbein 1981).

6.2.2 Water

Estimated releases of 114,852 pounds of chromium to surface water from 938 domestic manufacturing and processing facilities in 2006, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). Estimated releases of 574,728 pounds of chromium compounds to surface water from 1,521 domestic manufacturing and processing facilities in 2006, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008).

Total chromium has been identified in surface water and groundwater samples at 427 of 1,699 and 813 of 1,699 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Chromium[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	0	0	21,000	22,000	0	43,000	0	43,000
AL	20	4,558	298	0	52,862	185,896	7,667	235,947	243,614
AR	12	5,637	269	0	13,686	0	5,644	13,948	19,592
AZ	12	163,323	32	0	532,831	11,705	688,637	19,253	707,891
CA	39	1,430	493	0	79,064	6,434	46,152	41,270	87,422
CO	6	21	27	0	32,156	27,070	32,039	27,235	59,274
CT	13	139	1,617	0	47,929	14,315	194	63,806	64,000
DE	2	5	0	0	364	0	5	364	369
FL	15	1,955	59	0	134,519	722	48,148	89,107	137,255
GA	20	1,765	372	0	57,841	2,012	7,127	54,863	61,990
IA	23	4,049	709	0	38,226	92,627	4,476	131,135	135,611
ID	2	56	0	0	334,455	0	334,511	0	334,511
IL	48	5,578	21,374	0	77,246	16,042	5,964	114,277	120,241
IN	57	15,780	5,443	0	2,043,519	85,506	17,947	2,132,301	2,150,248
KS	11	1,895	1,013	0	3,173	4,800	2,370	8,511	10,881
KY	30	8,287	1,255	0	141,687	15,575	9,129	157,674	166,803
LA	19	2,455	115	0	17,611	5	4,985	15,200	20,185
MA	21	1,765	413	0	11,206	21,137	4,000	30,522	34,522
MD	1	258	15	0	0	250	258	265	523
ME	5	144	1,123	0	102	405	154	1,620	1,774
MI	37	12,336	1,149	0	90,611	10,492	13,929	100,658	114,587
MN	8	1,758	54	0	5,866	1	1,758	5,921	7,679
MO	24	7,789	5,731	0	9,668	559	8,312	15,435	23,747
MS	12	7,045	527	0	20,851	250	7,067	21,607	28,673
MT	2	32	0	0	687,248	0	687,280	0	687,280
NC	22	1,199	123	0	19,368	68,337	1,306	87,722	89,028
ND	2	22	6	0	4,953	0	24	4,957	4,981
NE	7	1,072	517	0	74,072	2,450	1,072	77,039	78,111
NH	3	90	8	0	253	18,567	90	18,829	18,919
NJ	8	790	20	0	14,411	0	793	14,428	15,221
NM	2	15	0	0	218,200	0	218,215	0	218,215
NV	9	985	241	0	333,614	930	332,702	3,067	335,769
NY	30	3,591	3,831	0	126,761	22,484	3,782	152,884	156,667
OH	90	12,810	11,949	69	663,116	215,357	398,183	505,118	903,301
OK	16	3,742	920	0	24,379	255	4,006	25,290	29,296
OR	8	1,811	69	0	138,906	4	134,460	6,330	140,790

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Chromium[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
PA	87	17,076	3,949	0	1,021,579	76,723	69,470	1,049,856	1,119,326
PR	2	11,148	0	0	5	0	11,148	5	11,153
RI	2	6	250	0	0	32	6	282	287
SC	22	4,725	524	0	251,022	3,488	6,185	253,573	259,759
SD	5	79	0	0	16,948	0	16,579	448	17,027
TN	21	3,305	1,433	0	122,693	7,882	106,296	29,017	135,313
TX	50	8,436	25,278	467,512	446,753	1,922	900,179	49,722	949,901
UT	6	583	14	0	67,972	1,189	21,198	48,560	69,757
VA	11	553	983	0	67,637	2,706	1,054	70,825	71,878
VT	2	23	15	0	0	3,229	23	3,244	3,267
WA	12	6,355	18,695	0	32,792	14,277	7,647	64,472	72,119
WI	74	10,761	3,927	0	896,104	28,906	12,125	927,573	939,698
WV	5	25	5	0	26,059	251	19,025	7,315	26,340
WY	2	69	8	0	28,658	250	28,477	508	28,985
Total	938	337,330	114,852	488,581	9,050,976	965,042	4,274,796	6,681,985	10,956,781

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI06 2008 (Data are from 2006)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Chromium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	3	5	2	0	1,319,096	0	1,319,103	0	1,319,103
AL	47	13,993	3,753	0	1,286,925	130,962	1,209,640	225,993	1,435,633
AR	26	2,962	1,237	0	52,072	196,825	43,413	209,683	253,096
AZ	19	3,337	1,848	0	2,744,366	11,427	2,742,448	18,530	2,760,978
CA	59	1,521	43,301	1,467	368,099	109,292	269,108	254,573	523,681
CO	12	550	3	0	68,120	309	45,180	23,802	68,982
CT	13	886	1,309	0	14,000	52,417	949	67,664	68,613
DE	9	2,273	825	0	228,879	31,033	75,776	187,234	263,010
DL	37	4,736	537	0	579,255	16,676	515,478	85,726	601,204
GA	47	8,471	3,549	0	779,139	9,673	752,026	48,806	800,832
HI	1	0	0	0	0	0	0	0	0
IA	15	5,283	1,841	0	183,140	20,675	46,619	164,320	210,938
ID	1	3,330	5	0	435,548	0	438,883	0	438,883
IL	93	8,438	37,556	1,458	2,105,214	267,923	667,536	1,753,052	2,420,589
IN	92	60,518	169,387	1,900	2,947,399	362,957	1,521,315	2,020,847	3,542,162
KS	23	52,599	2,923	250	312,827	201,641	138,199	432,041	570,240
KY	48	37,387	7,866	0	842,740	106,458	737,981	256,469	994,451
LA	19	1,862	1,192	0	225,541	25,554	153,523	100,626	254,149
MA	13	802	34	0	123,335	18,418	30,059	112,530	142,589
MD	23	3,519	1,247	5	117,989	175,703	75,846	222,617	298,463
ME	6	26	45,771	0	39,978	20,486	486	105,775	106,261
MI	83	12,043	19,271	14,202	550,023	105,809	269,032	432,316	701,349
MN	24	1,680	32,504	0	120,801	75,465	81,013	149,438	230,451
MO	30	4,152	774	0	384,845	20,519	114,340	295,950	410,290
MS	25	2,349	1,146	844,400	960,595	284,408	1,797,876	295,022	2,092,898
MT	7	3,172	0	0	307,563	660	200,490	110,904	311,394
NC	47	13,844	2,000	0	1,478,427	198,532	1,434,308	258,495	1,692,803
ND	7	4,833	243	0	328,820	1,587	151,221	184,262	335,483
NE	12	4,333	3,817	0	106,858	6,997	87,413	34,592	122,005
NH	3	56	0	0	2,200	2	1,856	402	2,258
NJ	21	2,543	3,178	0	70,282	51,995	12,637	115,360	127,998
NM	4	987	140	0	193,622	0	194,369	380	194,749
NV	9	406	350	0	3,139,144	0	3,139,886	14	3,139,900
NY	31	3,873	1,160	0	92,555	132,591	72,200	157,979	230,179
OH	115	36,176	48,506	1,395,849	3,242,604	2,760,101	2,877,140	4,606,096	7,483,236
OK	18	19,020	714	11,502	463,558	10,538	439,890	65,442	505,332
OR	20	713	154	0	233,263	2,733	198,714	38,149	236,863

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Chromium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
PA	119	81,454	81,764	0	2,869,224	613,481	1,267,287	2,378,635	3,645,922
PR	5	560	0	0	179	0	560	179	739
RI	4	82	5	0	375	0	87	375	462
SC	33	7,058	13,395	0	767,121	27,752	190,802	624,524	815,326
SD	2	0	0	0	0	0	0	0	0
TN	47	6,027	17,121	0	2,499,080	4,200	2,039,524	486,903	2,526,428
TX	107	30,761	5,206	24,558	1,448,331	109,977	741,400	877,432	1,618,832
UT	16	2,954	567	0	2,137,746	32,207	1,911,981	261,493	2,173,474
VA	25	2,393	2,801	0	282,803	4,409	253,251	39,155	292,406
VT	1	0	0	0	250	0	0	250	250
WA	15	521	791	0	183,135	29,607	165,742	48,312	214,053
WI	52	5,014	5,557	0	402,601	104,162	8,132	509,202	517,334
WV	27	27,051	9,245	0	1,303,237	57,066	864,358	532,241	1,396,599
WY	6	3,994	135	0	117,102	0	121,231	0	121,231
Total	1521	490,546	574,728	2,295,591	38,460,006	6,393,229	29,420,309	18,793,790	48,214,098

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI06 2008 (Data are from 2006)

On a worldwide basis, the major chromium source in aquatic ecosystems is domestic waste water effluents (32.2% of the total) (Barceloux 1999). The other major sources are metal manufacturing (25.6%), ocean dumping of sewage (13.2%), chemical manufacturing (9.3%), smelting and refining of nonferrous metals (8.1%), and atmospheric fallout (6.4%) (Nriagu and Pacyna 1988). Annual anthropogenic input of chromium into water has been estimated to exceed anthropogenic input into the atmosphere (Nriagu and Pacyna 1988). However, land erosion, a natural source of chromium in water, was not included in the Nriagu and Pacyna (1988) estimation of chromium contributions to the aquatic environment.

6.2.3 Soil

Estimated releases of 9,050,976 pounds of chromium to soils from 938 domestic manufacturing and processing facilities in 2006, accounted for about 82% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). An additional 965,042 pounds of chromium were transferred to waste broker for disposal. Estimated releases of 38,460,006 pounds of chromium compounds to soils from 1,521 domestic manufacturing and processing facilities in 2006, accounted for about 80% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). An additional 1,131,559 million pounds, constituting about 3.4% of the total environmental emissions, were released ***via*** underground injection (TRI06 2008). An additional 6,393,229 pounds were transferred to waste broker for disposal. These releases are summarized in Tables 6-1 and 6-2.

Total chromium has been identified in soil and sediment samples at 696 of 1,699 and 471 of 1,699 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

On a worldwide basis, the disposal of commercial products that contain chromium may be the largest contributor, accounting for 51% of the total chromium released to soil (Nriagu and Pacyna 1988). Other significant sources of chromium release into soil include the disposal of coal fly ash and bottom fly ash from electric utilities and other industries (33.1%), agricultural and food wastes (5.3%), animal wastes (3.9%), and atmospheric fallout (2.4%) (Nriagu and Pacyna 1988). Solid wastes from metal manufacturing constituted <0.2% to the overall chromium release in soil. However, the amount of chromium in sludge or residue that is disposed of in landfills by manufacturing and user industries that

treat chromate wastes in ponds and lagoons is not included in the estimation by Nriagu and Pacyna (1988).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Chromium is present in the atmosphere primarily in particulate form; naturally occurring gaseous forms of chromium are rare (Cary 1982; Kimbrough et al. 1999; Seigneur and Constantinous 1995). The transport and partitioning of particulate matter in the atmosphere depends largely on particle size and density. Atmospheric particulate matter is deposited on land and water via wet and dry deposition. Wet, dry, and total deposition rates of chromium and several other trace metals in remote, rural and urban areas were summarized by Schroeder et al. (1987). Deposition rates tended to be highest in urban areas that had greater atmospheric levels of chromium as compared to rural and remote locations. The rates of wet and dry deposition are dependent upon several factors, including particle and aerosol size distribution (Kimbrough et al. 1999). The mass mean aerodynamic diameter (MMAD) of chromium aerosols or particulates emitted from several industrial sources are $\leq$10 µm and it has been estimated that chromium-containing particulates emitted from these industrial sources can remain airborne for 7–10 days and are subject to long-range transport (Kimbrough et al. 1999). Based on a troposphere to stratosphere turnover time of 30 years (EPA 1979), atmospheric particles with a residence time of <10 days are not expected to transport from the troposphere to the stratosphere and there are no data in the reviewed literature indicating that chromium particles are transported from the troposphere to the stratosphere (Pacyna and Ottar 1985).

Since chromium compounds cannot volatilize from water, transport of chromium from water to the atmosphere is not likely, except by transport in windblown sea sprays. Most of the chromium released into water will ultimately be deposited in the sediment. A very small percentage of chromium in the water column is present in both soluble and insoluble forms. In the aquatic phase, chromium(III) occurs mostly as suspended solids adsorbed onto clayish materials, organics, or iron oxide (Fe_2O_3) present in water. Approximately 10.5–12.6% of chromium in the aquatic phase of the Amazon and Yukon Rivers was in solution, the rest being present in the suspended solid phase (Cary 1982; King 1988). The ratio of chromium in suspended solids to dissolved form in an organic-rich river in Brazil was 2.1 (Malm et al. 1988).

The bioconcentration factor (BCF) for chromium(VI) in rainbow trout (*Salmo gairdneri*) is 1. In bottom-feeder bivalves, such as the oyster (*Crassostrea virginica*), blue mussel (*Mytilus edulis*), and soft shell clam (*Mya arenaria*), the BCF values for chromium(III) and chromium(VI) range from 86 to 192 (EPA 1980, 1984a; Fishbein 1981; Schmidt and Andren 1984). The bioavailability of chromium(III) to freshwater invertebrates (*Daphnia pulex*) decreased with the addition of humic acid (Ramelow et al. 1989). This decrease in bioavailability was attributed to lower availability of the free form of the metal due to its complexation with humic acid. Based on this information, chromium is not expected to biomagnify in the aquatic food chain. Although higher concentrations of chromium have been reported in plants growing in high chromium-containing soils (e.g., soil near ore deposits or chromium-emitting industries and soil fertilized by sewage sludge) compared with plants growing in normal soils, most of the increased uptake in plants is retained in roots, and only a small fraction is translocated in the aboveground part of edible plants (Cary 1982; WHO 1988). Therefore, bioaccumulation of chromium from soil to aboveground parts of plants is unlikely (Petruzzelli et al. 1987). There is no indication of biomagnification of chromium along the terrestrial food chain (soil-plant-animal) (Cary 1982).

The mobility of chromium in soil is dependent upon the speciation of chromium, which is a function of redox potential and the pH of the soil. In most soils, chromium will be present predominantly in the chromium(III) oxidation state. This form has very low solubility and low reactivity, resulting in low mobility in the environment (Barnhart 1997; Jardine et al. 1999; Robson 2003). Under oxidizing conditions, chromium(VI) may be present in soil as CrO_4^{-2} and $HCrO_4^-$ (James et al. 1997). In this form, chromium is relatively soluble and mobile. A leachability study comparing the mobility of several metals, including chromium, in soil demonstrated that chromium had the least mobility of all of the metals studied (Sahuquillo et al. 2003). These results support previous data finding that chromium is not very mobile in soil, especially in the trivalent oxidation state (Balasoiu et al. 2001; Jardine et al. 1999; Lin et al. 1996; Robson 2003). These results are further supported by a leachability investigation in which chromium mobility was studied for a period of 4 years in a sandy loam (Sheppard and Thibault 1991). The vertical migration pattern of chromium in this soil indicated that after an initial period of mobility, chromium forms insoluble complexes and little leaching is observed. Chromium present as insoluble oxide, $Cr_2O_3 \cdot nH_2O$, exhibited limited mobility in soil (Rifkin et al. 2004). Flooding of soils and the subsequent anaerobic decomposition of plant detritus matters may increase the mobilization of chromium(III) in soils due to formation of soluble complexes (Stackhouse and Benson 1989). This complexation may be facilitated by a lower soil pH.

A smaller percentage of total chromium in soil exists as soluble chromium(VI) and chromium(III) complexes, which are more mobile in soil. Chromium that is irreversibly sorbed onto soil (e.g., in the interstitial lattice of geothite, FeOOH) will not be bioavailable to plants and animals under any condition. Organic matter in soil is expected to convert soluble chromate, chromium(VI), to insoluble chromium(III) oxide, Cr_2O_3 (Calder 1988). Surface runoff from soil can transport both soluble and bulk precipitate of chromium to surface water. Soluble and unadsorbed chromium(VI) and chromium(III) complexes in soil may leach into groundwater. The leachability of chromium(VI) in the soil increases as the pH of the soil increases. On the other hand, lower pH present in acid rain may facilitate leaching of acid-soluble chromium(III) complexes and chromium(VI) compounds in soil. Chromium has a low mobility for translocation from roots to aboveground parts of plants (Cary 1982). However, depending on the geographical areas where the plants are grown, the concentration of chromium in aerial parts of certain plants may differ by a factor of 2–3 (Cary 1982).

6.3.2 Transformation and Degradation

6.3.2.1 Air

In the atmosphere, chromium(VI) may be reduced to chromium(III) at a significant rate by vanadium (V^{2+}, V^{3+}, and VO^{2+}), Fe^{2+}, HSO^{3-}, and As^{3+} (EPA 1987b; Kimbrough et al. 1999). Conversely, chromium(III), if present as a salt other than Cr_2O_3, may be oxidized to chromium(VI) in the atmosphere in the presence of at least 1% manganese oxide (EPA 1990b). The estimated atmospheric half-life for chromium(VI) reduction to chromium(III) was reported in the range of 16 hours to about 5 days (Kimbrough et al. 1999).

6.3.2.2 Water

The reduction of chromium(VI) to chromium(III) and the oxidation of chromium(III) to chromium(VI) in water has been investigated extensively. Reduction of chromium(VI) to chromium(III) can occur under suitable conditions in the aqueous environment, if an appropriate reducing agent is available. The most significant reducing agents present in aqueous systems include (in order of decreasing reduction ability) organic matter, hydrogen sulfide, sulfur, iron sulfide, ammonium, and nitrate (Kimbrough et al. 1999). The reduction of chromium(VI) by S^{-2} or Fe^{+2} ions under anaerobic conditions occurs rapidly, with the reduction half-life ranging from instantaneous to a few days (Seigneur and Constantinous 1995). However, the reduction of chromium(VI) by organic sediments and soils was much slower and depended on the type and amount of organic material and on the redox condition of the water. The reduction half-

life of chromium(VI) in water with soil and sediment ranged from 4 to 140 days, with the reaction typically occurring faster under anaerobic rather than aerobic conditions (Saleh et al. 1989). Generally, the reduction of chromium(VI) to chromium(III) is also favored under acidic conditions (Kimbrough et al. 1999).

Oxidation of chromium(III) to chromium(VI) can also occur in the aqueous environment, depending on several factors. Although oxygen is known to oxidize chromium(III) to chromium(VI), dissolved oxygen by itself in natural waters did not cause any measurable oxidation of chromium(III) to chromium(VI) over a period of 128 days (Saleh et al. 1989). When chromium(III) was added to lake water, a slow oxidation of chromium(III) to chromium(VI) occurred, corresponding to an oxidation half-life of nine years. Addition of 50 mg/L manganese oxide accelerated the process, decreasing the oxidation half-life to approximately 2 years (Saleh et al. 1989). The oxidation of chromium(III) to chromium(VI) during chlorination of water was highest in the pH range of 5.5–6.0 (Saleh et al. 1989). However, the process would rarely occur during chlorination of drinking water because of the low concentrations of chromium(III) in these waters, and the presence of naturally occurring organics that may protect chromium(III) from oxidation, either by forming strong complexes with chromium(III) or by acting as a reducing agent to free available chlorine (EPA 1988c). In chromium(III)-contaminated waste waters having pH ranges of 5–7, chlorination may convert chromium(III) to chromium(VI) in the absence of chromium(III)-complexing and free chlorine reducing agents (EPA 1988c).

Chromium speciation in groundwater also depends on the redox potential and pH conditions in the aquifer. Chromium(VI) predominates under highly oxidizing conditions; whereas chromium(III) predominates under reducing conditions. Oxidizing conditions are generally found in shallow, oxygenated aquifers, and reducing conditions generally exist in deeper, anaerobic groundwaters. In natural groundwater, the pH is typically 6–8, and CrO_4^{-2} is the predominant species of chromium in the hexavalent oxidation state, while $Cr(OH)_2^{+1}$ will be the dominant species in the trivalent oxidation state. This species and other chromium(III) species will predominate in more acidic pH; $Cr(OH)_3$ and $Cr(OH)_4^{-1}$ predominate in more alkaline waters (Calder 1988).

6.3.2.3 Sediment and Soil

The fate of chromium in soil is greatly dependent upon the speciation of chromium, which is a function of redox potential and the pH of the soil. In most soils, chromium will be present predominantly in the chromium(III) state. This form has very low solubility and low reactivity resulting in low mobility in the

environment and low toxicity in living organisms (Ashley et al. 2003; Barnhart 1997; EPA 1994b). Under oxidizing conditions, chromium(VI) may be present in soil as CrO_4^{-2} and $HCrO_4^-$ (James et al. 1997). In this form, chromium is relatively soluble, mobile, and toxic to living organisms. In deeper soil where anaerobic conditions exist, chromium(VI) will be reduced to chromium(III) by S^{-2} and Fe^{+2} present in soil. The reduction of chromium(VI) to chromium(III) is possible in aerobic soils that contain appropriate organic energy sources to carry out the redox reaction, with the reduction of chromium(VI) to chromium(III) facilitated by low pH (Cary 1982; EPA 1990b; Saleh et al. 1989).

The oxidation of chromium(III) to chromium(VI) in soil is facilitated by the presence of organic substances, oxygen, manganese dioxide, moisture, and the elevated temperatures in surface soil that result from brush fires (Calder 1988; Cary 1982). Organic forms of chromium(III) (e.g., humic acid complexes) are more easily oxidized than insoluble oxides. However, oxidation of chromium(III) to chromium(VI) was not observed in soil under conditions of maximum aeration and a maximum pH of 7.3 (Bartlett and Kimble 1976). It was later reported that soluble chromium(III) in soil can be partly oxidized to chromium(VI) by manganese dioxide in soil, and the process is enhanced at pH values >6 (Bartlett 1991). Because most chromium(III) in soil is immobilized due to adsorption and complexation with soil materials, the barrier to this oxidation process is the lack of availability of mobile chromium(III) to immobile manganese dioxide in soil surfaces. Due to this lack of availability of mobile chromium(III) to manganese dioxide surfaces, a large portion of chromium in soil will not be oxidized to chromium(VI), even in the presence of manganese dioxide and favorable pH conditions (Bartlett 1991; James et al. 1997).

The microbial reduction of chromium(VI) to chromium(III) has been discussed as a possible remediation technique in heavily contaminated environmental media or wastes (Chen and Hao 1998; EPA 1994b). Factors affecting the microbial reduction of chromium(VI) to chromium(III) include biomass concentration, initial chromium(VI) concentration, temperature, pH, carbon source, oxidation-reduction potential, and the presence of both oxyanions and metal cations. Although high levels of chromium(VI) are toxic to most microbes, several resistant bacterial species have been identified that could ultimately be employed in remediation strategies (Chen and Hao 1998; EPA 1994b). Elemental iron, sodium sulfite, sodium hydrosulfite, sodium bisulfite, sodium metabisulfite sulfur dioxide, and certain organic compounds such as hydroquinone have also been shown to reduce chromium(VI) to chromium(III) and have been discussed as possible remediation techniques in heavily contaminated soils (Higgins et al. 1997; James et al. 1997). The limitations and efficacy of these and all remediation techniques are dependent upon the ease in which the reducing agents are incorporated into the contaminated soils.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to chromium depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of chromium in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on chromium levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring chromium in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Levels of total chromium in the ambient air in U.S. urban and nonurban areas during 1977–1984 are reported in EPA's National Aerometric Data Bank (EPA 1984a, 1990b). According to this databank, the arithmetic mean total chromium concentrations from a total of 2,106 monitoring stations ranged from 5 to 525 ng/m^3. The two locations that showed the highest total arithmetic mean chromium concentrations were in Steubenville, Ohio, in 1977 (525 ng/m^3) and in Baltimore, Maryland, in 1980 (226 ng/m^3) (EPA 1990b). Arithmetic mean total chromium concentrations in only 8 of 173 sites monitored in 1984 were >100 ng/m^3 (EPA 1990b).

An indoor/outdoor air study was conducted in southwestern Ontario to measure levels of chromium(VI) and the size fraction of chromium(VI). Indoor and outdoor samples were taken from 57 homes during the summer months of 1993. The concentrations were 0.1–0.6 ng/m^3 indoors (geometric mean 0.2 ng/m^3) and were 0.10–1.6 ng/m^3 outdoors (geometric mean 0.55 ng/m^3). The indoor concentrations were less than half of the outdoor concentrations. Analysis of airborne chromium(VI) particles showed that they were inhalable in size (Bell and Hipfner 1997). A study measured the levels of chromium(VI) and total chromium in the ambient air in Hudson County, New Jersey. The concentrations of chromium(VI) in the indoor air of residences in Hudson County in 1990 ranged from 0.38 to 3,000 ng/m^3, with a mean of 1.2 ng/m^3 (Falerios et al. 1992).

Another study analyzed the relationship between soil levels of chromium and chromium content of the atmosphere. An indoor/outdoor study was conducted at 25 industrial sites in Hudson County, New Jersey to analyze soils containing chromite ore processing residues. The industrial sites include industrial, manufacturing, trucking, and warehouse facilities. The study found industrial indoor chromium(VI) and

total chromium concentrations to be 0.23–11 and 4.1–130 ng/m^3 and industrial outdoor chromium(VI) and total chromium concentrations to be 0.013–15.3 and 1.9–84.5 ng/m^3. The results of this study found that higher levels of chromium(VI) in soil do not necessarily result in higher levels of chromium(VI) in air (Finley et al. 1993). The mean concentration of total chromium at the same sites was 7.1 ng/m^3, with a concentration range of 3.7–12 ng/m^3. Monitoring data in Hudson County, New Jersey has shown a background chromium(VI) concentration of 0.2–3.8 ng/m^3 with a mean concentration of 1.2 ng/m^3 (Scott et al. 1997a). The airborne total chromium concentration range was 1.5–10 ng/m^3 with a mean concentration of 4.5 ng/m^3 (Scott et al. 1997a). The mean airborne chromium(VI) and total chromium concentrations in the indoor air of industrial sites in Hudson County, New Jersey, contaminated by chromite ore-processing residue were 3 ng/m^3 (range, 0.23–11 ng/m^3) and 23 ng/m^3 (range, 4.11–130 ng/m^3), respectively. The mean airborne chromium(VI) and total chromium concentrations in outdoor air for the same sites were 9.9 ng/m^3 (range, 0.13–110 ng/m^3) and 37 ng/m^3 (range, 1.9–250 ng/m^3), respectively (Falerios et al. 1992).

An air dispersion model was developed which accurately estimated chromium(VI) concentrations at two of these industrial sites in Hudson County, New Jersey (Scott et al. 1997b). The background corrected airborne concentrations in ng/m^3 for seven sampling dates are reported as measured (modeled values in parentheses): 0.0 (0.41); 6.2 (7.7); 0.9 (1.7); 2.8 (2.7); 0.0 (0.08); 0.3 (0.1); and 1.2 (0.12). The estimated percent levels of chromium(III) and chromium(VI) in the U.S. atmosphere from anthropogenic sources are given in Table 6-3 (EPA 1990b). Fly ash from a coal-fired power plant contained 1.4–6.1 mg/kg chromium(VI) (Stern et al. 1984). In a field study to assess inhalation exposure to chromium during showering and bathing activities, the average chromium(VI) concentration in airborne aerosols ranged from 87 to 324 ng/m^3 when water concentrations of 0.89–11.5 mg/L of chromium(VI) were used in a standard house shower (Finley et al. 1996a).

The concentrations of atmospheric chromium in remote areas range from 0.005 to 2.6 ng/m^3 (Barrie and Hoff 1985; Cary 1982; Schroeder et al. 1987; Sheridan and Zoller 1989). Saltzman et al. (1985) compared the levels of atmospheric chromium at 59 sites in U.S. cities during 1968–1971 with data from EPA's National Aerometric Data Bank file for 1975–1983. They concluded that atmospheric chromium levels may have declined in the early 1980s from the levels detected in the 1960s and 1970s.

Table 6-3. Estimates of U.S. Atmospheric Chromium Emissions from Anthropogenic Sources

Source category	Estimated number of sources	Chromium emissions (metric tons/year)	Estimated hexavalent chromium (percent)
Combustion of coal and oil	Many	1,723	0.2
Chromium chemical manufacturing	2	18	67
Chemical manufacturing cooling towers	2,039	43	100
Petroleum refining cooling towers	475	32	100
Specialty/steel production	18	103	2.2
Primary metal cooling towers	224	8	100
Chrome plating	4,000	700	~100
Comfort cooling towers	38,000	7.2–206	100
Textile manufacturing cooling towers	51	0.1	100
Refractory production	10	24	1.3
Ferrochromium production	2	16	5.4
Sewage sludge incineration	133	13	<0.1
Tobacco cooling towers	16	0.2	100
Utility industry cooling towers	6	1.0	100
Chrome ore refining	6	4.8	<0.1
Tire and rubber cooling towers	40	0.2	100
Glass manufacturing cooling towers	3	0.01	100
Cement production	145	3	0.2
Municipal refuse incineration	95	2.5	0.3
National total			2,700–2,900

Source: EPA 1990b

6.4.2 Water

Chromium concentrations in U.S. river water usually range from <1 to 30 μg/L (EPA 1984a; Malm et al. 1988; Ramelow et al. 1987), with a median value of 10 μg/L (Eckel and Jacob 1988; Smith et al. 1987). Chromium concentrations in lake water generally do not exceed 5 μg/L (Borg 1987; Cary 1982), with higher levels of chromium related to anthropogenic pollution sources. Dissolved chromium concentrations of 0.57–1.30 μg/L were reported in the Delaware River near Marcus Hook and Fieldsboro, Pennsylvania in January 1992, with chromium(III) composing 67% of the total (Riedel and Sanders 1998). In March 1992, these concentrations decreased to 0.03–0.23 μg/L. In general, the concentration of chromium in ocean water is much lower than that in lakes and rivers. The mean chromium concentration in ocean water is 0.3 μg/L, with a range of 0.2–50 μg/L (Cary 1982). The mean concentration of chromium in rainwater is 0.14–0.9 μg/L (Barrie et al. 1987; Dasch and Wolff 1989).

The concentrations of total chromium in groundwater at the Idaho National Engineering Laboratory, where chromate is used as a corrosion inhibitor, ranged from <1 to 280 μg/L (USGS 1989). The water from a village well situated near a waste pond receiving chromate waste in Douglas, Michigan, contained 10,800 μg/L chromium(VI). Similarly, water from a private well adjacent to an aircraft plant in Nassau County, New York, contained 25,000 μg/L chromium(VI), while water from a public well adjacent to another aircraft plant in Bethpage, New York, contained 1,400 μg/L chromium(VI) (Davids and Lieber 1951). In a later study, water from an uncontaminated well in Nassau County, New York, contained an undetectable level of chromium(VI), whereas a contaminated well in the vicinity of a plating plant contained 6,000 μg/L chromium(VI) (Lieber et al. 1964). A high chromium concentration (120 μg/L) was detected in private drinking water wells adjacent to an NPL site in Galena, Kansas (Agency for Toxic Substances and Disease Registry 1990a).

The chromium levels detected in drinking water in an earlier study (1962–1967 survey) may be erroneous due to questionable sampling and analytical methods (see Section 7.1) (EPA 1984a). Total chromium levels in drinking water were reported to range from 0.2 to 35 μg/L (EPA 1984a). Most drinking water supplies in the United States contain <5 μg/L of of total chromium (WHO 2003). The concentration of chromium in household tap water may be higher than supply water due to corrosion of chromium-containing pipes. At a point of maximum contribution from corrosion of the plumbing system, the peak chromium in tap water in Boston, Massachusetts was 15 μg/L (Ohanian 1986). A survey that targeted drinking waters from 115 Canadian municipalities during 1976–1977 reported the median and the range of chromium concentrations to be <2.0 μg/L (detection limit) and <2.0–8.0 μg/L, respectively (Meranger

et al. 1979). A recent monitoring survey of drinking water by the California Department of Public Health found that levels of chromium(VI) were <10 µg/L in 86% (2,003 out of 2,317 sources) of the drinking water sources sampled; however, levels above 50 µg/L were noted in six sources (CDPH 2007). In this survey, a source was defined as those reporting more than a single detection of chromium(VI) and may include both raw and treated sources, distribution systems, blending reservoirs, and other sampled entities. These data did not include agricultural wells, monitoring wells, or more than one representation of the same source (e.g., a source with both raw and treated entries is counted a single source).

6.4.3 Sediment and Soil

The chromium level in soils varies greatly and depends on the composition of the parent rock from which the soils were formed. Basalt and serpentine soils, ultramafic rocks, and phosphorites may contain chromium as high as a few thousand mg/kg (Merian 1984) whereas soils derived from granite or sandstone will have lower concentrations of chromium (Swaine and Mitchell 1960). The concentration range of chromium in 1,319 samples of soils and other surficial materials collected in the conterminous United States was 1–2,000 mg/kg, with a geometric mean of 37 mg/kg (USGS 1984). Chromium concentrations in Canadian soils ranged from 5 to 1,500 mg/kg, with a mean of 43 mg/kg (Cary 1982). In a study with different kinds of soils from 20 diverse sites including old chromite mining sites in Maryland, Pennsylvania, and Virginia, the chromium concentration ranged from 4.9 to 71 mg/kg (Beyer and Cromartie 1987). A polynuclear aromatic hydrocarbon (PAH) soil study was conducted to determine the metal levels in soil at the edge of a busy road that runs through the Aplerbecker Forest in West Germany. Chromium(VI) concentrations of 64 mg/kg were measured, and these concentrations were 2- to 4-fold higher along the road than in the natural forest (Munch 1993). The soil beneath decks treated with chrominated copper arsenate (CCA), a wood preservative, had an average chromium content of 43 mg/kg (Stilwell and Gorny 1997).

Chromium has been detected at a high concentration (43,000 mg/kg) in soil at the Butterworth Landfill site in Grand Rapid City, Michigan, which was a site listed on the NPL (Agency for Toxic Substances and Disease Registry 1990b).

Chromium was detected in sediment obtained from the coastal waters of the eastern U.S. seashore at concentrations of 3.8–130.9 µg/g in 1994 and 0.8–98.1 µg/g in 1995 (Hyland et al. 1998).

6.4.4 Other Environmental Media

The concentration of chromium in the particulate portion of melted snow collected from two urban areas (Toronto and Montreal) of Canada ranged from 100 to 3,500 mg/kg (Landsberger et al. 1983). In the suspended materials and sediment of water bodies, chromium levels ranged from 1 to 500 mg/kg (Byrne and DeLeon 1986; EPA 1984a; Mudroch et al. 1988; Ramelow et al. 1987). The chromium concentration in incinerated sewage sludge ash may be as high as 5,280 mg/kg (EPA 1984a).

Total chromium levels in most fresh foods are extremely low (vegetables [20–50 μg/kg], fruits [20 μg/kg], and grains and cereals [40 μg/kg]) (Fishbein 1984). The chromium levels of various foods are reported in Table 6-4. In a study to find the concentrations of chromium in edible vegetables in Tarragon Province, Spain, the highest levels of chromium were found in radish root and spinach, with a nonsignificant difference between the samples collected in two areas (northern industrial and southern agricultural). The samples ranged in concentration from 0.01 to 0.21 μg/g (industrial) and from 0.01 to 0.22 μg/g (agricultural) (Schuhmacker et al. 1993). Acidic foods that come into contact with stainless steel surfaces during harvesting, processing, or preparation for market are sometimes higher in chromium content because of leaching conditions. Processing, however, removes a large percentage of chromium from foods (e.g., whole-grain bread contains 1,750 μg/kg chromium, but processed white bread contains only 140 μg/kg; and molasses contains 260 μg/kg chromium, but refined sugar contains only 20 μg/kg chromium) (Anderson 1981; EPA 1984a).

Chromium levels in oysters, mussels, clams, and mollusks vary from <0.1 to 6.8 mg/kg (dry weight) (Byrne and DeLeon 1986; Ramelow et al. 1989). Fish and shellfish collected from ocean dump sites off New York City, Delaware Bay, and New Haven, Connecticut, contained <0.3–2.7 mg/kg chromium (wet weight) (Greig and Jones 1976). The chromium concentration in fish sampled from 167 lakes in the northeastern United States was 0.03–1.46 μg/g with a mean concentration of 0.19 μg/g (Yeardley et al. 1998). Higher levels of chromium in forage of meat animals have been reported for plants grown in soils with a high concentration of chromium (see Section 6.3.1). Cigarette tobacco reportedly contains 0.24–14.6 mg/kg chromium, but no estimates were available regarding the chromium levels in inhaled cigarette smoke (Langård and Norseth 1986). Cigarette tobacco grown in the United States contains ≤6.3 mg/kg chromium (IARC 1980).

Cement-producing plants are a potential source of atmospheric chromium. Portland cement contains 41.2 mg/kg chromium (range 27.5–60 mg/kg). Soluble chromium accounts for 4.1 mg/kg (range 1.6–

Table 6-4. Chromium Content in Various U.S. Foods

Sample	Mean concentration (µg/kg)	Reference
Fresh vegetables	30–140	EPA 1984a
Frozen vegetables	230	EPA 1984a
Canned vegetables	230	EPA 1984a
Fresh fruits	90–190	EPA 1984a
Fruits	20	EPA 1984a
Canned fruits	510	EPA 1984a
Dairy products	100	EPA 1984a
Chicken eggs	160–520	Kirpatrick and Coffin 1975
Chicken eggs	60	Kirpatrick and Coffin 1975
Whole fish	50–80	EPA 1984a
Edible portion of fresh fin fish	<100–160	Eisenberg and Topping 1986
Meat and fish	110–230	EPA 1984a
Seafoods	120–470	EPA 1984a
Grains and cereals	40–220	EPA 1984a
Sugar, refined[a]	<20	WHO 1988

[a]Value in Finnish sugar

8.8 mg/kg) of which 2.9 mg/kg (range 0.03–7.8 mg/kg) is chromium(VI) (Fishbein 1981). The wearing down of vehicular brake linings that contain asbestos represents another source of atmospheric chromium. Asbestos may contain ≈1,500 mg/kg of chromium. The introduction of catalytic converters on U.S. automobiles in 1975 in the United States represented an additional source of atmospheric chromium. Catalysts, such as copper chromite, emit $<10^6$ metal-containing condensation nuclei per cubic centimeter in vehicular exhaust, under various operating conditions (Fishbein 1981).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to chromium by inhaling ambient air, ingesting food, and drinking water containing chromium. Home-based exposures can occur to the families of occupational workers in what is known as worker-to-family exposures. Home exposures can also occur through proximity to hazardous waste sites (Pellerin and Booker 2000). A study measured the relationships between chromium in household dust and chromium in the urine of Hudson County, New Jersey residents (Pellerin and Booker 2000). Three major producers of chromium (VI) in the form of chromate were active in the area for over 70 years, and produced over 2 million tons of chromium containing slag waste (Pellerin and Booker 2000). Chromium (VI) levels as high as several hundred parts per million were measured in some of the soil samples extracted from the area (Pellerin and Booker 2000).

Dermal exposure of the general public to chromium can occur from skin contact with consumer products that contain chromium. Some of the consumer products known to contain chromium are certain wood preservatives, cement, cleaning materials, textiles, and leather tanned with chromium (WHO 1988). Both chromium(III) and chromium(VI) are known to penetrate the skin, although chromium(VI) penetrates to a higher degree (Robson 2003). However, no quantitative data for dermal exposure to chromium-containing consumer products were located. Levels of chromium in ambient air (<0.01–0.03 μg/m^3) (Fishbein 1984; Pellerin and Booker 2000) and tap water (<1 μg/L) (Pellerin and Booker 2000) have been used to estimate the daily intake of chromium via inhalation (<0.2–0.6 μg) and tap water (<4 μg). These estimates are based on an air inhalation rate of 20 m^3/day and a drinking water consumption rate of 2 L/day. The daily chromium intake for the U.S. population from consumption of selected diets (diets with 25 and 43% fat) has been estimated to range from 25 to 224 μg with an average of 76 μg (Kumpulainen et al. 1979). The chromium concentrations in tissues and body fluids of the general population are given in Table 6-5.

Table 6-5. Chromium Content in Tissues and Body Fluids of the General Population

Sample	Median or mean	Range	Reference
Serum	0.006 µg/L	0.01–0.17 µg/L	Sunderman et al. 1987
Urine	0.4 µg/L	0.24–1.8 µg/L	Iyengar and Woittiez 1988
Lung	201 µg/kg (wet weight)	28–898 µg/kg (wet weight)	Raithel et al. 1987
Breast milk	0.30 µg/L	0.06–1.56 µg/L	Casey and Hambidge 1984
Hair	0.234 mg/kg	Not available	Takagi et al. 1986
Nail	0.52 mg/kg	No applicable	Takagi et al. 1988

Workers in industries that use chromium can be exposed to concentrations of chromium two orders of magnitude higher than exposure to the general population, and that workers in some 80 different professions may be exposed to chromium (VI) (Hemminki and Vainio 1984; Pellerin and Booker 2000). Occupational exposure to chromium occurs mainly from chromate production, stainless steel production and welding, chromium plating, ferrochrome alloys and chrome pigment production, and working in tanning industries (Ashley et al. 2003). A list of industries that may be sources of chromium exposure is given in Table 6-6. For most occupations, exposure is due to both chromium(III) and chromium(VI) present as soluble and insoluble fractions. However, exceptions include the tanning industry, where exposure is mostly from soluble chromium(III), and the plating industry, where exposure is due to soluble chromium(VI). The typical concentration ranges of airborne chromium(VI) to which workers in these industries were exposed during an average of 5–20 years of employment were: chromate production, 100–500 μg/m^3; stainless steel welding, 50–400 μg/m^3; chromium plating, 5–25 μg/m^3; ferrochrome alloys, 10–140 μg/m^3; and chrome pigment, 60–600 μg/m^3 (Stern 1982). In the tanning industry, except for two bath processes, the typical exposure range due to chromium(III) was 10–50 μg/m^3. A study of chromium (VI) levels of in the air of a chrome plating shop measured concentrations of chromium (VI) in the range of 10–30 μg/m^3 for chrome plating shops with local exhaust (Pellerin and Booker 2000). In plating shops without local exhaust, the levels were much higher, up to 120 μg/m^3 (Pellerin and Booker 2000). In an occupational exposure study of chromium in an aircraft construction factory, airborne samples were collected over a 4-hour period; urinary samples were collected at the beginning (Monday), end (Friday), and after the work shift in order to analyze the absorption of chromium during working hours (Gianello et al. 1998). The air sampling results were 0.02–1.5 mg/m^3, and the urine sampling results were 0.16–7.74 μg/g creatinine. Compared to the ACGIH and BEI-ACGIH Hygiene Standard of 50 μg/m^3, both sets of results indicated a very low risk of exposure. The National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 304,829 workers in the United States were potentially exposed to chromium(VI) (NIOSH 1989). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey only estimates the number of workers potentially exposed to chemicals in the workplace.

In a survey of workers in pigment factories in England that produced strontium and lead chromate, the concentrations of chromium in the whole blood in exposed workers ranged from 3 to 216 μg/L, compared to a level of <1 μg/L for the nonoccupationally exposed population (McAughey et al. 1988). The corresponding concentrations in the urine of exposed workers and the unexposed population were 1.8–575 μg chromium/g creatinine and <0.5 μg chromium/g creatinine, respectively (McAughey et al. 1988).

Table 6-6. Industries that May be Sources of Chromium Exposure

Abrasives manufacturers	Laboratory workers
Acetylene purifiers	Leather finishers
Adhesives workers	Linoleum workers
Aircraft sprayers	Lithographers
Alizarin manufacturers	Magnesium treaters
Alloy manufactures	Match manufacturers
Aluminum anodizers	Metal cleaners
Anodizers	Metal workers
Battery manufacturers	Milk preservers
Biologists	Oil drillers
Blueprint manufacturers	Oil purifiers
Boiler scalers	Painters
Candle manufacturers	Palm-oil bleachers
Cement workers	Paper water proofers
Ceramic workers	Pencil manufacturers
Chemical workers	Perfume manufacturers
Chromate workers	Photoengravers
Chromium-alloy workers	Photographers
Chromium-alum workers	Platinum polishers
Chromium platers	Porcelain decorators
Copper etchers	Pottery frosters
Copper-plate strippers	Pottery glazers
Corrosion-inhibitor workers	Printers
Crayon manufacturers	Railroad engineers
Diesel locomotive repairmen	Refractory-brick manufacturers
Drug manufacturers	Rubber manufacturers
Dye manufacturers	Shingle manufacturers
Dyers	Silk-screen manufacturers
Electroplaters	Smokeless-powder manufacturers
Enamel workers	Soap manufacturers
Explosive manufacturers	Sponge bleachers
Fat purifiers	Steel workers
Fireworks manufacturers	Tanners
Flypaper manufacturers	Textile workers
Furniture polishers	Wallpaper printers
Fur processors	Wax workers
Glass-fibre manufacturers	Welders
Glue manufacturers	Wood-preservative workers
Histology technicians	Wood stainers
Jewelers	

Source: IARC 1990

Other investigators have found a higher lung burden for chromium in occupational groups than in unexposed groups. The median concentration of chromium in the lungs of deceased smelter workers in Sweden was 450 μg/kg (wet weight), compared to a value of 110 μg/kg (wet weight) for rural controls and 199 μg/kg (wet weight) for urban controls (Gerhardsson et al. 1988).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes ingest inappropriate materials (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children living in vicinities where there are chromium waste sites nearby may be exposed to chromium to a greater extent than adults through inhalation of chromium particulates and through contact with contaminated soils. One study has shown that the average concentration of chromium in the urine of children at ages five and younger was significantly higher than in adults residing near sites where chromium waste slag was used as fill material (Fagliano et al. 1997), and the soil levels of a hazardous waste disposal site in New Jersey were measured at levels up to 120 μg/m^3 (Pellerin and Booker 2000). The tendency of young children to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity, is well documented and can result in ingestion of chromium present in soil and dust. Soil may affect the bioavailability of contaminants in several ways, most likely by acting as a competitive sink for the contaminants. In the presence of soil, the contaminants will partition between absorption by the gut and sorption onto the soil particles. If a soil has a longer residence time in the gut than food particles, then sorption may enhance the overall absorption of the contaminant (Sheppard et al. 1995). If the contaminant is irreversibly bound to soil particles, then the contaminant is unlikely to be absorbed in the gastrointestinal tract. Hexavalent chromium exists in soils as a relatively soluble anion

and may be present in bioavailable form, possibly with enhanced absorption due to the presence of the soil itself. In contrast, chromium(III) present in soil is generally not very soluble or mobile under most environmental conditions and is not readily bioavailable (James et al. 1997). Studies discussing the oral absorption of chromium in rats from a soil surface in which 30% of the chromium was in hexavalent form and 70% was in trivalent form suggested that while absorption in animals is quite low, chromium appeared to be better absorbed from soil than from soluble chromate salts (Witmer et al. 1989, 1991). However, less than half of the administered dose of chromium could be accounted for in this study, and in separate experiments with low dosages administered to the rats, the control animals actually had higher concentrations of chromium than the animals that were administered the oral dose. Children may accidently ingest chromium picolinate in households whose members use this product as a dietary supplement unless it is well stored and kept away from children. Small amounts of chromium are used in certain consumer products such as toners in copying machines and printers, but childhood exposure from these sources are expected to be low. Children may also be exposed to chromium from parents' clothing or items removed from the workplace if the parents are employed in a setting where occupational exposure is significant (see Section 6.5). Chromium has been detected in breast milk at concentrations of 0.06–1.56 µg/L (Casey and Hambidge 1984), suggesting that children could be exposed to chromium from breast-feeding mothers. Studies on mice have shown that chromium crosses the placenta and can concentrate in fetal tissue (Danielsson et al. 1982; Saxena et al. 1990a).

A study done on the potential exposure of teenagers to airborne chromium from steel dust in the New York City subway system found significantly higher concentrations of chromium than in home and ambient samples. The conclusion from the study was that the increased concentration was most likely due to steel dust present in the subway system as the source of chromium (Chillrud et al. 2004). Chromium levels in the New York City subway system are greater than ambient levels by approximately two orders of magnitude. Levels observed in the study of chromium ≈84 ng/m^3 are similar to chronic reference guidelines in both Canada and the United States and were 40–100 times the adult range in the estimated 10^{-5} lifetime cancer risk (Chillrud et al. 2004). The reference values for exposure to chromium range from 2 to 100 ng/m^3 (Wu et al. 2001). The study measured total chromium levels, without separating the species of chromium into chromium (III) and chromium (VI). Previous studies have suggested that airborne chromium generated from steel welding have a significant amount of chromium(VI) present, extending the possibility that there is a possibility for chromium(VI) to be present in the steel dust in the New York City subway system as well (Chillrud et al. 2004; Edme et al. 1997).

Another study done on the bones of deceased neonatal humans in Poland found that statistically significant differences in chromium concentrations were observed. In addition, a positive correlation between pairs of metals was observed, specifically between the pairing of chromium and lead. (Baranowski et al. 2002). Bones were chosen to examine, since they are a useful reference in regards to heavy metal exposure and accumulation, and are therefore an accurate measure of chronic exposure.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to chromium (see Section 6.5), there are several groups within the general population that have potentially high exposures (higher-than-background levels) to chromium. Persons using chromium picolinate as a dietary supplement will also be exposed to higher levels of chromium than those not ingesting this product (Anderson 1998b). Like many other products used to promote weight loss or speed metabolism, there is also the potential for overuse of this product by some members of the population in order to achieve more dramatic results (Wasser et al. 1997). People may also be exposed to higher levels of chromium if they use tobacco products, since tobacco contains chromium (IARC 1980).

Workers in industries that use chromium are one segment of the population that is especially at high risk to chromium exposure. Many industrial workers are exposed to chromium(VI) levels in air that exceed the accepted occupational exposure limits (Blade et al. 2007). Occupational exposure from chromate production, stainless steel welding, chromium plating, and ferrochrome and chrome pigment production is especially significant since the exposure from these industries is to chromium(VI). Occupational exposure to chromium(III) compounds may not be as great a concern as exposure to chromium(VI) compounds. Among the general population, residents living near chromate production sites may be exposed to higher levels of chromium(VI) in air. Ambient concentrations as high as 2.5 $\mu g/m^3$ chromium in air were detected in a 1977 sample from Baltimore, Maryland (EPA 1984a). People who live near chromium waste disposal sites and chromium manufacturing and processing plants may be exposed to elevated levels of chromium. The airborne concentrations of chromium(VI) and total chromium in a contaminated site in Hudson County, New Jersey were studied (Falerios et al. 1992). The mean concentrations of both chromium(VI) and total chromium in indoor air of the contaminated site were about three times higher than the mean indoor air concentrations of uncontaminated residential sites in Hudson County. Although the mean concentration of chromium(VI) in outdoor air was much lower than the current occupational exposure limit of 50 $\mu g/m^3$, levels in 10 of 21 samples at the contaminated site exceeded the background urban outdoor chromium(VI) concentration of 4 ng/m^3. Similarly, the total

chromium concentration in 11 of 21 outdoor air samples from the contaminated site exceeded the outdoor mean concentration of 15 ng/m^3 for urban New Jersey. However, recent sampling data from Hudson County, New Jersey have shown that more than two-thirds of previously sampled sites contaminated with chromite ore processing residue did not have statistically significant mean concentrations greater than the background levels (Scott et al. 1997a). These data, as well as the results of a soil dispersion model (Scott et al. 1997b), suggest that heavy vehicular traffic over unpaved soil surfaces containing chromium(VI) are required for high levels of atmospheric chromium(VI) at these sites. Persons using contaminated water for showering and bathing activities may also be exposed via inhalation to potentially high levels of chromium(VI) in airborne aerosols (Finley et al. 1996a). In a field study to simulate daily bathing activity, airborne chromium(VI) concentrations were about 2 orders of magnitude greater than ambient outdoor air concentrations when water concentrations of 5.4 and 11.5 mg/L were used in the shower.

A study was conducted from September to November 1989 to determine the levels of chromium in urine and red blood cells of state employees who worked at a park (with only indirect exposure potential) adjacent to chromium-contaminated sites in Hudson County, New Jersey (Bukowski et al. 1991). The chromium levels in red blood cells and urine of 17 of these employees showed no differences compared to 36 employees who worked at state parks outside Hudson County. The authors concluded that urinary and blood levels of chromium are poor biological markers in gauging low-level environmental exposure to chromium. This study also concluded that chromium levels in blood and urine depended on other confounding variables, such as exercise, past employment in a chromium-exposed occupation, beer drinking, and diabetic status. Other lifestyle (e.g., smoking), dietary, or demographic factors had no measurable effect on blood and urinary chromium. These conclusions are consistent with the results of a study that measured the urinary excretion of chromium following oral ingestion of chromite ore processing residue material for three days (Finley and Paustenbach 1997). These results indicate no statistical difference in mean urinary chromium concentrations in groups of individuals exposed to chromite ore processing residue material versus the control group. High levels of chromium were detected in the urine and hair of individuals living near a chromite ore-processing plant in Mexico (Rosas et al. 1989), which suggests the possibility of using these media as biological markers in gauging long term, high-level environmental exposure to chromium.

Elevated levels of chromium in blood, serum, urine, and other tissues and organs have been observed in patients with cobalt-chromium knee and hip arthroplasts (Coleman et al. 1973; Michel et al. 1987; Sunderman et al. 1989).

The chromium content in cigarette tobacco from the United States has been reported to be 0.24–6.3 mg/kg (IARC 1980), but neither the chemical form nor the amount of chromium in tobacco smoke is known. People who use tobacco products may be exposed to higher-than-normal levels of chromium.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chromium is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chromium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. As seen in Section 4.2, the relevant physical and chemical properties of chromium and its compounds are known (Hartford 1979; NIOSH 2008; Weast 1985) and prediction of environmental fate and transport of chromium in environmental media is possible. However, the physical or chemical forms and the mode by which chromium(III) compounds are incorporated into biological systems are not well characterized. The determination of the solubilities of hexavalent chromium compounds in relevant body fluids (e.g., the solubility of chromates in lung fluid) may also be helpful.

Production, Import/Export, Use, Release, and Disposal. Knowledge of a chemical's production volume is important because it may indicate environmental contamination and human exposure. If a chemical's production volume is high, there is an increased probability of general population exposure via consumer products and environmental sources, such as air, drinking water, and food. Data concerning the production (Hartford 1979; Papp and Lipin 2001; SRI 1997; USGS 2008b), import (USGS 2008b), and use (CMR 1988a, 1988b; EPA 1984a; IARC 1990; Papp and Lipin 2001;

USDI 1988a; USGS 2008b) of commercially significant chromium compounds are available. Chromium is not generally used to process foods for human consumption or added to foods other than diet supplements. Thus, consumer exposure to chromium occurs mostly from natural food sources (Bennett 1986; EPA 1984a; Kumpulainen et al. 1979), but this exposure will increase particularly for people who consume acidic food cooked in stainless steel utensils (Anderson 1981; EPA 1984a). Exposure to chromium occurs to a much lesser extent from products such as toners of photocopying machines, some wood treatment chemicals, and through other chromium-containing consumer products (CMR 1988a, 1988b; EPA 1984a; IARC 1990; USDI 1988a).

As seen in Tables 6-1 and 6-2, the largest amount of chromium from production and user facilities is disposed of on land or transferred to an off-site location. More detailed site-and medium-specific (e.g., air, water, or soil) release data for chromium that is disposed of off-site are necessary to assess the exposure potential to these compounds from different environmental media and sources. There are EPA guidelines regarding the disposal of chromium wastes and OSHA regulations regarding the levels of chromium in workplaces (EPA 1988a; OSHA 1998a).

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2006, became available in May of 2008. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Information is available to permit assessment of the environmental fate and transport of chromium in air (Pacyna and Pacyna 2001; Schroeder et al. 1987; Scott et al. 1997a, 1997b), water (Cary 1982; Comber and Gardner 2003; EPA 1980, 1984a; Fishbein 1981; Schmidt and Andren 1984; WHO 2003) and soil (Ashley et al. 2003; Avudainayagam et al. 2003; Balasoiu et al. 2001; Bartlett 1991; Calder 1988; Cary 1982; Jardine et al. 1999; Rifkin et al. 2004). Chromium is primarily removed from the atmosphere by fallout and precipitation. By analogy with copper, the residence time of chromium in the atmosphere is expected to be <10 days (Nriagu 1979). Most of the chromium in lakes and rivers will ultimately be deposited in the sediments. Chromium in the aquatic phase occurs in the soluble state or as suspended solids adsorbed onto clayish materials, organics, or iron oxides (Cary 1982). Most of the soluble chromium is present as chromium(VI) or as soluble chromium(III) complexes and generally accounts for a small percentage of the total (Cary 1982). Additional data, particularly regarding chromium's nature of speciation, would be useful to fully assess chromium's fate in air. For example, if chromium(III) oxide forms some soluble salt in the air due to speciation, its removal by wet deposition

will be faster. No data regarding the half-life of chromium in the atmosphere or a measure of its persistence are available. In aquatic media, sediment will be the ultimate sink for chromium, although soluble chromates may persist in water for years (Cary 1982; EPA 1984a). Additional data elucidating the nature of speciation of chromium in water and soil would also be desirable and a direct measurement of the chromium residence time in the atmosphere would be useful.

Bioavailability from Environmental Media. The bioavailability of chromium compounds from contaminated air, water, soil, or plant material in the environment has not been adequately studied. Absorption studies of chromium in humans and animals provide information regarding the extent and rate of inhalation (Cavalleri and Minoia 1985; Kiilunen et al. 1983; Langård et al. 1978) and oral exposure (Anderson 1981, 1986; Anderson et al. 1983; Donaldson and Barreras 1966; Randall and Gibson 1987; Suzuki et al. 1984). A sorption study has measured the amount of chromium(VI) when iron particles are present in the water samples; the conclusion was that soluble chromium(VI) present in the water could sorb on to iron particles present in the acidic environment of the stomach, and thus, be less bioavailable (Parks et al. 2004). These available absorption studies indicate that chromium(VI) compounds are generally more readily absorbed from all routes of exposure than are chromium(III) compounds. This is consistent, in part, with the water solubilities of these compounds (Bragt and van Dura 1983). The bioavailability of both forms is greater from inhalation exposure than from ingestion or dermal exposure. The bioavailability of chromium from soil depends upon several factors (Witmer et al. 1989). Factors that may increase the mobility of chromium in soils include the speculated conversion of chromium(III) to chromium(VI), increases in pH, and the complexation of chromium(III) with organic matter from water-soluble complexes. Data on the bioavailability of chromium compounds from actual environmental media and the difference in bioavailability for different media need further development.

Food Chain Bioaccumulation. It is generally believed that chromium does not bioconcentrate in fish (EPA 1980, 1984a; Fishbein 1981; Schmidt and Andren 1984) and there is no indication of biomagnification of chromium along the aquatic food chain (Cary 1982). However, recent skin biopsy data indicate that North Atlantic right whales are exposed to hexavalent chromium and accumulate a range of 4.9–10 μg chromium/g tissue with a mean of 7.1 μg chromium/g tissue (Wise et al. 2008). Some data indicate that chromium has a low mobility for translocation from roots to aboveground parts of plants (Cary 1982; WHO 1988). However, more data regarding the transfer ratio of chromium from soil to plants and biomagnification in terrestrial food chains would be desirable.

Exposure Levels in Environmental Media. The atmospheric total chromium concentration in the United States is typically <10 ng/m^3 in rural areas and 10–30 ng/m^3 in urban areas (Fishbein 1984; WHO 2003). Most drinking water supplies in the United States contain <5 µg/L of chromium (WHO 2003). The chromium level in soils varies greatly and depends on the composition of the parent rock from which the soils were formed. Basalt and serpentine soils, ultramafic rocks, and phosphorites may contain chromium as high as a few thousand mg/kg (Merian 1984), whereas soils derived from granite or sandstone will have lower concentrations of chromium (Swaine and Mitchell 1960). The concentration range of chromium in 1,319 samples of soils and other surficial materials collected in the conterminous United States was 1–2,000 mg/kg, with a geometric mean of 37 mg/kg (USGS 1984). There is a large variation in the available data regarding the levels of chromium in foods (EPA 1984a). Concentrations ranges are 30–230 µg/kg in vegetables, 20–510 µg/kg in fruits, 40–220 µg/kg in grains and cereals, and 110–230 µg/kg in meats and fish (EPA 1984a). It would be useful to develop nationwide monitoring data on the levels of chromium in U.S. ambient air and drinking water, and these data should quantitate levels of both chromium(III) and chromium(VI) and not just total chromium.

Exposure Levels in Humans. The general population is exposed to chromium by inhaling ambient air and ingesting food and drinking water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products that contain chromium or from contact with chromium contaminated soils. Some of the consumer products known to contain chromium are certain wood preservatives, cement, cleaning materials, textiles, and leather tanned with chromium (WHO 1988). However, no quantitative data for dermal exposure to chromium-containing consumer products were located. Levels of chromium in ambient air (<0.01–0.03 µg/m^3) (Fishbein 1984; WHO 2003) and tap water (<2 µg/L) (WHO 2003) have been used to estimate the daily intake of chromium via inhalation (<0.2–0.6 µg) and tap water (<4 µg). These estimates are based on an air inhalation rate of 20 m^3/day and a drinking water consumption rate of 2 L/day. The daily chromium intake for the U.S. population from consumption of selected diets (diets with 25 and 43% fat) has been estimated to range from 25 to 224 µg, with an average of 76 µg (Kumpulainen et al. 1979). This value is within the range established by the World Health Organization (WHO) as a mean chromium intake form food and water of 52–943 µg/day (WHO 2003). However, few data on the levels of chromium in body tissues or fluids for populations living near hazardous waste sites are available. Such data could be a useful tool as an early warning system against harmful exposures. In addition, there is a need for data on the background levels of chromium in body fluids of children. Such data would be important in assessing the exposure levels of this group of people.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Limited data exist regarding exposure and body burdens of chromium in children. Chromium has been detected in breast milk at concentrations of 0.06–1.56 μg/L (Casey and Hambidge 1984), suggesting that children could be exposed to chromium from breast-feeding mothers. Studies in mice have shown that chromium crosses the placenta and can concentrate in fetal tissue (Danielsson et al. 1982; Saxena et al. 1990a). Because children living near areas contaminated with chromium have been shown to have elevated chromium levels in urine as compared to adults (Fagliano et al. 1997), additional body burden studies are required to evaluate the exposures and the potential consequences that this might have upon children. This is particularly important around heavily contaminated soils where children may be exposed dermally or through inhalation of soil particulates during play activities. These studies may determine if children may be more susceptible than adults to the toxic effects of chromium including immunosensitivity. Studies are necessary that examine children's weight-adjusted intake of chromium and determine how it compares to that of adults. Since chromium is often detected in soil surfaces and children ingest soil either intentionally through pica or unintentionally through hand-to-mouth activity, pica is a unique exposure pathway for children. Studies have shown that although absorption of chromium is low, it may be enhanced slightly from contaminated soil surfaces (Witmer et al. 1989, 1991).

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for chromium were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2008) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1 (see Table 6-7).

Table 6-7. Ongoing Studies on Chromium

Principal investigator	Affiliation	Research description
David Brautigan	University of Virginia	Define the biochemical basis of chromium enhancement of insulin action
William Cefalu	Pennington Biomedical Research Center	Study the changes in insulin uptake on chromium supplementation
Mitchell Cohen	New York University School of Medicine	Study biological interactions of metals and improve deign of metallopharmaceuticals
Jeffrey Elmendorf	Indiana University: Purdue University at Indianapolis	Chromium action and role in the glucose transport system
Emily Horvath	Indiana University: Purdue University at Indianapolis	Cellular insulin resistance mechanisms
Joshua Jacobs	Rush University Medical Center	Metal release and effects in people with metal-on-hip replacements
Sushil Jain	Louisiana State University	Cytokine production; role of chromium in preventing oxidative stress
Umesh Masharani	University of California, San Francisco	The effects of chromium on insulin action
Mahmood Mozaffari	Medical College of Georgia	Effect of chromium on glucose metabolism
Charles Myers	Medical College of Wisconsin	Study the mechanisms of chromium(VI) in the human lung system
Patricia Opresko	University of Pittsburgh at Pittsburgh	Understand the mechanisms of genomic instability associated with aging
Viresh Rawal	University of Chicago	Investigation of metal-salen complexes for use in C-C bond forming reactions; Diels-Alder catalyst development
James Rigby	Wayne State University	Study metal mediated cyclo-addition reactions to synthesize natural products
Diane Stearns	Northern Arizona University	Study the difference in mutations caused by soluble chromium vs. insoluble chromium; discover mechanism of cellular entry by soluble chromium compounds
Kent Sugden	University of Montana	Study the role of chromium in DNA mutations and cancer
Bo Xu	Southern Research Institute	The effect of chromium exposure on DNA damage
Ziling Xue	University of Tennessee, Knoxville	Development of an analytical method to determine chromium levels in biological fluids
Anatoly Zhitkovich	Brown University	Study the role of chromium in genetic alteration of cells after exposure

Source: FEDRIP 2008

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring chromium compounds, their metabolites, and other biomarkers of exposure to chromium compounds. The intent is not to provide an exhaustive list of analytical methods, but to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to lower detection limits and/or to improve accuracy and precision in detection.

7.1 BIOLOGICAL MATERIALS

Several methods are available for the analysis of chromium in different biological media, with some recent methods of chromium determination reported in Table 7-1. Multiple reviews on the subject provide more detailed descriptions of the available analytical methods (EPA 1984a; Fishbein 1984; IARC 1986a, 1990; Torgrimsen 1982; WHO 1988). Frequently used methods for determining low levels of chromium in biological samples include neutron activation analysis (NAA); mass spectrometry (MS); graphite spark atomic emission spectrometry (AES); and graphite furnace atomic absorption spectrometry (GFAAS) (Greenberg and Zeisler 1988; Plantz et al. 1989; Urasa and Nam 1989; Veillon 1989). A newly added technique includes the use of total reflection X-ray fluorescence (TXRF) for analysis of total chromium in the air (Adekola and Eletta 2007).

There are numerous issues and considerations in collecting and analyzing the chromium content in presented samples. Some of these issues include problems with collection, contamination, and determining accurate concentration levels of the chromium content in the samples. The determination of trace quantities of chromium in biological materials requires special precautionary measures, from the initial sample collection process to the final analytical manipulations of the samples.

Contaminates including dust contamination or losses of the samples during collection, transportation, and storage should be avoided (EPA 1984a). Chromium-containing grinding and homogenizing equipment should not be used for preparation of biological samples. Reagents of the highest purity should be used to

Table 7-1. Analytical Methods for Determining Chromium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plasma	Wet ashing with $HNO_3/HClO_4/H_2SO_4$; residue complexed with APDC and extracted with MIBK; evaporated residue dissolved deposited in HNO_3/HCE, and solution on a polycarbonate foil	PIXE	0.3 µg/L	87% at 4.5 µg/g	Simonoff et al. 1984
Blood, serum	Sample after wet digestion converted to a volatile chelate usually with fluorinated acetylacetone	GC/ECD	0.03 pg 0.5 pg 1.0 ng	No data	Fishbein 1984
Serum	$Mg(NO_3)_3$ added to serum, dried by Lyophilization, ashed, and dissolved in 0.1 N HCl	GFAAS	0.005 µg/L	103% at 0.30 µg/L	Randall and Gibson 1987
Blood	Diluted with 0.1% EDTA and 5% isopropanol	GFAAS-Zeeman-effect background correction	0.09 µg/L	No data	Dube 1988
Blood or tissue	Wet ashing with $HNO_3/HClO_4/H_2SO_4$	ICP-AES	1 µg/100 g blood 0.2 µg/g tissue	114% recovery at 10 µg/sample	NIOSH 1994a (Method No. 8005)
Erythrocytes	Dilution with Triton X100	GFAAS	No data	No data	Lewalter et al. 1985
Serum and urine	HNO_3 de-proteinization	GFAAS with pyrolytic graphite tube and Zeeman background correction	0.02 µg/L (serum) 0.1 µg/L (urine)	No data	Sunderman et al. 1989
Body fluids (milk, urine, etc.)	Dried sample ashed by oxygen plasma, H_2O_2 addition, drying, dilution in 1N HCl	GFAAS with tungsten iodide or deuterium arc or CEWM background correction	<0.25 µg/L	91% at 0.55 µg/L	Kumpulainen 1984
Urine	None	GFAAS	0.05 µg/L	91% at 0.22 µg/L	Randall and Gibson 1987

Table 7-1. Analytical Methods for Determining Chromium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	None	GFAAS with CEWM background correction and WM-AES	0.09 µg/L (CEWM-AAS) 0.02 µg/L (WM-AES)	No data	Harnly et al. 1983
Urine	No sample preparation other than addition of yttrium internal standard	ICP-AES	12 µg/L	77% at 13 µg/L	Kimberly and Paschal 1985
Urine	Sorption onto polydithiocarbonate resin, ash sorbate in low temperature oxygen plasma and dissolve in $HNO_3/HClO_4$	ICP-AES	0.1 µg/sample	100% recovery at 1 µg/50mL urine	NIOSH 1994b (Method 8310)
Urine	None	GFAAS	0.0052 µg/L	No data	Kiilunen et al. 1987
Urine	Sample spiked with standard chromium (standard addition)	GFAAS	0.03–0.04 µg/L	No data	Veillon et al. 1982
Urine	Diluted with water	GFAAS-Zeeman-effect-background correction	0.09 µg/kg	No data	Dube 1988
Milk powder	Mixed with water	GFAAS	5 µg/kg	134–141% at 17.7 µg/kg	Wagley et al. 1989
Tissue(Chromium(V))	Injection of sodium dichromate	EPR	0.1 mmol/kg	No data	Liu et al. 1994

AAS = atomic absorption spectrophotometry; APDC = ammonium pyrrolidine dithiocarbonate; CEWM = continuum source echelle monochromator wavelength-modulated; ECD = electron capture detector; EDTA = ethylenediaminetetraacetic acid; EPR = electron paramagnetic resonance spectroscopy; GC = gas chromatography; GFAS = graphite furnace AAS; H_2O_2 = hydrogen peroxide; H_2SO_4 = sulfuric acid; HCI = hydrochloric acid; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; ICP-AES = inductively coupled plasma-atomic emission spectrometry; $Mg(NO_3)_3$ = magnesium nitrate; MIBK = methylisobutyl ketone; MS = mass spectrometry; PIXE = proton-induced X-ray emission spectrometry; XRF = X-ray fluorescence analysis; WM-AES = wavelength-modulated atomic emission spectrometry

avoid contamination, and the potential loss of chromium due to volatilization during wet and dry ashing should be minimized (EPA 1984a).

The determination of chromium in most biological samples is difficult because of the matrix interference and the very low concentrations present in these samples. Prior to 1978, numerous erroneous results were reported for the chromium level in urine using electrothermal atomic absorption spectrometry (EAAS) because of the inability of conventional atomic absorption spectrometry systems to correct for the high nonspecific background absorption. Similarly, the reported serum and plasma chromium concentrations of normal subjects have varied more than 5,000-fold since the early 1950s. The chromium levels in human serum or plasma as reported in the mid-1980s ranged from 0.01 to 0.3 μg/L, and the daily urinary excretion rate of chromium in healthy and nonoccupationally exposed humans is <1 μg/day (Anderson 1987; Harnly et al. 1983; Sunderman et al. 1989; Veillon 1989).

The problem of generating accurate data for chromium in biological samples is further complicated by the lack of Standard Reference Materials (SRM). Standards in chromium certified materials, such as brewer's yeast (DOC 1976c), bovine liver (DOC 1977b, 1982), human serum (DOC 1985, 1993b, 2003), urine (DOC 1993c), orchard leaves (DOC 1977a), spinach leaves (DOC 1976b, 1996), pine needles (DOC 1993a), oyster tissue (DOC 1983, 1989), and tomato leaves (DOC 1976a), have been issued by the National Institute of Standards and Technology (formerly the National Bureau of Standards). However, due to the previous lack of SRMs, older data should be interpreted with caution (EPA 1984a), unless the data are verified by interlaboratory studies (WHO 1988).

In addition to the consideration of contamination and potential loss of sample, it should be noted that chromium may exist as several different oxidation states in biological media. Two of the most common oxidation states are chromium (III) and chromium (VI). Each of these oxidation states displays very different physical and biological properties. In biological samples where chromium is generally present as chromium(III), the choice of a particular method is dictated by several factors, including the type of sample, its chromium level, and the scope of the analysis (Kumpulainen 1984).

The preceding factors, in combination with the desired precision and accuracy and the cost of analysis, should be considered in selecting a particular analytical method. Although the methods reported in Table 7-1 represent some of the more recent methods, they are not necessarily the ones most commonly used. A comparison of the various standard methods and approaches for maintaining sample purity and integrity during sampling, handling, and analysis are provided by Kumpulainen (1984).

7.2 ENVIRONMENTAL SAMPLES

Analytical methods for determining chromium in environmental samples are reported in Table 7-2. The three commonly used methods that have the greatest sensitivity for chromium detection in air are GFAAS, instrumental neutron activation analysis (INAA), and graphite spark atomic emission spectrometry (Schroeder et al. 1987). Measurements of low levels of chromium concentrations in water have been made by specialized methods, such as inductively coupled plasma mass spectrometry (ICP-MS), capillary column gas chromatography (HRGC) of chelated chromium with electron capture detection (ECD), and electrothermal vaporization inductively coupled plasma mass spectrometry (Gonzalez et al. 2005; Henshaw et al. 1989; Malinski et al. 1988; Parks et al. 2004; Schaller and Neeb 1987). A method using high performance liquid chromatography (HPLC) interfaced with direct current plasma emission spectrometer has been used for the determination of chromium(III) and chromium(VI) in water samples (Krull et al. 1983). An acid digestion procedure followed by AAS has been developed that can quantify chromium(VI) in soil, sediment, and sludge (Ayyamperumal 2006; Oygard et al. 2004). The preferred methods for digestion of environmental samples have been discussed by Griepink and Tolg (1989).

Many of the same issues with the biological samples are also present in environmental analysis, including issues of collection, contamination, and detection. Chromium may be present in both the trivalent and hexavalent oxidation states in most ambient environmental and occupational samples, and the distinction between soluble and insoluble forms of chromium(VI) is sometimes necessary. The quantification of soluble and insoluble chromium is done by determining chromium concentrations in aqueous filtered and unfiltered samples. However, soluble chromium(VI) may be reduced to chromium(III) on filtering media, particularly at low concentrations, and under acidic conditions. Teflon® filter and alkaline solution are most suitable to prevent this reduction (Sawatari 1986). Routine analytical methods are not available that can quantify the concentration of both chromium(VI) and chromium(III) in air samples when present at a total concentration of <1 $\mu g/m^3$ (EPA 1990a), although two methods described in Table 7-2 can determine chromium(VI) concentrations alone in air at a minimum detection limit of 0.1 ng/m^3 for a 20-m^3 sample (CARB 1990).

As in the case of biological samples, contamination and chromium loss in environmental samples during sample collection, storage, and pretreatment should be avoided. Chromium loss from aqueous samples

Table 7-2. Analytical Methods for Determining Chromium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (total chromium)	Air particulate matter collected on filter is cut out and irradiated with X-ray photons	XRF	0.017 µg/m^3	No data	Wiersema et al. 1984
Air (total chromium)	The collected particulates in filter dissolved in HNO_3, dried and redissolved in acidified water	ICP-AES	0.05–0.2 ng/m^3	No data	Barrie and Hoff 1985
Air (total chromium)	Particulate matter collected on cellulose ester filter, digested with aqua regia	ICP-AES	1 µg/m^3	87–102% at 0.5–100 µg	Lo and Arai 1988
Air (total chromium)	Air particulate collected on cellulose ester filter, wet wash with HCI/HNO_3	Flame atomic absorption	0.06 µg/sample	98% at 45–90 µg/sample	NIOSH 1994c (Method 7024)
Air (total chromium)	Sample collected on cellulose ester membrane filter dissolved in acid mixtures	ICP-AES	1 µg/sample	98% at 2.5 µg/filter	NIOSH 1994d (Method 7300)
Air (chromium(VI))	Sample collected on sodium carbonate-impregnated cellulose filter leached with sodium bicarbonate	Ion chromato-graphy/ coulometric	0.1 ng/m^3 for 20 m^3 sample	89–99% at 100 ng	CARB 1990
Air (chromium(VI))	Sample collected in filters containing sodium bicarbonate buffer at 15 L/minute	Ion chromato-graphy/ coulometric	0.01 ng/m^3 for 20 m^3 sample	94%	Sheehan et al. 1992
Occupational air (welding fumes)	The particular matter on filter wet ashed with H_2SO_4 and chromium(III) oxidized to chromium(VI) by addition of Na_2O_2; the centifuged solution was acidified with HCl and reduced to chromium(III) by SO_2; the solution was complexed with β-isoproyl tropolone in $CHCl_3$	HPLC-UV	10 pg	No data	Maiti and Desai 1986

Table 7-2. Analytical Methods for Determining Chromium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air (chromium (VI))	Extract with 0.05 M $(NH_4)_2SO_4$–0.5 M $(NH_4)_2SO_4$.1 M NH_3.	FIA-UV/VIS	0.11 ng	>90%	Wang et al. 1997a
Welding fumes (total chromium(VI))	Air particulate collected on PVC filter is extracted with hot 3% Na_2CO_3 and 2% NaOH, acidified with H_2SO_4 and complexed with diphenyl carbazide	Spectro-photometry at 540 nm	0.05 µg/sample	No data	NIOSH 1994e (Method 7600); Zatka 1985
Welding fumes (total chromium(VI))	Air particulate collected on PVC filter, extracted with H_2SO_4 and complexed with diphenylcarbazide	Chromato-graphy at 540 nm Spectro-photometry at 540 nm	3.5 µg/sample	No data	NIOSH 1994f (Method 7604)
Simultaneous determination of chromium(III) and chromium(VI) in water extract from metal fumes	Sample solution at pH 5 reacted with disodium ethylenediamine tetraacetic acid at 50 °C for 1 hour	HPLC on anion exchange column with Na_2CO_3 eluting solution and simultan-eous UV and AAS detection	0.2 ng by UV for chromium(VI) 2.0 ng by UV 5.0 ng by AAS for chromium (IV) 5 ng by AAS for chromium (III)	95–105% at 0.002–2.0 µg	Suzuki and Serita 1985
Atmospheric deposition (snow); determination in soluble (chromium(VI)) and particulate (chromium(III)) part	The melted snow filtered through Nucleopore filter; the filtrate acidified with HNO_3; and dried by freeze-drier; residue dissolved in HNO_3; this preconcentrated solution placed in plastic tubes; both plastic tube and Nucleopore filter irradiated with protons	PIXE	2 µg/L (soluble portion) 26 µg/L (snow particle)	No data	Jervis et al. 1983; Landsberger et al. 1983
	Either the above Nucleopore filter or the preconcentrated liquid placed in plastic vial is irradiated by thermal neutron	INAA	5 µg/L (soluble portion) 115 µg/g (snow particle)	No data	Jervis et al. 1983; Landsberger et al. 1983

Table 7-2. Analytical Methods for Determining Chromium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water, surface water, and certain domestic and industrial effluents (dissolved chromium(VI))	Complex chromium(VI) in water with APDC at pH 2.4 and extracted with MIBK	Furnace AAS	2.3 µg/L	No data	EPA 1983c (Method 218.5)
Drinking water, groundwater and water effluents (chromium(VI))	Buffer solution introduced into ion chromatograph. Derivitized with dipenylcarbazide	Ion chromato-graphy spectro-photometry at 530 mm	0.3 µg/L	100% at 100 µg/L	EPA 1996a (Method 7199)
Waste water and industrial effluent for chromium(VI) only	Buffered sample mixed with $AlCl_3$ and the precipitate separated by centrifugation or filtration	DPPA at pH 10–12	30 µg/L	90% at 0.2 mg/L	Harzdorf and Janser 1984
Waste water 1986 (chromium(VI))	Sample mixed with a masking agent and cetyltrimethyl-ammonium bromide solution at pH 4.7–6.6, heated in water bath at 50 °C for 10 minutes	Spectro-photometry at 583 nm	Lower than diphenyl-carbazone method	No data	Qi and Zhu 1986
Water (total chromium)	Calcium nitrate added to water and chromium is converted to chromium(III) by acidified H_2O_2	GFAAS or ICP/AES	1.0 µg/L (GFAAS) 7.0 µg/L	97–101% at 19–77 µg/L	EPA 1983a, 1986a (Method 218.2 and 7191)
Industrial wastes, soils, sludges, sediments, and other solid wastes (total chromium)	Digest with nitric acid/hydrogen peroxide	ICP-AES	4.7 µg/L	101% at 3.75 mg/L	EPA 1996b (Method 6010b)
Oil wastes, oils, greases, waxes, crude oil (soluble chromium)	Dissolve in xylene or methyl isobutyl ketone	AAS or GFAAS	0.05 mg/L	107% at 15 µg/L	EPA 1986b (Method 7190)

Table 7-2. Analytical Methods for Determining Chromium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater, domestic and industrial waste (chromium[VI])	Chromium(VI) is coprecipitated with lead sulfate, reduced, and resolubilized in nitric acid	AAS or GFAAS	0.05 mg/L (AAS) 2.3 µg/L (GFAAS)	93–96% at 40 µg/L	EPA 1986c (Method 7195)
Groundwater-EP extract, domestic, and industrial waste (chromium[VI])	Chelation with ammonium pyrrolidine dithiocarbonate and extraction with methyl isobutyl ketone	AAS	No data	96% at 50 µg/L	EPA 1983b, 1986d (Method 218.4 and 7197)
Water, waste water, and EP extracts (chromium(VI))	Direct	DPPA	10 µg/L	93% at 5 mg/L	EPA 1986e (Method 7198)
Soil, sediment and sludges (chromium(VI))	Acid digestion extraction using HNO_3	AAS	No data	85–115%	Ayyamperumal 2006; Oygard et al. 2004

AAS=atomic absorption spectrophotometry; $AlCl_3$=aluminum chloride; APDC=ammonium pyrrolidine dithiocarbonate; $CHCl_3$=chloroform; DPPA=differential pulse polarographic analysis; EAAS=electrothermal atomic absorption spectrometry; EP=extraction procedure (for toxicity testing); FIA/uv/vis=flow injection analysis-ultraviolet/visible spectroscopy; GFAAS=graphite furnace atomic absorption spectrometry; H_2SO_4=sulfuric acid; HCI=hydrochloric acid; HNO_3=nitric acid; HPLC=high pressure liquid chromatography; ICP-AES=inductively coupled plasma-atomic emission spectrometry; INAA=instrumental neutron activation analysis; MIBK=methylisobutyl ketone; Na_2O_2=sodium peroxide; NaOH=sodium hydroxide; Na_2CO_3=sodium carbonate; $(NH_4)_2SO_4$=ammonium sulfate; NH_3=ammonia; PIXE=proton-induced X-ray emission spectrometry; SO_2=sulfur dioxide; UV=ultraviolet; XRF=X-ray fluorescence analysis

due to adsorption on storage containers should be avoided by using polyethylene or similar containers and acidifying the solution to the proper pH.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chromium compounds is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chromium compounds.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. There are studies correlating chromium in urine (Cocker et al. 2007; Gylseth et al. 1977; Kilburn et al. 1990; Lindberg and Vesterberg 1983a; McAughey et al. 1988; Minoia and Cavalleri 1988; Mutti et al. 1985b; Sjogren et al. 1983; Tola et al. 1977), blood (Kilburn et al. 1990; Lewalter et al. 1985; McAughey et al. 1988; Wiegand et al. 1988), hair (Randall and Gibson 1987, 1989; Takagi et al. 1986), hair in children (Chiba et al. 2004), nails (Takagi et al. 1988), and erythrocytes (Lukanova et al. 1996) to occupational exposure levels. Since chromium is an essential element, levels of chromium compounds have to be relatively high in humans before they signify an increase due to exposure. Hair has been useful in determining chronic occupational exposure to chromium in high concentrations (Randall and Gibson 1989), although the utility of this method for detecting prior exposures has a limited timespan of months (Simpson and Gibson 1992). Analytical methods to detect chromium concentrations in urine (Randall and Gibson 1987), whole blood (Case et al. 2001; Dube 1988; Fahrni 2007), serum/plasma (Simonoff et al. 1984), and tissue (Fahrni 2007; Liu et al. 1994) have been reported. Generally, the detection limits are in the sub ppb to ppb range, and recoveries are good (>70%).

Chromium induced DNA-protein complexes were prepared as a biomarker of exposure, as discussed in Section 3.12.2. These complexes can be detected by potassium chloride-sodium dodecyl sulfate mediated precipitation. These methods have a number of inherent limitations including tedious methodology and being subject to considerable interindividual and interlaboratory variations (Singh et al. 1998b). Only one study has attempted to utilize this biomarker, and it was found that volunteers exposed to chromium in drinking water showed no increase in protein-DNA crosslinking in blood cells (Kuykendall et al. 1996). This suggests that this procedure may not be sensitive enough for use in environmental monitoring unless an individual has received a potentially toxic level of exposure. In addition, chromium forms chromium-DNA complexes inside of cells, and these complexes constitute a potential biomarker for the assessment of environmental or occupational exposure. A novel method has been described for the sensitive detection of chromium-DNA adducts using inductively coupled plasma mass spectrometry (Singh et al. 1998b). The detection limits of this method are in the parts per trillion range and allow for the detection of as few as 2 chromium adducts per 10,000 bases, which coupled with the low DNA sample requirements, make this method sensitive enough to measure background levels in the population. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available and in use for detecting chromium in air, water, and soil environments. Air contaminated with chromium(VI), particularly in occupational settings, is of great concern. Methods have been developed that can determine low levels of total chromium and chromium(VI) in the air, with detection limits in the ng/m^3 range and excellent recoveries (90% or better) (Ashley et al. 2003; Barrie and Hoff 1985; CARB 1990; NIOSH 1994c, 1994d; Sheehan et al. 1992). These methods are sufficient to determine background chromium levels in the environment and levels at which health effects may occur. Chromium can be detected in water at concentrations in the ppb range (Abu-Saba and Flegal 1997; EPA 1983a, 1996a; Harzdorf and Janser 1984 Parks et al. 2004) and household and bottled drinking water (Al-Saleh and Al-Doush 1998), with recoveries of ≥90% being reported in some studies. In addition, there are also methods that can differentiate chromium(VI) from chromium(III) in water samples (EPA 1986c). A reliable analytical method for extracting and quantifying chromium, including chromium(VI), from soil surfaces has also been reported (Ayyamperumal et al. 2006; Oygard et al. 2004). Analytical methods exist that are sufficient for measuring background levels of chromium in soil (Ayyamperumal et al. 2006; EPA 1996b; Finley and Paustenbach 1997; Oygard et al. 2004) and water (EPA 1983a, 1983b, 1983c, 1986a, 1996a; Finley and Paustenbach 1997) and also water samples collected from various geological sites of interest (Gonzalez et al. 2005; Parks et al. 2004).

7.3.2 Ongoing Studies

Analytical methods for the detection of chromium compounds at increasingly lower concentrations are currently under development. Targeted areas of interest include air, water, and soil monitoring, with special emphasis being placed on populations considered vulnerable or potentially at risk, such as children and occupational workers. Additionally, more reliable methods to separate chromium(III) analysis from chromium(VI) analysis in collected samples is a source of interest and active research.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

An MRL of $5x10^{-6}$ mg chromium(VI)/m^3 has been derived for intermediate- and chronic-duration inhalation exposure to chromium(VI) as chromium trioxide mist and other dissolved hexavalent chromium aerosols and mists. The MRL is based on a LOAEL of 0.002 mg chromium(VI)/m^3 for upper respiratory effects in humans in the occupational exposure study by Lindberg and Hedenstierna (1983), which spanned both intermediate and chronic durations.

An MRL of 0.0003 mg chromium(VI)/m^3 has been derived for intermediate-duration inhalation exposure to chromium(VI) as particulate hexavalent chromium compounds. The MRL is based on a benchmark concentration of 0.016 mg chromium(VI)/m^3 for increases in lactate dehydrogenase activity in bronchiolavage fluid from rats in the study by Glaser et al. (1990).

An MRL of 0.005 mg chromium(VI)/kg/day has been derived for intermediate-duration oral exposure to hexavalent chromium compounds for hematological effects (e.g., microcytic, hypochromic anemia) in rats using data from a study by NTP (2008a). Because several hematological parameters are used to define the clinical picture of anemia, the MRL is based on the average $BMDL_{2sd}$ values for hemoglobin, MCV, and MCH of 0.52 mg chromium(VI)/kg/day.

An MRL of 0.001 mg chromium(VI)/kg/day has been derived for chronic-duration oral exposure to hexavalent chromium compounds. The MRL is based on a benchmark dose of 0.09 mg chromium(VI)/kg/day for diffuse epithelial hyperplasia of the duodenum in mice in a study by NTP (2008a).

An MRL of 0.005 mg chromium(III)/m^3 has been derived for intermediate-duration inhalation exposure to insoluble trivalent chromium particulate compounds. The MRL is based on a minimal LOAEL of 3 mg chromium(III)/m^3 for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in rats in the study by Derelanko et al. (1999).

An MRL of 0.0001 mg chromium(III)/m^3 has been derived for intermediate-duration inhalation exposure to soluble trivalent chromium particulate compounds. The MRL is based on a LOAEL of 3 mg chromium(III)/m^3 for nasal and larynx lesions in rats in the study by Derelanko et al. (1999).

A chronic oral reference dose (RfD) of 0.003 mg chromium(VI)/kg/day has been derived and verified by EPA for soluble salts of chromium(VI) (e.g., potassium chromate, sodium chromate, potassium dichromate, and sodium dichromate) (IRIS 2008). The RfD is based on a NOAEL for systemic effects in rats exposed to 2.5 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year in the study by MacKenzie et al. (1958).

A chronic inhalation RfC of 0.008 µg chromium(VI)/m^3 has been derived and verified by EPA for chromic acid mists and dissolved chromium(VI) aerosols (IRIS 2008). The RfC is based on a LOAEL for nasal septum atrophy in workers exposed to 0.002 mg chromium(VI)/m^3 (Lindberg and Hedenstierna 1983).

A chronic inhalation RfC of 0.0001 mg chromium(VI)/m^3 has been derived and verified by EPA for chromium(VI) particulates (IRIS 2008). The RfC is based on a benchmark concentration of 0.016 mg chromium(VI)/m^3 derived from data for lactate dehydrogenase activity in bronchoalveolar lavage fluid in rats exposed to sodium dichromate (Glaser et al. 1990).

A chronic oral RfD of 1.5 mg chromium(III)/kg/day has been derived and verified by EPA for insoluble salts of chromium(III) (e.g., chromium oxide and chromium sulfate) (IRIS 2008). The RfD is based on a NOAEL for systemic effects in rats fed 1,800 mg chromium(III)/kg/day for 5 days/week for 600 feedings (840 total days) in the study by Ivankovic and Preussmann (1975). EPA has determined that the data are inadequate for the development of an RfC for chromium(III) due to the lack of relevant toxicity study addressing the respiratory effects of chromium(III) (IRIS 2008).

The Institute of Medicine (IOM) of the National Academy of Sciences (NAS) determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 µg chromium(III)/day for adolescents and adults (IOM 2001)

The international and national regulations, advisories, and guidelines regarding chromium in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2008
	Chromium, metallic	Group 3[a]	
	Chromium (III) compounds	Group 3[a]	
	Chromium (VI)	Group 1[b]	
WHO	Air quality guidelines		WHO 2000
	Chromium (VI)	1 µg/m^3 for a lifetime risk of 4x10^{-2}	
	Drinking water quality guidelines		WHO 2004
	Chromium (for total chromium)	0.05 mg/L[c]	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2007
	Calcium chromate (as Cr)	0.001 mg/m^3	
	Chromium and inorganic compounds (as Cr)		
	Metal and chromium (III) compounds	0.5 mg/m^3	
	Water-soluble chromium (VI) compounds	0.05 mg/m^3	
	Insoluble chromium (VI) compounds	0.01 mg/m^3	
	Lead chromate		
	As Pb	0.05 mg/m^3	
	As Cr	0.012 mg/m^3	
	Strontium chromate (as Cr)	0.0005 mg/m^3	
	Zinc chromates (as Cr)	0.01 mg/m^3	
	TLV basis (critical effects)		
	Calcium chromate (as Cr)	Lung cancer	
	Chromium		
	Metal and chromium (III) compounds	Upper respiratory tract and skin irritation	
	Water-soluble chromium (VI) compounds	Upper respiratory tract irritation and cancer	
	Insoluble chromium (VI) compounds	Lung cancer	

Table 8-1. Regulations and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
ACGIH	TLV basis (critical effects)		ACGIH 2007
	Lead chromate As Pb As Cr	Male reproductive damage, teratogenic effects, and vasoconstriction	
	Strontium chromate (as Cr)	Cancer	
	Zinc chromates (as Cr)	Nasal cancer	
EPA	AEGL-1, -2, and -3	No data	EPA 2007a
	Second list of AEGL priority chemicals for guideline development		EPA 2008a
	Chromium (III) chloride	Yes	
	Hazardous air pollutant		EPA 2007b 42 USC 7412
	Chromium compounds	Yes	
NIOSH	REL (8-hour TWA)		NIOSH 2005
	Chromium, metal, chromium (II), and chromium (III) compounds	0.5 mg/m^3	
	REL (10-hour TWA)		
	Chromium (VI) trioxide (as Cr)[d,e]	0.001 mg/m^3	
	IDLH		
	Chromium, metal (as Cr)	250 mg/m^3	
	Chromium (VI) trioxide (as chromium [VI])[e]	15 mg/m^3	
	Target organs		
	Chromium, metal	Eyes, skin, and respiratory system	
	Chromium (VI) trioxide	Blood, respiratory system, liver, kidneys, eyes, and skin	
	Category of pesticides		NIOSH 1992
	Potassium chromate	Group 1 pesticide	
	Potassium dichromate	Group 1 pesticide	
	Sodium chromate	Group 1 pesticide	
OSHA	PEL (8-hour TWA) for general industry (ceiling limit)		OSHA 2007a 29 CFR 1910.1000, Table Z-2
	Chromium (II) compounds (as Cr)	0.5 mg/m^3	
	Chromium (III) compounds (as Cr)	0.5 mg/m^3	
	Chromium metal and insoluble salt (as Cr)	1.0 mg/m^3	,
	Chromium (VI) compounds	5 µg/m^3	OSHA 2007d 29 CFR 1910.1026

Table 8-1. Regulations and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	PEL (8-hour TWA) for shipyard industry (ceiling limit)		OSHA 2007c 29 CFR 1915.1000
	Chromium (II) compounds (as Cr)	0.5 mg/m^3	
	Chromium (III) compounds (as Cr)	0.5 mg/m^3	
	Chromium metal and insoluble salt (as Cr)	1.0 mg/m^3	
	Chromium (VI) compounds	0.5 µg/m^3	OSHA 2007e 29 CFR 1915.1026
OSHA	PEL (8-hour TWA) for construction industry (ceiling limit)		OSHA 2007b 29 CFR 1926.55, Appendix A
	Chromium (II) compounds (as Cr)	0.5 mg/m^3	
	Chromium (III) compounds (as Cr)	0.5 mg/m3	
	Chromium metal and insoluble salt (as Cr)	1.0 mg/m^3	
	Chromium (VI) compounds	0.5 µg/m^3	OSHA 2007f 29 CFR 1926.1126
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2008b 40 CFR 116.4
	Ammonium dichromate	Yes	
	Calcium chromate	Yes	
	Chromium (III) sulfate	Yes	
	Potassium chromate	Yes	
	Strontium chromate	Yes	
	Drinking water standards and health advisories		EPA 2006a
	Chromium (total)		
	1-day health advisory for a 10-kg child	1 mg/L	
	10-day health advisory for a 10-kg child	1 mg/L	
	DWEL	0.1 mg/L	
	Lifetime	No data	
	National secondary drinking water standards		EPA 2003
	Chromium (total)		
	MCL	0.1 mg/L	
	Public health goal	0.1 mg/L	

Table 8-1. Regulations and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	National recommended water quality criteria[g]	No data	EPA 2006b
	Chromium (III)		
	Freshwater CMC	570 µg/L	
	Freshwater CCC	74 µg/L	
	Chromium (VI)		
	Freshwater CMC	16 µg/L	
	Freshwater CCC	11 µg/L	
	Saltwater CMC	1,100 µg/L	
	Saltwater CCC	50 µg/L	
EPA	Toxic pollutants designated pursuant to Section 307(a)(1) of the Clean Water Act		EPA 2008i 40 CFR 401.15
	Chromium and compounds	Yes	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2008c 40 CFR 117.3
	Chromium (III) sulfate	100 pounds	
	Potassium chromate	10 pounds	
	Strontium chromate	10 pounds	
c. Food			
EPA	Inert ingredients permitted for use in nonfood use pesticide products		EPA 2008e
	Chromium (III) oxide	Yes	
	Sodium chromate	Yes	
FDA	Bottled drinking water		FDA 2007a 21 CFR 165.110
	Chromium	0.1 mg/L	
	EAFUS[h]	No data	FDA 2008
	Indirect food additives: adhesives and components of coatings		FDA 2007b 21 CFR 175.105
	Sodium chromate	Yes	
	Recommended daily intake		FDA 2007c 21 CFR 101.9
	Chromium	120 µg	

Table 8-1. Regulations and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2007
	Calcium chromate (as Cr)	A2[l]	
	Chromium		
	Metal and chromium (III) compounds	A4[j]	
	Water-soluble chromium (VI) compounds	A1[k]	
	Insoluble chromium (VI) compounds	A1[k]	
	Lead chromate		
	As Pb	A2[i]	
	As Cr	A2[i]	
	Strontium chromate (as Cr)	A2[l]	
	Zinc chromates (as Cr)	A1[k]	
ACGIH	Biological exposure indices		ACGIH 2007
	Chromium		
	Water-soluble chromium (VI) fume		
	Total chromium in urine at end of shift at end of workweek	25 µg/L	
	Total chromium in urine increase during shift	10 µg/L	
EPA	Carcinogenicity classification		IRIS 2008
	Chromium(III), insoluble salts	Group D[l]	
	Chromium (VI)		
	Inhalation route of exposure	Group A[m]	
	Oral route of exposure	Group D[l]	
	RfC		
	Chromium(III), insoluble salts	Not available	
	Chromium (VI)		
	Chromic acid mists and dissolved Cr (VI) aerosols	$8x10^{-6}$ mg/m^3	
	Cr(VI) particulates	$1x10^{-4}$ mg/m^3	
	RfD		
	Chromium(III), insoluble salts	1.5 mg/kg/day	
	Chromium (VI)	$3x10^{-3}$ mg/kg/day	
	Master Testing List	Yes[n]	EPA 2008f
	RCRA waste minimization PBT priority chemical list		EPA 1998c 63 FR 60332
	Chromium	Yes	

Table 8-1. Regulations and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list		EPA 2008d 40 CFR 264, Appendix IX
	Chromium (total)	Yes	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2008j 40 CFR 302.4
	Ammonium dichromate	Yes[o]	
	Calcium chromate	Yes[o,p]	
	Chromium	Yes[q]	
	Chromium and compounds	Yes[r]	
	Chromium (III) sulfate	Yes[o]	
	Potassium chromate	Yes[o]	
	Strontium chromate	Yes[o]	
EPA	Superfund, emergency planning, and community right-to-know		
	Reportable quantity		EPA 2008j 40 CFR 302.4
	Ammonium dichromate	10 pounds	
	Chromium	5,000 pounds	
	Calcium chromate	10 pounds	
	Chromium and compounds	None[s]	
	Chromium (III) sulfate	1,000 pounds	
	Potassium chromate	10 pounds	
	Strontium chromate	10 pounds	
	Effective date of toxic chemical release reporting		EPA 2008h 40 CFR 372.65
	Chromium	01/01/1987	
	Extremely Hazardous Substances		EPA 2008g 40 CFR 355, Appendix A
	Chromium (III) chloride		
	Reportable quantity	1 pound	
	Threshold planning quantity	1,000 pounds	

Table 8-1. Regulations and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification		NTP 2005
	Chromium (VI) compounds	Known to be human carcinogens	
	Calcium chromate		
	Chromium (VI) trioxide		
	Ferrochromite		
	Lead chromate		
	Strontium chromate		
	Zinc chromate		

[a]Group 3: The agent is not classifiable as to its carcinogenicity to humans.
[b]Group 1: The agent is carcinogenic to humans.
[c]Provisional guideline value, as there is evidence of a hazard, but the available information on health effects is limited.
[d]The NIOSH REL (10-hour TWA) is 0.001 mg Cr(VI)/m^3 for all hexavalent chromium (Cr[(VI]) compounds. NIOSH considers all chromium (VI) compounds (including chromic acid, tert-butyl chromate, zinc chromate, and chromyl chloride) to be potential occupational carcinogens.
[e]NIOSH potential occupational carcinogen.
[f]Group 1 pesticides: contains the pesticides that pose a significant risk of adverse acute health effects at low concentrations.
[g]The CMC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed briefly without resulting in an unacceptable effect. The CCC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed indefinitely without resulting in an unacceptable effect.
[h]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[i]A2: Suspected human carcinogen.
[j]A4: Not classifiable as a human carcinogen.
[k]A1: Confirmed human carcinogen.
[l]Group D: not classified as to its human carcinogenicity.
[m]Group A: known human carcinogen by the inhalation route of exposure.
[n]Chromium was recommended to the MTL by ATSDR in 1994 and the testing needs development is currently underway. The testing needs include acute toxicity, neurotoxicity, reproductive, and immunotoxicity health effects.
[o]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.
[p]Designated CERCLA hazardous substance pursuant to Section 3001 of the Resource Conservation and Recovery Act.
[q]Designated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water.
[r]Designated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water Act and Section 112 of the Clean Air Act.
[s]Indicates that no reportable quantity is being assigned to the generic or broad class.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CCC = Criterion Continuous Concentration; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CMC = Criteria Maximum Concentration; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FR = Federal Register; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MTL = Master Testing List; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PBT = persistant, bioacumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Concervation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSD = transport, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(VI) aerosols and mists
CAS number: 18540-29-9
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [X] Chronic
Key to figure: 11, 29
Species: Human

Minimal Risk Level: $5x10^{-6}$ mg chromium(VI)/m^3 for dissolved hexavalent chromium aerosols and mists.

Reference: Lindberg E, Hedenstierna G. 1983. Chrome plating: Symptoms, findings in the upper airways, and effects on lung function. Arch Environ Health 38:367-374.

Experimental design: Eighty-five male and 19 female chrome-plating workers exposed to chromic acid were assessed for nose, throat, and chest symptoms, were inspected for effects in nasal passages, and were given pulmonary function tests. Study participants were compared to a reference group of 119 auto mechanics who were not exposed to chromium. The length of worker exposures to chromic acid ranged from 0.1 to 36 years, spanning intermediate- and chronic-exposure durations. Since the study population included workers exposed for both intermediate and chronic durations, data are considered appropriate for derivation of the intermediate- and chronic-duration inhalation MRLs. Chromium exposures were measured using personal air samplers and stationary equipment positioned close to the baths containing chromic acid. The exposure categories were defined as high average daily concentrations >0.002 mg chromium(VI)/m^3], low (average daily concentrations <0.002 mg chromium(VI)/m^3), and mixed category (chromium(VI) was <0.002 mg chromium(VI)/m^3, with exposure to other acids and metallic salts). Correlations with nasal irritation and respiratory functions were also determined for peak exposures. Statistical analyses were performed using the chi-square test with Yate's correction when comparing nasal findings, and the Student's two tail t-test was used when comparing lung function findings.

Effects noted in study and corresponding doses: Nasal irritation ($p<0.05$), mucosal atrophy ($p<0.05$), and ulceration ($p<0.01$), and decreases in spirometric parameters (forced vital capacity, forced expired volume in 1 second, and forced mid-expiratory flow) were observed in workers occupationally exposed to ≥0.002 mg chromium(VI)/m^3 as chromic acid with a median exposure period of 2.5 years. About 60% of the exposed subjects were smokers, but no consistent association between exposure and cigarette smoking was observed. Short-term peak exposures to chromic acid correlated better with nasal septum damage than with 8-hour mean concentrations.

Dose end point used for MRL derivation: 0.002 mg chromium(VI)/m^3 (nasal irritation, mucosal atrophy, decreased FVC, FEP_1, and FEV)

[ ] NOAEL [X] LOAEL [ ] benchmark concentration (BMC)

The LOAEL of 0.002 mg chromium(VI)/m^3 for upper respiratory effects was selected as the point of departure for derivation of the intermediate- and chronic-duration inhalation MRLs for dissolved hexavalent chromium aerosols and mists. The LOAEL was duration-adjusted to a $LOAEL_{ADJ}$ of 0.0005 mg chromium(VI)/m^3 for continuous exposure. The intermediate- and chronic-duration inhalation MRLs of 0.000005 mg chromium(VI)/m^3 for dissolved hexavalent chromium aerosols and mists were

derived by dividing the $LOAEL_{ADJ}$ of 0.0005 mg chromium(VI)/m^3 by a composite uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Uncertainty factors used in MRL derivation:

[X] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: No. Not applicable.

Was a conversion used from intermittent to continuous exposure? Yes, the LOAEL of 0.002 mg chromium(VI)/m^3 was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL ($LOAEL_{ADJ}$) of 0.0005 mg chromium(VI)/m^3.

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. In workers exposed to dissolved hexavalent chromium aerosols and mists (as chromium trioxide mist) for intermediate durations, nasal irritation, ulceration, and mucosal atrophy and rhinorrhea have been reported, with LOAEL values ranging from 0.09 to 0.1 mg chromium(VI)/m^3 (Gibb et al. 2000a; Gomes 1972; Kleinfeld and Rosso 1965). Similarly, studies in rats and mice have shown that the upper respiratory tract is a primary target of exposure to inhaled chromium trioxide mist, with LOAEL values ranging from 0.49 to 3.63 mg chromium(VI)/m^3 (Adachi 1987; Adachi et al. 1986; Kim et al. 2004). In addition, numerous intermediate- and chronic-duration exposure studies of workers to chromium(VI) compounds in general identify the respiratory tract as the primary target of exposure, with reports of epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulceration of the nasal septum, bronchitis, pneumonoconiosis, decreased pulmonary function, and pneumonia (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gomes 1972; Greater Tokyo Bureau of Hygiene 1989; Hanslian et al. 1967; Keskinen et al. 1980; Kleinfeld and Rosso 1965; Lee and Goh 1988; Letterer 1939; Lieberman 1941; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Pastides et al. 1991; PHS 1953; Royle 1975b; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al. 1987; Taylor 1966).

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(VI) particulates
CAS number: 18540-29-9
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 14
Species: Rat

Minimal Risk Level: 0.0003 mg chromium (VI)/m^3 for hexavalent chromium particulate compounds

Reference: Glaser U, Hochrainer D, Steinholf D. 1990. Investigation of irritating properties of inhaled CrVI with possible influence on its carcinogenic action. Environ Hyg 2:235-245.

Experimental design: Eight-week-old male Wistar rats (30 animals in each group) were exposed 22 hours/day, 7 days/week to 0, 0.05, 0.1, 0.2, or 0.4 mg chromium(VI)/m^3 as sodium dichromate aerosol particulates. Groups of 10 animals were sacrificed after 30 or 90 days of exposure or after 90 days of exposure and a 30-day recovery period. The respective mass median mean diameters (MMAD) and geometric standard deviation were 0.28 μm and 1.63 for the 0.5 and 0.1 mg chromium(VI)/m^3 concentrations and 0.39 μm and 1.72 for the 0.2 and 0.4 mg chromium(VI)/m^3 concentrations. Hematological, clinical chemistry, and urinalysis tests were performed. Gross and histological examinations were limited to the upper airway epithelia, left lung lobes, and the kidneys. In addition, lung lavage fluid was analyzed for total protein, albumin, lactate dehydrogenase, and β-glucuronidase activities.

Effects noted in study and corresponding doses: No deaths or abnormal clinical signs occurred at any of the exposures. Body weight was significantly ($p<0.001$) decreased at 0.2 and 0.4 mg chromium(VI)/m^3 for 30 days, at 0.4 mg chromium(VI)/m^3 for 90 days ($p<0.05$), and at 0.2 ($p<0.01$) and 0.4 mg chromium(VI)/m^3 ($p<0.05$) in the recovery group. No differences in urinary protein and no exposure-related histopathological lesions were noted. No differences were seen in analysis of serum levels or activities of alanine aminotransferese, alkaline phosphatase, glucose, urea, total bilirubin, total cholesterol, or phospholipids. There were no hematological effects on red blood cells, but the white blood cell counts increased significantly in a dose-related manner at ≥0.1 mg chromium(VI)/m^3 after 30 days and at ≥0.05 mg chromium(VI)/m^3 after 90 days. White blood cells counts were not increased in 90 day exposure plus 30-day observation group.

Obstructive respiratory dyspnea occurred at ≥0.2 mg chromium(VI) chromium(VI)/m^3 after 30 and 90 days. Mean lung weight was increased in all exposure groups and was statistically increased at ≥0.05 mg chromium(VI)/m^3 for 30 days, and at ≥0.1 mg chromium(VI)/m^3 for 90 days and in the 90-day plus recovery period group. Histological examination revealed slight hyperplasia in high incidence at ≥0.05 mg chromium(VI)/m^3 at 30 days. With longer exposure, the incidence declined, indicating repair. Lung fibrosis occurred at ≥0.1 mg chromium(VI)/m^3 for 30 days, but was not seen in rats exposed for 90 days. Accumulation of macrophages was observed in all exposed rats, regardless of exposure concentration or duration. This histiocytosis probably accounts for the increased lung weight. Histology of upper airways revealed focal inflammation. Results of bronchoalveolar lavage (BAL) analysis provided further information of the irritation effect. Total protein in BAL fluid was significantly increased in all exposed groups, but declined in the recovery period. Albumin in BAL fluid increased in a dose-related manner at all concentrations in the 30-day group, but recovery started during 90-day exposure and continued during the 30-day observation period. The activities of lactate dehydrogenase

and β-glucuronidase, measures of cytotoxicity, were elevated at 0.2 and 0.4 mg chromium(VI)/m^3 for 30 and 90 days, but returned to control values during the recovery period. The number of macrophages in the BAL fluid had significantly increased after 30 and 90 days, but normalized during the recovery period. The macrophages were undergoing cell division or were multinucleate and larger. This activation of macrophages was not observed in the recovered rats. The study authors concluded that inflammation is essential for the induction of most chromium inhalation effects and may influence the carcinogenicity of chromium(VI) compounds.

Dose end point used for MRL derivation: 0.016 mg/m^3 (alterations in lactate dehydrogenase levels in bronchoalveolar lavage), converted to a $BMCL_{HEC}$ of 0.010 mg chromium(VI)/m^3

[ ] NOAEL [ ] LOAEL [X] benchmark concentration (BMC)

The Agency adopted the benchmark concentration (BMC) analysis of the Glaser et al. (1990) data conducted by Malsch et al. (1994) for deriving an intermediate-duration inhalation MRL for hexavalent chromium particulate compounds. Using the 90-day exposure data (as described above), Malsch et al. (1994) developed BMCLs for lung weight and BAL fluid levels of lactate dehydrogenase, protein, and albumin. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure. Duration-adjusted data were then fitted to a polynomial mean response regression model by the maximum likelihood method to derive BMCLs (defined as the 95% lower confidence limit on the concentration corresponding to a 10% relative change in the end point compared to the control). The BMCL values for lung weight, lactate dehydrogenase in the BAL fluid, protein in BAL fluid, and albumin in BAL fluid were 0.067, 0.016, 0.035, and 0.031 mg chromium(VI)/m^3, respectively. The lowest BMCL, 0.016 mg chromium(VI)/m^3 for alterations in lactate dehydrogenase levels in BAL fluid, was selected to derive the intermediate-duration inhalation MRL. The BMCL of 0.016 mg chromium(VI)/m^3 was converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.010 mg chromium(VI)/m^3, as described below. The intermediate-duration inhalation MRL of 0.0003 mg chromium (VI)/m^3 for hexavalent chromium particulate compounds was derived by dividing the $BMCL_{HEC}$ of 0.010 mg chromium(VI)/m^3 by a composite uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Uncertainty factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans, with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.
Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
The BMCL of 0.016 mg chromium(VI)/m^3 was converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.010 mg chromium(VI)/m^3 using the RDDR (regional deposited dose ratio) program (EPA 1994c) as follows:

$$BMCL_{HEC} = BMCL \times RDDR$$
$$BMCL_{HEC} = 0.016 \text{ mg chromium(VI)/m}^3 \times 0.630 = 0.010 \text{ mg chromium(VI)/m}^3$$

where
RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal to the predicted inhalation particulate exposure concentration for a human. The RDDR

multiplier of 0.630 for the thoracic region tract was determined using the default subchronic body weight of 217 g for male Wistar rats (EPA 1988d) and a particle size MMAD±GSD of 0.5±1.63 μm reported in the Glaser et al. (1984) study. Although the actual mean particle size reported in the critical study was 0.28 μm, the RDDR program (EPA 1994c) can only run be run for particle sizes ranging from 0.5 to 30 μm; therefore, 0.5 μm was used as the default particle size to calculated the RDDR. Since the critical study did not report body weight, the default subchronic body weight of 217 g for male Wistar rats was used.

Was a conversion used from intermittent to continuous exposure? Yes. Animals were exposed for 22 hours/day, 7 days/week. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure (22 hours/day) by multiplying data points for all outcome measures by 22 hours/24 hours.

Other additional studies or pertinent information that lend support to this MRL: The findings in this study are supported by another 90-day study conducted by the same group (Glaser et al. 1985). In this study, groups of 20 male Wistar rats were exposed to 0, 0.025, 0.05, 0.1, or 0.2 mg chromium(VI)/m^3 as sodium dichromate for 22 hours/day, 7 days/week for 90 days. No deaths occurred at any of the exposures. All exposed animals showed normal histologic findings in lung, kidney, liver, stomach, and gonads. Lung and spleen weights were increased significantly at doses above 0.025 mg chromium(VI)/m^3. Serum levels of triglycerides and phospholipid were increased in rats exposed to 0.2 mg chromium(VI)/m^3. Serum contents of total immunoglobulins were significantly increased in the 0.05 and 0.1 mg chromium(VI)/m^3 groups. At 0.025 and 0.2 mg chromium(VI)/m^3, serum immunoglobulin contents were no different than controls. The SRBC antibody response was increased in all dosed groups over control values. Chromium treatment at 0.2 mg chromium(VI)/m^3 also enhanced the mitogenic-stimulation of splenic Concanavalin T-lymphocytes. At 0.025 mg chromium(VI)/m^3, there were significant increases in polynuclear macrophages and the number of macrophages in telophase, and increases in lymphocytes in bronchoalveolar lavage samples. At 0.05 and 0.2 mg chromium(VI)/m^3, there were significant decreases in total numbers of macrophages. The percentages of polynuclear macrophages, lymphocytes, and granulocytes were increased at chromium exposures of 0.05 mg chromium(VI)/m^3, but at 0.2 mg chromium(VI)/m^3, the percentage of granulocytes cells was lower than control values. At 0.025 and 0.05 mg chromium(VI)/m^3 exposures, phagocytosis of latex particles by alveolar macrophages was increased over controls. However, at 0.2 mg chromium(VI)/m^3, the phagocytic activity was less than controls and there was a decrease in lung clearance of iron oxide particulates.

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chromium(VI)
CAS Numbers: 18540-29-9
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 45
Species: Rat

Minimal Risk Level: 0.005 [X] mg chromium(VI)/kg/day [ ] ppm

Reference: NTP. 2008a. NTP technical report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate (CAS No. 7789-12-0) in F344/N rats and B6C3F1 mice (drinking water studies). Washington, DC: National Toxicology Program. NTP TR 546. http://ntp.niehs.nih.gov/files/546_web_FINAL.pdf. August 13, 2008.

Experimental design: Male F344/N rats (6–7 weeks old) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study. Male rats (50/group) were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. In a subgroup of 10 male rats, blood was collected from the retroorbital sinus after exposure durations of 4 days, 22 days, 3 months, 6 months, and 1 year and evaluated for hematology (Hct; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; MCV; MCH; MCHC; and leukocyte count and differentials) and clinical chemistry (urea nitrogen, creatinine, total protein, albumin, ALT, AP, creatine kinase, SDH, and bile acids). Clinical signs of toxicity were assessed over the course of exposure. NTP calculated mean daily doses of sodium dichromate dihydrate in male rats of 0, 0.6, 2.2, 6, or 17 mg/kg (equivalent to 0, 0.21, 0.77, 2.1, or 5.9 mg chromium(VI)/kg/day, respectively) over the course of the 2-year study. Since observations were made at various time points during the chronic study (e.g., 22 days to 1 year), rather than using different dosage scales for each observation and outcome in the dose-response modeling, time-averaged dosages for the chronic duration (i.e., 101 weeks) were used to represent the dosage received during the intermediate- (i.e., >2–<52 weeks) and chronic- (>2–101 weeks) duration periods. This is an approximation of the actual dosages received, which varied as a function of body weight, and therefore, time of observation, with the differences most pronounced at the earliest periods of the intermediate-duration exposure (e.g., 3–12 weeks). The rationale for this simplification of the dose-response analysis is as follows: (1) outcomes observed at specific time points in the study (e.g., blood effects) after the acute period (>2 weeks) were considered to be relevant to the entire intermediate-duration period (>2–<52 weeks), if observed at multiple observation times during the intermediate-duration period; (2) chronic duration dosages were nearly identical to the time-averaged dosages for intermediate-duration exposure (e.g., <12% difference in the rat study); and (3) the possible bias introduced into estimates of BMDLs as a result of using chronic-duration dosages to represent intermediate-duration dosages is small (<12%) and conservative (i.e., BMDLs based on the chronic-duration dosages may be slightly lower than BMDLs based on actual intermediate-duration dosages).

Effect noted in study and corresponding doses: No treatment-related clinical signs of toxicity were observed in rats over the course of this study. Hematological effects consistent with microcytic, hypochromic anemia were observed at all intermediate-duration time points (22 days to 6 months) in male rats exposed to sodium dichromate dihydrate in drinking water; severity exhibited dose-dependence. At the 22-day assessment in rats, decreases were observed in Hct, Hgb, MCV, and MCH at ≥0.77 mg chromium(VI)/kg/day; effects at higher doses included decreased MCHC and platelet count at ≥2.1 mg chromium(VI)/kg/day, and decreased erythrocyte and reticulocyte counts, and increased nucleated

erythrocytes at 5.9 mg chromium(VI)/kg/day). At the 3-month assessment in rats, decreases were observed for MCV and MCH at ≥0.77 mg chromium(VI)/kg/day; effects at higher doses included decreased Hgb at ≥2.1 mg chromium(VI)/kg/day and decreased Hct and increased erythrocyte, reticulocyte, platelet, leukocyte, and segmented neutrophil counts at ≥5.9 mg chromium(VI)/kg/day. Increases in cell counts indicate a compensatory hematopoietic response to anemia. At 6 months in rats, decreased MCV, MCH, and MCHC were observed at ≥0.77 mg chromium(VI)/kg/day; at 5.9 mg chromium(VI)/kg/day, decreased Hgb was observed. For all intermediate-duration exposures (22 days to 6 months), NOAEL and LOAEL values in male rats for hematological effects were 0.21 and 0.77 mg chromium(VI)/kg/day, respectively. Although effects in rats were similar at the 22-day and 3-month assessments, NTP (2008a) concluded that effects were more severe at 22 days than at 3 months based on the magnitude of changes and the number of parameters affected in rats exposed to 0.77 mg chromium(VI)/kg/day. Effects at 6 months were less severe than those observed at the 22-day and 3-month assessments. Although the magnitude of the decreases in hematological parameters was small at 0.77 mg chromium(VI)/kg/day compared to the control group (6.1–10.6%), there is clear indication of damage to the hematological system and this dose level was considered a minimal LOAEL. At the next highest dose (2.1 mg chromium(VI)/kg/day), these parameters were 16–25% lower than controls. As defined by ATSDR, an effect that enhances the susceptibility of an organism to the deleterious effects of other chemical, physical, microbiological, or environmental influences should be considered adverse. Thus, the slight, but statistically significant, decrease in hematological parameters at 0.77 mg chromium(VI)/kg/day was considered minimally adverse.

Evaluation of clinical chemistry parameters in male rats showed significant alterations in serum liver enzyme activities, although changes were not consistent over all intermediate-duration exposures. At the 22-day assessment, increases were observed for ALT (≥0.77 mg chromium(VI)/kg/day) and AP (5.9 mg chromium(VI)/kg/day), but no change was observed for SDH. At 3 months, ALT was increased (≥0.77 mg chromium(VI)/kg/day), but AP was decreased (≥0.21 mg chromium(VI)/kg/day) and no change was observed for SDH. At 6 months, increases were observed for ALT and SDH (≥2.1 mg chromium(VI)/kg/day), but AP was decreased (0.77 mg chromium(VI)/kg/day). Due to the inconsistent changes in serum liver enzyme activities, NTP (2008a) concluded that alterations in liver enzymes (specifically ALT) were suggestive of enzyme induction, rather than hepatocellular damage. Thus, altered serum liver enzyme activities were not considered indicative of an adverse effect on the liver.

Dose and end point used for MRL derivation: 0.52 mg chromium(VI)/kg/day (microcytic, hypochromic anemia)

[ ] NOAEL [ ] LOAEL [X] benchmark dose (BMD)

Exposure to sodium dichromate dihydrate in drinking water resulted in microcytic, hypochromic anemia in male rats at all intermediate-duration exposures (22 days to 6 months). The severity was greatest at the 22-day assessment compared to the 3- and 6-month assessments; therefore, microcytic, hypochromic anemia observed at the 22-day assessment was identified as the critical effect for derivation of the intermediate-duration oral MRL. In male rats, decreases in Hct, Hgb, MCV, and MCH were the most sensitive measures of hematological effects, with NOAEL and LOAEL values of 0.21 and 0.77 mg chromium(VI)/kg/day, respectively; data sets for these end points are summarized in Table A-1.

Table A-1. Hematological Effects in Male F/344 Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

	Dose (mg chromium(VI)/kg/day)				
	0	0.21	0.77	2.1	5.9
Male rats					
Hematocrit (percent)	46.0±1.1[a]	44.4±0.4	43.2±0.6[b]	38.7±0.6[c]	33.5±0.8[c]
Hemoglobin (g/dL)	15.5±0.3	15.1±0.2	14.2±0.2[c]	12.0±0.3[c]	10.1±0.2[c]
MCV (fL)	59.5±0.4	58.6±0.5	54.9±0.5[c]	47.4±0.4[c]	45.0±0.7[c]
MCH (pg)	19.8±0.1	19.5±0.2	17.7±0.2[c]	14.8±0.2[c]	16.3±0.5[c]

[a]Mean±standard error: number of rats/group=10; number of mice/group=10
[b]Significantly different ($p \leq 0.05$) from the control group by Dunn's or Shirley's test
[c]Significantly different ($p \leq 0.01$) from the control group by Dunn's or Shirley's test

MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume

Source: NTP 2008a

To determine the point of departure for derivation of the intermediate-duration oral MRL, available continuous-variable models in the EPA BMDs (version 1.4.1) were fit to the data for Hct, Hgb, MCV, and MCH in male rats (NTP 2008a; Table A-1). The BMD and the 95% lower confidence limit (BMDL) calculated is an estimate of the doses associated with a change of 2 standard deviations from the control ($BMDL_{2sd}$); the use of 2 standard deviations takes into consideration of the normal variability in the population and decreases the possibility of misclassifying a small change as anemia. The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the tests for both constant and nonconstant variance are negative, then the data set is considered not to be suitable for BMD modeling.

A summary of the BMDs and BMDLs for the best fitting models for each hematological end point are shown in Table A-2. For male rats, $BMDL_{2sd}$ values ranged from 0.37 mg chromium(VI)/kg/day for MCH to 0.71 mg chromium(VI)/kg/day for hemoglobin. None of the models provided adequate fit to the data, even with the two highest doses dropped from the analysis, for Hct. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. Because several hematological parameters are used to define the clinical picture of anemia, the $BMDL_{2sd}$ values for hemoglobin, MCV, and MCH were averaged resulting in a $BMDL_{2sd}$ of 0.52 mg chromium(VI)/kg/day. The intermediate-duration MRL of 0.005 mg chromium(VI)/kg/day was derived by dividing the average $BMDL_{2sd}$ by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Table A-2. Summary of BMDs and BMDLs From the Best Fitting Models for Hematological End Points in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

End point	Model	Number of doses	BMD_{2sd} (mg/kg/day)[b]	$BMDL_{2sd}$ (mg/kg/day)[b]
Hematocrit (percent)[a]	——	——	——	——
Hemoglobin (g/dL)	Polynomial (2-degree)	5	0.88	0.71
MCV (fL)	Hill	4	0.63	0.49
MCH (pg)	Linear	4	0.44	0.37

[a]None of the models provided an adequate fit to the data.
[b]Units of BMD_{1sd} and $BMDL_{1sd}$ are mg chromium(VI)/kg/day.

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; 2sd = a 2 standard deviation change from the control

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Daily doses for each exposure group based on measured body weight and drinking water intake were reported by study authors (NTP 2008a). Additional information on daily doses used for intermediate-duration exposure is discussed in the experimental design section above.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Identification of anemia, as defined by significant alterations in hematocrit, hemoglobin, MCH, and MCV, as the critical end point for deriving an intermediate-duration oral MRL is supported by results of a 22-day study in female mice (NTP 2008a), 3-month drinking water study on sodium dichromate dihydrate in rats and mice (NTP 2007), and dietary studies on potassium dichromate in rats and mice (NTP 1996a, 1996b, 1997). In the 3-month sodium dichromate dihydrate drinking water study in male and female F344/N rats (NTP 2007), blood was collected for hematology assessments after 23 days and after 3 months of exposure; for B6C3F1 mice, hematological assessments were conducted only after 3 months. Dose-dependent hematological effects consistent with microcytic, hypochromic anemia, including decreased Hct, Hgb, MCV, and MCH, were observed in rats at the 23-day and 14-week hematological assessments; the LOAEL value at both time points in males and females was 1.7 mg chromium(VI)/kg/day (a NOAEL was not established). Hematological effects were more severe at the 23-day assessment compared to the 14 week assessment. Similar hematological effects were observed in male and female B6C3F1 mice and male BALB/c and C57BL/6 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, with a LOAEL value of 3.1 mg chromium(VI)/kg/day (a NOAEL was not established). Results of the 3-month study in rats and mice (NTP 2007) were not selected as the basis for the

intermediate-duration MRL because a lower LOAEL value (0.77 mg chromium(VI)/kg/day) was observed for intermediate-duration exposures in the 2-year study (NTP 2008a). In a dietary studies on potassium dichromate, microcytic, hypochromic anemia was observed in male and female Sprague-Dawley rats exposed for 9 weeks, with NOAEL and LOAEL values in males of 2.1 and 8.4 mg chromium(VI)/kg/day, respectively, and of 2.5 and 9.8 mg chromium(VI)/kg/day, respectively, in females (NTP 1996b). Similar hematological effects were observed in male and female BALB/c mice exposed to potassium dichromate in the diet for 9 weeks with NOAEL and LOAEL values in males of 7.3 and 32.2 mg chromium(VI)/kg/day, respectively, and in females of 12 and 48 mg chromium(VI)/kg/day, respectively (NTP 1996a). In a multigeneration study on dietary potassium dichromate in BALB/c mice, a LOAEL value of 7.8 for hematological effects was reported (a NOAEL was not established) (NTP 1997). Compared to the LOAEL values for hematological effects at 22 days and 3 months in male rats (0.77 mg chromium(VI)/kg/day) and female mice (0.38 mg chromium(VI)/kg/day) observed in the critical study on sodium dichromate dihydrate in drinking water, higher LOAEL values were reported in the 9-week dietary study on potassium dichromate in rats (8.4 and 9.8 mg chromium(VI)/kg/day in males and females, respectively) (EPA 1996b) and mice (32.2 and 48 mg chromium(VI)/kg/day in males and females, respectively) (NTP 1996a). The reason for the differences in LOAEL values has not been established, but could be due to different exposure media (drinking water versus feed) or differences in strain sensitivity (rats).

The erythrocyte has a high capacity for chromium(VI) uptake and binding. Chromium(VI) enters the erythrocyte though a sulfate ion channel; once inside the cell, it is rapidly reduced to reactive intermediates (chromium(V) and chromium(IV)) and binds to hemoglobin and other ligands. The chromium-hemoglobin complex is stable and remains sequestered within the cell over the life-span of the erythrocyte (Paustenbach et al. 2003). Thus, chromium(VI) uptake and subsequent sequestration as a chromium-Hgb complex by erythrocytes provides supporting information regarding the plausibility of adverse hematological effects following intermediate-duration oral exposure to chromium(VI).

Details of Benchmark Dose Analysis for the Intermediate-duration Oral MRL

Hematocrit in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data (Table A-3). The linear model was applied to the data again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model also did not provide an adequate fit (as assessed by the p-value for variance). In an attempt to achieve an adequate fitting model, the highest doses were dropped from the data set. As with the full data set, statistical tests indicated that the variances were not constant across exposure groups without the highest doses. Similar to the full data set, applying the nonhomogenous variance model also did not provide an adequate fit (as assessed by the p-value for variance); therefore, the data set is considered not suitable for benchmark dose modeling.

Table A-3. Model Predictions for Changes in Hematocrit (Percent) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

Model	Variance p-value[a]	p-Value for the means[a]	AIC	BMD_{2sd} (mg/kg/day)	$BMDL_{2sd}$ (mg/kg/day)
All doses					
Linear[b,c]	0.03	0.02	145.49	—	—
Linear[c,d]	0.01	0.02	147.49	—	—
Polynomial (1-degree)[c,d]	0.01	0.02	147.49	—	—
Polynomial (2-degree)[c,d]	0.01	0.02	147.49	—	—
Polynomial (3-degree)[c,d]	0.01	0.02	147.49	—	—
Polynomial (4-degree)[c,d]	0.01	0.02	147.49	—	—
Power[d]	0.01	0.02	147.49	—	—
Hill[d]	0.01	0.28	142.76	—	—
Highest dose dropped					
Linear[b,c]	0.01	0.64	109.33	—	—
Linear[c,d]	0.02	0.43	109.21	—	—
Polynomial (1-degree)[c,d]	0.02	0.43	109.21	—	—
Polynomial (2-degree)[c,d]	0.02	0.43	109.21	—	—
Polynomial (3-degree)[c,d]	0.02	0.43	109.21	—	—
Power[d]	0.02	0.43	109.21	—	—
Hill[d]	0.02	0.21	111.09	—	F[e]
Two highest doses dropped					
Linear[b,c]	0.01	0.37	86.65	—	—
Linear[c,d]	0.02	0.15	85.61	—	—
Polynomial (1-degree)[c,d]	0.02	0.15	85.61	—	—
Polynomial (2-degree)[c,d]	0.02	0.15	85.61	—	—
Power[d]	0.02	0.15	85.61	—	—
Hill[d]	NA[f]				

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance
[c]Restriction = non-positive
[d]Nonconstant variance
[e]F = BMDL computation failed
[f]NA = model failed to generate output

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

Hemoglobin in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. Only the Hill model provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-4); however, the model failed to generate a figure. Without a visual representation of the model, an assessment of model fit is not complete. In order to obtain an appropriate

assessment for model fit adequacy, the highest dose was dropped from the dataset. After dropping the highest dose from the dataset, all models provided an adequate fit to the constant variance model and to the means (as assessed by the p-values for variance and means). Most models, with the exception of the Hill model, took the form of a linear model. Comparing across models, the best fitting model is generally determined by the lowest AIC. As assessed by the AIC, the linear model provides the best fit to the data. The predicted BMD_{2sd} and $BMDL_{2sd}$ for the data are 0.88 and 0.71 mg chromium(VI)/kg/day (Figure A-1).

Table A-4. Model Predictions for Changes in Hemoglobin (g/dL) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

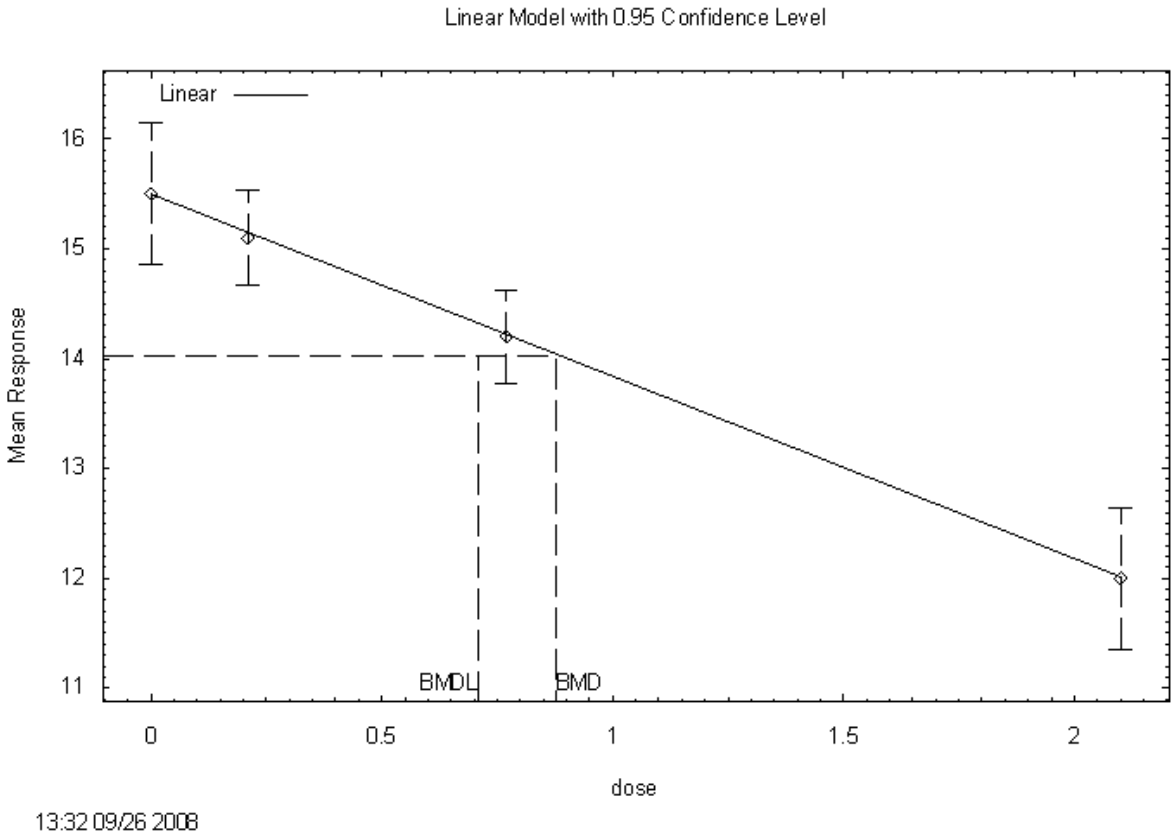
Model[a]	Variance p-value[b]	p-Value for the means[b]	AIC	BMD_{2sd} (mg/kg/day)	$BMDL_{2sd}$ (mg/kg/day)
Linear[c]	0.40	<0.0001	46.98	—	—
Polynomial (1-degree)[c]	0.40	<0.0001	46.98	—	—
Polynomial (2-degree)[c]	0.40	<0.0001	46.98	—	—
Polynomial (3-degree)[c]	0.40	<0.0001	46.98	—	—
Polynomial (4-degree)[c]	0.40	<0.0001	46.98	—	—
Power	0.40	<0.0001	46.98	—	—
Hill	0.40	0.51	24.37	0.83	0.55
Highest dose dropped					
Linear	**0.36**	**0.99**	**20.37**	**0.88**	**0.71**
Polynomial (1-degree)[c]	0.36	0.99	20.37	0.88	0.71
Polynomial (2-degree)[c]	0.36	0.99	20.37	0.88	0.71
Polynomial (3-degree)[c]	0.36	0.99	20.37	0.88	0.71
Power	0.36	0.99	20.37	0.88	0.71
Hill	0.36	0.99	22.36	0.87	0.57

[a]Constant variance assumed for all models
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Restriction = non-positive

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

Figure A-1. Predicted and Observed Changes in Hemoglobin in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days*



*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Mean Cell Volume in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. The Hill model was the only model which provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-5). Using the constant-variance Hill model, the BMD_{2sd} and $BMDL_{2sd}$ are 0.63 mg chromium(VI)/kg and 0.49 mg chromium(VI)/kg, respectively (Figure A-2).

Table A-5. Model Predictions for Changes in MCV (fL) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

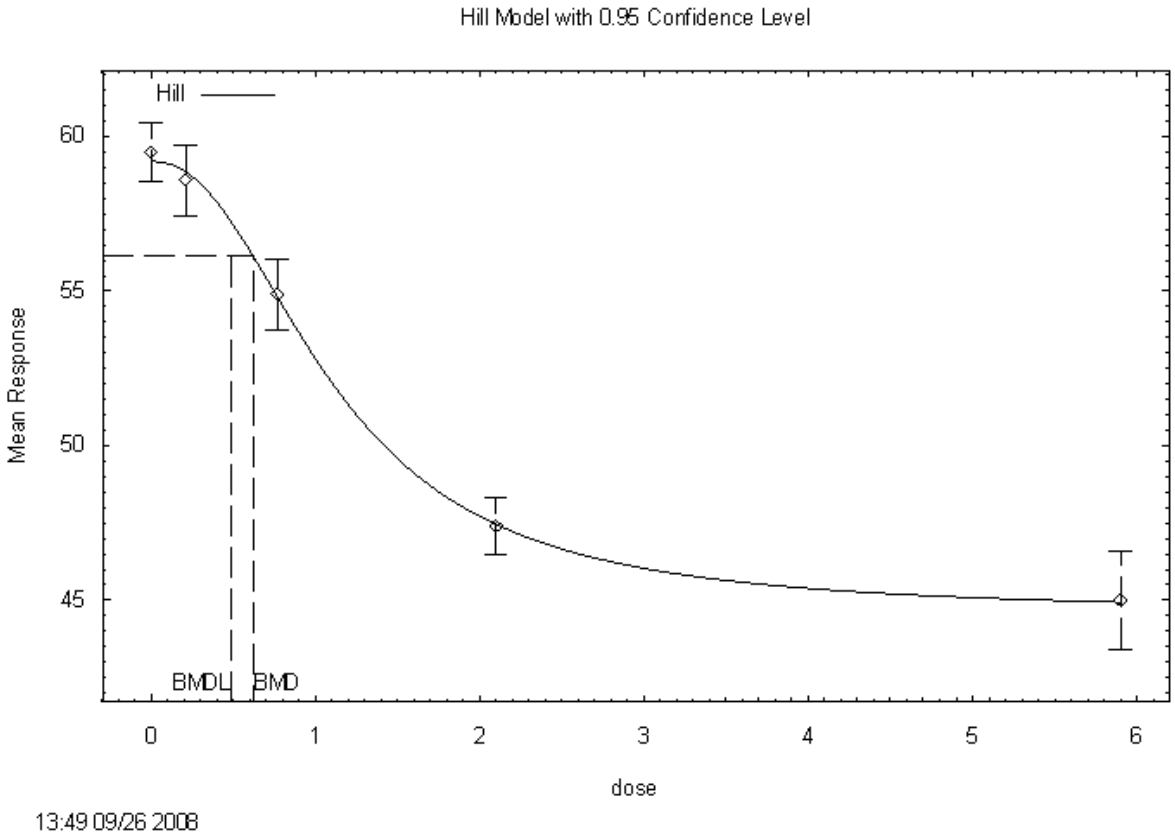
Model[a]	Variance p-value[b]	p-Value for the means[b]	AIC	BMD_{2sd} (mg/kg/day)	$BMDL_{2sd}$ (mg/kg/day)
Linear[c]	0.41	<0.0001	168.50	—	—
Polynomial (1-degree)[c]	0.41	<0.0001	168.50	—	—
Polynomial (2-degree)[c]	0.41	<0.0001	168.50	—	—
Polynomial (3-degree)[c]	0.41	<0.0001	168.50	—	—
Polynomial (4-degree)[c]	0.41	<0.0001	168.50	—	—
Power	0.41	<0.0001	168.50	—	—
Hill	**0.41**	**0.41**	**104.52**	**0.63**	**0.49**

[a]Constant variance assumed for all models
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Restriction = non-positive

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

Figure A-2. Predicted and Observed Changes in MCV in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days*



*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day

Source: NTP 2008a

Mean Cell Hemoglobin in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model also did not provide an adequate fit (as assessed by the p-value for variance). In an attempt to achieve an adequate fitting model, the highest dose was dropped from the data-set. Unlike the full data-set, statistical tests indicated that the variances were constant across exposure groups without the highest dose. All of the models reverted to the linear model and provided an adequate fit to the means (Table A-6). Using the constant-variance Linear model (without the highest dose), the BMD_{2sd} and $BMDL_{2sd}$ are 044 and 0.37 mg chromium(VI)/kg, respectively (Figure A-3).

Table A-6. Model Predictions for Changes in MCH (pg) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

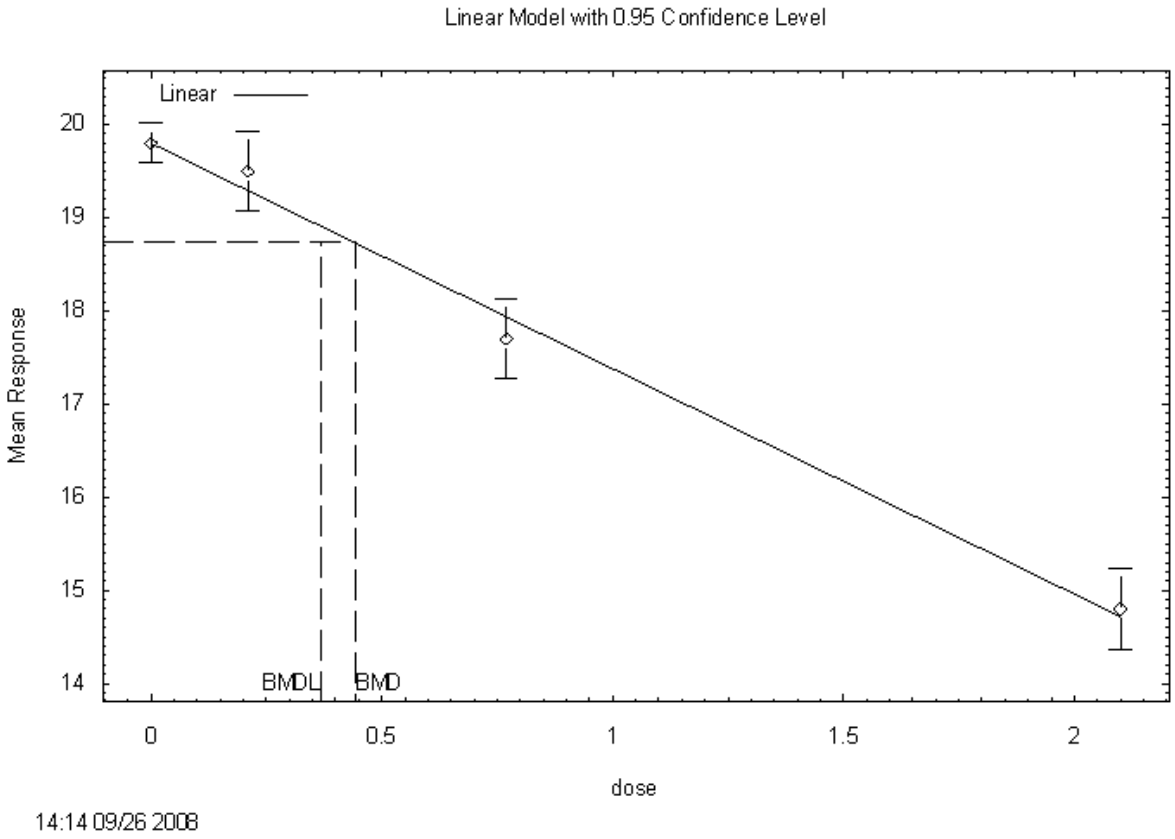
Model	Variance p-value[b]	p-Value for the means[b]	AIC	BMD_{2sd} (mg/kg/day)	$BMDL_{2sd}$ (mg/kg/day)
All doses					
Linear[b,c]	<0.0001	<0.0001	107.27	—	—
Linear[c,d]	0.00	<0.0001	57.60	—	—
Polynomial (1-degree)[c,d]	0.00	<0.0001	57.60	—	—
Polynomial (2-degree)[c,d]	0.00	<0.0001	57.60	—	—
Polynomial (3-degree)[c,d]	0.00	<0.0001	57.60	—	—
Polynomial (4-degree)[c,d]	0.00	<0.0001	57.60	—	—
Power[d]	0.00	<0.0001	57.60	—	—
Hill[d]	0.00	0.02	34.64	—	—
Highest dose dropped (four doses)					
Linear[b,c]	**0.14**	**0.15**	**-3.57**	**0.44**	**0.37**
Polynomial (1-degree)[b,c]	0.14	0.15	-3.57	0.44	0.37
Polynomial (2-degree)[b,c]	0.14	0.15	-3.57	0.44	0.37
Polynomial (3-degree)[b,c]	0.14	0.15	-3.57	0.44	0.37
Power[b]	0.14	0.15	-3.57	0.44	0.37
Hill[b]	0.14	NA[e]	-3.39	0.46	0.32

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance
[c]Restriction = non-positive
[d]Nonconstant variance
[e]NA = degrees of freedom are ≤0; the Chi-Square test for fit is not valid.

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

Figure A-3. Predicted and Observed Changes in MCH in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days*



*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chromium(VI)
CAS Numbers: 18540-29-9
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 95
Species: Mouse

Minimal Risk Level: 0.001 [X] mg chromium(VI)/kg/day [ ] ppm

Reference: NTP. 2008a. NTP technical report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate (CAS No. 7789-12-0) in F344/N rats and B6C3F1 mice (drinking water studies). Washington, DC: National Toxicology Program. NTP TR 546. http://ntp.niehs.nih.gov/files/546_web_FINAL.pdf. August 13, 2008.

Experimental design: Groups of F344/N rats (50/sex/group) and B6C3F1 mice (50/sex/group) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study. Rats and female mice were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. NTP (2008a) calculated mean daily doses of sodium dichromate dihydrate in male rats of 0, 0.6, 2.2, 6, or 17 mg/kg (equivalent to 0, 0.21, 0.77, 2.1, or 5.9 mg chromium(VI)/kg/day, respectively), in female rats of 0, 0.7, 2.7, 7, or 20 mg/kg (equivalent to 0, 0.24, 0.94, 2.4, and 7.0 mg chromium(VI)/kg/day, respectively), and in female mice of 0, 1.1, 3.9, 9, or 25 mg/kg (equivalent to 0, 0.38, 1.4, 3.1, or 8.7 mg chromium(VI)/kg/day, respectively) over the course of the 2-year study. Male mice were exposed to 0, 14.3, 28.6, 85.7, or 257.4 mg sodium dichromate dihydrate/L. NTP (2008a) calculated mean daily doses of sodium dichromate dihydrate in male mice of 1.1, 2.6, 7, or 17 mg/kg (equivalent to 0, 0.38, 0.91, 2.4, and 5.9 mg chromium(VI)/kg/day, respectively). Mortality, clinical signs of toxicity, body weight, and water intake were assessed over the course of exposure. In a subgroup of 10 male rats and 10 female mice, blood was collected from the retroorbital sinus after exposure durations of 4 days (rats only), 22 days, 3 months, 6 months, and 1 year and evaluated for hematology (Hct; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; MCV; MCH; MCHC; and leukocyte count and differentials) in rats and mice and clinical chemistry (urea nitrogen, creatinine, total protein, albumin, ALT, AP, creatine kinase, SDH, and bile acids) in rats only. Blood for hematology and clinical chemistry was not obtained at the end of the 2-year treatment period. At the end of the 2-year treatment period, necropsies and histopathological assessment of comprehensive tissues, gross lesions and tissue masses were performed on all animals. No data on organ weights were presented in the study report (NTP 2008a).

Effect noted in study and corresponding doses: Study results presented in the following discussion are noncancer findings associated with chronic-duration exposures only; results of hematological and clinical chemistry assessments conducted at 4 days and from 22 days to 6 months are described in the acute- and intermediate-duration MRL worksheets, respectively; carcinogenic effects are reviewed in Section 3.2.2.7 (Oral Exposure, Cancer). In rats, no treatment-related effects were observed on survival and no clinical signs of toxicity were observed. Final body weight was significantly decreased by 12% in male and 11% in females exposed to the highest drinking water concentration. Study authors attributed alterations in body weight to decreased water intake (due to decreased palatability) rather than to a toxicological effect. Hematological assessments conducted in male rats at 1-year showed dose-dependent effects indicative of microcytic, hypochromic anemia: decreased MCH (≥0.77 mg chromium(VI)/kg/day), decreased MCV and MCHC (≥2.1 mg chromium(VI)/kg/day), and decreased Hgb (5.9 mg chromium(VI)/kg/day). No

hematological effects were observed at 2.1 mg chromium(VI)/kg/day. Other hematological effects observed were decreased leukocyte (5.9 mg chromium(VI)/kg/day) and segmented neutrophil counts (≥0.77 mg chromium(VI)/kg/day). Alterations in clinical chemistry parameters observed after 1 year of exposure were increased ALT and decreased AP (≥0.77 mg chromium(VI)/kg/day), increased BUN and creatine kinase (≥2.1 mg chromium(VI)/kg/day), and decreased total protein (5.9 mg chromium(VI)/kg/day). Regarding the toxicological significance of elevated ALT, as discussed below, histopathological assessment of the liver showed minimal-to-mild chronic inflammation in males (≥2.1 mg chromium(VI)/kg/day) and females (≥0.24 mg chromium(VI)/kg/day). However, since serum activities of AP, SDH, or bile acids were not increased, elevated serum ALT activity may have resulted from enzyme induction rather than hepatocellular injury. Histopathological evaluations revealed an increased incidence of nonneoplastic lesions in the liver (males and females), small intestine (males and females), mesenteric lymph nodes (males and females), pancreatic lymph nodes (females only) and salivary gland (females only). Hepatic lesions observed in male rats included minimal-to-mild chronic inflammation (≥0.77 mg chromium(VI)/kg/day) and histiocytic cellular infiltration (5.9 mg chromium(VI)/kg/day); hepatic lesions in females included chronic inflammation (≥0.24 mg chromium(VI)/kg/day), histiocytic cellular infiltration (≥0.94 mg chromium(VI)/kg/day) and fatty change (≥0.94 mg chromium(VI)/kg/day). Although chronic hepatic inflammation is commonly observed in aging rats, the incidence was significantly enhanced by exposure. Histiocytic cellular infiltration (minimal-to-mild) of the duodenum, was observed in males (≥0.77 mg chromium(VI)/kg/day) and females (≥2.4 mg chromium(VI)/kg/day). Nonneoplastic lesions of lymph nodes included the following: histocytic cellular infiltration of mesenteric lymph nodes in males and females at ≥0.77 and ≥2.4 mg chromium(VI)/kg/day, respectively; hemorrhage of mesenteric lymph nodes in males and females at ≥0.77 and ≥7.0 mg chromium(VI)/kg/day, respectively; and histocytic cellular infiltration of pancreatic lymph nodes in females at ≥2.4 mg chromium(VI)/kg/day only. The incidence of salivary gland atrophy was significantly in female rats at 2.4 mg chromium(VI)/kg/day; although the incidence was also increased at 7.0 mg chromium(VI)/kg/day, the change was not significantly different from control. Salivary atrophy was not observed in male rats. No data on organ weights were presented in the study report (NTP 2008a).

In mice, no treatment-related effects on survival or signs of toxicity were observed. Final body weight was significantly decreased by 15% in male and 8% in females exposed to the highest drinking water concentration. The study authors attributed the alterations in body weight to decreased water intake (due to decreased palatability) rather than to a toxicological effect. Hematological assessments conducted in female mice at 1 year showed dose-dependent effects indicative of microcytic, hypochromic anemia and compensatory erythropoiesis: decreased MCV and MCH (≥3.1 mg chromium(VI)/kg/day) and increased erythrocyte count at ≥3.1 mg chromium(VI)/kg/day. Platelet count and segmented neutrophil count were decreased at 8.7 mg chromium(VI)/kg/day. Severity of hematological effects on mice was less than in rats. Clinical chemistry was not evaluated in male or female mice. Histopathological evaluations revealed an increased incidence of nonneoplastic lesions in the liver (females), small intestine (male and females), and mesenteric and pancreatic lymph nodes (males and females). Histiocytic cellular infiltration of the liver was observed in all treatment groups, with incidence and severity exhibiting dose-dependence. Chronic inflammation of the liver was also observed in females at ≥3.1 mg chromium(VI)/kg/day. In males, only pre-neoplastic (clear cell and eosinophilic foci) lesions were observed at the highest dose tested. Diffuse epithelial hyperplasia of the duodenum was observed in all treatment groups in males and females (≥0.38 mg chromium(VI)/kg/day), with histiocytic cellular infiltration of the duodenum in males and females at ≥2.4 and 3.1 mg chromium(VI)/kg/day, respectively. Histiocytic cellular infiltration was observed in mesenteric lymph nodes in all treatment groups in males and females (≥0.38 mg chromium(VI)/kg/day) and in pancreatic lymph nodes at ≥2.4 and ≥3.1 mg chromium(VI)/kg/day in males and females, respectively. Increased incidence of cytoplasm alteration of the pancreas (depletion of zymogen granules from acinar epithelial cells) was observed in males at

≥2.4 mg chromium(VI)/kg/day and in females in all treatment groups (≥0.38 mg chromium(VI)/kg/day); the toxicological significance of this finding is not clear.

Dose and end point used for MRL derivation: 0.09 mg chromium(VI)/kg/day (diffuse epithelial hyperplasia of the duodenum)

[ ] NOAEL [ ] LOAEL [X] benchmark dose (BMD)

Chronic-duration exposure of rats and mice to sodium dichromate dihydrate in drinking water resulted in microcytic, hypochromic anemia and nonneoplastic lesions of the liver, duodenum, mesenteric and pancreatic lymph nodes, pancreas and salivary gland. Based on comparison of LOAEL values (Table A-7), the lowest LOAELs were observed for histopathological changes of the liver (chronic inflammation in female rats and histiocytic cellular infiltration in female mice), duodenum (diffuse epithelial hyperplasia in male and female mice), mesenteric lymph node (histiocytic cellular infiltration in male and female mice) and pancreas (cytoplasm cellular alteration of acinar epithelial cells in female mice), with effects occurring in all treatment groups. Therefore, all effects with LOAEL values of the lowest dose tested were considered as the possible the critical effect for derivation of the chronic-duration oral MRL. Incidence data for these lesions are summarized in Table A-8.

Table A-7. NOAEL and LOAEL Values for Effects in Rats and Mice Exposed to Sodium Dichromate Dihydrate in Drinking Water for 1–2 Years

	NOAEL/LOAEL value (mg chromium(VI)/kg/day)			
Effect or tissue with lesion	Male rats	Female rats	Male mice	Female mice
Hematological effects	0.21/0.77	N/A	N/A	1.4/3.1
Liver	0.21/0.77	0.24[a]	2.4/5.9[c]	0.38[a]
Duodenum	0.21/0.77	0.94/2.4	0.38[a]	0.38[a]
Mesenteric lymph node	0.21/0.77	0.94/2.4	0.38[a]	0.38[a]
Pancreatic lymph node	N/O	0.94/2.4	0.91/2.4	1.4/3.1
Pancreas	N/O	N/O	0.91/2.4	0.38[a]
Salivary gland	N/O	2.4[b]	N/O	N/O

[a]No NOAEL value was identified; effects occurred in all treatment groups
[b]Not observed at other doses
[c]Pre-neoplastic lesions

LOAEL = lowest-observed-adverse-effect level; N/A = not assessed; N/O = effect not observed; NOAEL = no-observed-adverse-effect level

Source: NTP 2008a

Table A-8. Incidence Data for Nonneoplastic Lesions[a] Occurring in All Treatment Groups of Female F/344 Rats and Male and Female B6C3F1 Mice Exposed to Sodium Dichromate Dihydrate in Drinking Water for 2 Years

	Dose (mg chromium(VI)/kg/day)				
	0	0.24	0.94	2.4	7.0
Female rats					
Liver, chronic inflammation	12/50[b] (1.3)	21/50[c] (1.2)	28/50[d] (1.3)	35/50[d] (1.6)	39/50[d] (2.1)
	Dose (mg chromium(VI)/kg/day)				
	0	0.38	0.91	2.4	5.9
Male mice					
Duodenum: diffuse epithelial hyperplasia	0/50	11/50[d] (2.0)	18/50[d] (1.6)	42/50[d] (2.1)	32/50[c] (2.1)
Mesenteric lymph node: histiocytic cellular infiltration	14/47 (1.2)	38/47[d] (1.1)	31/49[d] (1.2)	32/49[d] (1.5)	42/46[c] (2.5)
	Dose (mg chromium(VI)/kg/day)				
	0	0.38	1.4	3.1	8.7
Female mice					
Duodenum: diffuse epithelial hyperplasia	0/50	16/50[d] (1.6)	35/50[d] (1.7)	31/50[d] (1.6)	42/50[d] (2.2)
Mesenteric lymph node: histiocytic cellular infiltration	3/46 (1.0)	29/48[d] (1.3)	26/46[d] (1.1)	40/50[d] (1.9)	42/50[d] (2.7)
Liver: histiocytic cellular infiltration	2/49 (1.0)	15/50[d] (1.1)	23/50[d] (1.0)	32/50[d] (1.0)	45/50[d] (1.9)
Pancreas: acinus, cytoplasmic alteration	0/48	6/50[c] (2.5)	6/49[c] (2.0)	14/50[d] (2.4)	32/50[d] (2.6)

[a]Lesion severity (1=minimal, 2=mild, 3=moderate, 4=marked)
[b]Number of animals with lesions/number of animals examined
[c]Significantly different (p≤0.05) from the control group by Dunn's or Shirley's test
[d]Significantly different (p≤0.01) from the control group by Dunn's or Shirley's test

Source: NTP 2008a

To determine the specific end point for derivation of the chronic-duration oral MRL, all available dichotomous models in the EPA (version 1.4.1) were fit to the incidence data for selected end points in female rats and male and female mice exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a) (Table A-8). To provide potential points of departure for MRL derivation, 10% extra risk was selected as the benchmark response in accordance with U.S. EPA (2000) technical guidance for benchmark dose analysis to select a response level near the lower range of detectable observations. The BMD_{10s} and $BMDL_{10s}$ from the best fitting models for nonneoplastic lesions of the liver (female rats and mice), duodenum (male and female mice), mesenteric lymph nodes (male and female mice), and pancreas (female mice) are shown in Table A-9. For chronic inflammation of the liver in female rats, the log-logistic model provided the best fit, with BMD_{10} and $BMDL_{10}$ values of 0.22 and 0.14 mg chromium(VI)/kg/day, respectively. For diffuse epithelial hyperplasia in male mice, the multistage and quantal linear models provided the best fit, with BMD_{10} and $BMDL_{10}$ values of 0.16 and 0.13 mg chromium(VI)/kg/day, respectively. For diffuse epithelial hyperplasia in female mice, the best

fit was provided by several models (gamma, multistage, quantal linear, and weibull) with BMD_{10} and $BMDL_{10}$ values of 0.12 and 0.09 mg chromium(VI)/kg/day, respectively. For histiocytic alteration of the liver and cytoplasm alteration of the pancreas in female mice, the log-logistic model provided the best fit, with BMD_{10} and $BMDL_{10}$ values of 0.17 and 0.12 mg chromium(VI)/kg/day, respectively, for liver lesions and of 0.68 and 0.52 mg chromium(VI)/kg/day, respectively, for pancreas lesions. For lesions of the mesenteric lymph nodes in male and female mice, none of the models provided adequate fit to the data, even with the two highest doses dropped from the analysis; thus, data sets for these lesions were considered not suitable for BMD analysis. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. Based on the lowest $BMDL_{10}$ value of 0.09 mg chromium(VI)/kg/day, diffuse epithelial hyperplasia of the duodenum in female mice was selected as the point of departure for derivation of the chronic-duration oral MRL. The chronic-duration oral MRL based on nonneoplastic lesions of the duodenum in female mice is expected to be protective for all other adverse effects observed in the 2-year drinking water study (e.g., hematological effects and lesions of the liver, lymph nodes, pancreas, and salivary gland). The chronic-duration MRL of 0.001 mg chromium(VI)/kg/day was derived by dividing the $BMDL_{10}$ by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Table A-9. Summary of BMD_{10} and $BMDL_{10}$ from the Best Fitting Models for Nonneoplastic Lesions of the Liver, Duodenum, Mesenteric Lymph Nodes, and Pancreas in Female Rats and Male and Female Mice After Exposure to Sodium Dichromate Dihydrate in Drinking Water for 2 Years

End point	Species/sex	Model	Number of doses	BMD[a] (mg/kg/day)	BMDL[a] (mg/kg/day)
Liver, chronic inflammation	Rat/female	Log-logistic	5	0.22	0.14
Duodenum: diffuse epithelial hyperplasia	Mouse/male	1-Degree polynomial multistage/quantal linear	4	0.16	0.13
Mesenteric lymph node: histiocytic cellular infiltration[b]	Mouse/male	—	—	—	—
Duodenum: diffuse epithelial hyperplasia	**Mouse/female**	**Gamma/Multistage/quantal linear/weibull**	**3**	**0.12**	**0.09**
Mesenteric lymph node: histiocytic cellular infiltration[b]	Mouse/female	—	—	—	—
Liver: histiocytic cellular infiltration	Mouse/female	Log-logistic	5	0.17	0.12
Pancreas: acinus, cytoplasmic alteration	Mouse/female	Log-logistic	5	0.68	0.52

[a]BMDs and BMDLs from dichotomous data are associated with a 10% extra risk; doses are in terms of mg chromium(VI)/kg/day.
[b]None of the models provided an adequate fit to the data.

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Daily doses for each treatment group were reported by study authors (NTP 2008a) based on body weights and water intake over the 2-year exposure period.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Selection of nonneoplastic lesions of the duodenum in female mice is as the critical effect for the chronic-duration oral MRL is supported by observations from the same study showing adverse gastrointestinal effects in male mice (diffuse epithelial hyperplasia at ≥0.38 mg chromium(VI)/kg/day and histiocytic cellular infiltration at 5.9 mg chromium(VI)/kg/day) and in male and female rats (histiocytic cellular infiltration at ≥0.77 and ≥0.94 mg chromium(VI)/kg/day, respectively) exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a). Although no other chronic-duration studies on oral chromium(VI) in animals were identified, a 3-month study on sodium dichromate dihydrate in drinking water revealed adverse gastrointestinal effects in rats and mice (including a comparative study in 3 mouse strains) (NTP 2007). Epithelial hyperplasia and histiocytic cellular infiltration of the duodenum was observed at ≥3.1 and ≥5.9 mg chromium(VI)/kg/day, respectively, in male and female B6C3F1 mice. Similar nonneoplastic lesions of the duodenum were also reported in the 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice, with epithelial hyperplasia at ≥2.8 mg chromium(VI)/kg/day in B6C3F1 and BALB/c strains and ≥5.2 in the C57BL/6 strain, and histiocytic cellular infiltration at ≥2.8 mg chromium(VI)/kg/day in B6C3F1 and C57BL/6 strains and ≥5.2 mg chromium(VI)/kg/day in the BALB/c strain. In male and female F344/N rats, histiocytic cellular infiltration was observed at ≥3.5 mg chromium(VI)/kg/day. At a higher daily dose (20.9 mg chromium(VI)/kg/day), ulcer, epithelial regenerative focal hyperplasia, and epithelial focal squamous metaplasia of the glandular stomach were observed.

Details of Benchmark Dose Analysis for the Chronic-duration Oral MRL

Chronic Inflammation of the Liver in Female Rats. As assessed by the chi-square goodness-of-fit statistic, only the log-logistic model provided an adequate fit (X^2 p-value ≥0.1) to the data (Table A-10). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.22 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.14 mg chromium(VI)/kg/day (Figure A-4).

Table A-10. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Chronic Inflammation of the Liver in Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

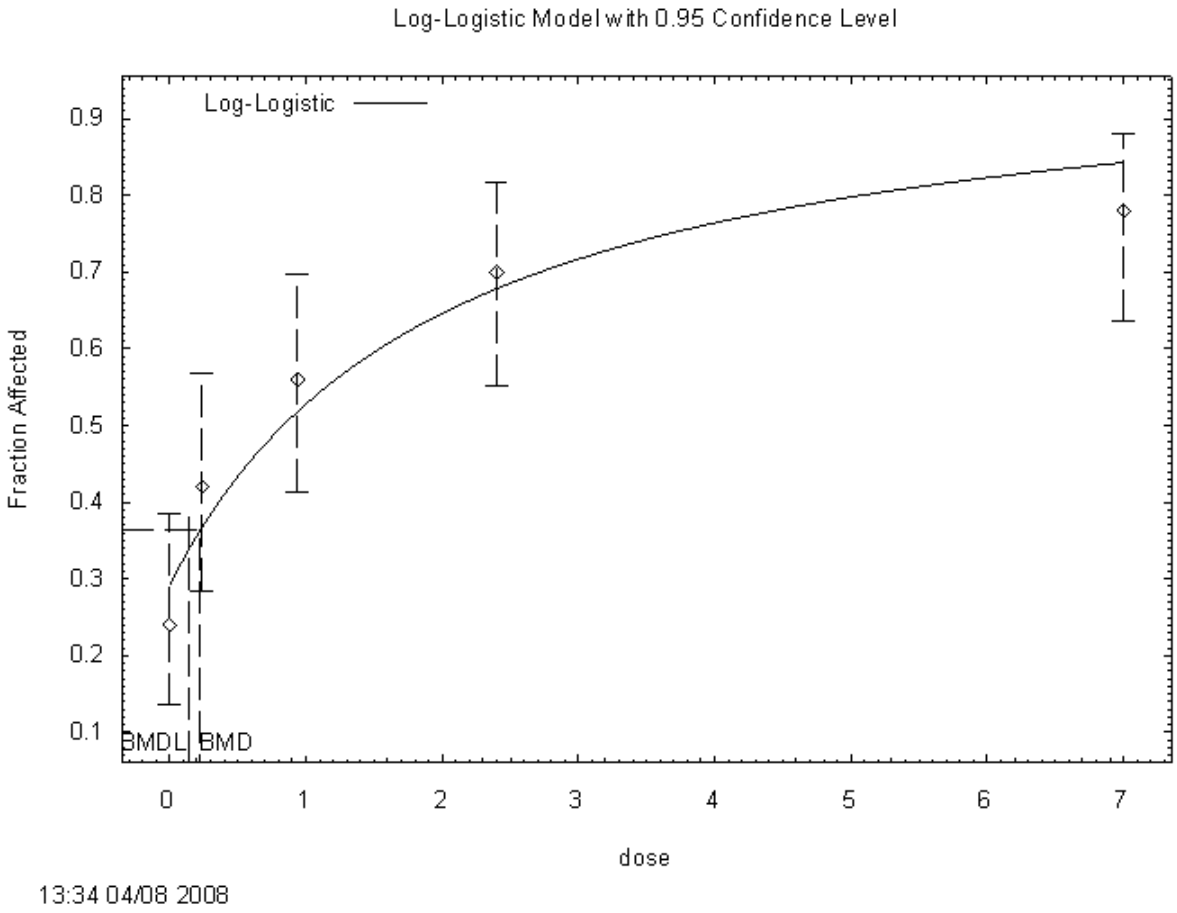
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
Gamma[a]	0.51	0.37	0.04	317.97
Logistic	0.84	0.65	0.01	321.45
Log-logistic[b]	**0.22**	**0.14**	**0.37**	**312.57**
Multi-stage[c]	0.51	0.37	0.04	317.97
Probit	0.88	0.70	0.01	321.80
Log-probit[b]	0.89	0.61	0.01	320.86
Quantal linear	0.51	0.37	0.04	317.97
Weibull[a]	0.51	0.37	0.04	317.97

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Figure A-4. Predicted and Observed Incidence of Chronic Inflammation of the Liver in Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Diffuse Epithelial Hyperplasia of the Duodenum in Male Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value $\geq$0.1) to the full dataset (Table A-11). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. After dropping the highest dose, the gamma, log-logistic, multistage, log-probit, quantal linear, and weibull models provided adequate fits to the data (X^2 p-value >0.1). Comparing across models, a better fit is generally indicated by a lower AIC (EPA 2000). As assessed by AIC, the 1-degree polynomial multistage model provided the best fit to the data (Figure A-5). Based on the multistage model, the BMD associated with a 10% extra risk was 0.16 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.13 mg chromium(VI)/kg/day.

Table A-11. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Diffuse Epithelial Hyperplasia in the Duodenum in Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

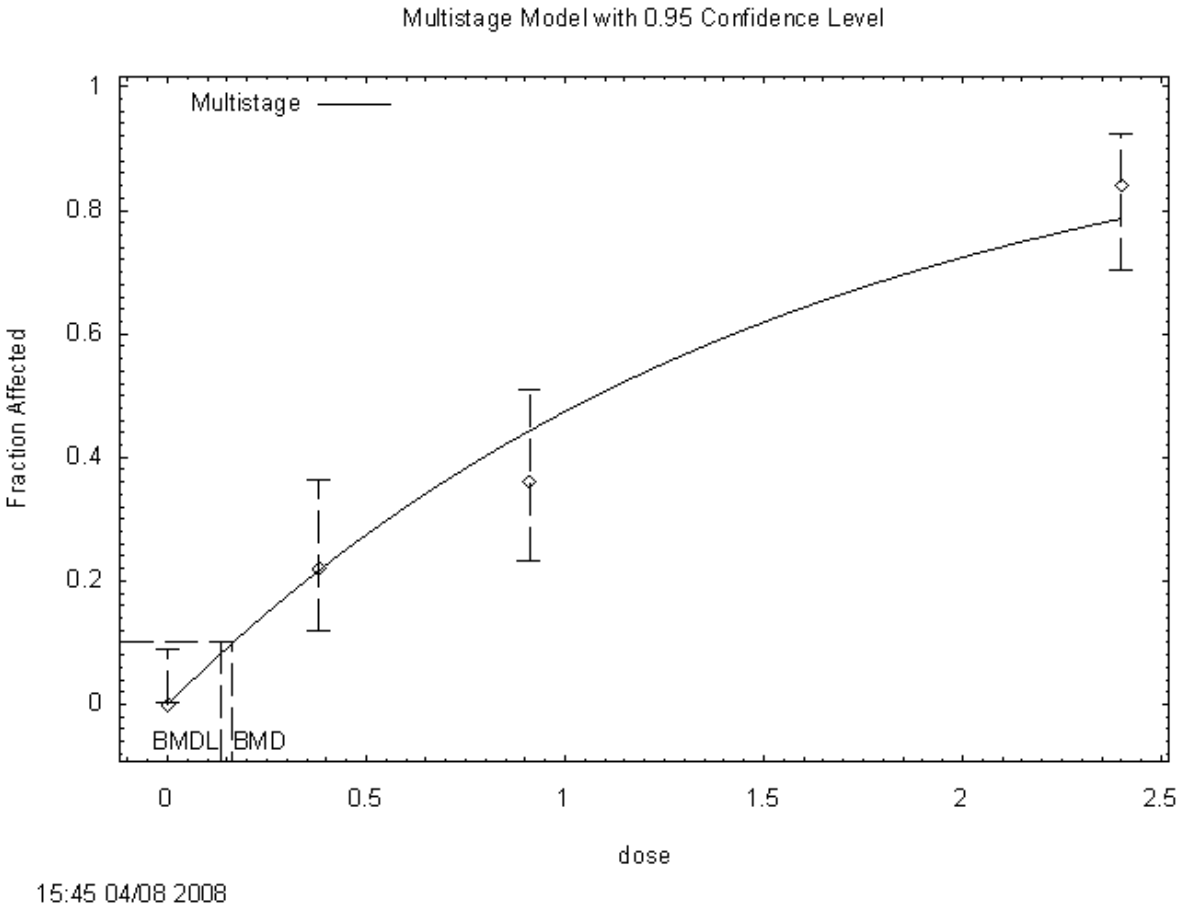
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
All doses				
Gamma[a]	0.31	0.25	0.00	270.99
Logistic	0.90	0.74	0.00	296.25
Log-logistic[b]	0.15	0.12	0.00	247.93
Multi-stage[c]	0.31	0.25	0.00	270.99
Probit	0.90	0.76	0.00	296.18
Log-probit[b]	0.48	0.36	0.00	274.38
Quantal linear	0.31	0.25	0.00	270.99
Weibull[a]	0.31	0.25	0.00	270.99
Highest dose dropped (four doses modeled)				
Gamma[a]	0.22	0.14	0.43	167.67
Logistic	0.47	0.39	0.03	177.09
Log-logistic[b]	0.26	0.15	0.20	169.23
Multi-stage[d]	0.16	**0.13**	**0.52**	**166.34**
Probit	0.45	0.37	0.04	176.19
Log-probit[b]	0.28	0.23	0.33	167.41
Quantal linear	0.16	**0.13**	**0.52**	**166.34**
Weibull[a]	0.22	0.14	0.47	167.50

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.
[d]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; degree polynomial =1.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Figure A-5. Predicted and Observed Incidence of Diffuse Epithelial Hyperplasia in the Duodenum of Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Histiocytic Cellular Infiltration of the Mesenteric Lymph Nodes in Male Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value ≥ 0.1) to the full dataset (Table A-12). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. Dropping the highest dose did not result in adequately fitting models, nor did dropping the two highest doses. This dataset is considered not suitable for benchmark dose modeling.

Table A-12. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in Mesenteric Lymph Nodes of Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
All doses				
Gamma[a]	0.38	0.26	0.00	285.94
Logistic	0.53	0.39	0.00	286.38
Log-logistic[b]	0.16	0.08	0.00	284.48
Multi-stage[c]	0.43	0.26	0.00	287.88
Probit	0.56	0.43	0.00	286.35
Log-probit[b]	0.83	0.52	0.00	289.36
Quantal linear	0.38	0.26	0.00	285.94
Weibull[a]	0.38	0.26	0.00	285.94
Highest dose dropped (four doses modeled)				
Gamma[a]	0.47	0.24	0.00	258.50
Logistic	0.61	0.35	0.00	259.04
Log-logistic[b]	0.21	0.08	0.00	256.81
Multi-stage[d]	0.47	0.24	0.00	258.50
Probit	0.63	0.37	0.00	259.08
Log-probit[b]	1.24	0.56	0.00	261.28
Quantal linear	0.47	0.24	0.00	258.50
Weibull[a]	0.47	0.24	0.00	258.50
Two highest doses dropped (three doses modeled)				
Gamma[a]	0.11	0.07	0.00	187.77
Logistic	0.17	0.12	0.00	189.97
Log-logistic[b]	0.05	0.03	0.00	183.77
Multi-stage[e]	0.11	0.07	0.00	187.77
Probit	0.17	0.12	0.00	190.12
Log-probit[b]	0.17	0.11	0.00	190.37
Quantal linear	0.11	0.07	0.00	187.77
Weibull[a]	0.11	0.07	0.00	187.77

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.
[d]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.
[e]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Diffuse Epithelial Hyperplasia of the Duodenum in Female Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value $\geq$0.1) to the data (Table A-13). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. After dropping the highest dose, an adequate fit was still not achieved. After dropping the two highest doses, all of the models except for the logistic and probit models provided an adequate fit (X^2 p-value $\geq$0.1) to the data. Comparing across models, a better fit is generally indicated by a lower AIC (EPA 2000). As assessed by AIC, the gamma, multistage, quantal linear, and weibull models generated identical goodness of fit statistics and benchmark doses, as these models all took the form of a 1-degree polynomial multistage model which provides the best fit (Figure A-6). Based on these models, the BMD associated with a 10% extra risk was 0.12 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.09 mg chromium(VI)/kg/day.

Table A-13. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Diffuse Epithelial Hyperplasia in the Duodenum of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

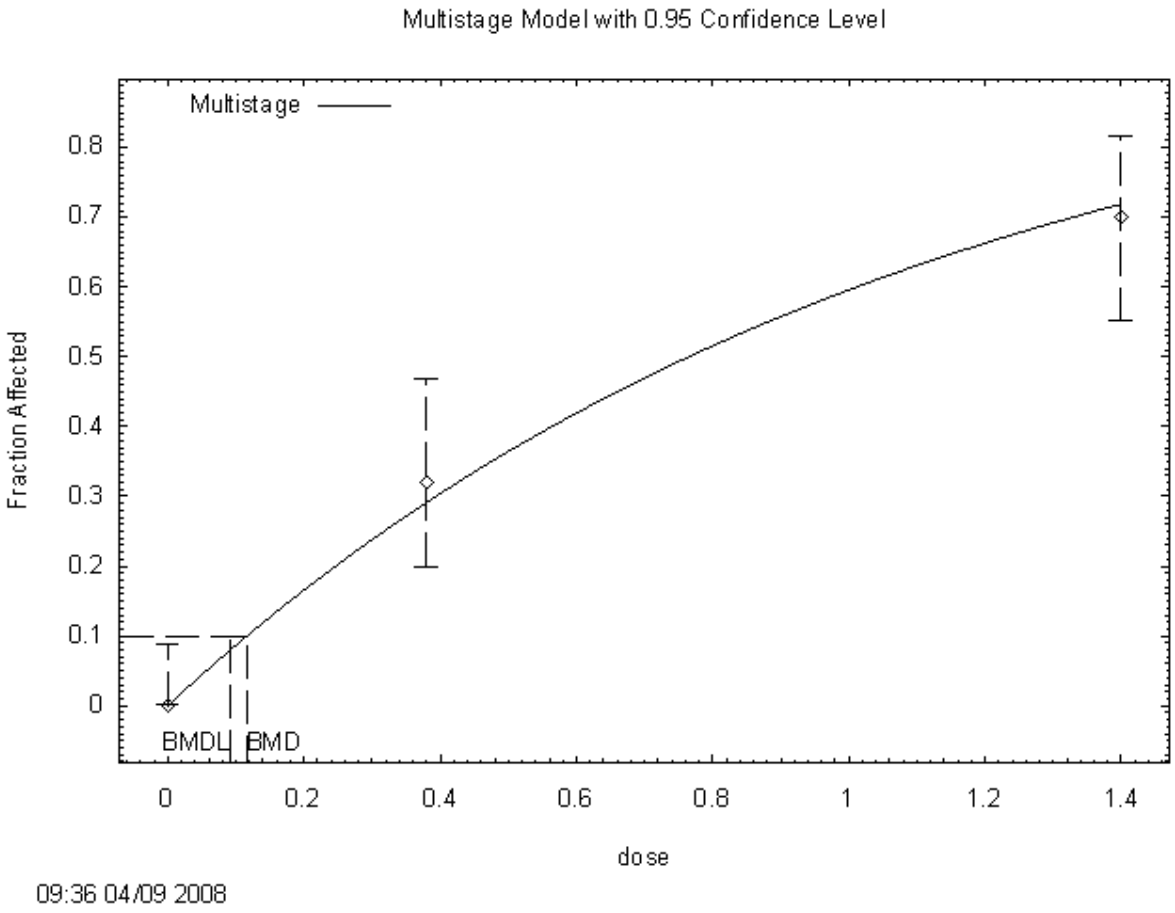
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
All doses				
Gamma[a]	0.34	0.27	0.00	275.34
Logistic	0.88	0.72	0.00	293.17
Log-logistic[b]	0.12	0.09	0.04	245.54
Multi-stage[c]	0.34	0.27	0.00	275.34
Probit	0.93	0.78	0.00	294.03
Log-probit[b]	0.52	0.38	0.00	279.54
Quantal linear	0.34	0.27	0.00	275.34
Weibull[a]	0.34	0.27	0.00	275.34
Highest dose dropped (four doses modeled)				
Gamma[a]	0.20	0.16	0.00	213.41
Logistic	0.55	0.46	0.00	236.10
Log-logistic[b]	0.11	0.08	0.04	200.07
Multi-stage[d]	0.20	0.16	0.00	213.41
Probit	0.54	0.45	0.00	235.61
Log-probit[b]	0.29	0.24	0.00	220.04
Quantal linear	0.20	0.16	0.00	213.41
Weibull[a]	0.20	0.16	0.00	213.41
Two highest doses dropped (three doses modeled)				
Gamma[a]	**0.12**	**0.09**	**0.87**	**126.06**
Logistic	0.34	0.27	0.00	141.77
Log-logistic[b]	0.12	0.06	1.00	127.77
Multi-stage[e]	**0.12**	**0.09**	**0.87**	**126.06**
Probit	0.32	0.26	0.00	140.65
Log-probit[b]	0.20	0.16	0.48	127.17
Quantal linear	**0.12**	**0.09**	**0.87**	**126.06**
Weibull[a]	**0.12**	**0.09**	**0.87**	**126.06**

[a]Restrict power >=1
[b]Slope restricted to >1
[c]Restrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.
[d]Restrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.
[e]Restrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Figure A-6. Predicted and Observed Incidence of Diffuse Epithelial Hyperplasia in the Duodenum of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium (VI)/kg/day.

Source: NTP 2008a

Histiocytic Cellular Infiltration of the Mesenteric Lymph Nodes in Female Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value ≥ 0.1) to the full dataset (Table A-14). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. Dropping the highest dose did not result in adequately fitting models, nor did dropping the two highest doses. This dataset is not suitable for benchmark dose modeling.

Table A-14. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in Mesenteric Lymph Nodes of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
All doses				
Gamma[a]	0.41	0.30	0.00	282.46
Logistic	0.77	0.61	0.00	290.18
Log-logistic[b]	0.09	0.06	0.00	263.55
Multi-stage[c]	0.41	0.30	0.00	282.46
Probit	0.85	0.69	0.00	291.41
Log-probit[b]	0.68	0.47	0.00	285.85
Quantal linear	0.41	0.30	0.00	282.46
Weibull[a]	0.41	0.30	0.00	282.46
Highest dose dropped (four doses modeled)				
Gamma[a]	0.20	0.15	0.00	224.84
Logistic	0.40	0.33	0.00	230.81
Log-logistic[b]	0.07	0.05	0.00	215.19
Multi-stage[d]	0.20	0.15	0.00	224.84
Probit	0.40	0.34	0.00	230.85
Log-probit[b]	0.37	0.24	0.00	231.76
Quantal linear	0.20	0.15	0.00	224.84
Weibull[a]	0.20	0.15	0.00	224.84
Two highest doses dropped (three doses modeled)				
Gamma[a]	0.14	0.10	0.00	172.32
Logistic	0.31	0.24	0.00	178.99
Log-logistic[b]	0.07	0.04	0.00	164.47
Multi-stage[e]	0.14	0.10	0.00	172.32
Probit	0.30	0.23	0.00	178.74
Log-probit[b]	0.21	0.15	0.00	178.11
Quantal linear	0.14	0.10	0.00	172.32
Weibull[a]	0.14	0.10	0.00	172.32

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.
[d]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.
[e]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Histiocytic Cellular Infiltration of the Liver in Female Mice. As assessed by the chi-square goodness-of-fit statistic, only the log-logistic model provided an adequate fit (X^2 p-value ≥ 0.1) to the data (Table A-15). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.17 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.12 mg chromium(VI)/kg/day (Figure A-7).

Table A-15. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in the Liver of Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

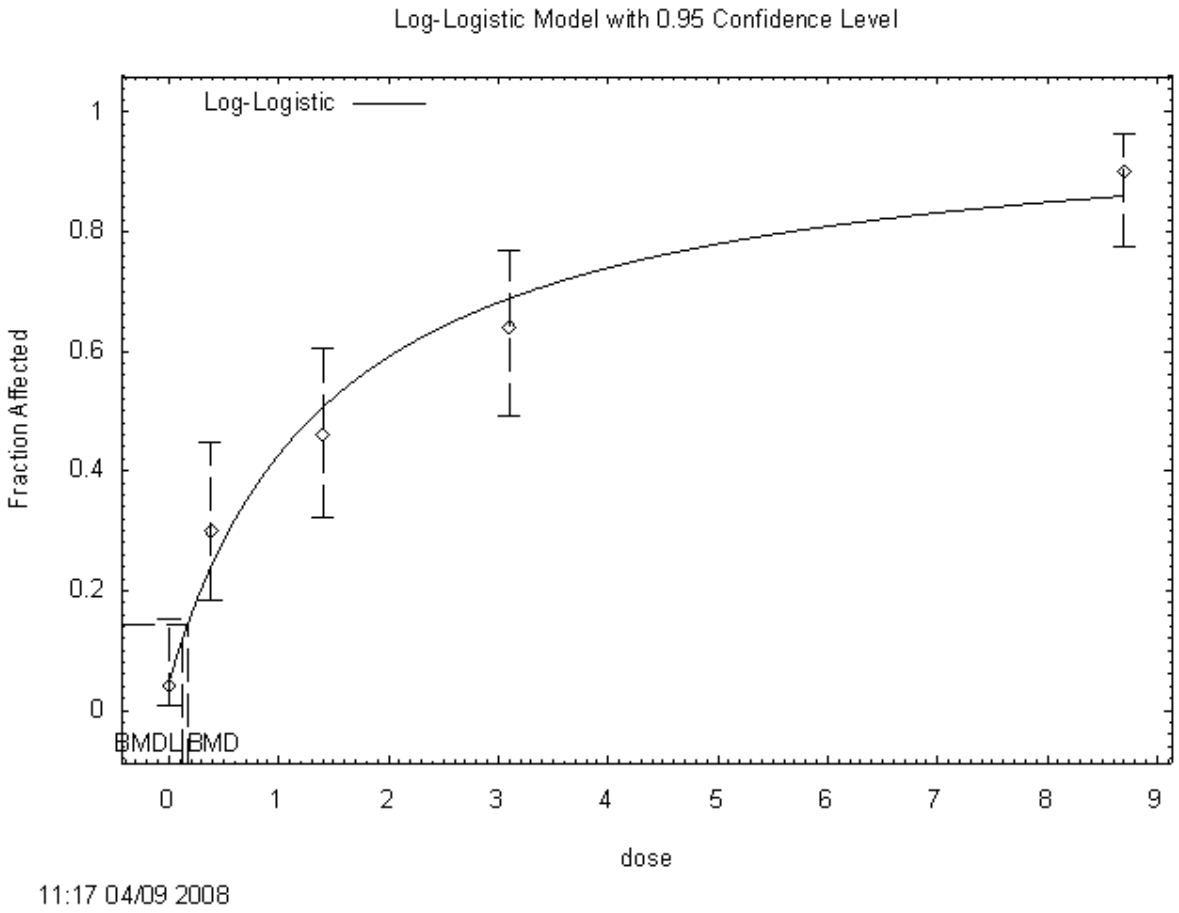
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
Gamma[a]	0.35	0.28	0.08	255.40
Logistic	0.85	0.70	0.00	267.56
Log-logistic[b]	**0.17**	**0.12**	**0.44**	**251.36**
Multi-stage[c]	0.35	0.28	0.08	255.40
Probit	0.88	0.75	0.00	268.64
Log-probit[b]	0.62	0.48	0.01	260.00
Quantal linear	0.35	0.28	0.08	255.40
Weibull[a]	0.35	0.28	0.08	255.40

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Figure A-7. Predicted and Observed Incidence of Histiocytic Cellular Infiltration in the Livers of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium (VI)/kg/day.

Source: NTP 2008a

Cytoplasmic Alteration of Acinar Epithelial Cells of the Pancreas in Female Mice. As assessed by the chi-square goodness-of-fit statistic, all of the models provide adequate fits (X^2 p-value ≥ 0.1) to the data (Table A-16). Comparing across models, a better fit is generally indicated by a lower Akaike's Information Criteria (AIC) (EPA 2000). As assessed by AIC, the log-logistic model provides the best fit (Figure A-8). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.68 mg chromium (VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.52 mg chromium (VI)/kg/day.

Table A-16. BMD_{10} and $BMDL_{10}$ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Pancreas: Acinus, Cytoplasmic Alteration in Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

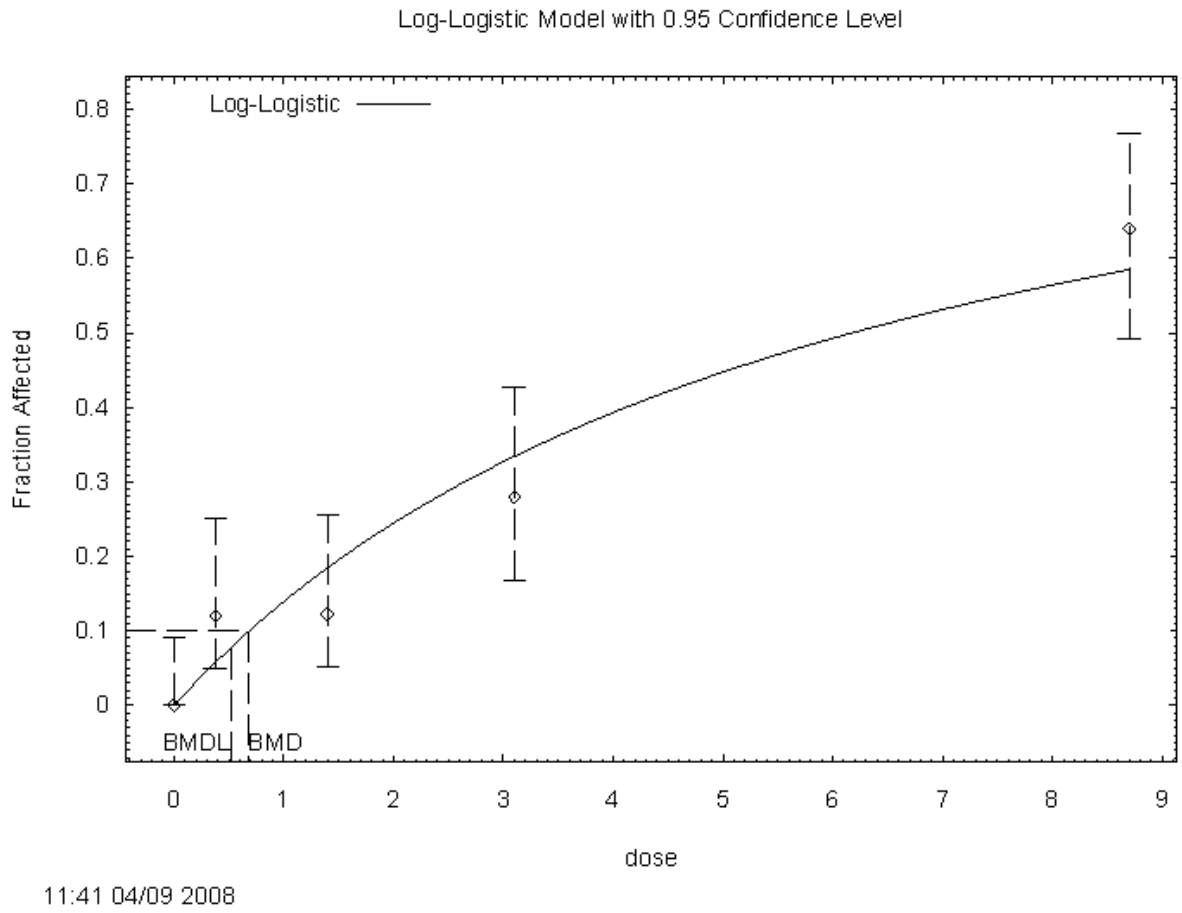
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	x^2 p-value	AIC
Gamma[a]	0.92	0.72	0.13	206.82
Logistic	2.43	2.03	0.09	211.78
Log-logistic[b]	**0.68**	**0.52**	**0.19**	**205.22**
Multi-stage[c]	0.92	0.72	0.13	206.82
Probit	2.24	1.89	0.11	210.99
Log-probit[b]	1.77	1.40	0.11	209.99
Quantal linear	0.92	0.72	0.13	206.82
Weibull[a]	0.92	0.72	0.13	206.82

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial (up to n-2) with an adequate fit is reported; a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

Figure A-8. Predicted and Observed Incidence of Pancreas: Acinus, Cytoplasmic Alteration in Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium (VI)/kg/day.

Source: NTP 2008a

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(III) insoluble particulates
CAS number: 16065-83-1
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 2
Species: Rat

Minimal Risk Level: 0.005 mg chromium(III)/m^3 for insoluble trivalent chromium particulate compounds

Reference: Derelanko MJ, Rinehart WE, Hilaski RJ, et al. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chromic acid and basic chromium sulfate. Toxicol Sci 52(2):278-288.

Experimental design: Groups of 15 male and female CDF (Fisher 344/Crl BR VAF/Plus) rats were exposed to chromic oxide or basic chromium sulfate by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m^3 (measured concentrations) 6 hours/day, 5 days/week for 13 weeks. Mean particle sizes (in microns±GSD, based on 21 samples/test group evaluated over the 13-week exposure period) in the 3, 10, and 30 mg chromium(III)/m^3 groups, were 1.8±1.93, 1.9±1.84, and 1.9±1.78, respectively, for chromic oxide and 4.2±2.48, 4.2±2.37, and 4.5±2.50, respectively, for basic chromium sulfate; no chromium(VI) was detected in samples. Of these 15 rats/sex/group, 10 rats/sex/group were examined and sacrificed after 13 weeks of exposure and 5 rats/sex/group were examined and sacrificed after an additional 13-week recovery (e.g., no exposure) period. Throughout the exposure and recovery periods, rats were examined daily for mortality and clinical signs of toxicity; body weight was recorded weekly, but food consumption was not measured. Ophthamalmoscopic examinations were conducted prior to treatment and before terminal sacrifice. At the end of the treatment and recovery phases, blood was analyzed for "standard" hematology and clinical chemistry, and urinalysis was conducted; specific outcome measures evaluated for these assessments were not reported. In five rats/sex/group, urine was also analyzed for β_2-microglobulin. Gross necropsy was performed on all animals at terminal sacrifice and organ weights were recorded for heart, liver, lungs/trachea (combined), spleen, kidneys, brain, adrenal, thyroid/parathyroid, testes, and ovaries. Bone marrow was examined and differential cell counts of bone marrow were conducted. Microscopic examination of comprehensive tissues (described as "tissues typically harvested for subchronic studies") was conducted for all animals and the control and 30 mg chromium(III)/m^3 groups. For all animals in the 3 and 30 mg chromium(III)/m^3 groups, the following tissues were examined microscopically: kidneys, liver, nasal tissues, trachea, lungs, larynx, mediastinal and mandibular lymph nodes, and all tissues with gross lesions. Histopathological lesions were described, but no incidence data were reported. Sperm morphology, count, and motility were assessed in all males at the end of the 13-week treatment period only.

Effects noted in study and corresponding doses: The following study results are for rats exposed to chromic oxide only; detailed results of animals exposed to basic chromium sulfate are presented in the following intermediate-duration inhalation MRL worksheet for soluble chromium(III) compounds. No mortalities, clinical signs of toxicity, changes in body weight, findings on ophthalmologic examination, or alterations of sperm count, motility, or morphology were observed. Evaluations of hematology, clinical chemistry, and urinalysis did not reveal any treatment-related differences compared to controls; β_2-microglobulin was not detected in urine of rats from any group. Absolute and relative lung/trachea weights were significantly increased by 12 and 13%, respectively, in males in the 30 mg

chromium(III)/m^3 group compared to control. Lung weights were not increased in females. Other significant changes in organ weight changes were limited to small increases in absolute thyroid/parathyroid weight in females in the 10 mg chromium(III)/m^3 group and in relative thyroid/parathyroid weight (combined) in females in the 10 and 30 mg chromium(III)/m^3 groups. The study authors stated that the biological significance of changes in thyroid/parathyroid weight could not be determined; however, no histopathological changes were observed in these tissues in female rats exposed to 30 mg chromium(III)/m^3. On necropsy, most animals (incidence not reported) in the chromic oxide group had green discoloration of the lungs and mediastinal lymph nodes; the degree of discoloration increased with exposure level and was presumed to represent deposition of the test material. Mediastinal lymph node enlargement was noted in the 30 mg chromium(III)/m^3 group. Microscopic examination of the lung revealed foci or aggregates of dark-pigmented (presumably the test material) macrophages within alveolar spaces adjacent to junctions of terminal bronchioles and alveolar ducts; black pigment was observed at the tracheal bifurcation and in periobronchial lymphoid tissue and the medistinal lymph node in all chromic oxide treatment groups. These findings are consistent with normal physiological clearance mechanisms for particulates deposited in the lung and are not considered adverse. Lymphoid hyperplasia of the mediastinal node was observed in rats of all treatment groups (severity not reported). In rats exposed to 10 and 30 mg chromium(III)/m^3, trace-to-mild chronic interstitial inflammation of the lung, characterized by inflammatory cell infiltration, was observed in alveolar septa, and hyperplasia of Type II pneumocytes (severity not reported) were observed. Histopathological changes were isolated to the lungs and respiratory lymphatic tissues and were not observed in other tissues, including nasal tissues and the larynx. Thus, for evaluations conducted at the end of the 13-week treatment period, a LOAEL of 3 mg chromium(III)/m^3 for hyperplasia of the mediastinal node was identified for both males and females; the severity of this effect was not reported. Following the 13-week recovery period, pigmented macrophages and black pigment were observed in peribronchial tissues and the mediastinal lymph node in animals from all treatment groups. Septal cell hyperplasia and chronic interstitial inflammation of the lung, both trace-to-mild in severity, were observed in males of all treatment groups and in females exposed to 10 and 30 mg chromium(III)/m^3. For evaluations conducted at the 13-week posttreatment recovery period, a minimal LOAEL (classified as minimal based on severity) of 3 mg chromium(III)/m^3 for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was identified.

Dose end point used for MRL derivation: 3 mg chromium(III)/m^3 (trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung), adjusted to 0.54 mg chromium(III)/m^3 for intermittent exposure and converted to a $LOAEL_{HEC}$ of 0.43 mg chromium(III)/m^3

[ ] NOAEL [X] LOAEL

The LOAEL of 3 mg chromium(III)/m^3 for hyperplasia of the mediastinal node in males and females (observed at the end of the 13-week treatment period) and the minimal LOAEL (based on severity) of 3 mg chromium(III)/m^3 for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in males (observed at the end of the 13-week recovery period) were further evaluated as potential critical effects for derivation of the intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds. A BMCL for these effects could not be determined since incidence data for lesions of the lung and respiratory lymphatic tissue were not reported; thus, a NOAEL/LOAEL approach was used. Following adjustment of LOAELs for intermittent exposure ($LOAEL_{ADJ}$) and human equivalent concentrations ($LOAEL_{HEC}$), as described below, trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was selected as the critical effect, based on the lowest $LOAEL_{HEC}$ of 0.43 mg chromium(III)/m^3 (Table A-17). The intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds of 0.005 mg chromium(III)/m^3 was derived by dividing the minimal $LOAEL_{HEC}$ of 0.43 mg chromium(III)/m^3 by a composite uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Table A-17. LOAEL Values (Expressed in Terms Of HEC) for Nonneoplastic Lesions in Rats Exposed to Chromic Oxide by Inhalation For 13 Weeks

Species/sex	Lesion type (RDDR location)	RDDR multiplier	$LOAEL_{ADJ}$ (mg chromium(III)/m^3)[a]	$LOAEL_{HEC}$ (mg chromium(III)/m^3)[b]
Rat/male	Septal cell hyperplasia and chronic interstitial inflammation of the lung (thoracic)	0.789	0.54	0.43
Rat/male	Hyperplasia of the mediastinal node (tracheobronchial)	1.225	0.54	0.66
Rat/female	Hyperplasia of the mediastinal node (tracheobronchial)	1.084	0.54	0.59

[a]Duration-adjusted for intermittent exposure ($LOAEL_{ADJ}$ = LOAEL x 6 hours/24 hours x 5 days/7 days = 3 mg chromium(III)/m^3 x 6 hours/24 hours x 5 days/7 days = 0.54 mg chromium(III)/m^3)
[b]$LOAEL_{HEC}$ = $LOAEL_{ADJ}$ x RDDR

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; RDDR = regional deposited dose ratio

Source: Derelanko et al. 1999

Uncertainty factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans, with dosimetric adjustment
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: To determine the $LOAEL_{HEC}$, the $LOAEL_{ADJ}$ in rats was multiplied by the RDDR multiplier determined for lesions in various areas of the respiratory tract in male and female rats (Table A-17). The RDDR computer program was used to determine the RDDR multipliers as follows.

For interstitial inflammation of the lung in male rats (specific location of lesion within the lung was not reported by study authors) observed after the 13-week recovery period, the thoracic region for the RDDR program was selected since the observed effect could occur in the both the tracheobronchial and pulmonary regions of the lung. The RDDR multiplier of 0.789 for the thoracic region of the respiratory tract in male rats was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study (data for body weights of male rats in the chromic oxide portion of the study were not reported) and the average particle size (MMAD±GSD) of 1.9±1.85 reported in the Derelanko et al. (1999) study.

For hyperplasia of the mediastinal node in male and female rats observed at the end of the 13-week treatment period, the tracheobronchial region of the respiratory tract was selected for the RDDR program. Although the mediastinal lymph node is not a respiratory tissue, for the purposes of HEC conversions, it is considered part of the tracheobronchial region of the respiratory system rather than a systemic tissue;

classification of the mediastinal lymph node as a systemic tissue is not appropriate, since the test material reaches the respiratory lymphatic tissues by the pulmonary macrophage clearance system and not by first entering the systemic circulation. For male rats, the RDDR multiplier of 1.225 for the tracheobronchial region of the respiratory tract in male rats was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study (data for body weights of male rats in the chromic oxide portion of the study were not reported) and the average particle size MMAD±GSD of 1.9±1.85 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 1.084 for the tracheobronchial region tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 1.9±1.85 reported in the Derelanko et al. (1999) study; the default value for female body weights was used because female body weights were not reported in the critical study.

Was a conversion used from intermittent to continuous exposure? Rats were exposed for 6 hours/day, 5 days/week for 13 weeks.

$LOAEL_{ADJ}$ = 3 mg chromium(III)/m^3 x 6 hours/24 hours x 5 days/7 days
$LOAEL_{ADJ}$ = 0.54 mg chromium(III)/m^3

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(III) and chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. The available occupational studies for exposure to chromium(III) compounds include, or likely include, concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors. Studies evaluating respiratory effects of intermediate-duration inhalation exposure of animals are limited to the critical study evaluating 13-week exposure to chromic oxide or basic chromium sulfate (Derelanko et al. 1999). Results of this study show that intermediate-duration inhalation exposure to chromic oxide or basic chromium sulfate produced adverse respiratory effects, as indicated by histopathological changes and increased lung weight. However, effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung and respiratory lymph tissues). The authors suggest that differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, separate intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds.

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(III) soluble particulates
CAS number: 16065-83-1
Date: October 2008
Profile status: Final Draft Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 3
Species: Rat

Minimal Risk Level: 0.0001 mg chromium(III)/m^3 for soluble trivalent chromium particulate compounds

Reference: Derelanko MJ, Rinehart WE, Hilaski RJ, et al. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chromic acid and basic chromium sulfate. Toxicol Sci 52(2):278-288.

Experimental design: Groups of 15 male and female CDF (Fisher 344/Crl BR VAF/Plus) rats were exposed to chromic oxide or basic chromium sulfate by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m^3 (measured concentrations) 6 hours/day, 5 days/week for 13 weeks. Mean particle sizes (in microns±GSD, based on 21 samples/test group evaluated over the 13-week exposure period) in the 3, 10, and 30 mg chromium(III)/m^3 groups, were 1.8±1.93, 1.9±1.84, and 1.9±1.78, respectively, for chromic oxide and 4.2±2.48, 4.2±2.37, and 4.5±2.50, respectively, for basic chromium sulfate; no chromium(VI) was detected in samples. Of these 15 rats/sex/group, 10 rats/sex/group were examined and sacrificed after 13 weeks of exposure and 5 rats/sex/group were examined and sacrificed after an additional 13-week recovery (e.g., no exposure) period. Throughout the exposure and recovery periods, rats were examined daily for mortality and clinical signs of toxicity; body weight was recorded weekly but food consumption was not measured. Ophthamalmoscopic examinations were conducted prior to treatment and before terminal sacrifice. At the end of the treatment and recovery phases, blood was analyzed for "standard" hematology and clinical chemistry, and urinalysis was conducted; specific outcome measures evaluated for these assessments were not reported. In five rats/sex/group, urine was also analyzed for β_2-microglobulin. Gross necropsy was performed on all animals at terminal sacrifice and organ weights were recorded for heart, liver, lungs/trachea (combined), spleen, kidneys, brain, adrenal, thyroid/parathyroid, testes, and ovaries. Bone marrow was examined and differential cell counts of bone marrow were conducted. Microscopic examination of comprehensive tissues (described as "tissues typically harvested for subchronic studies") was conducted for all animals and the control and 30 mg chromium(III)/m^3 groups. For all animals in the 3 and 30 mg chromium(III)/m^3 groups, the following tissues were examined microscopically: kidneys, liver, nasal tissues, trachea, lungs, larynx, mediastinal and mandibular lymph nodes, and all tissues with gross lesions. Histopathological findings were described, but no incidence data were reported. Sperm morphology, count, and motility were assessed in all males at the end of the 13-week treatment period only.

Effects noted in study and corresponding doses: The following study results are for rats exposed to basic chromium sulfate only; detailed results of animals exposed to chromic oxide are presented in the preceding intermediate-duration inhalation MRL worksheet for insoluble chromium(III) compounds. No treatment-related mortalities were observed; one male rat in the 30 mg chromium(III)/m^3 group died on day 4 of exposure; the study authors did not attribute this death to treatment since no significant signs of toxicity were observed in this animals or in other animals in this treatment group. Females in the 30 mg chromium(III)/m^3 group exhibited sporadic labored breathing; no additional information on this observation was reported. No findings on ophthalmologic examination or alterations of sperm count, motility, or morphology were observed. At the end of the 13-week treatment period, body weight was

significantly decreased in males in the 10 and 30 mg chromium(III)/m^3 groups and females in the 30 mg chromium(III)/m^3 group. The study authors stated that "most" hematological, clinical chemistry, and urinalysis values in all exposure groups were similar to controls, although data were not reported. A significant, dose-related increase in absolute and relative lung/trachea weights was observed in male rats in all treatment groups. Other organ weight changes in males were decreased absolute and increase relative brain weights (30 mg chromium(III)/m^3), increased relative kidney weight (30 mg chromium(III)/m^3), decreased absolute liver weight (30 mg chromium(III)/m^3), increased relative thyroid/parathyroid weight (30 mg chromium(III)/m^3), decreased relative spleen weight (10 and 30 mg chromium(III)/m^3), and increased relative testes weight (30 mg chromium(III)/m^3). In females, absolute and relative lungs weights were increased in a dose-dependent fashion in all treatment groups. Other organ weight changes in females were increased absolute and relative thyroid/parathyroid weight (30 mg chromium(III)/m^3) and decreased absolute spleen weight (30 mg chromium(III)/m^3). With the exception of increased absolute and relative lung weights in males and females, small changes in other organs weights were not considered adverse in the absence of histopathological changes. On necropsy, grey lung discoloration was observed in animals exposed to 10 and 30 mg chromium(III)/m^3; the degree of discoloration increased with exposure level. Microscopic examination of the lung revealed the following changes in all treatment groups: chronic inflammation of the alveoli; alveolar spaces filled with macrophages, neutrophils, lymphocytes and cellular debris; foci of "intense" inflammation and thickened alveolar walls; chronic interstitial inflammation with cell infiltration; hyperplasia of Type II pneumocytes; and granulomatous inflammation, characterized by infiltration of macrophages and multinucleated giant cells. Macrophage infiltration and granulomatous inflammation of the larynx, acute inflammation and suppurative and mucoid exudates of nasal tissues, and histiocytosis and hyperplasia of peribronchial lymphoid tissues and the mediastinal lymph node were also observed in all treatment groups. Following the 13-week recovery period, enlargement of the mediastinal lymph node was observed on gross necropsy in all treatment groups. Microscopic examination of respiratory tissues showed changes to the lung (chronic alveolar inflammation, interstitial inflammation, septal cell hyperplasia, and granulomatous inflammation) in all treatment groups, larynx (granulomatous inflammation) in the 10 and 30 mg chromium(III)/m^3 groups, nasal tissues (trace suppurative exudates) in one to two animals in each groups, and mediastinal lymph node (histiocytosis and hyperplasia) in all treatment groups chromium(III)/m^3 groups. Following the 13-week recovery period, test material was observed in the respiratory tract on necropsy; however, incidence was decreased compared to observations made immediately following treatment (data not presented). In addition, chronic alveolar and interstitial inflammation and septal cell hyperplasia (all trace-to-moderate in severity) were observed in the 10 and 30 mg chromium(III)/m^3 groups, with severity similar to that observed immediately following treatment; in the 3 mg chromium(III)/m^3 group, severity was slightly reduced.

Dose end point used for MRL derivation: 3 mg chromium(III)/m^3 (nasal and larynx lesions), adjusted to 0.54 mg chromium(III)/m^3 for intermittent exposure and converted to a $LOAEL_{HEC}$ of 0.04 mg chromium(III)/m^3

[ ] NOAEL [X] LOAEL

The respiratory tract was identified as the target for inhaled soluble trivalent chromium particulate compounds. Similar effects were observed in male and female rats exposed to inhaled basic chromium sulfate for 13 weeks, with histopathological changes to the nose, larynx, lung, and respiratory lymphatic tissues and increased relative lung weight occurring at ≥3 mg chromium(III)/m^3. Therefore, data for histopathological changes in various regions of the respiratory tract and increased relative lung weights were further evaluated to determine the point of departure for derivation of the intermediate-duration MRL for soluble trivalent chromium particulate compounds.

Benchmark dose analysis could not be conducted for respiratory tract lesions, since incidence data were not reported by Derelanko et al. (1999); therefore, a NOAEL/LOAEL approach was used. The LOAEL value of 3 mg chromium(III)/m^3 for lesions in different regions of the respiratory tract was further evaluated as a potential point of departure. LOAEL values were adjusted for intermittent exposure ($LOAEL_{ADJ}$) and converted to a human equivalent concentration ($LOAEL_{HEC}$), as shown in (Table A-18).

Table A-18. LOAEL Values (Expressed in Terms of HEC) for Nonneoplastic Lesions in Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

Species/sex	Lesion type (RDDR location)	RDDR multiplier	$LOAEL_{ADJ}$ (mg chromium(III)/m^3)[a]	$LOAEL_{HEC}$ (mg chromium(III)/m^3)[b]
Rat/male	Granulomatous inflammation of larynx; inflammation of nasal tissue (extrathoracic)	0.129	0.54	0.07
Rat/male	Interstitial and alveolar inflammation; alveolar hyperplasia (thoracic)	0.470	0.54	0.25
Rat/female	Granulomatous inflammation of larynx; inflammation of nasal tissue (extrathoracic)	0.078	0.54	0.04
Rat/female	Interstitial and alveolar inflammation; alveolar hyperplasia (thoracic)	0.483	0.54	0.26

[a]Duration-adjusted for intermittent exposure ($LOAEL_{ADJ}$ = LOAEL x 6 hours/24 hours x 5 days/7 days = 3 mg chromium(III)/m^3 x 6 hours/24 hours x 5 days/7 days = 0.54 mg chromium(III)/m^3)
[b]$LOAEL_{HEC}$ = $LOAEL_{ADJ}$ x RDDR

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; RDDR = regional deposited dose ratio

Soucre: Derelanko et al. 1999

To determine the BMC for increased lung weights, available continuous-variable models in the EPA Benchmark Dose (version 1.4.1) were fit to the data for relative lung weights in male and female rats (Derelanko et al. 1999; Table A-19). The BMC and the 95% lower confidence limit (BMCL) calculated is an estimate of the concentrations associated with a change of 1 standard deviation from the control ($BMCL_{1sd}$). The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of

constant variance ($p \geq 0.1$), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest Akaike's Information Criteria (AIC) for the fitted model is selected for BMC derivation. If the test for constant variance is negative, then the linear model is run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMC derivation. If the tests for both constant and nonconstant variance are negative, then the data set is considered not to be suitable for BMC modeling. For male rats, the best model fit (Hill model) did not provide graphic output of the model; since model fit could not be evaluated by visual inspection, the $BMDL_{1sd}$ from the Hill model was not selected. All other models took the form of a linear model (nonconstant variance), yielding predicted BMC_{1sd} and $BMCL_{1sd}$ values of 2.89 and 2.05 mg chromium(III)/m^3, respectively. For female rats, the linear model (nonconstant variance) provided the best fit, with predicted BMC_{1sd} and $BMCL_{1sd}$ values of 6.33 and 3.96 mg/m^3, respectively. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. The $BMCL_{1sd}$ values for the best fitting models in male and female rats were adjusted for intermittent exposure ($BMCL_{1sd, ADJ}$) and human equivalent concentrations ($BMCL_{1sd, HEC}$), yielding $BMCL_{1sd, HEC}$ values of 0.17 and 0.34 mg chromium(III)/m^3 in males and females, respectively, as shown below (Table A-20).

Table A-19. Relative Lung Weights[a] of CDF Rats[b] Exposed to Basic Chromium Sulfate by Nose-Only Inhalation 6 Hours/Day, 5 Days/Week for 13 Weeks

	Concentrations (mg chromium(III)m^3)			
Relative weight (percent x 10)	0	3	10	30
Basic chromium sulfate, males	4.42±0.187[c]	5.60±0.271[d]	7.1 5± 0.252[d]	10.69±0.688[d]
Basic chromium sulfate, females	5.65±0.418	6.99±0.619[d]	9.24±1.036[d]	12.89±1.134[d]

[a]Combined lung and trachea
[b]10 rat in all groups except male rats in the basic chromium sulfate 30 mg/m^3 group (n=9)
[c]mean±Standard deviation
[d]$p<0.01$

Source: Derelanko et al. 1999

Table A-20. $BMCL_{1sd}$ Values (Expressed in Terms of HEC) for Increased Relative Lung Weight in Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

Species/sex	RDDR multiplier[a]	Duration-adjusted $BMCL_{1sd, ADJ}$ (mg chromium(III)/m^3)[b]	$BMCL_{1sd, HEC}$ (mg chromium(III)/m^3)[c]
Rat/male	0.470	0.37	0.17
Rat/female	0.483	0.71	0.34

[a]For thoracic region
[b]Duration-adjusted for continuous exposure ($BMCL_{1sd, ADJ}$ = $BMCL_{1sd}$ x 6 hours/24 hours x 5 days/7 days); $BMCL_{1sd}$ for the best fitting models for male and female rats were 2.05 and 3.96 mg chromium(III)/m^3, respectively.
[c]$BMCL_{1sd, HEC}$ = $BMCL_{1sd, ADJ}$ x RDDR

BMCL = lower confidence limit (95%) on the benchmark concentration; HEC = human equivalent concentration; RDDR = regional deposited dose ratio

Source: Derelanko et al. 1999

Based on comparison of $LOAEL_{HEC}$ values for respiratory tract lesions and $BMCL_{1sd, HEC}$ values for increased lung weight, the lowest value of 0.04 mg chromium(III)/m^3 (the $LOAEL_{HEC}$ for lesions of the larynx and nose in female rats) was selected as the point of departure. The intermediate-duration inhalation MRL for soluble trivalent chromium particulate compounds of 0.0001 mg chromium(III)/m^3 was derived by dividing the $LOAEL_{HEC}$ of 0.04 mg chromium(III)/m^3 by a composite uncertainty factor of 300 (10 for use of a LOAEL, 3 for pharmacodynamic variability between animals to humans, and 10 for human variability).

Uncertainty factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: To determine human equivalent concentrations, $LOAEL_{ADJ}$ values for lesions in various areas of the respiratory tract (Table A-18) and $BMCL_{1sd, ADJ}$ values for changes in changes in lung weights (Table A-20) were multiplied by the RDDR multiplier determined for lesions in various areas of the respiratory tract as follows.

For histopathological changes to the nose and larynx, the extrathoracic region for the RDDR program was selected. For male rats, the RDDR multiplier of 0.129 for the extrathoracic region of the respiratory tract was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study and the average particle size (MMAD±GSD) of 4.3±2.45 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 0.078 for the extrathoracic region of the respiratory tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 4.3±2.45 reported in Derelanko et al. (1999); the default value for female body weights was used because female body weights were not reported in Derelanko et al. (1999).

For histopathological changes to the lung and increased relative lung weight, the thoracic region (a combination of tracheobronchial and pulmonary regions) was selected. For male rats, the RDDR multiplier of 0.470 for the thoracic region of the respiratory tract was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study and the average particle size (MMAD±GSD) of 4.3±2.45 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 0.483 for the thoracic region of the respiratory tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 4.3±2.45 reported in Derelanko et al. (1999); the default value for female body weights was used because female body weights were not reported in Derelanko et al. (1999).

Was a conversion used from intermittent to continuous exposure? Rats were exposed for 6 hours/day, 5 days/week for 13 weeks. The LOAEL and $BMCL_{1sd}$ values were adjusted for continuous exposure as follows:

$$LOAEL_{ADJ} \text{ or } BMCL_{1sd,\ ADJ} = LOAEL \text{ or } BMCL_{1sd} \text{ x 6 hours/24 hours x 5days/7 days}$$

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(III) and chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. The available occupational studies for exposure to chromium(III) compounds include, or likely include, concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors. Studies evaluating respiratory effects of intermediate-duration inhalation exposure of animals are limited to the critical study evaluating 13-week exposure to chromic oxide or basic chromium sulfate (Derelanko et al. 1999). Results of this study show that intermediate-duration inhalation exposure to chromic oxide or basic chromium sulfate produced adverse respiratory effects, as indicated by histopathological changes and increased lung weight. However, effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung and respiratory lymph tissues). The authors suggest that differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, separate intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds.

Details of Benchmark Dose Analysis for the Intermediate-duration Inhalation MRL for Soluble Trivalent Chromium Particulates

Lung Weights in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was applied to the data again while applying the power model integrated into the BMCs to account for nonhomogenous variance. The nonconstant variance model did provide an adequate fit (as assess by the p-value for variance). The polynomial, power, and Hill models were then fit to the data with nonconstant variance assumed. All of the models provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-21). Comparing across models, a better fit is generally indicated by a lower AIC. As assessed by AIC, the Hill model provides the best fit to the data; however, the BMDS software did not generate the graph output needed to assess visual fit of the model to the data. All other models took the form of a linear model, so the

nonconstant variance-linear model is selected for BMC derivation. The predicted BMC_{1sd} and $BMCL_{1sd}$ for the data are 2.89 and 2.05 mg chromium(III)/m^3, respectively (Figure A-9).

Table A-21. Model Predictions for Changes in Relative Lung Weights of Male CDF Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

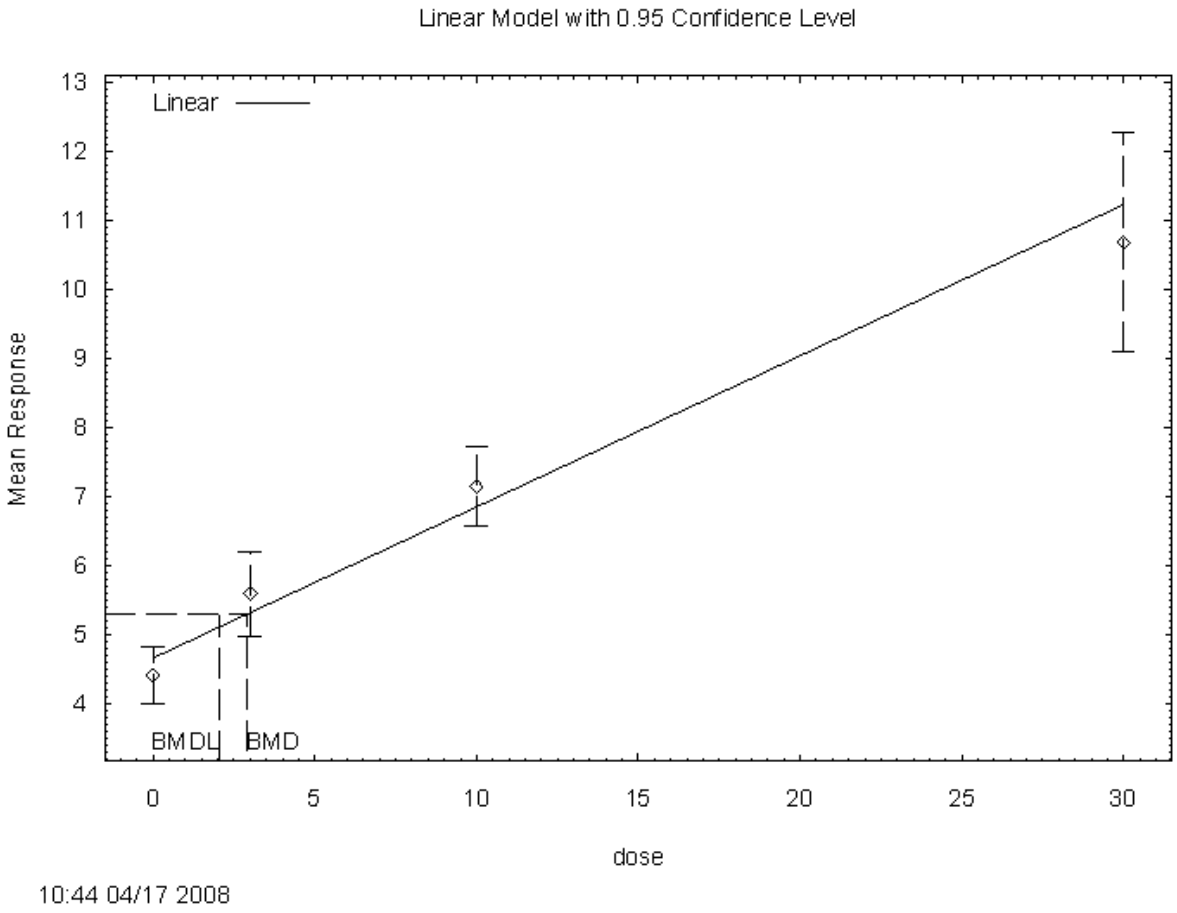
Model	Variance p-value[a]	p-Value for the means[a]	AIC	BMC_{1sd} (mg chromium(III)/m^3)	$BMCL_{1sd}$ (mg chromium(III)/m^3)
Linear[b,c]	0.00	0.30	56.75	5.79	4.70
Linear [c,d]	**0.40**	**0.10**	**44.09**	**2.89**	**2.05**
Polynomial (1-degree)[c,d]	0.40	0.10	44.09	2.89	2.05
Polynomial (2-degree)[c,d]	0.40	0.10	44.09	2.89	2.05
Polynomial (3-degree)[c,d]	0.40	0.10	44.09	2.89	2.05
Power[d]	0.40	0.10	44.09	2.89	2.05
Hill[d]	0.40	0.26	42.79	1.74	1.07

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Nonconstant variance model applied

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; 1sd = a 1 standard deviation change from the control

Source: Derelanko et al. 1999

Figure A-9. Predicted and Observed Changes in Relative Lung Weights in Male Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks*



*BMD=BMC; BMDL=BMCL; BMCs and BMCLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg chromium(III)/m^3.

Source: Derelanko et al. 1999

Lung Weights in Female Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was applied to the data again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model did provide an adequate fit (as assess by the p-value for variance). The polynomial, power, and Hill models were then fit to the data with nonconstant variance assumed. All of the models provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-22). Comparing across models, a better fit is generally indicated by a lower AIC. As assessed by AIC, the linear model provides the best fit to the data. The predicted BMC_{1sd} and $BMCL_{1sd}$ for the data are 6.33 and 3.96 mg chromium(III)/m^3, respectively (Figure A-10).

Table A-22. Model Predictions for Changes in Relative Lung Weights of Female CDF Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

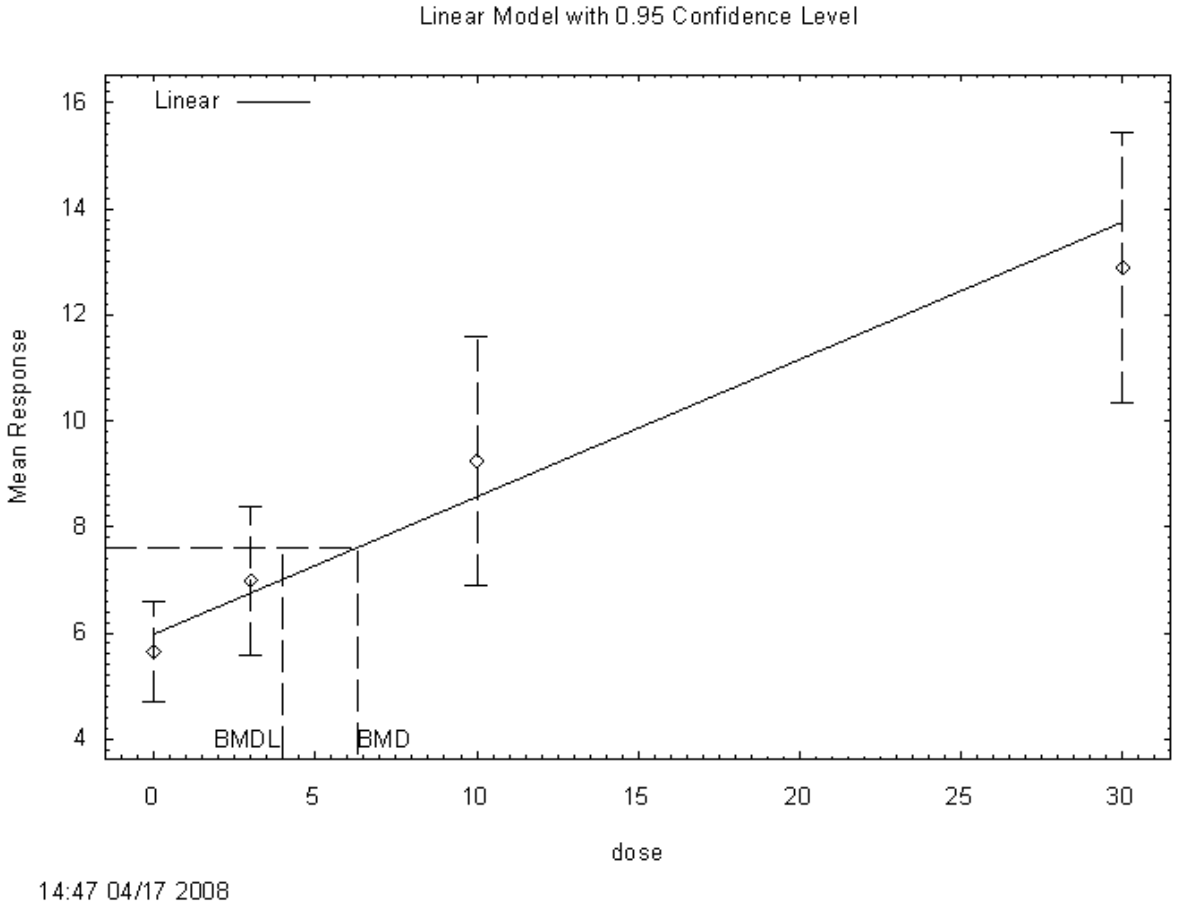
Model	Variance p-value[a]	p-Value for the means[a]	AIC	BMC $_{1sd}$ (mg chromium(III)/m^3)	BMCL $_{1sd}$ (mg chromium(III)/m^3)
Linear[b,c]	0.01	0.51	122.61	11.28	8.59
Linear [c,d]	**0.59**	**0.14**	**117.05**	**6.33**	**3.96**
Polynomial (1-degree)[c,d]	0.59	0.14	117.05	6.33	3.96
Polynomial (2-degree)[c,d]	0.59	0.14	117.05	6.33	3.96
Polynomial (3-degree)[c,d]	0.59	0.14	117.05	6.33	3.96
Power[d]	0.59	0.14	117.05	6.33	3.96
Hill[d]	0.59	NA[e]	117.13	2.84	1.32

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Nonconstant variance model applied
[e]NA = degrees of freedom are ≤0; the Chi-Square test for fit is not valid.

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; 1sd = a 1 standard deviation change from the control

Source: Derelanko et al. 1999

Figure A-10. Predicted and Observed Changes in Relative Lung Weights in Female Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks*



*BMD=BMC; BMDL=BMCL; BMCs and BMCLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg chromium(III)/m^3.

Source: Derelanko et al. 1999

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

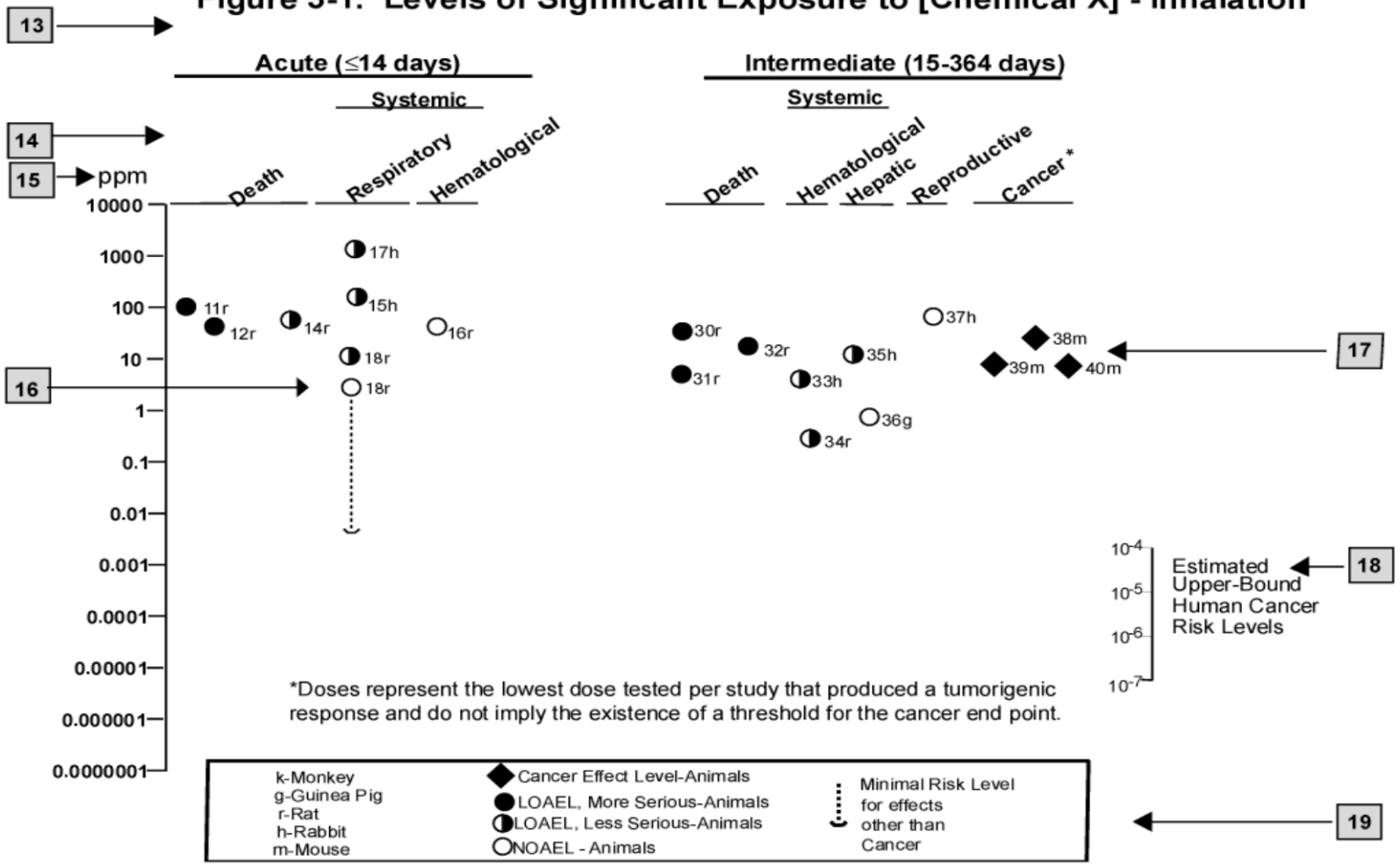
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMDX	dose that produces a X% change in response rate of an adverse effect
BMDLX	95% lower confidence limit on the BMDX
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense

DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid

MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration

OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX

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TOXICOLOGICAL PROFILE FOR COBALT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

April 2004

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for cobalt, Draft for Public Comment was released in July 2001. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE,
Mailstop F-32
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

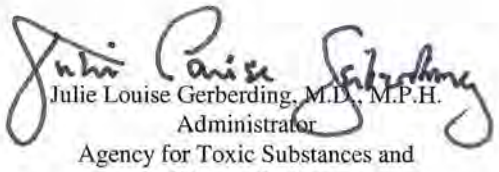
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Julie Louise Gerberding, M.D., M.P.H.
Administrator
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Disease Registry

Background Information

The toxicological profiles are developed by ATSDR pursuant to Section 104(i) (3) and (5) of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund) for hazardous substances found at Department of Energy (DOE) waste sites. CERCLA directs ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. ATSDR and DOE entered into a Memorandum of Understanding on November 4, 1992 which provided that ATSDR would prepare toxicological profiles for hazardous substances based upon ATSDR's or DOE's identification of need. The current ATSDR priority list of hazardous substances at DOE NPL sites was announced in the Federal Register on July 24, 1996 (61 FR 38451).

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.8 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.9 Biomarkers of Exposure and Effect
Section 3.12 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (770) 488-4178
E-mail: atsdric@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Radiation Emergency Assistance Center/Training Site (REAC/TS) provides support to the U.S. Department of Energy, the World Health Organization, and the International Atomic Energy Agency in the medical management of radiation accidents. A 24-hour emergency response program at the Oak Ridge Institute for Science and Education (ORISE), REAC/TS trains, consults, or assists in the response to all kinds of radiation accidents. Contact: Oak Ridge Institute for Science and Education, REAC/TS, PO Box 117, MS 39, Oak Ridge, TN 37831-0117 • Phone 865-576-3131 • FAX 865-576-9522 • 24-Hour Emergency Phone 865-576-1005 (ask for REAC/TS) • e-mail: cooleyp@orau.gov • website (including emergency medical guidance): http://www.orau.gov/reacts/default.htm

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Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact:

AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for cobalt. The panel consisted of the following members:

1. Dr. Herman Cember, C.H.P., Ph.D., PE., Adjunct Professor, School of Health Sciences, Purdue University, Lafayette, Indiana;

2. Dr. James Hansen, Ph.D., Environmental Contaminant Specialist, U.S. Fish and Wildlife Service, Spokane, WA;

3. Dr. Dominique Lison, M.D., Ph.D., Vice-Chairman of the Doctoral School in Genetics and Immunology, Catholic University of Louvain, Brussels, Belgium, and

4. Dr. Nancy Pedigo, Ph.D., Research Assistant Professor, Department of Pharmacology, University of Kentucky Medical Center, Lexington, KY.

These experts collectively have knowledge of cobalt's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about cobalt and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Stable cobalt has been found in at least 426 of the 1,636 current or former NPL sites. Radioactive cobalt, as ^{60}Co, has been found in at least 13 of the 1,636 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which cobalt is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact. External exposure to radiation may occur from natural or man-made sources. Naturally occurring sources of radiation are cosmic radiation from space or radioactive materials in soil or building materials. Man-made sources of radioactive materials are found in consumer products, industrial equipment, atom bomb fallout, and to a smaller extent from hospital waste and nuclear reactors.

If you are exposed to cobalt, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS COBALT?

Cobalt is a naturally-occurring element that has properties similar to those of iron and nickel. It has an atomic number of 27. There is only one stable isotope of cobalt, which has an atomic mass number of 59. (An element may have several different forms, called isotopes, with different weights depending on the number of neutrons that it contains. The isotopes of an element, therefore, have different atomic mass numbers [number of protons and neutrons], although the atomic number [number of protons] remains the same.) However, there are many unstable or radioactive isotopes, two of which are commercially important, cobalt-60 and cobalt-57, also written as Co-60 or ^{60}Co and Co-57 or ^{57}Co, and read as cobalt sixty and cobalt fifty-seven. All isotopes of cobalt behave the same chemically and will therefore have the same chemical behavior in the environment and the same chemical effects on your body. However, isotopes have different mass numbers and the radioactive isotopes have different radioactive properties, such as their half-life and the nature of the radiation they give off. The half-life of a cobalt isotope is the time that it takes for half of that isotope to give off its radiation and change into a different isotope. After one half-life, one-half of the radioactivity is gone. After a second half-life, one-fourth of the original radioactivity is left, and so on. Radioactive isotopes are constantly changing into different isotopes by giving off radiation, a process referred to as radioactive decay. The new isotope may be a different element or the same element with a different mass.

Small amounts of cobalt are naturally found in most rocks, soil, water, plants, and animals, typically in small amounts. Cobalt is also found in meteorites. Elemental cobalt is a hard, silvery grey metal. However, cobalt is usually found in the environment combined with other elements such as oxygen, sulfur, and arsenic. Small amounts of these chemical compounds can be found in rocks, soil, plants, and animals. Cobalt is even found in water in dissolved or ionic form, typically in small amounts. (Ions are atoms, collections of atoms, or molecules containing a positive or negative electric charge.) A biochemically important cobalt compound is vitamin B_{12} or cyanocobalamin. Vitamin B_{12} is essential for good health in animals and humans. Cobalt is not currently mined in the United States, but has been mined in the past. Therefore, we

obtain cobalt and its other chemical forms from imported materials and by recycling scrap metal that contains cobalt.

Cobalt metal is usually mixed with other metals to form alloys, which are harder or more resistant to wear and corrosion. These alloys are used in a number of military and industrial applications such as aircraft engines, magnets, and grinding and cutting tools. They are also used in artificial hip and knee joints. Cobalt compounds are used as colorants in glass, ceramics, and paints, as catalysts, and as paint driers. Cobalt colorants have a characteristic blue color; however, not all cobalt compounds are blue. Cobalt compounds are also used as trace element additives in agriculture and medicine.

Cobalt can also exist in radioactive forms. A radioactive isotope of an element constantly gives off radiation, which can change it into an isotope of a different element or a different isotope of the same element. This newly formed nuclide may be stable or radioactive. This process is called radioactive decay. ^{60}Co is the most important radioisotope of cobalt. It is produced by bombarding natural cobalt, ^{59}Co, with neutrons in a nuclear reactor. ^{60}Co decays by giving off a beta ray (or electron), and is changed into a stable nuclide of nickel (atomic number 28). The half-life of ^{60}Co is 5.27 years. The decay is accompanied by the emission of high energy radiation called gamma rays. ^{60}Co is used as a source of gamma rays for sterilizing medical equipment and consumer products, radiation therapy for treating cancer patients, and for manufacturing plastics. ^{60}Co has also been used for food irradiation; depending on the radiation dose, this process may be used to sterilize food, destroy pathogens, extend the shelf-life of food, disinfest fruits and grain, delay ripening, and retard sprouting (e.g., potatoes and onions). ^{57}Co is used in medical and scientific research and has a half-life of 272 days. ^{57}Co undergoes a decay process called electron capture to form a stable isotope of iron (^{57}Fe). Another important cobalt isotope, ^{58}Co, is produced when nickel is exposed to a source of neutrons. Since nickel is used in nuclear reactors, ^{58}Co may be unintentionally produced and appear as a contaminant in cooling water released by nuclear reactors. ^{58}Co also decays by electron capture, forming another stable isotope of iron (^{58}Fe). ^{60}Co may be similarly produced from cobalt alloys in nuclear reactors and

released as a contaminant in cooling water. ^{58}Co has a half-life of 71 days and gives off beta and gamma radiation in the decay process.

Quantities of radioactive cobalt are normally measured in units of radioactivity (curies or becquerels) rather than in units of mass (grams). The becquerel (Bq) is a new international unit, and the curie (Ci) is the traditional unit; both are currently used. A becquerel is the amount of radioactive material in which 1 atom transforms every second, and a curie is the amount of radioactive material in which 37 billion atoms transform every second. For an overview of basic radiation physics, chemistry, and biology see Appendix D of this profile. For more information on radiation, see the *ATSDR Toxicological Profile for Ionizing Radiation*.

To learn more about the properties and uses of cobalt, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO COBALT WHEN IT ENTERS THE ENVIRONMENT?

Cobalt may enter the environment from both natural sources and human activities. Cobalt occurs naturally in soil, rock, air, water, plants, and animals. It may enter air and water, and settle on land from windblown dust, seawater spray, volcanic eruptions, and forest fires and may additionally get into surface water from runoff and leaching when rainwater washes through soil and rock containing cobalt. Soils near ore deposits, phosphate rocks, or ore smelting facilities, and soils contaminated by airport traffic, highway traffic, or other industrial pollution may contain high concentrations of cobalt. Small amounts of cobalt may be released into the atmosphere from coal-fired power plants and incinerators, vehicular exhaust, industrial activities relating to the mining and processing of cobalt-containing ores, and the production and use of cobalt alloys and chemicals. ^{58}Co and ^{60}Co may be released to the environment as a result of nuclear accidents (i.e, Chernobyl), radioactive waste dumping in the sea or from radioactive waste landfills, and nuclear power plant operations.

Cobalt cannot be destroyed in the environment. It can only change its form or become attached or separated from particles. Cobalt released from power plants and other combustion processes

is usually attached to very small particles. Cobalt contained in windborne soil is generally found in larger particles than those released from power plants. These large particles settle to the ground or are washed out of the air by rain. Cobalt that is attached to very small particles may stay in the air for many days. Cobalt released into water may stick to particles in the water column or to the sediment at the bottom of the body of water into which it was released, or remain in the water column in ionic form. The specific fate of cobalt will depend on many factors such as the chemistry of the water and sediment at a site as well as the cobalt concentration and water flow. Cobalt deposited on soil is often strongly attached to soil particles and therefore would not travel very far into the ground. However, the form of the cobalt and the nature of the soil at a particular site will affect how far cobalt will penetrate into the soil. Both in soil and sediment, the amount of cobalt that is mobile will increase under more acidic conditions. Ultimately, most cobalt ends up in the soil or sediment.

Plants can accumulate very small amounts of cobalt from the soil, especially in the parts of the plant that you eat most often, such as the fruit, grain, and seeds. While animals that eat these plants will accumulate cobalt, cobalt is not known to biomagnify (produce increasingly higher concentrations) up the food chain. Therefore, vegetables, fruits, fish, and meat that you consume will generally not contain high amounts of cobalt. Cobalt is an essential element, required for good health in animals and humans, and therefore, it is important that foodstuffs contain adequate quantities of cobalt.

^{60}Co and ^{58}Co are moderately short-lived, manufactured radioactive isotopes that are produced in nuclear reactors. Although these isotopes are not produced by nuclear fission, small amounts of these radioisotopes are also produced by the neutron interaction with the structural materials found in the reactor of nuclear plants, and are produced during the routine operation of nuclear plants. Small amounts may be released to the environment as contaminants in cooling water or in radioactive waste. Since these isotopes are not fission products, they are not produced in nuclear weapons testing and are not associated with nuclear fallout. In the environment, radioactive isotopes of cobalt will behave chemically like stable cobalt. However, ^{60}Co and ^{58}Co

will also undergo radioactive decay according to their respective half-lives, 5.27 years and 71 days.

For more information about what happens to cobalt in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO COBALT?

Cobalt is widely dispersed in the environment in low concentrations. You may be exposed to small amounts of cobalt by breathing air, drinking water, and eating food containing it. Children may also be exposed to cobalt by eating dirt. You may also be exposed by skin contact with soil, water, cobalt alloys, or other substances that contain cobalt. Analytical methods used by scientists to determine the levels of cobalt in the environment generally do not determine the specific chemical form of cobalt present. Therefore, we do not always know the chemical form of cobalt to which a person may be exposed. Similarly, we do not know what forms of cobalt are present at hazardous waste sites. Some forms of cobalt may be insoluble or so tightly attached to particles or embedded in minerals that they are not taken up by plants and animals. Other forms of cobalt that are weakly attached to particles may be taken up by plants and animals.

The concentration of cobalt in soil varies widely, generally ranging from about 1 to 40 ppm (1 ppm=1 part of cobalt in a million parts of soil by weight), with an average level of 7 ppm. Soils containing less than about 3 ppm of cobalt are considered cobalt-deficient because plants growing in them do not have sufficient cobalt to meet the dietary requirements of cattle and sheep. Such cobalt-deficient soils are found in some areas in the southeast and northeast parts of the United States. On the other hand, soils near cobalt-containing mineral deposits, mining and smelting facilities, or industries manufacturing or using cobalt alloys or chemicals may contain much higher levels of cobalt.

Usually, the air contains very small amounts of cobalt, less than 2 nanograms (1 nanogram=one-billionth part of a gram) per cubic meter (ng/m^3). The amount of cobalt that you breathe in a day

is much less than what you consume in food and water. You may breathe in higher levels of cobalt in dust in areas near cobalt-related industries or near certain hazardous waste sites.

The concentration of cobalt in surface and groundwater in the United States is generally low—between 1 and 10 parts of cobalt in 1 billion parts of water (ppb) in populated areas; concentration may be hundreds or thousands times higher in areas that are rich in cobalt-containing minerals or in areas near mining or smelting operations. In most drinking water, cobalt levels are less than 1–2 ppb.

For most people, food is the largest source of cobalt intake. The average person consumes about 11 micrograms of cobalt a day in their diet. Included in this food is vitamin B_{12}, which is found in meat and diary products. The recommended daily intake of vitamin B_{12} is 6 micrograms (1 microgram=one-millionth part of a gram).

You may also be exposed to higher levels of cobalt if you work in metal mining, smelting, and refining, in industries that make or use cutting or grinding tools, or in other industries that produce or use cobalt metal and cobalt compounds. If good industrial hygiene is practiced, such as the use of exhaust systems in the workplace, exposure can be reduced to safe levels. Industrial exposure results mainly from breathing cobalt-containing dust.

When we speak of exposure to ^{60}Co, we are interested in exposure to the radiation given off by this isotope, primarily the gamma rays. The general population is rarely exposed to this radiation unless a person is undergoing radiation therapy. However, workers at nuclear facilities, irradiation facilities, or nuclear waste storage sites may be exposed to ^{60}Co or ^{58}Co. Exposures to radiation at these facilities are regulated and carefully monitored and controlled.

You can find more information on how you may be exposed to cobalt in Chapter 6.

1.4 HOW CAN COBALT ENTER AND LEAVE MY BODY?

Cobalt can enter your body when you breathe in air containing cobalt dust, when you drink water that contains cobalt, when you eat food that contains cobalt, or when your skin touches materials that contain cobalt. If you breathe in air that contains cobalt dust, the amount of inhaled cobalt that stays in your lungs depends on the size of the dust particles. The amount that is then absorbed into your blood depends on how well the particles dissolve. If the particles dissolve easily, then it is easier for the cobalt to pass into your blood from the particles in your lungs. If the particles dissolve slowly, then they will remain in your lungs longer. Some of the particles will leave your lungs as they normally clean themselves out. Some of the particles will be swallowed into your stomach. The most likely way you will be exposed to excess cobalt is by eating contaminated food or drinking contaminated water. Levels of cobalt normally found in the environment, however, are not high enough to result in excess amounts of cobalt in food or water. The amount of cobalt that is absorbed into your body from food or water depends on many things including your state of health, the amount you eat or drink, and the number of days, weeks, or years you eat foods or drink fluids containing cobalt. If you do not have enough iron in your body, the body may absorb more cobalt from the foods you eat. Once cobalt enters your body, it is distributed into all tissues, but mainly into the liver, kidney, and bones. After cobalt is breathed in or eaten, some of it leaves the body quickly in the feces. The rest is absorbed into the blood and then into the tissues throughout the body. The absorbed cobalt leaves the body slowly, mainly in the urine. Studies have shown that cobalt does not readily enter the body through normal skin, but it can if the skin has been cut.

Further information on how cobalt can enter or leave your body can be found in Chapter 3.

1.5 HOW CAN COBALT AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body. In the case of a radioactive chemical, it is also important to gather information concerning the radiation dose and dose rate to the body. For some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Cobalt has both beneficial and harmful effects on human health. Cobalt is beneficial for humans because it is part of vitamin B_{12}, which is essential to maintain human health. Cobalt (0.16–1.0 mg cobalt/kg of body weight) has also been used as a treatment for anemia (less than normal number of red blood cells), including in pregnant women, because it causes red blood cells to be produced. Cobalt also increases red blood cell production in healthy people, but only at very high exposure levels. Cobalt is also essential for the health of various animals, such as cattle and sheep. Exposure of humans and animals to levels of cobalt normally found in the environment is not harmful.

When too much cobalt is taken into your body, however, harmful health effects can occur. Workers who breathed air containing 0.038 mg cobalt/m^3 (about 100,000 times the concentration normally found in ambient air) for 6 hours had trouble breathing. Serious effects on the lungs, including asthma, pneumonia, and wheezing, have been found in people exposed to 0.005 mg cobalt/m^3 while working with hard metal, a cobalt-tungsten carbide alloy. People exposed to 0.007 mg cobalt/m^3 at work have also developed allergies to cobalt that resulted in asthma and skin rashes. The general public, however, is not likely to be exposed to the same type or amount of cobalt dust that caused these effects in workers.

In the 1960s, some breweries added cobalt salts to beer to stabilize the foam (resulting in exposures of 0.04–0.14 mg cobalt/kg). Some people who drank excessive amounts of beer (8–25 pints/day) experienced serious effects on the heart. In some cases, these effects resulted in

death. Nausea and vomiting were usually reported before the effects on the heart were noticed. Cobalt is no longer added to beer so you will not be exposed from this source. The effects on the heart, however, may have also been due to the fact that the beer-drinkers had protein-poor diets and may have already had heart damage from alcohol abuse. Effects on the heart were not seen, however, in people with anemia treated with up to 1 mg cobalt/kg, or in pregnant women with anemia treated with 0.6 mg cobalt/kg. Effects on the thyroid were found in people exposed to 0.5 mg cobalt/kg for a few weeks. Vision problems were found in one man following treatment with 1.3 mg cobalt/kg for 6 weeks, but this effect has not been seen in other human or animal studies.

Being exposed to radioactive cobalt may be very dangerous to your health. If you come near radioactive cobalt, cells in your body can become damaged from gamma rays that can penetrate your entire body, even if you do not touch the radioactive cobalt. Radiation from radioactive cobalt can also damage cells in your body if you eat, drink, breathe, or touch anything that contains radioactive cobalt. The amount of damage depends on the amount of radiation to which you are exposed, which is related to the amount of activity in the radioactive material and the length of time that you are exposed. Most of the information regarding health effects from exposure to radiation comes from exposures for only short time periods. The risk of damage from exposure to very low levels of radiation for long time periods is not known. If you are exposed to enough radiation, you might experience a reduction in white blood cell number, which could lower your resistance to infections. Your skin might blister or burn, and you may lose hair from the exposed areas. This happens to cancer patients treated with large amounts of radiation to kill cancer. Cells in your reproductive system could become damaged and cause temporary sterility. Exposure to lower levels of radiation might cause nausea, and higher levels can cause vomiting, diarrhea, bleeding, coma, and even death. Exposure to radiation can also cause changes in the genetic materials within cells and may result in the development of some types of cancer.

Studies in animals suggest that exposure to high amounts of nonradioactive cobalt during pregnancy might affect the health of the developing fetus. Birth defects, however, have not been

found in children born to mothers who were treated with cobalt for anemia during pregnancy. The doses of cobalt used in the animal studies were much higher than the amounts of cobalt to which humans would normally be exposed.

Nonradioactive cobalt has not been found to cause cancer in humans or in animals following exposure in the food or water. Cancer has been shown, however, in animals who breathed cobalt or when cobalt was placed directly into the muscle or under the skin. Based on the animal data, the International Agency for Research on Cancer (IARC) has determined that cobalt is possibly carcinogenic to humans.

Much of our knowledge of cobalt toxicity is based on animal studies. Cobalt is essential for the growth and development of certain animals, such as cows and sheep. Short-term exposure of rats to high levels of cobalt in the air results in death and lung damage. Longer-term exposure of rats, guinea pigs, hamsters, and pigs to lower levels of cobalt in the air results in lung damage and an increase in red blood cells. Short-term exposure of rats to high levels of cobalt in the food or drinking water results in effects on the blood, liver, kidneys, and heart. Longer-term exposure of rats, mice, and guinea pigs to lower levels of cobalt in the food or drinking water results in effects on the same tissues (heart, liver, kidneys, and blood) as well as the testes, and also causes effects on behavior. Sores were seen on the skin of guinea pigs following skin contact with cobalt for 18 days. Generally, cobalt compounds that dissolve easily in water are more harmful than those that are hard to dissolve in water.

Much of what we know about the effects of radioactive cobalt comes from studies in animals. The greatest danger of radiation seen in animals is the risk to the developing animal, with even moderate amounts of radiation causing changes in the fetus. High radiation doses in animals have also been shown to cause temporary or permanent sterility and changes in the lungs, which affected the animals' breathing. The blood of exposed animals has lower numbers of white blood cells, the cells that aid in resistance to infections, and red blood cells, which carry oxygen in the blood. Radioactive cobalt exposures in animals have also caused genetic damage to cells, cancer, and even death.

More information on how cobalt can affect your health can be found in Chapter 3.

1.6 HOW CAN COBALT AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Children can be exposed to cobalt in the same ways as adults. In addition, cobalt may be transferred from the pregnant mother to the fetus or from the mother to the infant in the breast milk. Children may be affected by cobalt the same ways as adults. Studies in animals have suggested that children may absorb more cobalt from foods and liquids containing cobalt than adults. Babies exposed to radiation while in their mother's womb are believed to be much more sensitive to the effects of radiation than adults.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO COBALT

If your doctor finds that you have been exposed to significant amounts of cobalt, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Since cobalt is naturally found in the environment, people cannot avoid being exposed to it. However, the relatively low concentrations present do not warrant any immediate steps to reduce exposure. If you are accidentally exposed to large amounts of cobalt, consult a physician immediately.

Children living near waste sites containing cobalt are likely to be exposed to higher environmental levels of cobalt through breathing, touching soil, and eating contaminated soil. Some children eat a lot of dirt. You should discourage your children from eating dirt. Make sure

they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or hand-to-mouth activity.

You are unlikely to be exposed to high levels of radioactive cobalt unless you are exposed as part of a radiotherapy treatment, there is an accident involving a cobalt sterilization or radiotherapy unit, or there is an accidental release from a nuclear power plant. In such cases, follow the advice of public health officials who will publish guidelines for reducing exposure to radioactive material when necessary. Workers who work near or with radioactive cobalt should follow the workplace safety guidelines of their institution carefully to reduce the risk of accidental irradiation.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO COBALT?

We have reliable tests that can measure cobalt in the urine and the blood for periods up to a few days after exposure. The amount of cobalt in your blood or urine can be used to estimate how much cobalt you had taken into your body. The tests are not able to accurately predict potential health effects following exposure to cobalt.

It is difficult to determine whether a person has been exposed only to external radiation from radioactive cobalt unless the radiation dose was rather large. Health professionals examining people who have health problems similar to those resulting from radiation exposure would need to rely on additional information in order to establish if such people had been near a source of radioactivity. It is relatively easy to determine whether a person has been internally exposed to radioactive cobalt, as discussed in Chapter 7. More information on medical tests can be found in Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), the Food and Drug Administration (FDA), and the U.S. Nuclear Regulatory Commission (USNRC).

Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR), the National Institute for Occupational Safety and Health (NIOSH), and the FDA.

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; they are then adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for cobalt include the following:

EPA requires that the federal government be notified if more than 1,000 pounds of cobalt (as the bromide, formate, and sulfamate compounds) are released into the environment in a 24-hour period. OSHA regulates levels of nonradioactive cobalt in workplace air. The limit for an 8-hour workday, 40-hour workweek is an average of 0.1 mg/m^3. The USNRC and the Department of Energy (DOE) regulate occupational exposures as well as exposures of the general public to radioactive cobalt.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, your regional Nuclear Regulatory Commission office, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles CD-ROM by calling the information and technical assistance toll-free number at 1-888-42ATSDR (1-888-422-8737), by email at atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

For-profit organizations may request a copy of final profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO COBALT IN THE UNITED STATES

Cobalt is a naturally-occurring element that has properties similar to those of iron and nickel. The largest use of metallic cobalt is in superalloys that are used in gas turbine aircraft engines. Cobalt compounds are used as pigments in glass, ceramics, and paints; as catalysts in the petroleum industry; as paint driers; and as trace element additives in agriculture and medicine.

Cobalt may be released to the environment by human activities, as well by weathering of rocks and soil. The primary anthropogenic sources of cobalt in the environment are from the burning of fossil fuels, application of cobalt-containing sludge or phosphate fertilizers, mining and smelting of cobalt-containing ores, processing of cobalt-containing alloys, and industries that use or process cobalt compounds. Cobalt released to the atmosphere is deposited onto soil or water surfaces by wet and dry deposition. In soils, cobalt generally has low mobility and strong adsorption. However its mobility increases in moist, acidic soils. In water, cobalt largely partitions to sediment and to suspended solids in the water column; however, the amount that is adsorbed to suspended solids is highly variable.

Exposure of the general population to cobalt occurs through inhalation of ambient air and ingestion of food and drinking water. In general, intake from food sources is much greater than from drinking water and air. The cobalt intake in food has been estimated to be 5.0–40.0 µg/day. Occupational exposure to cobalt occurs for workers in the hard metal industry (tool production, grinding, etc.) and in industries such as coal mining, metal mining, smelting and refining, cobalt dye painters, and the cobalt chemical production industry. The concentrations of cobalt in the air of hard metal manufacturing, welding, and grinding factories may range from 1 to 300 µg/m^3, compared to normal atmospheric levels of 0.4–2.0 ng/m^3.

While there is only one stable isotope of cobalt, ^{59}Co, there are many radioactive isotopes of cobalt. Of these radioactive isotopes, two are commercially important, ^{60}Co and ^{57}Co. ^{60}Co is produced by irradiating ^{59}Co with thermal neutrons in a nuclear reactor, and is used as a source of gamma rays for sterilizing medical equipment or consumer products, food irradiation, radiation therapy for treating cancer

patients, and for manufacturing plastics. The general population is not significantly exposed to radioactive forms of cobalt. Cancer patients being treated with radiation therapy may be exposed to gamma rays from a ^{60}Co source; however, the effects of external exposure to gamma radiation is not unique to ^{60}Co, but is similar for all gamma-emitting radionuclides. Workers at nuclear facilities and nuclear waste storage sites may be exposed to potentially high levels of radioactive cobalt.

2.2 SUMMARY OF HEALTH EFFECTS

As a component of cyanocobalmin (vitamin B_{12}), cobalt is essential in the body; the Recommended Dietary Allowance of vitamin B_{12} is 2.4 µg/day, which contains 0.1 µg of cobalt. Cobalt has been identified in most tissues of the body, with the highest concentrations found in the liver.

Following inhalation exposure to cobalt-containing particles, the primary target of exposure is the respiratory tract. Occupational exposure of humans to cobalt metal or cobalt-containing hard metal have reported primarily respiratory effects, including decreased pulmonary function, asthma, interstitial lung disease, wheezing, and dyspnea; these effects were reported at occupational exposure levels ranging from 0.015–0.13 mg Co/m^3. Animal studies have further identified respiratory tract hyperplasia, pulmonary fibrosis, and emphysema as sensitive effects of inhaled cobalt on respiratory tissues. Many of the respiratory tract effects are believed to be the result of the generation of oxidants and free radicals by the cobalt ion. In particular, hard metal (a tungsten carbide/cobalt alloy) is a potent generator of free electrons, resulting in the generation of active oxygen species. However, some of the respiratory effects, such as cobalt-induced asthma, are likely the result of immunosensitization to cobalt.

Other sensitive targets of cobalt inhalation in humans include effects on the thyroid and allergic dermatitis, manifesting as eczema and erythema; it is believed that the allergic dermatitis is due, at least in part, to concurrent dermal exposure and the development of immunosensitization to cobalt.

Adequate chronic studies of the oral toxicity of cobalt or cobalt compounds in humans and animals are not presently available. The most sensitive endpoint following oral exposure to cobalt in humans appears to be an increase in erythrocyte numbers (polycythemia). This effect has been observed in both normal subjects and in patients who were anemic as a result of being anephric. However, treatment of pregnant women with cobalt did not prevent the reduction in hematocrit and hemoglobin levels often found during

pregnancy. Exposure of humans to beer containing cobalt as a foam stabilizer resulted in severe effects on the cardiovascular system, including cardiomyopathy and death, as well as gastrointestinal effects (nausea, vomiting) and hepatic necrosis. However, the subjects in these studies were alcoholics, and it is not known what effect excessive alcohol consumption may have played in the development of the observed effects.

Following dermal exposure, the most commonly observed effect is dermatitis, as demonstrated by a large number of human studies. Using patch tests and intradermal injections, it has been demonstrated that the dermatitis is probably caused by an allergic reaction to cobalt, with the cobalt ion functioning as a hapten.

Available studies of the carcinogenic effects of cobalt in occupationally-exposed humans have reported mixed results, with both positive and negative results. Lifetime inhalation of cobalt sulfate resulted in increased tumor incidences in both rats and mice; NTP reported that there was some evidence of carcinogenicity in male Fischer 344 (F344) strain rats, and clear evidence of carcinogenicity in female F344 strain rats and male and female B6C3F1 strain mice following inhalation exposure. Oral data on the carcinogenic effects of cobalt and cobalt compounds are not available. IRIS does not report a cancer classification for cobalt or cobalt compounds. IARC has classified cobalt and cobalt compounds as *possibly carcinogenic to humans (Group 2B)*.

A more detailed discussion of the health effects of cobalt and cobalt compounds is presented in Chapter 3. An enhanced discussion of sensitive end points of stable cobalt toxicity is presented below.

Respiratory Effects. The primary effects of cobalt on respiratory tissues are seen following inhalation exposure, and include diminished pulmonary function, increased frequency of cough, respiratory inflammation, and fibrosis; reported effect levels in occupationally-exposed humans have ranged from 0.015–0.13 mg Co/m^3. Animal studies have further identified respiratory tract hyperplasia, pulmonary fibrosis, and emphysema as sensitive effects of cobalt on respiratory tissues. A number of these effects are believed to be the result of the generation of oxidants and free radicals by the cobalt ion. *In vitro* exposure to soluble cobalt increases indices of oxidative stress, including diminished levels of reduced glutathione, increased levels of oxidized glutathione, activation of the hexose monophosphate shunt, and free-radical-induced DNA damage. Cobalt exposure also results in sensitization of the immune system, which may result in asthmatic attacks following inhalation of cobalt in sensitized individuals.

Hard metal is a metal alloy with a tungsten carbide and cobalt matrix. It is used to make cutting tools because of its hardness and resistance to high temperature. Exposure to hard metal has been shown in a number of studies to cause respiratory effects, including respiratory irritation, diminished pulmonary function, asthma, and fibrosis, at exposure levels lower than those that would produce similar effects following exposure to cobalt metal alone (0.007–0.14 mg Co/m^3). Studies suggest that cobalt and not tungsten carbide is the probable causative agent for the respiratory effects observed in hard metal workers (see Section 3.5). A mechanism by which hard metal may exert its effects has been proposed by a group of Belgian researchers. In this proposed mechanism, tungsten carbide, which is a very good conductor of electrons, facilitates the oxidation of cobalt metal to ionic cobalt (presumably Co^{2+}) by transferring electrons from the cobalt atom to molecular oxygen adjacent to the tungsten carbide molecule. The result is an increased solubility of cobalt, relative to cobalt metal alone, and the generation of active oxygen species. *In vitro* evidence for this mechanism includes the ability of hard metal particles, but neither cobalt nor tungsten carbide alone at the same concentrations, to generate oxidant species and cause lipid peroxidation. Hard metal particles have also been shown to increase the levels of inducible nitric oxide synthase (iNOS), a gene responsive to oxidant stress.

Hematological Effects. Exposure to cobalt and cobalt compounds has been demonstrated to increase levels of erythrocytes and hemoglobin in both humans and animals. Davis and Fields reported increased (~16–20%) erythrocyte levels in six of six healthy men exposed orally to cobalt chloride (~1 mg Co/kg-day); erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. Increased levels of erythrocytes were also found following oral treatment of anephric patients (with resulting anemia) with cobalt chloride. The increase in hemoglobin resulted in a decreased need for blood transfusions. Treatment of pregnant women for 90 days with cobalt chloride, however, did not prevent the reduction in hematocrit and hemoglobin levels often found during pregnancy.

Increased levels of hemoglobin were observed in rats and guinea pigs, but not in dogs, exposed to cobalt hydrocarbonyl by inhalation. Polycythemia was reported in rats, but not mice, exposed to airborne cobalt sulfate. Significantly increased erythrocyte (polycythemia), hematocrit, and hemoglobin levels were found in animals treated orally with cobalt as either a single dose or with longer-term exposure. Of particular note is an 8-week study in rats, which reported dose- and time-related increases in erythrocyte number following oral administration of cobalt chloride.

The mechanisms regarding cobalt-induced polycythemia are not well understood. Cobalt is thought to inhibit heme synthesis *in vivo* by acting upon at least two different sites in the biosynthetic pathway. This inhibitory activity might result in the formation of cobalt protoporphyrin rather than heme. Cobalt treatment also stimulates heme oxidation in many organs, due to the induction of heme oxygenase. Conversely, cobalt acts, through a mechanism believed to involve a heme-containing protein, to increase erythropoietin, which stimulates the production of red blood cells. The regulatory mechanisms behind this apparent dichotomy have not been fully elucidated.

Cardiac Effects. Cardiomyopathy has been reported in both humans and animals following exposure to cobalt. Occupational exposure of humans to cobalt-containing dust, either as cobalt metal or as hard metal, is believed to result in cardiomyopathy characterized by functional effects on the ventricles and enlargement of the heart, but the exposure levels associated with cardiac effects of inhaled cobalt in humans have not been determined. Rats exposed to 11.4 mg Co/m^3 for 13 weeks developed a mild cardiomyopathy; however, rats and mice exposed to 1.14 mg Co/m^3 for 2 years showed no signs of cardiomyopathy.

Beer-cobalt cardiomyopathy was observed in people who heavily consumed beer that contained cobalt sulfate as a foam stabilizer. The beer drinkers ingested an average of 0.04 mg Co/kg/day to 0.14 mg Co/kg/day for a period of years. The cardiomyopathy was characterized by sinus tachycardia, left ventricular failure, cardiogenic shock, diminished myocardial compliance, absence of a myocardial response to exercise or catecholamine, enlarged heart, pericardial effusion, and extensive intracellular changes (changes in the myofibers, mitochondria, glycogen, and lipids). The beer-cobalt cardiomyopathy appeared to be similar to alcoholic cardiomyopathy and beriberi, but the onset of beer-cobalt cardiomyopathy was very abrupt. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein-poor diets and may have had prior cardiac damage from alcohol abuse. Studies in animals, and limited human data, have supported this possibility, as much greater oral exposure levels (on the order of 8-30 mg Co/kg-day) are necessary to induce cardiac effects.

The mechanism for cobalt-induced cardiomyopathy is not presently understood. Exposure to cobalt may result in accumulation in cardiac tissues, and is thought to stimulate carotid-body chemoreceptors, mimicking the action of hypoxia. Microscopic analysis of the hearts of those with beer-cobalt cardiomyopathy revealed fragmentation and degeneration of myofibers and aggregates of abnormal mitochondria. These mitochondrial changes are indicative of disturbances in energy production or

utilization may possibly be related to cobalt effects on lipoic acid. Cobalt irreversibly chelates lipoic acids under aerobic conditions. Lipoic acid is a required cofactor for oxidative decarboxylation of pyruvate to acetyl CoA and of α-ketoglutarate to succinate. In the myocardium of rats treated with cobalt, oxidation of pyruvate or fatty acids is impaired. However, the relative contribution of these mechanisms to the cardiac effects of cobalt has not been determined.

Dermal Effects. Dermatitis is a common result of dermal exposure to cobalt in humans. Using patch tests and intradermal injections, it has been demonstrated that the dermatitis is probably caused by an allergic reaction to cobalt. Exposure levels associated with the development of dermatitis have not been identified. It appears that cobalt metal may be a more potent allergen than some cobalt salts, as Nielsen et al. demonstrated that daily repeated exposure to aqueous cobalt salts did not result in hand eczema in patients known to have cobalt allergy. In animals, scabs and denuded areas were found after six doses of 51.75 mg Co/kg (5 days/week) as dicobalt octacarbonyl were applied to the shaved abdomens (uncovered area of approximately 50 cm^2) of guinea pigs. By the 11th dose, the lesions disappeared. No adverse effects were observed in vehicle controls (methyl ethyl ketone). It is not known whether or not a similar reaction would result from metallic or inorganic forms of cobalt.

Immunological Effects. Exposure of humans to cobalt by the inhalation and dermal routes has resulted in sensitization to cobalt. Exposure to inhaled cobalt chloride aerosols can precipitate an asthmatic attack in sensitized individuals, believed to be the result of an allergic reaction within the lungs. Similarly, the dermatitis seen in dermally-exposed subjects is likely the result of an allergic reaction, with cobalt functioning as a hapten. IgE and IgA antibodies specific to cobalt have been reported in humans. There is evidence that cobalt sensitivity in humans may also be regulated by T-lymphocytes; a human helper T-lymphocyte cell line specific for cobalt ($CoCl_2$) has been established. Cobalt may also interact directly with immunologic proteins, such as antibodies or Fc receptors, to result in immunosensitization. *In vitro*, cobalt(III) has been shown to reduce the proliferation of both B and T lymphocytes, as well as the release of the cytokines IL-2, IL-6, and IFN-Gamma. Interrelationships exist between nickel and cobalt sensitization, with cross-reactivity between the two having been reported in several studies.

Radioactive Cobalt. Exposure to radioisotopes of cobalt is also a human health concern. Energy released by radioactive isotopes can result in significant damage to living cells. Both ^{60}Co and ^{57}Co emit beta particles and gamma rays, which may ionize molecules within cells penetrated by these emissions and result in tissue damage and disruption of cellular function. The most important exposure route for

radioisotopes of cobalt is external exposure to the radiation released by the radioisotopes. It should be noted that there is nothing unique about the effects of external exposure to ^{60}Co and ^{57}Co when compared to other gamma- and beta-emitting radionuclides.

Generally, acute radiation doses below 15 rad (0.15 Gy) do not result in observable adverse health effects. At doses in the range of 15–50 rad (0.15–0.5 Gy), subclinical responses such as chromosomal breaks and transient changes in formed elements of the blood may be seen in sensitive individuals. Symptoms of acute radiation syndrome begin to be observed at radiation doses above 50 rad, characterized by transient hematopoietic manifestations, nausea and vomiting, and moderate leukopenia at doses near 100 rad (1 Gy), progressing through more serious hematopoietic symptoms, clinical signs, and gastrointestinal symptoms with increasing dose (100–800 rad or 1–8 Gy), and usually death in persons receiving total doses ≥1,000 rad (10 Gy). Other health effects from acute or continued high-level exposure to ionizing radiation may include reproductive, developmental, and latent cancer effects.

Signs and symptoms of acute toxicity from external and internal exposure to high levels of radiation from ^{60}Co and ^{57}Co are typical of those observed in cases of high exposure to ionizing radiation in general. Depending on the radiation dose, symptoms may include those typical of acute radiation syndrome (vomiting, nausea, and diarrhea), skin and ocular lesions, neurological signs, chromosomal abnormalities, compromised immune function, and death.

Acute or repeated exposure of humans or animals to ionizing radiation (from radioisotopes of cobalt or other radioactive elements) may result in reduced male fertility, abnormal neurological development following exposure during critical stages of fetal development, and genotoxic effects such as increased frequencies of chromosomal aberrations, sister-chromatid exchanges, and micronucleus formation.

Due to the ionizing properties of radionuclides such as ^{60}Co and ^{57}Co, increased cancer risk would be expected among exposed individuals. However, studies of increased cancer risk specifically associated with exposure of humans to radioactive cobalt isotopes were not located. Similarly, studies of the carcinogenic effects of radioactive cobalt isotopes in animals were not located.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

- An MRL of 0.0001 mg cobalt/m^3 has been derived for chronic-duration inhalation exposure (>365 days) to cobalt.

An MRL for inhalation exposure to cobalt was derived for chronic duration only. The chronic inhalation MRL of 0.0001 mg cobalt/m^3 was based on a no-observed-adverse-effect-level (NOAEL) of 0.0053 mg cobalt/m^3 and a LOAEL of 0.0151 mg cobalt/m^3 (both NOAEL and LOAEL values were adjusted for continuous exposure prior to MRL derivation) for decreases in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory flow between 25 and 75% of the FVC (MMEF), and mean peak expiratory flow rate (PEF) in diamond polishers (Nemery et al. 1992); a further discussion of the results and limitations of this study is presented in Appendix A.

The National Toxicology Program (NTP) has conducted a chronic-duration carcinogenicity study in rats and mice. Exposure of rats and mice to aerosols of cobalt (as cobalt sulfate) at concentrations ranging from 0.11 to 1.14 mg cobalt/m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice (NTP 1998). Squamous metaplasia of the larynx occurred in rats and mice at exposure concentrations of 0.11 mg cobalt/m^3, with severity of the lesion increasing with increased exposure concentration. Hyperplastic lesions of the nasal epithelium occurred in rats at concentrations of 0.11 mg cobalt/m^3, and in mice at concentrations of 0.38 mg cobalt/m^3. Both sexes of rats had greatly increased incidences (>90% incidence) of alveolar lesions at all exposure levels, including inflammatory changes, fibrosis, and metaplasia. Similar changes were seen in mice at all exposure levels, though the changes in mice were less severe. The study in diamond polishers, being a well-conducted study in humans, was selected as the critical study for the derivation of a MRL because it examined a human population and identified a NOAEL, neither of which occurred in the NTP study. The chronic inhalation MRL was derived by adjusting the NOAEL of 0.0053 mg Co/m^3 for intermittent exposure (adjusted to 0.0013 mg/m^3 to simulate continuous exposure), and applying an uncertainty factor of 10 (for human variability). It should be noted that this MRL may not be protective for individuals already sensitive to cobalt.

An acute inhalation MRL was not derived because the threshold was not defined for human effects and animal studies reported effects that were serious and occurred at levels above those reported in the few

human studies. An acute-duration study of hard metal exposure in humans (Kusaka et al. 1986b) was not utilized for MRL derivation because the toxicity of hard metal is not directly due to cobalt metal, but rather to an interaction between cobalt metal and tungsten carbide. An intermediate-duration MRL was not derived because available studies did not examine the dose-response relationship at low doses; the chronic inhalation MRL should be protective for intermediate exposures (see Appendix A).

Oral MRLs

- An MRL of 0.01 mg Co/kg-day has been derived for intermediate-duration oral exposure (<365 days) to cobalt.

An intermediate-duration MRL of 0.01 mg Co/kg/day was derived based on a LOAEL of 1 mg cobalt/kg-day for polycythemia as reported in a study by Davis and Fields (1958). The authors exposed six men to 120 or 150 mg/day of cobalt chloride (~1 mg Co/kg/day) for up to 22 days. Exposure to cobalt resulted in the development of polycythemia in all six patients, with increases in red blood cell numbers ranging from 0.5 to 1.19 million (~16–20% increase above pre-treatment levels). Polycythemic erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. An 8–week study in rats (Stanley et al. 1947) also reported increases in erythrocyte number, with a no-observed-effect-level (NOEL) of 0.6 mg/kg-day and a lowest-observed-effect-level (LOEL) of 1 mg/kg/day. The intermediate oral MRL was derived by dividing the LOAEL of 1 mg Co/kg-day by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Oral MRL values were not derived for acute or chronic exposure to cobalt. An acute MRL was not derived because the reported effects in animals were serious and occurred at levels above those reported in the few human oral studies. No chronic oral studies were available in animals; the chronic studies of beer-cobalt cardiomyopathy (Alexander 1969, 1972; Bonenfant et al. 1969; Morin et al. 1967, 1971; Sullivan et al. 1969) were not used because the effects were serious (death) and because the effects of concurrent alcoholism were not controlled for. Therefore, a chronic oral MRL was not derived for cobalt.

MRLs for External Exposure to Cobalt Isotopes

Two MRLs have been derived for ionizing radiation (Agency for Toxic Substances and Disease Registry 1999) and are applicable to external exposure to radioisotopes of cobalt:

- An MRL of 400 mrem (4.0 mSv) has been derived for acute-duration external exposure to ionizing radiation (14 days or less).

The acute MRL is based on results of a study by Schull et al. (1988) in which neurological effects of radiation, measured by intelligence test scores, were evaluated in children 10–11 years of age who had been exposed at critical stages of fetal development (gestation weeks 8–15) during the atomic bombing of Hiroshima and Nagasaki. When IQ scores were regressed on radiation dose estimates, IQ diminished linearly with increasing dose, resulting in an estimated decrease in IQ score of approximately 25 points per 100 rad (or 100 rem in dose equivalent) or 0.25 points/rem (25 points/Sv). To derive the MRL of 400 mrem (4.0 mSv), Agency for Toxic Substances and Disease Registry (1999) divided the dose associated with a predicted change of 0.25 IQ points/rem by an uncertainty factor of 3 (for human variability and/or the potential existence of sensitive populations). Agency for Toxic Substances and Disease Registry (1999) noted that a change in IQ points of 0.25 is less than the reported difference of 0.3 IQ points between separated and unseparated identical twins (Burt 1966).

The USNRC set a radiation exposure limit of 500 mrem (5 mSv) for pregnant working women over the full gestational period (USNRC 1991). For the critical gestational period of 8–15 weeks, Agency for Toxic Substances and Disease Registry believes that the acute MRL of 400 mrem (4 mSv) is consistent with the USNRC limit and could be applied to either acute (0–14-day) or intermediate (15–365-day) exposure periods.

- An MRL of 100 mrem/year (1.0 mSv/year) above background has been derived for chronic-duration external ionizing radiation (365 days or more).

The MRL is based on the BEIR V (1990) report that the average annual effective dose of ionizing radiation to the U.S. population is 360 mrem/year (3.6 mSv/year), a dose not expected to produce adverse noncancerous health effects. This dose is obtained mainly by naturally-occurring radiation from external sources, medical uses of radiation, and radiation from consumer products. An uncertainty factor of 3 (for human variability) was applied to the NOAEL of 360 mrem/year to derive the MRL of 100 mrem/year.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of cobalt. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. Section 3.2 contains a discussion of the chemical toxicity of stable cobalt; radiation toxicity associated with exposure to radioactive cobalt (primarily ^{60}Co) is discussed in Section 3.3. The chemical properties of stable and radioactive cobalt isotopes are identical and are described in Chapter 4.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

Section 3.2 discusses the chemical toxicity of stable cobalt. Radiation toxicity resulting from exposure to radioactive cobalt is discussed in Section 3.3.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death,

or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for cobalt. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic

bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Studies have shown that soluble cobalt compounds are generally more acutely toxic than insoluble cobalt compounds. When expressed in terms of the cobalt ion for the sake of comparison, however, the differences in lethality values from the available studies are within an order of magnitude and therefore do not warrant presentation in separate LSE tables and figures. Therefore, data regarding both soluble and insoluble cobalt compounds are presented in Tables 3-1, 3-2, and 3-3.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Conclusive evidence for human deaths related to inhalation exposure to cobalt has not been reported; however, results of several studies and case reports suggest a possible relationship between exposure and deaths from lung cancer and cardiomyopathy, respectively.

In general, available cohort studies in humans have not reported a significant increase in total mortality as a result of cobalt exposure. Several studies have noted increased mortality rates resulting from lung cancer following occupational exposure to cobalt, either as a mixture of cobalt compounds (Mur et al. 1987) or as hard metal, a metal alloy with a tungsten carbide and cobalt matrix (Lasfargues et al. 1994; Moulin et al. 1998). Fatal cases of hard metal disease (Figueroa et al. 1992; Ruokonen et al. 1996) and cardiomyopathy (Barborik and Dusek 1972) believed to have resulted from occupational cobalt exposure have also been reported. However, in the majority of these and other reported occupational studies, co-exposure to other substances was common, and was unable to be corrected for in the analysis.

Cobalt inhalation can be lethal in animals if exposure is sufficiently high or prolonged. The acute LC^{50} for a 30-minute inhalation exposure in rats was 165 mg cobalt/m^3 as cobalt hydrocarbonyl (Palmes et al. 1959). Exposure to 9 mg cobalt/m^3 as cobalt hydrocarbonyl for 6 hours/day, 5 days/week for

3 months resulted in 16 deaths out of 75 rats (Palmes et al. 1959). Death was reported in rats and mice exposed to 19 mg cobalt/m^3 (but not 1.9 mg cobalt/m^3) as cobalt sulfate over 16 days, but exposure to 11.4 mg cobalt/m^3 over 13 weeks was lethal only to mice and not to rats (Bucher et al. 1990; NTP 1991). Exposure to 1.14 mg cobalt/m^3 as cobalt sulfate for 104 weeks resulted in no increase in mortality in rats and mice of either sex (Bucher et al. 1999; NTP 1998). Lethal levels for each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No data were located regarding dermal effects in humans or animals after inhalation exposure to stable cobalt. Inhalation of stable cobalt by humans and/or animals resulted in respiratory, cardiovascular, hematological, hepatic, renal, endocrine, ocular, and body weight effects. For each effect, the highest NOAEL values and all reliable LOAEL values for each species and duration category are reported in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Hard metal is a metal alloy with a tungsten carbide and cobalt matrix. It is used to make cutting tools because of its hardness and resistance to high temperature. Studies (Davison et al. 1983; Harding 1950) suggest that cobalt (and not tungsten carbide) is the probable causative agent for the respiratory effects observed in hard metal workers (see Section 3.6).

The effects of chronic occupational exposure to cobalt and cobalt compounds on the respiratory system in humans are well-documented. These effects include respiratory irritation, diminished pulmonary function, wheezing, asthma, pneumonia, and fibrosis and occurred at exposure levels ranging from 0.007 to 0.893 mg cobalt/m^3 (exposure from 2 to 17 years) (Anttila et al. 1986; Davison et al. 1983; Demedts et al. 1984a, 1984b; Deng et al. 1991; Gennart and Lauwerys 1990; Gheysens et al. 1985; Hahtola et al. 2000; Hartung et al. 1982; Kusaka et al. 1986a, 1986b, 1996a, 1996b; Nemery et al. 1992; Raffn et al. 1988; Rastogi et al. 1991; Ruokonen et al. 1996; Shirakawa et al. 1988, 1989; Sprince et al. 1988; Sundaram et al. 2001; Swennen et al. 1993; Tabatowski et al. 1988; Van Cutsem et al. 1987; Zanelli et al. 1994). These effects have been observed in workers employed in cobalt refineries, as well as hard metal workers, diamond polishers, and ceramic dish painters (painting with cobalt blue dye).

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
	ACUTE EXPOSURE								
	Systemic								
1	Human	6 hr	Resp		0.038	(bronchial irritation, reduced FVC)			Kusaka et al. 1986b Hard Metal
2	Rat SD-Jcl	5 hr	Resp	2.72					Kyono et al. 1992 Metal
3	Rat SD-Jcl	4 d	Resp		2.12 M	(Slight damage to respiratory tissues, assessed by electron microscopy)			Kyono et al. 1992 Metal
4	Rat	30 min	Resp	7	26	(edema)	83	(severe edema)	Palmes et al. 1959 Hydrocarbonyl
	INTERMEDIATE EXPOSURE								
	Death								
5	Rat	16 d 5 d/wk 6 hr/d		1.9			19	(2/5 males died)	NTP 1991 Sulfate

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
6	Mouse	13 wk 5 d/wk 6 hr/d		3.8			11.4	(2 males died)	NTP 1991 Sulfate
	Systemic								
7	Rat	13 wk 5 d/wk 6 hr/d	Resp		0.11	(laryngial squamous metaplasia and polyps)	0.38	(chronic inflammation of larynx)	NTP 1991 Sulfate
			Cardio		11.4	(increase in severity of cardiomyopathy)			
			Hemato		1.14[b] M	(polycythemia)			
			Renal	11.4					
			Bd Wt		11.4	(15% lower body weight in males)			
8	Rat	3 mo 5 d/wk 7 h/d	Resp		9	(lung inflamm)			Palmes et al. 1959 Hydrocarbonyl
			Hemato		9[b]	(10% increase in hemoglobin)			
			Bd Wt	9					

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
9	Mouse	16d 5 d/wk 6 hr/d	Resp	0.2	1.9	(respiratory tract inflammation)	19	(necrosis)	NTP 1991 Sulfate
			Cardio	76					
			Gastro	76					
			Musc/skel	76					
			Hepatic				19	(necrosis)	
			Renal	76					
			Dermal	76					

[a]

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
10	Mouse	13 wk 5 d/wk 6 hr/d	Resp		0.11 (larynx metaplasia)	3.8 M (acute inflam of nose) 1.14[c] F (acute inflam of nose)	NTP 1991 Sulfate
			Gastro	11.4			
			Hemato	11.4			
			Musc/skel	11.4			
			Hepatic	11.4			
			Renal	11.4			
			Dermal	11.4			
			Bd Wt		11.4 (13-20% decrease in body weight)		
11	Gn Pig (Hartley)	66 d	Resp			2.4 F (Increased lung weight, increased retention of lavage fluid)	Camner et al. 1993 Chloride

[a] Key to figure

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
12	Gn Pig	3 mo 5 d/wk 7 h/d	Hemato		9[b] (5% increase in hemoglobin)		Palmes et al. 1959 Hydrocarbonyl
13	Dog	3 mo 3d/wk 7h/d	Hemato	9			Palmes et al. 1959 Hydrocarbonyl
			Bd Wt		9 (wt loss)		
14	Rabbit	4 mo 5 d/wk 6 h/d	Resp		0.4 (moderate lung inflammation)	2 (severe lung inflammation)	Johansson et al. 1987
15	Rabbit	4 mo	Resp	0.5 M			Johansson et al. 1991 Chloride
16	Rabbit	4 mo	Resp		0.6 M (Histologic alterations in pulmonary tissue; altered BAL parameters)		Johansson et al. 1992 Chloride

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
17	Pig	3 mo 5d/wk 6hr/d	Resp		0.1 (decr compliance)		Kerfoot 1975 Metal
			Cardio		0.1 (EKG changes)		
			Hepatic	1			
			Renal	1			
			Bd Wt		0.1 (decr wt gain)		
	Immuno/ Lymphoret						
18	Rat	16 d 5 d/wk 6 hr/d			19 (necrosis of thymus)		NTP 1991 Sulfate
19	Mouse	13 wk 5 d/wk 6 hr/d			11.4 (lymph node hyperplasia)		NTP 1991 Sulfate
	Neurological						
20	Rat	16 d 5 d/wk 6 hr/d			19 (congestion of vessels in brain)		NTP 1991 Sulfate
21	Mouse	16 d 5 d/wk 6 hr/d			19 (congestion of vessels in brain)		NTP 1991 Sulfate

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
	Reproductive						
22	Rat	16 d 5 d/wk 6 hr/d				19 M (testes atrophy)	NTP 1991 Sulfate
23	Mouse	13 wk 5 d/wk 6 hr/d			1.14 M (decreased sperm motility)	11.4 (testes atrophy- increased length estrous cycle)	NTP 1991 Sulfate
	CHRONIC EXPOSURE						
	Systemic						
24	Human	occup (occup)	Resp	0.0175			Deng et al. 1991 Metal
25	Human	occup (occup)	Resp		0.1355 (Decreased FEV1 and FVC ~10%; increased cough, sputum, dyspnea)		Gennart and Lauwerys 1990 Hard-Metal
26	Human	occup (occup)	Resp	0.0053[d]	0.0151 (Decreased FEV1, FVC increased cough and upper airway irritation)		Nemery et al. 1992 Metal
27	Human	occup (occup)	Endocr		0.05 F (Decreased thyroid volume; increases in T4 and FT4I levels)		Prescott et al. 1992 Zinc-Silicate Dye

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
28	Human	occup	Resp				0.007	(asthma)	Shirakawa et al. 1988 Hard Metal
29	Human	occup	Resp				0.051	(interst lung dis)	Sprince et al. 1988 Hard Metal
30	Human	8 yr (occup)	Resp		0.125	(Dyspnoea and wheezing)			Swennen et al. 1993 Metal
			Hemato		0.125	(Decreased red cell counts ~5%; decreased total hemoglobin ~4%)			
			Endocr		0.125	(Slight (~7%) decrease in T3 levels)			
			Dermal		0.125	(Eczema and erythema)			
31	Rat (Fischer- 344)	104 wk	Resp				0.11	(Hyper- and metaplasia of respiratory tract tissues; pulmonary fibrosis)	NTP 1998 Sulfate
32	Mouse (B6C3F1)	104 wk	Resp		0.11	(Laryngial metaplasia)			NTP 1998 Sulfate

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
33	Hamster	life 5d/wk 7h/d	Resp			7.9 (emphysema)	Wehner et al. 1977 Oxide
			Bd Wt	7.9			
	Immuno/ Lymphoret						
34	Human	occup			0.007 (sensitization)		Shirakawa et al. 1986a Hard Metal
35	Human	8 yr (occup)			0.125 (Increased white cell count by 19%)		Swennen et al. 1993 Metal
	Cancer						
36	Rat (Fischer- 344)	104 wk				1.14 M (alveoloar/bronchiolar neoplasms)	NTP 1998 Sulfate
						1.14 F (pheochromocytoma)	
						0.38 F (alveoloar/bronchiolar neoplasms)	

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
37	Mouse (B6C3F1)	104 wk				1.14 M (Combined alveolar/bronchiolar adenoma/carcinoma)	NTP 1998 Sulfate
						0.38 F (Combined alveolar/bronchiolar adenoma/carcinoma)	

[a] The number corresponds to entries in Figure 3-1.

[b] An increase in hemoglobin or red blood cells (polycythemia) is not necessarily considered an adverse effect.

[c] Differences in levels of health effects and cancer effect between males and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

[d] Used to derive a chronic inhalation Minimal Risk level (MRL) of 0.0001 mg Co/m3., dose adjusted for intermittent exposure, and divided by an uncertainty factor of 10 (for human variability).

Bd = body weight; Cardio = cardiovascular, d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; (occup) = occupational; Resp = respiratory; wk = week(s); yr = year(s).

Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation

Acute (≤14 days)

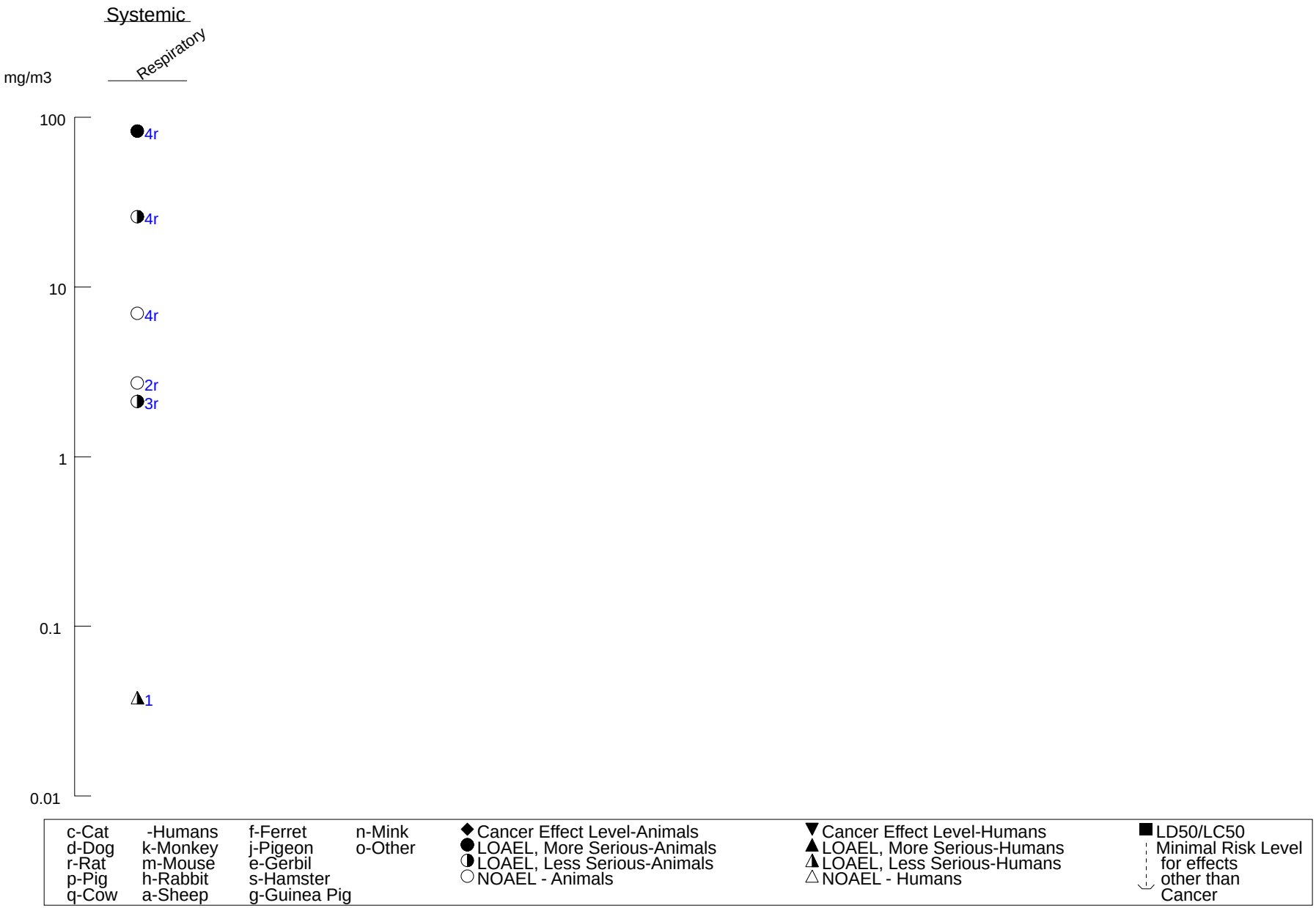


Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (*Continued*)

Intermediate (15-364 days)

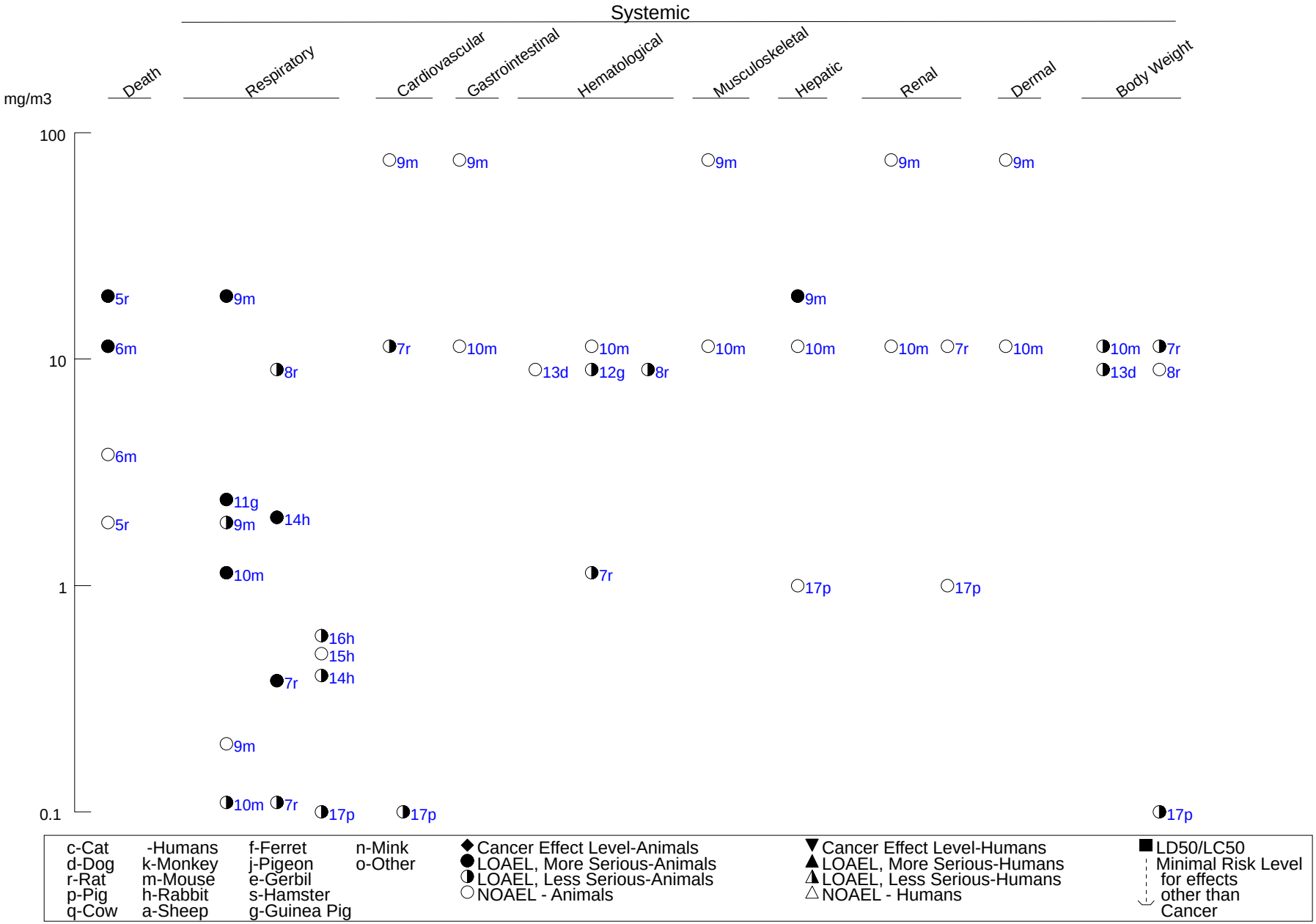


Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (*Continued*)

Intermediate (15-364 days)

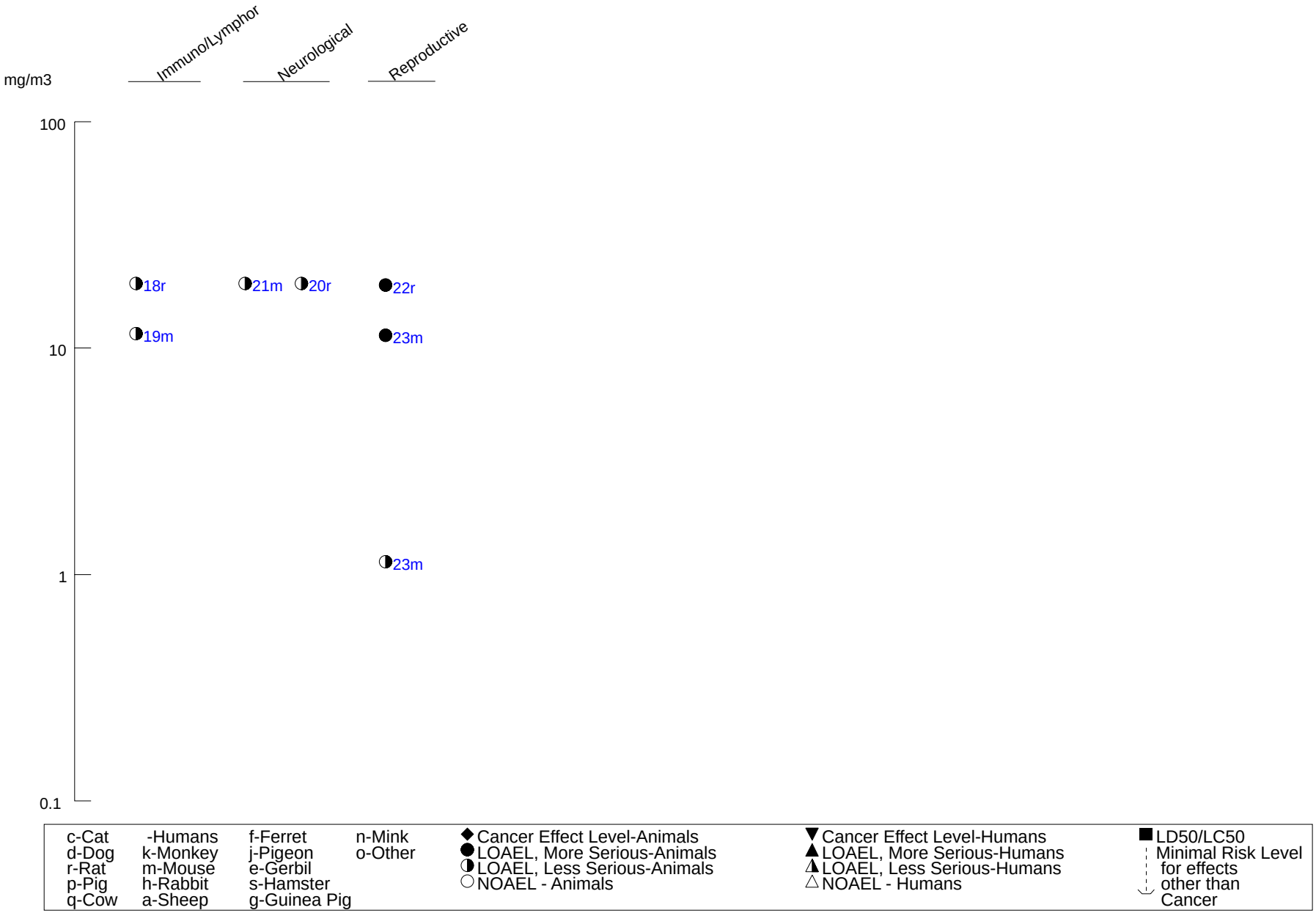
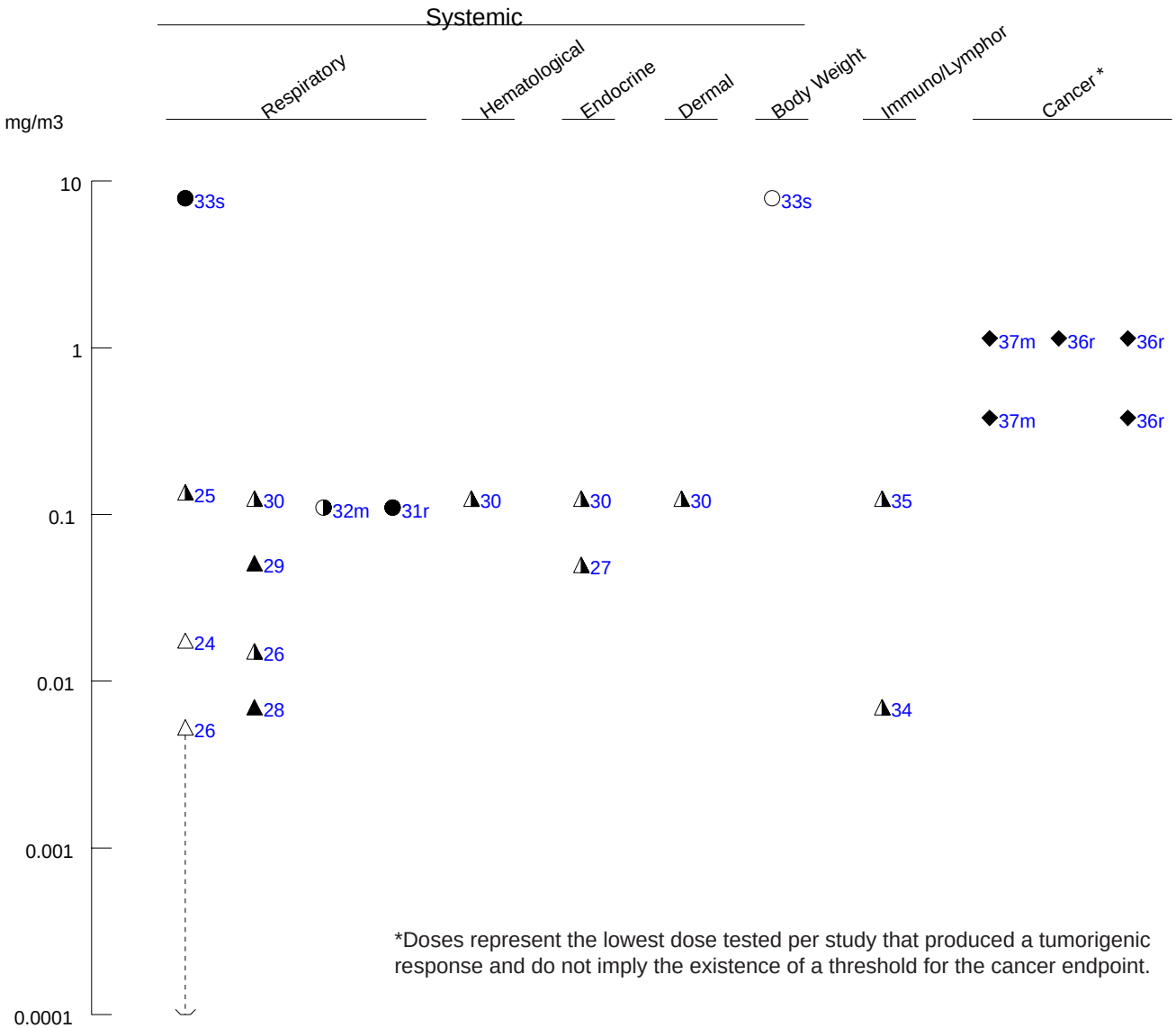


Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (*Continued*)

Chronic (≥365 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Kusaka et al. (1986b) described an acute exposure of 15 healthy young men to atmospheres of hard metal dust containing 0.038 mg cobalt/m^3 for 6 hours. Forced vital capacity (FVC) was reduced, but no dose-response relation could be discerned. By contrast, 42 workers occupationally exposed to hard metal showed no decrease in ventilatory function at 0.085 mg cobalt/m^3, but significant changes in FEV_1 (forced expiratory volume in 1 second) at 0.126 mg cobalt/m^3 (Kusaka et al. 1986b). Several other studies of hard metal workers have shown respiratory effects, including decreased ventilatory function, wheezing, asthma, and fibrosis (Kusaka et al. 1996a, 1996b; Ruokonen et al. 1996; Zanelli et al. 1994), but have had less complete reports of exposure.

Swennen et al. (1993) performed a cross-sectional study on 82 workers in a cobalt refinery. Workers were examined for cobalt in blood and urine, a number of erythropoietic variables, thyroid metabolism, pulmonary function, skin lesions, and several serum enzymes. The concentrations of cobalt in blood and in urine after the shift were significantly correlated with those in air. Workers exposed to airborne cobalt metal, salts, or oxides (mean concentration 0.125 mg/m^3, range 0.001–7.7 mg/m^3) showed an increased ($p<0.05$) prevalence of dyspnea and wheezing and had significantly more skin lesions (eczema, erythema) than control workers. A dose-effect relation was found between the reduction of the FEV_1 and the intensity of the current exposure to cobalt, as assessed by measurement of cobalt in blood, air, or urine.

Gennart and Lauwerys (1990) examined the ventilatory functions of 48 diamond polishing workers, relative to 23 control workers. Exposure occurred mainly in one of two rooms, with mean airborne concentrations of 0.0152 and 0.1355 mg cobalt/m^3; control subjects worked in other areas of the facilities, where no exposure to cobalt occurred. Significant decreases in ventilatory function were found in the exposed workers relative to the control workers. Duration of exposure played a significant factor, with no significant differences in workers who had been exposed for ≤5 years; reported decreases in ventilatory function were noted in workers exposed for > 5 years. Inhalation exposure to cobalt salts (exposure levels not reported) among glass bangle workers resulted in decreases in decreased ventilatory function, generally restrictive in nature, relative to controls (Rastogi et al. 1991).

Nemery et al. (1992) conducted a cross-sectional study of cobalt exposure and respiratory effects in diamond polishers. Exposure occurred mainly from the generation of airborne cobalt resulting from the use of cobalt-containing polishing discs. The study groups were composed of 194 polishers working in 10 different workshops, and were divided into control, low-, and high-exposure groups. The low-exposure group (n=102) was exposed to an average of 0.0053 mg cobalt/m^3, based on personal sampling

measurements, while the exposure level for the high dose group (n=92) was 0.0151 mg cobalt/m^3; there was considerable overlap in the total range of concentrations for the low- and high-exposure groups. Workers in the high-exposure group were more likely than those in the other groups to complain about respiratory symptoms; the prevalence of eye, nose, and throat irritation and cough, as well as the fraction of these symptoms related to work, were significantly increased in the high-exposure group. Workers in the high-exposure group also had significantly reduced lung function compared to controls and low-exposure group workers, as assessed by FVC, FEV_1, MMEF (forced expiratory flow between 25 and 75% of the FVC) and mean PEF (peak expiratory flow rate). Results in the low-exposure group did not differ from controls. Based on the NOAEL of 0.0053 mg cobalt/m^3 for decreased ventilatory function in exposed workers, a chronic inhalation MRL of 1x10-4 mg cobalt/m^3 was calculated as described in footnote (d) in Table 3-1. It should be noted that this MRL value may not be protective for some hypersensitive individuals.

As with exposures in humans, exposures of animals to cobalt-containing aerosols have resulted in pronounced respiratory effects. Animals exposed to aerosols of cobalt oxides and cobalt sulfate developed respiratory effects that varied in severity with exposure level and duration. A single 30-minute exposure of rats to relatively high levels (26–236 mg cobalt/m^3 as cobalt hydrocarbonyl) resulted in congestion, edema, and hemorrhage of the lung (Palmes et al. 1959). Prolonged exposure (3–4 months) of rats and rabbits to mixed cobalt oxides (0.4–9 mg cobalt/m^3) resulted in lesions in the alveolar region of the respiratory tract characterized histologically by nodular accumulation of Type II epithelial cells, accumulations of enlarged highly vacuolated macrophages, interstitial inflammation, and fibrosis (Johansson et al. 1984, 1987, 1991, 1992; Kyono et al. 1992; Palmes et al. 1959). In at least one instance, the lesions appeared to regress when exposure was terminated (Palmes et al. 1959). Guinea pigs sensitized to cobalt by repeated dermal application and then exposed to 2.4 mg cobalt/m^3 as cobalt chloride showed pulmonary inflammatory changes (altered BAL fluid recovery, increased neutrophils and eosinophils in the recovered BAL fluid) that were different than those in exposed animals not sensitized to cobalt (Camner et al. 1993). Decreased lung compliance was found in pigs exposed to 0.1 mg cobalt/m^3 as cobalt dust for 3 months (Kerfoot 1975). Lifetime exposure of hamsters to 7.9 mg cobalt/m^3 as cobalt oxide resulted in emphysema (Wehner et al. 1977).

Necrosis and inflammation of the respiratory tract epithelium (nasal turbinates, larynx, trachea, bronchioles) were reported in rats exposed to 19 mg cobalt/m^3 and mice exposed to 1.9 mg cobalt/m^3 or greater as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991). Exposure of rats and mice to

cobalt as cobalt sulfate for 13 weeks resulted in adverse effects on all parts of the respiratory tract, with the larynx being the most sensitive part (Bucher et al. 1990; NTP 1991). At concentrations of ≥0.11 mg cobalt/m^3, rats and mice developed squamous metaplasia of the larynx. Histiocytic infiltrates in the lung were also reported at similar levels in both the rats and mice. In rats, chronic inflammation of the larynx was found at ≥0.38 mg cobalt/m^3, and more severe effects on the nose, larynx, and lung were reported at higher exposures. In mice, acute inflammation of the nose was found at ≥1.14 mg cobalt/m^3, and more severe effects on the nose, larynx, and lung were reported at higher exposures. Exposure of rats and mice to aerosols of cobalt (as cobalt sulfate) at concentrations from 0.11 to 1.14 mg cobalt/m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice (Bucher et al. 1999; NTP 1998). Squamous metaplasia of the larynx occurred in rats and mice at exposure concentrations of ≥0.11 mg cobalt/m^3, with severity of the lesion increasing with increased cobalt concentration. Hyperplastic lesions of the nasal epithelium occurred in rats at concentrations of ≥0.11 mg cobalt/m^3, and in mice at concentrations of ≥0.38 mg cobalt/m^3. Both sexes of rats had greatly increased incidences (>90% incidence) of alveolar lesions at all exposure levels, including inflammatory changes, fibrosis, and metaplasia. Similar changes were seen in mice at all exposure levels, though the changes in mice were less severe.

Cardiovascular Effects. Occupational exposure of humans to cobalt-containing dust, either as cobalt metal or as hard metal, has been shown to result in cardiomyopathy, characterized by functional effects on the ventricles (Horowitz et al. 1988) and/or enlargement of the heart (Barborik and Dusek 1972; Jarvis et al. 1992), but the exposure levels associated with cardiac effects of inhaled cobalt in humans have not been determined. Jarvis et al. (1992) reported on two patients (exposure histories not specified) who had been admitted to the emergency room for cardiac failures; these failures were believed to be associated with cobalt exposure. Barborik and Dusek (1972) reported a case of a 41-year-old man who was admitted to the hospital with cardiac failure following occupational exposure to cobalt; cobalt concentrations in heart, liver, lung, spleen, and kidney were elevated over two control patients. Horowitz et al. (1988) reported that in a cohort of 30 hard metal workers (exposure histories not specified), significant decreases in exercise right ventricular ejection fraction (EF) were seen in workers with abnormal chest x-rays relative to those with normal chest x-rays. It is possible that these effects were secondary to the respiratory effects of inhaled cobalt. It was concluded that cobalt is a weak cardiomyopathic agent following occupational exposure (Horowitz et al. 1988). Cardiomyopathy is a characteristic toxic effect of cobalt following oral exposure in both humans and animals (Section 3.2.2.2).

In rats, exposure to 11.4 mg cobalt/m^3 as cobalt sulfate over 13 weeks resulted in a marginal increase in the severity of cardiomyopathy as compared to controls (minimal-mild in treated animals versus minimal in controls; 3/10 animals affected in either group) (Bucher et al. 1990; NTP 1991). Cardiomyopathy was not observed in mice exposed to ≤76 mg cobalt/m^3 as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991), nor in mice or rats exposed to up to 1.14 mg cobalt/m^3 for 2 years (Bucher et al. 1999; NTP 1998). Electrocardiogram abnormalities that may reflect ventricular impairment have been observed in miniature swine (n=5) exposed to 0.1 mg cobalt dust/m^3 for 6 hours/day, 5 days/week for 3 months (Kerfoot 1975).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to stable cobalt.

No histological lesions were reported in the esophagus, stomach, duodenum, ileum, jejunum, cecum, colon, or rectum of rats or mice of either sex exposed to 76 mg cobalt/m^3 or less as cobalt sulfate for 16 days, up to 11.4 mg cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998).

Hematological Effects. Swennen et al. (1993) reported slightly, but statistically significantly, decreased levels of red cells and total hemoglobin (~4–5% decreases) in a group of 82 workers occupationally exposed to a mean concentration of 0.125 mg cobalt/m^3 as cobalt metal dust. No other studies were located regarding hematological effects in humans after inhalation exposure to cobalt.

Increased levels of hemoglobin and increased numbers of basophils and monocytes have been observed in rats and guinea pigs, but not in dogs, exposed to 9 mg cobalt/m^3 as cobalt hydrocarbonyl for 3 months (Palmes et al. 1959). Polycythemia was reported in rats, but not mice, exposed to 1.14 mg cobalt/m^3 as cobalt sulfate for 13 weeks (Bucher et al. 1990; NTP 1991).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to cobalt.

No histological lesions were reported in the sternebrae (segments of the sternum), including the bone marrow, of rats or mice exposed to ≤76 mg cobalt/m^3 as cobalt sulfate for 16 days, up to 11.4 mg

cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998) (see the above section on respiratory effects for detailed descriptions of exposure conditions).

Hepatic Effects. Congestion of the liver was observed upon autopsy of a metal worker (exposure history not reported) who had been occupationally exposed to an unknown level of cobalt for 4 years (Barborik and Dusek 1972). The cause of death was determined to be cardiomyopathy.

Necrosis and congestion of the liver were observed in both rats and mice that died following exposure to 19 mg cobalt/m^3 as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991). No histological effects on the liver were found in pigs exposed to up to 1.0 mg cobalt/m^3 as cobalt metal dust for 3 months (Kerfoot 1975).

Renal Effects. Congestion of the kidneys was observed upon autopsy of a metal worker who had been occupationally exposed to an unknown level of cobalt for 4 years (Barborik and Dusek 1972). The cause of death was determined to be cardiomyopathy.

A significant increase in the relative weight of the kidneys was reported in male rats exposed to 0.11 mg cobalt/m^3 or greater as cobalt sulfate for 13 weeks (Bucher et al. 1990; NTP 1991). No effects were observed upon histological examination of the kidneys in rats or mice following exposure to $\leq$76 mg cobalt/m^3 as cobalt sulfate for 16 days, up to 11.4 mg cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998). No histological effects on the kidneys were found in pigs exposed to up to 1.0 mg cobalt/m^3 as cobalt metal for 3 months (Kerfoot 1975).

Dermal Effects. No studies were located regarding dermal effects in humans or animals after inhalation exposure to stable cobalt.

Endocrine Effects. A group of female workers occupationally exposed to a semisoluble cobalt glaze (cobalt-zinc silicate, estimated concentrations of 0.05 mg Co/m^3) showed significantly elevated levels of serum thyroxine (T4) and free thyroxine, but no change in T3 levels (Prescott et al. 1992). In contrast to this, Swennen et al. (1993) reported no significant change in serum T4 levels, but a significant reduction in serum T3 in workers occupationally exposed to cobalt oxides, cobalt salts, and cobalt metal.

Ocular Effects. Congestion of the conjunctiva was observed in a metal worker after occupational exposure to an unknown level of cobalt for 4 years (Barborik and Dusek 1972); however, due to the nature of the exposure, this effect may also have been the result of direct dermal or ocular contact. Upon autopsy, the cause of death was determined to be cardiomyopathy.

No histological lesions were reported in the eyes or on the skin of rats or mice exposed to ≤76 mg cobalt/m^3 as cobalt sulfate for 16 days, up to 11.4 mg cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998).

Body Weight Effects. Weight loss, measured individually from time of initial examination throughout followup, was observed in a group of five diamond polishers suffering from cobalt-induced interstitial lung disease (Demedts et al. 1984b), but the exposure level of cobalt was not reported.

Decreased body weight, relative to controls at study termination, was reported in both rats and mice exposed to 19 mg cobalt/m^3 as cobalt sulfate over 16 days or to 11.4 mg cobalt/m^3 for 13 weeks (Bucher et al. 1990; NTP 1991). A 13-week exposure to 11.4 mg cobalt /m^3 resulted in ruffled fur in male rats, with no clinical signs reported in female rats or either sex of mice (Bucher et al. 1990; NTP 1991). Chronic exposure of rats and mice to up to 1.14 mg cobalt/m^3 did not result in decreased body weight (Bucher et al. 1999; NTP 1998).

Weight loss was found in dogs, but not rats or guinea pigs, exposed for 3 months to cobalt at a level of 9 mg cobalt/m^3 as cobalt hydrocarbonyl (Palmes et al. 1959). Lifetime exposure of hamsters to a similar concentration (7.9 mg cobalt/m^3 as cobalt oxide) did not result in decreased body weight gain (Wehner et al. 1977).

3.2.1.3 Immunological and Lymphoreticular Effects

Cobalt is known to function as a hapten, resulting in the generation of antibodies against cobalt-protein complexes. Although the minimum exposure level associated with cobalt sensitization has not been determined, sensitization has been demonstrated in hard metal workers with work-related asthma who have experienced prolonged occupational exposure (>3 years) to levels ranging from 0.007 to 0.893 mg cobalt/m^3 (Shirakawa et al. 1988, 1989). The lower end of this range, 0.007 mg/m^3, is reported in

Table 3-1 and plotted in Figure 3-1 as a LOAEL. The sensitization phenomenon includes the production of IgE and IgA antibodies to cobalt (Bencko et al. 1983; Shirakawa et al. 1988, 1989). Exposure to inhaled cobalt chloride aerosols can precipitate an asthmatic attack in sensitized individuals (Shirakawa et al. 1989), believed to be the result of an allergic reaction within the lungs.

Necrosis of the thymus was reported in rats exposed to 19 mg cobalt/m^3 as cobalt sulfate over 16 days, and hyperplasia of the mediastinal lymph nodes was found in mice exposed to 11.4 mg cobalt/m^3 for 13 weeks (Bucher et al. 1990; NTP 1991). Tests of immunological function, however, were not performed on the rats or mice.

3.2.1.4 Neurological Effects

Occupational exposure to cobalt in humans has been reported to cause several effects on the nervous system, including memory loss (Wechsler Memory Scale-Revised), nerve deafness, and a decreased visual acuity (Jordan et al. 1990; Meecham and Humphrey 1991). It should be noted, though, that both of these studies had small numbers of subjects (n=38 for Jordan et al. 1990, n=1 for Meecham and Humphrey 1991), and exposure characterization was not reported.

Congestion in the vessels of the brain/meninges was reported in rats and mice exposed to 19 mg cobalt/m^3 or greater as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991).

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to cobalt.

In animals, long-term exposure to cobalt-containing aerosols has resulted in effects on reproductive end points. Testicular atrophy was reported in rats, but not in mice, exposed to 19 mg cobalt/m^3 as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991). Following exposure of mice to cobalt (as cobalt sulfate) for 13 weeks, a decrease in sperm motility was found at 1.14 mg cobalt/m^3, and testicular atrophy was found at 11.4 mg cobalt/m^3. A significant increase in the length of the estrous cycle was reported in female mice exposed to 11.4 mg cobalt/m^3 for 13 weeks (Bucher et al. 1990; NTP 1991). No effects on

the male or female reproductive systems were observed in rats similarly treated for 13 weeks (Bucher et al. 1990; NTP 1991), or in mice or rats exposed to up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1999; NTP 1998).

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to cobalt.

3.2.1.7 Cancer

Several studies have evaluated the effects of inhalation of cobalt-containing compounds on possible carcinogenicity in humans. The mortality of a cohort of 1,143 workers in a plant that refined and processed cobalt and sodium was analyzed (Mur et al. 1987); the French national population mortality data were used as a reference population. An increase in deaths due to lung cancer was found in workers exposed only to cobalt (standardized mortality ratio [SMR] of 4.66; four cases in the exposed group versus one case in the controls). In a study within the cohort that controlled for date of birth, age at death, and smoking habits, 44% (four workers) in the group exposed to cobalt and 17% (three workers) in the group not exposed to cobalt died of lung cancer. The authors, however, indicated that the difference was not statistically significant and that the workers were exposed to both arsenic and nickel as well as cobalt. The nonneoplastic lung diseases commonly found in cobalt-exposed workers (see Section 3.2.1.2) were not reported in this group. These lung diseases may have been present in these workers, but if they were not listed as the cause of death on the death certificate, they would not have been mentioned. Inhalation was probably a prominent route of exposure to cobalt; however, oral and dermal exposure probably occurred as well. No adjustments were made for smoking habits in the larger study, and the exposure levels of cobalt were not reported for either study. However, a followup study of this cohort (Moulin et al. 1993) did not report significant increases in mortality due to respiratory or circulatory diseases. Similarly, no increase in the SMR for lung cancer was noted in exposed workers, relative to controls. While an elevated SMR for lung cancer was seen in maintenance workers (SMR=1.80, 95% confidence interval [CI]=0.78–3.55), it was not statistically significant, since the 95% confidence interval included an SMR of 1.

Lasfargues et al. (1994) reported on the mortality of a cohort of 709 male workers in a French hard metal plant, using the national rates for French males for comparison. The overall mortality did not differ from expected, but there was a significant increase in mortality due to cancer of the trachea, bronchus, and lung (SMR=2.13, 95% CI=1.02–3.93). Smoking alone did not account for the lung cancer excesses, although the influence of smoking on the observed mortality could not be entirely ruled out.

A cohort of 5,777 males and 1,682 females who were exposed occupationally to cobalt (concentrations ranging from 1 to 515 μg/m^3, means of exposure levels ranging from 39.37 to 169.0 μg/m^3) and tungsten carbide (as hard metal dust) was examined by Moulin et al. (1998). A significantly increased mortality rate (SMR=1.30, 95% CI=1.00–1.66) was seen for lung cancer in exposed workers, when compared to the national average. Within this study group, 61 cases and 180 controls were selected for a case-control study of cancer risk. When exposures during the last 10 years were ignored, presumably because cancer is a late-developing disease, a significant increase in lung cancer mortality (OR=1.93, 95% CI=1.03–3.62) relative to controls was seen among workers simultaneously exposed to cobalt and tungsten carbide. Significant trends for increasing cancer risk with increasing cumulative exposure and exposure duration were noted. Adjustments for smoking and for coexposures to other carcinogens did not change the results, though occupational risk was greatest among smokers.

A later study by the same group (Moulin et al. 2000) examined the lung cancer mortality of 4,288 male and 609 female workers employed in the production of stainless and alloyed steel from 1968 to 1992. No significant changes in mortality rate from lung cancer were seen among exposed workers (SMR=1.19, 95% CI=0.88–1.55), and a concurrent case control study identified no correlation between lung cancer excess and for exposure to cobalt (OR=0.64, 95% CI=0.33–1.25).

Wild et al. (2000) reported on a cohort of 2,216 male hard metal workers who had been employed for at least 3 months; this cohort was the same as that in Moulin et al. (2000), with some modifications. The total mortality was not increased in workers, relative to local mortality rates. However, lung cancer mortality was significantly increased (SMR=1.70, 95% CI=1.24–2.26). The risks increased with increasing exposure scores, even after adjustment for smoking and coexposure to other known or suspected carcinogens.

Inhalation exposure to 7.9 mg cobalt/m^3 as cobalt oxide intermittently for a lifetime did not increase the incidence of malignant or benign tumors in hamsters (Wehner et al. 1977).

NTP (1998) exposed groups of rats and mice of both sexes to 0, 0.11, 0.38, or 1.14 mg cobalt/m^3 as cobalt sulfate for 2 years. Increased incidence of alveolar/bronchiolar neoplasms was noted following lifetime exposure of male rats to 1.14 mg cobalt/m^3 and in female rats exposed to 0.38 mg cobalt/m^3 (Bucher et al. 1999; NTP 1998). Statistical analysis revealed that tumors occurred with significantly positive trends in both sexes of rats. Similarly, mice of both sexes exposed to 1.14 mg cobalt/m^3 showed an increase in alveolar/bronchiolar neoplasms, again with lung tumors occurring with significantly positive trends.

3.2.2 Oral Exposure

3.2.2.1 Death

In several studies, lethal cardiomyopathy was reported in people who consumed large quantities of beer containing cobalt sulfate (Alexander 1969, 1972; Bonenfant et al. 1969; Morin et al. 1967, 1971; Sullivan et al. 1969). The deaths occurred during the early to mid 1960s, at which time, breweries in Canada, the United States, and Europe were adding cobalt to beer as a foam stabilizer (Alexander 1969, 1972; Bonenfant et al. 1969; Morin et al. 1967, 1971; Sullivan et al. 1969); this practice has been discontinued. Deaths occurred following ingestion of beer containing 0.04–0.14 mg cobalt/kg/day for a period of years (approximately 8–30 pints of beer each day). "Acute mortality" (death within several days of admission) accounted for 18% of the deaths (Alexander 1972). Approximately 43% of the patients admitted to the hospital with cardiomyopathy died within several years of the initial hospital visit. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein-poor diets and may have had prior cardiac damage from alcohol abuse.

Treatment of both pregnant and nonpregnant anemic patients with doses of cobalt (0.6–1 mg/kg/day) that were much higher than the doses in the beer did not result in mortality (Davis and Fields 1958; Holly 1955). A 19-month-old male child who swallowed an unknown amount of a cobalt chloride solution died approximately 6.5 hours after ingestion, despite repeated induced vomiting, gastric lavage, and supportive therapy (Jacobziner and Raybin 1961).

Oral LD_{50} values for several cobalt compounds have been determined in Wistar rats (FDRL 1984a, 1984b, 1984c; Singh and Junnarkar 1991; Speijers et al. 1982). The LD_{50} values ranged from 42.4 mg cobalt/kg as cobalt chloride to 317 mg cobalt/kg as cobalt carbonate. An LD_{50} of 3,672 mg cobalt/kg was also found for tricobalt tetraoxide, a highly insoluble cobalt compound (FDRL 1984c). The exact cause of death in rats is unknown, but effects on the heart, liver, gastrointestinal tract, and kidneys have been observed. In Sprague-Dawley rats, death has been reported to occur at 161 mg cobalt/kg given by gavage as cobalt chloride (Domingo and Llobet 1984). In male Swiss mice, the LD_{50} values for cobalt chloride and cobalt sulfate have been reported to be 89.3 and 123 mg cobalt/kg, respectively (Singh and Junnarkar 1991).

Following 5 weeks of exposure to 20 mg cobalt/kg/day as cobalt sulfate by gavage, 20–25% of the guinea pigs died (Mohiuddin et al. 1970). The animals were given cobalt sulfate alone or in combination with ethanol (as part of a liquid diet) to compare the effects seen in animals to those seen in humans suffering from beer-cobalt cardiomyopathy. Although effects on the heart were found in the treated animals, alcohol did not appear to intensify the toxic effect.

The LD_{50} and all reliable LOAEL values for each species and duration category are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

Oral cobalt exposure in humans and/or animals resulted in respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, dermal, ocular, hypothermic, and body weight effects. For each effect, the highest NOAEL values and all reliable LOAEL values for each species and duration category are reported in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. In 50 patients with beer-cobalt cardiomyopathy, pulmonary rales and pulmonary edema were observed and were attributed to cobalt-induced cardiac failure (Morin et al. 1971). These patients had ingested, over a period of years, an average of 0.04 mg cobalt/kg/day in beer containing cobalt sulfate that was added to stabilize the foam. It should be noted that these patients consumed significant quantities of alcohol, and the effect that this may have had on the symptoms seen is not known.

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	1x (GW)				161.1 (LD50)	Domingo and Llobet 1984 Chloride
2	Rat (Wistar)	1x (GW)				42.4 (LD50)	Singh and Junnarkar 1991 Chloride
3	Rat (Wistar)	1x (GW)				194 (LD50)	Singh and Junnarkar 1991 Sulfate
4	Rat (Wistar)	1 x (GO)				91 (LD50)	Speijers et al. 1982 Fluoride
5	Rat (Wistar)	1 x (GO)				187 (LD50)	Speijers et al. 1982 Phosphate
6	Rat (Wistar)	1 x (GW)				109 (LD50)	Speijers et al. 1982 Bromide
7	Rat (Wistar)	1 x (GO)				159 (LD50)	Speijers et al. 1982 Oxide

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
8	Rat (Wistar)	1 x (GW)				168 (LD50)	Speijers et al. 1982 Acetate
9	Rat (Wistar)	1 x (GW)				190 (LD50)	Speijers et al. 1982 Chloride
10	Rat (Wistar)	1 x (GW)				140 (LD50)	Speijers et al. 1982 Bromide
11	Rat (Wistar)	1 x (GW)				161 (LD50)	Speijers et al. 1982 Sulfate
12	Mouse (Swiss-Webster)	1x (GW)				123 (LD50)	Singh and Junnarkar 1991 Sulfate
13	Mouse (Swiss-Webster)	1x (GW)				89.3 (LD50)	Singh and Junnarkar 1991 Chloride
	Systemic						
14	Human	2 wk (C)	Endocr		1 (decreased Iodine uptake in thyroid)		Roche and Layrisse 1958 Chloride

[a]

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
15	Rat	1x (GW)	Hemato		161.1[b]	(increased hematocrit 8%)			Domingo and Llobet 1984 Chloride
16	Rat	1 x (GW)	Other	110	209	(Clinical signs, including decreased activity, ataxia, diarrhea, salivation)			FDRL 1984a Sulfate
17	Rat (Sprague-Dawley)	1 x (GO)	Other		149	(Decreased activity, diarrhea)			FDRL 1984b Carbonate
18	Rat (Wistar)	1x (GW)	Renal		19.4	(Increased urinary output)			Singh and Junnarkar 1991 Sulfate
19	Rat (Wistar)	1 x (GO)	Cardio	109.6			176.6	(proliferative interstitial tissues, swollen muscle fibers, focal myocardial degeneration)	Speijers et al. 1982 Fluoride
			Hepatic	42.6			68.2	(hyperemia)	
			Renal		42.6	(swollen proximal tubules)	176.6	(degeneration of proximal tubules)	
			Other				109.6	(hypothermia)	

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
20	Rat (Wistar)	1 x (GO)	Cardio			794.5 (hemorrhage)	Speijers et al. 1982 Oxide
			Hepatic			157.3 (hyperemia)	
			Renal			157.3 (hyperemia)	
			Other			157.3 (hypothermia)	
21	Mouse (Swiss-Webster)	48 hr (W)	Hemato		76.4 M (Alteration in electrophoretic profile of serum proteins)		Bryan and Bright, 1973 Chloride
22	Mouse (Swiss-Webster)	3 mo (W)	Hemato	76.4 M			Bryan and Bright, 1973 Chloride
	Neurological						
23	Rat (Wistar)	1x (GW)			19.4 (Mild depression of spontaneous activity, muscle tone, and respiration)		Singh and Junnarkar 1991 Sulfate

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
24	Rat (Wistar)	1x (GW)			4.25	(Mild depression of spontaneous activity, muscle tone, and respiration)			Singh and Junnarkar 1991 Chloride
	Developmental								
25	Rat	Gd 6-15 (GW)		24.8					Paternian et al. 1988 Chloride
26	Mouse	Gd 8-12 (GW)		81.7					Seidenberg 1986 Chloride
	INTERMEDIATE EXPOSURE								
	Death								
27	Human	NR (W)					0.04	(death)	Morin et al. 1971 Sulfate
28	Gn Pig	5 wk (F)					20	(death)	Mohiuddin et al. 1970 Sulfate
	Systemic								
29	Human	NR (W)	Cardio				0.07	(beer-cobalt cardiomyopathy)	Alexander 1972 Sulfate

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
30	Human	1x/d 25 d (C)	Hemato		1[c]	(polycythemia)			Davis and Fields 1958 Chloride
31	Human	12-32 wk (C)	Gastro		0.18	(nausea)			Duckham and Lee 1976b Chloride
			Hemato		0.18[b]	(increased hemoglobin, 23-102% increase)			
32	Human	90 d (C)	Gastro		0.5	(gastric intolerance)			Holly 1955 Chloride
			Hemato	0.6					
			Hepatic	0.6					
33	Human	NR (W)	Resp		0.04	(edema)			Morin et al. 1971 Sulfate
			Cardio				0.04	(beer-cobalt cardiomyopathy)	
			Gastro		0.04	(vomiting, nausea)			
			Hepatic		0.04	(necrosis)			

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
34	Human	10-25 d 1x/d (C)	Other		0.54 (decreased Iodine uptake)		Paley et al. 1958
35	Human	12-32 wk 7d/wk (C)	Hemato		0.16[b] (increased hemoglobin)		Taylor et al. 1977 Chloride
36	Rat (Sprague-Dawley)	4 wk (F)	Bd Wt		3.79 M (45-65% reduction in body weight gain)		Chetty et al. 1979 Chloride
37	Rat	8 wk 1x/d (F)	Bd Wt		4.2 (33% decrease in body weight gain)		Clyne et al. 1988

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rat	3 mo (W)	Resp		30.2 (increased lung weight 33%)		Domingo et al. 1984
			Cardio		30.2 (increased heart weight 9.4%)		
			Gastro	30.2			
			Hemato		30.2 (increased hematocrit 29%)c		
			Musc/skel	30.2			
			Hepatic	30.2			
			Renal	30.2			
39	Rat	8 wk (F)	Cardio			26 (degeneration)	Grice et al. 1969
40	Rat (Sprague-Dawley)	24 wk (F)	Cardio			8.4 M (Left ventricular hypertrophy and impaired ventricular function)	Haga et al. 1996 Sulfate

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
41	Rat	4 mo (G)	Resp	18			Holly 1955 Chloride
			Cardio	18			
			Gastro	18			
			Hemato		18[b] (erythrocytosis)		
			Hepatic	18			
			Renal			18 (tubular necrosis)	
42	Rat	7 mo 6 d/wk (GW)	Hemato	0.05	0.5[b] (increased RBC, hemoglobin)		Krasovskii and Fridlyand 1971
			Hepatic	2.5			
43	Rat CFY	3 wk (G)	Cardio			12.4 M (Incipient, multifocal myocytolysis, with degeneration of myofibrilles)	Morvai et al. 1993 Chloride
			Bd Wt		12.4 M (Decreased body weight 8%)		

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
44	Rat	150 d 5 d/wk (GW)	Hemato		10[b] (increased hemoglobin)		Murdock 1959 Chloride
			Hepatic		10 (increased weight 17%)		
			Renal			10 (necrosis of tubular lining cells)	
			Bd Wt	10			
45	Rat (Sprague-Dawley)	8 wk	Hemato	8.4 M			Pehrsson et al. 1991 Sulfate
			Bd Wt			8.4 M (>20% decrease from appropriate control)	
46	Rat (Sprague-Dawley)	12-16 d (W)	Bd Wt	10.6 M			Saker et al. 1998 Chloride
			Metab		10.6 M (Decreased serum glucose levels in diabetic rats, but not control rats)		

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
47	Rat	6 wk 7 d/wk (C)	Hemato	0.6	2.5[b] (polycythemia)		Stanley et al. 1947 Chloride
48	Rat (Long- Evans)	3 d (F)	Bd Wt	20 M	100 M (<20% reduction of body weights)		Wellman et al. 1984 Chloride
49	Mouse Parkes	45 d (W)	Endocr			26 F (Necrosis and inflammation of thyroid)	Shrivastava et al. 1996 Chloride
50	Gn Pig	5 wk (F)	Cardio			20 (cardiomyopathy)	Mohiuddin et al. 1970
			Bd Wt	20			
51	Dog	4 wk 7 d/wk (F)	Hemato		5[b] (polycythemia)		Brewer 1940
	Immuno/ Lymphoret						
52	Rat (Sprague-Dawley)	4 wk (F)				3.79 M (Atrophy of the thymus)	Chetty et al. 1979 Chloride

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
53	Rat	7 mo 6 d/wk (GW)		0.05	0.5 (decreased phagocytic ability)		Krasovskii and Fridlyand 1971 Chloride
	Neurological						
54	Rat (Sprague-Dawley)	57 d (W)			20 M (Increased latency during retention testing)		Bourg et al. 1985 Chloride
55	Rat	57 d (W)			20 (increased reactivity)		Bourg et al. 1985 Chloride
56	Rat	7 mo 6 d/wk (GW)		0.05	0.5 (mildly increased latent reflex)	2.5 (pronounced increase in latent reflex)	Krasovskii and Fridlyand 1971 Chloride
57	Rat (Wistar)	30 d (W)			4.96 M (Alterations in sympathetically-induced contractility of vas deferens)		Mutafova-Yambolieva et al. 1994 Chloride
58	Rat	69 d (F)		5	20 (changes in schedule training, conditioned suppression, and mixed schedule training tests)		Nation et al. 1983

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
59	Rat (Wistar)	30 d (W)			6.44 M (Alterations in cholinergic sensitivity)		Vassilev et al. 1993 Nitrate
60	Rat (Long- Evans)	3 d (F)		20 M	100 M (Saccharin and food aversion)		Wellman et al. 1984 Chloride
	Reproductive						
61	Rat (Sprague-Dawley)	98 days (F)				20 M Pronounced histologic alteration of seminiferous tubules	Corrier et al. 1985 Chloride
62	Rat (Sprague-Dawley)	90 d (W)			30.2 M 26% decrease in testicular weight		Domingo et al. 1984 Chloride
63	Rat	98 d 7 d/wk (F)				13.25 (testicular degeneration)	Mollenhauer et al. 1985
64	Rat	69 d (F)		5		20 M (testicular atrophy)	Nation et al. 1983 Chloride

[a]

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
65	Mouse (CD-1)	13 wk (W)				43.4 M (Irreversible testicular degeneration)	Anderson et al. 1992 Chloride
66	Mouse (CD-1)	13 wk (W)				43.4 M (Testicular degeneration)	Anderson et al. 1993 Chloride
67	Mouse	13 wk (W)			23 (reversible testicular degeneration)		Pedigo et al. 1988 Chloride
68	Mouse (B6C3F1)	10 wk (W)				58.9 M (Reduced pregnant females and pups per litter; reduced fertility)	Pedigo et al. 1993 Chloride
	Developmental						
69	Human	90 d (C)		0.6			Holly 1955 Chloride

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
70	Rat	Gd 14- Ld 21 (G)				5.4	(stunted pup growth)	Domingo et al. 1985 Chloride

[a] The number corresponds to entries in Figure 3-2.

[b] An increase in hemoglobin or red blood cells is not necessarily considered an adverse effect.

[c] Used to derive an intermediate oral MRL; concentration was divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability), resulting in an MRL of 0.01 mg/kg/day.

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = female; (G) = gavage; Gd = gestation day; (GO) = gavage oil; (GW) = gavage-water, Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); Ld = lactation day; LD50 = dose producing 50% death; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; mo = month(s); NOAEL = no observed-adverse-effect level; NS = not specified; (W) = drinking water; wk = week(s); x = times.

Figure 3-2. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral

Acute (≤14 days)

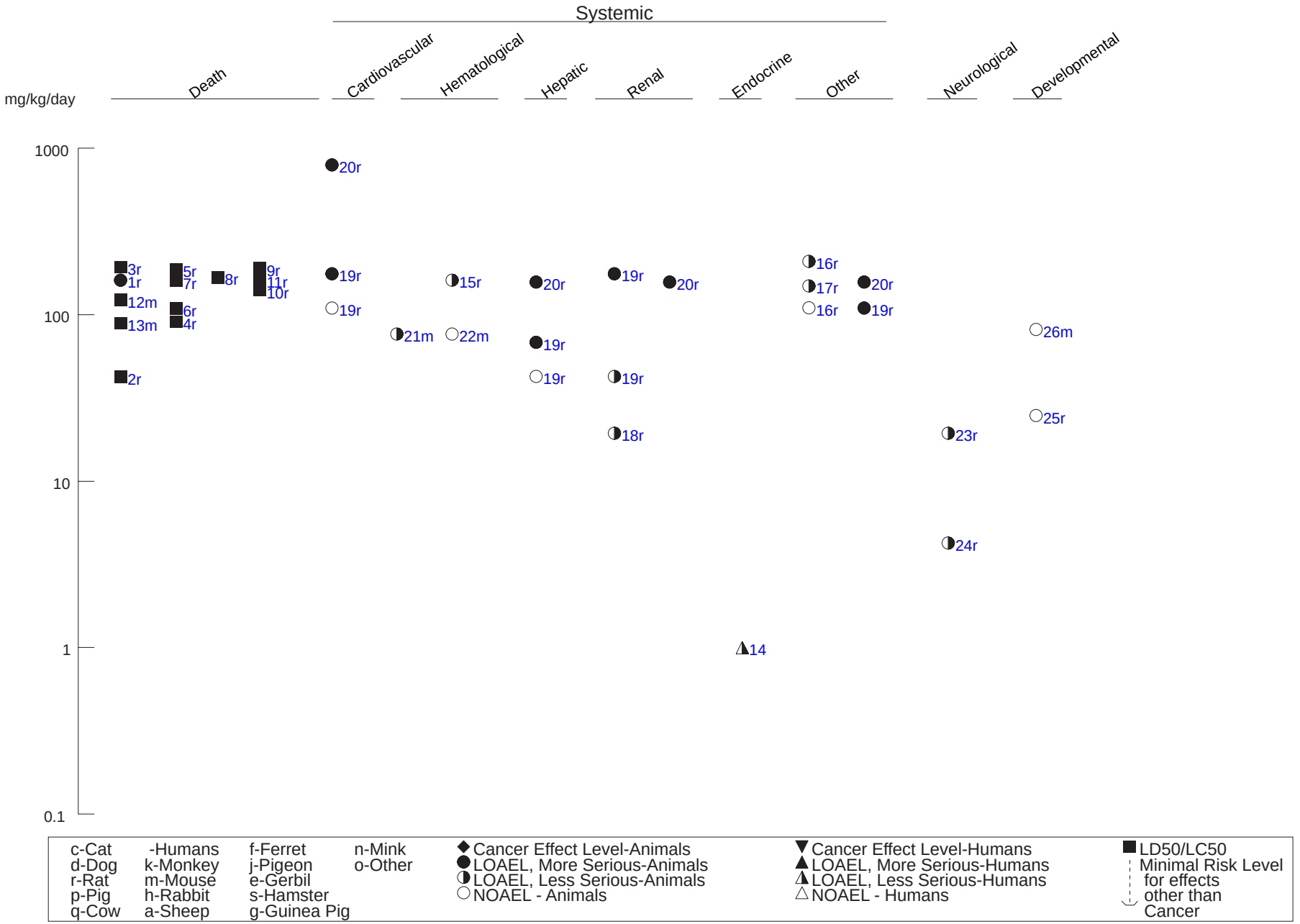


Figure 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (*Continued*)

Intermediate (15-364 days)

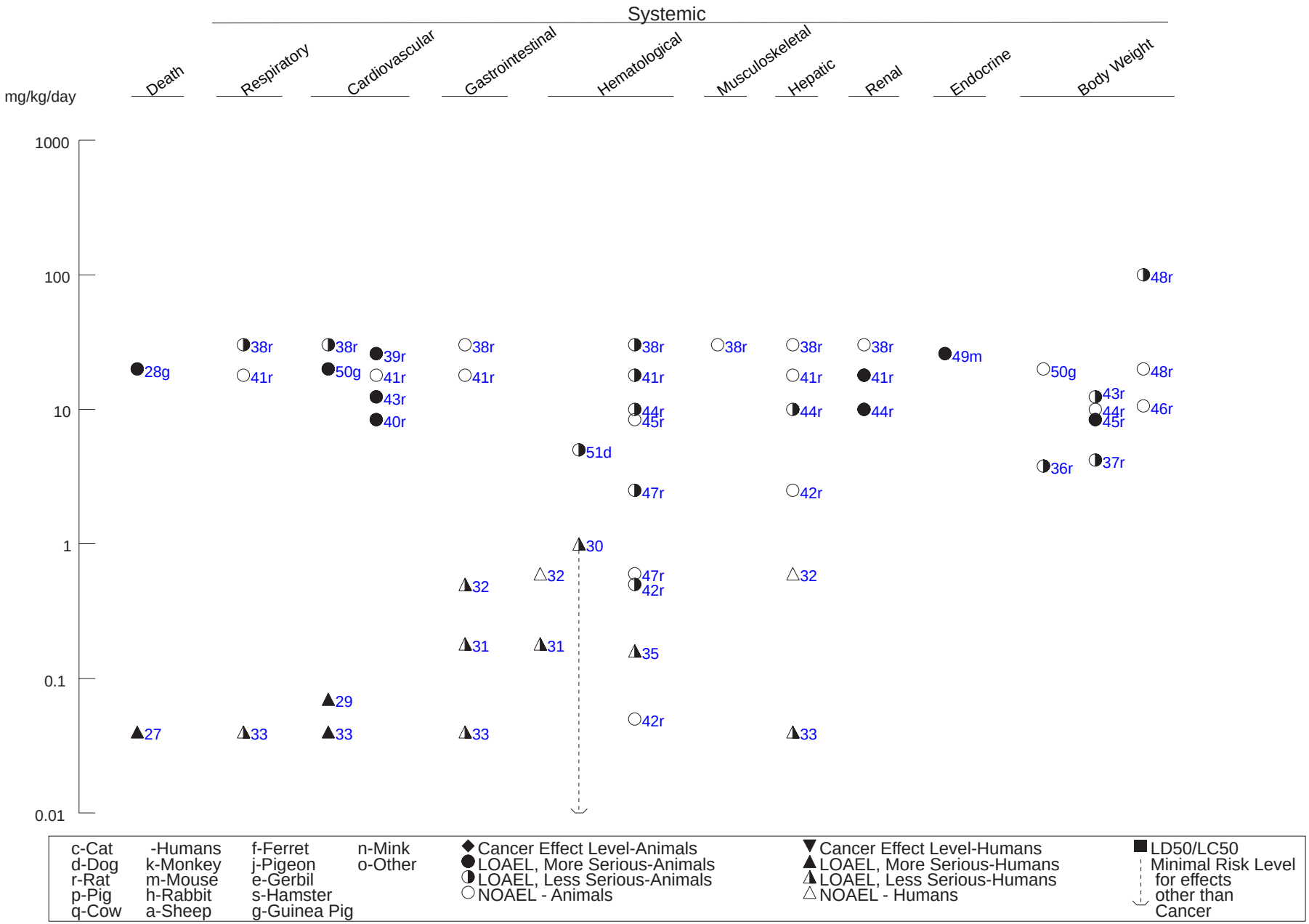
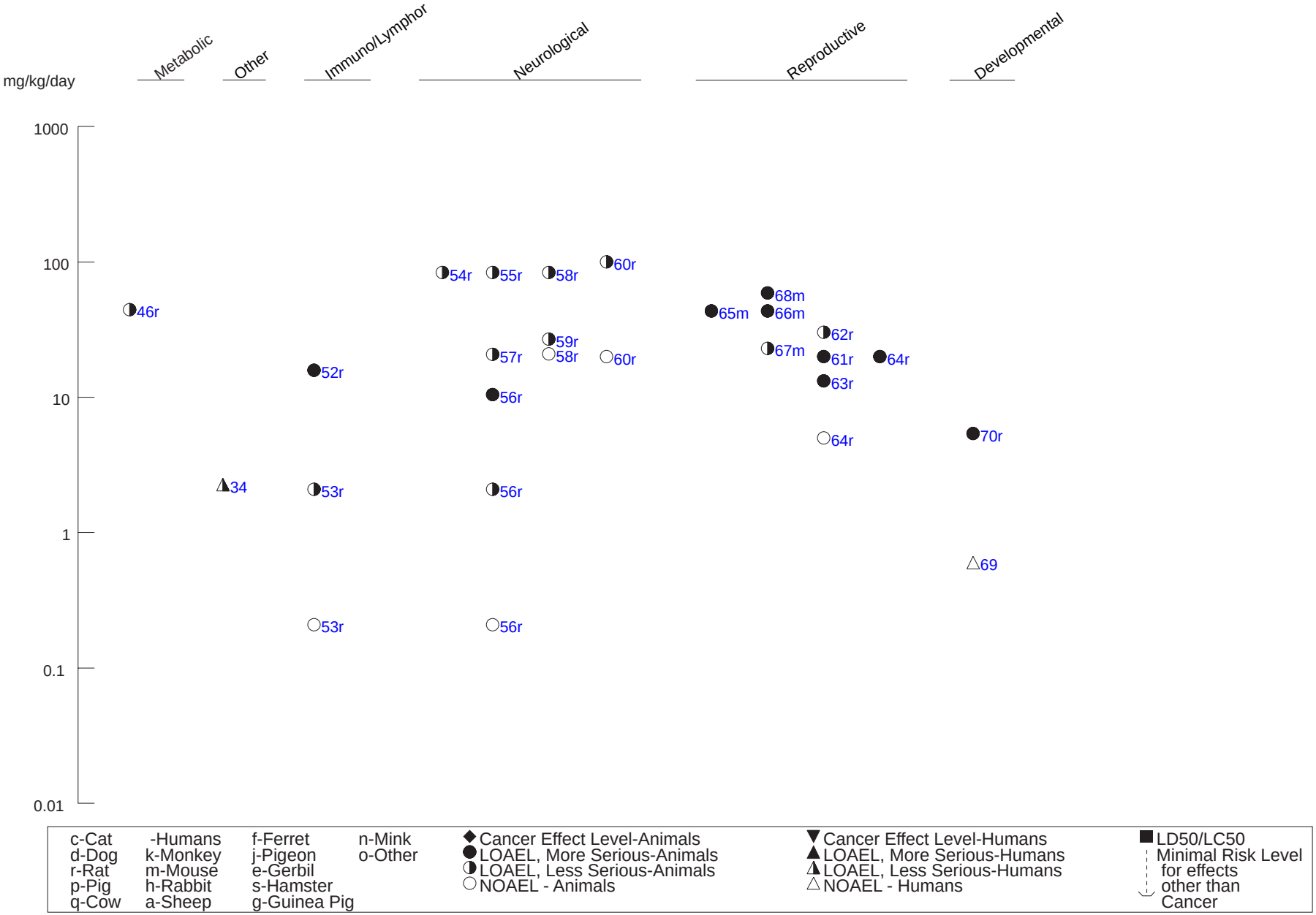


Figure 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (*Continued*)

Intermediate (15-364 days)



A significant increase in the weight of the lungs, without morphological or histological changes, was found in rats that received 30.2 mg cobalt/kg/day as cobalt chloride in drinking water for 3 months, as compared with controls (Domingo et al. 1984). No morphological changes were seen in the lungs of rats treated with 18 mg cobalt/kg/day for 4 months (Holly 1955).

Cardiovascular Effects. Beer-cobalt cardiomyopathy was observed in people who heavily consumed beer containing cobalt sulfate as a foam stabilizer (Alexander 1969, 1972; Bonenfant et al. 1969; Kesteloot et al. 1968; Morin et al. 1967, 1971; Sullivan et al. 1969). The beer drinkers ingested an average of 0.04 mg cobalt/kg/day (Morin et al. 1971, n=50) to 0.14 mg cobalt/kg/day for a period of years (Alexander 1969, 1972, n=28). The cardiomyopathy was characterized by sinus tachycardia, left ventricular failure, cardiogenic shock, diminished myocardial compliance, absence of a myocardial response to exercise or catecholamine, enlarged heart, pericardial effusion, and extensive intracellular changes (changes in the myofibers, mitochondria, glycogen, and lipids). The beer-cobalt cardiomyopathy appeared to be similar to alcoholic cardiomyopathy and beriberi, but the onset of beer-cobalt cardiomyopathy was very abrupt. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein-poor diets and may have had prior cardiac damage from alcohol abuse. Treatment of both pregnant and nonpregnant anemic patients for 90 days with doses of cobalt (0.6–1 mg/kg/day as cobalt chloride) that were much higher than the doses in the beer did not result in effects on the heart (Davis and Fields 1958; Holly 1955).

Approximately 40–50% of the patients admitted to the hospital with cardiomyopathy died within several years of diagnosis. In a followup study of four different sites, 0–43% of the survivors, depending on the site, showed a residual cardiac disability and 23–41% had abnormal electrocardiograms (Alexander 1972).

In an experiment designed to simulate conditions leading to beer-cobalt cardiomyopathy in humans, guinea pigs were given 20 mg cobalt/kg/day as cobalt sulfate by gavage either alone or in combination with ethanol (as part of a liquid diet) for 5 weeks (Mohiuddin et al. 1970). The experiment resulted in cardiomyopathy, which was characterized by abnormal EKGs; increased heart weights; lesions involving the pericardium, myocardium, and endocardium; and disfigured mitochondria. Alcohol did not intensify the cardiac effects. Myocardia changes (proliferative interstitial tissue, swollen muscle fibers, and focal degeneration) were also found in rats following a single dose of 176.6 mg cobalt/kg administered by

gavage as cobalt fluoride or a single dose of 795 mg cobalt/kg administered as cobalt oxide (Speijers et al. 1982).

Three weeks of exposure to 12.4 mg cobalt/kg/day as cobalt chloride in male rats resulted in cardiac damage, presenting as incipient, multifocal myocytolysis, with degeneration of myofibrilles (Morvai et al. 1993). After longer-term exposure (2–3 months) of rats to 26–30.2 mg cobalt/kg/day as cobalt sulfate in the diet or as cobalt chloride in the drinking water, degenerative heart lesions (Grice et al. 1969) and an increase in heart weight were found (Domingo et al. 1984). Exposure of rats to 8.4 mg cobalt/kg/day as cobalt sulfate resulted in left ventricular hypertrophy and impaired left ventricular systolic and diastolic functions in an isolated working rat heart model (Haga et al. 1996). Clyne et al. (2001) reported that exposure of rats to 8.4 mg cobalt/kg/day, as cobalt sulfate, in the diet for 24 weeks resulted in significant reductions in a number of enzymes in cardiac tissues, including manganese-superoxide dismutase, succinate-cytochrome c oxidase, NADH-cytochrome c reductase, and cytochrome c oxidase, as well as reducing the mitochondrial ATP production rate.

Gastrointestinal Effects. The first signs of the beer-cobalt cardiomyopathy syndrome were gastrointestinal effects and included nausea, vomiting, and diarrhea (Morin et al. 1971). Signs of heart failure subsequently appeared. These individuals had ingested an average of 0.04 mg cobalt/kg/day for a period of years during which cobalt sulfate was added to beer as a foam stabilizer; however, it is likely that alcohol consumption was also a factor.

In pregnant women given cobalt supplements (alone or combined with iron) to prevent the decrease in hematocrit and hemoglobin levels commonly found during pregnancy (n=78), a small percentage of those treated complained of gastric intolerance (Holly 1955). The women were treated with 0.5–0.6 mg cobalt/kg/day as cobalt chloride for 90 days. Nausea was reported in one anemic patient following treatment with 0.18 mg cobalt/kg/day as cobalt chloride (Duckham and Lee 1976b).

No morphological changes in the gastrointestinal system were observed following exposure of 20 male rats for 3 months to 30.2 mg cobalt/kg/day as cobalt chloride in the drinking water (Domingo et al. 1984) or exposure for 4 months to 18 mg cobalt/kg/day as cobalt chloride by gavage (Holly 1955).

Hematological Effects. Cobalt has been shown to stimulate the production of red blood cells in humans. Davis and Fields (1958) exposed six apparently normal men, ages 20–47, to a daily dose of

cobalt chloride, administered as a 2% solution diluted in either water or milk, for up to 22 days. Five of the six received 150 mg cobalt chloride per day for the entire exposure period, while the sixth was started on 120 mg/day and later increased to 150 mg/day. Blood samples were obtained daily from free-flowing punctures of fingertips at least 2 hours after eating, and at least 15 hours after the last dosage of cobalt. Blood was analyzed for red blood cell counts, hemoglobin percentage, leukocyte counts, reticulocyte percentages, and thrombocyte counts. Exposure to cobalt resulted in the development of polycythemia in all six subjects, with increases in red blood cell numbers ranging from 0.5 to 1.19 million (~16–20% increase above pretreatment levels). Polycythemic erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. Hemoglobin levels were also increased by cobalt treatment, though to a lesser extent than the erythrocyte values, with increases of 6–11% over pretreatment values. In five of the six subjects, reticulocyte levels were elevated, reaching at least twice the pre-experiment values. Thrombocyte and total leukocyte counts did not deviate significantly from pretreatment values. From the LOAEL of 1 mg/kg-day identified by this study, an intermediate-duration oral MRL of $1x10^{-2}$ mg/kg-day was derived (for derivation, see Section 2.3 and Appendix A).

Increased levels of erythrocytes were also found following oral treatment of anephric patients (with resulting anemia) with 0.16–1.0 mg cobalt/kg/day daily as cobalt chloride for 3–32 weeks (Duckham and Lee 1976b; Taylor et al. 1977). The increase in hemoglobin resulted in a decreased need for blood transfusions. Treatment of pregnant women for 90 days with 0.5–0.6 mg cobalt/kg/day as cobalt chloride, however, did not prevent the reduction in hematocrit and hemoglobin levels often found during pregnancy (Holly 1955).

Significantly increased erythrocyte (polycythemia), hematocrit, and hemoglobin levels were found in animals treated orally with cobalt chloride as a single dose of 161 mg cobalt/kg (Domingo and Llobet 1984) or with longer-term exposure (3 weeks to 2 months) to ≥0.5 mg/kg/day (Brewer 1940; Davis 1937; Domingo et al. 1984; Holly 1955; Krasovskii and Fridlyand 1971; Murdock 1959; Stanley et al. 1947). Of particular note is an 8-week study in rats (Stanley et al. 1947), which reported dose- and time-related increases in erythrocyte number following oral administration of cobalt chloride, with an apparent NOAEL of 0.6 mg cobalt/kg/day and a LOAEL of 2.5 mg cobalt/kg/day. Changes in the levels of other blood proteins (transferrin, several haptoglobulins, and ceruloplasmin) were noted in male Swiss mice following 4, 24, and 48 hours of treatment with 76.4 mg cobalt/kg as cobalt chloride in the drinking water (Bryan and Bright 1973). Exposure for 3 weeks or 3 months to 76.4 mg cobalt/kg as cobalt chloride in the drinking water resulted in no alterations in serum proteins examined.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to cobalt.

No morphological changes were found in the skeletal muscle of rats exposed to 30.2 mg cobalt/kg/day as cobalt chloride in the drinking water for 3 months (Domingo et al. 1984). This NOAEL in rats for intermediate-duration exposure is reported in Table 3-2 and plotted in Figure 3-2.

Hepatic Effects. Liver injury was evident in patients with beer-cobalt cardiomyopathy, characterized by central hepatic necrosis accompanied by increased levels of serum bilirubin and serum enzymes (serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], lactate dehydrogenase [LDH]), creatine phosphokinase, ornithine carbamyl transferase, isocitric dehydrogenase, aldolase) (Alexander 1972; Morin et al. 1971). The hepatic injury may have resulted from ischemia, secondary to the cardiac effects of cobalt, and/or from excessive alcohol consumption. The cardiomyopathy resulted from the ingestion of beer containing 0.04 mg cobalt/kg/day as cobalt sulfate that had been added as a foam stabilizer (Morin et al. 1971). Liver function tests were found to be normal in pregnant women receiving up to 0.6 mg cobalt/kg/day as cobalt chloride for 90 days for treatment of the decreases in hematocrit and hemoglobin levels commonly found during pregnancy (Holly 1955).

Data from animals have also indicated that cobalt has hepatic effects. Hyperemia of the liver and cytoplasmic changes in hepatocytes (clumpy cytoplasm located along the cell membrane) were found in rats administered a single dose of 68.2 mg cobalt/kg as cobalt fluoride or a single dose of 157.3 mg cobalt/kg as cobalt oxide (Speijers et al. 1982).

Increased liver weight (17%) was found in rats exposed to 10 mg cobalt/kg/day (as cobalt chloride) for 5 months (Murdock 1959). No morphological or enzymatic changes were found in the livers of rats exposed to 2.5–30.2 mg cobalt/kg as cobalt chloride by gavage or as cobalt chloride in the drinking water for 3–7 months (Domingo et al. 1984; Holly 1955; Krasovskii and Fridlyand 1971).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to cobalt.

Acute and prolonged exposure to cobalt results in renal tubular degeneration in rats. Renal injury, evidenced by histologic alteration of the proximal tubules, was observed in rats after a single oral exposure to 42 mg cobalt/kg as cobalt fluoride (Speijers et al. 1982) and after exposure to 10–18 mg cobalt/kg/day as cobalt chloride for 4–5 months (Holly 1955; Murdock 1959). A slightly decreased urinary output was observed in rats exposed to 19.4 mg cobalt/kg as cobalt sulfate, but not in rats exposed to 4.25 mg cobalt/kg as cobalt chloride (Singh and Junnarker 1991).

Endocrine Effects. Roy et al. (1968) reported on 20 Québécois patients who died of beer drinkers' myocardosis. Of these, 14 thyroids were available for examination. Three of those were normal, and the other 11 formed the basis of the study. "Abnormal" thyroids did not show gross changes, but upon histologic examination, they showed irregular follicle morphology and decreased follicular size.

Kriss et al. (1955) reported on five patients who had been receiving cobalt therapy for sickle-cell anemia or renal amyloidosis. Three of five developed goiter, one severe, while four of five showed microscopic alterations of the thyroid gland. Two of the patients died from non-cobalt-related causes, while the other three recovered once cobalt treatment was removed. A similar study was reported by Gross et al. (1955) in which stable cobalt was used therapeutically in four cases of sickle-cell anemia. Treatment with cobalt resulted in an enlargement of the thyroid gland, which was reversible upon cessation of cobalt therapy. Similar effects on the thyroid, including enlargement, hyperplasia, and an increased firmness, have been reported in several other cases where cobalt therapy for anemia was used (Chamberlain 1961; Little and Sunico 1958; Soderholm et al. 1968; Washburn and Kaplan 1964). No other studies examining the endocrine effects of stable cobalt in humans were located.

NTP (1998; Bucher et al. 1999) reported increased incidence of pheochromocytoma, a tumor of the adrenal medulla, in female rats exposed to 1.14 mg cobalt/m^3 for 2 years, but did not measure any other endocrine effects. Female mice exposed to 26 mg cobalt/kg-day in the drinking water for up to 45 days showed histopathological changes to the thyroid gland (Shrivastava et al. 1996). Cobalt significantly stimulated serum testosterone in mice treated orally with 23 mg cobalt/kg as cobalt chloride, though no dose-response relationship was present (Pedigo et al. 1988).

Dermal Effects. Allergic dermatitis has been reported in some cobalt-sensitized people following oral challenge with cobalt. Several patients with eczema of the hands were challenged orally with 1 mg cobalt as cobalt sulfate given in tablet form once per week for 3 weeks (0.014 mg/kg/day). A flaring of the

eczema was considered to be a positive allergic response to cobalt (Veien et al. 1987). No other studies were located regarding dermal effects in humans or animals after oral exposure to cobalt.

Ocular Effects. Severe visual disturbances (optic atrophy, impaired choroidal perfusion) developed in a man who was treated with cobalt chloride for pancytopenia and hypercellular bone marrow (Licht et al. 1972). He received 1.3 mg cobalt/kg daily for four series of treatments with a total duration of 6 weeks. However, no other cases of visual disturbances due to therapeutic administration of cobalt have been reported, and no such effects have been observed in animals.

Body Weight Effects. No effects on body weight in animals were found following longer-term (1–5 months) exposure of rats to 10–30.2 mg cobalt/kg/day as cobalt chloride (Bourg et al. 1985; Domingo et al. 1984; Murdock 1959) or of guinea pigs to 20 mg cobalt/kg/day as cobalt sulfate (Mohiuddin et al. 1970). A significant decrease (33%) in body weight gain was observed following 8 weeks of exposure of rats to 4.2 mg cobalt/kg/day as cobalt sulfate (Clyne et al. 1988).

Metabolic Effects. Treatment of rats with 10.6 mg Co/kg/day as $CoCl_2$ in the drinking water for 12–16 days resulted in a significant decrease in serum glucose levels in diabetic rats, but not in control rats (Saker et al. 1998).

Other Systemic Effects. Hypothermia occurred in rats following a single oral dose of 157 mg cobalt/kg given as cobalt oxide or a single oral dose of 110 mg cobalt/kg given as cobalt fluoride (Speijers et al. 1982). The hypothermia was time- and dose-related. Hypothermia was reported as an effect during LD_{50} studies with other cobalt compounds, but the exact dose for the onset of hypothermia with these compounds was not reported (Speijers et al. 1982). Other physiological signs noted in LD_{50} studies include decreased activity, ataxia, diarrhea, and salivation (FDRL 1984a, 1984b).

3.2.2.3 Immunological and Lymphoreticular Effects

Cobalt is known to function as a hapten, resulting in the generation of antibodies against cobalt-protein complexes. Allergic dermatitis has been reported in some cobalt-sensitized people following oral challenge with cobalt. Several patients with eczema of the hands were challenged orally with 1 mg cobalt as cobalt sulfate given in tablet form once per week for 3 weeks (0.014 mg/kg/day). A flaring of the

eczema was considered to be a positive allergic response to cobalt (Veien et al. 1987). Using both the oral challenge test and dermal patch tests, it was determined that the cobalt allergy was systemically induced. The exposure level associated with sensitization to cobalt was not established. After sensitization, allergic reactivity may be independent of dose. Cobalt has been found to be a sensitizer following inhalation exposure (Section 3.2.1.3). This LOAEL value was not reported in Table 3-2 because sensitized individuals only represent a small percent of the population.

A case report of a 6-year-old boy who had ingested approximately 1.7 mg of cobalt chloride reported neutropenia by 7 hours post-exposure (Mucklow et al. 1990).

Thymic atrophy was reported in male Sprague-Dawley rats exposed to 3.79 mg cobalt/kg/day as cobalt chloride in the feed for 4 weeks (Chetty et al. 1979). A deterioration in immunological reactivity, manifested by a decline in phagocytic activity, was reported in rats following 6–7 months of treatment with 0.5 mg cobalt/kg or greater as cobalt chloride (Krasovskii and Fridlyand 1971). This value is presented in Table 3-2 and Figure 3-2.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to stable cobalt.

Several rodent studies have identified neurological effects following cobalt exposure. In Wistar rats, a single gavage dose of 4.25 mg cobalt/kg as cobalt chloride resulted in a moderate reduction in spontaneous activity, muscle tone, touch response, and respiration, while 19.4 mg cobalt/kg as cobalt sulfate caused a mild reduction the same parameters (Singh and Junnarkar 1991). In rats exposed to 4.96 mg cobalt/kg/day as cobalt chloride for 30 days in the drinking water, cobalt led to changes in sympathetically mediated contractile activity of isolated rat vas deferens (Mutafova-Yambolieva et al. 1994). Rats exposed to 6.44 mg cobalt/kg/day as cobalt nitrate in the drinking water showed an increased sensitivity and decreased maximal response to a cholinergic agonist (Vassilev et al. 1993). In rats exposed to 20 mg cobalt/kg/day as cobalt chloride for 57 days in the drinking water, cobalt enhanced behavioral reactivity to stress (the animals were less likely to descend from a safe platform to an electrified grid) (Bourg et al. 1985). Rats exposed to the same dose in the diet for 69 days showed a slower rate of lever pressing than controls, but no change in behavioral reactivity to stress (Nation et al.

1983). Longer-term exposure of rats to cobalt chloride (7 months) resulted in a significant increase in the latent reflex period at ≥0.5 mg cobalt/kg as cobalt chloride and a pronounced neurotropic effect (disturbed conditioned reflexes) at 2.5 mg cobalt/kg (Krasovskii and Fridlyand 1971).

The NOAEL value and the LOAEL value for rats for intermediate duration are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to stable cobalt.

Testicular degeneration and atrophy have been reported in rats exposed to 13.3–58.9 mg cobalt/kg/day as cobalt chloride for 2–3 months in the diet or drinking water (Corrier et al. 1985; Domingo et al. 1984; Mollenhauer et al. 1985; Nation et al. 1983; Pedigo and Vernon 1993; Pedigo et al. 1988), or in mice exposed to 43.4 mg cobalt/kg/day as cobalt chloride for 13 weeks in the drinking water (Anderson et al. 1992, 1993).

The highest NOAEL and all reliable LOAEL values for rats in the intermediate-duration category are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No developmental effects on human fetuses were observed following treatment of pregnant women with cobalt chloride to raise hematocrit and hemoglobin levels that are often depressed during pregnancy. Dosages up to 0.6 mg cobalt/kg/day for 90 days were given (Holly 1955). Examination of the fetuses, however, was limited to the reporting of obvious birth defects, and exposure only occurred in the final trimester.

Oral exposure of female rats to cobalt chloride at 5.4 or 21.8 mg cobalt/kg/day from gestation day 14 through lactation day 21 has been shown to result in stunted growth and decreased survival, respectively, of newborn pups (Domingo et al. 1985b). The effects on the offspring occurred at levels

that also caused maternal toxicity (reduced body weight and food consumption, and altered hematological measurements) and might therefore have been an indirect effect of maternal toxicity rather than a direct effect of cobalt on the fetus (Domingo et al. 1985b). Teratogenic effects were not observed.

Szakmary et al. (2001) reported that exposure of pregnant rats to 0–38 mg Co/kg-day as cobalt sulfate did not result in changes in fetal death rates, maternal body weigh gain, average litter size, or average fetal or placental weights; however, a dose-related trend was seen for the percent of fetuses with retarded body weights. In contrast, no effects on fetal growth or survival were found following exposure of rats to 24.8 mg cobalt/kg/day as cobalt chloride during gestation days 6–15 (Paternian et al. 1988). In mice, exposure to 81.7 mg cobalt/kg/day as cobalt chloride during gestation days 8–12 was reported to have no effect on fetal growth or mortality in mice (Seidenberg et al. 1986). In a later mouse study that exposed pregnant mice to 19 mg Co/kg-day as cobalt sulfate, no changes in litter size, postimplantation loss, or average fetal or placental weights were seen; the only difference seen was an increase in the percent of fetuses with retarded body weights (Szakmary et al. 2001). The same study reported that rabbits exposed to ≥ 38 mg Co/kg-day, as cobalt sulfate, showed nearly complete maternal lethality, and complete fetal loss. Rabbits exposed to 7.6 mg Co/kg, as cobalt sulfate, showed significant increases in mortality and fetal resorption, as well as an increase in fetuses with retarded body weight (Szakmary et al. 2001). The highest NOAEL and all reliable LOAEL values for each species and duration category are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

In a survey assessing the correlation between cancer mortality and trace metals in water supplies (10 basins) throughout the United States, no correlation was found between cancer mortality and the level of cobalt in the water (Berg and Burbank 1972). Cobalt levels of 1–19 µg/L, with resulting human intakes ranging from 0.03 to 0.54 µg/kg/day, were reported.

No studies were located regarding carcinogenic effects in animals after oral exposure to stable cobalt.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding lethal effects in humans after dermal exposure to cobalt.

No mortality was observed in guinea pigs dermally exposed to 51.75 mg cobalt/kg for 5 days/week as dicobalt octacarbonyl for a total of 18 applications (Kincaid et al. 1954).

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or ocular effects in humans or animals after dermal exposure to stable cobalt.

Dermal Effects. Dermatitis is a common result of dermal exposure to cobalt in humans that has been verified in a large number of studies (Alomar et al. 1985; Bedello et al. 1984; Dooms-Goossens et al. 1980; Fischer and Rystedt 1983; Goossens et al. 2001; Kanerva et al. 1988, 1998; Kiec-Swierczyńska and Krecisz 2002; Marcussen 1963; Minamoto et al. 2002; Pryce and King 1990; Swennen et al. 1993; Romaguera et al. 1982; Valer et al. 1967). Using patch tests and intradermal injections, it has been demonstrated that the dermatitis is probably caused by an allergic reaction to cobalt. Contact allergy was reported in 22 of 223 (9.9%) nurses who were tested with a patch test of 1.0% cobalt chloride (Kieć-Świerczyńska and Kręcisz 2000), as well as 16 of 79 (20.3%) of examined dentists (Kieć-Świerczyńska and Kręcisz 2002). Persons with body piercings showed an increased prevalence of allergy to cobalt, with the incidence of contact allergy being proportional to number of piercings (Ehrlich et al. 2001). The prevalence of sensitivity to cobalt following exposure to cobalt as a component of metal implants is low, with only 3.8% of patients developing a new sensitivity to cobalt following insertion of the implant (Swiontkowski et al. 2001). Exposure levels associated with the development of dermatitis have not been identified. It appears that the allergic properties of cobalt result mainly from exposure to the metal itself, rather than a salt, as Nielsen et al. (2000) demonstrated that daily repeated exposure to aqueous cobalt salts did not result in hand eczema in patients known to have cobalt allergy.

In animals, scabs and denuded areas were found after six doses of 51.75 mg cobalt/kg (5 days/week) as dicobalt octacarbonyl were applied to the shaved abdomens (uncovered area of approximately 50 cm^2) of guinea pigs (Kincaid et al. 1954). By the 11^{th} dose, the lesions disappeared. No adverse effects were observed in vehicle controls (methyl ethyl ketone). It is not known whether or not a similar reaction would result from metallic or inorganic forms of cobalt. This LOAEL value is reported in Table 3-3.

3.2.3.3 Immunological and Lymphoreticular Effects

Cobalt-induced dermatitis is well documented in the literature, and the studies indicate that cobalt is a sensitizer (Alomar et al. 1985; Dooms-Goossens et al. 1980; Fischer and Rystedt 1983; Goh et al. 1986; Kanerva et al. 1988; Marcussen 1963; Valer et al. 1967). Patch testing and intradermal injections were performed, but exposure levels of cobalt were not reported. Interrelationships exist between nickel and cobalt sensitization (Bencko et al. 1983; Rystedt and Fisher 1983); however, the extent of any potential interactions between the two metals on immunologic end points is not well understood. In guinea pigs, nickel and cobalt sensitization appear to be interrelated and mutually enhancing (Lammintausta et al. 1985), though cross-reactivity was not reported to occur.

Single or multiple dermal exposures of BALB/c mice to $CoCl_2$ in dimethylsulfoxide or in ethanol resulted in an increased cellular proliferation in the local lymph node assay in a concentration-dependant manner (Ikarashi et al. 1992a). The effect of three consecutive exposures to varying concentrations of $CoCl_2$ in DMSO on lymph node proliferation was measured in rats, mice, and guinea pigs (Ikarashi et al. 1992b). Stimulation Indices of 3 or greater, indicated by the authors as a significant response, were reported for mice exposed to 1, 2.5, or 5% $CoCl_2$, rats exposed to 2.5 or 5% $CoCl_2$, and guinea pigs exposed to 5% $CoCl_2$; these treatments resulted in dose levels of 10.8, 27, or 54.1 mg cobalt/kg/day for mice, 9.60 or 19.2 mg cobalt/kg/day for rats, and 14.7 mg cobalt/kg/day for guinea pigs.

No studies were located regarding the following health effects in humans or animals after dermal exposure to stable cobalt:

Table 3-3 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious		Serious	
ACUTE EXPOSURE							
Immuno/ Lymphoret							
Rat (Fischer- 344)	1x/d 3d		3.84 F mg/kg/day	9.6 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992b Chloride
Mouse (BALB/c)	1x or 1x/d for 3 d			10.8 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992a Chloride
Mouse CBA/N	1x/d 3 d		5.4 F mg/kg/day	10.8 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992b Chloride
Gn Pig (Hartley)	1x/d 3 d		7.39 F mg/kg/day	14.7 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992b Chloride
INTERMEDIATE EXPOSURE							
Systemic							
Gn Pig (NS)	18 d 5 d/wk	Dermal		51.75 mg/kg/day	(skin lesions (scabs and denuded areas) at application site)		Kincaid et al. 1954

d =day(s); F = female; LOAEL = lowest-observed-adverse-effect level; NOAEL = no observed-adverse-effect level; wk = week(s); x = times.

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to cobalt.

3.2.4 Other Routes of Exposure

Endocrine Effects. Patients (n=12) injected with a single diagnostic dose of radioactive iodine, and then treated 48 hours later with 1 mg cobalt/kg/day as cobalt chloride for 2 weeks, resulted in a greatly reduced uptake of radioactive iodine by the thyroid in 1 week, with uptake nearing 0 by the second week (Roche and Layrisse 1956). When the cobalt treatment ended, the uptake values returned to normal. The decrease of radioactive iodine uptake found in patients administered 0.54 mg cobalt/kg/day for 10–25 days prior to iodine injection was found to result from cobalt blocking the organic binding of iodine (Paley et al. 1958).

In various species of animals, parenteral administration of cobalt resulted in cytotoxic effects on the alpha cells of the pancreas (Beskid 1963; Goldner et al. 1952; Hakanson et al. 1974; Lacy and Cardeza 1958; Lazarus et al. 1953; Van Campenhout 1955). Because this effect has never been reported in humans or animals following inhalation, oral, or dermal exposure to cobalt, the relevance of the effect to humans is not known.

Moger (1983) exposed primary cultures of mouse Leydig cells to 0–2.5 mM cobalt as cobalt for 3 hours, and measured the effects on androgen production. Cobalt exposure caused a dose-related decrease in both basal and LH-stimulated androgen production, with no effects on protein synthesis. The author suggested that these effects are the result of cobalt inhibition of calcium influx across the plasma membrane.

3.3 DISCUSSION OF HEALTH EFFECTS OF RADIOACTIVE COBALT BY ROUTE OF EXPOSURE

Section 3.3 discusses radiation toxicity associated with exposure to radionuclides of cobalt and is organized in the same manner as that of Section 3.2, first by route of exposure (inhalation, oral, and external) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing NOAELs or LOAELs reflect the actual dose (levels of exposure) used in the studies. Refer to Section 3.2 for detailed discussion of the classification of endpoints as a NOAEL, less serious LOAEL, or serious LOAEL.

Refer to Appendix B for a User's Guide, which should aid in the interpretation of the tables and figures for Levels of Significant Exposure.

3.3.1 Inhalation Exposure

No studies were located regarding the following health effects in humans or animals after inhalation exposure to radioactive cobalt:

3.3.1.1 Death

3.3.1.2 Systemic Effects

3.3.1.3 Immunological and Lymphoreticular Effects

3.3.1.4 Neurological Effects

3.3.1.5 Reproductive Effects

3.3.1.6 Developmental Effects

3.3.1.7 Cancer

3.3.2 Oral Exposure

No studies were located regarding the following health effects in humans or animals after oral exposure to radioactive cobalt:

3.3.2.1 Death

3.3.2.2 Systemic Effects

3.3.2.3 Immunological and Lymphoreticular Effects

3.3.2.4 Neurological Effects

3.3.2.5 Reproductive Effects

3.3.2.6 Developmental Effects

3.3.2.7 Cancer

3.3.3 External Exposure

This section contains information regarding health effects related to external exposure to radioactive cobalt sources. Radionuclides of cobalt may emit beta particles and/or gamma rays, which may be a health hazard in living organisms because they ionize the atoms that they hit while passing through the tissues of the body (see Table 3-4 and Figure 3-3). Beta particles can travel appreciable distances in air, but travel only a few millimeters in solids. External exposure to beta particles may result in damage to skin and superficial body tissues at sufficiently high doses. Beta radiation is only a threat to internal organs if the radiation source is internalized. Gamma radiation, on the other hand, can easily pass completely through the human body and cause ionization of atoms in its path. For most radionuclides of public interest, the fraction of gamma rays that actually deposits energy and contributes to the radiation

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL: Less Serious (rad)	LOAEL: Serious (rad)	Reference / Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Human					2250 M (Death)	Stavem et al. 1985
2	Mouse (BALB/c)					627 (30-day LD50 value, single exposure)	Darwezah et al. 1988
3	Mouse CBA/Ca.Lac.C	1x				1420 M (Death)	Down et al. 1986
	Systemic						
4	Human	(occup)	Gastro	12.7			House et al. 1992
			Hemato	12.7			
5	Human		Dermal			159 M (Severe alterations to skin of left hand)	Klener et al. 1986
			Ocular			159 M (Progressive occlusion of vision of left eye)	

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
6	Human		Cardio			2250 M (left ventricular hypertrophy)	Stavem et al. 1985
			Gastro			2250 M (Pronounced atrophy in intestines; less severe in stomach)	
			Hemato			2250 M (>35% decrease in hemogolbin and >90% decrease in thrombocytes)	
			Renal		2250 M (Enlarged kidneys)		
7	Monkey (Rhesus)	30 min	Cardio		1000 M (Minor changes: increased heart rate; decreased blood pressure; variable cardiac output and total peripheral resistance)		Bruner 1977
8	Monkey (Rhesus)	1 hr	Cardio			10000 M (Pronounced decreases in mean arterial blood pressure and blood flow to the brain)	Cockerham et al. 1986
9	Rat (Wistar)		Cardio		2500 M (Increased brain uptake index)		Bezek et al. 1990

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
10	Rat (Sprague-Dawley)	1x	Resp			1500 M (Severe inflammation, pulmonary histopathology, fibrosis)	Lafuma et al. 1987
11	Mouse (Swiss-Webster)		Gastro		1000 M (Intestinal crypt cell damage, including necrosis and altered mitotic figures)		Devi et al. 1979
12	Mouse CBA/Ca.Lac.C	1x	Resp		1330 M (Increased breathing rate)		Down et al. 1986
			Dermal		1800 M (Mild epilation)		
13	Mouse (Swiss-Webster)	24 hr	Hepatic		1000 M (Transient decrease in total liver protein)		Mazur et al. 1991
14	Dog (Mongrel)	198 d	Cardio			4355 (Cardiac arrhythmia)	Dick et al. 1979
15	Dog (Beagle)	10.44 min	Gastro		800 (Repeated emesis)		Gomez-de-Segura et al. 1998

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)		LOAEL Serious (rad)		Reference Chemical Form
16	Rabbit (New Zealand)	1x	Dermal		1730 M	(Alopecia)			Cox et al. 1981
17	Pig Large White	1x	Resp		900 F	(Reversible decrease in ventilation capacity)	1090 F	(Irreversible decrease in ventilation capacity, histopathology, pulmonary atrophy)	Rezvani et al. 1989
18	Pig Large White	1x	Renal				874 F	(50% loss in effective renal plasma flow)	Robbins et al. 1989a
19	Pig Large White	1x	Hemato		780 F	(Slight decreases in erythrocytes, hemoglobin, and hematocrit)	1190 F	(Severe decreases in erythrocytes, hemoglobin, and hematocrit)	Robbins et al. 1989b
			Renal		780 F	(Reversible changes in effective renal plasma flow and glomerular filtration rate)	980 F	(Persistent changes in effective renal plasma flow and glomerular filtration rate)	
20	Pig Large White	1x	Renal				557 F	(50% loss in effective renal plasma flow)	Robbins et al. 1989c

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
21	Pig Large White	1x	Renal			980 F (Progressive inflammatory and degenerative changes in the glomerulus)	Robbins et al. 1991
22	Baboon	3-4 wk, 1x/wk	Resp			3000 (Severe pulmonary fibrosis)	Collins et al. 1978
23	Ferret	2 hr	Gastro	49 M	77 M (Emesis with wretching)		King 1988
	Immuno/ Lymphoret						
24	Human	(occup)		12.7			House et al. 1992
25	Human				159 M (Minor reduction in white cell counts)		Klener et al. 1986
26	Human					2250 M (Pronounced decrease in lymphocytes and granulocytes)	Stavem et al. 1985

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
27	Mouse (Swiss-Webster)	24 hr			1000 M (>50% decrease in spleen weight and protein; increased spleen acid phosphatase)		Mazur et al. 1991
	Neurological						
28	Rat (CD)	140 d		150 M	450 M (Reversible deficits in fixed-ratio behavior parameters)		Mele et al. 1988
29	Mouse (Swiss-Webster)	97 d		300 M	500 M (Reversible decreases in aggressive behavior)		Maier and Landauer 1989
30	Rabbit Burgundy fawn	12 hr			450 M (Altered firing rates and patterns of hippocampal neurons)		Bassant and Court 1978
	Reproductive						
31	Rat (Sprague-Dawley)	1x			330 M (Decreased testis weight and altered spermatogenesis, with some evidence of recovery)		Cunningham and Huckins 1978
32	Rat (Wistar)	1x			80 M (Reversible decrease in testicular weight)		Laporte et al. 1985

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)		LOAEL Serious (rad)		Reference Chemical Form
	Developmental								
33	Monkey Squirrel	1x					100	(Developmental retardation, neurobehavioral deficits)	Brizzee et al. 1978
34	Rat (Sprague-Dawley)	1x					50 F	(Defective eye development and spinal curvature)	Bruni et al. 1994
35	Rat	1x					260	(Testicular trophy; adrenal atrophy)	Inano et al. 1989
36	Rat (Wistar)	1x			260 M	(Reduced NADPH cytochrome p450 reductase)			Inano et al. 1990
37	Rat (Wistar)	4d or 6d		11	16	(slightly decreased (2.6%) brain weight in offspring)	560	(decreased (13.1%) brain weight in offspring)	Reyners et al. 1992
38	Rat (Wistar)	1x					210 M	(Testicular atrophy)	Suzuki et al. 1990

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)		LOAEL Serious (rad)		Reference Chemical Form
39	Mouse (Swiss-Webster)	1x		5	10	(Decreased brain weight 3-4%, significantly increased microphthalmia)	50	(Increased fetal mortality and growth retardation)	Devi et al. 1994
40	Mouse (Swiss-Webster)	1x			25	(Decreased body weight 5%, liver weight 5%, and spleen weight 12%. Decreased spleen cellularity.)			Devi et al. 1998
41	Mouse (B6C3F1)	1x					100 M	(Increased number of tumor-bearing animals after in utero exposure)	Nitta et al. 1992
42	Mouse (Swiss-Webster)	1x					200	(Atrophy or lack of development of corpus callosum)	Schmidt and Lent 1987
43	Mouse	6d					20 F	(Altered neurobehavioral parameters, growth retardation)	Want et al. 1993

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
44	Mouse LACA	1x				50 (Delayed development, altered hindlimb splay)	Zhong et al. 1996
45	Hamster (Golden Syrian)	1x				200 F (Severe developmental abnormalities of multiple organ systems, embryo death)	Harvey et al. 1962
46	Dog (Beagle)	1x				83 (Increased risk of thyroid neoplasia)	Benjamin et al. 1997
47	Dog (Beagle)	1x				15.6 (Increased cancer-related mortality - multiple tumor types)	Benjamin et al. 1998b
48	Dog (Beagle)	1x		16	83 (Hypodontia)		Lee et al. 1989
49	Dog (Beagle)	1x				96 (Optic atrophy/degeneration)	Schweitzer et al. 1987

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
	Cancer						
50	Dog (Beagle)	1x				15.6 (Increased cancer-related mortality)	Benjamin et al. 1998b
	INTERMEDIATE EXPOSURE						
	Death						
51	Human					7500 F (Death)	Roscher and Woodard 1969
	Systemic						
52	Human		Ocular			4800 F (Progressive visual impairment and blindness)	Fishman et al. 1976
53	Human	22 - 35 d teletherapy	Cardio			4623 (Persistent pericarditis)	Martin et al. 1975
54	Human	18 d	Gastro		3600 (Loose bowel movements, impaired absorption of vitamin B12)		McBrien 1973
55	Human	17 d	Dermal		4056 F (Comedones, which were resolved with treatment)		Myskowski and Safai 1981

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
56	Human		Gastro			7500 F (Severe gastrointestinal necrosis and fibrosis)	Roscher and Woodard 1969
57	Human	3 yr	Other	2400			Thibadoux et al. 1980
58	Human	7 wk	Dermal		4700 (Reversible changes in skin pigmentation)		van Oort et al. 1984
59	Rat (albino)	10 wk	Other	2400 M	4800 M (Transient alterations in incisor histopathology)	7200 M (Lasting alterations in incisor histopathology)	Sweeney et al. 1977
60	Dog (Beagle)	150-300 d	Hemato			1125 M (Aplastic anemia)	Seed et al. 1989
	Immuno/ Lymphoret						
61	Dog (Beagle)	150-300 d				1125 M (Dose- and time-related reduction in granulocytes, monocytes, and lymphocytes)	Seed et al. 1989

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
	Neurological						
62	Human					4800 F (Optic nerve damage, resulting in visual impairment and blindness)	Fishman et al. 1976
63	Human	9 mo				13150 F (Neural necrosis and gliosis)	Llena et al. 1976
64	Human					5500 M (Partial paralysis secondary to radiation myelopathy) 5000 F[b] (Partial paralysis secondary to radiation myelopathy)	Sanyal et al. 1979
	Reproductive						
65	Human	47 d				6600 M (Calcification of the prostate)	Keys and Reed 1980
66	Mouse	32 wk				1282 F (Decreased offspring per litter and sterility)	Searle et al. 1980
	Cancer						
67	Human	NS				1800 F (Basal cell carcinoma)	Garcia-Silva et al. 1996
68	Human	8 mo				25150 M (Multiple basal cell carcinomas)	Wollenberg et al. 1995

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
69	Human	3 yr	Cardio			13150 F (Endothelial hyperplasia, dysplasia, and fibrosis)	Llena et al. 1976

[a] The number corresponds to entries in Figure 3-3.

[b] Differences in levels of health and cancer effects between males and females are not indicated in Figure 3-3. Where such differences exits, only the levels of effect for the most sensitive gender are represented.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; min = minute(s); mo = month(s); NOAEL = no observed-adverse-effect level; NS = not specified; (occup) = occupational; Resp = respiratory; wk = week(s); yr = year(s).

Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation

Acute (≤14 days)

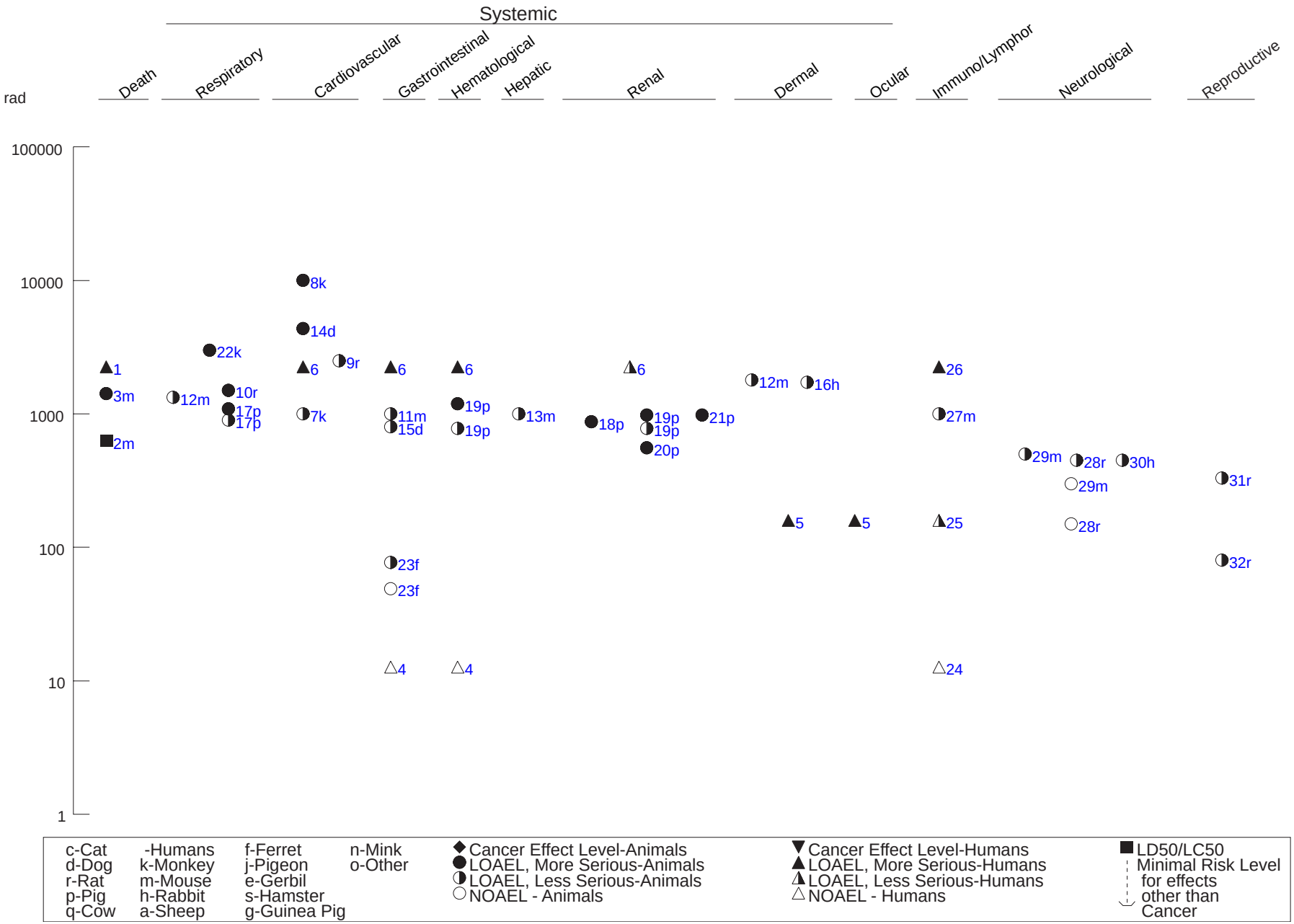


Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (*Continued*)

Acute (≤14 days)

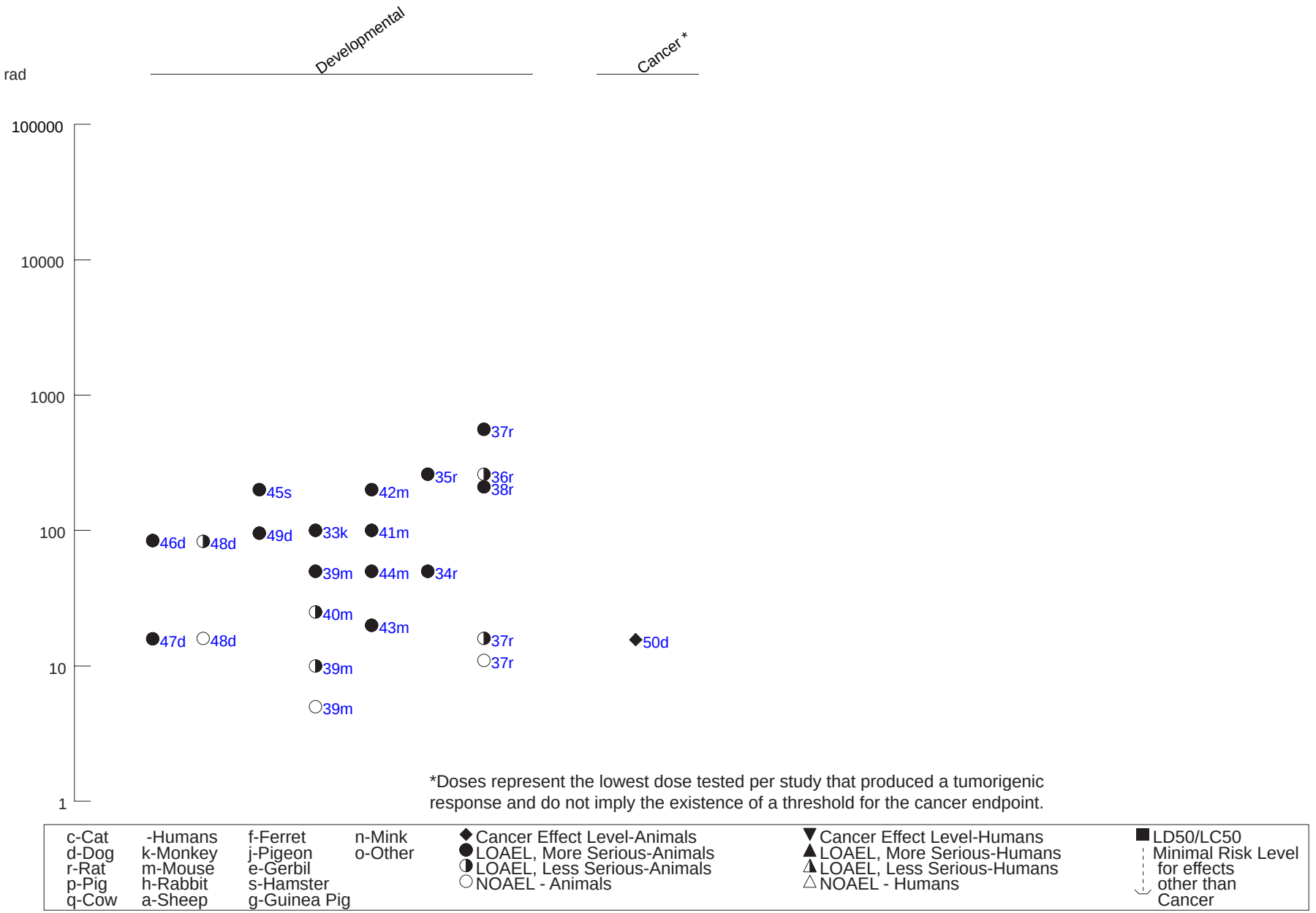


Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (*Continued*)

Intermediate (15-364 days)

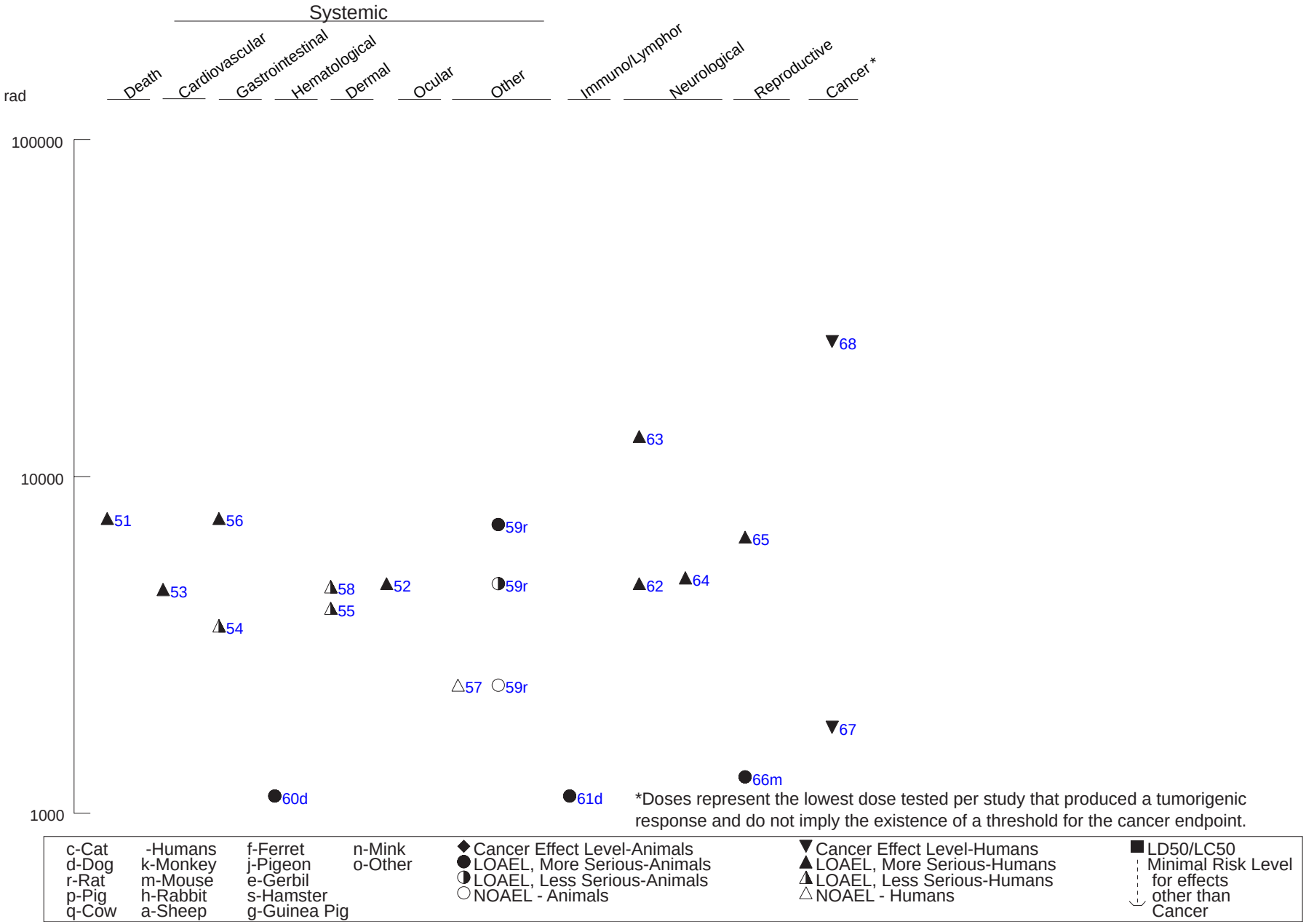
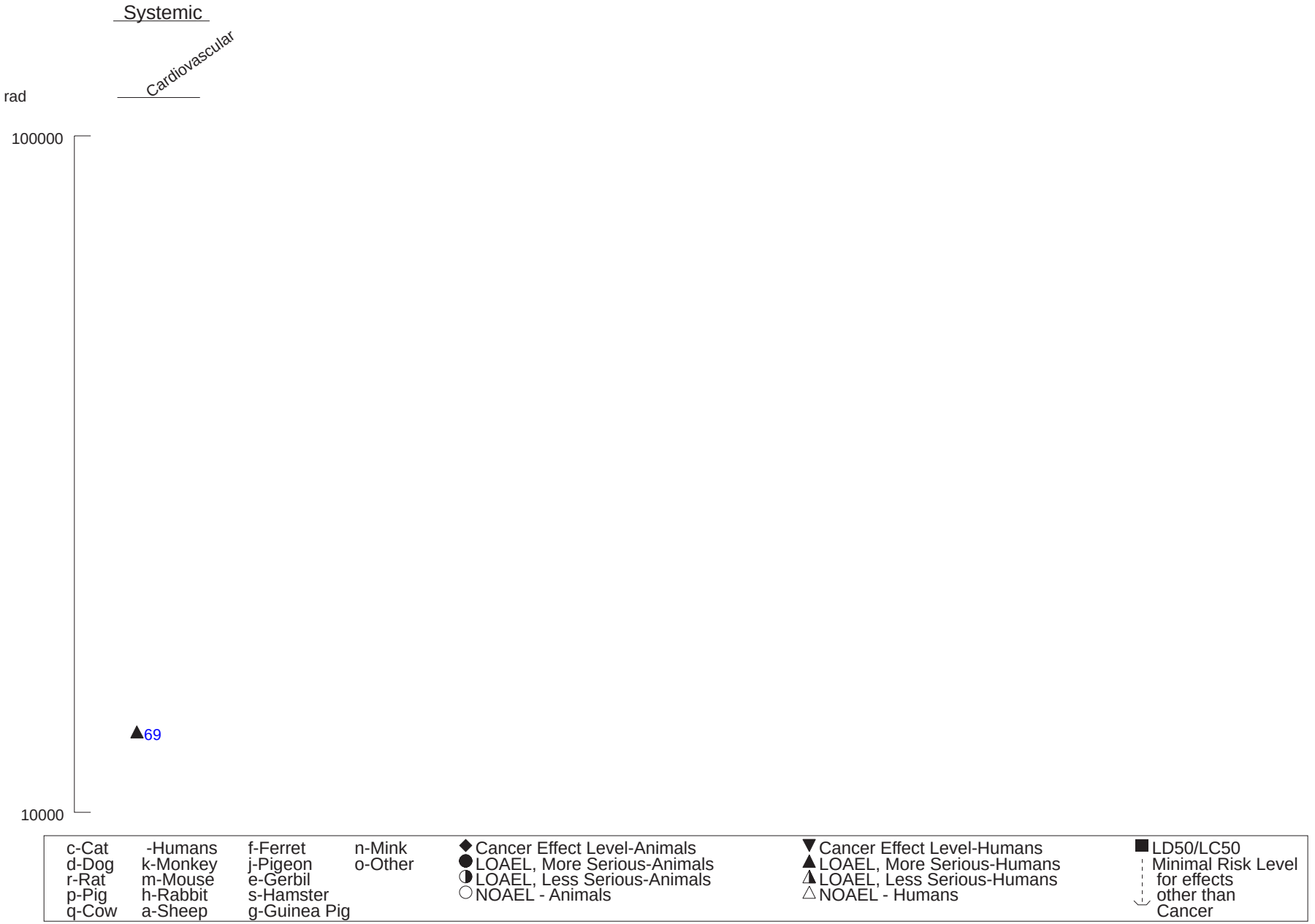


Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (*Continued*)

Chronic (≥365 days)



dose increases with tissue density (resulting in a higher dose to bone than soft tissue) and decreases with energy. Several feet of concrete or a few inches of lead are typical shield thicknesses for protection from gamma rays. Because it is so highly penetrating, gamma radiation released by radionuclides such as cobalt may be a radiation hazard to internal organs (Agency for Toxic Substances and Disease Registry 1999; EPA 1997b). ^{60}Co gamma rays are commonly used for human radiotherapy. The purpose of this section is to provide information regarding health effects associated with external exposure to a radioactive cobalt source. These health effects are not specific to cobalt, but apply to any radionuclide delivering the same beta and gamma radiation dose at a comparable dose rate. Refer to Agency for Toxic Substances and Disease Registry (1999) for a detailed description of health effects from external exposure to ionizing radiation in general.

3.3.3.1 Death

Exposure to high levels of external radiation, including radiation from cobalt radionuclides, may result in mortality when the whole body dose exceeds 300 rads. Stavem et al. (1985) reported a case in which a worker was exposed to 2,250 rad (22.5 Gy) within a few minutes time, resulting in death due to acute radiation sickness (depressed leukocyte counts, vomiting, diarrhea, etc.). Complications resulting from cobalt radiotherapy resulted in the death of a patient from severe gastrointestinal complications (Roschler and Woodard 1969).

Norris and Poole (1969) reported on the mortality of dogs exposed to ^{60}Co gamma rays at a rate of 35 rad (0.35 Gy) per day for 40 days, resulting in a cumulative exposure of 1,400 rad (14 Gy). Twelve of 40 animals died prior to termination of the 40-day exposure period, 13 of 40 died within the 23-day post-exposure observation period, and 15 survived to the end of the study period, indicating an LD_{50} of <1,400 rad at 35 rad/day. Darwezah et al. (1988) reported single, whole-body exposure LD_{50} values in mice of 913 rad (9.13 Gy) and 627 rad (6.27 Gy) at 6 and 30 days post-irradiation, respectfully. Down et al. (1986) reported a slightly higher LD_{50} of 1,400–1,450 rad (14–14.5 Gy) for ^{60}Co thoracic irradiation in mice at 26 days postirradiation. Several studies have demonstrated that decreasing the dose rate or the portion of the body exposed will increase the LD_{50} for ^{60}Co gamma rays (Darwezah et al. 1988; Down et al. 1986; Hanks et al. 1966; Page et al. 1968).

3.3.3.2 Systemic Effects

Respiratory Effects. Ionizing radiation is known to exert dramatic effects on the tissue of the lung (Agency for Toxic Substances and Disease Registry 1999; Davis et al. 1992; Libshitz 1993; Roswit and White 1977), particularly at the high doses used in radiotherapy. The first phase of damage usually consists of radiation pneumonitis, which occurs between 3 and 13 weeks after irradiation and is characterized by low-grade fever, mild exertional dyspnea, congestion, and unproductive cough. The second phase is characterized by radiation-induced lung fibrosis, emphysema, and pleural thickening. Patients receiving radiotherapy treatment regimens of ≥4,000 rad (40 Gy) to the chest region almost always develop radiographic changes in the lung (Davis et al. 1992), whereas lower therapeutic doses (2,500–3,000 rad, 25–30 Gy) generally result in a lower risk of adverse pulmonary symptoms (Davis et al. 1992; Roswit and White 1977). Prophylactic protective measures may be taken, and these symptoms may be treated later if detected early enough in their progression (Roswit and White 1977).

At similar doses, studies in animals, including rats, mice, baboons, and pigs, using ^{60}Co radiation have also shown radiation pneumonitis and fibrosis, similar to effects seen in humans (Collins et al. 1978; Down et al. 1986; Lafuma et al. 1987; Rezvani et al. 1989). Other respiratory changes seen in animal experiments included an increased breathing rate, effects on the surfactant system, edema, increased pleural fluid content, pulmonary atrophy, and histologic alterations of the lung parenchyma (Bellet-Barthas et al. 1980; Collins et al. 1978; Down et al. 1986; Lafuma et al. 1987).

Cardiovascular Effects. Martin et al. (1975) reported that 24 of 81 patients who underwent ^{60}Co teletherapy for Hodgkin's disease, using an upper mantle treatment regimen of 4,000 rad (40 Gy) over 22–35 days, developed radiation-related pericarditis. In 14 of these patients, the condition was transient, while it persisted in the other 10 patients. Llena et al. (1976) presented a case wherein a 51-year-old woman who had received a localized dose of 13,150 rad (131.5 Gy) of ^{60}Co radiation between the nasopharynx and cervical lymph nodes as part of radiotherapy developed severe alterations in the endothelial cells of the brain, including proliferation, increased cytoplasmic organelles, and infoldings of the plasma membrane.

Whole-body exposure of Rhesus monkeys to 10,000 rad (100 Gy) over a 90-second period resulted in dramatic decreases in mean systemic arterial blood pressure, as well as in mean blood flow in the pons and pre-central gyrus, beginning at 10 minutes post-irradiation and persisting throughout the 60-minute

observation period (Cockerham et al. 1986). Bruner (1977) examined cardiovascular parameters in Rhesus monkeys exposed to 1,000 rad (10 Gy) at rates of 129–164 rad/minute (1.29–1.64 Gy/minute). Heart rate was elevated post-exposure, blood pressure was reduced near the end of exposure and thereafter, cardiac output increased at the end of exposure, but thereafter fell to below control levels, and total peripheral resistance to blood flow decreased at early times post-exposure, but thereafter rose to above control levels. Ten of 12 dogs irradiated with 4,355–5,655 rad (43.6–56.6 Gy), focused on the interatrial septum of the heart, developed cardiac arrhythmias (Dick et al. 1979). The permeability of the blood-brain barrier was significantly increased, particularly for hydrophillic compounds, in rats exposed to 2,500 rad (25 Gy) from a ^{60}Co source (Bezek et al. 1990).

Gastrointestinal Effects. A worker accidentally exposed to an acute whole-body dose of 2,250 rad (22.5 Gy) showed slight atrophy of the stomach glands, marked atrophy in the small intestine, and total atrophy of the glands in the large intestine (Stavem et al. 1985). Two years after a woman received ^{60}Co radiation therapy amounting to 4,000 rad (40 Gy) anteriorly and 3,500 rad (35 Gy) posteriorly over a 6-week period, she reported severe gastrointestinal difficulties, including epigastric pain, vomiting, bloody stools, and weight loss (Roschler and Woodard 1969), eventually resulting in death. Autopsy revealed dense fibrous layers around the sacrum, with severe fibrosis confirmed by microscopic examination. Cobalt radiotherapy for carcinoma of the bladder (~3,100–3,600 rad, 31–36 Gy, over 18 days) resulted in loose bowel movements and a decreased absorption of vitamin B12 following oral exposure in 8 of 14 patients (McBrien 1973). No gastrointestinal symptoms were reported in three workers who were accidentally exposed to much lower exposure levels, ranging from 2.24 to 12.7 rad (0.022–0.127 Gy) (House et al. 1992).

Exposure of male Sprague-Dawley rats to 850 rad (8.5 Gy) of ^{60}Co gamma radiation resulted in marked alterations in drug absorption, primarily due to a decrease in gastric emptying rate (Brady and Hayton 1977b). Exposure of young adult beagle dogs to 800 rad (8 Gy) of ^{60}Co radiation at a rate of 177.5 rad/minute (1.775 Gy/minute) resulted in a 100% emesis rate within 10 hours post-irradiation, with an average of 2.4 episodes per animal and an average time to emesis of 82 minutes (Gomez-d-Segura et al. 1998). King (1988a) reported a NOAEL of 49 rad (0.49 Gy) and an EC_{50} of 77 rad (0.77 Gy) for emesis and wretching following exposure of male ferrets to ^{60}Co gamma radiation. Exposure of male Swiss mice to 1,000 rad (10 Gy) of ^{60}Co radiation resulted in necrosis of the intestinal crypt cells (Devi et al. 1979).

Hematological Effects. No changes in hematologic parameters were reported in three workers who were accidentally exposed to levels ranging from 2.24 to 12.7 rad (0.022–0.127 Gy) (House et al. 1992). Hashimoto and Mitsuyasu (1967) reported that in 50 of 58 patients receiving local radiotherapy, irradiated bone marrow was more hypoplastic in the hematopoietic elements than in non-irradiated marrow in the same individual. A male worker exposed to 159 rad (1.59 Gy) showed minor reductions in leukocytes, neutrophils, and lymphocytes (Klener et al. 1986). Stavem et al. (1985) reported that a male worker exposed to 2,250 rad (22.5 Gy) showed a progressive decrease in hemoglobin and circulating thrombocytes prior to death. Autopsy showed a pronounced hypocellularity of the bone marrow.

Seed et al. (1989) exposed male Beagle dogs to 7.5 rad/day (0.075 Gy/day) gamma radiation for 150–700 days from a ^{60}Co source. The irradiated dogs initially showed a significant suppression, compared with levels from the control animals, of the five circulating types of cells studied (granulocytes, monocytes, platelets, erythrocytes, and lymphocytes), which lasted ~250 days; this was followed by a recovery phase for the remainder of the study period. Hashimoto and Mitsuyasu (1967) exposed guinea pigs to whole-body ^{60}Co radiation, and reported an initial hypoplasia of the bone marrow followed by recovery of hematopoietic activity by 3 weeks post-irradiation. Robbins et al. (1989b) reported significant reductions in erythrocyte count, hematocrit, and hemoglobin levels within 6–8 weeks of irradiation of the kidneys of female pigs with 980–1,400 rad (9.8–14 Gy) of ^{60}Co gamma rays.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals following external exposure to ^{60}Co radiation. These tissues are among the most radioresistant in both humans and animals.

Hepatic Effects. No studies were located regarding hepatic effects in humans following external exposure to ^{60}Co radiation.

No changes in liver weight were seen in male Swiss mice exposed to 1,000 rad (10 Gy) of ^{60}Co radiation and examined every 4 hours for 24 hours post-irradiation (Mazur et al. 1991). Andrzejewski et al. (1980) reported increased respiration rates in rat liver mitochondria after whole-body exposure to 1,000 or 3,000 rad (10 or 30 Gy) of ^{60}Co radiation; the increase was greater and more persistent at the higher dose level.

Renal Effects. Stavem et al. (1985) reported that a 64-year-old man who accidentally received a fatal dose (2,250 rad) of cobalt radiation developed enlarged kidneys. No other studies were located regarding renal effects in humans after external exposure to cobalt radiation.

Robbins et al. (1989a, 1989b, 1989c, 1991a, 1991b) performed a series of studies in female White pigs wherein the kidneys of the animals were exposed to single doses of 780–1,400 rad (7.8–14 Gy) of ^{60}Co radiation and examined for periods up to 24 weeks postirradiation. Irradiation resulted in an initial increase in glomerular filtration rate (GFR), followed by a dose-related decrease in the GFR, beginning at 4 weeks postexposure. Effective renal plasma flow (ERPF) was also decreased in a dose-related manner beginning at 4 weeks postexposure, but did not show the initial increase seen in GFR. Some recovery of GFR and ERPF occurred by 24 weeks postirradiation, though values were still significantly reduced below controls in all groups but the 780 rad (7.8 Gy) group. Histology was performed on animals exposed to 980 rad (9.8 Gy) and killed between 2 and 24 weeks after exposure. Beginning at 2 weeks postirradiation, increased numbers of inflammatory cells were present within the glomerulus, and there was an increase in mesangial matrix and number of mesangial cells. The glomerular changes continued to progress in severity throughout the observation period, with generalized thickening of the capillary walls, extensive duplication of the basement membrane, and progressive inflammation. Tubular changes appeared to be maximal at 6 weeks, including focal degeneration and necrosis, with partial recovery at later timepoints.

Endocrine Effects. Prager et al. (1972) reported that 5 of 23 patients receiving cobalt radiotherapy (3,900–4,600 rad, 39–46 Gy) for Hodgkin's disease developed hypothyroidism, with substantial decreases in levels of T4 relative to patients with normal thyroids. Chang et al. (2001) examined the residents of ^{60}Co-contaminated buildings for effects on the thyroid. There was an increased prevalence of goiter in males of all ages and females <15 years of age, as well as a dose-related increase in the prevalence of thyroid cysts in females of all ages, and elevated tri-iodothyronine levels in males <15 years of age. No other studies examining the endocrine effects of radioactive cobalt exposure, either internal or external, in humans were located.

Whole-body acute exposure of rats to 330 rad (3.3 Gy) did not affect FSH, LH, or testosterone levels (Cunningham and Huckins 1978). Similarly, male Wistar rats exposed to a single dose of 80 rad (0.8 Gy) of testicular radiation showed no changes in FSH, LH, prolactin, or testosterone (Laporte et al. 1985). No

other studies examining the endocrine effects of radioactive cobalt exposure, either internal or external, in animals were located.

Dermal Effects. Several studies in humans have demonstrated that high-dose exposure to cobalt radiation can result in damage to the skin. Klener et al. (1986) described the accidental irradiation of a worker who was attempting to bring under control a sealed ^{60}Co source. The patient's left palm (the patient was left-handed) developed an irregular oval defect 3x4 cm with whitish edges and bleeding, as well as superficial lesions on the third and fourth finger. Considerable spontaneous pain required the administration of analgesics. The lesions showed no tendency to heal, instead spreading to the adjacent digits. After several failed skin graft attempts, the condition worsened, necessitating the amputation of fingers five through two. Walter (1980) reported that a patient who had undergone ^{60}Co radiotherapy (dose not reported) of the forehead and scalp developed a pronounced acneform reaction, characterized primarily by alopecia with multiple open comedones on the scalp and forehead, and hair loss. With treatment, the comedones were 80% cleared at 9 months post-diagnosis (13 months post-treatment), but no hair regrowth was noted. Myskowski and Safai (1981) have likewise reported localized comedones in a patient following 4,056 rad (40.6 Gy) of ^{60}Co radiotherapy. Van Oort et al. (1984) reported that patients receiving 4,700–6,000 rad (47–60 Gy) of ^{60}Co radiotherapy over a 7-week period showed significant differences in baseline color of the skin, primarily erythema, and pigmentation, beginning the third week of exposure and persisting throughout the fifth week postirradiation (study week 12). Johansson et al. (2000) reported that 86% of women who had been treated with 5,400–5,700 rad (54–57 Gy) after a radical mastectomy developed fibrosis of the skin of the treated area.

Cox et al. (1981) reported a dose-related loss of hair in rabbits exposed to 1,730–3,210 rad (17.3–32.1 Gy) ^{60}Co gamma rays, targeted at the skin near the eyes or of the ears, with recovery initially noted in animals exposed to 2,140 rad (<21.4 Gy) by day 200 postirradiation. Beginning at day 500 postirradiation, a substantial loss of hair again was seen, persisting throughout the end of the study. Mice exposed to 1,800 rad (18 Gy) of ^{60}Co radiation showed a slight increase in epilation score (Down et al. 1986).

Ocular Effects. Exposure to high-dose radiation from cobalt sources has been shown to result in effects on the eye, in particular the development of cataracts. Augsburger and Shields (1985) described 13 patients who developed cataracts following ^{60}Co plaque radiotherapy; estimated doses to the eyes ranged from 2,000 to 10,000 rad (20–100 Gy). Fishman et al. (1976) reported on two patients who

received head-only 60Co radiotherapy, in combination with chemotherapy, for the treatment of acute lymphocytic leukemia. Both patients, who received 2,400 rad (24 Gy) over an initial 16-day course of treatment followed later by either 2,400 or 2,500 rad (24 or 25 Gy) in followup therapy, developed progressively severe vision disorders, resulting in partial or total blindness. Exposure of a male worker to a whole-body dose of 159 rad (1.59 Gy) of ^{60}Co radiation resulted in a progressive deterioration of visual acuity, due to cataract development, in the left eye (which was more exposed than the right) over time (Klener et al. 1986). Chen et al. (2001) evaluated subjects that had been exposed to 120–194 mSv (range: 1.11–1493.4 mSv) for an undisclosed period of time for lenticular opacities. Subjects <20 years old showed a dose-dependent increase in the numbers of focal lens defects, while for those aged 20–40 and >40, no such statistical correlation was seen.

Other Systemic Effects. Thibadoux et al. (1980) reported that of 61 children receiving a course of 2,400 rad (24 Gy) of cranial radiotherapy, none developed significant reductions in hearing levels by the end of the third year after irradiation.

Taiwanese children (48 boys, 37 girls) who were raised in apartments contaminated with ^{60}Co were compared to 21,898 age- and sex-matched nonexposed children from a nationwide surveillance program (Wang et al. 2001). After adjusting for effects from parental heights and body mass index, clear dose-related decreases in height percentile (HP) and age-specific relative height differences (RHD) were seen in exposed boys, but not in exposed girls. Average cumulative doses were 120.8 and 129.9 mSv for the boys and girls, respectively.

Sweeney et al. (1977) examined the effects of 60Co radiation on the teeth of rats exposed to 0, 2,400, 4,800, or 7,200 rad (0, 24, 48, or 72 Gy). Animals exposed to 4,800 rad (48 Gy) showed transient effects on the incisors only, while at 7,200 rad (72 Gy), the effects lasted throughout the 10-week study period.

3.3.3.3 Immunological and Lymphoreticular Effects

A worker accidentally exposed to an acute dose of 2,250 rad (22.5 Gy) showed a rapid fall in circulating lymphocytes and granulocytes prior to death (Stavem et al. 1985). Chronic exposure to low amounts of ^{60}Co radiation in people living in a contaminated building significantly reduced the numbers of circulating CD4+ lymphocytes in the blood (Chang et al. 1997, 1999b); mean total radiation dose was estimated to be

0.169 Gy (16.9 rad) over a 2–13-year period. Similarly, children chronically-exposed to low levels (estimated dose of 0.002–0.085 Gy [0.2–8.5 rad]) of ^{60}Co radiation in a contaminated kindergarten building showed significant decreases in total leucocytes and neutrophils, but an increase in eosinophils, 5–7 years after exposure had ceased (Chang et al. 1999a).

In male Swiss mice exposed to 1,000 rad (10 Gy) of ^{60}Co radiation, significant decreases in weight of the spleen were seen as early as 1 hour post-exposure and persisted throughout the following 24 hours (Mazur et al. 1991). Spleen acid phosphatase activity, expressed as activity per gram of protein, was significantly increased in irradiated animals beginning at 13 hours post-exposure.

3.3.3.4 Neurological Effects

Exposure of both humans and animals to high doses of cobalt radiation has been shown to result in damage to nervous tissue, particularly peripheral nerves. Llena et al. (1976) presented a case wherein a 51-year-old woman who had received 13,150 rad (131.5 Gy) of 60Co radiation between the nasopharynx and cervical lymph nodes as part of radiotherapy developed focal necrosis of the brain in the frontal lobe, as confirmed by gross and microscopic examination. Fishman et al. (1976) reported on two patients who received head-only ^{60}Co radiotherapy, in combination with chemotherapy, for the treatment of acute lymphocytic leukemia. Both patients, who received 2,400 rad (24 Gy) over an initial 16-day course of treatment followed later by either 2,400 or 2,500 rad (24 or 25 Gy) in followup therapy, developed progressively severe vision disorders, resulting in partial or total blindness. Histopathology from one patient demonstrated severe alterations in the optic nerve, including severe atrophy, terminal beading, lack of myelin, and calcification. Sanyal et al. (1979) reported on five patients who received doses of 4,500–6,000 rad (45–60 Gy) ^{60}Co radiation as radiotherapy, who developed varying degrees of myelopathy, resulting in minimal to mild paralysis. In patients that had been treated with ^{60}Co radiation (total dose of 54–57 Gy, or 5,400–5,700 rad) following mastectomy, 63% developed brachial plexus neuropathy and 5% developed vocal chord paresis over the 30-year period reported by the study (Johansson et al. 2000).

Mele et al. (1988) exposed male rats to 50, 150, or 450 rad (0.5, 1.5, or 4.5 Gy) 3 times, at 43-day intervals, and examined them for changes in behavior daily for 30 days following each exposure. Rats exposed to 450 rad (4.5 Gy), but not those exposed to 150 rad (1.5 Gy) or 50 rad (0.5 Gy), showed

significant deficits in fixed-ratio response rates and running rates after each exposure, beginning the day after exposure and persisting for 4–5 days, after which both rates returned to normal. After the third exposure, all rats were exposed to 650 rad (6.5 Gy), which resulted in similar performance decrements as were seen in the 450 rad (4.5 Gy) animals, again beginning 24 hours after exposure, with previous exposure resulting in no differences in behavioral parameters. Maier and Landauer (1989) reported significant decreases in offensive behavior in mice acutely exposed to whole-body doses of 500 or 700 rad (5 or 7 Gy), but not those exposed to 300 rad (3 Gy), with changes occurring in the second week postirradiation and responses returning to normal by day 19 postirradiation. Rabin et al. (1998) reported that exposure of rats to ^{60}Co radiation (up to 30 Gy or 3,000 rad) showed a dose-related decrease in the acquisition of controlled taste aversion behavior. Bassant and Court (1978) reported that rabbits exposed to 450 rad (4.5 Gy) of ^{60}Co radiation whole-body showed an altered activity of hippocampal cells, with a slowed mean discharge rate and increased interspike variability persisting for at least 12 hours postirradiation.

3.3.3.5 Reproductive Effects

Ionizing radiation in general, and gamma-emitting isotopes in particular, is known to have profound effects on reproductive tissues, with effects seen primarily in rapidly-dividing germ cells resulting in temporary or permanent sterility in both sexes, as well as other effects (Agency for Toxic Substances and Disease Registry 1999). These effects are usually observed only at high radiation doses. Keys and Reed (1980) reported a case of a man who, as treatment for a prostate tumor, received an estimated dose of 6,600 rad (66 Gy) to the prostate over a 47-day period, and who later developed a severe prostatic calcification necessitating surgical correction.

^{60}Co radiation at high doses has been shown to elicit profound decrements in reproductive ability in animal species. Whole-body acute exposure of rats to 330 rad (3.3 Gy) decreased testicular weights beginning at 22 days postirradiation, with recovery of testicular weight beginning about day 65 (Cunningham and Huckins 1978). Histologic examination of the testes revealed destruction of the spermatogonial population, with a slow recovery as the spermatogonial population was rebuilt from the surviving stem cells. Searl et al. (1976) reported that exposure of male mice to 1,128 rad (11.3 Gy) over a 28-week period resulted in significant reductions of testis mass and epididymal sperm count. Male Wistar rats exposed to a single dose of 80 rad (0.8 Gy) to the testes showed increased tubular fluid production

and decreased testicular weight at 30 and 45 days postirradiation, but not at later time points (Laporte et al. 1985). Single doses of >100 rad (1 Gy) of ^{60}Co radiation caused decreased fertility in exposed female mice (Philippe 1975). Continuous exposure of female mice to an average daily dose of 8 or 16 rad/day (0.08 or 0.16 Gy/day) caused a decreased number of offspring per litter and decreased reproductive performance, with 100% sterility occurring at 32 weeks of exposure at 8 rad/day (0.08 Gy/day) or 20 weeks of exposure at 16 rad/day (0.16 Gy/day) (Searl et al. 1980). Female rabbits exposed to 400 rad (4 Gy) prior to implantation showed dramatic decreases in implantation (Chang et al. 1963).

3.3.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after external exposure to cobalt radiation.

In utero exposure to cobalt radiation has been extensively studied in animal species, and may elicit substantial effects across many organ systems of the developing organism. Effects have been noted following single-dose exposures as low as 10 rad (0.10 Gy) in mice (Devi et al. 1994; Wang et al. 1993), 50 rad (0.5 Gy) in rats (Bruni et al. 1994), 200 rad (2 Gy) in hamsters (Harvey and Chang 1962), 250 rad in rabbits (Chang et al. 1963), 15.6 rad (0.16 Gy) in dogs (Benjamin et al. 1998a, 1998b), and 100 rad (1 Gy) in monkeys (Brizzee et al. 1978). Organs known to be affected include the brain (Brizzee et al. 1978; Bruni et al. 1994; Devi et al. 1994; Hamilton et al. 1989; Reyners et al. 1992; Schmidt and Lent 1987), eyes (Brizzee et al. 1978; Bruni et al. 1994; Schweitzer et al. 1987), hair (Hirobe 1994; Hirobe and Zhou 1990), kidney (Benjamin et al. 1998a; Brizzee et al. 1978), liver (Devi et al. 1998), ovaries (Inano et al. 1989), pituitary (Brizzee et al. 1978), skeleton (including cleft palate, shortened digits, fused digits, and other gross abnormalities) (Bruni et al. 1994; Chang et al. 1963; Harvey and Chang 1962), spleen (Devi et al. 1998), teeth (Lee et al. 1989), testes (Inano et al. 1989; Suzuki et al. 1990), and thyroid (Benjamin et al. 1997). ^{60}Co radiation *in utero* has also shown to cause functional alterations, including postnatal growth retardation (Wang et al. 1993; Zhong et al. 1996), neurobehavioral changes (Brizzee et al. 1978; Wang et al. 1993), hormonal production (Brizzee et al. 1978; Inano et al. 1989; Suzuki et al. 1990), alterations in hepatic enzymes (Inano et al. 1990), and diabetes mellitus (Benjamin et al. 1998a). *In utero* irradiation with cobalt also leads to increased tumor incidence later in life (Benjamin et al. 1991, 1997, 1998b; Nitta et al. 1992).

Devi et al. (1994) exposed pregnant mice to a single dose of 0–50 rad (0–0.50 Gy) of ^{60}Co radiation on day 11.5 of gestation. A significant decrease in pup brain weight and an increase in the incidence of microphthalmia was seen at 10 rad (0.10 Gy), with decreases in head width, head length, body length, and body weight occurring at higher doses. A later study (Devi et al. 1998) found decreases in body weight, liver weight, and spleen weight in pups 72 hours after irradiation with 25 rad (0.25 Gy) of ^{60}Co radiation on day 17 of gestation. Male offspring, but not female offspring, of mice exposed to 50 rad (0.5 Gy) on gestation day 9 showed decreased body weights on postnatal days 0, 3, and 7, while offspring of both sexes showed delays in pinna detachment, incisor eruption, eye opening, and testes descent (Zhong et al. 1996). Wang et al. (1993) reported that mice exposed to a cumulative *in utero* dose of 10 rad (0.10 Gy) showed alterations in visual placing reflex tests, while those exposed to 20 or 40 rad (0.20 or 0.40 Gy) showed decreased mean body weight, delayed eye opening, and alterations in the air righting reflex.

Rats exposed to 50 rad (0.50 Gy) of ^{60}Co radiation on gestational day 9.5 showed histologic damage to the neuro-epithelium 4 hours post-exposure, with abnormal flexion of the embryo and abnormal flexion of the head at 48 hours post-exposure (Bruni et al. 1994). At birth, rats showed increased incidence of defective eye development, spinal curvature, and visceral anomalies. Reyners et al. (1992) reported decreased brain weight in 3-month-old rats that had been exposed to cumulative doses of 160 rad (1.6 Gy) over gestation days 12–16 or 170 rad (1.7 Gy) over gestation days 14–20. Male rats exposed to 210 rad (2.1 Gy) on day 20 of gestation showed atrophy of the testes, prostates, and seminal vesicles, as well as a complete disappearance of germinal cells within the testes, on postnatal day 70 (Suzuki et al. 1990). Inano et al. (1989) exposed rats on gestation day 20 to 260 rad (2.6 Gy) of ^{60}Co radiation. Seminiferous tubules of male offspring and ovaries of female offspring showed pronounced atrophy, and steroid hormone production was significantly altered.

Benjamin et al. (1997, 1998a, 1998b) exposed groups of pregnant Beagle dogs to 15.6–17.5 or 80.8–88.3 rad (0.15–0.175 or 0.8–0.88 Gy) of ^{60}Co radiation on day 8, 28, or 55 post-breeding. Animals were allowed to live their full life span and were observed for radiation-related illnesses and cause of death. No change in the mean age at death was seen as a result of exposure. Males exposed to either exposure level at day 55 post-breeding, but not females at any time or males exposed at days 8 or 28, showed an increase in deaths due to renal disease. High-dose females exposed on days 28 or 55 showed an increase in the frequency of diabetes mellitus. Both sexes showed an increase in malignant neoplasias in general when exposed to radiation at 8 or 55 days postcoitus, but not at 28 days, while females exposed on day 55 also showed an increase in lymphoid neoplasia. A similar exposure on day 28 or 55 postcoitus

also resulted in a dose-dependent decrease in brain weight (Hamilton et al. 1989). *In utero* radiation of dogs to higher doses (100–380 rad [1–3.8 Gy]) resulted in retinal dysplasia and atrophy (Schweitzer et al. 1987).

3.3.3.7 Cancer

The carcinogenic effects of high doses of ionizing radiation have been well documented (Agency for Toxic Substances and Disease Registry 1999), though the effects of lower doses are less clearly defined. Duncan et al. (1977) reported on a cohort of patients who had received radiotherapy for carcinoma of the cervix. Eight of 2,674 patients developed bladder tumors within 6 months to 20 years following irradiation; the incidence rate was over 57 times greater than the general female population. All eight patients had received high (therapeutic) doses of ^{60}Co irradiation, though five of the eight also received radium therapy in conjunction with ^{60}Co irradiation. Wollenberg et al. (1995) presented a case of a 55-year-old farmer who received a total of 25,150 rad (251.5 Gy) distributed over six areas of the body over an 8-month period as a ^{60}Co teletherapy treatment regimen. Twenty years after irradiation, the patient developed a total of 43 basal cell carcinomas of the skin over the treated areas, all of which were successfully removed with cryosurgery. A 2-year-old girl exposed to 1,800 rad (18 Gy) of ^{60}Co radiation as part of a treatment regimen for acute lymphoblastic leukemia L1 developed, at age 12, a basal cell carcinoma of the scalp (Garcia-Silva et al. 1996). Three patients receiving cobalt irradiation as part of a chemotherapy/radiation treatment developed basal cell carcinoma of the scalp 8–15 years after treatment in the area of radiation treatment (Dinehart et al. 1991).

3.3.4 Other Routes of Exposure

This section includes injection and *in vitro* studies that provide evidence for the biological basis of toxicity of stable and radioactive cobalt in humans and animals. Since these studies are not directly relevant to general population exposure conditions, no LSE tables have been created for this section.

3.4 GENOTOXICITY

Stable Cobalt. No studies were located regarding genotoxic effects in humans following oral or dermal exposure to cobalt. No studies were located regarding genotoxic effects in animals following inhalation exposure to cobalt.

Gennart et al. (1993) examined a cohort of 26 male workers who had been occupationally-exposed to cobalt, chromium, nickel, and iron. Analysis of variance on sister-chromatid exchange rank values revealed that exposure status (exposed vs. controls) and smoking habits had statistically significant effects. De Boeck et al. (2000) reported no significant change in the comet assay on lymphocytes from nonsmoking workers who had been occupationally exposed to cobalt or hard metal dusts; a positive association was found between hard metal exposure and increased micronucleus formation in smokers only.

Single oral exposure of male Swiss mice to 0, 4.96, 9.92, or 19.8 mg cobalt/kg as cobalt chloride resulted in significantly increased percentages of both chromosomal breaks and chromosomal aberrations in bone marrow cells, with significant linear trends toward increasing aberrations with increased exposure (Palit et al. 1991a, 1991b, 1991c, 1991d).

Results of genetic testing of cobalt are presented in Table 3-5. Several different forms of cobalt, including cobalt chloride and cobalt sulfide, were tested. No profound differences were found among the various forms.

Cobalt was found to be generally nonmutagenic in bacteria (*Salmonella typhimurium, Escherichia coli*) and yeast when compounds with a valence state of II were tested (Arlauskas et al. 1985; Fukunaga et al. 1982; Kanematsu et al. 1980; Kharab and Singh 1985; Ogawa et al. 1986; Singh 1983; Tso and Fung 1981). A very weak mutagenic response was found with *Bacillus subtilis* (Kanematsu et al. 1980). A mutagenic response to cobalt was found, however, when compounds with a valence state of III were tested in *S. typhimurium* and *E. coli* (Schultz et al. 1982). The authors suggested that this may be due to the formation of cobalt(III) complexes that are inert to ligand substitution, allowing optimal interaction of cobalt with genetic material (Schultz et al. 1982). Other studies have shown cobalt to be a comutagen in combination with 4-substituted pyridines in *S. typhimurium* (Ogawa et al. 1988). It has been reported that cobalt acts as an antimutagen in bacterial (*S. typhimurium, B. subtilis, E. coli*) and yeast test systems

Table 3-5. Genotoxicity of Cobalt *In Vitro*

Species (test system)	End point	Results		Reference	Valence state
		With activation	Without activation		
Stable Cobalt					
Prokaryotic organisms:					
Salmonella typhimurium (plate incorporation)	Gene mutations	No data	–	Tso and Fung 1981	II
S. typhimurium (plate incorporation)	Gene mutations	No data	–	Arlauskas et al. 1985	II
S. typhimurium (plate incorporation)	Gene mutations	No data	–	Ogawa et al. 1986	II
S. typhimurium (plate incorporation)	Gene mutations	No data	+	Schultz et al. 1982	III
Bacillus subtilis (rec assay)	Gene mutations	No data	(+)	Kanematsu et al. 1980	II
Escherichia coli (reversion assay)	Gene mutations	No data	–	Kanematsu et al. 1980	II
E. coli (repair assay)	DNA damage	No data	+	Schultz et al. 1982	III
Eukaryotic organisms:					
Fungi:					
Saccharomyces cerevisiae (plate assay)	Reversion	No data	–	Kharab and Singh 1985	II
S. cerevisiae (plate assay)	Reversion	No data	–	Fukunaga et al. 1982	II
S. cerevisiae (plate assay)	Reversion	No data	–	Singh 1983	II
S. cerevisiae (plate assay)	Conversion	No data	+	Kharab and Singh 1985	II
S. cerevisiae (plate assay)	Conversion	No data	+	Fukunaga et al. 1982	II
S. cerevisiae (plate assay)	Conversion	No data	+	Singh 1983	II
Mammalian cells:					
Hamster ovary cells	Clastogenic effects	No data	+	Hamilton-Koch et al. 1986	II
Hamster embryo cells	Transformation	No data	+	Costa et al. 1982	II
Human lymphocytes	Sister chromatid exchange	No data	+	Andersen 1983	II
Human HeLa cells	Inhibition of DNA synthesis	No data	+	Painter and Howard 1982	II
Human diploid fibroblasts	DNA damage	No data	+	Hamilton-Koch et al. 1986	II

Table 3-5. Genotoxicity of Cobalt *In Vitro*

Species (test system)	End point	Results		Reference	Valence state
		With activation	Without activation		
Radioactive Cobalt					
Mammalian cells:					
Chinese hamster ovary cells	DNA amplification	No data	+	Luecke-Huhle et al. 1986	N/A
Hamster embryo cells	DNA amplification	No data	+	Luecke-Huhle et al. 1990	N/A
Mouse lymphosarcoma cells	Chromosomal aberrations	No data	+	Juraskova and Drasil 1987	N/A
Mouse lymphosarcoma cells	Sister-chromatid exchanges	No data	+	Juraskova and Drasil 1987	N/A
Human lymphocytes	Chromosomal aberrations	No data	+	Koksal et al. 1995	N/A
Human lymphocytes	Micronucleus formation	No data	+	Koksal et al. 1996	N/A
Human leukocytes	DNA strand breaks	No data	+	Rueff et al. 1993	N/A
Human leukocytes	Chromosomal aberrations	No data	+	Rueff et al. 1993	N/A
Human leukocytes	Chromosome breaks	No data	+	Lindahl-Kiessling et al. 1970	N/A
Human fibroblasts	Transformation	No data	+	Namba et al. 1981	N/A
Human fibroblasts	Transformation	No data	+	Namba et al. 1985	N/A
Human fibroblasts	DNA strand breaks	No data	+	Coquerelle et al. 1987	N/A
Human fibroblasts	Transformation	No data	+	Namba et al. 1988	N/A
Human fibroblasts	Retinoblastoma gene alterations	No data	+	Endo et al. 1993	N/A
Human fibroblasts	DNA strand breaks	No data	+	Dolling et al. 1998	N/A
Human kidney cells	DNA strand breaks	No data	+	Feinendegen et al. 1977	N/A
Human kidney cells	DNA strand breaks	No data	+	Feinendegen et al. 1978	N/A

DNA = deoxyribonucleic acid; + = positive results; – = negative results; (+) = weakly positive results

(*Saccharomyces cerevisiae*) (Inoue et al. 1981; Kada et al. 1986; Kuroda and Inoue 1988). A possible explanation was that cobalt acts by correcting the error-proneness of deoxyribonucleic acid (DNA) replicating enzymes by improving their performance in DNA synthesis (Inoue et al. 1981; Kada et al. 1986; Kuroda and Inoue 1988). However, cobalt has also been shown to increase the frequency of genetic conversions in *S. cerevisiae* (Kharab and Singh 1985; Singh 1983). The reasons for this apparent dichotomy in yeast cells is not known.

In contrast to the results seen in bacteria, stable cobalt compounds were generally found to be genotoxic or mutagenic in mammalian assay systems. Exposure to cobalt compounds (metal, salts, or hard metal) has been shown to produce clastogenic effects in mammalian cells, including human lymphocytes (Anard et al. 1997; Hamilton-Koch et al. 1986; Painter and Howard 1982); transformation in hamster cells (Costa et al. 1982); sister chromatid exchanges in human lymphocytes (Andersen 1983); and micronucleus formation in mouse bone marrow cells (Suzuki et al. 1993) and human lymphocytes (Capomazza and Botta 1991; Olivero et al. 1995; Van Goethem et al. 1997). Hard metal is generally more genotoxic in *in vitro* tests than other cobalt compounds. Cobalt ions are also thought to inhibit DNA repair in mammalian cells by interaction with zinc-finger proteins involved in DNA excision repair (Asmuß et al. 2000; De Boeck et al. 1998; Hartwig et al. 1991; Kasten et al. 1997; Sarkar 1995).

Thirty hours following single intraperitoneal injection of cobalt(II) chloride in BALB/c mice, an increase in micronucleus formation was seen at 12.4 or 22.3 mg cobalt/kg (as cobalt chloride), but not at 6.19 mg/kg (Suzuki et al. 1993). Single injection of mg cobalt/kg (as cobalt chloride) resulted in significantly increased micronucleus formation at 24 hours post-injection, but not at 12, 48, 72, or 96 hours. Two or 10 days following intraperitoneal injection of male and female F344 rats with 3 or 6 mg cobalt/kg, increased levels of oxidatively-damaged DNA bases were noted in the liver, kidney, and to a lesser extent, the lung (Kasprzak et al. 1994).

Radioactive Cobalt. The ability of ionizing radiation to induce genotoxic damage is well-documented (Agency for Toxic Substances and Disease Registry 1999). Chang et al. (1999c) reported increased micronucleus frequency, both of single and multiple nucleates, in 48 people who had been exposed to 12–1,600 rad (0.12–16 Gy) over a 2–10-year period as a result of a building contaminated with ^{60}Co-containing steel. Subjects who had left the building showed a decrease in micronucleus formation that correlated with time since cessation of exposure. Three workers accidentally exposed to 2.2–12.7 rad (0.022–0.127 Gy) showed no elevation in frequency of chromosome alterations (House et al. 1992). Ten

children who received chemotherapy and 1,725–2,405 rad (17.25–24.05 Gy) as cobalt radiotherapy for acute lymphatic leukemia showed no clastogenic changes after chemotherapy but before irradiation. After radiotherapy, significant dose-related increases in chromosomal aberrations were seen (Rauscher and Bauchinger 1983).

Radiation from cobalt isotopes has been shown to induce numerous genetic changes, including translocations (Gilot-Delhalle et al. 1988; Grahn and Carnes 1988; Grahn et al. 1983; Searl et al. 1976), decreased DNA synthesis (Lohmann et al. 1966), dominant lethal mutations (Grahn et al. 1988; Searl et al. 1976; Zhou et al. 1986), chromosome deletions (Brooks et al. 1971b, 1974), polycentrics (Brooks et al. 1971a, 1974), and aberrations (Brooks et al. 1971a, 1971b) in exposed animals.

Radiation from cobalt isotopes was genotoxic in several assay systems in mammalian cells: DNA amplification in hamster cells (Lucke-Huhle et al. 1986, 1990); chromosomal aberrations and sister-chromatid exchanges in mouse lymphosarcoma cells (Juraskova and Drasil 1987); chromosomal aberrations and micronucleus formation in human lymphocytes (Koksal et al. 1995, 1996; Schmid et al. 2002); DNA breakage in human leukocytes (Lindahl-Kiessling et al. 1970; Reuff et al. 1993), kidney cells (Feinendegen et al. 1977), and fibroblasts (Coquerelle et al. 1987; Dolling et al. 1998); chromosomal aberrations in human leukocytes (Reuff et al. 1993); transformation of human fibroblasts (Namba et al. 1981, 1985, 1988); and retinoblastoma gene alterations in human fibroblasts (Endo et al. 1993).

3.5 TOXICOKINETICS

3.5.1 Absorption

3.5.1.1 Inhalation Exposure

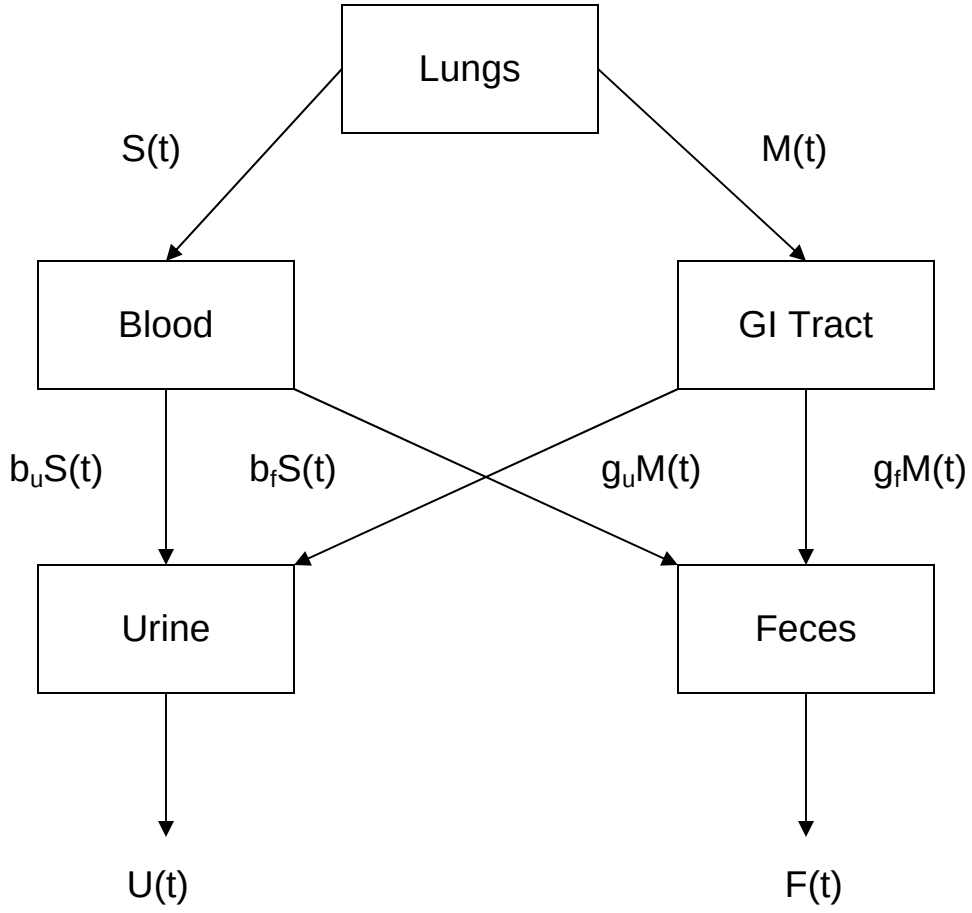
Inhaled cobalt particles are deposited in the upper and lower respiratory tract and cobalt is subsequently absorbed by several mechanisms (Casarett and Doull 1986); however, two of these mechanisms in particular appear to be most relevant. The deposition pattern in the respiratory tract is related to particle size, which determines the degree to which particles are affected by inertial impaction, sedimentation, diffusion, and electrostatic precipitation. Large particles (diameter >2 μm) tend to deposit in the upper respiratory tract where high airstream velocities and airway geometry promote inertial impaction of larger particles. Smaller particles escape inertial impaction and enter the lower respiratory tract where lower

airstream velocities and airway geometry favor the process of sedimentation, diffusion, and electrostatic precipitation of small particles. Fractional deposition can be expected to vary considerably with age, particle size, and breathing patterns (see Table 3-10). Fractional deposition of inhaled cobalt oxide particles in humans varied from approximately 50% of the inhaled dose for particles with a geometric mean diameter of 0.8 µm to approximately 75% of the inhaled dose for particles with a geometric mean diameter of 1.7 µm (Foster et al. 1989).

The transfer pathways of cobalt oxide (^{57}Co used as a tracer) from the lungs in humans and animals are shown in Figure 3-4. Particles of cobalt deposited in the respiratory tract can be absorbed into the blood after dissolution (S(t)) or mechanically transferred to the gastrointestinal tract by mucociliary action of the respiratory tract and swallowing action (M(t)). Only a portion (probably <50%) of the cobalt that enters the gastrointestinal tract will be absorbed into the body. The relative magnitude of the translocation and mechanical clearance pathways depends on the size and solubility of the cobalt particles that are inhaled. Large particles (>2 µm) will tend to deposit in the middle and upper airways where mechanical clearance mechanisms predominate over translocation. Smaller particles that enter the lower respiratory tract will tend to remain until dissolved or phagocytized by macrophages and translocation occurs. The sum of the activities of translocation and mechanical clearance determine the kinetics of absorption of inhaled cobalt. In humans, the ratio of translocation (S(t)) to mechanical clearance (M(t)) is approximately 5–1 for particle sizes ranging from 0.8 to 1.7 µm (mean geometric diameter) (Foster et al. 1989).

Data on retention of cobalt oxide (^{57}Co used as a tracer) in the respiratory tracts of humans and several animal species are summarized in Table 3-6. Considerable variability exists among species. In humans, almost one-half of the original lung burden persisted 6 months after exposure; in rats, clearance of cobalt from the lungs was nearly complete after 6 months. The elimination half-time for cobalt in the human lung increased with increasing time after exposure (Foster et al. 1989; Sedlet et al. 1958). This may reflect slower clearance of cobalt that is bound to cellular components in the lung (Kreyling et al. 1985, 1986).

Figure 3-4. Transfer Parameters for Cobalt Following Inhalation of Cobalt Oxide* (CO_3O_4) Particles, Showing the Fractions of the Lung Content, L(t), and Time, t, Cleared Per Day by Each Route**



GI tract = gastrointestinal tract;
$b_fS(t)$ = fraction of cobalt excreted in the feces after translocation;
$b_uS(t)$ = fraction of cobalt excreted in the urine after translocation;
F(t) = fecal excretion rate;
$g_fM(t)$ = fraction of cobalt excreted in the feces after mechanic clearance to the gastrointestinal tract;
$g_uM(t)$ = fraction of cobalt excreted in the urine after mechanic clearance to the gastrointestinal tract;
M(t) = rate of mechanical transport of cobalt particles from the lungs to the gastrointestinal tract;
S(t) = rate of translocation of cobalt from the lungs to the blood;
U(t) = urinary excretion rate

*Cobalt-57 tracer used
**Derived from Bailey et al. 1989

Table 3-6. Initial (Day 3) Lung Deposits of Cobalt Oxide and Summary of Lung Retention at 90 and 180 Days[a,b]

	Mean initial ^{57}Co activity in lung L(3) (kBq)		Lung retention L(90)/L(3) (%)		Lung retention L(180)/L(3) (%)	
Species (strain)	0.8 µm	1.7 µm	0.8 µm	1.7 µm	0.8 µm	1.7 µm
Human	53	42	64	75	45	56
Baboon	2,100	1,700	55	55	26	37
Beagle dog	1,150	1,450	27	45	5.5	12
Guinea pig (Harwell)	8.4	1.4	49	46	8.3	15
Rat (HMT, 1985)	10.8	4.7	5.2	20	1.3	8.0
Rat (HMT, 1986)	3.2	0.7	5.3	18	1.2	9.2
Rat (F344, SPF)	8.8	4.4	14	25	4.7	9.2
Rat (Sprague-Dawley)	0.9	0.10	8	39	1	15
Syrian hamster	4.0	1.2	21	35	3.4	12
Mouse (CBA/H)	1.8	No data	15	No data	2.8	No data

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer

3.5.1.2 Oral Exposure

Gastrointestinal absorption of cobalt in humans varies considerably (18–97% of the given dose) based on the type and dose of cobalt compound given and the nutritional status of the subjects (Harp and Scoular 1952; Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). More cobalt was absorbed through the gastrointestinal tract of humans when the body was deficient in iron (31–71% in iron deficiency; 18–44% in controls) (Sorbie et al. 1971; Valberg et al. 1969). One study in humans has shown that oral exposure to cobalt chloride resulted in significantly higher urinary excretion in females relative to males (Christensen et al. 1993).

In animal studies, many factors have been shown to influence the absorption of cobalt compounds following oral exposure. In several studies in rats (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Schade et al. 1970; Taylor 1962), soluble cobalt chloride was absorbed in the range of 13–34%, whereas physiologically insoluble cobalt oxide particles have been shown to be poorly absorbed, in the range of 1–3% (Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989). The particle size of the given dose of cobalt oxide had no significant effect on gastrointestinal absorption (Table 3-7). Administration of cobalt chloride labeled with radioactive 58Co and complexed with histidine, lysine, glycylglycine, ethylenediaminetetraacetic acid (EDTA), casein, or glycine resulted in decreased gastrointestinal absorption of cobalt; administration of cobalt chloride (with 58Co tracer) in cows' milk permitted a significantly greater (about 40%) absorption through the gastrointestinal tract (Taylor 1962). The same study found that while there was no difference in the chlorides of cobalt(II) and cobalt(III), a cobalt(II) glycine complex was absorbed in greater quantities than a cobalt(III) glycine complex. Other studies have also demonstrated that the chemical form of the cobalt compound can affect the absorption of cobalt following oral exposure (Deka et al. 1981; Firriolo et al. 1999; Inaba et al. 1980; Kinoshita and Fujita 1972), with more water-soluble compounds generally showing greater absorption.

Iron deficiency led to increased absorption of cobalt from the gastrointestinal tract, and simultaneous administration of cobalt and iron reduced the amount of cobalt absorbed (Reuber et al. 1994; Schade et al. 1970). Increasing oral doses of cobalt resulted in decreased fractional absorption (Houk et al. 1946; Kirchgessner et al. 1994; Taylor 1962), and more soluble forms of cobalt were better absorbed than less soluble compounds (Kreyling et al. 1986). Absorption is 3- to 15-fold greater in younger animals (rats and guinea pigs examined from days 1–60 of life) than in adult (200 days of age) animals (Naylor and

Table 3-7. Summary of Measurements of Retention and Excretion After Intragastric Administration of Cobalt Oxide (Co_3O_4) Particles (Mean Percentage of Recovered Activity at 7 Days After Administration)[a,b]

Species (strain)	Cumulative fecal excretion		Whole body retention		Cumulative urinary excretion		Absorption	
	0.8 µm	1.7 µm	0.8 µm	1.7 µm	0.8 µm	1.7 µm	0.8 µm	1.7 µm
Baboon	97.8	98.4	0.12	0.20	2.0	1.4	2.6	1.9
Guinea pig	98.7	97.6	0.16	0.66	1.1	1.9	1.3	2.3
Rat (HMT)	96.3	99.4	0.09	0.02	2.8	0.6	3.9	1.0
Rat (F-344)	99.6	99.7	0.04	0.03	0.4	0.3	0.4	0.3
Hamster	96.0	96.3	0.50	0.18	3.5	3.5	5.1	5.1
Mouse (CBA/H)	99.1	No data	0.3	No data	0.6	No data	0.8	No data

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer

Harrison 1995). Species differences in absorption of cobalt oxide do not appear to exist (Bailey et al. 1989), but absorption of soluble cobalt compounds is greater in rats (13–34%) than in dairy cows (1–2%) and guinea pigs (4–5%) following oral exposure (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Naylor and Harrison 1995; Schade et al. 1970; Taylor 1962; van Bruwaene et al. 1984).

3.5.1.3 Dermal Exposure

Four humans who placed their right hands into a box filled with hard metal dust (~5–15% cobalt metal, 95–85% tungsten carbide) for 90 minutes showed an increase in urinary cobalt levels by an order of magnitude in the post-exposure samples, remaining elevated for as long as 48–60 hours (Scansetti et al. 1994). Similarly, cobalt was detected in the fingernails of three volunteers who placed their fingers in cobalt solution 10 minutes/day for 7 days (Nielsen et al. 2000), even after the cessation of exposure. These findings demonstrate that cobalt from these metal dusts can be absorbed through the skin. The absorption of $2.2x10^{-5}$ mg ^{60}Co/kg as cobalt chloride in 1.4N HCl through 1 cm^2 of intact or abraded skin of guinea pigs was examined by Inaba and Suzuki-Yasumoto (1979). Absorption through intact skin was very small (<1%), while absorption through abraded skin was almost 80% 3 hours after exposure. A study in hamsters (Lacy et al. 1996) also reported a low amount of absorption of cobalt through unabraded skin.

3.5.1.4 Other Routes of Exposure

No studies were located regarding absorption of cobalt in humans or animals after other routes of exposure.

3.5.2 Distribution

As a component of vitamin B_{12}, cobalt is an essential element and, therefore, is found in most body tissues. It has been identified in liver, muscle, lung, lymph nodes, heart, skin, bone, hair, stomach, brain, pancreatic juice, kidneys, plasma, and urinary bladder of nonexposed subjects, with the highest cobalt concentration found in the liver (Collecchi et al. 1986; Forbes et al. 1954; Hewitt 1988; Ishihara et al.

1987; Muramatsu and Parr 1988; Teraoka 1981; Yamagata et al. 1962; Yukawa et al. 1980) (see Chapter 6 for more information). Tissue levels reflected exposure from all routes. The total body content of cobalt has been estimated at 1.1–1.5 mg (ICRP 1979; Yamagata et al. 1962); about 0.11 mg was found in the liver (ICRP 1979).

In patients with laryngeal carcinoma, levels of cobalt in the tumor were significantly higher ($p<0.001$) than levels in the nonmalignant tissues around the tumor (68.7 ng/g tissue versus 39.6 ng/g) (Collecchi et al. 1986). The mean cobalt concentrations in plasma (18.3 ng/mL) were also significantly higher in these patients than in the comparison population (0.73 ng/mL). The clinical significance of these findings is not known.

3.5.2.1 Inhalation Exposure

In workers occupationally exposed to airborne cobalt, increased cobalt levels were found in tissues at death. Significant increases in cobalt in the lung have been found in copper smelter and metal workers and coal miners occupationally exposed to cobalt (Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Teraoka 1981). No increase in liver or kidney cobalt levels were found in the copper smelter workers as compared to controls (Gerhardsson et al. 1984). In metal workers, increased cobalt levels were also found in the lymph nodes, liver, spleen, and kidneys (Hillerdal and Hartung 1983; Teraoka 1981).

The tissue distribution of cobalt in animals is similar to that in humans, with marked increases in the concentration of cobalt in the lungs following inhalation exposure (Barnes et al. 1976; Brune et al. 1980; Collier et al. 1991; Kreyling et al. 1986; Kyono et al. 1992; Patrick et al. 1989; Talbot and Morgan 1989). Histologically, the particles of cobalt in the lung are found in macrophages within the bronchial wall or in the interstitium close to the terminal bronchioli (Brune et al. 1980). Significant concentrations of cobalt have been found in the liver, kidney, trachea, spleen, bones, and heart (Barnes et al. 1976; Brune et al. 1980; Kerfoot 1975; Kreyling et al. 1986; Wehner and Craig 1972), with the greatest concentrations in the liver and the kidney (Kerfoot 1975; Wehner and Craig 1972).

3.5.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to cobalt.

In animals, the cobalt absorbed through the gastrointestinal tract was primarily retained in the liver (Ayala-Fierro et al. 1999; Greenberg et al. 1943; Simesen 1939). Appreciable levels were also found in the kidneys, heart, stomach, and intestines (Ayala-Fierro et al. 1999; Persson et al. 1992; Simesen 1939). Following a single oral dose of cobalt napthenate, appreciable levels of cobalt were found in the heart, liver, and kidney, but not in the spleen or testes (Firriolo et al. 1999). Following oral exposure to pregnant rats, a dose-dependent increase in cobalt levels in fetal blood and amniotic fluid was seen (Szakmary et al. 2001).

Following longer-term exposure (8 weeks) to cobalt sulfate in the diet, exposed rats showed a 30-fold increase in the cobalt concentration in the myocardium, a 26-fold increase in the concentration in the soleus muscle, and a 100-fold increase in the concentration in serum compared with nonexposed controls (Clyne et al. 1988; Pehrsson et al. 1991). Long-term oral exposure of rats to cobalt chloride resulted in significantly increased levels of cobalt in the liver, kidney, muscle, brain, and testes of treated rats (Barnaby et al. 1968; Bourg et al. 1985; Thomas et al. 1976).

3.5.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to cobalt.

3.5.2.4 Other Routes of Exposure

Following intravenous injection of cobalt chloride (as a combination of radioactive $^{55}CoCl_2$ and $^{56}CoCl_2$) in two humans, the liver and bladder contained the highest portions of cobalt (Jansen et al. 1996).

Distribution in animals after an intravenous dose appears to be similar to what we know of cobalt distribution in humans following injection of cobalt compounds. Two hours after intravenous injection of cobalt chloride (with a radioactive ^{57}Co tracer) in rats, accumulation was found in the liver (22.8% of the dose), kidneys (10.2%), and intestines (3.16%) (Gregus and Klaassen 1986). Similar results (29% liver,

10% kidneys, 4.6% intestines) were found following intracardiac injection of cobalt nitrate in rats (Patrick et al. 1989) or intravenous injection of a combination of radioactive $^{55}CoCl_2$ and $^{56}CoCl_2$ in rats (exact percentages were not provided) (Jansen et al. 1996). One hundred days after intravenous injection of $^{60}CoCl_2$ in rats, the greatest concentrations were found in spleen>heart>bone, while liver and kidney, initially the highest in cobalt, contained comparatively low amounts of cobalt (Thomas et al. 1976). Similar results were seen 132 days following an intraperitoneal injection of $^{60}CoCl_2$ in rats (Barnaby et al. 1968). Intramuscular injection of cobalt mesoporphyrin in rats yielded the greatest levels of cobalt in liver and blood, followed by kidney, lung, spleen, adrenal glands, and heart at 7 days post-injection and later (Feng et al. 1998). Four weeks after subcutaneous administration of cobalt protoporphyrin, the greatest tissue levels of cobalt occurred in the kidney, followed by spleen, liver, lung, thymus, and gonads (Rosenberg 1993). When cobalt (with a ^{57}Co tracer) encapsulated in liposomes was intravenously injected into rats, decreased distribution to the heart (40% less than animals receiving cobalt chloride), kidneys, and carcass, and increased distribution to the spleen and bones were found (Szebeni et al. 1989).

3.5.3 Metabolism

Cobalt is essential in the body because it is a component of cyanocobalamin (vitamin B_{12}) (Vouk 1986). Vitamin B_{12} acts as coenzyme in many enzymatic reactions, most notably a methyl transfer reaction that converts homocysteine to methionine and for a separate reaction that converts L-methylmalonylcoenzyme A (CoA) to succinyl-CoA (Institute of Medicine 2000). Vitamin B_{12} is also a part of some enzymes involved in hematopoiesis; deficiency can lead to pernicious anemia (Domingo 1989). No other essential function of cobalt has been reported. The Recommended Dietary Allowance (RDA) for vitamin B_{12} for adults is 2.4 µg/day, which contains 0.1 µg of cobalt (Institute of Medicine 2000).

3.5.4 Elimination and Excretion

3.5.4.1 Inhalation Exposure

No data are available on the clearance of soluble cobalt particles in humans. Following exposure of humans to physiologically insoluble cobalt compounds (cobalt metal, cobalt oxides), clearance from the body, assessed by both urinary/fecal clearance and a reduction in whole-body retention, appears to follow

three-phase kinetics. The first phase, likely representing mucociliary clearance of particles deposited in the tracheobronchial region, has a half-time on the order of 2–44 hours (Apostoli et al. 1994; Mosconi et al. 1994b). The second phase, with a half-time on the order of 10–78 days, may represent macrophage-mediated clearance of cobalt particles from the lung (Beleznay and Osvay 1994; Mosconi et al. 1994b). The third clearance phase, representing long-term clearance from the lungs, has a half-time on the order of years (Bailey et al. 1989; Beleznay and Osvay 1994; Mosconi et al. 1994b; Newton and Rundo 1971). Following a controlled aerosol exposure in humans, about 40% of the initial lung burden of inhaled cobalt oxide (with a 57Co tracer) was retained for a period of 6 months after exposure (Foster et al. 1989). Within the first week, about 17% of the initial lung burden was eliminated, with the majority (about 90%) mechanically cleared to the gastrointestinal tract and excreted in the feces (Foster et al. 1989). Six months after exposure, a cumulative elimination of 33% of the initial lung burden was found in the urine and 28% was found in the feces (Foster et al. 1989). The ratio of peak absorption rate to average mechanical clearance rate (Figure 3-4 and Table 3-8) was about 5 to 1. The elimination of cobalt following inhalation exposure was affected by the time after exposure (urinary excretion increases as time increases) and particle size (more cobalt is initially mechanically cleared to the gastrointestinal tract when the aerosol consists of bigger particles) (Bailey et al. 1989; Foster et al. 1989).

In animals, the solubility of the cobalt compound appears to greatly affect its long-term clearance. Studies with cobalt oxides have shown that the more soluble CoO is cleared from the lungs at a greater rate than the less soluble Co_3O_4 (Barnes et al. 1976; Kreyling 1984a). More soluble cobalt compounds are absorbed into the blood at a greater rate, and excreted in the urine and, to a lesser extent, the feces (Barnes et al. 1976). The rate of urinary excretion appears to correlate with the rate of translocation of cobalt from the lungs to the blood, and the rate of fecal clearance with the rate of mechanical clearance of cobalt from the lungs to the gastrointestinal tract (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kreyling et al. 1986, 1989; Patrick et al. 1989; Talbot and Morgan 1989). Following an initial high rate of fecal clearance, urinary excretion was the primary route of cobalt elimination after a single inhalation exposure (2 weeks of observation) (Palmes et al. 1959) or 3 months of exposure (Kerfoot 1975; Palmes et al. 1959). In several species of animals, most of the inhaled Co_3O_4 (with a ^{57}Co tracer) following a single exposure was cleared from the lungs by 6 months after exposure (Table 3-6) (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kreyling et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). The peak translocation and average mechanical clearance of cobalt from the lungs for different species are reported in Table 3-8, with the rate (high to low) following as mouse > rat > hamster > guinea pig > baboon, human > beagle dog.

Table 3-8. Peak Translocation and Average Mechanical Clearance Rates After Inhalation of Cobalt Oxide[a,b]

Species (strain)	Percent of lung content cleared per day				
	Translocation at peak				Average mechanical clearance[c]
	0.8 µm	Peak day	1.7 µm	Peak day	
Human	0.45	180	0.5	180	0.1
Baboon	0.6	180	0.2	d	0.1
Beagle dog	2.1	85	1.7	180	0.03
Guinea pig	2.1	180	1.0	75	0.3
Rat HMT	2.4	40	0.6	d	0.9
Rat (F-344)	1.1	10	0.4	d	1.0
Hamster	1.8	180	0.7	180	0.8
Mouse	1.7	180	No data	No data	1.05

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer
[c]Clearance rates were virtually identical in both particle size groups
[d]Constant value over 180 days

3.5.4.2 Oral Exposure

In humans orally exposed to cobalt, fecal elimination, which is the primary route of elimination, varies considerably (3–99% of the dose) and depends on the amount and type of cobalt given and on the nutritional status of the subjects (Section 3.5.1.2) (Harp and Scoular 1952; Paley et al. 1958; Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). Within days after oral exposure, 10 times more cobalt was excreted in feces than in the urine (Paley et al. 1958). Less cobalt was eliminated in the feces (more was absorbed) in subjects with an iron deficiency (Sorbie et al. 1971; Valberg et al. 1969).

Fecal elimination of cobalt is the primary route of elimination in animals following oral exposure and depends mainly upon the particle solubility (decreasing fecal clearance with increasing solubility) of the cobalt compound. The cumulative urinary and fecal elimination in several species following oral administration of Co_3O_4 (with a ^{57}Co tracer) is reported in Table 3-7 (Bailey et al. 1989). Following oral administration in several species, very little Co_3O_4 was absorbed through the gastrointestinal tract and most (>96%) was quickly eliminated in the feces. No significant differences in elimination of Co_3O_4 were found among species of animals (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). For the more soluble cobalt(II) chloride, reported fecal elimination levels have ranged from 70 to 83% of the administered dose for rats, with urinary excretion accounting for the majority of the remainder of the dose (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971). In lactating dairy cows, about 97% of an oral dose of cobalt chloride was recovered in the feces by day 70 post-exposure, while the urine and milk contained 0.26 and 0.012% of the dose, respectively (van Bruwaene et al. 1984). Following a single exposure in beagle dogs, more Co_3O_4 (physiologically insoluble) was eliminated in the feces (90% in the feces and 5% in the urine) than following an exposure to cobalt nitrate (soluble) (70% in the feces and 25% in the urine) (Kreyling et al. 1986).

As is the case for absorption of cobalt compounds, the iron status of the animal also appears to affect the elimination of cobalt compounds. Following oral exposure, iron-deficient rats eliminated less of a given dose in the feces than normal rats, while co-administration of iron compounds resulted in an increased fecal excretion of cobalt compounds (Reuber et al. 1994; Schade et al. 1970).

3.5.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to cobalt.

Lacy et al. (1996) reported that the majority of the absorbed dose of $CoCl_2$ was excreted in the urine 48 hours after a single dermal exposure in Syrian hamsters. No other studies were located regarding excretion in animals after dermal exposure to cobalt.

3.5.4.4 Other Routes of Exposure

Following intravenous injection of cobalt chloride in humans, about 30% of the dose was excreted in the urine within 24 hours (Smith et al. 1972), 56–73% was excreted within 48 hours (Paley et al. 1958), and 57% was excreted within 2 weeks (Kent and McCance 1941).

Following intravenous injection of cobalt nitrate (with a 57Co tracer) in various species of animals, most of the injected dose was excreted in the urine; about 80% of the given dose was excreted in the urine within 21 days (Table 3-9) (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). Other investigators have also found that the urine is the primary route of cobalt excretion following intravenous administration (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Gregus and Klaassen 1986; Kreyling et al. 1986; Onkelinx 1976; Thomas et al. 1976). Most of the remaining cobalt (5–30% of the total dose) after intravenous exposure was excreted in the feces, with the majority of studies reporting very little long-term retention. Excretion of cobalt (about 2–7% of the injected dose) in the bile was also reported (Cikrt and Tich 1981; Gregus and Klaasen 1986; Sheline et al. 1945). Elimination following intraperitoneal injection is similar to that seen following intravenous exposure, with urinary excretion being the major route of elimination, and fecal excretion accounting for the majority of the remainder of the dose (Barnaby et al. 1968; Hollins and McCullough 1971; Talbot and Morgan 1989), though long-term clearance may be more balanced between the two (Hollins and McCullough 1971). Following subcutaneous injection, both $CoCl_2$ and $Co(NO_3)_2$ were cleared rapidly from the body (Rosenberg 1993; Talbot and Morgan 1989), with the urine being the major route of clearance (Talbot and Morgan 1989).

Table 3-9. Summary of Measurements of Retention and Excretion of Cobalt Following Injection of Cobalt Nitrate $Co(NO_3)_2$ Solution (Mean Percent Recovery)[a,b]

Species (strain)	Whole body retention on day			Cumulative urinary excretion on day			Cumulative fecal excretion on day		
	1	7	21	1	7	21	1	7	21
Baboon	No data	No data	No data	57	74	80	5	17	20
Beagle dog	No data	No data	No data	71	86	87	3.4	4.4	4.9
Guinea pig	34	8	3.5	64	82	85	2.2	10	12
Rat (HMT)	18	4.2	1.9	64	72	74	18	24	24
Rat (F-344)	No data	No data	2.9	No data	No data	80	No data	No data	18
Hamster	27	4.3	1.9	55	68	69	17	28	29
Mouse	23	2.9	1.1	59	71	72	18	26	27

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer

Following injection, studies have shown that the chemical form of the cobalt compound can affect its elimination. Subcutaneous injection of cobalt protoporphyrin in rats, in which the cobalt atom is chelated within the porphyrin ring, resulted in a slower elimination from the body than cobalt chloride, with significant cobalt levels (~20% of initial injection) still present in the body 14 days after exposure (Rosenberg 1993). Likewise, intramuscular injection of cobalt mesoporphyrin resulted in primarily in fecal excretion, with a high systemic retention (Feng et al. 1998). It therefore appears that a greater solubility leads to fast elimination, mainly in the urine, while a less soluble compound will be retained for longer periods and eliminated to a greater extent in the feces.

3.5.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of

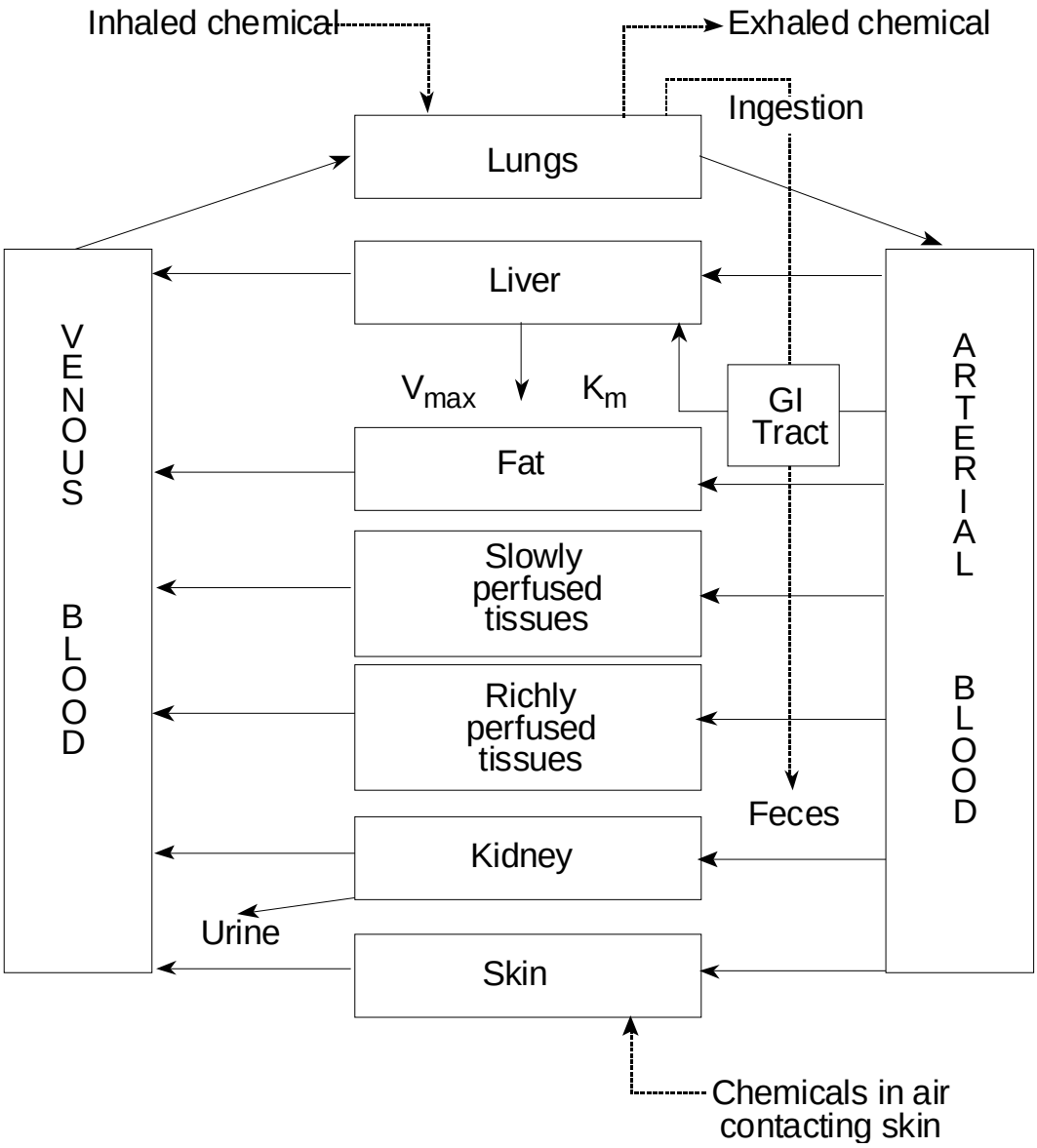
toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). Similar models have been developed for radionuclides. These PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model. Figures 3-6 through 3-9 show models for radionuclides in general or specifically for cobalt.

The ICRP (1995) developed a Human Respiratory Tract Model for Radiological Protection, which contains respiratory tract deposition and clearance compartmental models for inhalation exposure that may be applied to particulate aerosols of cobalt compounds. The ICRP (1993) also developed a 3-compartment biokinetic model for human oral exposure that applies to cobalt. EPA (1998) has adopted the ICRP (1993, 1995) models for assessment of radiologic cancer risks from cobalt exposures. The National Council on Radiation Protection and Measurement (NCRP) has also developed a respiratory tract model for inhaled radionuclides (NCRP 1997). At this time, the NCRP recommends the use of the

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

ICRP model for calculating doses for radiation workers and the general public. Readers interested in this topic are referred to NCRP Report No. 125; *Deposition, Retention and Dosimetry of Inhaled Radioactive Substances* (NCRP 1997). In the appendix to the report, NCRP provides the animal testing clearance data and equations fitting the data which supported the development of the human model for cobalt

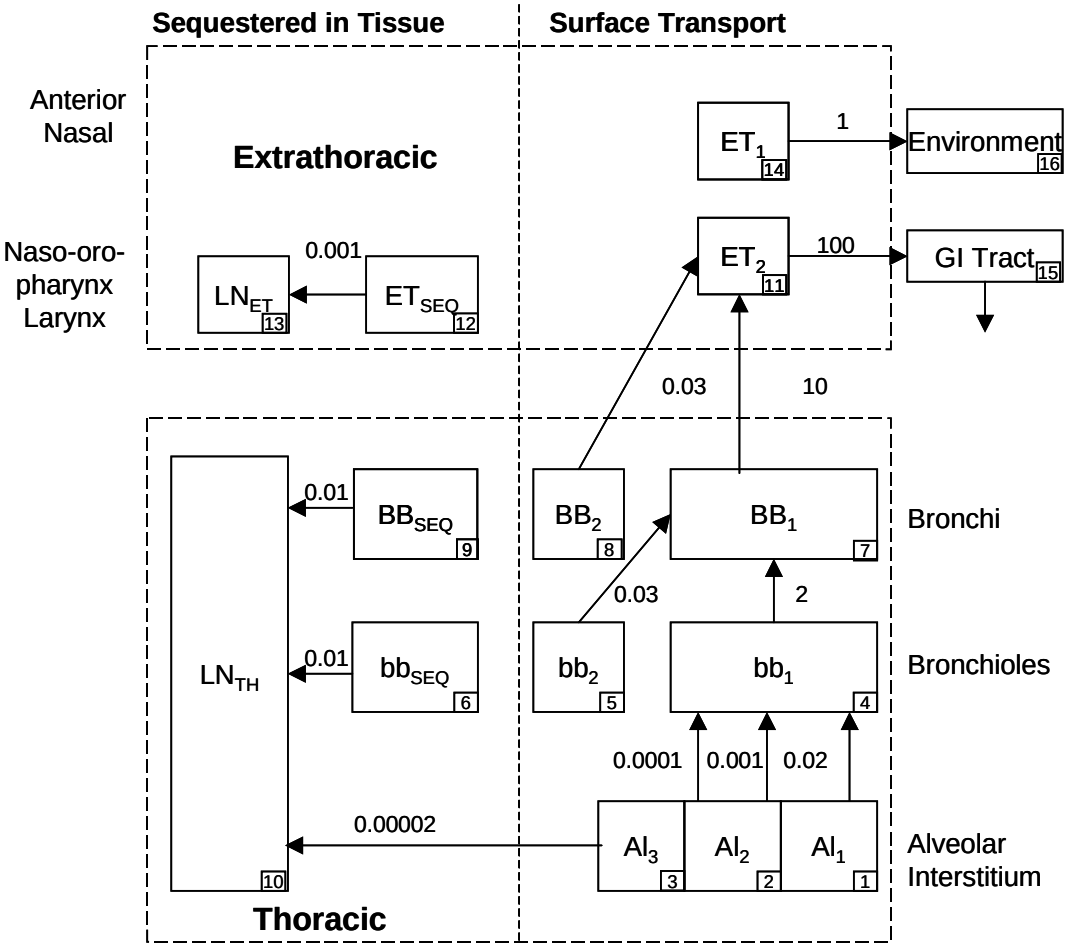
Human Respiratory Tract Model for Radiological Protection (ICRP 1994).

Respiratory Tract Deposition. The ICRP (1994) has developed a physiologically-based pharmacokinetic model for behavior of aerosols and vapors in the respiratory tract. ICRP (1994) provides inhalation dose coefficients that can be used to estimate the committed equivalent and the effective doses to organs and tissues throughout the body based on a unit intake of radioactive material and the anticipated distribution and retention of the material, its radioactive decay, and the energy of the radiationemitted from the material and absorbed by tissues. The model applies to three levels of particle solubility, a wide range of particle sizes (approximately 0.0005–100 μm in diameter), and parameter values that can be adjusted for various segments of the population (e.g., sex, age, level of physical exertion). This model also allows one to evaluate the bounds of uncertainty in deposition estimates. Uncertainties arise from natural biological variability among individuals and the need to interpret some experimental evidence that remains inconclusive. It is applicable to particulate aerosols containing cobalt, and was developed for a wide variety of radionuclides and their chemical forms.

The ICRP deposition model estimates the fraction of inhaled particle mass that initially deposits in each compartment (Figure 3-6). The model was developed with 5 compartments: (1) the anterior nasal passages (ET_1); (2) all other extrathoracic airways (ET_2) (posterior nasal passages, the naso- and oropharynx, and the larynx); (3) the bronchi (BB); (4) the bronchioles (bb); and (5) the alveolar interstitium (AI). Particles deposited in each of the regions may be removed from each region and redistributed either upward into the respiratory tree or to the lymphatic system and blood by different particle removal mechanisms.

For extrathoracic deposition of particles, the model uses experimental data, where deposition is related to particle size and airflow parameters, and scales deposition for women and children from adult male data. Similarly to the extrathoracic region, experimental data served as the basis for lung (bronchi, bronchioles, and alveoli) aerosol transport and deposition. A theoretical model of gas transport and particle deposition

Figure 3-6. Compartment Model to Represent Particle Deposition and Time-Dependent Particle Transport in the Respiratory Tract*



*Compartment numbers shown in lower right corners are used to define clearance pathways. The clearance rates, half-lives, and fractions by compartment, as well as the compartment abbreviations are presented in Table 3-11.

Source: ICRP 1994b

was used to interpret data and to predict deposition for compartments and subpopulations other than adult males. Table 3-10 provides reference respiratory values for the general Caucasian population under several levels of activity.

Deposition of inhaled gases and vapors is modeled as a partitioning process, which depends on the physiological parameters noted above as well as the solubility and reactivity of compound in the respiratory tract (Figure 3-7). The ICRP (1994) model defines three categories of solubility and reactivity: SR-0, SR-1, and SR-2:

- Type SR-0 compounds include insoluble and nonreactive gases (e.g., inert gases such as H2, He). These compounds do not significantly interact with the respiratory tract tissues and essentially all compound inhaled is exhaled. Radiation doses from inhalation of SR-0 compounds are assumed to result from the irradiation of the respiratory tract from the air spaces.

- Type SR-1 compounds include soluble or reactive gases and vapors that are expected to be taken up by the respiratory tract tissues and may deposit in any or all of the regions of the respiratory tract, depending on the dynamics of the airways and properties of the surface mucous and airway tissues, as well as the solubility and reactivity of the compound.

- Type SR-2 compounds include soluble and reactive gases and vapors that are completely retained in the extrathoracic regions of the respiratory tract. SR-2 type compounds include sulfur dioxide (SO2) and hydrogen fluoride (HF).

Respiratory Tract Mechanical (Particle) Clearance. This portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention of various chemical materials. The compartmental model is linked to the deposition model (see Figure 3-6) and to reference values presented in Table 3-11. This table provides deposition fractions and clearance rates for each compartment for insoluble particles. The table provides rates of insoluble particle transport for each of the compartments, expressed as a fraction of the deposit per day and also as clearance half-time. ICRP (1994) also developed modifying factors for some of the parameters, such as age, smoking, and disease status. Parameters of the clearance model are based on human evidence for the most part, although particle retention in airway walls is based on experimental data from animal experiments.

The clearance of deposited particles from the respiratory tract is a dynamic process. The rate of clearance generally changes with time from each region and by each route. Following deposition of large numbers

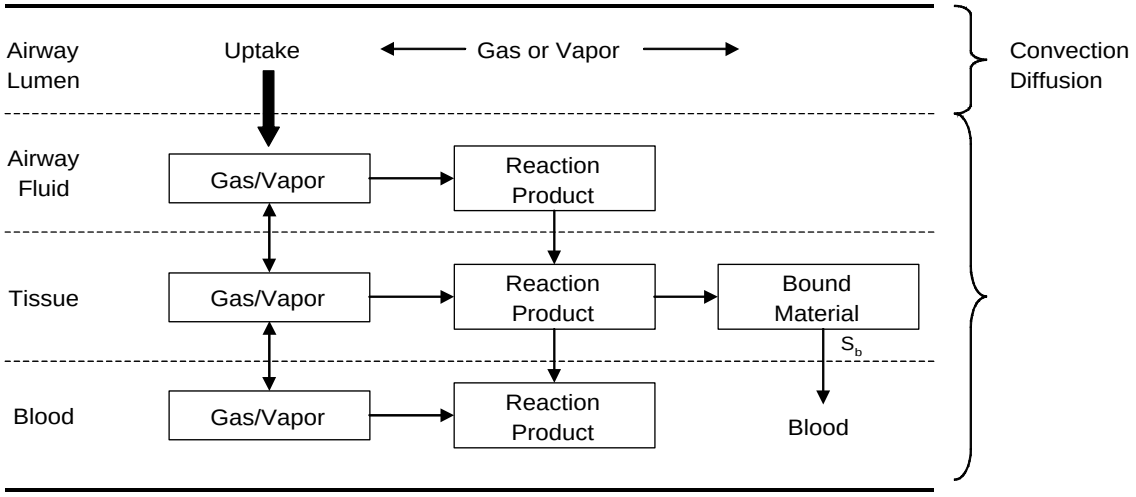
Table 3-10. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity[a]

Activity:		Resting (sleeping)			Sitting awake			Light exercise			Heavy exercise		
Maximal workload:		8%			12%			32%			64%		
Breathing parameters[b]		V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})
Age	Sex												
3 months		0.04	0.09	38	N/A	N/A	N/A	0.07	0.19	48	N/A	N/A	N/A
1 year		0.07	0.15	34	0.1	0.22	36	0.13	0.35	46	N/A	N/A	N/A
5 years		0.17	0.24	23	0.21	0.32	25	0.24	0.57	39	N/A	N/A	N/A
10 years	Male:										0.841	2.22	44
	Female:										0.667	1.84	46
	Both:	0.3	0.31	17	0.33	0.38	19	0.58	1.12	32			
15 years	Male:	0.50	0.42	14	0.533	0.48	15	1.0	1.38	23	1.352	2.92	36
	Female:	0.42	0.35	14	0.417	0.40	16	0.903	1.30	24	1.127	2.57	38
Adult	Male:	0.63	0.45	12	0.750	0.54	12	1.25	1.5	20	1.923	3.0	26
	Female:	0.44	0.32	12	0.464	0.39	14	0.992	1.25	21	1.364	2.7	33

[a]See Annex B (ICRP 1994) for data from which these reference values were derived.
[b]V_T = Tidal volume, B = ventilation rate, f_R = respiration frequency

h = hour; L = liter(s); min = minute(s); N/A = not applicable

Figure 3-7. Reaction of Gases or Vapors at Various Levels of the Gas-Blood Interface



Source: ICRP 1994b

Table 3-11. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part A

Clearance rates for insoluble particles

Pathway	From	To	Rate (d^{-1})	Half-time[a]
$m_{1,4}$	AI_1	bb_1	0.02	35 days
$m_{2,4}$	AI_2	bb_1	0.001	700 days
$m_{3,4}$	AI_3	bb_1	0.0001	7,000 days
$m_{3,10}$	AI_3	LN_{TH}	0.00002	—
$m_{4,7}$	bb_1	BB_1	2	8 hours
$m_{5,7}$	bb_2	BB_1	0.03	23 days
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 days
$m_{7,11}$	BB_1	ET_2	10	100 minutes
$m_{8,11}$	BB_2	ET_2	0.03	23 days
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 days
$m_{11,15}$	ET_2	GI tract	100	10 minutes
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 days
$m_{14,16}$	ET_1	Environment	1	17 hours

See next page for Part B

Table 3-11. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part B

Partition of deposit in each region between compartments[b]		
Region or deposition site	Compartment	Fraction of deposit in region assigned to compartment[c]
ET_2	ET_2	0.9995
	ET_{seq}	0.0005
BB	BB_1	0.993-f_s
	BB_2	f_s
	BB_{seq}	0.007
bb	bb_1	0.993-f_s
	bb_2	f_s
	bb_{seq}	0.007
AI	AI_1	0.3
	AI_2	0.6
	AI_3	0.1

[a]The half-times are approximate since the reference values are specified for the particle transport rates and are rounded in units of day^{-1}. A half-time is not given for the transport rate from AI_3 to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-time of compartment AI_3 is determined by the sum of the clearance rates from it.
[b]See paragraph 181, Chapter 5 (ICRP 1994) for default values used for relating f_s to d_{ae}.
[c]It is assumed that f_s is size-dependent. For modeling purposes, f_s is taken to be:

$$f_s = 0.5 \text{ for } d_{ae} \le 2.5\sqrt{\rho/\chi}\ \mu m \text{ and}$$

$$f_s = 0.5e^{0.63(d_{ae}\sqrt{\rho/\chi}-2.5)} \text{ for } d_{ae} > 2.5\sqrt{\rho/\chi}\ \mu m$$

where:

f_s	=	fraction subject to slow clearance
d_{ae}	=	aerodynamic particle diameter/(µm)
ρ	=	particle density (g/cm^3)
χ	=	particle shape factor

AI = alveolar-interstitial region; BB = bronchial region; bb = bronchiolar region; BB_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchial region; bb_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchiolar region; ET = extrathoracic region; Et_{seq} = compartment representing prolonged retention in airway tissue of small fraction of particles deposited in the nasal passages; LN_{ET} = lymphatics and lymph nodes that drain the extrathoracic region; LN_{TH} = lymphatics and lymph nodes that drain the thoracic region

Source: ICRP 1994

of particles (acute exposure), transport rates change as particles are cleared from the various regions. Physical and chemical properties of deposited material determine the rate of dissolution and as particles dissolve; absorption rates tend to change over time. By creating a model with sub-compartments of different clearance rates within each region (e.g., BB_1, BB_2, BBseq), the ICRP model overcomes problems associated with time-dependent functions. Each compartment clears to other compartments by constant rates for each pathway.

Particle transport from all regions is toward both the lymph nodes and the pharynx, and a majority of deposited particles end up being swallowed. In the front part of the nasal passages (ET_1), nose blowing, sneezing, and wiping remove most of the deposited particles. Particles remain here for about a day. For particles with AMADs a few micrometers or greater, the ET_1 compartment is probably the largest deposition site. The majority of particles deposited at the back of the nasal passages and in the larynx (ET_2) are removed quickly by the fluids that cover the airways. In this region, particle clearance is completed within 15 minutes. Ciliary action removes deposited particles from both the bronchi and bronchioles. Though it is generally thought that mucocilliary action rapidly transports most particles deposited here toward the pharynx, a fraction of these particles are cleared more slowly. Evidence for this is found in human studies. For humans, retention of particles deposited in the lungs (BB and bb) is apparently biphasic. The “slow” action of the cilia may remove as many as half of the bronchi- and bronchiole-deposited particles. In human bronchi and bronchiole regions, mucus moves more slowly the closer to the alveoli it is. For the faster compartment, it has been estimated that it takes about 2 days for particles to travel from the bronchioles to the bronchi and 10 days from the bronchi to the pharynx. The second (slower) compartment (BB_2 and bb_2) is assumed to have fractions of the inhaled particles, depending on the particle size, deposited in BB_2 and bb_2; both have clearance half-times estimated at 20 days. A small fraction of particles deposited in the BB and bb regions is retained in the airway wall for even longer periods (BBseq and bbseq).

If particles reach and become deposited in the alveoli, they tend to stay imbedded in the fluid on the alveolar surface or move into the lymph nodes. The one mechanism by which particles are physically resuspended and removed from the AI region is coughing. For modeling purposes, the AI region is divided into three subcompartments to represent different clearance rates, all of which are slow.

Particle clearance from the alveolar-interstitial region has been measured in human subjects. The ICRP model uses 2 half-times to represent clearance: about 30% of the particles have a 30-day half-time, and

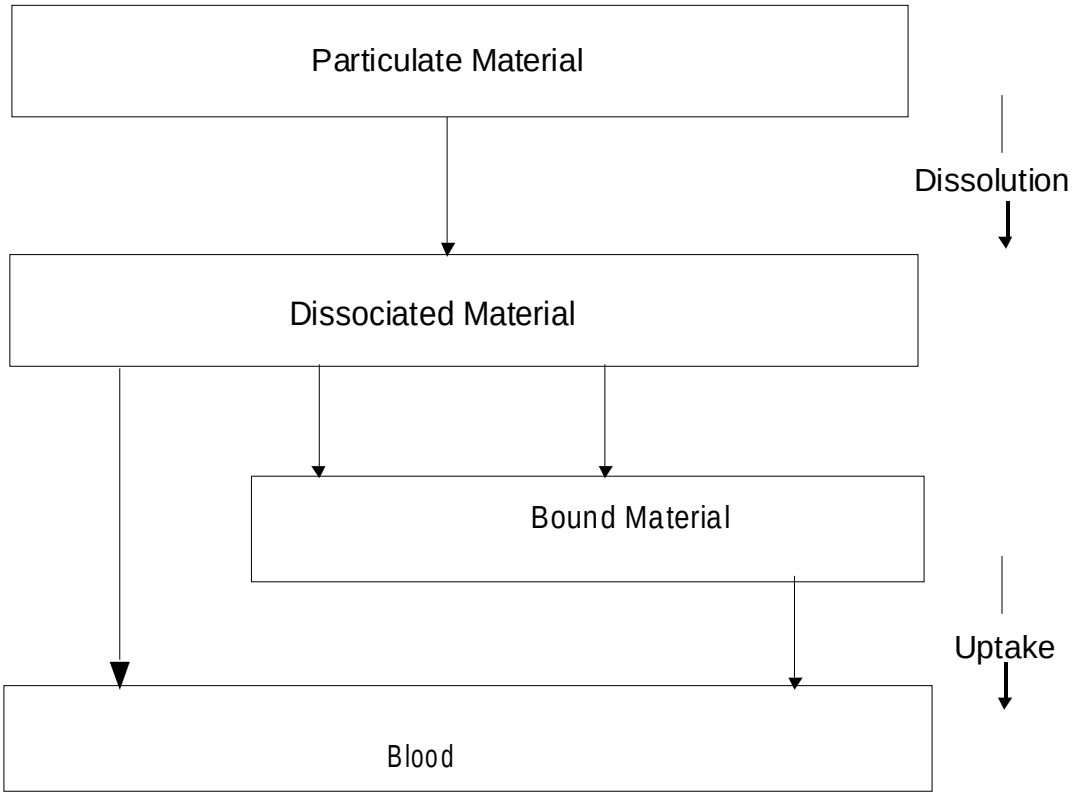
the remaining 70% are given a half-time of several hundred days. Over time, the AI particle transport rate falls and some compounds have been found in lungs 10–50 years after exposure.

Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages (ET_1), where no absorption occurs. It is essentially a 2-stage process, as shown in Figure 3-8. First, there is a dissociation (dissolution) of particles; then, the dissolved molecules or ions diffuse across capillary walls and are taken up by the blood. Immediately following dissolution, rapid absorption is observed. For some elements, rapid absorption does not occur because of binding to respiratory-tract components. In the absence of data for specific compounds, the model uses the following default absorption rate values for those compounds that are classified as Types F (fast), M (medium), S (slow), and V (instantaneous):

- For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB, bb, and AI regions, and 50% of material deposited in ET_2. Thus, for nose breathing, there is rapid absorption of approximately 25% of the deposit in ET and 50% for mouth breathing.
- For Type M, about 70% of the deposit in AI reaches the blood eventually. There is rapid absorption of about 10% of the deposit in BB and bb, and 5% of material deposited in ET_2. Thus, there is rapid absorption of approximately 2.5% of the deposit in ET for nose breathing, and 5% for mouth breathing.
- For Type S, 0.1% is absorbed within 10 minutes and 99.9% is absorbed within 7,000 days, so there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI reaches the blood eventually.
- For Type V, complete absorption (100%) is considered to occur instantaneously.

ICRP (1995) considers the experimental and human data to support the following classifications: cobalt chloride and nitrate, Type F; cobalt oxides, Type M or S; cobalt in fused aluminosilicate or polystyrene, Type S; cobalt in mineral dusts such as fly ash and volcanic ash, Type M; cobalt metal and metal alloys, M or S. ICRP (1995) recommends assigning all cobalt aerosols to Type M in the absence of specific information supporting an alternative classification.

Figure 3-8. The Human Respiratory Tract Model: Absorption into Blood



Source: ICRP 1994

ICRP (1993) Cobalt Biokinetics Model.

Description of the model.

ICRP (1979, 1993) developed a 3-compartment model of the kinetics of ingested cobalt in humans that is applicable to infants, children, adolescents, and adults. Absorption of ingested cobalt is assumed to be 60% in infants up to 3 months of age, 30% from 3 months to 15 years of age, and 10% after age 15 years. Absorbed cobalt is assumed to distribute as follows: 50% is excreted (urine and feces combined in a 6:1 ratio), 5% is transferred to the liver, and 45% is transferred to other tissues (Figure 3-9). Elimination from tissue compartments is described by three first order rate constants representing slow, medium, and fast elimination pools with half-times of 6, 60, and 800 days, respectively. The elimination half-times are assumed to be independent of age.

Validation of the model.

The extent to which the ICRP model has been validated is not described in ICRP (1993).

Risk assessment.

The model has been used to establish radiation dose equivalents (Sv/Bq) of ingested ^{57}Co, ^{58}Co, and ^{60}Co for ages 3 months to 70 years (ICRP 1993).

Target tissues.

The model can be used to estimate the radiation dose from cobalt radionuclides to all major organs and can be applied to environmental and occupational exposures.

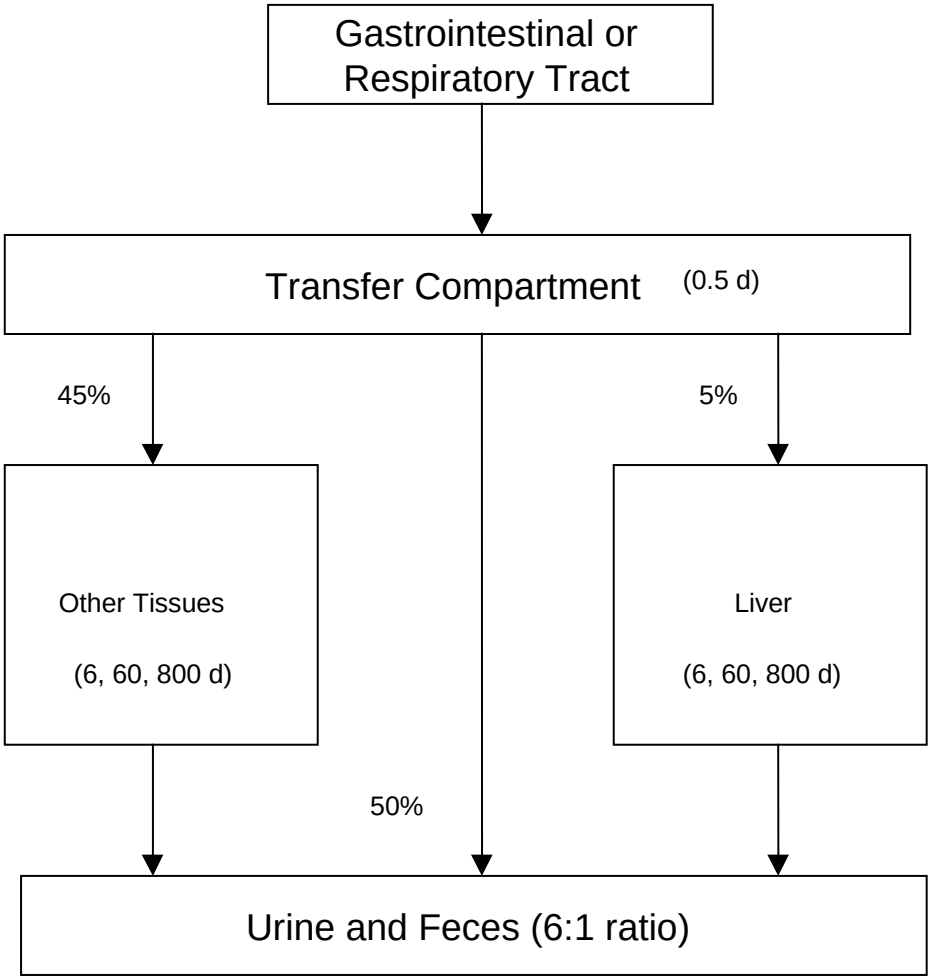
Species extrapolation.

The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

*Inter*route extrapolation.

The model is designed to simulate oral exposures to cobalt and cannot be applied to other routes of exposure without modification.

Figure 3-9. ICRP Biokinetics Model for Cobalt



Absorbed cobalt enters a virtual transfer compartment from which unidirectional transfer to tissues is assumed to occur. Percentages shown are of the initial amounts absorbed. Numbers in parentheses are elimination half-times to urine and feces combined (d=days. Liver other tissues are assumed to have fast, medium, and slow elimination pools.

3.6 MECHANISMS OF ACTION

3.6.1 Pharmacokinetic Mechanisms

Absorption. Following inhalation exposure, the absorption of deposited cobalt compounds seems to be related to their biological solubility. Cobalt compounds deposit in the lungs based on their aerosol characteristics. Physiologically insoluble cobalt particles are generally cleared by phagocytosis and/or mucociliary transport, and thus, have a low systemic absorption. To some extent, cobalt particles may be dissolved within alveolar macrophages (Kreyling et al. 1990). More soluble forms of cobalt may enter the bloodstream through the alveolar or bronchial walls.

Following oral exposure, the absorption of cobalt varies with the amount given, with a greater dose leading to 4- to 20-fold greater fractional absorption (Smith et al. 1972). Nutritional status also seems to be an important factor in cobalt absorption, with both overnight fasting and iron deficiency resulting in increased cobalt absorption (Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). It has been suggested that cobalt and iron share a common absorptive pathway in the intestines, though the cobalt absorption takes place without ferritin (Reuber et al. 1994; Schade et al. 1970; Thomson et al. 1971). Solubility of the cobalt compound is also an important factor regarding the absorption following oral exposure, with increasing solubility resulting in increasing absorption (Christensen et al. 1993). One study in humans showed that oral exposure to cobalt resulted in significantly higher urinary excretion in females relative to males (Christensen et al. 1993), but these results have not been verified by other studies. A complex, specific pathway exists for the absorption of vitamin B_{12}, whereby the molecule interacts with several factors in the stomach and intestine to facilitate absorption (for review, see Russel-Jones and Alpers 1999).

Dermal absorption of cobalt compounds depends greatly on whether the skin is intact or damaged. Absorption through intact skin is comparatively low, while absorption through damaged skin is much higher (Inaba and Suzuki-Yasumoto 1979; Lacy et al. 1996).

Distribution. As a component of vitamin B_{12}, cobalt is found in most body tissues. Absorbed cobalt is transported throughout the body in the blood, with greatest levels found in the liver, followed by the kidney (Ayala-Fierro et al. 1999; Greenberg et al. 1943; Gregus and Klaassen 1986; Patrick et al. 1989).

Following inhalation exposure, significant levels of cobalt are found in the lungs of exposed humans and animals (Barnes et al. 1976; Brune et al. 1980; Collier et al. 1991; Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Kreyling et al. 1986; Kyono et al. 1992; Patrick et al. 1989; Talbot and Morgan 1989; Teraoka 1981). Within the lung, physiologically insoluble cobalt particles tend to be located within macrophages within the bronchial wall or in the interstitium close to the terminal bronchioli (Brune et al. 1980).

Excretion. Following inhalation exposure, the rate of urinary excretion appears to correlate with the rate of translocation of cobalt from the lungs to the blood, and the rate of fecal clearance with the rate of mechanical clearance of cobalt from the lungs to the gastrointestinal tract (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kerfoot 1975; Kreyling et al. 1986, 1989; Palmes et al. 1959; Patrick et al. 1989; Talbot and Morgan 1989). Likewise, the majority of absorbed cobalt following oral exposure is rapidly removed from the body by excretion in the urine, and to a lesser extent in the bile and feces, with fecal elimination being the primary method of excretion for physiologically insoluble cobalt compounds in both humans and animals (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Harp and Scoular 1952; Paley et al. 1958; Patrick et al. 1989; Smith et al. 1972; Sorbie et al. 1971; Talbot and Morgan 1989; Valberg et al. 1969). The primary route for excretion following dermal exposure is the urine (Lacy et al. 1996; Scansetti et al. 1994).

3.6.2 Mechanisms of Toxicity

Stable Cobalt. The exact mechanisms by which cobalt exerts its effects on cells are not completely understood. However, a number of potential mechanisms have been identified. Several studies have demonstrated that hard metal, a metal alloy with a tungsten carbide and cobalt matrix, is considerably more toxic than either cobalt or tungsten carbide alone. A mechanism by which hard metal may exert its effects has been proposed by a group of Belgian researchers (Lasfargues et al. 1995; Lison et al. 1995, 1996). In this proposed mechanism, tungsten carbide, which is a very good conductor of electrons, facilitates the oxidation of cobalt metal to ionic cobalt (presumably Co^{2+}) by transferring electrons from the cobalt atom to molecular oxygen adjacent to the tungsten carbide molecule. The result is an increased solubility of cobalt, relative to cobalt metal alone, and the generation of active oxygen species. The cobalt ions formed may be absorbed into the blood and transported throughout the body, where they may elicit effects by the above mechanisms. *In vitro* evidence for this mechanism includes the ability of hard

metal particles, but neither cobalt nor tungsten carbide alone, to generate substantial levels of oxidant species and cause significant lipid peroxidation (Lison et al. 1995; Zanetti and Fubini 1997). Hard metal particles have also been shown to increase the levels of inducible nitric oxide synthase (iNOS), a gene responsive to oxidant stress (Rengasamy et al. 1999).

Another potential mechanism for cobalt toxicity is through oxidant-based and free radical-based processes. Exposure to soluble cobalt increases indices of oxidative stress, including diminished levels of reduced glutathione, increased levels of oxidized glutathione, activation of the hexose monophosphate shunt, and free-radical-induced DNA damage (Hoet et al. 2002; Kasprzak et al. 1994; Lewis et al. 1991; Zhang et al. 1998a); hydrogen peroxide appears to be a necessary cofactor for cobalt-induced oxidative DNA damage (Ivancsits et al. 2002). Cobalt has been shown to generate oxygen radicals, including superoxide, both *in vitro* and *in vivo* (Kadiiska et al. 1989; Kawanishi et al. 1994; Moorhouse et al. 1985), through what may be a Fenton-type mechanism (Lloyd et al. 1997). *In vivo* exposure to cobalt in rats and guinea pigs resulted in increased lipid peroxidation in the liver (Christova et al. 2001, 2002; Sunderman and Zaharia 1988), as well as changes in reduced glutathione and hepatic levels of superoxide dismutase, catalase, heme oxygenase, and glutathione peroxidase (Christova et al. 2001, 2002). Exposure to cobalt results in accumulation in cardiac tissues, and is thought to stimulate carotid-body chemoreceptors, mimicking the action of hypoxia (Di Giulio et al. 1990, 1991; Hatori et al. 1993; Morelli et al. 1994). Cobalt administration to a neuroblastoma/glioma cell line resulted in an upregulation of opioid delta receptors, through a mechanism similar to that of hypoxia (Mayfield et al. 1994). Exposure to cobalt also elicits effects on a number of genes known to be sensitive to oxidant status, including hypoxia-inducible factor 1, erythropoietin, vascular endothelial growth factor, catalase, and monooxygenase enzymes (Bunn et al. 1998; Daghman et al. 1999; Dalvi and Robbins 1978; Di Giulio et al. 1991; Goldberg et al. 1988, 1994; Ho and Bunn 1996; Hoet et al. 2002; Ladoux and Frelin 1994; Legrum et al. 1979; Semenza et al. 1994; Yasukochi et al. 1974), and may also lead, through these genes or other pathways, to the induction of apoptosis (Zou et al. 2001).

Soluble cobalt has also been shown to alter calcium influx into cells, functioning as a blocker of inorganic calcium channels (Henquin et al. 1983; Moger 1983; Yamatani et al. 1998). This mechanism has been linked to a reduction of steroidogenesis in isolated mouse Leydig cells (Moger 1983). Additionally, soluble cobalt has been shown to alter the inorganic calcium influx in liver cells after exposure to glucagon (Yamatani et al. 1998), and calcium influx into pancreatic β cells (Henquin et al. 1983) and

isolated rat islets (Henquin and Lambert 1975). Cobalt may also affect neuromuscular transmission though antagonism with calcium (Weakly 1973).

Another potential mechanism of cobalt toxicity is relevant to cobalt cardiomyopathy. As mentioned previously, cobalt accumulated in the heart of beer drinkers. Microscopic analysis revealed fragmentation and degeneration of myofibers and aggregates of abnormal mitochondria (Ferrans et al. 1964). These mitochondrial changes are indicative of disturbances in energy production or utilization possibly related to cobalt effects on lipoic acid. Cobalt irreversibly chelates lipoic acids under aerobic conditions (Webb 1982). Lipoic acid is a required cofactor for oxidative decarboxylation of pyruvate to acetyl CoA and of α-ketoglutarate to succinate (Lehninger 1982). In the myocadrium of rats treated with cobalt, oxidation of pyruvate or fatty acids is impaired (Wiberg 1968).

A number of investigators have reported that cobalt ions can result in increased damage to DNA when co-exposed with oxidants *in vitro*, such as UV radiation or H_2O_2 (De Boeck et al. 1998; Hartwig et al. 1991; Nackerdien et al. 1991). It is believed that cobalt acts by inhibition of DNA repair, particularly the incision and polymerization steps (Asmuß et al. 2000; Kasten et al. 1997), accomplishing this through interaction with zinc finger DNA repair proteins (Asmuß et al. 2000; Sarkar 1995).

Another potentially important mechanism by which cobalt may exert effects is through its effects on heme and heme-containing enzymes. Cobalt is thought to inhibit heme synthesis *in vivo* by acting upon at least two different sites in the biosynthetic pathway: synthesis of 5-aminolevulinate and conversion of 5-aminolevulinate into heme (de Matteis and Gibbs 1977). This inhibitory activity might result in the formation of cobalt protoporphyrin rather than heme (Sinclair et al. 1979). Cobalt treatment also stimulates heme oxidation in many organs, due to the induction of heme oxygenase (for review, see Sunderman 1987). Effects on heme synthesis may potentially affect a wide variety of heme-containing proteins, including monooxygenase enzymes (i.e., cytochromes P450) and catalase (Legrum et al. 1979; Yasukochi et al. 1974). Conversely, cobalt acts, through a mechanism believed to involve a heme-containing protein, to increase erythropoietin, which stimulates the production of red blood cells (Di Giulio et al. 1991; Goldberg et al. 1988; Smith and Fisher 1973). The regulatory mechanisms behind this apparent dichotomy have not been fully elucidated.

Another potential mechanism by which cobalt may exert its effects is through interactions with the immune system. Exposure of humans to cobalt by the inhalation and dermal routes have resulted in

sensitization to cobalt (Alomar et al. 1985; Bencko et al. 1983; Dooms-Goossens et al. 1980; Fischer and Rystedt 1983; Goh et al. 1986; Kanerva et al. 1988; Marcussen 1963; Shirakawa et al. 1988, 1989; Valer et al. 1967). Exposure to inhaled cobalt chloride aerosols can precipitate an asthmatic attack in sensitized individuals (Shirakawa et al. 1989), suggesting cobalt sensitization as one mechanism by which cobalt-induced asthma may be produced. IgE and IgA antibodies specific to cobalt have been reported in humans (Bencko et al. 1983; Shirakawa et al. 1988, 1989). There is evidence that cobalt sensitivity in humans may to be regulated by T-lymphocytes (Katsarou et al. 1997). A human helper T-lymphocyte cell line specific for cobalt (CoCl2) has been established (Löfström and Wigzell 1986). Cobalt may also interact directly with immunologic proteins, such as antibodies or Fc receptors, to result in immunosensitization (Cirla 1994). *In vitro*, cobalt(II) has been shown to reduce the proliferation of both B and T lymphocytes, as well as the release of the cytokines IL-2, IL-6, and IFN-Gamma (Wang et al. 1996). Interrelationships exist between nickel and cobalt sensitization (Bencko et al. 1983; Rystedt and Fisher 1983); however, the extent of any potential interactions between the two metals on immunologic end points is not well understood. In guinea pigs, nickel and cobalt sensitization appear to be interrelated and mutually enhancing (Lammintausta et al. 1985), though cross-reactivity was not reported to occur.

Cobalt has been shown to have a number of effects on glucose metabolism. Treatment of animals with cobalt results in a depression of serum (Eaton and Pommer 1973; Ybarra et al. 1997) or tissue (Wiberg 1968) glucose levels. In rats made diabetic by pretreatment with streptozotocin, this depression was persistent, whereas it was transient in normal rats (Ybarra et al. 1997). Many of the effects of cobalt on glucose metabolism are thought to result from alterations in the expression of the glut family of glucose transport proteins, a family of facilitative Na+-independent transport proteins thought to mediate non-insulin-dependent transport of glucose. Exposure to soluble cobalt results in increased expression of these genes, particularly GLUT1, in cells of the liver, kidney cortex, myocardium, skeletal muscle, and cerebrum (Behrooz and Ismail-Beigi 1997; Ybarra et al. 1997). Cobalt also reduces the amount of glucose produced in liver cells following stimulation with glucagon (Eaton and Pommer 1973; Yamatani et al. 1998), as well as reducing insulin release in isolated rat islets (Henquin and Lambert 1975).

Radioactive Cobalt. Due to the nature of its ionizing radiation, radioactive cobalt can present a health hazard. Highly-penetrating gamma emissions are the major source of damage to tissues and internal organs following external exposure to radioactive cobalt isotopes. If radioactive cobalt is internalized, nearby tissues are at highest risk for damage due to the release of beta particles. In either case, exposure to ionizing radiation results in an increased risk of cellular damage. Both beta and gamma radiations are

capable of producing ionization events when they hit cellular molecules, including DNA, RNA, or lipids. Ionized molecules within irradiated cells may be repaired quickly to prevent further damage. On the other hand, irreparable damage may be imposed on cellular materials, such as DNA, which might ultimately result in either cell death or the formation of cancerous tumors. Very large acute radiation doses can damage or kill enough cells to cause the disruption of organ systems, resulting in acute radiation syndrome or even death. Human and animal data indicate that sufficiently high exposures to cobalt radiation can result in adverse effects such as reduced fertility, abnormal development, genotoxicity, pulmonary fibrosis, gastrointestinal atrophy and fibrosis, hematological and lymphoreticular disorders, cancer, and death (Chang et al. 1999b; Davis et al. 1992; Dinehart et al. 1991; Hashimoto and Mitsuyasu 1967; Klener et al. 1986; Libshitz 1993; Myskowski and Safai 1981; Rauscher and Bauchinger 1983; Roschler and Woodard 1969; Roswit and White 1977; Stavem et al. 1985; Van Oort et al. 1984). For a more complete discussion of the mechanisms associated with the toxic effects of ionizing radiation, refer to Chapter 5 of the Toxicological Profile for Ionizing Radiation (Agency for Toxic Substances and Disease Registry 1999).

3.6.3 Animal-to-Human Extrapolations

Bailey et al. (1989) reported a wide variation across species, including man, in the retention and clearance of inhaled physiologically insoluble 57Co particles (see Table 3-8), noting that this variation illustrates the potential difficulty of extrapolating the results of animal lung retention experiments to human even qualitatively. Species differences in absorption of physiologically insoluble cobalt oxide following oral exposure do not appear to exist (Bailey et al. 1989), although humans were not examined. Absorption of soluble cobalt compounds is greater in rats (13–34%) than in dairy cows (1–2%) and guinea pigs (4–5%) following oral exposure (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Naylor and Harrison 1995; Schade et al. 1970; Taylor 1962; van Bruwaene et al. 1984).

3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate

terminology to describe such effects remains controversial. The terminology endocrine disruptors, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997c). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

The available human and animal data suggest that the endocrine system, particularly the thyroid gland, may be a target of stable and radioactive cobalt toxicity. These effects are discussed in Sections 3.2 and 3.3 under Systemic Effects.

3.8 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential

effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also

have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Though human data are lacking, animal studies have suggested several differences in pharmacokinetic behavior of cobalt compounds between children and adults. Following inhalation exposure to Co_3O_4, deposition tended to increase with age, though no significant differences were reported (Collier et al. 1991). The youngest animals exposed (3 weeks postnatal) had the lowest fractional retention 182 days postexposure, though no differences were seen at day 7 or 83. The authors attributed this to a faster rate of translocation of cobalt from the lung to the blood, which could enhance subsequent excretion. Naylor and Harrison (1995) reported that in rats and guinea pigs, fractional absorption of cobalt following oral exposure was highest at 1 day after birth, and diminished rapidly with time thereafter. Collier et al. (1991) reported no difference in absorption of cobalt nitrate following oral exposure to animals aged 3–46 weeks, which is in agreement with the results of the later portion of the Naylor and Harrison (1995) study. No PBPK models specific for cobalt exposures to children were located. However, the ICRP Human Respiratory Tract Model is applicable to children, and may be used for children if the appropriate values for the parameters are used.

Once in the bloodstream, soluble cobalt compounds have been shown, in animal studies, to cross the placenta and enter the fetus. Twenty-four hours after intravenous injection of cobalt chloride in rats, 0.14% of the dose was found in the fetus, 0.19% in the chorioallantoic placenta, and 0.22% in the yolk sac (Zylicz et al. 1975). Several other rat studies (Nishimura et al. 1978; Zylicz et al. 1975, 1976) have demonstrated that the amount of cobalt crossing the placenta following intravenous injection is greater in later gestation stages, though the percent of the maternal dose reaching the fetus is still relatively low (in <1% of the maternal dose). The fetal uptake of cobalt following intravenous administration to the mother was increased when the cobalt was given as cyanocobalmin, relative to cobalt chloride (~5% of the maternal dose for cyanocobalmin, compared to <1% for cobalt chloride) (Nishimura et al. 1978), indicating that the form of the cobalt compound may affect its availability to the fetus.

Cobalt has been detected in human breast milk (Byczkowski et al. 1994; Kratchler et al. 1998). In general, physiological concentrations of cobalt in breast milk are very low, on the order of parts per billion (Byczkowski et al. 1994). Animal studies are in agreement with this observation. By day 70 post-exposure in lactating dairy cows orally exposed to cobalt chloride, the milk contained 0.012% of the dose (van Bruwaene et al. 1984). One to two percent of cobalt given intravenously to mother rats as cyanocobalmin was transferred to offspring via the breast milk (Nishimura et al. 1978).

Health Effects from Exposure to Stable Cobalt. Available data have not clearly defined whether children are at greater risk from exposure to stable cobalt than adults. Studies in adult humans have identified several health effects of cobalt compounds following inhalation, oral, or dermal exposure. Data on effects of cobalt in children following inhalation exposures are lacking. Jacobziner and Raybin (1961) reported on two cases of children who had accidentally ingested unknown amounts of cobalt chloride; a 19-month-old male died approximately 6.5 hours after ingestion, whereas a 3-year-old male was given medical treatment and showed no symptoms after ingestion. Several studies (Chamberlain 1961; Little and Sunico 1958; Sederholm et al. 1968; Washburn and Kaplan 1964) have reported enlarged thyroid glands in children given cobalt chloride for treatment of anemia; removal of cobalt therapy resulted in a return to normal thyroid size. Patch testing of children aged 4–14 years revealed a 13.3% dermal sensitization rate to cobalt chloride (Romaguera and Vilaplana 1998). More girls reacted positively than boys, which the authors attributed to the wearing of costume jewelry, which often contains cobalt, and the resulting exposure.

Offspring of mice intravenously injected with approximately 1.2 mg cobalt/kg at day 8 of gestation, but not at day 3, showed a significant increase in the number of skeletons with delayed ossification (Wilde 1984). Other studies, however, have not shown developmental effects of stable cobalt compounds, or have shown effects only at maternally toxic doses (Domingo et al. 1985b; Paternian et al. 1988; Seidenberg 1986).

Health Effects from Exposure to Radioactive Cobalt. Taiwanese children (48 boys, 37 girls) who were raised in apartments contaminated with ^{60}Co were compared to 21,898 age- and sex-matched non-exposed children from a nationwide surveillance program (Wang et al. 2001). After adjusting for effects from parental heights and body mass index, clear dose-related decreases in height percentile (HP) and age-specific relative height differences (RHD) were seen in exposed boys, but not in exposed girls. Average

cumulative exposures were 120.8 and 129.9 mSv (equivalent to ~12.1 or 13 rad) for the boys and girls, respectively.

No other studies of human children exposed to radioactive cobalt or cobalt radiation were located. As rapidly-dividing cells are more sensitive to radiation, the developing fetus and growing children are expected to be more sensitive to cobalt radiation than adults.

Animal studies have shown that exposures to external radiation from cobalt isotopes (as low as 10 rad [0.1 Gy] in mice) may have a dramatic effect on the developing fetus (see Section 3.2.4.6 and Agency for Toxic Substances and Disease Registry 1999). Exposure duration, gestational day, and dose all influence the effect of cobalt radiation on the developing organism. Radiation exposure to very young dogs (80 rad [0.8 Gy] on day 2 or 70 postpartum) has resulted in an increased incidence of diabetes mellitus, renal disease, and cancer (Benjamin et al. 1998a, 1998b).

3.9 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous

substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to cobalt are discussed in Section 3.9.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by cobalt are discussed in Section 3.9.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.11 “Populations That Are Unusually Susceptible”.

3.9.1 Biomarkers Used to Identify or Quantify Exposure to Cobalt

Biomonitoring data exist that demonstrate a positive correlation between occupational exposure levels of cobalt and the levels of cobalt in both the urine and blood (Table 3-12) (Alexandersson 1988; Ichikawa et al. 1985; Lison et al. 1994; Nemery et al. 1992; Scansetti et al. 1985). Available studies of unexposed humans have reported cobalt blood levels of 0.05–0.19 µg/dL and urinary cobalt levels of 0.04–2 µg/dL (Alexandersson 1988; Ichikawa et al. 1985). Figure 3-10 graphically presents the cobalt exposure data and cobalt in blood data presented in Table 3-12 (Ichikawa et al. 1985). The highest excretion rate of cobalt in urine occurs during the first 24 hours after short-term exposure; therefore, subjects should be tested quickly to assess whether cobalt exposure has occurred (Alexandersson 1988). Occupational exposure to 0.1 mg/m^3 cobalt resulted in blood levels of cobalt ranging (95% CI) from 0.57 to 0.79 µg/dL, compared to 0.19 µg/dL in unexposed workers, and urinary levels from 59 to 78 µg/L, compared to 2 µg/L in unexposed workers (Ichikawa et al. 1985). Correlations between recent exposure and cobalt levels in the blood or urine are more consistent for soluble cobalt compounds (metal, salts, and hard

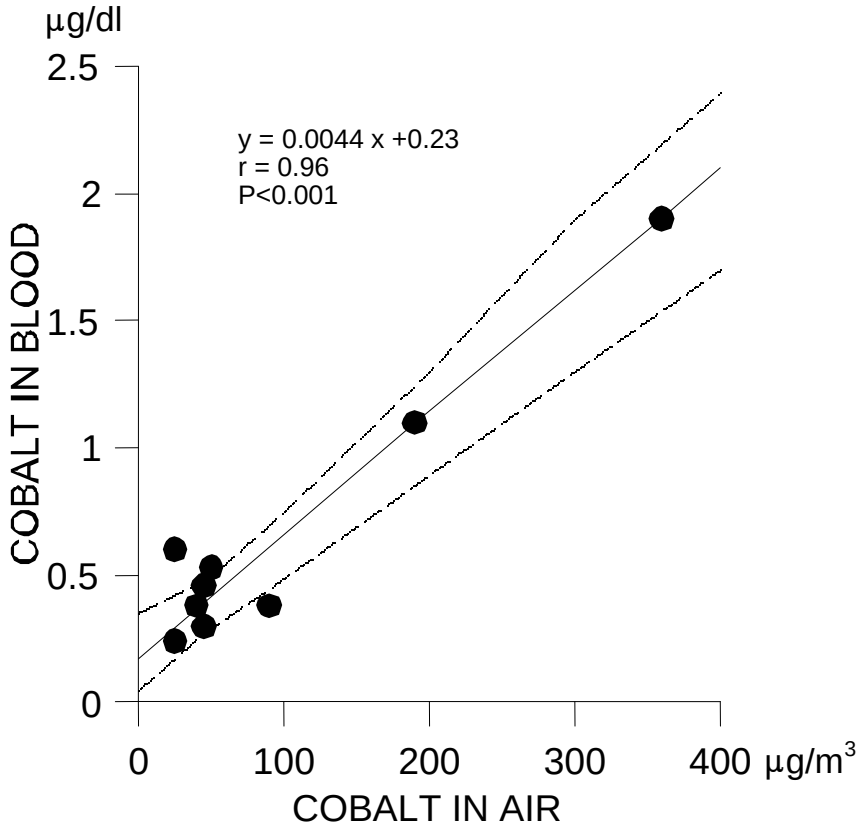
Table 3-12. Cobalt Exposure Concentrations and Amounts in the Blood and Urine of Subjects Examined[a]

Subjects	Number	Cobalt in air[b] mean±SD µg/m^3		Cobalt in blood[b] mean±SD µg/dL		Cobalt in urine[b] mean±SD µg/L	
Powder handlers	2	186±108	(110–262)	1.08±0.28	(0.88–1.28)	148±13	(138–158)
Rubber press operators	6	367±324	(92–859)	1.87±1.96	(0.40–5.30)	235±182	(41–392)
Automatic press operators	11	56±60	(9–210)	0.57±0.53	(0.10–0.95)	34±43	(4–73)
Shapers (lathing)	7	33±15	(15–62)	0.67±0.44	(0.14–1.34)	33±30	(11–95)
Shapers (sawing)	21	50±35	(8–144)	0.52±0.31	(0.15–1.15)	41±60	(6–266)
Sintering workers	21	28±30	(4–145)	0.26±0.10	(0.09–0.45)	10±10	(2–46)
Wet grinders							
A	27	44±48	(4–227)	0.42±0.31	(0.10–1.30)	35±34	(2–180)
B	18	45±50	(3–161)	0.33±0.10	(0.16–0.52)	19±15	(2–67)
C	12	92±92	(15–291)	0.43±0.39	(0.12–1.90)	68±87	(3–265)
D	25	44±54	(3–205)	0.35±0.20	(0.10–1.00)	17±16	(1–69)
Workers using respirators	25	317±307	(7–1,203)	0.65±0.86	(0.20–3.90)	26±30	(1–119)
Office workers	20	No data		0.19±0.11	(0.08–0.40)	2±1	(1–4)

[a]Adapted from Ichikawa et al. 1985
[b]The range of each value is given in parentheses.

SD = standard deviation

Figure 3-10. Relation Between Mean Cobalt Exposure and Mean Blood Concentration of Cobalt in Exposed Workers*



*Adapted from Ichikawa et al. 1985

metals), while blood and/or urinary cobalt levels are less reflective of recent exposure for less soluble compounds (cobalt oxides) (Lison et al. 1994).

Sensitive serum protein responses were found in animals exposed to cobalt at levels below those necessary to produce hematopoietic effects (Stokinger and Wagner 1958). These serum protein responses included an increase in alpha globulin fractions of serum proteins and associated serum neuraminic acid. The responses were observed in rabbits and dogs following both inhalation and injection of cobalt. The authors indicated that this increase was a unique response to cobalt exposure. The characteristics of the response were similar to those of the erythropoietic response found following exposure to higher levels of cobalt; the response is delayed, does not occur in all animals within a given exposure group, is not of great magnitude, and is not persistent (Stokinger and Wagner 1958).

Biomarkers specific for exposure to cobalt radioisotopes have not been reported.

3.9.2 Biomarkers Used to Characterize Effects Caused by Cobalt

Sensitization to cobalt results in cobalt-specific changes in serum antibodies (IgE and IgA) that may be monitored to determine if sensitization, or additional exposure, to cobalt has occurred (Bencko et al. 1983; Shirakawa et al. 1988, 1989).

No biomarkers specific for effects of radioactive cobalt isotopes have been reported. Biomarkers for response to ionizing radiation are discussed in Agency for Toxic Substances and Disease Registry (1999).

3.10 INTERACTIONS WITH OTHER CHEMICALS

A major medical use of cobalt is in combination with bleomycin, an antineoplastic antibiotic, as a tumor-localizing and therapeutic agent (Goodwin and Meares 1976; Hansen et al. 1976; Kapstad 1978, 1979). The anti-tumor effects of the two agents are amplified when given in combination with each other. The complex, wherein cobalt is coordinately bound to the bleomycin molecule, is intravenously injected and acts by binding to and cleaving the DNA in the tumor cells (Kakinuma and Orii 1982).

The interaction of cobalt with various chelators has been investigated in animals for mitigation of the toxicity of cobalt (Baker et al. 1987; Domingo et al. 1983; Llobet et al. 1988). Glutathione, N-acetyl-L-cysteine (NAC) and diethylenetriaminepentaacetic acid (DTPA), administered to rats previously exposed to cobalt, significantly increased urinary excretion of cobalt, while EDTA, NAC, and 2,3-di-mercaptosuccinic acid (DMSA) increased fecal excretion. NAC was the most effective chelator because it increased both urinary and fecal excretion of cobalt while decreasing its levels in liver and spleen (Llobet et al. 1988). Cysteine, also acting as a chelator, mitigated the toxicity of cobalt when both chemicals were given to chicks in the feed (Baker et al. 1987).

A number of studies have suggested an association between cobalt ions and calcium ions. Soluble cobalt has also been shown to alter calcium influx into cells, functioning as a blocker of inorganic calcium channels (Henquin et al. 1983; Moger 1983; Yamatani et al. 1998). This mechanism has been linked to a reduction of steroidogenesis in isolated mouse Leydig cells (Moger 1983). Additionally, soluble cobalt has been shown to alter the inorganic calcium influx in liver cells after exposure to glucagon (Yamatani et al. 1998), and calcium influx into pancreatic β cells (Henquin et al. 1983) and isolated rat islets (Henquin and Lambert 1975). Cobalt may also affect neuromuscular transmission through antagonism with calcium (Weakly 1973).

Hard metal, consisting of 5–10% cobalt with the balance being tungsten carbide, has been shown to be considerably more toxic than cobalt alone, resulting from interactions between particles of cobalt metal and tungsten carbide particles. The mechanisms responsible for this interaction are discussed in Section 3.6.2.

An interrelationship between cobalt and nickel sensitization has been reported in individuals exposed to the two metals (Rystedt and Fisher 1983; Veien et al. 1987), as well as in animal studies (Wahlberg and Lidén 2000). It was concluded that the combination of nickel sensitivity and irritant eczema resulted in a high risk for developing an allergy to cobalt. Studies of cultured alveolar type II cells showed a synergistic (greater than additive) response to co-exposure to cobalt and nickel chlorides (Cross et al. 2001).

3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to cobalt than will most persons exposed to the same level of cobalt in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of cobalt, or compromised function of organs affected by cobalt. Populations who are at greater risk due to their unusually high exposure to cobalt are discussed in Section 6.7, Populations With Potentially High Exposures.

Individuals who are already sensitized to cobalt may be unusually susceptible because cobalt exposure may trigger asthmatic attacks (Shirakawa et al. 1988, 1989). Sensitization to cobalt results in cobalt-specific changes in serum antibodies (IgE and IgA) (Bencko et al. 1983; Shirakawa et al. 1988, 1989). Potolicchio et al. (1997, 1999) have suggested that individuals with a polymorphism in the HLA-DP gene (presence of glutamate 69 in the β chain) may be more susceptible to hard metal lung disease. Individuals with ongoing respiratory illness may also be more susceptible to the effects of inhaled cobalt. Following oral exposure, individuals with iron deficiency may at greater risk, as animal studies have shown an increased absorption of cobalt compounds in iron-deficient animals (Reuber et al. 1994; Schade et al. 1970). Studies of beer-cobalt cardiomyopathy have suggested that individuals with high alcohol consumption may be more susceptible to health effects of cobalt (Alexander 1969, 1972; Morin et al. 1971).

Ionizing radiation has greater effects on rapidly-dividing cells than on those that divide at a slower rate. The most sensitive population to exposure to cobalt radiation is likely to be the developing fetus, as even moderate exposures to cobalt radiation have been shown to cause dramatic effects on the developing fetus in animal studies (see Section 3.2.4.6), Likewise, growing children are likely to be more susceptible to cobalt radiation than adults, and people who are immunocompromised, have existing lung diseases, or who have defects in genetic repair enzymes would be expected to show an increased susceptibility to cobalt radiation. A detailed discussion on the effects of ionizing radiation in children can be found in Agency for Toxic Substances and Disease Registry (1999).

3.12 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to cobalt. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to cobalt. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to cobalt:

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd edition. Baltimore, MD: Williams & Wilkins, 1682–1723.

Goldfrank, LR, Flomenbaum, NE, Lewin, NA, et al., eds. 1998. Toxicological emergencies. 6th edition. Connecticut: Appleton & Lange, 481t, 489, 490t, 1338–1339.

REAC/TS. Radiation Emergency Assistance Center/Training Site. www.orau.gov/reacts/.

3.12.1 Reducing Peak Absorption Following Exposure

Methods for reducing peak absorption are similar for both the stable and radioactive forms of cobalt. General management and treatment of patients following acute exposure to cobalt includes removal of the victim from the contaminated area, and removal and isolation of contaminated clothing, jewelry, and shoes (Bronstein and Currance 1988; Stutz and Janusz 1988). The excess solid contaminant is gently brushed away, and excess liquids are blotted with absorbent material. If the victim is in respiratory distress, ventilation assistance is provided and oxygen is administered. Measures that are appropriate to the route of exposure are then taken to remove cobalt from the body. Following ocular exposure, the eyes are immediately flushed thoroughly with water. Skin is washed immediately with soap or mild detergent and water. Some evidence has been presented that the use of cheating creams on the skin can reduce the occurrence of symptoms in allergic persons (Wöhrl et al. 2001). Following ingestion of cobalt, two conflicting forms of treatment have been recommended. Stutz and Janusz (1988) recommend that victims over 1 year old be given ipecac, followed by activated charcoal (after vomiting). A cathartic, such as magnesium sulfate in water, is then administered to adults and children. Bronstein and Currance (1988) recommend that the victim be given water for dilution of the cobalt; however, they recommend that emetics not be administered. Following all routes of exposure, victims are monitored for pulmonary edema, circulatory collapse, and shock, and treated as necessary.

3.12.2 Reducing Body Burden

Chelation therapy with EDTA or dimercaprol can be effectively used if necessary (Goldfrank et al. 1990; Haddad and Winchester 1990; Stutz and Janusz 1988). Animal studies have investigated the effectiveness of various chelating agents for mitigating the toxicity of cobalt (Baker et al. 1987; Domingo et al. 1983; Llobet et al. 1988). NAC was found to be the most effective chelator because it increased both urinary and fecal excretion of cobalt as well as decreased the levels of cobalt in the liver and spleen (Llobet et al. 1988). These chelators react chemically with cobalt, so they are effective for both stable and radioactive cobalt isotopes. For more complete information on treatment of specific symptoms, refer to Bronstein and Currance (1988) and Stutz and Janusz (1988).

3.12.3 Interfering with the Mechanism of Action for Toxic Effects

No studies were located in humans or animals regarding interfering with the mechanism of action of stable or radioactive cobalt compounds.

3.13 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cobalt is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cobalt.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.13.1 Existing Information on Health Effects of Cobalt

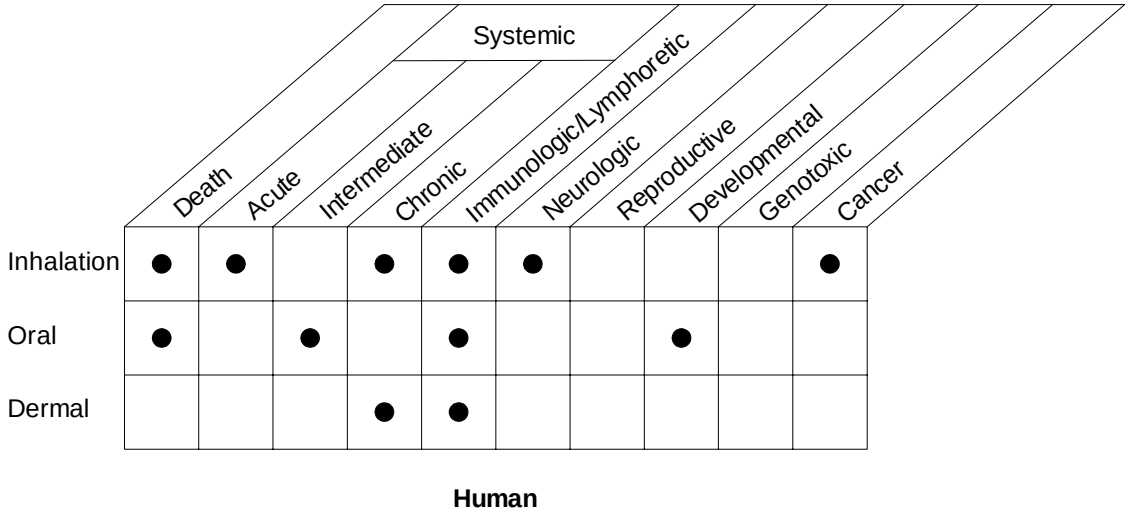
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals are summarized in Figure 3-11 for stable cobalt and in Figure 3-12 for radioactive cobalt. The purpose of these figures is to illustrate the existing information concerning the health effects of cobalt. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figures 3-11 and 3-12 represent studies conducted with all forms of cobalt. The effects of cobalt have been studied in humans following both inhalation and oral exposure. Human dermal studies designed to investigate nondermal systemic effects of cobalt have been reported. Similarly, the effects of cobalt in animals have been studied following inhalation and oral exposure. Few dermal studies are available.

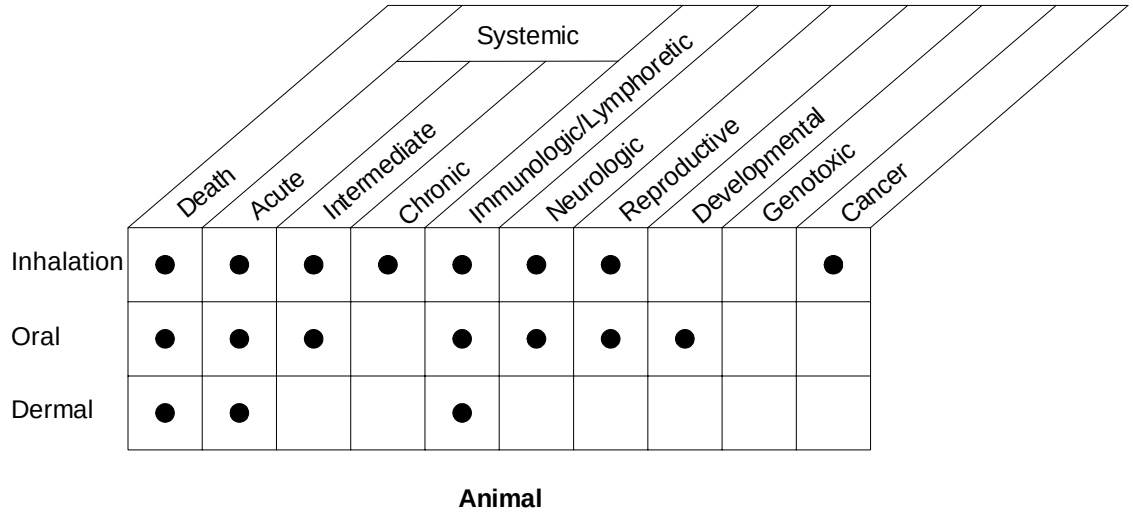
3.13.2 Identification of Data Needs

Stable Cobalt. Effects in humans following acute inhalation, oral, and dermal exposures to cobalt have been reported. In humans, the primary targets following acute exposure to cobalt include the respiratory system following inhalation exposure (Kusaka et al. 1986a), the thymus following oral exposure (Roche and Layrisse 1956), and the immunological system following dermal exposure (Alomar et al. 1985; Fischer and Rystedt 1983; Kanerva et al. 1988). Acute oral studies in animals have also identified the cardiovascular and hematopoietic systems as targets of cobalt toxicity (Domingo and Llobet 1984; Speijers et al. 1982). Although acute exposure levels associated with some of these effects in humans have been reported, the minimal acute exposure levels required to produce these effects are not known because few acute human studies exist. The results of animal studies of the acute toxicity of cobalt have been used to determine dose levels that produce death and respiratory effects following inhalation exposure, death and various systemic effects following oral exposure, and dermal and immunological effects following dermal exposure.

Figure 3-11. Existing Information on Health Effects of Stable Cobalt



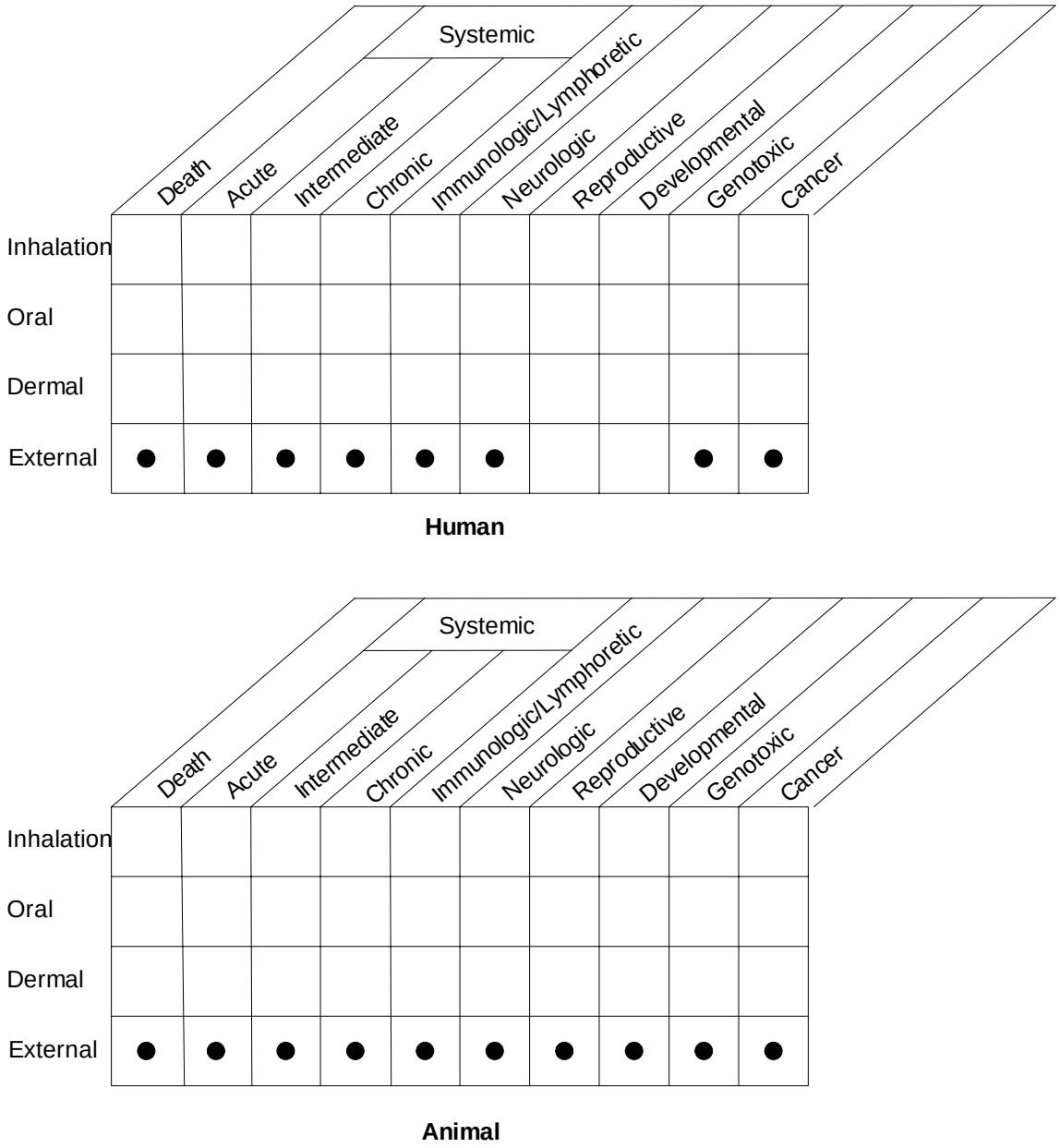
Human



Animal

● Existing Studies

Figure 3-12. Existing Information on Health Effects of Radioactive Cobalt



● Existing Studies

There were insufficient data for derivation of inhalation or oral acute MRLs because reported effects were severe and occurred at levels above those reported in the few human studies. Animal studies that identify minimally effective inhalation and oral exposure levels for the various cobalt compounds would be useful in estimating acute MRLs for each cobalt compound. Acute dermal studies would enable the determination of hazardous levels for this route of exposure. Because a small portion of the cobalt taken into the body is retained for a relatively long time, studies on the long-term consequences of acute exposure on the heart, respiratory tract, hematological system, and immune response could provide information about the potential for chronic effects of acute exposures in humans. Knowledge about the acute toxicity of cobalt is important because people living near hazardous waste sites might be exposed for brief periods.

Radioactive Cobalt. Data on health effects following acute exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because all cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. A number of health effects have been seen following cases of accidental acute exposure to high levels of external cobalt radiation in humans, including death, gastrointestinal disorders, hematological alterations, and dermal lesions (Klener et al. 1986; Stavem et al. 1985). Acute-exposure animal studies have shown pronounced effects, including death, cardiovascular changes, gastrointestinal effects, kidney effects, and neurobehavioral changes (Brady and Hayton 1977b; Bruner 1977; Cockerham et al. 1986; Darwezah et al. 1988; Down et al. 1986; Gomez-d-Segura et al. 1998; Hanks et al. 1966; King 1988a; Mele et al. 1988; Page et al. 1968; Robbins 1989a, 1989b, 1989c, 1991a). The most pronounced effects in animals following acute exposure to cobalt radiation have been reproductive and developmental effects (see Sections 3.2.4.5 and 3.2.4.6). Agency for Toxic Substances and Disease Registry (1999) has derived an acute MRL for external exposure to ionizing radiation, which is applicable to external exposures to cobalt radiation, so additional data for the derivation of an MRL are not needed.

Intermediate-Duration Exposure.

Stable Cobalt. Information on oral exposure of humans to cobalt, in the form of cobalt chloride added to beer as a foam stabilizer, provides the only human data available for exposure of intermediate duration (Alexander 1969, 1972; Morin et al. 1971). Inhalation and dermal data in humans were not located for this duration of exposure. The cardiac and hematopoietic systems are the primary targets in humans following oral exposure to cobalt. Some exposure levels associated with cardiomyopathy have been

reported following oral exposure, but the minimal exposure level required to produce this effect in humans is not known (Alexander 1969, 1972; Morin et al. 1971). Oral studies in animals reported dose levels associated with death, various systemic and neurological effects, and effects on reproduction and development (Domingo et al. 1984, 1985b; Krasovskii and Fridlyand 1971; Mohiuddin 1970; Mollenhauer et al. 1985; Pedigo et al. 1988). Intermediate-duration inhalation studies in animals reported that the respiratory tract is the target of the toxicity of inhaled cobalt (Bucher et al. 1990; Johansson et al. 1987; Kerfoot 1975; NTP 1991; Palmes et al. 1959). Animal studies were insufficient for derivation of an intermediate-duration MRL for oral exposure, since the reported effects were severe and the effects occurred at levels above those reported in the few human studies. Dermal data in animals were not located. Animal studies that investigate the possible toxic interaction between cobalt and alcohol may be helpful in understanding the role of cobalt in the cardiomyopathy reported in the heavy beer drinkers (Alexander 1969, 1972; Morin et al. 1971). One such study in guinea pigs already exists (Mohiuddin et al. 1970), but this study used a single, high dose of cobalt. Studies using a series of lower doses, both with and without alcohol preexposure, would be helpful in determining the threshold for the cardiac effects. Intermediate-duration dermal studies would enable determination of hazardous levels for this route of exposure. Intermediate-duration toxicity information is important because people living near hazardous waste sites might be exposed for corresponding time periods.

Radioactive Cobalt. Data on health effects following acute exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Substantial human data exist concerning intermediate-duration exposure to external radiation, as radiotherapy treatment regimens fall into this duration category. Animal data from intermediate-duration external exposure also exist, but are less numerous. Additional intermediate-duration studies are not likely to provide substantial additions to our knowledge of radiation-induced toxic effects.

Chronic-Duration Exposure and Cancer.

Stable Cobalt. Chronic inhalation exposure levels in humans associated with respiratory effects have been reported (Gennart and Lauwerys 1990; Nemery et al. 1992; Shirakawa et al. 1988; Sprince et al. 1988). In humans, the respiratory system is the primary target following chronic inhalation exposure. A chronic-duration inhalation MRL was derived from a NOAEL for decreased ventilatory function in exposed workers (Nemery et al. 1992). Wehner et al. (1977) reported no adverse effects in hamsters

exposed chronically to cobalt oxide. NTP (1998; Bucher et al. 1999) exposed rats and mice to cobalt sulfate for 2 years, reporting pronounced effects on the respiratory tract, including hyperplasia, inflammation, fibrosis, and metaplasia; an increased incidence of cancer was also reported. Chronic oral or dermal studies have not been reported in either humans or animals. Animal studies that identify minimally effective chronic oral exposure levels would be useful for estimating a chronic MRL. Chronic dermal studies would enable determination of hazardous levels for this route of exposure. Chronic toxicity information is important because people living near hazardous waste sites might be exposed to cobalt for many years.

Several studies of hard metal exposure in humans have reported increases in lung cancer mortality from occupational inhalation exposure to hard metal (Lasfargues et al. 1994; Moulin et al. 1998; Wild et al. 2000). In humans, cancer has not been reported following exposure to cobalt by the oral or dermal routes. An increased incidence of alveolar/bronchiolar neoplasms was noted following lifetime exposure of male rats to 1.14 mg cobalt/m^3 and in female rats to 0.38 mg cobalt/m^3 as cobalt sulfate, with tumors occurring in both sexes with significantly positive trends (Bucher et al. 1999; NTP 1998). Similarly, mice of both sexes exposed to 1.14 mg cobalt/m^3 showed an increase in alveolar/bronchiolar neoplasms, again with lung tumors occurring with significantly positive trends. Parenteral exposure to cobalt has been found to induce tumors (Gilman 1962; Gilman and Ruckerbauer 1962; Heath 1956, 1969; Heath and Daniel 1962; Shabaan et al. 1977). Further chronic exposure studies by the oral and dermal routes may determine the actual carcinogenic potential of cobalt. Also, studies examining the effect of cobalt speciation (i.e., cobalt metal vs. cobalt sulfate) would add to our understanding of the carcinogenic potential of cobalt.

Radioactive Cobalt. Data on health effects following chronic exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Limited data exist on chronic exposure to cobalt radiation in humans, with genotoxicity, immunologic effects, and cancer being the primary end points examined. Animal data are similarly limited. Additional human or animal data following chronic exposure to external cobalt radiation would be useful in further identifying possible long-term health effects or susceptible populations. Agency for Toxic Substances and Disease Registry (1999) has derived a chronic-duration MRL for external radiation exposure, which is applicable to external exposures to cobalt radiation, so additional data for the derivation of an MRL are not needed.

Genotoxicity.

Stable Cobalt. Gennart et al. (1993) reported an increase in sister-chromatid exchanges in workers exposed to a mixture of cobalt, chromium, nickel, and iron. De Boeck et al. (2000) reported no significant change in the comet assay on lymphocytes from nonsmoking workers who were occupationally exposed to cobalt or hard metal dusts; a positive association was found between hard metal exposure and increased micronucleus formation in smokers only.

Data regarding the mutagenic action of cobalt in bacterial cell lines and mammalian cell lines have been reported in the literature (Hamilton-Koch et al. 1986; Kharab and Singh 1985; Ogawa et al. 1986). *In vivo* mutagenicity studies in animals following inhalation, oral, or dermal exposure to cobalt would be helpful in ascertaining its true mutagenic potential. Further studies examining the differences in genotoxicity between different valence states of cobalt would also be useful.

Radioactive Cobalt. Data on genotoxic effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Several studies have demonstrated genotoxic effects in humans exposed to external cobalt radiation (Chang et al.1999c; House et al. 1992; Rauscher and Bauchinger 1983). Numerous data from animal studies exist demonstrating the genotoxic effects of ionizing radiation, including cobalt radiation.

Reproductive Toxicity.

Stable Cobalt. No studies were located regarding the reproductive effects of cobalt in humans following exposure by any route. Inhalation and oral studies in male animals have demonstrated adverse effects on reproductive organs (Anderson et al. 1992, 1993; Bucher et al. 1990; Corrier et al. 1985; Domingo et al. 1985b; Mollenhauer et al. 1985; NTP 1991; Pedigo et al. 1988). One study also reported effects on the estrous cycle in mice following inhalation exposure (Bucher et al. 1990; NTP 1991). Multigenerational studies would be helpful in assessing the significance of these effects on reproductive performance.

Radioactive Cobalt. Data on reproductive effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Human data on reproductive effects following external exposure to cobalt radiation are lacking,

but are sufficiently understood for gamma radiation. Available animal studies are limited, but have demonstrated radiation-induced deficits on reproductive ability in both genders (Cunningham and Huckins 1978; Laporte et al. 1985; Searl et al. 1976, 1980). Additional data in humans and animals would be helpful in refining minimal effective doses for radiation effects on reproduction.

Developmental Toxicity.

Stable Cobalt. No developmental effects were observed in the children of 78 women given cobalt chloride orally during pregnancy for treatment of anemia (Holly 1955); however, only a limited examination of offspring was reported, and details of examined end points were not reported. No studies of developmental effects by other routes of exposure in humans were located. Developmental effects in animals following oral exposure during gestation, however, have been observed (Domingo et al. 1985b). Further developmental studies in animals by all relevant routes of exposure (inhalation, oral, dermal) may clarify the potential developmental effects of cobalt in humans.

Radioactive Cobalt. Data on developmental effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. No human studies describing developmental effects of exposure to external cobalt radiation were located. Extensive data from animal studies have shown that even acute exposures to small amounts of cobalt radiation may elicit profound effects on the developing organism (see Section 3.2.4.6). The effects of ionizing radiation on the developing organism are also described in the Agency for Toxic Substances and Disease Registry Toxicological Profile for Ionizing Radiation (1999).

Immunotoxicity.

Stable Cobalt. Humans have been shown to develop sensitivity to cobalt following occupational exposure (Bencko et al. 1983; Shirakawa et al. 1988, 1989). No immunological effects were observed following oral exposure of humans to cobalt. Similar evidence of sensitization has been reported in animals (Lammintausta et al. 1985). Studies examining the mechanism of sensitization might be helpful in fully understanding and treating this effect in humans. A battery of immune function tests would further assess the immunotoxicity of cobalt in humans and animals.

Radioactive Cobalt. Data on immunotoxic effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Following external exposure to cobalt radiation, above levels normally encountered except for medical procedures, decreases in white blood cell counts have been seen in both humans and animals. Further studies on the immunotoxic effects of external cobalt radiation would be useful in refining the minimum effective dose.

Neurotoxicity.

Stable Cobalt. No studies were located regarding neurotoxic effects of cobalt in humans following oral or dermal exposure. Two occupational inhalation exposure studies have reported memory deficits, optic atrophy, or nerve deafness in humans exposed to cobalt (Jordan et al. 1990; Meecham and Humphrey 1991). In animals, alterations in several neurologic parameters were found following oral exposure (Bourg et al. 1985; Krasovskii and Fridlyand 1971; Mutafova-Yambolieva et al. 1994; Nation et al. 1983; Singh and Junnarkar 1991; Vassilev et al. 1993; Wellman et al. 1984). Additional studies in animals would assist in determining whether these neurological effects have any relevance to potential effects in humans.

Radioactive Cobalt. Data on neurotoxic effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Human data following cobalt radiotherapy have demonstrated effects believed to result from neurological damage, but data are limited, doses were extreme, and effects have not been well-characterized. Several animal studies have shown neurobehavioral or neurophysiological changes following exposure to cobalt radiation (Bassant and Court 1978; Maier and Landauer 1989; Mele et al. 1988).

Epidemiological and Human Dosimetry Studies.

Stable Cobalt. Epidemiological studies relating to cobalt exposure are available in the literature. Studies of persons exposed to cobalt occupationally are available (Kusaka et al. 1986a, 1986b; Shirakawa et al. 1988, 1989; Sprince et al. 1988), dietetically (beer drinkers) (Alexander 1969, 1972; Morin et al. 1971), and medically (cobalt given to alleviate anemia) (Davis and Fields 1958; Holly 1955; Taylor et al. 1977).

Further studies assessing the cause/effect relationship between cobalt exposure and human health effects would be helpful in monitoring individuals living near a hazardous waste site to verify that documented exposure levels are not associated with adverse health effects.

Radioactive Cobalt. Epidemiological data on exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Human external exposures to cobalt radiation have been documented in the literature. Radiotherapy exposures, though to extremely high radiation doses, are generally well-controlled and documented, whereas environmental and accidental workplace exposures are less frequent and less well-documented.

Biomarkers of Exposure and Effect.

Exposure.

Stable Cobalt. Information is available on the monitoring of cobalt exposure by the quantification of cobalt in urine and blood (Alexandersson 1988; Ichikawa et al. 1985; Scansetti et al. 1985). A portion of inhaled cobalt is rapidly excreted in the feces, and the amount retained in the body tends to be steadily excreted over time. Levels in body fluids, therefore, can be monitored up to several days after exposure. Many different methods for the detection of cobalt in body fluids have been reported (Section 7.1).

Radioactive Cobalt. No information is available regarding biomarkers specific for exposure to cobalt radionuclides by the inhalation, oral, dermal, or external exposure routes. Biomarkers for exposure to ionizing radiation are discussed in Agency for Toxic Substances and Disease Registry (1999). Personal dosimeters (film or luminescent) are an artificial surrogate to measure the amount of exposure to external beta or gamma radiation, though these are not specific for radiation from cobalt radionuclides.

Effect.

Stable Cobalt. Alterations in serum proteins and changes in serum antibodies have been found that are specific for cobalt exposure (Stokinger and Wagner 1958). These changes may be the earliest indication of the effects of cobalt exposure. Further studies may reveal other cobalt-specific biomarkers that, in

combination with these changes, may alert health professionals to cobalt exposure before serious toxicological effects occur.

Radioactive Cobalt. While in many cases radioactive cobalt itself can be measured following exposure, no information is available regarding biomarkers specific for effects of cobalt radionuclides following exposure by the inhalation, oral, dermal, or external exposure routes. Biomarkers for effects of ionizing radiation are discussed in Agency for Toxic Substances and Disease Registry (1999), and include changes in levels of formed elements of the blood as some of the most sensitive indicators. These biomarkers are believed to be suitable for monitoring exposure to cobalt radiation.

Absorption, Distribution, Metabolism, and Excretion. Pharmacokinetic data in humans indicate that cobalt is absorbed through the lungs (Foster et al. 1989) and the gastrointestinal tract (Harp and Scoular 1952; Sorbie et al. 1971; Valberg et al. 1969), that cobalt is well distributed in the body with the highest concentration being found in the lungs following inhalation (Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Teraoka 1981), and that some of the inhaled or ingested cobalt is rapidly excreted in the feces, with the amount retained in the body being excreted slowly, primarily in the urine (Foster et al. 1989; Paley et al. 1958; Smith et al. 1972). Pharmacokinetic studies in animals following inhalation and oral exposure have demonstrated similar responses (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Foster et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). Few data exist regarding the pharmacokinetics of cobalt following dermal exposure, though what data are available demonstrate that cobalt can be absorbed in small quantities through human (Scansetti et al. 1994) and animal (Inaba and Suzuki-Yasumoto 1979; Lacy et al. 1996) skin, with greater absorption occurring through damaged than intact skin.

Comparative Toxicokinetics. Several inhalation and oral studies have compared the toxicokinetics of cobalt in several different species of animals, including humans (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Foster et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). No comparative pharmacokinetic studies following dermal exposure were located. These studies would be useful because humans are exposed via the skin in the workplace and may potentially be exposed via this route at waste sites.

Methods for Reducing Toxic Effects.

Stable and Radioactive Cobalt. Chelation therapy is expected to apply equally well to stable and radioactive cobalt isotopes. EDTA or British anti-lewisite (BAL) has been shown to effectively mitigate the toxicity of cobalt in humans (Goldfrank et al. 1990; Haddad and Winchester 1990; Stutz and Janusz 1988). In animal studies examining the effectiveness of various chelators, n-acetyl cysteine (NAC) was shown to be the most effective (Llobet et al. 1988). It would be useful to determine the effective dose of NAC in humans. Studies examining the effectiveness of other chelating agents may be helpful in determining the most effective chelation therapy for humans.

Children's Susceptibility.

Stable Cobalt. Data comparing the susceptibility of children to cobalt compounds are limited. Animal studies have suggested that absorption following inhalation or oral exposure may be greater in very young animals, resulting in increased systemic dose. Data are not available on the differences between children and adults following dermal exposure. Further studies on the susceptibility of young animals relative to adult animals may be useful in determining whether children are at greater risk from exposure to cobalt in the environment than adults.

Radioactive Cobalt. No data are available on whether children are more susceptible to the effects of radioactive cobalt compounds than adults. Animal studies have shown that exposure *in utero* to even moderate amounts of cobalt radiation can cause dramatic effects in the developing organism. It would be expected that children would be more susceptible to the effects of external cobalt radiation, due to the greater percentage of rapidly-dividing cells during growth.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.13.3 Ongoing Studies

Relevant ongoing studies were not located for cobalt.

4. CHEMICAL, PHYSICAL, AND RADIOLOGICAL INFORMATION

4.1 CHEMICAL IDENTITY

Cobalt is a naturally-occurring element that appears in the first transition series of Group 9 (VIII) of the periodic table along with iron and nickel. There is only one stable isotope of cobalt, ^{59}Co. There are about 26 known radioactive isotopes of cobalt, of which only two are of commercial importance, ^{60}Co and ^{57}Co. ^{60}Co, a commonly-used source of gamma radiation, is the most important radionuclide. It may be a low-level contaminant of cooling water released by nuclear reactors. Table 4-1 summarizes information on the chemical identity of elemental cobalt and some common cobalt compounds.

4.2 PHYSICAL, CHEMICAL, AND RADIOLOGICAL PROPERTIES

Cobalt commonly occurs in the 0, +2, and +3 valence states. Compounds containing cobalt in the -1, +1, +4, and +5 oxidation state are few and uncommon (Cotton and Wilkinson 1980). Cobalt (II) is much more stable than Co(III), and Co^{3+} is a sufficiently powerful oxidizing agent to oxidize water, liberating oxygen. Table 4-2 summarizes important physical and chemical properties of elemental cobalt and some common cobalt compounds. These properties are similar to those of its neighbors in Group 9 of the periodic table, iron and nickel. Metallic cobalt, Co(0), occurs as two allotropic forms, hexagonal and cubic; the hexagonal form is stable at room temperature. A biochemically important cobalt compound is vitamin B_{12}, or cyanocobalamin, in which cobalt is complexed with four pyrrole nuclei joined in a ring called the corrinoid ligand system (similar to porphyrin).

The Chemical Abstract Service (CAS) registry numbers, decay modes, half-lives, and specific activity of the three principal radioactive cobalt isotopes, ^{57}Co, ^{58}Co, and ^{60}Co, are presented in Table 4-3. ^{60}Co (half-life of 5.27 years) decays by beta decay to nickel-60, a stable isotope (ICRP 1983; Lide 1998).

$$^{60}_{27}\mathrm{Co} \rightarrow ^{60}_{28}\mathrm{Ni} + ^{0}_{-1}e + \gamma$$

Table 4-1. Chemical Identity of Cobalt and Selected Compounds

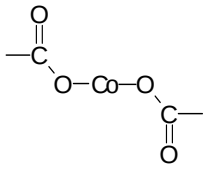
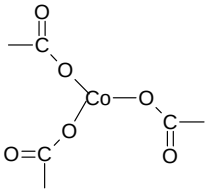
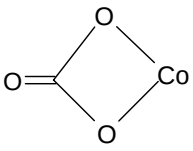
Characteristic	Cobalt	Cobalt(II) acetate	Cobalt(III) acetate	Cobalt(II) carbonate
Synonym(s)	Cobalt-59, cobalt metal	Cobaltous acetate, cobalt diacetate	Cobaltic acetate, cobalt triacetate	Cobaltous carbonate; carbonic acid; cobalt (+2) salt
Registered trade name(s)	No data	No data	No data	No data
Chemical formula	Co	$Co(C_2H_4O_2)_2$	$Co(C_2H_4O_2)_3$	$CoCO_3$
Chemical structure	Co			
Identification numbers:				
CAS registry	7440-48-4	71-48-7	917-69-1	513-79-10
NIOSH RTECS	GF8750000	AG3150000	No data	FF9450050
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping[a]	UN1318	No data	No data	No data
HSDB	519	997	No data	No data
NCI	C60311	No data	No data	No data

Table 4-1. Chemical Identity of Cobalt and Selected Compounds

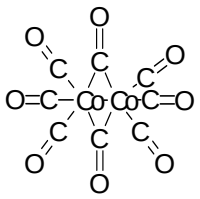
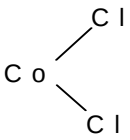
Characteristic	Cobalt carbonyl	Cobalt(II) chloride	Cobalt(II) hydroxide	Cobalt(II) meso-porphyrin
Synonym(s)	Dicobalt octa-carbonyl; cobalt tetracarbonyl	Cobalt dichloride; cobaltous chloride	Cobaltous hydr-oxide; cobalt dihydroxide	Cobalt meso-porphyrin IX Cobalt-iprotoporphyrin
Registered trade name(s)	No data	No data	No data	No data
Chemical formula	$Co_2(CO)_8$	$CoCl_2$	$Co(OH)_2$	$C_{34}H_{34}CoN_4O_4$
Chemical structure			HO—Co—OH	No data
Identification numbers:				
CAS registry	10210-68-1	7646-79-9	21041-93-0	21158-51-0
NIOSH RTECS	GG0300000	GF9800000	No data	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	7217328	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	6345	1000	No data	No data
NCI	No data	No data	No data	No data

Table 4-1. Chemical Identity of Cobalt and Selected Compounds

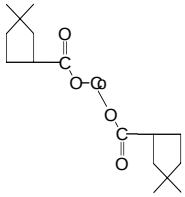
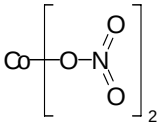
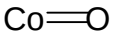
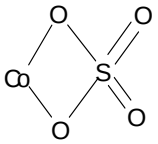
Characteristic	Cobalt(II) naphthenate	Cobalt(II) nitrate	Cobalt(II) oxide	Cobalt(III) oxide
Synonym(s)	Naftolite; naphthenic acid, cobalt salt	Cobaltous nitrate	Black 13; C.I. 77322; cobalt monoxide; cobaltous oxide	Cobalt black; cobaltic oxide; cobalt sesquioxide; cobalt trioxide; C.I. 77323
Registered trade name(s)	No data	No data	C.I. Pigment Black 13; Zaffre	No data
Chemical formula	$Co(C_{11}H_{10}O_2)_2$	$Co(No_3)_2•6H_20$	CoO	Co_2O_3
Chemical structure				
Identification numbers:				
CAS registry	10210-68-1	7646-79-9	21041-93-0	21158-51-0
NIOSH RTECS	GG0300000	GF9800000	No data	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	7217328	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	6345	1000	No data	No data
NCI	No data	No data	No data	No data

Table 4-1. Chemical Identity of Cobalt and Selected Compounds

Characteristic	Cobalt(II, III) oxide	Cobalt(II) sulfate
Synonym(s)	Cobaltic-cobaltous oxide; cobalt tetra-oxide, tricobalt tetraoxide, cobaltosic oxide; cobalt black; C.I. Pigment Black 13	Cobalt sulfate; cobaltous sulfate
Registered trade name(s)	No data	No data
Chemical formula	Co_3O_4	$CoSO_4$
Chemical structure	Co=OO=Co–O–Co=O	
Identification numbers:		
CAS registry	1308-06-1	10124-43-3
NIOSH RTECS	No data	GG3100000
EPA hazardous waste	No data	No data
OHM/TADS	No data	7217330
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	No data	240
NCI	No data	No data

[a]The identification number for radioactive materials is UN2910

CAS = Chemical Abstract Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Source: Budavari 1996; HSDB 2001; RTECS 1987

Table 4-2. Physical and Chemical Properties of Cobalt and Selected Compounds

Property	Cobalt	Cobalt(II) acetate	Cobalt(III) acetate	Cobalt(II) carbonate
Molecular weight	58.93	177.03	236.07	118.94
Color	Silvery gray	Light pink	Dark green	Red
Physical state	Solid	Solid	Solid	Solid
Melting point, °C	1,495	No data	Decomposes at 100 °C	Decomposes
Boiling point, °C	2,870	No data	Not relevant	Not relevant
Density, g/cm^3	8.9 (20 °C)	No data	No data	4.13
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	Soluble	Soluble	0.18 g/100 g H_2O at 15 °C
Organic solvent(s)	Insoluble	2.1 g/100 g methanol at 15 °C	soluble in alcohol, acetic acid	Insoluble in ethanol
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1 mmHg at 1,910 °C	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	760 °C for dust cloud	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[a]	Not relevant[a]	Not relevant[a]	Not relevant[a]
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Cobalt and Selected Compounds

Property	Cobalt carbonyl	Cobalt(II) chloride	Cobalt(II) hydroxide	Cobalt(II) mesoporphyrin
Molecular weight	341.9	129.84	92.95	621.2[b]
Color	Orange (white when pure)	Blue	Rose red or blue green	No data
Physical state	Solid	Solid	Solid	No data
Melting point, °C	51	724	No data	No data
Boiling point, °C	Decomposes	1,049	No data	No data
Density, g/cm^3	1.73 at 18 °C	3.356 (36 °C)	3.597 at 15 °C	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	450 g/L at 7 °C	0.0032 g/L	No data
Organic solvent(s)	Soluble in ether; insoluble in naphtha	544 g/L in ethanol; 86 g/L in acetone	No data	No data
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	199.5 at 25 °C	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature, °C	No data	No data	No data	No data
Flashpoint, °C	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[a]	Not relevant[a]	Not relevant[a]	Not relevant[a]
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Cobalt and Selected Compounds

Property	Cobalt(II) naphthenate	Cobalt(II) nitrate	Cobalt(II) oxide	Cobalt(III) oxide
Molecular weight	407	182.94	74.93	165.86
Color	No data	Red	Pink	Black-gray
Physical state	Solid	Solid	Solid	Solid
Melting point, °C	140	Decomposes at 100–105[b]	1,795	895 (decomposes)
Boiling point, °C	No data	Not relevant	No data	Not relevant
Density g/cm^3	0.9	2.49[b]	6.45	5.18
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	133.8 at 0 °C[c]	Insoluble	Insoluble
Organic solvent(s)	No data	Soluble in ethanol, acetone	Insoluble in alcohol	Insoluble in ethanol
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{ow}	No data	No data	No data	No data
Vapor pressure	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[a]	Not relevant[a]	Not relevant[a]	Not relevant[a]
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Cobalt and Selected Compounds

Property	Cobalt(II, III) oxide	Cobalt(II) sulfate
Molecular weight	250.80	154.99
Color	Black	Dark blue
Physical state	Solid	Solid
Melting point, °C	-O_2 at 900–950	Decomposes at 735 °C
Boiling point, °C	Not relevant	Not relevant
Density g/cm^3	6.07	3.71
Odor	No data	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water	Insoluble	3.83 g/100 mL H_2O at 25 °C
Organic solvent(s)	No data	1.04 g/100 mL methanol at 18 °C
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{ow}	No data	No data
Vapor pressure	No data	No data
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	Not relevant[a]	Not relevant[a]
Explosive limits	No data	No data

[a]Substances exist in the atmosphere in the particulate state, and the concentration is expressed in weight per cubic meter
[b]CAS Online
[c]Hexahydrate

Source: Budavari 1996; HSDB 2001, 2004; Lide 1994; Stockinger 1981; Weast 1985

Table 4-3. Principal Radioactive Cobalt Isotopes

				Beta radiation		Gamma radiation		
Isotope	CAS registry no.	Decay mode (product)	Decay mode energy (MeV)	Energy (MeV)	Intensity (percent)	Energy (MeV)	Intensity (percent)	Half-life
^{55}Co	13982-25-7	E.C. β^+ (^{55}Fe)	3.452	1.498	46	0.9312	75	17.53 hours
				1.021	25.6	0.4772	20	
				2.043	10.7	1.408	16.88	
^{57}Co	13981-50-5	E.C. (^{57}Fe)	0.836	0.700	99.8	0.1221	85.6	271.8 days
						0.1365	10.7	
						0.014	9.2	
^{58}Co	13981-38-9	E.C. β^+ (^{58}Fe)	2.30	1.4966	83.9	0.811	99	70.86 days
				0.4746	14.9			
^{60}Co	10198-40-0	β^- (^{60}Ni)	2.824	0.3181	99.9	1.173	100	5.271 years
						1.332	100	

B^- = negative beta emission; β^+ = positron emission; E.C. = orbital electron capture

Source: ICRP 1983; LBNL 2000; Lide 1998

The decay is accompanied by the emission of 1.173 and 1.332 MeV gamma rays. ^{57}Co (half-life of 271.8 days) and ^{58}Co (half-life of 70.9 days) decay by electron capture and electron capture/position (β+) emission to ^{57}Fe and ^{58}Fe, respectively. These decay processes are also accompanied by gamma emissions (Table 4-3).

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Cobalt is the 33rd most abundant element, comprising approximately 0.0025% of the weight of the earth's crust. It is often found in association with nickel, silver, lead, copper, and iron ores and occurs in mineral form as arsenides, sulfides, and oxides. The most import cobalt minerals are: linnaeite, Co_3S_4; carrolite, $CuCo_2S_4$; safflorite, $CoAs_2$; skutterudite, $CoAs_3$; erythrite, $Co_3(AsO_4)_2 \cdot 8H_2O$; and glaucodot, CoAsS (Hodge 1993; IARC 1991; Merian 1985; Smith and Carson 1981). The largest cobalt reserves are in the Congo (Kinshasa), Cuba, Australia, New Caledonia, United States, and Zambia. Most of the U.S. cobalt deposits are in Minnesota, but other important deposits are in Alaska, California, Idaho, Missouri, Montana, and Oregon. Cobalt production from these deposits, with the exception of Idaho and Missouri, would be as a byproduct of another metal (USGS 2004). Cobalt is also found in meteorites and deep sea nodules.

The production of pure metal from these ores depends on the nature of the ore. Sulfide ores are first finely ground (i.e., milled) and the sulfides are separated by a floatation process with the aid of frothers (i.e., C_5–C_8 alcohols, glycols, or polyethylene or polypropylene glycol ethers). The concentrated product is subjected to heating in air (roasting) to form oxides or sulfates from the sulfide, which are more easily reduced. The resulting matte is leached with water and the cobalt sulfate leachate is precipitated as its hydroxide by the addition of lime. The hydroxide is dissolved in sulfuric acid, and the resulting cobalt sulfate is electrolyzed to yield metallic cobalt. For the cobalt-rich mineral cobaltite, a leaching process with either ammonia or acid under pressure and elevated temperatures has been used to extract cobalt. The solution is purified to remove iron and is subsequently reduced by hydrogen in the presence of a catalyst under elevated temperature and pressure to obtain fine cobalt powder (Duby 1995; Nagaraj 1995; Planinsek and Newkirk 1979).

Except for a negligible amount of byproduct cobalt produced from some mining operations, no cobalt is presently mined or refined in the United States. In addition to byproduct production, U.S. production is derived from scrap (secondary production). In 2003, an estimated 2,200 metric tons of cobalt were recycled from scrap (USGS 2004). Since 1993, production has been supplemented by sales of excess cobalt from the National Defense Stockpile (NDS), which the government maintains for military,

industrial, and essential civilian use during national emergencies. In fiscal year 2002, 2,720 metric tons of cobalt were released from the NDS. In 2001, the United States did not mine or refine cobalt, with the exception of small amounts of byproduct cobalt produced from mining operations in Missouri and Montana. The 2002 U.S. consumption of cobalt metal, organic and inorganic cobalt compounds, and purchased scrap (in terms of cobalt content) was 3,870, 1,270, and 2,800 metric tons, respectively (USGS 2002).

Current U.S. manufacturers of selected cobalt compounds are given in Table 5-1. Table 5-2 lists facilities in each state that manufacture, process, or use cobalt or cobalt compounds, the intended use, and the range of maximum amounts of these substances that are stored on site. In 2000, there were 618 reporting facilities that produced, processed, or used cobalt or cobalt compounds in the United States. The data listed in Table 5-2 are derived from the Toxics Chemicals Release Inventory (TRI) (TRI01 2004). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

^{60}Co is produced by irradiating stable cobalt, ^{59}Co, with thermal neutrons in a nuclear reactor: $^{59}Co(n,\gamma)^{60}Co$. The neutron flux employed is 10^{12}–10^{15} *n*/cm^2-sec and the conversion is 99%. The maximum specific activity obtained is $3.7x10^{13}$ Bq/g (1,000 Ci/g). Commercial ^{60}Co sources used for bacterial sterilization are made into rods with double metal shielding. The individual sources have an activity of about $2x10^{14}$–$6x10^{14}$ Bq (6–15 kCi). The annual output of ^{60}Co was about $2x10^{18}$–$3x10^{18}$ Bq (50–80 MCi) in the early 1990s. In 1991, there were 170 gamma irradiation systems operating in 45 countries having a total activity of about $6x10^{18}$ Bq (160 MCi) (Zyball 1993). Producers of ^{60}Co include MDS Nordion in Canada, AEA Technology (formerly Amersham QSA) in the United Kingdom, and Neutron Products in Dickerson, Maryland.

^{58}Co is not produced commercially. It can be produced by irradiating ^{58}Ni, a stable isotope, with neutrons, followed by positron decay: $^{58}Ni(n,\gamma)^{58}Co$. It can be produced in a nuclear reactor or a cyclotron. Both ^{60}Co and ^{58}Co may be produced unintentionally in reactors. These are the dominant sources of residual radiation in the primary circuit outside the reactor core of nuclear plants and are formed by neutron absorption of ^{59}Co and ^{58}Ni, both stable isotopes commonly used in plant construction materials (Taylor 1996). ^{60}Co is commonly found as one of the radionuclides present in the low-level radioactive waste discharges from many nuclear power plants; however, amounts rarely make a significant contribution to the radiation exposure of the public (Leonard et al. 1993a). The geometric

Table 5-1. Current U.S. Manufacturers of Cobalt Metal and Selected Cobalt Compounds[a]

Company	Location
Cobalt metal[b]:	
Kennametal, Inc.	Latrobe, Pennsylvania
OM Group, Inc.	Cleveland, Ohio
Cobalt (II) acetate:	
The IMC Group	Shelby, North Carolina
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OM Group, Inc.	Franklin, Pennsylvania
The Shepard Chemical Company	Cincinnati, Ohio
Cobalt (II) carbonate:	
The IMC Group	Shelby, North Carolina
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OMG Apex	St. George, Utah
OM Group, Inc.	Franklin, Pennsylvania
The Shepherd Chemical Co.	Cincinnati, Ohio
Cobalt (II) chloride:	
The IMC Group	Shelby, North Carolina
Johson Matthey, Inc., Alfa Aesar	Ward Hill, Massachusetts
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OM Group. Inc.	Franklin, Pennsylvania
The Shepard Chemical Company	Cincinnati, Ohio
Cobalt (II) hydroxide:	
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OM Group, Inc.	Franklin, Pennsylvania
The Shepard Chemical Company	Cincinnati, Ohio
Cobalt (II) nitrate:	
The IMC Group	Shelby, North Carolina
Johnson Matthey, Inc., Alfa Aesar	Ward Hill, Massachusetts
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OMG Apex	St. George, Utah
OM Group, Inc.	Franklin, Pennsylvania
The Shepard Chemical Company	Cincinnati, Ohio
Umicore USA, Inc., Cobalt Products	Laurinburg, North Carolina
Cobalt (II) oxide:	
OMG Apex	St. George, Utah
The Shepard Chemical Company	Cincinnati, Ohio

Table 5-1. Current U.S. Manufacturers of Cobalt Metal and Selected Cobalt Compounds[a]

Cobalt (III) oxide:	
Johnson Matthey, Inc., Alfa Aesar	Ward Hill, Massachusetts
Mallinckrodt Baker, Inc.	Phillipsburg, New Jersey
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OM Group, Inc.	Franklin, Pennsylvania
Osram Sylvania Inc.	Towanda, Pennsylvania
Cobalt (II) sulfate:	
The IMC Group	Shelby, North Carolina
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OMG Apex	St. George, Utah
OM Group, Inc.	Franklin, Pennsylvania
The Shepard Chemical Company	Cincinnati, Ohio

[a]Derived from Stanford Research Institute (SRI) 2003, except where otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed

[b]U.S. members of The Cobalt Development Institute that are listed as producers of cobalt powder or hard metal products

Table 5-2. Facilities that Produce, Process, or Use Cobalt and Cobalt Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	2	10,000	999,999	1, 5, 7, 12
AL	22	100	999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 12, 13
AR	9	100	99,999	1, 5, 7, 8,9
AZ	12	1,000	49,999,999	1, 2, 3, 5, 7, 8,9, 10, 12, 13, 14
CA	28	0	9,999,999	1, 2, 3, 5, 6, 7, 8,9, 10, 11, 12
CO	1	10,000	99,999	12
CT	9	0	999,999	2, 3, 7, 8
DE	2	1,000	9,999	1, 5,9, 13
FL	11	0	99,999	1, 2, 3, 4, 5, 6, 7, 8,9, 12, 13, 14
GA	17	100	999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 11, 12, 13
IA	6	100	99,999	3, 4, 7, 8, 12
ID	2	100,000	999,999	1, 3, 5, 12
IL	24	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 13, 14
IN	42	100	999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 13, 14
KS	5	10,000	99,999	1, 3, 5, 6, 7, 8,9, 10, 11, 12, 13
KY	22	100	999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 12, 13, 14
LA	15	1,000	999,999	1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14
MA	11	100	99,999	1, 5, 8,9, 12
MD	6	1,000	99,999	1, 2, 3, 4, 5, 6, 7,9, 13
ME	2	100	99,999	1, 5, 8
MI	24	0	999,999	1, 2, 3, 4, 5, 7, 8,9, 11, 12, 13, 14
MN	6	100	99,999	1, 2, 5, 7, 8,9, 10, 12, 13, 14
MO	5	1,000	999,999	1, 2, 3, 4, 5, 6, 8,9, 12, 13, 14
MS	7	100	99,999	1, 5, 6, 7, 8, 10
MT	1	10,000	99,999	1, 5, 12, 14
NC	24	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 12, 13, 14
ND	4	1,000	99,999	1, 5, 7, 12, 13, 14
NE	1	1,000	9,999	8, 11
NH	1	100	999	8
NJ	14	1,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 10, 12, 14
NM	6	1,000	9,999,999	1, 3, 4, 5, 7, 8,9, 11, 12, 13
NV	8	1,000	10,000,000,000	1, 5, 6, 8, 12, 13, 14
NY	12	1,000	99,999	1, 2, 3, 4, 5, 7, 8,9, 11, 12
OH	44	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 11, 12, 13, 14
OK	14	100	999,999	1, 2, 3, 5, 6, 7, 8,9, 10, 11, 12
OR	6	1,000	99,999	1, 5, 7, 8, 12
PA	44	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Cobalt and Cobalt Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PR	2	1,000	99,999	8,9
RI	1	100,000	999,999	8
SC	26	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 13
SD	1	10,000	99,999	7
TN	18	0	999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 12, 13
TX	45	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 13, 14
UT	6	1,000	9,999,999	1, 3, 4, 5, 7, 8,9, 12, 13
VA	9	10,000	999,999	1, 2, 3, 4, 5, 6, 7, 8
VI	1	10,000	99,999	10
WA	2	10,000	99,999	1, 3, 4, 5,9, 10, 11, 12, 13
WI	20	100	999,999	1, 3, 4, 5, 7, 8,9, 11, 12, 13, 14
WV	13	100	999,999	1, 2, 3, 4, 5, 7, 8,9, 11, 12, 13, 14
WY	2	0	99,999	1, 5,9, 12, 13

Source: TRI01 2004

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

mean release of ^{60}Co in liquid effluents of light-water nuclear power stations was reported as in the early 1970s as 0.0805 Ci/year (3.0 GBq) (Morgan 1976).

The ^{60}Co activities for a representative pressurized-water reactor (PWR) and boiling water reactor (BWR) fuel assemblies are 1,100 and 170 Ci (41 and 6.3 TBq), respectively. There are 78 PWR and 40 BWR reactors in the United States, several of which have ceased operation. The postirradiation cobalt content of typical PWR and BWR reactor fuel assemblies are 38 g (0.01%) and 26 g (0.01%), respectively (DOE 2002).

^{55}Co may be produced by applying 12 MeV indirect deuteron energy to ^{54}Fe (^{54}Fe(d,n)^{55}Co), 40 MeV protons to natural iron (^{56}Fe(p,2n)^{55}Co), or 20 MeV protons to natural nickel foil (^{58}Ni(p,α)^{55}Co) followed by separation of the ^{55}Co on an ion exchange column (Wolf 1955). Due to the short half-life (17.5 hours), however, ^{55}Co would not be persistent in the environment or in waste sites. ^{57}Co (half-life of 270 days) is produced by AEA Technology (formerly Amersham QSA) in the United Kingdom (Web Research Co. 1999).

5.2 IMPORT/EXPORT

In 2002, 8,450 metric tons of cobalt were imported into the United States compared with 7,670, 8,150, 8,770, and 9,410 metric tons in 1998, 1999, 2000, and 2001 (USGS 2002). Between 1999 and 2002, Finland, Norway, Russia, and Canada supplied 24, 18, 13, and 10% of cobalt, respectively (USGS 2004). Imports for 2002 by form included (form, metric tons cobalt content): metal, 6,800; oxides and hydroxides, 936; acetates, 84; carbonates, 60; chlorides, 22; and sulfates 545. Cobalt exports for 1999, 2000, 2001, and 2002 were 1,550, 2,630, 3,210, and 2,080 metric tons, respectively; exports estimated in 2002 are 2,500 metric tons (USGS 2002; 2004).

^{60}Co and ^{57}Co are produced in Canada and in the United Kingdom and are imported from these countries. No import and export quantities for cobalt radioisotopes were available.

5.3 USE

The United States is the world's largest consumer of cobalt. Cobalt is used in a number of essential military and industrial applications. The largest use of metallic cobalt is in superalloys that are used in gas turbines aircraft engines. Superalloys are alloys developed for applications where elevated temperatures and high mechanical stress are encountered. It is also used in magnetic alloys and alloys that are required for purposes requiring hardness, wear resistance, and corrosion resistance. Cobalt is used as a binder for tungsten carbide (cemented carbides) cutting tools to increase impact strength. Cobalt compounds are used as pigments in glass, ceramics, and paints; as catalysts in the petroleum industry; as paint driers; and as trace element additives in agriculture and medicine.

Over 40% of nonmetallic cobalt is used in catalysis, and most cobalt catalysts are used in hydrotreating/desulfurization in the oil and gas industry, the production of terephthalic acid and dimethylterephthalate, and the production of aldehydes using the high pressure oxo process (hydroformylation). Cobalt chemicals primarily used as catalysts include cobalt(III) acetate, cobalt(II) bromide, carbonate, manganate, oxalate, and sulfide, cobalt carbonyl, and cobalt naphthenate. Cobalt carbonate and chromate are mainly used as pigments and cobalt(II) acetate, 2-ethylhexanoate, linoleate, naphthenate, nitrate, oleate, and stearate are mainly used as driers. Cobalt has been used for hundreds of years as a blue colorant in glass, ceramics, and paints (Richardson 1993).

A growing use for cobalt is as an addition to the Ni/Cd, Ni-metal hydride battery or as the main component of the lithium ion cell ($LiCoO_2$). In 2002, the reported U.S. cobalt consumption was 7,930 metric tons with a use pattern of (end use, metric tons cobalt content, percent): superalloys, 3,700, 46.7%; steel alloys, 555, 7.0%; other alloys, including magnetic alloys, 1,050, 13.2%; cemented carbides, 617, 7.8%; chemical and ceramic use, 1,950, 24.6%; and miscellany, 63, 0.8%. Cobalt is also used a target material in electrical x-ray generators (Cobalt Development Institute 2004; Donaldson 1986; Hodge 1993; IARC 1991; Richardson 1993; USGS 2002).

Gamma rays from ^{60}Co are used medically to treat cancer and industrially to sterilize medical and consumer products, to crosslink, graft and degrade plastics, and as an external source in radiography and radiotherapy. ^{60}Co, along with iridium 192 (^{192}Ir), are the most commonly used isotopes in industrial radiography. In this application, ^{60}Co is used for nondestructive testing of high-stress alloy parts, such as pipeline weld joints, steel structures, boilers, and aircraft and ship parts. Radiography may be conducted

at permanent, specially shielded facilities or temporary sites in the field (USNRC 1999). ^{60}Co is used in chemical and metallurgical analysis and as a tracer in biological studies. In 1990, about 95% of installed ^{60}Co activity was used for the sterilization of medical devices; about 45% of medical devices were sterilized using radiation. ^{60}Co is also a source of gamma rays used for food irradiation; depending on the dose levels, irradiation may be used to sterilize food, destroy pathogens, extend the shelf-life of food, disinfest fruits and grain, delay ripening, and retard sprouting (e.g., potatoes and onions). Sludge, waste water, and wood may also be treated with gamma rays to kill harmful organisms.

^{57}Co decays to an excited state of ^{57}Fe, the most widely used x-ray source in Mössbauer spectroscopy (Hodge 1993; Richardson 1993). It is also made into standards and sources for dose calibrators, gamma cameras, and gauges, and is used as markers and rulers to help estimate organ size/location. It is also used in *in vitro* diagnostic kits for the study of anemia related to vitamin B_{12} deficiency/malabsorption (MDS Nordion 2000). ^{55}Co-bleomycin has been used for scanning malignant tumors (e.g., lung and brain cancer) and is a practical isotope for positron emission tomography (PET) studies because it mainly (81%) decays by positron emission.

5.4 DISPOSAL

There is a paucity of data on the methods of disposal of cobalt and its compounds. Due to the lack of natural sources of economically extractable ores in the United States, cobalt is entirely imported in the United States, and it is considered a strategic mineral. It is economical to recycle certain cobalt wastes rather than to dispose of them. Recycling of superalloy scrap is an important method for the recovery of cobalt. About 2,200 metric tons of cobalt were recycled from purchased scrap in 2003. This was about 28% of reported consumption for the year (USGS 2004). According to TRI (TRI01 2004), 7.14 and 1.42 million pounds of cobalt and cobalt compounds combined were recycled onsite and offsite, respectively, in 2001. Waste containing cobalt dust and, presumably, waste containing cobalt in the solid state may be placed in sealed containers and disposed of in a secured sanitary landfill (HSDB 1989). Waste water containing cobalt can be treated before disposal, for instance, by precipitation of carbonate or hydroxide of cobalt or by passage through an ion-exchange resin (Clifford et al. 1986). According to TRI (TRI01 2004), 1,619,874 pounds of cobalt and cobalt compounds, were transferred offsite for disposal, in processes such as solidification/stabilization and waste water treatment, including publicly operated treatment plants (POTWs). The amount of cobalt so transferred by state is shown in Table 6-1.

In August 1998, EPA issued a final rule listing spent hydrotreated and hydrorefined catalysts as hazardous waste under the Resource Conservation and Recovery Act (USGS 1998). Listing under this act requires that releases of these substances will be subject to certain management and treatment standards and emergency notification requirements. Information regarding effluent guidelines and standards for cobalt may be found in Title 40 of the Code of Federal Regulations, Parts 421.230, 421.310, and 471.30.

^{60}Co sources used for irradiation purposes are valuable and are not to be discarded. However, some radioactive cobalt isotopes may occur in waste material from nuclear reactors. Radioactive waste is categorized according to origin, type of waste present, and level of activity. Radioactive cobalt isotopes may be commingled with other radioactive isotopes. The first distinction in radioactive waste is between defense waste and commercial waste, the former being generated during and after World War II principally at the Department of Energy (DOE) facilities at Hanford, Washington; Savannah River, South Carolina; and Idaho Falls, Idaho, where plutonium and other isotopes were separated from production reactor spent fuel or nuclear-powered naval vessels. Commercial wastes are produced predominantly by nuclear power plants as well as the long defunct commercial reprocessing facility at West Valley, New York and manufacturers of radioisotopes used in nuclear medicine for the treatment and diagnosis of disease. Nuclear waste is also classified as high-level waste (HLW), transuranic waste (TRU), and low-level waste (LLW). LLW is further differentiated into three classes, A, B, and C, according to increasing of the level of activity. A fourth category, commercial greater-than-class-C LLW (listed in 10 CFR 61.55 Tables 1 and 2 for long and short half-life radionuclides, respectively) is not generally suitable for near-surface disposal. This could include operating and decommissioning waste from nuclear power plant and sealed radioisotope sources. The final disposition for this waste has not been determined. If LLW also contains nonradioactive hazardous material (i.e., that which is toxic, corrosive, inflammable, or explosive), it is termed mixed waste. Mine tailings from uranium mining is yet another category of radioactive waste (DOE 1999; Murray 1994). While radioactive cobalt would not ordinarily be found in HLW or TRU, the definitions of these are included below for completion.

TRUs are those containing isotopes, like plutonium, that are above uranium in the periodic table and whose half-lives are >20 years. If their level of activity is <100 nanocuries (nCi) (<3,700 becquerels[Bq]) of alpha-emitters per gram of waste material (up from 10 nCi/g in 1982), the waste could be disposed of by shallow burial. Otherwise, the waste must be placed in retrievable storage for eventual transfer to a

permanent repository. The level of radioactivity in TRUs is generally low; they generate very little heat and can be handled by ordinary means without remote control (Eisenbud 1987, Murray 1994).

HLW includes spent fuels that are contained in fuel rods that have been used in a nuclear reactor. These may contain small amounts of transuranic elements. After removal from the reactor, these rods are placed into pools adjacent to the commercial nuclear power plants and DOE facilities where they were produced. It was originally intended that the fuel rods remain in these pools for only about 6 months to allow for a reduction in short-lived radioactivity and rate of heat production temperature and then be transferred to a reprocessing or storage facility. There is no commercial reprocessing facility or permanent disposal facility for HLW operating in the United States. The U.S. Nuclear Regulatory Commission (USNRC) has issued standards for the disposal of HLW (10 CFR 60), and the DOE is pursuing the establishment of an HLW facility in Yucca Mountain, Nevada. Efforts to establish an HLW facility, which began over 2 decades ago, have experienced many delays (Eisenbud 1987; Murray 1994). However, in July, 2002, the U.S. Congress and the President selected Yucca Mountain, Nevada as the nation's first long-term repository for HLW. The facility is projected to begin operation in 2010, and efforts are underway to consider establishing a nearby interim facility (DOE 2002b).

LLWs are officially defined as wastes other than those previously defined. These wastes come from certain reactor operations and from manufacturers of radioisotopes used in nuclear medicine and institutions such as hospitals, universities, and research centers. Most LLW contain very little radioactivity and contain practically no transuranic elements. It requires little or no shielding or special handling and may be disposed of by shallow burial. However, some LLW contains sufficient radioactivity as to require special treatment. Although USNRC regulations for LLW disposal (10 CFR 61) permit shallow land burial, many states have enacted more stringent regulations that require artificial containment of the waste in addition to natural containment (Eisenbud 1987; Murray 1994). The EPA has the authority to set generally acceptable environmental standards for LLW that would be implemented by the US NRC and DOE (EPA 2004). The Manifest Information Management System (MIMS), maintained by the Idaho National Engineering and Environmental Laboratory (INEEL), contains information on low-level radioactive waste shipments received at commercial low-level radioactive waste disposal facilities at Barnwell, South Carolina (1/1/86–present), Beaty, Nevada (4/1/86–12/31/92), Richland, Washington(1/1/86–present), and Envirocare, Utah (1/1/98–12/31/99). In 1999, 17 Ci (0.63 TBq) of ^{57}Co, 1,300 Ci (48 TBq) of ^{58}Co, and 1.08×10^{6} Ci (4.00×10^{4} TBq) of ^{60}Co contained in LLW was received at these facilities from academic, industrial, government, and utility generators throughout the United

States (INEL 2000). In addition, 4.26 Ci (0.158 TBq) of ^{57}Co of NARM ("naturally occurring and accelerator-related waste") was received.

At present, DOE stores most of its spent fuel at three primary locations: the Hanford site, Washington, the Idaho National Engineering and Environmental Laboratory (INEEL), Idaho, and the Savannah River site, South Carolina. Some spent fuel is also stored at the dry storage facility at Fort St. Vrain in Colorado. Much smaller amounts of spent nuclear fuel stored at other sites were to be shipped to the three prime sites for storage and preparation for ultimate disposal (DOE 1999). The DOE National Spent Fuel Program maintains a spent nuclear fuel database that lists the total volume, mass, and metric tons heavy metal (MTHM) of 16 DOE categories of spent nuclear fuel stored in each of the three locations. The categories having the highest ^{60}Co activities per spent nuclear fuel canister (decayed to 2030) are 'naval surface ship fuel' and 'naval submarine fuel'. The ^{58}Co and ^{60}Co solid wastes stored on the Hanford site in 1998 as LLW were 2,600 and 6,900 Ci (96 and 260 TBq), respectively (Hanford 1999). In addition, 40 Ci (1.5 TBq) of ^{60}Co was included in TRU.

In commercial irradiators, additional quantities of ^{60}Co are added, usually once a year to maintain preferred radiation levels of the source (MDS Nordion 2000). ^{60}Co sources are removed from the facility at the end of their useful life, which is typically 20 years. In general, manufacturers of ^{60}Co sources guarantee to accept the sources they originally supplied. These old sources may be reencapsulated, reprocessed, or recycled when technically, environmentally, and economically feasible.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Stable cobalt has been identified in at least 426 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). Radioactive cobalt as ^{60}Co has been identified in at least 13 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA NPL (HazDat 2004). However, the number of sites evaluated for stable cobalt and ^{60}Co is not known. The frequency of these sites can be seen in Figures 6-1 and 6-2, respectively. Of the cobalt sites, 421 are located within the United States, 1 is located in Guam (not shown), 3 are located in the Commonwealth of Puerto Rico (not shown), and 1 is located in the Virgin Islands (not shown). All of the sites at which ^{60}Co has been identified are located within the United States.

Cobalt occurs naturally in the earth's crust, and therefore, in soil. Low levels of cobalt also occur naturally in seawater and in some surface water and groundwater (Smith and Carson 1981). However, elevated levels of cobalt in soil and water may result from anthropogenic activities such as the mining and processing of cobalt-bearing ores, the application of cobalt-containing sludge or phosphate fertilizers to soil, the disposal of cobalt-containing wastes, and atmospheric deposition from activities such as the burning of fossil fuels and smelting and refining of metals (Smith and Carson 1981). Cobalt is released into the atmosphere from both anthropogenic and natural sources. However, emissions from natural sources are estimated to slightly exceed those from manufactured sources. Natural sources include windblown soil, seawater spray, volcanic eruptions, and forest fires. Primary anthropogenic sources include fossil fuel and waste combustion, vehicular and aircraft exhausts, processing of cobalt and cobalt-containing alloys, copper and nickel smelting and refining, and the manufacture and use of cobalt chemicals and fertilizers derived from phosphate rocks (Barceloux 1999; Lantzy and Mackenzie 1979; Nriagu 1989; Smith and Carson 1981). ^{60}Co and ^{58}Co, both radioactive forms of cobalt, may be released to the environment as a result of nuclear research and development, nuclear accidents, operation of nuclear power plants, and radioactive waste dumping in the sea or in radioactive waste landfills.

Cobalt compounds are nonvolatile and cobalt will be emitted to the atmosphere only in particulate form. Their transport in air depends on their form, particle size and density, and meteorological conditions. Cobalt so released will return to land or surface water as wet or dry deposition. Coarse particles, those

Figure 6-1. Frequency of NPL Sites with Cobalt Contamination

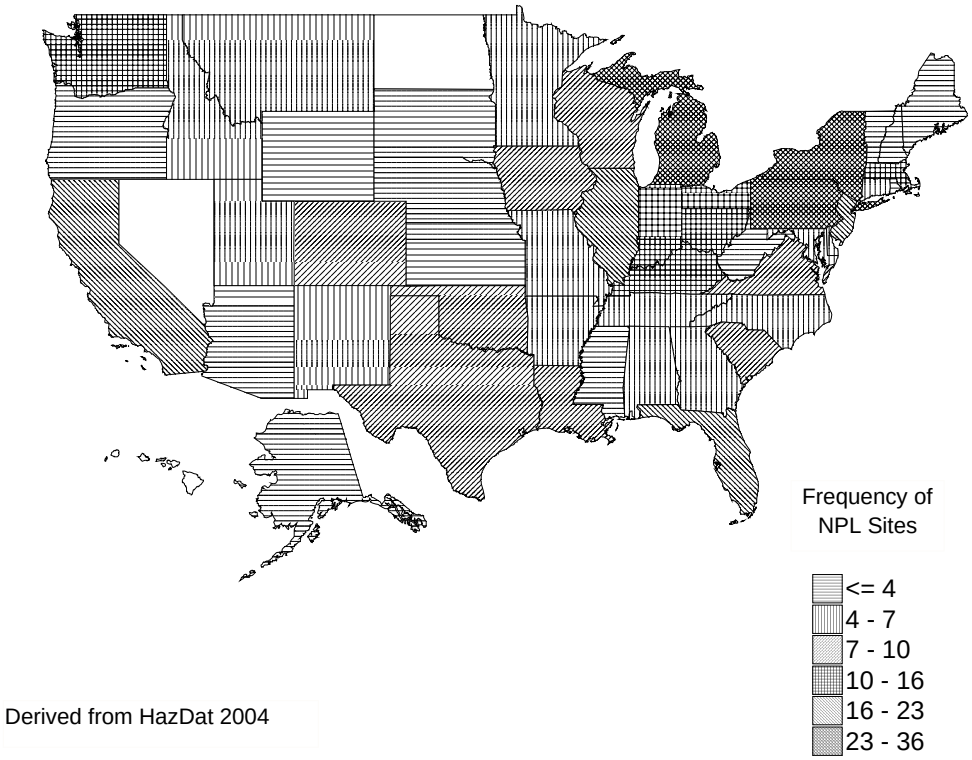


Figure 6-2. Frequency of NPL Sites with ^{60}Cobalt Contamination

Derived from HazDat 2004

with aerodynamic diameters >2 μm (such as those obtained during ore processing), may deposit within 10 km from the point of emission; finer particles (such as is obtained from thermal processes) may travel longer distances. It is generally assumed that anthropogenic cobalt originating from combustion sources exists primarily as the oxide; arsenides or sulfides may be released during mining and ore processing (Schroeder et al. 1987). Frequently, sediment and soil are the ultimate sinks for cobalt; however, this process is dynamic, and cobalt can be released into the water depending upon conditions. Soluble cobalt released into waterways will sorb to particles and may settle into the sediment or be sorbed directly by sediment. It may precipitate out as carbonates and hydroxides or with mineral oxides. It may also sorb to or complex with humic acid substances in the water. These processes are sensitive to environmental factors such as pH and the proportion of dissolved cobalt will be higher at low pH. In the case of ^{60}Co released into an experimental lake in northwestern Ontario, cobalt's half-life in the water column was 11 days; 5% of added ^{60}Co remained in the water after 100 days (Bird et al. 1998a). Cobalt can also be transported in dissolved form or as suspended sediment by rivers to lakes and the sea or by ocean currents. The proportion of cobalt transported in each form is highly variable (Smith and Carson 1981). In deep sediment where water is anoxic and hydrogen sulfide is present, some mobilization of cobalt from sediment may occur, probably due to the formation of bisulfides and polysulfides (Bargagli 2000; Brügmann 1988; Finney and Huh 1989; Glooschenko et al. 1981; Knauer et al. 1982; Nriagu and Coker 1980; Shine et al. 1995; Smith and Carson 1981; Szefer et al. 1996; Windom et al. 1989). Cobalt adsorbs rapidly and strongly to soil and sediment in which it is retained by metal oxides, crystalline minerals, and natural organic matter. The mobility of cobalt sediment depends on the nature of the soil or sediment; it increases with decreasing pH and redox potential (Eh) and in the presence of chelating/complexing agents (Brooks et al. 1998; Buchter et al. 1989; King 1988b; McLaren et al. 1986; Schnitzer 1969; Smith and Carson 1981; Swanson 1984; Yashuda et al. 1995).

While cobalt may be taken up from soil by plants, the translocation of cobalt from roots to above-ground parts of plants is not significant in most soils; the transfer coefficient (concentration in plant/concentration in soil) for cobalt is generally 0.01–0.3 (Mascanzoni 1989; Mermut et al. 1996, Smith and Carson 1981). However, in highly acidic soils (pH as low as 3.3) and in some higher plants (plants excluding algae), significantly higher transfer has been observed (Boikat et al. 1985; Francis et al. 1985; Jenkins 1980; Kloke et al. 1984; Mejstrik and Svacha 1988; Palko and Yli-Hala 1988; Tolle et al.1983; Watabe et al. 1984). The bioaccumulation factors (dry weight basis) for cobalt in marine fish and freshwater fish are ~100–4,000 and <10–1,000, respectively; accumulation is largely in the viscera and on the skin, as

opposed to the edible parts of the fish. Cobalt does not biomagnify up the food chain (Barceloux 1999; Evans et al. 1988; Freitas et al. 1988; Smith and Carson 1981).

Atmospheric cobalt is associated with particulate matter. Mean cobalt levels in air at unpolluted sites are generally <1–2 ng/m^3. In several open-ocean environments, geometric mean concentrations ranged from 0.0004 to 0.08 ng/m^3 (Chester et al. 1991). However, in source areas, cobalt levels may exceed 10 ng/m^3; the highest average cobalt concentration recorded was 48 ng/m^3 at the site of a nickel refinery in Wales (Hamilton 1994; Smith and Carson 1981). By comparison, the Occupational Safety and Health Administration (OSHA) limit for airborne stable cobalt is 100,000 ng/m^3. While ^{60}Co has been detected in some air samples at the Hanford, Washington site and Oak Ridge National Laboratories, Tennessee, levels were not reported (HazDat 2004; PNNL 1996).

The concentrations of stable cobalt in surface and groundwater in the United States are generally low; <1 µg/L in pristine areas and 1–10 µg/L in populated areas (Hamilton 1994; Smith and Carson 1981). However, cobalt levels may be considerably higher in mining or agricultural areas. Cobalt concentrations in surface water and groundwater samples collected in 1992 from area creeks near the Blackbird Mine in Idaho, one of the large deposits of cobalt in North America where mining occurred from the late 1800s to 1982, were reported to range from <1 to 625,000 µg/L, and from not detected to 315,000 µg/L, respectively (ATSDR 1995). Cobalt levels in most drinking water is <1–2 µg/L although levels as high as 107 µg/L have been recorded (Greathouse and Craun 1978; Meranger et al. 1981; NAS 1977; Smith and Carson 1981).

Little data are available on the levels of ^{60}Co in water. In 1989, subsequent to the largest effluent discharge from the Steam Generating Heavy Water Reactor at Winfrith on the south coast of England, ^{60}Co levels in offshore seawater from 18 sites contained 0.06–2.22 mBq/L (1.6–69 fCi) of particulate ^{60}Co, 0.30–10.3 mBq/L (8–280 fCi) of soluble ^{60}Co(II), and 0.12–1.55 mBq/L (3.2–42 fCi) of soluble ^{60}Co(III) (Leonard et al. 1993a). The U.S. NRC discharge limit is 111,000 mBq/L ($3x10^6$ fCi/L) (USNRC 1991).

The average concentrations of cobalt in the earth's crust are 20–25 mg/kg (Abbasi et al. 1989; Merian 1985; Smith and Carson 1981). Most soils contain 1–40 mg cobalt/kg; the average cobalt concentration in U.S. soils is 7.2 mg/kg (Smith and Carson 1981). Soils containing <0.5–3 mg cobalt/kg are considered cobalt-deficient because plants growing on them have insufficient cobalt (<0.08–0.1 mg/kg) to meet the

dietary requirements of cattle and sheep. Cobalt-deficient soils are found in some areas of the southeastern and northeastern United States. Soils near ore deposits, phosphate rocks, or ore smelting facilities, and soils contaminated by airport traffic, highway traffic, or other industrial pollution may contain high concentrations of cobalt; concentrations up to 800 mg/kg have been detected in such areas (Kloke et al. 1984; Smith and Carson 1981). Cobalt concentrations in 28 samples collected from surface deposits in the Big Deer and Blackbird Creek drainage basins near a site of former cobalt mining in Idaho ranged from 26.5 to 7,410 mg/kg (ATSDR 1995).

The level of cobalt in most foods is low. However, food is the largest source of exposure to cobalt in the general population. The estimated average daily dietary intake of cobalt in Canada was 11 µg/day. Food groups contributing most heavily to this intake were bakery goods and cereals (29.8%) and vegetables (21.9%) (Dabeka and McKenzie 1995). No estimates of the average dietary input of cobalt in the United States were located. People living near mining and smelting facilities or metal shops where cobalt is used in grinding tools may be exposed to higher levels of cobalt in air or soil. Similarly, people living near hazardous waste sites may be exposed to higher levels of cobalt in these media. Contaminated soils pose a hazardous exposure pathway to children because of both hand-to-mouth behavior and intentional ingestion of soil (pica) that contain metals and other contaminants (Hamel et al. 1998). However, much of the cobalt in soil may not be in a form that is available for uptake by the body. People who work in the hard metal industry, metal mining, smelting, and refining or other industries that produce or use cobalt and cobalt compounds may be exposed to substantially higher levels of cobalt, mainly from dusts or aerosols in air. Workers at nuclear facilities, irradiation facilities, or nuclear waste storage sites may be exposed to radioisotopes of cobalt. Exposure would generally be to radiation produced by these isotopes (e.g., gamma radiation from ^{60}Co).

6.2 RELEASES TO THE ENVIRONMENT

Stable cobalt has been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) collected at 426 of 1,636 current or former NPL hazardous waste sites (HazDat 2004). ^{60}Co has been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) collected at 13 of 1,636 current or former NPL hazardous waste sites (HazDat 2004).

According to the Toxic Chemical Release Inventory (TRI), in 2001, total releases of cobalt and cobalt compounds to the environment (including air, water, soil, and underground injection) from 605 reporting facilities that produced, processed, or used cobalt or cobalt compounds were 16,443,429 pounds (TRI01 2004). Table 6-1 lists amounts released from these facilities grouped by state. In addition, 1,619,874 pounds of cobalt and cobalt compounds were transferred offsite by these facilities (TRI01 2004). Starting in 1998, metal mining, coal mining, electric utilities, and Resource Conservation and Recovery Act (RCRA)/solvent recovery industries are required to report, to the TRI, industries with potentially large releases of cobalt and cobalt compounds. Industrial sectors producing, processing, or using cobalt that contributed the greatest environmental releases in 2001 were primary metals and RCRA/solvent recovery with 141,554 and 531,427 pounds, respectively. Industrial sectors producing, processing, or using cobalt compounds that contributed the greatest environmental releases in 2001 were metal mining and electrical utilities with 10,228,193 and 3,652,398, pounds, respectively. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

6.2.1 Air

The sources of cobalt in the atmosphere are both natural and anthropogenic (Barceloux 1999). Natural sources include wind-blown continental dust, seawater spray, volcanoes, forest fires, and continental and marine biogenic emissions. The worldwide emission of cobalt from natural sources has been estimated to range from 13 to 15 million pounds/year (Lantzy and Mackenzie 1979; Nriagu 1989). The global atmospheric emission of cobalt from anthropogenic sources is an estimated 9.7 million pounds/year. Therefore, natural sources contribute slightly more to cobalt emissions in the atmosphere than anthropogenic sources (Lantzy and Mackenzie 1979). The primary anthropogenic sources of cobalt in the atmosphere are the burning of fossil fuels and sewage sludge, phosphate fertilizers, mining and smelting of cobalt-containing ores, processing of cobalt-containing alloys, and industries that use or process cobalt compounds. Small amounts of cobalt are found in coal, crude oils, and oil shales. Therefore, burning of these fossil fuels for power generation will emit cobalt into the atmosphere. The cobalt contents of the fly ash and flue gases of a coal-burning power plant are approximately 25 mg/kg and 100–700 µg/L, respectively. Gasoline contains <0.1 mg cobalt/kg, but catalytic converters may contain cobalt; therefore, emissions from vehicular exhaust are also a source of atmospheric cobalt (Abbasi et al. 1989; Holcombe

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt and Cobalt Compounds[a]

State[c]	Number of facilities	Reported amounts released in pounds per year[b]						
		Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
AK	2	23	0	16,000	546,463	562,486	0	562,486
AL	21	5,893	8,612	0	315,853	330,358	30,040	360,398
AR	9	921	142	0	8,301	9,364	2,015	11,379
AZ	12	1,029	0	0	1,061,035	1,062,064	2,266	1,064,330
CA	26	646	20	0	307,654	308,320	7,463	315,783
CO	1	3	1	0	12,026	12,030	0	12,030
CT	9	632	65	0	0	697	4,133	4,830
DE	2	1,265	52	0	52	1,369	27,444	28,813
FL	11	2,397	345	0	93,049	95,791	15,464	111,255
GA	17	3,508	268	0	282,610	286,386	12,461	298,847
IA	6	566	0	0	0	566	2,123	2,689
ID	2	74	5	0	395,424	395,503	0	395,503
IL	23	1,630	1,278	0	16,999	19,907	102,088	121,995
IN	42	7,005	351	0	279,122	286,478	64,293	350,771
KS	5	4,269	0	0	10,200	14,469	3,859	18,328
KY	22	3,184	542	0	478,855	482,581	13,269	495,850
LA	15	385	8,477	2,700	66,858	78,420	91,274	169,694
MA	11	794	780	0	5	1,579	17,403	18,982
MD	6	2,472	15	0	6,629	9,116	45,382	54,498
ME	2	66	0	0	0	66	700	766
MI	24	4,699	559	0	125,405	130,663	33,737	164,400
MN	5	255	No data	0	0	255	7,666	7,921
MO	5	1,457	8	0	559,401	560,866	0	560,866
MS	7	386	120	12,000	44	12,550	3,044	15,594
MT	1	250	No data	0	31,000	31,250	505	31,755
NC	24	6,593	8,257	0	194,974	209,824	216,849	426,673
ND	4	1,165	21	0	108,300	109,486	39,842	149,328
NE	1	0	27	0	0	27	3,982	4,009
NH	1	0	No data	0	0	0	No data	0
NJ	12	1,191	26	0	413	1,630	26,894	28,524
NM	6	498	1	0	4,257,140	4,257,639	69	4,257,708
NV	8	678	0	0	4,099,136	4,099,814	9,950	4,109,764
NY	12	755	44	0	11,843	12,642	14,322	26,964
OH	44	4,977	771	1,100	310,653	317,501	96,116	413,617
OK	13	1,357	158	0	5,677	7,192	20,760	27,952

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt and Cobalt Compounds[a]

State[c]	Number of facilities	Reported amounts released in pounds per year[b]						
		Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
OR	6	1,262	20	0	16,487	17,769	2,862	20,631
PA	44	6,169	3,176	0	51,350	60,695	221,662	282,357
PR	2	2	No data	0	0	2	2,871	2,873
RI	1	1	1	0	0	2	50	52
SC	25	1,579	10,970	0	43,488	56,037	70,316	126,353
SD	1	0	No data	0	0	0	0	0
TN	18	5,560	4,013	0	330,615	340,188	36,520	376,708
TX	44	8,126	784	3,730	150,470	163,110	95,840	258,950
UT	6	278	No data	0	23,350	23,628	126,502	150,130
VA	9	1,451	518	0	89,388	91,357	9,683	101,040
VI	1	0	0	0	0	0	0	0
WA	2	72	91	0	106,618	106,781	5,112	111,893
WI	20	1,098	5	0	8	1,111	95,996	97,107
WV	13	1,341	566	0	212,254	214,161	37,047	251,208
WY	2	898	No data	0	38,927	39,825	0	39,825
Total	605	88,860	51,089	35,530	14,648,076	14,823,555	1,619,874	16,443,429

Source: TRI01 2004

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]The sum of fugitive and stack releases are included in releases to air by a given facility.
[e]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[f]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

et al. 1985; Ondov et al. 1982; Smith and Carson 1981). Cobalt has been detected in cigarette tobacco and therefore, smoking is a potential source of atmospheric cobalt that could impact on indoor air quality (Munita and Mazzilli 1986).

Stable cobalt has been identified in air samples collected at 5 of the 426 current or former NPL hazardous waste sites where it was detected in some environmental media (i.e., air, soil, sediment, or water) (HazDat 2004). ^{60}Co has been identified in air samples collected at 2 of the 13 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2004).

Air sampling data were used to estimate ^{60}Co release from the Savannah River Site (SRS) from the plant's start up in 1954 to 1989 (DOE 1991). From this monitoring, it was estimated that 0.092 Ci (3.4 GBq) of ^{60}Co was released to the atmosphere between 1968 and 1986. Total releases of ^{60}Co to the atmosphere from the SRS between 1968 and 1996 were 0.092 Ci (3.4 GBq) (DOE 1998). Data were not reported for all years in this interval. In 1999, atmospheric releases of ^{57}Co, ^{58}Co, and ^{60}Co as particulates were 4.71×10^{-8}, 1.27×10^{-4}, and 1.30×10^{-4} Ci (0.00174, 4.70, and 4.81 MBq), respectively (DOE 1999). The SRS was a major production facility to the U.S. defense program and included five nuclear reactors, a fuel fabrication plant, a naval fuel materials facility, two chemical separation plants, a heavy water production plant, and a laboratory. ^{60}Co has also been detected in air samples at the Hanford site and Oak Ridge National Laboratories (HazDat 2004; PNNL 1996).

According to the TRI, in 2001, releases of 88,860 pounds of cobalt and cobalt compounds to air from 605 reporting facilities accounted for 0.5% of the total onsite environmental releases of these substances (TRI01 2004). The industrial sectors contributing the largest release of cobalt and cobalt compounds to air were electrical utilities, chemicals, and primary metals. Table 6-1 lists the amounts of cobalt and cobalt compounds released to air from these facilities grouped by state. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

6.2.2 Water

Compounds of cobalt occur naturally in seawater and in some surface, spring, and groundwater (Smith and Carson 1981). Cobalt is also released into water from anthropogenic sources. While there has been

no mine production of cobalt in the United States in recent years, cobalt is a byproduct or coproduct of the refining of other mined metals such as copper and nickel. Historic mining operations that processed cobalt containing ores may continue to release cobalt into surface water and groundwater. Waste water from the recovery of cobalt from imported matte or scrap metal, refining of copper and nickel, or during the manufacture of cobalt chemicals are sources of cobalt in water (Smith and Carson 1981). Process water and effluent from coal gasification and residue from solvent-refined coal contain cobalt. The accidental discharge of activated sludge and sewage may be important sources of cobalamins in waterways, together with bioconcentration by benthic organisms (Smith and Carson 1981). The discharge of waste water by user industries, such as paint and pigment manufacture, also contributes to the release of cobalt into water. In one case, manufacturers of nickel-cadmium batteries operating between 1953 and 1979 discharged cobalt from a battery factory to the Hudson River in Foundry Cove, New York, of which 1.2 metric tons are estimated to be present in the eastern cove (Knutson et al. 1987). Atmospheric deposition is an additional source of cobalt in water. Lake Huron receives an estimated 76% of its cobalt input from natural sources and 24% from anthropogenic sources. The corresponding estimated values for Lake Superior are 85.4 and 14.6% (Smith and Carson 1981). In these Great Lakes, it therefore appears that natural inputs of cobalt far exceed anthropogenic ones.

Cobalt has been identified in groundwater and surface water at 255 and 106 sites, respectively, of the 426 NPL hazardous waste sites, where it was detected in some environmental media (i.e., air, soil, sediment, or water) (HazDat 2004). ^{60}Co has been identified in groundwater and surface water at 4 and 2 sites, respectively, of the 13 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2004).

According to the TRI, in 2001, the reported releases of 51,089 pounds of cobalt and cobalt compounds to water from 605 reporting facilities accounted for 0.3% of the total onsite environmental releases of these substances (TRI01 2004). Table 6-1 lists the amounts of cobalt and cobalt compounds released to water from these facilities grouped by state. As of 1998, TRI no longer separately collects data on substances released indirectly to Publicly-Owned Treatment Works (POTWs), part of which may ultimately be released to surface waters. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

^{60}Co is present in the low-level aqueous radioactive waste discharges from many nuclear power plants. Alloys that contain stable cobalt (^{59}Co), such as stellite, used in piping of nuclear reactors corrode and

may be activated, producing ^{60}Co, which accumulates in the reactor and must be periodically decontaminated. A common decontaminating agent includes a reducing metal ion (e.g., vanadium(II)) and a chelating agent (e.g., picolinate) resulting in low-level discharges of uncomplexed ^{60}Co(II) and complexed ^{60}Co(III). While soluble ionic and particulate forms predominate, at some sites stable, nonionic trivalent complexes of cobalt are present (Leonard et al. 1993a, 1993b; USNRC 2000d). For example, in 1987–1989 samples of treated effluent from the Steam Generating Heavy Water Reactor at Winfrith on the south coast of England, the percent of ^{60}Co as Co(III) picolinate ranged from 6.2 to 75.4%. Between 1978 and 1988, 12 TBq (320 Ci) of ^{60}Co was released into the Irish Sea by the British Nuclear Fuels reprocessing plant at Sellafield, United Kingdom (McCartney et al. 1994). These discharges are believed to be Co(II) (Leonard et al. 1993a). Both ^{58}Co and ^{60}Co are discharged into the Rhone River by the nuclear power plant at Bugey, France. This facility, which consists of a natural Uranium-Graphite-Gas unit and four pressurized water reactor (PWR) units, two of which are cooled by Rhone River water, discharged about 406 and 280 GBq (11.0 and 7.56 Ci) of ^{58}Co and ^{60}Co, respectively, in liquid waste during 1986–1990 (Beaugelin-Seiler et al. 1994).

Water sampling data were used to estimate effluent release from the SRS from the plant's start up in 1954 to 1989 (DOE 1991). From this monitoring, it was estimated that 17.8 Ci (659 GBq) of ^{60}Co were released into seepage basins and 66.4 Ci (2,460 GBq) were released into streams between 1955 and 1988. In addition, 2.7 Ci (100 GBq) of ^{58}Co were released into seepage basins between 1971 and 1988; no ^{58}Co was released into streams. Total releases of ^{60}Co to streams from the SRS for 1954–1995 were 66 Ci (2,400 GBq) (DOE 1998). No data were reported from 1985 to 1994. In 1999, 4.94×10^{-4} Ci (0.0183 GBq) of ^{60}Co was released to surface waters at the SRS (DOE 1999). ^{60}Co has also been reported in surface water at, Hanford, Washington, and Oak Ridge National Laboratories, and groundwater at Brook Industrial Park, New Jersey, the Hanford site and Oak Ridge National Laboratories, Tennessee (HazDat 2004). The Columbia River receives discharges from the unconfined aquifer underlying the Hanford Site via subsurface and surface (riverbank springs) discharges. This aquifer is contaminated by leachate from past waste-disposal practices at the site.

6.2.3 Soil

Cobalt occurs naturally in the earth's crust, and therefore, in soil. However, elevated levels of cobalt in soil may result from anthropogenic activities such as the mining and processing of cobalt-bearing ores,

the application of cobalt-containing sludge or phosphate fertilizers to soil, the disposal of cobalt-containing wastes, and atmospheric deposition from activities such as burning of fossil fuels, smelting, and metal refining (Smith and Carson 1981).

Cobalt has been identified in soil at 219 sites and sediment at 143 sites collected from 426 NPL hazardous waste sites, where it was detected in some environmental media (i.e., air, soil, sediment, or water) (HazDat 2004). ^{60}Co has been identified in soil at 8 sites and sediment at 2 sites collected from 13 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2004). ^{60}Co has been detected onsite in soils at the Hanford Site, Washington; INEEL, Idaho; Lawrence Livermore National Laboratory, Main Site, California; and Robins Air Force Base, Georgia at maximum concentrations of 87.7, 570, 0.21, and 0.07 pCi/g (3.24, 21, 0.0078, and 0.003 Bq/g) (HazDat 2004).

According to the TRI, in 2001, reported releases of 14,646,076 pounds of cobalt and cobalt compounds to land from 605 reporting facilities accounted for 98.8% of the total onsite environmental releases of these substances (TRI01 2004). An additional 35,530 pounds, accounting for 0.2% of the total onsite environmental releases were injected underground (TRI01 2004). Industrial sectors contributing the largest releases of cobalt and cobalt compounds to land were metal mining and electrical utilities with 10,210,508 and 3,197,209 pounds, respectively. Table 6-1 lists the amounts of cobalt and cobalt compounds released on land from these facilities grouped by state. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Cobalt compounds are nonvolatile, and thus, cobalt is emitted to the atmosphere in particulate form. The transport of cobalt in air depends on its particle size and density, and meteorological conditions; it can be returned to land or surface water by rain or it may settle to the ground by dry deposition. In nonarid areas, wet deposition may exceed dry deposition (Arimoto et al. 1985; Erlandsson et al. 1983). Coarse particles, with aerodynamic diameters >2 μm (such as those obtained during ore processing), may deposit within 10 km from the point of emission; finer particles may travel longer distances. It is the larger

particles that may be responsible for elevated local concentrations around emission sources. The mass median diameter for cobalt particles emitted from a power generator with a stack emission controlled by an electrostatic precipitator or scrubber ranged from <2 to 12 µm. The mass median diameter of cobalt in the ambient atmosphere is about 2.6 µm (Milford and Davidson 1985). Golomb et al. (1997) report average total (wet+dry) deposition rates of cobalt to Massachusetts Bay during the period September 15, 1992 to September 16, 1993. The total deposition rate was 58 µg/m^2-year, of which 47 µg/m^2-year was dry deposition and 12 µg/m^2-year was wet deposition. Total cobalt deposition flux at a site in the Rhone delta in southern France in 1988–1989 was 0.42±0.23 kg/km^2-year with 0.15 kg/km^2-year in the form of wet deposition (Guieu et al. 1991).

As with most metals, sediment and soil are frequently the final repository for cobalt released into the environment, although the process is dynamic, and cobalt can be released into the water depending upon conditions. Cobalt released into waterways may sorb to particles and settle into the sediment or be sorbed directly into the sediment. However, complexation cobalt to dissolved organic substances can significantly reduce sorption to sediment particles (Albrecht 2003). Studies by Jackman et al. (2001) suggest that interparticle migration of cobalt can influence the transport of metal ions, including cobalt, in sediments. For example, migration of a metal ion from a highly mobile sediment particle, such as clay, to less mobile gravels will slow the transport of that metal. Cobalt can also be transported in dissolved form or as suspended sediment by rivers to lakes and the sea or by ocean currents. Sediment in areas of active sedimentation would receive a large portion of the suspended sediment. In the case of the Peach Bottom Atomic Power Plant where ^{60}Co is released into the Conowingo Reservoir, an impoundment of the lower Susquehanna River, <20% of the radionuclide is trapped in the reservoir sediment, the rest being transported downstream and into the Chesapeake Bay (McLean and Summers 1990). It is often assumed that the primary mode of transport of heavy metals in aquatic systems is as suspended solids (Beijer and Jernelov 1986). However, in the case of cobalt, the percent that is transported by suspended solids is highly variable. Examples of the percentage of cobalt transported in suspended solids include (water body, percent): Main River (Germany), 33.4–42.2%; Susquehanna River (near its source in New York), 9%; New Hope River (North Carolina), 92%; Yukon River, >98%; Danube Rive (1961–1970), 27.4–85.9%; Columbia River (^{60}Co, downstream of the Hanford site), 95–98%; Strait of Juan de Fuca (Puget Sound, Washington), 11–15%; North Sea, 34%; and Lake Washington (Washington), 0% (Smith and Carson 1981).

In the oxic zones of many surface waters, dissolved cobalt levels decrease with increasing depth. This may be due to cobalt's continuous input into surface water from discharges or to increased adsorption and precipitation of the soluble forms with increasing depth. The fact that cobalt concentration profiles in deep water follow manganese and aluminum profiles strongly suggests that dissolved cobalt is precipitated in the adsorbed state with oxides of iron and manganese and with crystalline sediments such as aluminosilicate and goethite. A part of the cobalt may also precipitate out as carbonate and hydroxide in water. The higher concentration of organic pollutants in polluted water probably results in the formation of higher concentrations of soluble organic complexes. In a deep sediment where the water was anoxic and contained hydrogen sulfide, some mobilization of cobalt was observed, probably due to the formation of bisulfide and polysulfide complexes (Bargagli 2000; Brügmann 1988; Finney and Huh 1989; Glooschenko et al. 1981; Knauer et al. 1982; Nriagu and Coker 1980; Shine et al. 1995; Smith and Carson 1981; Szefer et al. 1996; Windom et al. 1989).

Cobalt strongly binds to humic substances naturally present in aquatic environments. Humic acids can be modified by UV light and bacterial decomposition, which may change their binding characteristics over time. The lability of the complexes is strongly influenced by pH, the nature of the humic material, and the metal-to-humic substance ratio. The lability of cobalt-humate complexes decreases in time ("aging effect") (Burba et al. 1994). The "aging effect" indicates that after a period of time (~12 hours), complexes that were initially formed are transformed into stronger ones from which the metal ion is less readily dislodged. In the Scheldt Estuary and the Irish Sea, between 45 and 100% of dissolved cobalt was found to occur in these very strong complexes (Zhang et al. 1990). Aquifer material from the contaminated aquifer at a low-level infiltration pit at the Chalk River Nuclear Laboratories in Canada was analyzed to assess the nature of the adsorbed ^{60}Co using sequential leaching techniques (Killey et al. 1984). Of the sediment-bound ^{60}Co, <10% was exchangeable, 5–35% was retained by iron oxide, and 55–>90% was fixed. Over 80% of the dissolved ^{60}Co was present as weakly anionic hydrophilic organic complexes. The average K_d for ^{60}Co between particulate matter and Po River (Italy) water was 451 m^3/kg over a 2-year monitoring period (Pettine et al. (1994). The mean K_d for ^{60}Co in Arctic surface sediment (Kara Sea) where large quantities of radioactive waste by the former Soviet Union was disposed was $1x10^5$ L/kg (range $1x10^3$–$7x10^5$), which is comparable to that in temperate coastal regions, $2x10^5$ L/kg (range, $2x10^4$–$1x10^6$) (Fisher et al. 1999).

The distribution coefficient of cobalt may vary considerably in the same sediment in response to conditions affecting the pH, redox conditions, ionic strength, and amount of dissolved organic matter

(Mahara and Kudo 1981b). Uptake of ^{60}Co from the water by sediment increased rapidly as the pH was increased from 5 to 7–7.5 and then slightly decrease (Benes et al. 1989a, 1989b). Therefore, pH would be an important factor affecting the migration of cobalt in surface water. Uptake was little affected by changes in liquid-to-solids ratio and ionic strength. ^{60}Co is more mobile in anaerobic marine aquatic environments than in freshwater aerobic ones (Mahara and Kudo 1981b). Therefore, ^{60}Co waste is most suitably stored underground in aerated zones away from possible seawater intrusions. In seawater-sediment systems under anaerobic conditions ^{60}Co was 250 times more mobile than ^{60}Co in freshwater-sediment systems under aerobic conditions. Under anaerobic conditions, 30% of the ^{60}Co added to a sediment-freshwater system was ‘exchangeable’ and therefore potentially mobile, while under aerobic conditions, 98% of the ^{60}Co was permanently fixed. Most of the mobile ^{60}Co produced under anaerobic conditions in seawater consisted of nonionic cobalt associated with low molecular weight organic substances that were stable to changes in pH; the exchangeable ^{60}Co appeared to be mostly ionic.

Bird et al. (1998b) added ^{60}Co to the anoxic hypolimnion of a Canadian Shield lake to simulate a nuclear waste scenario where radionuclides entered the bottom waters of a lake, and evaluated its behavior over 5 years. This situation was considered to be a likely pathway by which nuclear fuel waste stored deep underground in the plutonic (igneous) rock of this region would reach the surface environment via deep groundwater flow into the bottom waters of a lake. It was felt that adding a redox sensitive element such as cobalt to the anoxic hypolimnion might be different from adding it to the epilimnion. Monitoring vertical profiles in the lake established that the cobalt remained confined to the anoxic hypolimnion prior to the fall turnover (first 72 days) when mixing occurred throughout the water column. After 358 days, only about 4% of the ^{60}Co remained in the water. After the second year, approximately 2% of the ^{60}Co remained and after 5 years, only 0.4%. These results mirror previous experiments in which the ^{60}Co was added to the epilimnion, therefore establishing that there is little difference in the overall behavior of cobalt when added to the epilimnion or hypolimnion. The loss rate coefficient of ^{60}Co was 0.036/day (half-life=19 days) between days 90 and 131 (lake mixing) during which time, the cobalt sorbed to the suspended sediment and bottom sediment under anoxic conditions. Loss was to the sediment as there was no hydrological loss from the lake. In the previous experiment in which ^{60}Co was added to the epilimnion, the initial loss rate coefficient was somewhat higher, 0.056/day (half-life=12 days). Following the initial loss, ^{60}Co continued to be slowly removed from the water (loss rate coefficient 0.002/day; half-life=347 days); after 328 days, ^{60}Co was no longer detectable in the epilimnion. The half-life of ^{60}Co in the water column of an experimental lake in northwestern Ontario was 11 days; 5% of added ^{60}Co remained in the water after 100 days (Bird et al. 1998b). The redox potential also affects the

behavior of cobalt in sediment. Under moderately reducing conditions, cobalt is released from sediment as Co^{2+} and forms CoS in the presence of sulfide. The concentration of cobalt in the bottom water increases as the water becomes more anoxic (Brügmann 1988; Smith and Carson 1981).

The mobility of cobalt in soil is inversely related to how strongly it is adsorbed by soil constituents. Cobalt may be retained by mineral oxides such as iron and manganese oxide, crystalline materials such as aluminosilicate and goethite, and natural organic substances in soil. Sorption of cobalt to soil occurs rapidly (within 1–2 hours). Soil-derived oxide materials were found to adsorb greater amounts of cobalt than other materials examined, although substantial amounts were also adsorbed by organic materials. Clay minerals sorbed relatively smaller amounts of cobalt (McLaren et al. 1986). In addition, little cobalt was desorbed from soil oxides while substantial amounts desorbed from humic acids and montorillonite. In clay soil, adsorption may be due to ion exchange at the cationic sites on clay with either simple ionic cobalt or hydrolyzed ionic species such as $CoOH^+$. Adsorption of cobalt onto iron and manganese increases with pH (Brooks et al. 1998). In addition, as pH increases, insoluble hydroxides or carbonates may form, which would also reduce cobalt mobility. Conversely, sorption onto mobile colloids would enhance its mobility. In most soils, cobalt is more mobile than lead, chromium (II), zinc, and nickel, but less mobile than cadmium (Baes and Sharp 1983; King 1988b; Mahara and Kudo 1981b; Smith and Carson 1981). In several studies, the K_d of cobalt in a variety of soils ranged from 0.2 to 3,800. The geometric mean, minimum, median, and maximum K_ds of ^{60}Co in 36 Japanese agricultural soils were 1,840, 130, 1,735, and 104,000 L/kg, respectively (Yasuda et al. 1995). The soil properties showing the highest correlation with K_d were exchangeable calcium, pH, water content, and cation exchange capacity (CEC). In 11 U.S. soils, the mean Freundlich K_F and n values were 37 L/kg and 0.754, respectively; K_F values ranged from 2.6 to 363 L/kg and correlated with soil pH and CEC (Buchter et al. 1989). In 13 soils from the southeastern United States whose soil pH ranged from 3.9 to 6.5, cobalt sorption ranged from 15 to 93%; soil pH accounted for 84–95% of the variation in sorption (King 1988b).

Organic complexing agents such as ethylenediaminetetraacetic acid (EDTA), which are used for decontamination operations at nuclear facilities, greatly enhance the mobility of cobalt in soil. Other organic complexing agents, such as those obtained from plant decay, may also increase cobalt mobility in soil. However, both types of complexes decrease cobalt uptake by plants (Killey et al. 1984; McLaren et al. 1986; Toste et al. 1984). Addition of sewage sludge to soil also increases the mobility of cobalt, perhaps due to organic complexation of cobalt (Gerritse et al. 1982; Williams et al. 1985).

Leaching of cobalt has been observed from municipal and low-level radioactive waste sites (Cyr et al. 1987; Czyscinski et al. 1982; Friedman and Kelmers 1988). The mobility of cobalt was assessed in two soils from the Cabriolet and Little Feller event sites at the Nevada Test site as a function of various parameters such as pH, ionic strength, cobalt concentrations, soil solids concentrations, and particle size distribution (DOE 1996). Cobalt was quantitatively sorbed on these soils (at least 90% sorbed) when the pH was above 7 and the solid concentration was at least 20 g/L. The experiments suggest that binding is principally on amphoteric surface-hydroxyl surfaces. Since the pH of these soils is around 8, cobalt would bind strongly under normal environmental conditions. Migration would be severely retarded under all but the most extreme conditions, e.g., pH of 4 or below and high ionic strength soil solutions (approximately 0.1 M). In addition, unrealistically large quantities of water would be needed to displace cobalt from the upper layers of the soil profile.

Cobalt may be taken up from soil by plants. Surface deposition of cobalt on leaves of plants from airborne particles may also occur. Elevated levels of cobalt have been found in the roots of sugar beets and potato tubers in soils with high cobalt concentrations (e.g., fly ash-amended soil) due to absorption of cobalt from soil. However, the translocation of cobalt from roots to above-ground parts of plants is not significant in most soils, as indicated by the lack of cobalt in seeds of barley, oats, and wheat grown in high-cobalt soil (Mermut et al. 1996; Smith and Carson 1981). Mermut et al. (1996) found 0.01–0.02 mg/kg in 10 samples of durum wheat grain from different areas of Saskatchewan where surface soil cobalt levels ranged from 3.7 to 16.4 mg/kg. The enrichment ratio, defined as the concentration in a plant grown in amended soil (fly ash) over the concentration in unamended soil, was about 1. Other authors have determined the transfer coefficient (concentration in plant/concentration in soil) for cobalt to be 0.01–0.3. The mean ^{57}Co soil-plant transfer factors obtained for clover from eight soils over a 4-year period ranged from 0.02 to 0.35, in good agreement with results of other investigators (Mascanzoni 1989). However, in highly acidic soil (pH as low as 3.3), significantly higher than normal concentrations of cobalt were found in rye grass foliage, oats, and barley. For example, cobalt concentrations in rye grass grown in unlimed soil (pH<5.0) was 19.7 mg/kg compared with 1.1 mg/kg in rye grass grown in limed soil (pH>5.0) (Boikat et al. 1985; Francis et al. 1985; Kloke et al. 1984; Mejstrik and Svacha 1988; Palko and Yli-Hala 1988; Tolle et al. 1983; Watabe et al. 1984). Soil and plant samples taken in the 30-km zone around Chernobyl indicated that ^{60}Co was not accumulated by plants and mushrooms (Lux et al. 1995). Transfer factors obtained in 1992 ranged from 0.005 to 0.16 and those obtained in 1993 ranged from <0.001 to 0.008. Studies investigating the uptake of ^{60}Co by tomato plants watered with ^{60}Co-contaminated water showed that tomato plants absorbed <2% of the activity available from the soil. The

absorption was 6 times higher if the plants were watered aerially rather than ground watering. Using either watering method, >90% of the activity was absorbed by the stems and leaves (Sabbarese et al. 2002). Soil to plant transfer factors for ^{60}Co were determined for plants grown in containers with soil contaminated with ^{65}Zn and ^{60}Co over a 3-year period under outdoor tropical conditions. Average transfer factors for ^{60}Co over the 3-year period ranged from a high for spinach (1.030) to a low for rice (0.087) (Mollah and Begum 2001).

^{60}Co is taken up by phytoplankton and unicellular algae (*Senenastrum capricornutum*) with concentration factors (dry weight) ranging from 15,000 to 40,000 and 2,300 to 18,000, respectively (Corisco and Carreiro 1999). Elimination experiments with the algae indicate a two component biological half-life, 1 hour and 11 days, respectively, and suggest that the cobalt might be absorbed not only on the surface, but also intracellularly. Since these organisms are at the bottom of the food chain, they could play an important role in the trophic transfer of ^{60}Co released into waterways by nuclear facilities. However, cobalt levels generally diminish with increasing trophic levels in a food chain (Smith and Carson 1981).

The low levels of cobalt in fish may also reflect cobalt's strong binding to particles and sediment. The bioaccumulation factors (dry weight basis) for cobalt in marine and freshwater fish are ~100–4,000 and <10–1,000, respectively; accumulation in the muscle of marine fish is 5–500 (Smith and Carson 1981). Cobalt largely accumulates in the viscera and on the skin, as opposed to the edible parts of the fish. In carp, accumulation from water accounted for 75% of ^{60}Co accumulated from both water and food; accumulation from water and food was additive (Baudin and Fritsch 1989). Depuration half-lives were 53 and 87 days for fish contaminated from food and water, respectively. In the case of an accidental release of ^{60}Co into waterways, the implication is that effects would manifest themselves rapidly since the primary route of exposure is from water rather than food. Uptake of ^{60}Co by biota in lakes in northwestern Ontario was not affected by the tropic status of the lakes (Bird et al. 1998a). Uptake of ^{60}Co was very low in whitefish, with concentrations being highest in kidney and undetectable in muscle. Similarly, while accumulation of ^{60}Co by carp from food was dependent on food type, the transfer factor was very low, approximately 0.01, and no long-term bioaccumulation of the radionuclide occurred (Baudin and Fritsch 1987; Baudin et al. 1990). Accumulation of ^{60}Co from food for rainbow trout showed that after the 42-day exposure period, the highest concentrations of ^{60}Co were found in the kidneys, secondary gut, and viscera, and the trophic transfer factor was 0.0186. After 73 days of depuration, residual ^{60}Co concentrations were the highest in the kidneys, viscera, and fins (Baudin et al. 2000). In the experiment described above in which Bird et al. (1998a) added ^{60}Co to the anoxic

hypolimnion of a Canadian Shield lake to simulate a nuclear waste scenario where radionuclides entered the bottom waters of a lake, ^{60}Co levels in biota were low because of the rapid loss of cobalt to the sediment. Levels in forage fish, minnows, and sculpins were low, <0.3 Bq/g (8 pCi/g) dry weight; an occasional high level, ~4 Bq/g (110 pCi/g) dry weight, in slimy sculpin was thought to reflect the presence of detritus in the gut of the fish. Epilimnion additions of ^{60}Co in an earlier study resulted in lower maximum concentrations in fish, 0.07, 0.11, and 0.01 Bq/g (2, 3.0, and 0.3 pCi/g) dry weight in pearl dace, fathead minnows, and slimy sculpins, respectively, when similar quantities of radioactive cobalt were added to the lake.

Concentration factors have also been reported for various other aquatic organisms. Freshwater mollusks have concentration factors of 100–14,000 (~1–300 in soft tissue). Much of the cobalt taken up by mollusks and crustacae from water or sediment is adsorbed to the shell or exoskeleton; very little cobalt is generally accumulated in the edible parts (Amiard and Amiard-Triquet 1979; Smith and Carson 1981). A concentration factor for ^{60}Co of 265 mL/g (wet weight) was determined for *Daphnia magna* in laboratory studies. The rapid decrease in radioactivity during the depuration phase indicated that adsorption to the surface was the major contamination process (Adam et al. 2001). However, the digestive glands of crustaceans, which are sometimes eaten by humans, may accumulate high levels of ^{60}Co. Five different species of marine mollusks had whole-body ^{60}Co concentration factors between 6.3 and 84 after 1-month exposure to ^{60}Co in seawater (Carvalho 1987). The shell accounted for more than half of the body-burden. Among the soft tissue, the gills and viscera had the highest concentrations factors and the muscle had the lowest. Fisher et al. (1996) studied the release of ^{60}Co accumulated in mussels from water and ingested phytoplankton. In each case, there was a slow and fast component to the release; the rapid release was in the form of fecal pellets if uptake was from food and from desorption from the shell if uptake was from the dissolved phase. Biological half-lives obtained in laboratory studies were about 12–21 days from both the shell and soft parts. Higher absorption efficiencies and lower efflux rates were obtained for cobalamins than for inorganic cobalt, suggesting that it is a more bioavailable form of cobalt for mussels. Cobalt from fecal pellets is rapidly released into the overlying water and may play a role in its geochemical cycling (Fisher et al. 1996). The concentration of cobalt in clams in the Indian River Lagoon, Florida did not correlate with levels found in either water or sediment (Trocine and Trefry 1996). Kinetics of bioaccumulation of ^{57}Co from water and depuration by starfish (*Asterias rubens*) were carried out in laboratory studies. After 32 days of exposure to seawater containing ^{57}Co, whole body uptake from seawater reached a concentration factor of 23 (wet weight). ^{57}Co was released with a half-life of 27 days after removal to uncontaminated water. Comparison of the kinetics of loss of ^{57}Co following exposure to

^{57}Co-contaminated food versus exposure from ^{57}Co-contaminated water indicate that *A. rubens* accumulates ^{57}Co predominately from seawater rather than from food (Warnau et al. 1999).

6.3.2 Transformation and Degradation

6.3.2.1 Air

There is a paucity of data in the literature regarding the chemical forms of cobalt in air and their transformations in the atmosphere. It is generally assumed that anthropogenic cobalt originating from combustion sources exists primarily as the oxide (Schroeder et al. 1987). In addition, cobalt may be released into the atmosphere as its arsenide or sulfide during ore extraction processes. It is not clear if these species are transformed in the atmosphere. Should a relatively insoluble species such as the oxide be transformed into a more soluble form such as the sulfate, one would expect greater quantities to be washed out of the atmosphere in rain.

6.3.2.2 Water

Many factors control the speciation and fate of cobalt in natural waters and sediments. These include the presence of organic ligands (e.g., humic acids, EDTA), the presence and concentration of anions (Cl^-, OH^-, CO_3^{-2}, HCO_3^-, SO_4^{-2}), pH, and redox potential (Eh). Modeling the chemical speciation of a metal in water depends upon the environmental factors assumed and the stability constants of the various complexes. Mantoura et al. (1978) predicted the equilibrium levels of Co^{2+} species in fresh water to follow the order: free $Co^{+2} \geq CoCO_3 > CoHCO_3^+ >> CoSO_4 \geq$ Co•humic acid. However, the mole percent of various cobalt species in a Welsh lake was found to be: free Co^{+2}, 76%; $CoCO_3$, 9.8%; $CoHCO_3^+$, 9.6%; humate complexes, 4.0%; and $CoSO_4$, 0.4%. The rank order of species concentration in seawater was estimated to be: $CoCO_3$>free Co^{+2}>$CoSO_4 \geq CoHCO_3^+$. In another model, the speciation of cobalt was completely different with $CoCl^+$>free Co^{+2}>$CoCO_3$>$CoSO_4$ (Smith and Carson 1981). More recently, Tipping et al. (1998) estimated the equilibrium speciation of cobalt in riverine, estuarine, and marine surface water of the Humber system (England). In all but seawater, cobalt complexes with carbonate (HCO_3^- and CO_3^{2-}) constituted about 70% of dissolved cobalt while the free Co^{2+} ion, was a major

species, ~25%, which is much lower than the 61% predicted by Mantoura et al. (1978). As the alkalinity of the water increases, the proportion of cobalt complexed with carbonate increases at the expense of free Co^{2+}. The proportion, but not the concentration, of cobalt that exists as the free ion and the carbonate complexes in river water is independent of the level of fulvic acid in the water. In seawater, the carbonate species and the free aqua species assume roughly equal importance. The proportion of dissolved cobalt complexed with fulvic acid decreased with increasing salinity. About 20% of cobalt in seawater was estimated to be present as complexes with sulfate. In a bioconcentration study in which $CoCl_2$ was initially added to the seawater, at month's end, the cationic form of cobalt was progressively converted into anionic and neutral forms, possibly as a result of complexation with organic ligands (Carvalho 1987). Addition of humic acid to natural waters may merely increase the concentration of colloidal dispersed metal rather than form truly soluble humic complexes. In water that contains high organic wastes such as was the case in the Rhone River in France, cobalt was almost completely complexed. A recent study determined that the distribution of ^{60}Co in the Rhone River sampled at Arles, France was 45% in the particulate phase, 30% in the dissolved phase, and 25% in the colloidal phase (Eyrolle and Charmasson 2001). Cobalt forms complexes with EDTA that are very stable environmentally. EDTA is often used in agriculture, food and drug processing, photography, and textile and paper manufacturing, and therefore, it is a likely constituent of industrial discharges.

Acidity and redox potential have an effect on the behavior of cobalt in water. The adsorption of cobalt by particulate matter decreases with decreasing pH, since the increasing H^+ concentration competes with metal binding sites. This may lead to increased concentrations of dissolved cobalt at low pH. The effect of Eh (redox potential) on the speciation of cobalt has been shown by the increase in the concentration of dissolved cobalt by orders of magnitude with increasing depth in certain parts of Baltic waters. The increase in the concentration of dissolved cobalt may be due to the formation of soluble bisulfide and polysulfide complexes in the anoxic zones. The residence time of soluble cobalt in seawater has been estimated to range from <1 to 52 years (Brugmann 1988; Knauer et al. 1982; Smith and Carson 1981).

Vitamin B_{12}, which contains cobalt, is synthesized by 58 species of seven genuses of bacteria as well as blue-green algae and actinomycetes (mold-like bacteria). Consequently, vitamin B_{12} levels in marine water range from very low levels in some open ocean water to much higher levels in some coastal waters. Freshwater environments have comparable levels of vitamin B_{12}. The high level of cobalamins in coastal

water appears to be related to the occurrence of macrophytes in these areas with their high concentrations of vitamin B_{12}. Cobalamins are released into the water when the organisms die (Smith and Carson 1981).

Alkaline thermal groundwater in granitic areas have been studied as possible waste disposal sites for radioactive waste (Alaux-Negrel et al. 1993). Water in these areas is characterized by high pH, low CO_2 partial pressure, and generally low redox potential; sulfide concentrations are in the range of 10^{-4} to 10^{-3} mol/L. The solubility of cobalt is controlled by the solubility of CoS (log K_1 and log K_2 being 5.7 and 8.7 at 25°C) and therefore, levels of cobalt are very low, 10^{-8}–10^{-10} mol/L.

The ^{60}Co (III) picolinate complex that is released into water by some nuclear reactors does not break down immediately on release into seawater, but rather can coexist with the ^{60}Co (II) forms for lengthy periods in the environment (Leonard et al. 1993a, 1993b). Studies indicate that several processes occur to the Co(III) organic complexes, including reduction to the inorganic form, sorption of both species to particulate matter, and transformations of the uncomplexed species. It is possible that this more soluble and uncharged form of radioactive cobalt will increase the dispersion of ^{60}Co from its point of discharge.

6.3.2.3 Sediment and Soil

The speciation of cobalt in soil or sediment depends on the nature of the soil or sediment, concentration of chelating/complexing agents, pH, and redox potential (Eh) of the soil. Dissolved cobalt may be absorbed by ion exchange and other mechanisms, or may form complexes with fulvic acids, humic acid, or other organic ligands in soil. The humic and fulvic complexes of cobalt are not very stable compared with those of copper, lead, iron, and nickel. The speciation of cobalt in sediment from nine sites in the Red Sea, a sea that is unique in that it has no permanent streams flowing into it, was assessed using a sequential extraction technique (Hanna 1992). The mean percentages contained in the various fractions were: exchangeable, 5.5%; carbonate, 5%; Fe/Mn oxides, 24%; organic, 30.4%; sulfides, 13%; and lithogenous, 22%. While the mean concentration of cobalt in the sediment increased from 0.003 to 0.006 ppb between 1934 and 1984, its distribution among the different phases did not change appreciably.

The reduction of soil Eh, which may occur when soil is flooded or in deeper layers of soil that are oxygen-depleted, may change the speciation of cobalt. This may result in the reduction of soil iron and manganese and the subsequent release of adsorbed cobalt from the mineral oxides. Similarly, a decrease

in soil pH may result in the solubilization of precipitated cobalt and desorption of sorbed cobalt, resulting in increased cobalt mobility (Smith and Carson 1981). Co^{2+} may also be oxidized to Co^{3+} by manganese oxides, a common component of soils and aquifer material, with subsequent surface precipitation (Brusseau and Zachara 1993). This process may affect transport of cobalt in the subsurface environment.

EDTA complexes of cobalt are very stable and are likely to form in soils containing EDTA. EDTA is widely used as a decontaminating agent at nuclear facilities. Although cobalt-EDTA complexes are adsorbed by some soils, the mobility of cobalt in soil may increase as a result of complex formation (Schnitzer 1969; Smith and Carson 1981; Swanson 1984). ^{60}Co that is disposed of in shallow land trenches have sometimes been found to migrate more rapidly than expected from the disposal sites. Organic chelating agents are frequently present at these sites and would possibly increase the solubility and transport of the radionuclide.

Bacterial action can affect the mobility of a substance by mediating reactions or by participating in reactions that lower the pH. Another way of influencing radionuclide mobility is by degrading complexing agents used in cleaning reactors (e.g., citric acid), thereby releasing the radionuclide. However, experiments on the fate and transport of cobalt released upon the biodegradation of the complexing ligand indicate that results are not always predictable; the means of ligand removal and the geochemical environment are important factors that must be considered (Brooks et al. 1998).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Cobalt concentrations in environmental media, including food and human tissue, have been exhaustively tabulated by Smith and Carson (1981) and Young (1979). The International Agency for Research on Cancer (IARC 1991) contains reviews of more recent studies, but is primarily focused on occupational exposures and body burdens of cobalt.

6.4.1 Air

Atmospheric cobalt is associated with particulate matter. Mean cobalt levels in air at unpolluted sites are generally <1–2 ng/m^3 (Hamilton 1994; Smith and Carson 1981). At the South Pole, cobalt levels of 0.00049 ± 0.00015 ng/m^3 were recorded in 1974–1975 (Maenhaut et al. 1979). Geometric mean cobalt

levels in several open-ocean environments ranged from 0.0004 to 0.08 ng/m^3 (Chester et al. 1991). The average annual PM-10 (particles with diameters ≤10 µm) cobalt concentration at Nahant, Massachusetts (near Boston) in 1992–1993 was 1.7 ng/m^3 (Golomb et al. 1997). Half of the cobalt was contained in fine particles (<2.5 µm) and half in coarse particles (2.5–10 µm). The mean cobalt level in southern Norway in 1985–1986 (n=346) was 0.10 ng/m^3 with 35% of the samples falling below the detection limit of 0.04 ng/m^3 (Amundsen et al. 1992). Atmospheric cobalt levels in industrial settings may exceed 10 ng/m^3. The highest recorded average cobalt concentration in air was 48 ng/m^3 in Clydach, Wales at the site, where nickel and cobalt were refined (Smith and Carson 1981). Some ambient atmospheric levels of cobalt are given in Table 6-2. These data show the contribution of anthropogenic sources in increasing the level of cobalt in the ambient air. Typical occupational cobalt levels are 1.0x10^4–1.7x10^6 ng/m^3 (Barceloux 1999; IARC 1991). While ^{60}Co has been detected in air samples at the Hanford site and Oak Ridge National Laboratories, levels were not reported (HazDat 2004; PNNL 1996). In 1995, the concentration of ^{60}Co in air at the Hanford site was below the detection limit in over 88% of the air samples.

6.4.2 Water

The concentrations of cobalt in surface water and groundwater in the United States are generally low, <1 µg/L in pristine areas and 1–10 µg/L in populated areas (Hamilton 1994; Smith and Carson 1981). However, cobalt levels may be considerably higher in mining or agricultural areas. Levels as high as

4,500 µg/L were reported in Mineral Creek, Arizona, near a copper mine and smelter; levels of 6,500 µg/L were reported in the Little St. Francis River, which receives effluent from cobalt mining and milling operations (Smith and Carson 1981). Mining at Blackbird Mine in Idaho, one of the large deposits of cobalt in North America, occurred from the late 1800s to 1982. Cobalt concentration in surface water and groundwater samples collected in 1992 from area creeks near this mine were reported to range from <1 to 625,000 µg/L, and from not detected to 315,000 µg/L respectively (ATSDR 1995), Eckel and Jacob (1988) analyzed U.S. Geological Survey (USGS) data for 6,805 ambient surface water stations and estimated the geometric mean and median dissolved cobalt concentration as 2.9 and 2.0 µg/L, respectively. Mean cobalt levels reported in seawater range from 0.078 µg/L in the Caribbean Sea to 0.39 µg/L in the Indian Ocean (Hamilton 1994). Vitamin B_{12} is synthesized by bacteria, macrophytes,

Table 6-2. Concentration of Cobalt in the Atmosphere

Location	Possible source/activity	Concentration[a]	Units	Type	Reference
Ambient levels—remote					
South Pole, 1974–1975	Crustal material	0.00049±0.00015	ng/m^3	Mean±SD	Maenhaut et al. 1979
Open-ocean		0.0004–0.08	ng/m^3	Geomean range	Chester et al. 1991
North Atlantic		0.006–0.09	ng/m^3	Range	Smith and Carson 1981
Baltic Sea, 1983		0.09, 0.01–0.43	ng/m^3	Mean, range	Hasanen etal. 1990
Remote sites		0.001–0.9	ng/m^3	Range	Schroeder et al. 1987
Ambient levels—rural/suburban/urban					
Rural sites		0.08–10.1	ng/m^3	Range	Schroeder et al. 1987
Massachusetts, Nahant, 1992–1993		1.7	ng/m^3	Annual mean	Golomb et al. 1997
Urban sites					Schroeder et al. 1987
United States		0.2–83	ng/m^3	Range	
Canada		1–7.9			
Europe		0.4–18.3			
Texas state average (1978–1982)		2.0	ng/m^3	Mean	Wiersema et al. 1984
Illinois, urban air (<2.5 µm; 2.5–10 µm)					Sweet et al. 1993
Bondville, Ill (rural)	Background	0.2; 0.1	ng/m^3	Mean (fine; coarse)	
Southeast Chicago	Steel mills	0.4; 0.4			
East St. Louis	Smelters	0.5; 0.4			
Washington, DC (1974)	Urban area	1.1	ng/m^3	Mean	Smith and Carson 1981
Ambient levels—industrial					
Maryland, Baltimore Harbor Tunnel (1973–1974)					Ondov et al. 1982
Air outside	Vehicular exhaust	0.8–1.9	ng/m^3	Range	
Air inside	Vehicular exhaust	2.2–5.3			
Ohio, Cleveland	Be-Cu alloy and other industrial activities	610	ng/m^3	Maximum	Smith and Carson 1981
Texas, El Paso (1978–1982)	Industrial	127	ng/m^3	Maximum	Wiersema et al. 1984

Table 6-2. Concentration of Cobalt in the Atmosphere

Location	Possible source/activity	Concentration[a]	Units	Type	Reference
Texas, Houston (1978–1982)	Urban area	81	ng/m^3	Maximum	Wiersema et al. 1984
Arizona, Tucson					Smith and Carson 1981
Urban	Copper smelting	1.9	ng/m^3	Mean	
Rural		0.7			
Maryland, Chalk Point Generator	Coal-burning power plant	3.86	ng/m^3	Mean	Smith and Carson 1981
Wales, Clydach	Nickel refining	48, 3–300	ng/m^3	Mean, range	Smith and Carson 1981
Wales, Llausamlet and Trebanos	Towns near Clydach	3.8		Mean	Smith and Carson 1981
Occupational air levels					
Northern Italy, exposure survey, 1991, area monitoring (n=259)	Diamond abrasive mfg.				Mosconi et al. 1994a
	Mould-filling	220, 47–960	ng/m^3	Median, range	
	Sintering	101.5, 32–240			
	Grinding	22, 15–45			
	Mechanical-working	20, 12–44			
	Grinding	5, 2.5–94			
	Tool production	6, 5–47			
	Hard metal alloy filing	2, 0.8–3			
	Other	2.7, 2.3–15			
Northern Italy, exposure survey, 1991, personal sampling (n=259)	Diamond abrasive mfg.				Mosconi et al. 1994a
	Mould-filling	382, 76–2,600	ng/m^3	Median, range	
	Sintering	309, 238–413			
	Grinding	230, 82–690			
	Mechanical-working	40, 7.1–65			
	Grinding	9.3, 1.5–178			
	Tool production	17, 4–28			
	Hard metal alloy filling	5, 1–107			
	Other	50, 10–290			

Table 6-2. Concentration of Cobalt in the Atmosphere

Location	Possible source/activity	Concentration[a]	Units	Type	Reference
Japan, personal sampling, hard metal tool manufacture, 8-hour TWA, 356 workers (n=935)	Powder preparation				Kumagai et al. 1996
	Rotation	459, 7–6,390	$\mu g/m^3$	Mean, range	
	Full-time	147, 26–378			
	Press				
	Rubber	339, 48–2,910			
	Steel	47, 6–248			
	Shaping	97, 4–1,160			
	Sintering	24, 1–145			
	Blasting	2, 1–4			
	Electron discharging	3, 1–23			
	Grinding	45, 1–482			

geomean = geometric mean; SD = standard deviation; TWA = time weighted average

blue-green algae, and actinomycetes, and cobalt levels in oceans often correlate with biological productivity. In the Baltic Sea, dissolved cobalt levels that are 1.0 ng/L near the surface, increase to 71.0 ng/L at a depth of 200 m (Brügmann 1988). The rise in dissolved cobalt is coincident with the onset of anoxic conditions and the presence of hydrogen sulfide, indicating that soluble bisulfide and polysulfide complexes may be present. Some cobalt levels reported in water are given in Table 6-3.

In a 1962–1967 survey, cobalt was detected in 2.8% of 1,577 U.S. raw surface waters from which drinking water is derived; the detection limit was 1 µg/L and the maximum concentration was 48 µg/L (NAS 1977). Of 380 U.S. finished drinking waters, only 0.5% contained cobalt levels exceeding 1 µg/L; the maximum concentration found was 29 µg/L (NAS 1977). These values are higher than the respective median and maximum levels of <2.0 and 6.0 µg/L found in Canadian finished drinking water (Meranger et al. 1981). Meranger et al. (1981) tested source water and drinking water in 71 municipalities across Canada and concluded that, in general, both surface water and groundwater used for drinking water supplies contain negligible amounts of cobalt. Greathouse and Craun (1978) analyzed 3,834 grab samples of household tap water from 35 geographical areas in the United States for 28 trace elements. Cobalt was found in 9.8% of the samples at concentrations ranging from 2.6 to 107 µg/L. It is not clear whether these higher levels could indicate that cobalt was picked up in the distribution system. In the earlier National Community Water Supply Study (2,500 samples), 62% of the samples contained <1 µg Co/L; the average and maximum cobalt concentrations were 2.2 and 19 µg/L, respectively (Smith and Carson 1981). Cobalt was not detected (detection limit 8 µg/L) in a 1982–1983 survey of drinking water in Norway that covered 384 waterworks serving 70.9% of the Norwegian population (Flaten 1991).

The mean concentrations of cobalt in rain is around 0.03–1.7 µg/L, with levels generally ranging from 0.002 µg/L at Enewetak Atoll to about 2.9 µg/L in the Swansea Valley, Wales (Arimoto et al. 1985; Dasch and Wolff 1989; Hansson et al. 1988; Heaton et al. 1990; Helmers and Schrems 1995; Nimmo and Chester 1993; Nimmo and Fones 1997; Smith and Carson 1981). The highest recorded level of cobalt in precipitation was 68.9 µg/L in the vicinity of a nickel smelter in Monchegorsk in the Russian Arctic (Reimann et al. 1997). An analysis of rain in the Mediterranean and urban and coastal sites in northwest England showed that about 33–44% of the cobalt occurred as very stable dissolved organic complexes (Nimmo and Chester 1993; Nimmo and Fones 1997).

As it was pointed out in Section 6.3.2.2, ^{60}Co discharged from the Steam Generating Heavy Water Reactor at Winfrith on the south coast of England was shown to be largely in the form of the nonionic

Table 6-3. Cobalt Levels in Water

Nature/location of water	Level	Units	Type	Reference
Sea water				
Florida (Indian River Lagoon) (43 sites)	0.031, 50	µg/L	Mean, range	Trocine and Trefry 1996
California (Baja) 2–45 km offshore (n=11)	0.022–0.17	nM	Range	Sañudo-Wilhelmy and Flegal 1996
<100 m off shore (n=11)	0.11–0.59			
Agean Sea, 1994; 8 sites (dissolved)	0.168–0.632, 1.917	nM	Range of means, maximum	Voutsinou-Taliadouri 1997
Baltic Sea (Gotland Deep site)				Brügmann 1988
10 m	1.0	ng/L	Mean (dissolved Co)	
50 m	1.0			
100 m	3.5			
150 m	4.2			
200 m (anoxic)	71.0			
235 m (anoxic)	49.2			
Seawater background	0.04	µg/L		Bargagli 2000
Seawater	0.27	µg/L	Mean	Abbasi et al. 1989
Fresh surface water				
Freshwater background	0.05	µg/L		Bargagli 2000
U.S. ambient surface water (6,805 stations)	<2.9, 2.0	µg/L	Mean, median	Eckel and Jacob 1988
Five Great Lakes waters	ND–0.09	µg/L	Range	Rossmann and Barres 1988
Japan, unpolluted lake	<0.004	µg/L		Nojiri et al. 1985
Norway, 11 rivers	0.94	µg/L	Maximum	Flaten 1991
Streams near populated areas	1–10	µg/L	Range	Smith and Carson 1981
Streams in agricultural and mining areas	11–50	µg/L	Range	Smith and Carson 1981
Suspended solids in rivers	7–94	mg/kg	Range	Smith and Carson 1981
Groundwater				
Canada (Chalk River nuclear waste site)	0.0001–0.002	µg/L		Cassidy et al. 1982
Colorado (Denver)–shallow groundwater, (n=30)	<1 (<1–9)	µg/L	Median, range	Bruce and McMahon 1996

Table 6-3. Cobalt Levels in Water

Nature/location of water	Level	Units	Type	Reference
Drinking water				
Canadian drinking water (71 municipalities)				Meranger et al. 1981
Raw:	<2.0	µg/L	Median	
Treated:	<2.0			
Distributed:	≤2.0			
Precipitation				
Massachusetts, 1984 (12 events)	0.045 (0.008), 0.02–0.12	µg/L	Mean (SD), range	Dasch and Wolff 1989
Rhode Island (rain/snow), 1985 (n=269)	0.038 (0.067)	ppb	Median (mean)	Heaton et al. 1990
	0.001–0.80		Range	
Western Mediterranean, 1988–1989				Nimmo and Chester 1993
Total cobalt	0.029–0.134, 0.043	µg/L	Range, mean	
Labile cobalt	0.009–0.104, 0.025			
Organic cobalt	ND–0.613, 0.019			
Arctic (7 sites in Finland, Norway, Russia)	<0.02–1.07, 3.32	µg/L	Median range, maximum	Reimann et al. 1997
Russia (Monchegorsk), nickel smelter	11.8, 68.9		Median, maximum	

ND = not detected; SD = standard deviation

trivalent complex, ^{60}Co(III) picolinate. The ^{60}Co(III) species is not immediately reduced to the more particle-reactive divalent form, and both oxidation states may coexist for long periods of time in the environment. The proportion of the more soluble and mobile ^{60}Co(III) would be expected to increase with time and distance from the point of discharge. Shoreline water samples (n=22) taken in 1987–1988 at two locations in the vicinity of the discharge from the Steam Generating Heavy Water Reactor at Winfrith contained 0.3–16.2 mBq/L (8–437 fCi/L) of particulate ^{60}Co, 2.8–44.4 mBq/L (76–1,200 fCi/L) of soluble ^{60}Co(II), and 0.2–4.8 mBq/L (5–130 fCi/L) of soluble ^{60}Co(III) (Leonard et al. 1993). The percent of the soluble ^{60}Co present as Co(III) ranged from 4.3 to 18.6%. In 1989, in conjunction with the largest discharge of effluent from the plant, offshore seawater samples from 18 sites contained 0.06–2.22 mBq/L (2–60 fCi/L) of particulate ^{60}Co, 0.30–10.3 mBq/L (8.1–278 fCi/L) of soluble ^{60}Co(II), and 0.12–1.55 mBq/L (3.2–41.9 fCi/L) of soluble ^{60}Co(III). The percent of the soluble ^{60}Co present as Co(III) ranged from 6.0 to 28.6%.

6.4.3 Sediment and Soil

Cobalt is the 33rd most abundant element in the earth's crust. Its average concentrations in the earth's crust and in igneous rocks are 20–25 and 18 mg/kg, respectively (Abbasi et al. 1989; Merian 1985; Smith and Carson 1981). Trace metals in soils may originate from parent rock or from anthropogenic sources, primarily fertilizers, pesticides, and herbicides. Most soils contain 1–40 mg cobalt/kg. The average cobalt concentration in U.S. soils is 7.2 mg/kg (Smith and Carson 1981). Soils containing <0.5–3 mg cobalt/kg are considered cobalt-deficient because plants growing on them have insufficient cobalt (<0.08–0.1 mg/kg) to meet the dietary requirements of cattle and sheep. Cobalt-deficient soils include the humus podzols of the southeastern United States, and the podzols, brown podzolic soils, and humus groundwater podzols in the northeastern parts of the United States. (Podzols are generally coarse-textured soils.) The cobalt content of surface soils from 13 sites in the brown and dark brown soil zones of southwestern Saskatchewan ranged from 3.7 to 16.0 mg/kg and only in one case was the soil appreciably elevated above the corresponding parent material (Mermut et al. 1996). Fertilizers used in this agricultural area contained 0.12–102 mg Co/kg, with a median of 5.7 mg/kg.

Mean cobalt concentrations in surface soil from nine sites on two active volcanic islands off of Sicily ranged from 5.1 to 59.0 mg/kg (Bargagli et al. 1991). Soils near ore deposits, phosphate rocks, or ore

smelting facilities, and soils contaminated by airport traffic, highway traffic, or other industrial pollution may contain much higher concentrations of cobalt; concentrations up to 800 mg/kg have been detected in such areas (Kloke et al. 1984; Smith and Carson 1981). Cobalt concentrations from 28 samples collected from surface deposits in the Big Deer and Blackbird Creek drainage basins in Idaho near the Blackbird Mine ranged from 26.5 to 7,410 mg/kg (Agency for Toxic Substances and Disease Registry 1995). Soils around the large copper-nickel smelters in Sudbury, Ontario have been shown to contain high levels of cobalt. Fifty kilometers from the smelters, cobalt levels in surface soil were 19 mg/kg. These levels increased to 48 mg/kg at 19 km, 33 mg/kg at 10 km, and 42–154 mg/kg between 0.8 and 1.3 km from the smelter (Smith and Carson 1981). Soils around a cemented tungsten carbide tool grinding factory contained cobalt levels as high as 12,700 mg/kg, almost 2,000 times the average in U.S. soils (Abraham and Hunt 1995). However, neighborhood soils between 30 and 160 meters from the factory only contained 12–18 mg Co/kg.

Unpolluted freshwater sediment contains about the same levels of cobalt as does cobalt-sufficient soil, generally <20 mg/kg (Smith and Carson 1981). In the Hudson River Estuary, cobalt levels in suspended sediment were an order of magnitude higher than in bottom sediment (Gibbs 1994). This can be attributed to the finer grain size of suspended sediment or local sources. Cobalt levels in core samples (surface to 42 cm deep) from the Upper St. Lawrence Estuary were independent of depth, indicating the lack of any recent significant anthropogenic releases (Coakley et al. 1993). Cobalt levels in sediment are shown in Table 6-4.

No broad-based monitoring studies of ^{60}Co or other radioactive cobalt isotopes in soil or sediment were found in the literature. Soil samples from the O-horizon taken from three sites in the 30-km zone around Chernobyl in 1992 and again in 1993 contained 14–290 and 4.5–245 Bq/kg (380–7,800 and 120–6,620 pCi/kg) dry weight of ^{60}Co, respectively (Lux et al. 1995). The Columbia River receives radiological contaminants along the Hanford Reach primarily through seepage of contaminated groundwater. The regional median concentration of ^{60}Co in sediment was highest along the Hanford reach, approximately 0.09 pCi/g (0.003 Bq/g) (PNNL 1996). ^{60}Co activity in a sediment cores in water off of Southampton in southern England contained up to 28 Bq/kg (760 pCi/kg) in the upper 3 cm; no activity was found below 12.5 cm (Croudace and Cundy 1995). Discharges of treated effluent occurred on closing a steam generating heavy water reactor west of where the sampling was done. The maximum discharge occurred in 1980–1981; however, no value was reported (Croudace and Cundy 1995).

Table 6-4. Cobalt Levels in Sediment

Nature/location of sediment	Level	Units	Type	Reference
Freshwater				
Polluted lakes and rivers	0.16–133	mg/kg	Range	Smith and Carson 1981
Lake Ontario near Miesissaqua, Canada	4.1–19.8	mg/kg	Range	Glooschenko et al. 1981
Hudson River, Foundry Cove, 1983, Ni-Cd battery plant, 1953–1979, surficial (0–5 cm) sediment, 16 sites	18–700	mg/kg	Range	Knutson et al. 1987
Estuaries and Marine				
Hudson River Estuary (0–80 km from ocean), 1991				Gibbs 1994
Bottom sediment	1–13	mg/kg	Range	
Suspended sediment (near surface)	30–140			
Upper St. Lawrence Estuary, 1989–1990				Coakley et al. 1993
Core C168	3.1 (0.6)	mg/kg	Mean (SD)	
Cores LE and LO	2.7 (0.5)			
Massachusetts, New Bedford Harbor- core (0–25 cm)				Shine et al. 1995
Outer Harbor	7.03, 3.64–9.79, range			
Inner Harbor	6.38, 2.62–10.52			
Buzzards Bay (control site)	4.76, 1.64–8.19			
Indian River Lagoon, Florida (43 sites)	2.3, 0.4–6.3	mg/kg	Mean, range	Trocine and Trefry 1996
Gulf of Mexico				Villanueva and Botello 1998
Coastal areas (11 sites)	12.30–36.26	mg/kg	Range of means	
Continental shelf (3 sites)	6.39–21.00			
Antarctica (Ross Sea) continental shelf (n=12)	19, 0.10–13	mg/kg	Mean, range	Bargagli 2000
Northern Arctic Alaska, continental shelf (n=136)	9, 3.3–18	mg/kg	Mean, range	Bargagli 2000
Chukchi Sea, northeast Alaska (31 stations, surficial sediment)	32.7, 19–74	mg/kg	Mean, range	Naidu et al. 1997
Baltic Sea, southern, off Poland (surficial sediment)	0.69–18.10	mg/kg	Range	Szefer et al. 1996
Baltic Sea (Gotland Deep site)	19, 11–33	mg/kg	Mean, range	Brügmann 1988

SD = standard deviation

Sediment samples were analyzed from the Peconic River system on Long Island, New York, downstream of Brookhaven National Laboratory (BNL). Near the sewage treatment plant, closest to the BNL, mean concentrations of ^{60}Co from three locations at the depth intervals 0.00–0.06, 0.06–0.15, 0.15–0.24, and 0.24–0.37 meters were 9.6, 6.7, 9.6, and 10.5 Bq/kg (0.25, 0.18, 0.25, and 0.28 nCi/kg) dry weight, respectively. At one location at the BNL property boundary, mean concentrations of ^{60}Co, using the same depth intervals, were 5.8 Bq/kg (0.16 nCi/kg) dry weight for the 0.00–0.06 m depth and <4 Bq/kg (<0.11 nCi/kg) dry weight for the remaining depth intervals. Sediment samples from a control river, Connetquot River, were <4 Bq/kg (<0.11 nCi/kg) in two locations at two depths (0.00–0.06 and 0.06–0.15 m) (Rapiejko et al. 2001).

Mururoa and Fangataufa Atolls were used for underground testing of nuclear weapons from 1975 to 1996. ^{60}Co was detected in the particle fraction of water in measurable levels at two of the nine Mururoa Atoll sites, Aristee and Ceto, at 0.58 and 1.06 mBq/L (0.016 and 0.029 pCi/L), respectively. ^{60}Co levels were found at levels below the detection limit, <0.1 mBq/L (<0.003 pCi/L), at the two Fangataufa Atoll sites and at the seven other Muruoa Atoll sites (Mulsow et al. 1999). Concentrations of ^{60}Co of soil samples used for growing onion, potatoes, tomatoes, cabbage, and maize in the Bulgarian village, Ostrov, in the vicinity (approximately 25–30 km) of the “Kozloduy” nuclear power plant were <8, 3, 320, 330, and 180 mBq/kg (2, 8.1, 8.6, 8.9, and 4.9 pCi/kg), respectively (Djingova and Kuleff 2002).

6.4.4 Other Environmental Media

The cobalt content of plants depends on the plant, the cobalt content of the soil, and numerous environmental factors. The mean cobalt concentration reported for terrestrial plants was 0.48 µg/g, while the mean and median levels for freshwater vascular plants were 0.48 and 0.32 µg/g, respectively (Outridge and Noller 1991). The median cobalt level in freshwater vascular plants from polluted waters was about the same as in unpolluted waters, 0.37 µg/g, although extremely high levels of cobalt, up to 860 µg/g, was reported in one species, *Myriophyllum verticillatum*, from central Ontario lakes. Grasses normally contain 0.2–0.35 µg/g of cobalt, but grasses from cobalt-deficient regions contain only 0.02–0.06 µg/g of cobalt (Hamilton 1994). Durum wheat grown in southeastern Saskatchewan contained 0.01–0.02 mg/kg dry weight (Mermut et al. 1996). In view of the cobalt content of the soil and the fact that almost half of the cobalt in fertilizers used in the area was in a readily available form, the uptake of cobalt by wheat was negligible.

^{60}Co levels in plants and mushrooms in the 30-km zone around Chernobyl were mostly below the detection limit in samples obtained in 1992 and 1993; the highest activity recorded was 3.9 Bq/kg (110 pCi/kg) dry weight in *Athyrium filix femina* (Lux et al. 1995).

Cobalt concentrations have been reported in various aquatic animals and seabirds. Eel and a freshwater fish from three Dutch polder lakes contained 2.5–25.0 and 2.50–5.63 mg cobalt/kg wet weight, respectively, (Badsha and Goldspink 1988). Muscle tissue of ocean fish and rock crabs caught near dump sites off New York City, New Haven, Connecticut, and Delaware Bay contained 10–40 and 16.0 µg/kg, respectively (Greig and Jones 1976). In a study of the levels and distribution of 14 elements in oceanic seabirds, the concentration of cobalt, an essential element, appeared to be highly regulated, with over 80% of the body burden residing in the skeleton. The mean cobalt concentration in the livers of 11 seabird species ranged from 0.048 to 0.078 µg/g dry weight, and cobalt had the lowest coefficient of variation in the different species of the elements studied (Kim et al. 1998a). In another study in Antarctica, mean cobalt levels in fish and amphipods were 0.11–0.14 and 1.01 µg/g dry weight, respectively, while those in the tissue of penguin and other sea birds ranged from 0.09 to 0.11 µg/g (Szefer et al. 1993). The concentration of cobalt in the tissue of 14 bluefin tuna caught by various commercial fishing vessels off Newfoundland was essentially the same, 0.01±0.004 µg/g (Hellou et al. 1992a). Similarly, in a broad survey of contaminant levels in nine species of fish and fiddler crabs from 11 sites in the lower Savannah River, Georgia and the Savannah National Wildlife Refuge, mean cobalt levels among different species and sites were statistically indistinguishable (Winger et al. 1990). These and other studies indicate that cobalt does not biomagnify up the food chain (Smith and Carson 1981). While high levels of cobalt were found in sediment from the Tigris River in Turkey and low levels in the water, cobalt was not detected in two species of fish, *Cyprinion macrostomus* and *Garra rufa* (Gümgüm et al. 1994). Cobalt was detected in two other species of fish collect between 1995 and 1996 in the upper Sakarya river basin, Turkey. Cobalt concentrations ranged from 0.038 to 0.154 µg/g dry weight for *Cyprinus caprio* and from 0.045 to 0.062 µg/g dry weight for *Barbus plebejus* (Barlas 1999).

^{60}Co was not detected in fish and mussel samples analyzed from the Peconic River system on Long Island, New York, downstream of the BNL. The lower detection limit for ^{60}Co was 0.4 Bq/kg (10 pCi/kg). ^{60}Co had been detected in sediment samples from this area (Section 6.4.3) (Rapiejko et al. 2001).

Some female birds sequester metals into their eggs under certain conditions, a phenomenon that may jeopardize the developing embryos. The geometric mean concentrations of cobalt in tern eggs collected from coastal New Jersey in 1971 and 1982 were 0.48 and 0.50 mg/kg, respectively. Unlike the levels of seven other common metals (e.g., mercury, cadmium, copper, lead, manganese, nickel, and zinc), the level of cobalt in tern eggs (and in the environment) showed no decline over the 11-year period (Burger and Gochfeld 1988).

Table 6-5 shows the levels of cobalt in food items and food categories from different countries. The level of cobalt in most Canadian foods was low; items with the highest concentrations in this study were waffles (0.076 µg/g), corn cereal (0.074 µg/g), and potato chips (0.070 µg/g) (Dabeka and McKenzie 1995). Green leafy vegetables and fresh cereals are the richest sources of cobalt (0.2–0.6 µg/g dry weight), while dairy products, refined cereals, and sugar contain the least cobalt (0.1–0.3 µg/g dry weight) (Barceloux 1999). The levels of cobalt were determined in 50 different food items, mainly meat, fish, fruit, vegetables, pulses, and cereals on the Swedish market during the years 1983–1990 (Jorhem and Sundström 1993). Beef liver and seeds were fairly high in cobalt and fish, fruit, and root and leafy vegetables were under 0.01 µg cobalt/g fresh weight. The cobalt levels in µg/g fresh weight were highest in alfalfa seeds, 0.86; linseed, 0.56; milk chocolate, 0.34; dark chocolate, 0.24; white poppy seeds, 0.30; blue poppy seeds, 0.15; soya beans, 0.084; green lentils, 0.054; and beef liver, 0.043. The cobalt content of 20 brands of alcoholic and nonalcoholic beer widely consumed in Spain ranged from 0.16 to 0.56 µg/L with a median of 0.39 µg/L (Cameán et al. 1998). Cobalt, which was at one time added to beer to increase the foam head, has been associated with cardiomyopathies (heart disease) in heavy beer drinkers.

A study of radionuclide levels in various foods and drinks in Hong Kong found that the ^{60}Co content in nearly all foods and drinks used in the study were below the minimal detection limit (Yu and Mao 1999). Analysis of wild plants in Bulgaria in villages near the “Kozloduy” nuclear power plant showed that the concentrations of ^{60}Co were below the detection limit. Mean activity concentrations of ^{60}Co in edible plants in this region were mostly <0.04 Bg/kg (<1 pCi/kg) (Djingova and Kuleff 2002).

Stable cobalt is present in various consumer products including cleaners, detergents, and soaps, which have resulted in dermatitis in sensitive individuals (Kokelj et al. 1994; Vilaplana et al. 1987). Tobacco contains about <0.3–2.3 µg Co/g dry weight and approximately 0.5% of the cobalt appears in mainstream smoke (Barceloux 1999; Munita and Mazzilli 1986; Ostapczuk et al. 1987; Stebbens et al. 1992).

Table 6-5. Cobalt Levels in Food

Food item	Level	Units[a]	Type	Reference
Infant formulas/milk				
Evaporated milk (n=21)	0.74, 0.52–2.6	µg/kg[b]	Median, range	Dabeka 1989
Ready-to-use formula (n=49)	0.53, 0.21–5.2	µg/kg[b]	Median, range	Dabeka 1989
Milk-based (n=33)	0.40, 0.21–0.99			
No added iron (n=6)	0.36, 0.21–0.61			
Added iron (n=27)	0.87, 0.41–0.99			
Soy-based (n=16)	2.27, 1.71–5.2			
Concentrated liquid formula (n=50)	2.27,0.25–11.8	µg/kg[b]	Median, range	Dabeka 1989
Milk-based (n=34)	1.57, 0.25–3.11			
No added iron (n=20)	1.06, 0.25–1.77			
Added iron (n=14)	2.59, 2.03–3.11			
Soy-based (n=16)	4.33, 2.7–11.8			
Powdered formula (n=64)	9.54, 2.6–53	µg/kg[b]	Median, range	Dabeka 1989
Milk-based (n=36)	4.96, 2.6–10.6			
No added iron (n=23)	4.24, 2.6–9.6			
Added iron (n=13)	8.26, 5.1–10.6			
Soy-based (n=28)	20.0, 10.6–53			
Agricultural crops				
Cabbage, United States	0.2	mg/kg[c]	Typical level	NAS 1977
Corn seed, United States	0.01	mg/kg[c]	Typical level	NAS 1977
Fruits, 12 types, Poland	0.01–0.02	mg/kg	Range	Bulinski et al. 1986
Lettuce, Sweden 1983–1990 (n=7)	0.002, 0.006	mg/kg	Mean, maximum	Jorhem and Sundström 1993
Lettuce, United States	0.2	mg/kg[c]	Typical level	NAS 1977
Onions, 11 Danish sites (n=110)	1.51, 0.119–5.1	µg/kg	Median, range	Bibak et al. 1998a
Peas, 10 Danish sites (n=93)	4.6, 0.57–17	µg/kg	Median, range	Bibak et al. 1998b
Potatoes, Sweden (n=8)	0.008, 0.017	mg/kg	Mean, maximum	Jorhem and Sundström 1993
Spinach, United States	0.4–0.6	mg/kg[c]	Typical range	NAS 1977
Strawberries, Sweden (n=10)	0.004, 0.010	mg/kg	Mean, maximum	Jorhem and Sundström 1993
Vegetables, 30 types, Poland	0.008–0.032	mg/kg	Range	Bulinski et al. 1986
White flour, United States	0.003	mg/kg[c]	Typical level	NAS 1977
Meat, fish, beverages				
Beef, Sweden (n=3)	0.001, 0.001	mg/kg	Range, maximum	Jorhem and Sundström 1993
Beef liver, Sweden (n=3)	0.043, 0.074	mg/kg	Range, maximum	Jorhem and Sundström 1993
Beef kidney, Sweden (n=3)	0.008, 0.010	mg/kg	Range, maximum	Jorhem and Sundström 1993

Table 6-5. Cobalt Levels in Food

Food item	Level	Units[a]	Type	Reference
Beer, Spain, 20 brands	0.39, 0.16–0.56	µg/L	Median, range	Cameán et al. 1998
Cocoa, Germany	1.31	mg/kg[c]		Ostapczuk et al. 1987
Coffee (whole), South Africa	0.93	mg/kg[c]		Horwitz and Van der Linden 1974
Coffee (whole), Germany (61% water extractable)	0.11–0.31	mg/kg[c]	Range	Ostapczuk et al. 1987
Fish, Sweden, 10 varieties (n=40)	<0.001–.008, 0.020	mg/kg	Range of mean, maximum	Jorhem and Sundström 1993
Pork, Sweden (n=36)	0.001, 0.012	mg/kg	Range, maximum	Jorhem and Sundström 1993
Pork liver, Sweden (n=36)	0.010, 0.023	mg/kg	Range, maximum	Jorhem and Sundström 1993
Pork kidney, Sweden (n=36)	0.004, 0.011	mg/kg	Range, maximum	Jorhem and Sundström 1993
Tea (whole), South Africa	0.2	mg/kg[c]		Horwitz and Van der Linden 1974
Tea (whole), Germany (40% water extractable)	0.18–6.7	mg/kg[c]	Range	Ostapczuk et al. 1987
Food categories				
Bakery good/ cereals, Canada (n=24)	10.9, 75.7	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Beverages, Canada (n=7)	5.9, 9.1	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Fats and oils, Canada (n=3)	<2.6, 37.6	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Fish, Canada (n=6)	18.6, 14.3–29.4	µg/kg	Median, range	Dakeba and McKenzie 1995
Fruits and fruit juices, Canada (n=25)	<6.6, 35.7	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Meat and poultry, Canada (n=18)	<5.5, 38.2	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Milk and milk products, Canada (n=13)	<1.4, 18.9	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Soups, Canada (n=4)	5.6, 8.5	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Sugar and candy, Canada (n=7)	<0.4, 3.5	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Vegetables, Canada (n=38)	2.4, 18.1	µg/kg	Median, maximum	Dakeba and McKenzie 1995

[a]Produce on a fresh weight basis, unless otherwise specified
[b]As sold
[c]Dry weight basis

The cobalt content of sewage sludge, incinerator ash, fertilizers, soil amendments, and other substances appears in Table 6-6. The concentration of cobalt in U.S. coal averages about 5 mg/kg, levels in crude oil and fuel oil are 0.001–10 and 0.03–0.3 mg/kg, respectively, and those in gasoline are <0.1 mg/kg (Smith and Carson 1981). Cobalt levels were below the detection limit of 0.05 ppm dry weight in all but 1 of 26 samples of composted yard waste, sewage sludge, and municipal solid waste samples nationwide in 1991. The one positive sample of composted yard waste contained 1.53 ppm of cobalt (Lisk et al. 1992).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to cobalt occurs through inhalation of ambient air and ingestion of food and drinking water. In general, intake from food is much greater than from drinking water, which in turn, is much greater than from air. From the limited monitoring data available, the average concentration of cobalt in ambient air in the United States is approximately 0.4 ng/m^3. However, levels may be orders of magnitude higher in source areas. Therefore, intake to cobalt in air will vary substantially from nonsource areas to areas with cobalt-related industries. Similarly, the median cobalt concentration in U.S. drinking water is <2.0 µg/L; however, values as high as 107 µg/L have been reported in surveys of water supplies (Smith and Carson 1981). Therefore, exposure from drinking water may vary considerably from one location to another. In Canada, the daily cobalt intake of the average adult from drinking water is ≤2.6 µg; this could increase to 10 µg for those living in areas with the highest cobalt levels (Meranger et al. 1981).

General population exposure to cobalt from food is highly variable and normally higher than intake from drinking water. Most of the cobalt ingested is inorganic; vitamin B_{12}, which occurs almost entirely in food of animal origin, constitutes only a very small fraction of cobalt intake. The cobalt intake in food has been estimated to be 5.0–40.0 µg/day (Jenkins 1980). The daily cobalt intake, including food, water, and beverages of two men that were followed for 50 weeks was much higher, 310 and 470 µg (Smith and Carson 1981). The estimated average daily cobalt intake from diet in Canada was 11 µg/day; the intake varied from 4 to 15 µg/day between the various age/sex groups (Table 6-7) (Barceloux 1999; Dabeka and McKenzie 1995). The contributions of various food groups to cobalt intake in this study were (category, contribution of dietary intake): bakery goods and cereals, 29.8%; vegetables, 21.9%; beverages, 9.8%; milk and milk products, 9.4%; meat and poultry, 9.1%; soups, 6.4%; fruit and fruit juices, 5.0%; sugar

Table 6-6. Cobalt Content of Miscellaneous Substances

Substance/source	Level	Units	Type	Reference
Bituminous coal used for power generation	6.4	mg/kg	Median	Rubin 1999
Coal, United States	~5	mg/kg	Mean	Smith and Carson 1981
Fly ash	~25	mg/kg	Mean	Smith and Carson 1981
MSW Incinerator ash, Mississippi				Buchholz and Landsberger 1995
Fly ash (n=30)	11.3–13.5	µg/g	Range	
Bottom ash (n=30)	65.2–90.3			
Combined ash (n=30)	24.8–30.5			
MSW Incinerator ash, United States, 1987				Mumma et al. 1990
Fly ash (n=5)	18.2–54.0	µg/g	Range	
Bottom ash (n=7)	13.5–35.1			
Combined ash (n=8)	11.2–43.4			
Compost, Toronto				Evans and Tan 1998
Residential compost	8.1, 3.2–12	mg/kg	Median, range	
Greenhouse finished compost	6.1±1.03		Mean ± SD	
Sewage sludge				
16 large U.S. cities	11.3, 6.08–29.1	mg/kg	Median, range	Gutenmann et al 1994
32 U.S. cities	7.2, 2.4–30.1	mg/kg	Median, range	Mumma et al. 1984
Cow manure (comparison)	6.1	mg/kg		Mumma et al. 1984
Miscellaneous soil amendments[a]				Raven and Loeppert 1997
Compost	3.55, 3.57	mg/kg	Individual means	
Diammonium phosphate	3.24, 0.68			
Dolomite	0.33			
Manure	2.23			
Monoammonium phosphate	0.78, 3.38			
Rock phosphate, Tilemsi	19.6			
Rock phosphate, North Carolina	<0.08			
Sewage sludge, Austinite	4.10			
Sewage sludge, Milorganite	4.07			
Triple superphosphate	6.61, 2.24			
Street dust, New York City	8.7–12.9	µg/g	Range	Fergusson and Ryan 1984

[a]The rest of the 24 fertilizers and soil amendments tested were below the detection limit (typically <0.07 ppm)

MSW = municipal solid waste; SD = standard deviation

Table 6-7. Mean Daily Dietary Intake of Cobalt for Selected Population Groups in Canada

Group	Mean daily intake (µg/day)
1–4 years	7
5–11 years	10
12–19 years; male	14
12–19 years; female	10
20–39 years; male	15
20–39 years; female	9
40–65 years; male	12
40–65 years; female	9
65+; male	10
65+; male	8

Source: Dabeka and McKenzie 1995

and candies, 2.8%; fish, 2.7%; fats and oils, 2.2%; and miscellaneous, 1.1%. The average daily intake of cobalt in France was estimated to be 29 µg/day (Biego et al. 1998). In this study, foods were divided into nine categories. The foods accounting for the greatest contributions of cobalt intake were milk and dairy products, fish-crustaceans, and condiments-sugar oil, respectively contributing 32, 20, and 16% to the daily intake. The U.S. Department of Agriculture (USDA) conducted a special exploratory study in 1985–1986 to determine the concentration of trace metals in tissue of health livestock and poultry randomly selected from those slaughtered. Between 0.6 and 5.9% of samples in the 11 production classes had levels of cobalt that exceeded the lowest reliable quantitation level of 0.15 ppm (0.15 mg/kg) and the mean of positive samples ranged from 0.20 to 0.23 ppm in all classes but heifer/steer, which had a level of 1.92 ppm (Coleman et al. 1992). Cobalt, which has been added to beer to increase the foam head, has been associated with cardiomyopathies (heart disease) in heavy beer drinkers. However, according to a recent Spanish study, the low levels of cobalt presently found in beer do not make a significant contribution to the total cobalt intake in heavy beer drinkers (Cameán et al. 1998). Smokers may be exposed to cobalt in mainstream smoke, but the level of exposure has not been assessed (Barceloux 1999).

Since cobalt and other heavy metals have been used on hand-painted china, a study was conducted to see whether these metals are released into food under acidic conditions. Forty-six samples of porcelain dinnerware from Europe or Asia that were manufactured before the mid-1970s and had hand-painted designs over the glaze were filled with 4% acetic acid to within 7 mm of the rim and analyzed after 24 hours (Sheets 1998). Of these, 36 samples released <0.02 µg/mL of cobalt and 10 released 0.020–2.9 µg/mL. The Food and Drug Administration (FDA) has not established dinnerware extraction limits for cobalt.

Data are lacking on the levels of cobalt in tissues and fluids of the general populations in the United States; values from various countries are given in Table 6-8. This table shows that cobalt concentrations are greatest in nail, hair, and bone. The differences in cobalt levels in similar human tissues (e.g., hair, nail) in different countries may be due to differences in dietary and living habits and levels of cobalt in food (Takagi et al. 1988). The total amount of cobalt in the body of an adult as vitamin B_{12} is about 0.25 mg, of which 50–90% in contained in the liver (IARC 1991).

A recent study in the United States determined the concentrations of trace metals in seminal plasma in industrial workers in a petroleum refinery, smelter, and chemical plant as compared with those of hospital

Table 6-8. Cobalt Levels in Human Tissues and Fluids

Tissue or fluid	Level	Units[a]	Type	Reference
Urine, U.S., NHANES, representative population (n=1007)	0.36, 0.11–0.89	µg/L	Geomean, 10th–90th percentile	CDC 2001
Urine, U.S., NHANES 1999–2000, Total, age 6 and older (n=2,465)	0.372, 0.130–1.32	µg/L	Geomean, 10th–95th percentile	CDC 2003
6–11 years (n=340)	0.498, 0.130–1.32			
12–19 years (n=719)	0.517, 0.200–1.52			
20 years and older (n=1,406)	0.339, 0.120–1.28			
Males (n=1,227)	0.369, 0.150–1.01			
Females (n=1,238)	0.375, 0.120–1.49			
Mexican Americans (n=884)	0.415, 0.130–1.47			
Non-Hispanic blacks (n=568)	0.433, 0.160–1.45			
Non-Hispanic whites (n=822)	0.365, 0.120–1.29			
Urine, The Netherlands	<0.2–1.2	µg/L	Range	Bouman et al. 1986
Urine, Sweden	0.5, 0.1–2.2	µg/L	Mean, range	Alexandersson 1988
Urine, Denmark (3 reference groups)				Poulsen et al. 1994
Unexposed control females (n=46)	1.5, LOD–20.5	nmol[b]	Mean, range	
Unexposed males (n=12)	0.9, LOD–2.31			
Unexposed females (n=11)	5.9, LOD–25.02			
Urine, hip arthroplasty patients, observed 7–15 years (n=17)	0.9–1.05	µg/L	Range	IARC 1991
Urine, hip arthroplasty patients, observed 5–15.5 years (n=10)	3.8	µg/L	Mean	IARC 1991
Urine, 48 metal sharpening workers in 12 Italian factories	0–40.3, 86	µg/L	Range of means, maximum	Imbrogno et al. 1994
Urine, 12 female cobalt powder sintering workers, Italy				Ferdenzi et al. 1994
Monday, before shift	25, 1–51	µg/L	Mean, range	
Friday, before shift	29, 3–159			
Friday, end-of shift	85, 6–505			
After 3-week holiday	11, 4–34			
Urine, Italian workers wet grinding of hard metal tools (end of shift)				Sesana et al. 1994
Factory A no local exhausts (n=3)	138.3 (108), 123.7 (74)	µg/L	Mean (SD) Monday, Friday	
Factory B local exhausts (n=5)	15.3 (7.7), 24.4 (14.1)			
Factory C local exhausts (n=3)	48.2 (7.3), 74.7 (13)			

Table 6-8. Cobalt Levels in Human Tissues and Fluids

Tissue or fluid	Level	Units[a]	Type	Reference
Urine, Northern Italy, 1991, occupational exposure survey, 314 exposed people				Mosconi et al. 1994
Diamond abrasive production				
Mould-filling	320, 587, 39–2,100	µg/L	Median, mean, range	
Sintering	168, 193, 02–390			
Grinding	61, 151, 34–520			
Mechanical-working	50, 67, 143–165			
Grinding	15, 32, 0.8–730			
Tool production	12, 19, 0.8–100			
Hard metal alloy filling	5, 5, 0.8–18			
Other	1, 2.9, 0.8–72			
Blood, Denmark, porcelain factory				Raffn et al. 1988
Plate painters, off work for 6 weeks (n=46)	8.05, 1.70–22.1	nmol/L	Mean, range	
Plate painters, working 4 weeks (n=46)	36.7, 3.40–407			
Top glaze painters (unexposed) (n=51)	4.04, <1.70–10.2			
Urine, Denmark, porcelain factory				Raffn et al. 1988
Plate painters, off work for 6 weeks (n=46)	81.8, <1.70–445	nmol/L	Mean, range	
Plate painters, working 4 weeks (n=46)	1,308, 37.4–14,397			
Top glaze painters (unexposed) (n=51)	16.0, <1.70–234			
Plasma, Sweden	0.1–1.2	µg/L	Range	Alexandersson 1988
Whole Blood, Denmark (3 Reference groups)				Poulsen et al. 1994
Unexposed control females (n=46)	4.1, <1.7–10.2	nmol/L	Mean, range	
Unexposed males (n=12)	3.1, <1.7–6.8			
Unexposed females (n=11)	7.6, <1.7–30.5			
Lung, Sweden				Gerhardsson et al. 1988
Rural	0.007	mg/kg	Mean	
Urban	0.011			
Liver Tissue, United Kingdom, newborns and infants that died from SIDS (n=157)	17.4±11.3 (15.9)	ng/g wet mass	mean±SD (median)	Patriarca et al. 1999
Liver, New Zealand (n=96)	0.120	mg/kg	Mean	IARC 1991

Table 6-8. Cobalt Levels in Human Tissues and Fluids

Tissue or fluid	Level	Units[a]	Type	Reference
Tissue, Japan				Yamagata et al. 1962
Pectoral muscle	0.016	mg/kg	Mean	
Rib bone	0.036			
Stomach	0.021			
Liver	0.017			
Brain	0.0055			
Urinary bladder	0.0055			
Kidney	0.012			
Aorta	0.021			
Nails				Takagi et al. 1988
Canada (n=40)	0.09	mg/kg	Mean	
India (n=100)	0.06			
Japan (n=252)	0.17			
Poland (n=49)	0.04			
U.S. (n=71)	0.06			
Adipose tissue	0.035–0.078	mg/kg	Range	EPA 1986
Hair				Takagi et al. 1986
Canada (n=92)	0.043	mg/kg	Mean	
India (n=255)	0.051			
Japan (n=457)	0.18			
Poland (n=46)	0.022			
United States (n=55)	0.047			
Hair, Italy				Vienna et al. 1995
Male biology students (n=20)	0.007, 0.001–0.07	mg/kg	Geomean, range	
Female biology students (n=20)	0.017, 0.001–0.28			
Hair, Pakistan				Ashraf et al. 1995
Rural (n=28)	2.05, 0.10–4.80	mg/kg	Mean, range	
Urban (n=39)	3.86, 1.10–5.90			

[a]fresh weight, unless otherwise specified
[b]creatinine basis

geomean = geometric mean; LOD = limit of detection; NHANES = Nation Health and Nutrition Examination Survey; SD = standard deviation; SIDS = sudden infant death syndrome

workers (control group). There were four groups each with 50 adult men. The mean cobalt concentrations (µg/dL), including standard errors, were determined to be 31±2 (hospital workers), 25±0.8 (metal ore smelter workers), 19±0.6 (petroleum refinery workers), and 22±1 (chemical workers) (Dawson et al. 2000).

Surgical implants for knee and hip replacements often use cobalt-containing alloys, which may lead to elevated cobalt levels in body fluids. Indeed, cobalt levels in serum and urine have been used as an index of prosthesis wear. In some cases, significant increases in cobalt levels have been observed, while in other cases, elevations were much lower or only sporadic (IARC 1991). These differences have been ascribed to greater release rates from metal to metal than metal to polyethylene articular surfaces as well to differences in the cobalt-containing alloys.

There are several reports of cobalt exposure among occupational groups. The concentrations of cobalt in the air of hard metal manufacturing, welding, and grinding factories may range from 1 to 300 µg/m^3, compared to normal atmospheric levels of 0.4–2.0 ng/m^3 (Burr and Sinks 1989; Haddad and Zikovsky 1985; Koponen et al. 1982; Lichtenstein et al. 1975). The maximum OSHA permissible level is 100 µg/m^3. The concentration of cobalt in the dust of an electric welding factory was 4.2 µg/g compared to its normal dust level of 0.1–1.0 µg/g (Baumgardt et al. 1986). The higher rate of exposure to cobalt for occupational groups is also reflected in the higher cobalt content in tissues and body fluids of living and deceased workers in this group. The levels of cobalt in the urine of workers in the hard metal industry varied with the levels of cobalt concentration in the working atmosphere. At a concentration of 0.09 mg/m^3, the urinary excretion of cobalt exceeded normal values by orders of magnitude. When the cobalt concentration in the working atmosphere was 0.01 mg/m^3 or lower, urinary cobalt excretion was 4–10 times higher than normal level (Alexandersson 1988; Scansetti et al. 1985). At high exposure levels, the cobalt concentration in blood was 20 times higher than normal; in the low exposure group, it was only slightly higher than in the control group (Alexandersson 1988).

An extensive survey of workers potentially exposed to cobalt in the Bergamo Province in northern Italy in 1991 identified 403 exposed workers in different production areas (Mosconi et al. 1994a). Significant cobalt exposure occurred especially for operators working in diamond abrasive production, and in particular, in mold filling and sintering units where environmental limits are regularly exceeded. Exposure in tool production, tool sharpening, and hard metal alloy filling is much more restrained.

Occupational cobalt air levels and urinary excretion levels recorded in the survey appear in Tables 6-2 and 6-8.

Several studies of cobalt concentrations in air in the hard metal industry have been reported. In the hard metal industry in Japan, Kumagai et al. (1996) found that mean 8-hour time weighted averages (TWAs) of airborne cobalt were >50 μg/m^3 for workers involved in powder preparation (rotation), powder preparation (full-time), rubber press, and shaping operations; mean atmospheric concentrations were 459, 147, 339, and 97 μg/m^3, respectively. Workers involved in the manufacture and maintenance of hard metal and stellite blades in Finland were exposed to breathing zone cobalt concentrations ranging from 2 to 240 μg/m^3, with a geometric mean of 17 μg/m^3 (Linnainmaa et al. 1996). The average proportion of water soluble cobalt in airborne cobalt was 68% (range 14–100%). Wet grinding was not sufficient to adequately control cobalt levels and coolant cobalt levels were high. In a group of 12 factories in Italy in which 48 workers were tested who had been exposed to cobalt in operations such as sharpening with diamond grinding stones, the mean concentration of cobalt in air was 21.2 and 137.7 μg/m^3 (Permissible exposure limit [PEL]-TWA 100 μg/m^3) in work places with and without dust ventilation, respectively (Imbrogno et al. 1994).

Urine concentrations have been used to monitor workers' exposure to airborne cobalt. Ferdenzi et al. (1994) obtained a correlation between Friday TWA air cobalt levels and Friday end-of-shift urine levels among women in the powder sintering industry. Median urinary cobalt concentrations were 25 (range: 1–51) and 29 (3–159) μg/L, on Monday and Friday before the shift, respectively, and 85 (6–505) μg/L on Friday after the shift. Imbrogno and Alborghetti (1994) evaluated the levels of occupational exposure to cobalt during dry and/or wet hard metal sharpening. The mean urine cobalt level in the workers in 12 factories was found to range from 0 to 40.3 μg/L and the maximum was 86 μg/L. The average urinary cobalt level among workers using wet/mixed sharpening methods was 4 times higher than those using dry sharpening methods; 21.38 μg/L as compared to 5 μg/L, respectively. Gallorini et al. (1994) found that the ratio of inorganic to organic cobalt in the urine of hard metal workers was 2.3 compared to 1.01 in controls; the ratio was constant over the range of urinary cobalt levels analyzed (180–1,254 μg/L). Exposure to cobalt during the wet grinding of hard metal tools (Widia tools) used in the wood industry produced exposure to cobalt above the PEL-TWA of 100 μg/m^3 (Sesana et al. 1994). However, exhausts near the grinding wheels were shown to substantially reduce exposure levels (see Table 6-8). In the processing department of a small company producing carbide tip saw blades for the woodworking industry, area air sampling showed that exposure levels were low in all departments except tip grinding

where wet and dry tip grinding areas contained 55 and 21 μg/m^3 of cobalt, respectively, for the total collection method (Stebbins et al. 1992). For the method collecting respirable particles, cobalt levels ranged from 2 to 28 μg/m^3. Wet grinding is a traditional method for controlling dust during grinding. However, some coolants may contain significant concentrations of cobalt (in this case, 61–538 mg/mL) that can contribute to exposure during grinding (Stebbins et al. 1992). Among cobalt blue dye plate painters in a porcelain factory in Denmark, the blood and urine cobalt levels were, respectively, 2–4 and 5–15 times higher than in control groups (Raffn et al. 1988). Similarly, lungs taken from deceased, occupationally exposed workers also had higher levels of cobalt than lungs from control groups. Lungs of deceased hard metal industry workers in Sweden contained 2.5–4 times higher levels of cobalt than control lungs (Gerhardsson et al. 1988). Similarly, the lungs of coal miners from England contained 6 times higher cobalt levels than control lungs (Hewitt 1988).

Exposure to radioactive cobalt can occur through various means. Workers at nuclear facilities, irradiation facilities, or nuclear waste storage sites may be accidentally exposed to radioisotopes of cobalt. Also, workers using cobalt isotopes in tracer studies, in calibration or other devices, or ^{57}Co in Mössbauer spectroscopy, may be exposed to radioactive cobalt. Exposure would generally be to radiation produced by these isotopes (e.g., gamma radiation from ^{60}Co). Patients receiving ^{60}Co radiotherapy will obviously be exposed to its radiation. According to the USNRC (1999), the collective intake of ^{60}Co by ingestion and inhalation at power reactors in 1998 was 352 μCi (13 MBq) for 25 intake records and 27,000 μCi (1,000 MBq) for 281 intake records (USNRC 1999). The collective intake at fuel fabrication facilities was 0.486 μCi (0.180 MBq) for 502 intake records. The USNRC occupational inhalation annual limits of intake (ALIs) for ^{60}Co are 200 μCi (7.4 MBq) for all compounds, except oxides, hydroxides, halides, and nitrates, and 30 μCi (1.1 MBq) for compounds of oxides, hydroxides, halides, and nitrates (USNRC 2001k).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.8 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a

larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

As with adults, most children are exposed to cobalt largely through their diet. Dabeka and McKenzie (1995) estimated that the dietary cobalt intake by Canadian children ages 1–19 ranged from 7 to 14 mg/day (see Table 6-7). Milk constitutes a larger part of children's diets than that of adults, and infants may consume infant formula. Cobalt concentrations ranging from 0.3 to 0.8 ng/g in cow's milk were reported by Iyengar (1982). The levels of cobalt in human milk from Nigeria, Zaire, Guatemala, Hungary, Philippines, and Sweden ranged from 150 (Hungary) to 1,400 ng/g (Philippines), median 320 ng/g (Nriagru 1992). Garg et al. (1993) reported much lower cobalt levels in three samples of human milk in India, 2.42 ng/g, and reported a cobalt concentration of 5.07 ng/g in cow's milk in India. Dakeba (1989) determined cobalt levels in various infant formulas (see Table 6-5). Milk-based infant formulas and evaporated milk contained <1 ng/g of cobalt on a "ready-to-use" basis. Milk-based formulas with added iron contained about twice the cobalt as those with no added iron and soy-based formulas contained about 5 times more cobalt. The influence of added iron suggests that the cobalt in formula is not primarily from vitamin B_{12}. Using literature values of cobalt in food, Dakeba also estimated that infants 0–12 months old ingest an average of 0.52 µg Co/kg-day (3.93 µg/day) from food and water and that for an infant, 0–12 months old, the total dietary cobalt intake would range from 0.42 µg/kg-day (3.39 µg/day) for a breast or milk-based formula fed infant to 1.0 µg/kg-day (7.33 µg/day) for an infant fed soy-based formula powder. The recommended dietary allowance for Canadian infants is 0.012 µg/day cobalt as vitamin B_{12}. In a 1967 study of the total dietary intake of some trace elements, excluding drinking water, of institutionalized children aged 9–12 in 28 U.S. cities, cobalt intake ranged from 0.297 to 1.767 mg/day with a mean value of 1.024 mg/day (Murthy et al. 1971).

Exposure to stable cobalt in communities near mining and smelting facilities or metal shops where cobalt is used in grinding tools is a public health concern, especially for infants and children. Since cobalt remains in the surface soil indefinitely and long past land uses may be forgotten, people may not realize that they are living in areas where high levels of cobalt may occur in soil. Contaminated soils pose a particular hazard to children because of both hand-to-mouth behavior and intentional ingestion of soil that

contain metals and other contaminants (Hamel et al. 1998). In these communities, cobalt may have been tracked in from outdoors and contaminate carpeting. Cobalt-containing dust may be brought home in the clothing of parents working in industries where they are exposed to cobalt. Children may be exposed to this cobalt while crawling around or playing on contaminated carpeting. Exposure may also result from dermal contact with soil, or by inhaling dust and then swallowing it after mucociliary transport up out of the lungs. Because there is little absorption of cobalt through the skin following dermal exposure, and because much of the cobalt in soil is embedded in or adsorbed to soil particles or insoluble, it may not be in a form accessible for uptake by the body, and therefore may not pose a serious health hazard.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to workers in the hard metal industry (tool production, grinding, etc.) and industries such as coal mining, metal mining, smelting and refining, cobalt dye painters, and the cobalt chemical production, the general population living near these industrial sites may be exposed to high levels of cobalt in air and in soil. Exposure to cobalt during the wet grinding of hard metal tools is especially high when local exhausts are not in use (Sesana et al. 1994). People living near hazardous waste sites may be exposed to cobalt by inhaling dust from contaminated sites or through dermal contact with cobalt-contaminated soil. In the case of children playing in and around unrestricted landfill sites, exposure via dermal and ingestion routes is possible. The general populations in agricultural areas that use sewage sludge or cobalt-containing fertilizers or other soil amendments may be exposed to higher levels of cobalt via inhalation of dust or dermal contact with the soil. However, no experimental evidence of higher than normal exposures for these population groups was found in the literature. People who live in areas that naturally contain higher levels of cobalt minerals may also be exposed to higher levels of cobalt from both the inhalation and dermal contact routes.

The higher exposure of cobalt in patients with cobalt-chromium knee implants has been demonstrated by the slightly higher levels of cobalt in whole blood, serum, and urine, and by very high levels of cobalt in bone of these patients (IARC 1991; Ostapczuk et al. 1985; Sunderman et al. 1989). Prosthetic devices that contain polyethylene components to avoid metal-to-metal contact do not appear to cause elevated levels of cobalt in tissues and body fluids (IARC 1991; Ostapczuk et al. 1985; Sunderman et al. 1989). People who use cobalt supplements as a treatment for anemia and those who take large amounts of vitamin B-12 as a dietary supplement would have higher intakes of cobalt than the general population.

Workers at nuclear facilities and nuclear waste storage sites may be exposed to potentially high levels of radiation exposure from ^{60}Co and ^{58}Co. Workers at irradiation facilities using ^{60}Co may be exposed to potentially high levels of gamma radiation exposure from this isotope. Patients receiving ^{60}Co radiotherapy will intentionally be exposed to high levels of gamma radiation.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cobalt is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cobalt.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical, Chemical and Radiological Properties. As can be seen from Table 4-2 and Section 4.2, the relevant physical and chemical properties of cobalt and its compounds are sufficiently known to enable prediction of environmental fate and transport of cobalt compounds (Budavari 1996; Lide 1994; Stokinger 1981; Weast 1985). Information on the radiological properties of important cobalt isotopes are also well known (see Table 4-3) (ICRP 1983; Lide 1994). No data needs were identified.

Production, Import/Export, Use, Release, and Disposal. Information on the production, import/export, use, release, and disposal of a chemical is important because it is an indicator of possible environmental contamination and human exposure. Large releases and consumer use would indicate

higher general population exposure from environmental sources (e.g., air, drinking water, and food) and use of consumer products. Occupational exposure may also increase with increased production and use. U.S. production of cobalt is derived primarily from scrap (secondary production). Information is available on cobalt consumption derived from secondary production, import/export, and release of cobalt from the National Defense Stockpile (USGS 1998, 1999, 2002). However, production volumes of individual cobalt compounds are not available and information on the production of individual compounds would be useful in assessing exposure to specific cobalt compounds. Radioactive cobalt isotopes, primarily ^{60}Co and ^{57}Co, are not commercially produced in the United States, but rather are imported from Canada and the United Kingdom; consumption amounts are not available. Information on the uses of cobalt is available (Cobalt Development Institute 2004; Donaldson 1986; Hodge 1993; IARC 1991; Richardson 1993; USGS 1998, 2002). Cobalt-containing products are mostly used in the workplace, although some consumer products contain cobalt.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and offsite transfer information to the EPA. The TRI for 2001 is currently available (TRI01 2004). Starting in 1998, metal mining, coal mining, electric utilities, and RCRA/solvent recovery industries were required to report to the TRI. These sectors include those contributing greatest environmental releases of cobalt and cobalt compounds, giving us a much more complete picture of cobalt releases to the environment. The TRI also contains information on the onsite and offsite disposal and management of wastes (e.g., recycling, treatment, transfer to publicly owned treatment works [POTWs]). EPA guidelines address the disposal of hazardous cobalt wastes. The TRI database will be updated yearly and provides a list of industrial production facilities and emissions. The TRI data should be used with caution since the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

Environmental Fate. There are data that permit assessment of the environmental fate and transport of cobalt in water and soil (Section 6.3). Frequently, sediment and soil are the ultimate sinks for cobalt; however, this process is dynamic, and cobalt can be released into the water depending upon conditions. There is a paucity of data in the literature regarding the chemical forms of cobalt released to the atmosphere and their transformations in air and this information would facilitate the determination of the transport and persistence of cobalt in the atmosphere. Additional data elucidating the mode of speciation

of cobalt in water and soil would also be desirable. For example, under what circumstances Co(III) compounds might be formed in the environment and how long.

Bioavailability from Environmental Media. Absorption by the inhalation and oral routes in humans has been studied, but the results vary considerably (see Section 3.5.1) (Foster et al. 1989; Harp and Scoular 1952; Sedlet et al. 1958; Sorbie et al. 1971; Valberg et al. 1969). These variations were attributed to differences in the types and doses of cobalt compounds given, to the nutritional status of the subjects following oral exposure, and to particle size differences following inhalation exposure. Additional data assessing the absorption of cobalt following soil ingestion by children may be helpful. Data in animals are plentiful for both inhalation and oral routes and correlate well with the human data (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kreyling et al. 1986; Patrick et al. 1989; Talbot and Morgan 1989). Data in animals following dermal exposure suggested that cobalt is not absorbed well through intact skin, but is rapidly taken up through damaged skin. Data regarding the bioavailability of cobalt following dermal exposure are important because dermal exposure to cobalt in the workplace is probable.

Food Chain Bioaccumulation. Bioaccumulation in the food chain is important in assessing the human exposure to cobalt from the consumption of food. Data are available that indicate that cobalt is not taken up appreciably by plants and does not biomagnify up the food chain (Baudin and Fritsch 1987; Baudin et al. 1990; Boikat et al. 1985; Francis et al. 1985; Kloke et al. 1984; Lux et al. 1995; Mascanzoni 1989; Mejstrik and Svacha 1988; Mermut et al. 1996; Palko and Yli-Hala 1988; Smith and Carson 1981; Tolle et al. 1983; Watabe et al. 1984).

Exposure Levels in Environmental Media. Monitoring data on levels of cobalt in air, water, and food permits the estimation of exposure from these sources. Data are available on the cobalt levels in ambient air (Golomb et al. 1997; Hasanen et al. 1990; Schroeder et al. 1987; Smith and Carson 1981; Sweet et al. 1993; Wiersema et al. 1984). However, the data are not sufficiently recent or broad-based for estimating the current levels of exposure to cobalt in the general U.S. population and particularly those living near cobalt-containing hazardous waste sites. In addition, in only isolated studies was there an assessment of the concentration of cobalt associated with coarse and fine particles (Sweet et al. 1993) or an average annual level obtained at a site (Golomb et al. 1997). Similarly, levels of cobalt in ambient water, while generally low, are also not sufficiently broad-based or recent to be satisfactory (Bargagli 2000; Bruce and McMahon 1996; Cassidy et al. 1982; Eckel and Jacob 1988; Flaten 1991; Nojiri et al.

1985; Rossmann and Barres 1988; Smith and Carson 1981). This deficiency may be satisfied when the EPA's improved and updated STORET database becomes available. Cobalt levels in Canadian drinking water are ≤2.0 mg/L (Meranger et al. 1981). However, U.S. drinking water levels have not been reported and would be useful. The levels of cobalt in sediment are available (Bargagli 2000; Coakley et al. 1993; Gibbs 1994; Glooschenko et al. 1981; Knutson et al. 1987; Naidu et al. 1997; Shine et al. 1995; Smith and Carson 1981; Trocine and Trefry 1996; Villanueva and Botello 1998), but more data on levels in soil and in the vicinity of industrial and hazardous waste sites would be useful. Few data on the levels of cobalt in U.S. foods are available, although studies from Canada and Sweden are available that indicate that cobalt levels in food items are generally low (Barceloux 1999; Dabeka and McKenzie 1995; Jorhem and Sundström 1993). In particular, total diet studies of cobalt in U.S. food is lacking. A Canadian total diet study estimated average daily cobalt intake to range from 7 to 15 µg/day for different age-sex groups (Dabeka and McKenzie 1995).

Few data are available on levels of ^{60}Co and other cobalt isotopes in environmental media.

Exposure Levels in Humans. The levels of cobalt in hair, nail, and adipose tissues of the general U.S. population are known (EPA 1986; Takagi et al. 1986, 1988). No reliable data on the levels of this substance in blood (or plasma) and urine of the general U.S. population were found, although such data are available for certain European populations including occupationally-exposed groups (Table 6-8). These data may be important for establishing the background exposure level of cobalt. No data on the levels of cobalt in any body tissue or fluid for populations living near hazardous waste sites are available. Such data would be important in assessing the exposure levels of this group of people.

Exposures of Children. Dabeka (1989) reported the levels of cobalt in various formulas and milk products consumed by children in Canada, and Dabeka and McKenzie (1995) determined the mean dietary intake of Canadian children as young as 1–4 years of age. Nriagru (1992) reported levels of cobalt in human milk from several countries. No analogous U.S. studies were found. Cobalt levels is the tissue and body fluids of children have not been found.

Child health data needs relating to susceptibility are discussed in 3.13.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for cobalt were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to cobalt and its compounds.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2002, 2004) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-9.

Remedial investigations and feasibility studies conducted at the NPL sites known to be contaminated with cobalt, such as the Blackbird Mine in Idaho, will add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries, and will increase the current knowledge regarding the transport and transformation of cobalt in the environment.

The Cobalt Development Institute (CDI) is implementing a research program to assess environmental risks posed by the manufacture and use of cobalt and cobalt compounds. Studies that are underway include the assessment of seasonal and background variability of cobalt compounds in aquatic environment and a literature survey for existing data on the effects of cobalt and cobalt compounds in soils and sediment. Environmental studies proposed for 2002 included the assessment of seasonal and background variability of cobalt compounds in soils and sediments and a literature survey for existing data on the effects of cobalt and cobalt compounds on marine environments.

Table 6-9. Ongoing Studies on Cobalt

Investigator	Affiliation	Research description	Sponsor
Hamilton, JW	Dartmouth College, Hanover, New Hampshire	The overall goal of the Dartmouth Superfund Basic Research Program (SBRP) Project, Toxic Metals in the Northeast: From Biological to Environmental Implications is to determine the impact of toxic metals found at waste sites, including Superfund sites on human health and the environment. The program-wide focus of this research program is on toxic metals, particularly on arsenic, and also chromium, nickel, cadmium, mercury, cobalt, and lead.	NIH
Jones, BT	Wake Forest University, Winston-Salem, North Carolina	The investigators developing a novel, low-cost, portable instrument for the simultaneous determination of trace radioactive elements in nuclear forensic samples. At issue is the routine, inexpensive sampling for radioactivity that could be released on transport or storage of potential "dirty bomb" material. The instrument to be developed is expected to provide analytical figures comparable to inductively coupled plasma mass spectrometry, but the instrument is much lower cost and more portable. The specific objectives of the project include determination of the analytical figures of merit for elements including cobalt, cesium, and strontium, and analysis of real samples such as soil, urban dust, water and agricultural materials.	NSF
Kpomblekou-Ademawou, K Ankumah, RO	Tuskegee University, Tuskegee, Alabama	This project will investigate if excessive accumulation of some trace elements, added to poultry diet and excreted through feces, affects nitrogen transformation in broiler (chicken) litter amended soils and if this compromises safe food and feed production. The goals of this work are (1) to study the effects of concentrations of key trace elements (e.g., As, Cd, Co, Cr, Cu, Mn, Ni, Pb, Se, and Zn) found in broiler litter on nitrogen transformation in litter amended soils, (2) to assess the effects of temperature on the nitrogen transformation in the presence of trace elements and (3) to assess the fate of trace elements in sudax (Sorghum bicolor) grown in trace element-enriched broiler litter amended soils.	USDA
Longnecker, M	NIEHS, NIH	Evaluate the use of toenail levels as a measure of exposure by analyzing toenail and whole-diet homogenates by neutron activation analysis. Toenails reflect exposure over a longer period of time than do blood or urine measures, and are less likely to be influenced by contamination than hair.	NIEHS

Table 6-9. Ongoing Studies on Cobalt

Investigator	Affiliation	Research description	Sponsor
Saito, MA	Woods Hole Oceanographic Institution, Woods Hole, MA	This research will examine the influence of cobalt and cadmium speciation on *Synechococcus* and *Crocosphaera* at two sites in the Pacific Ocean. In addition, the distribution of cobalt across transects in the Eastern Equatorial Pacific will be determined to improve understanding of the global biogeochemical cycle of cobalt.	NSF
Tavlarides, LL	Syracuse University, Syracuse, New York	This work will be towards the development of sol-gel synthesis methods for organo-ceramic adsorbants for the extraction of toxic and valuable metal ions, such as cobalt, chromium, and arsenic ions from aqueous streams.	NSF

NIEHS = National Institute of Environmental Health Sciences; NIH = National Institute of Health; NSF = National Science Foundation USDA = U.S. Department of Agriculture; USDOE = U.S. Department of Energy

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring cobalt, its metabolites, and other biomarkers of exposure and effect to cobalt. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Entry of cobalt and its radioisotopes into the human body can be gained through ingestion, inhalation, or penetration through skin. The quantities of cobalt within the body can be assessed through the use of bioassays that are comprised of either *in vivo* and/or *in vitro* measurements. *In vivo* measurements can be obtained through techniques that directly quantitate internally deposited cobalt using, for example, whole body counters. These *in vivo* measurement techniques are commonly used to measure body burdens of cobalt radioisotopes (i.e., ^{60}Co), but cannot be used to assess the stable isotope of cobalt (^{59}Co). Instead, *in vitro* measurements provide an estimate of internally deposited cobalt (both the stable and radioactive isotopes), utilizing techniques that measure cobalt in body fluids, feces, or other human samples. Examples of these analytical techniques are given in NRCP Report No. 87 (1987) and are also listed in Tables 7-1 and 7-2.

7.1.1 Internal Cobalt Measurements

In vivo measurement techniques are the most direct and widely used approach for assessing the burden of cobalt radioisotopes within the body. The *in vivo* measurement of these radioisotopes within the body is

Table 7-1. Analytical Methods for Determining Stable Cobalt in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Direct injection	GF-AAS with Zeeman background correction	0.3 µg/L	101% at 40µg/L	Bouman et al. 1986
	Addition of magnesium nitrate and nitric acid matrix modifiers and equal volume dilution of sample with water	GF-AAS with Zeeman background correction	2.4 µg/L	107.6% at 50 µg/L	Kimberly et al. 1987
	Sample chelated with dithiocarbamic acid derivative, solvent extracted	GF-AAS with Zeeman background correction	0.1 µg/L	No data	Alexandersson 1988; Ichikawa et al. 1985
	Sample wet digested with acid and chelated with 2,3-butanedion dioxide and complex preconcentrated at hanging mercury drop electrode	DPCSV	0.2 µg/L	No data	Heinrick and Angerer 1984
	Direct injection	GF-AAS with Zeeman background correction	0.1 µg/L	No data	Sunderman et al. 1989
Whole blood	Sample diluted with a homogenizer	GF-AAS with D_2 background correction	2 µg/L	No data	Heinrick and Angerer 1984
	Sample wet digested with acid and chelated with 2,3-butanedion dioxine and complex preconcentrated at hanging mercury drop electrode	DPCSV	0.8 µg/L	No data	Heinrich and Angerer 1984
	Sample acid digested, complexed with thiocyanate and N-phenylcinnamo-hydroxamic acid and extracted into ethyl acetate	Colorimetric	0.15 mg/L	No data	Afeworki and Chandravanshi 1987
Serum	Direct injection	GF-AA with Zeeman background correction	0.02 µg/L	No data	Sunderman et al. 1989

Table 7-1. Analytical Methods for Determining Stable Cobalt in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood or tissue	Acid digestion	ICP-AES (NIOSH method 8005)	10 µg/g (blood); 0.2 µg/g (tissue)	81% at 110 µg/L (blood)	NIOSH 1984

D_2 = deuterium; DPCSV = differential pulse cathodic stripping voltammetry; GF-AAS = graphite furnace atomic absorption spectrometry; ICP-AES = inductively coupled plasma-atomic emission spectrometry; NIOSH = National Institute for Occupational Safety and Health

Table 7-2. Analytical Methods for Determining Radioactive Cobalt in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Urine	Direct count of sample	γ-spectrometry with NaI detector	No data (<MDL)	No data	Miltenberger et al. 1981
Soft tissue	Sample wet-ashed	γ-spectrometry (NaI)	No data	No data	Baratta et al. 1969
	Sample directly counted in detector	γ-spectrometry	5 pCi/g	No data	Rabon and Johnson 1973
	Sample digested in acid, oxidized with $HClO_4$, concentrated by precipitation with AMP, purified by resin column, precipitated with hexachloroplatinic acid	-counter	0.1 pCi/g	40–85%	Nevissi 1992
Feces	Direct count of sample	γ-spectrometry	No data	No data	Smith et al. 1972
Blood	Red cells separated from plasma and washed	γ-spectrometry with NaI detector	No data	No data	Smith et al. 1972

[a]1 Bq=2.7×10^{-11} Ci=27 pCi

AMP = ammonium molybdophosphate; MDL = minimum detectable level; NaI = sodium iodide

performed with various radiation detectors and associated electronic devices that are collectively known as whole body counters. These radiation detectors commonly utilize sodium iodide (NaI), hyperpure germanium, and organic liquid scintillation detectors to measure the 1,172 and 1,332 keV gamma rays from the decay of ^{60}Co. Because of the relatively low attenuation of the high energy gamma rays emitted from ^{60}Co by most tissues, cobalt radioisotopes can easily be detected and quantified using whole body counting techniques (Lessard et al. 1984; NCRP 1987; Raghavendran et al. 1978; Smith et al. 1972; Sun et al. 1997). Many configurations of the whole body counter and scanning methods have been utilized, ranging from unshielded single-crystal field detectors to shielded, multi-detector scanning detectors (IAEA 1962, 1970, 1972, 1976, 1985; NCRP 1987). Where appropriate, shielding of the room that houses the whole body counter and/or the detector is often used to increase the detection sensitivity of the equipment by minimizing background radiation. Additionally, care must be exercised to insure that external contamination with radioactive cobalt or other gamma-emitting radioisotopes on the clothing or skin of the individual to be scanned has been removed. Also, *in vitro* measurements of cobalt (see Section 7.1.2) are often used in conjunction with whole body counting when monitoring individuals working with cobalt, especially in conjunction with the assessment of individuals who have experienced accidental exposures to cobalt (Bhat et al. 1973).

Calibration of whole body counters is achieved through the use of tissue-equivalent phantoms. These phantoms are constructed to mimic the shape and density of the anatomical structure using tissue equivalent materials such as water-filled canisters or masonite (Barnaby and Smith 1971; Bhat et al. 1973; Sun et al. 1997). For example, the bottle mannequin absorber (BOMAB) consists of a series of water-filled polyethylene canisters constructed into seated or reclined human forms (Sun et al. 1997). ^{60}Co standards are measured either as point sources along the phantom or dissolved within the water-filled canisters. Comparisons of the actual counts obtained from the phantom to the known activity of the cobalt standards are used to determine the efficiency of the counting technique and, thus, provide the basis for calibrating the technique. Even so, differences in whole body measurement techniques, calibration methods, and background radiation count calculations between different laboratories can complicate the direct comparisons of body burden measurements and clearance rates for cobalt radioisotopes and should be taken into consideration when comparing data obtained from independent laboratories.

7.1.2 External Measurements

In vitro analyses of cobalt are routinely performed in situations where *in vivo* analyses can not be obtained or in support of an *in vivo* monitoring program. Urine and feces are the preferred samples for *in vitro* analyses of cobalt, although other sample types, such as tissue, bone, or blood, can also be used on a more limited basis. Urine provides for an analysis of soluble (inorganic) cobalt, fecal analysis can be used to assess the cobalt (organic) that is eliminated into the gut or the fraction of ingested cobalt not absorbed by the gut, and tissue/blood/bone are used to assess whole or regional body burdens of cobalt (NCRP 1987; Smith et al. 1972).

The analytical methods for determining the stable cobalt isotope, ^{59}Co, in biological matrices are given in Table 7-1. For accurate determination of cobalt, contamination of samples during sample collection, storage, and treatment must be avoided, particularly for biological samples containing low levels of cobalt. Cobalt contamination in blood samples has been reported from disposable syringes and technical-grade anticoagulants. Menghini needles, often used for liver biopsy, and mortar, pestles, and grinding devices used for homogeneous mixing may contaminate samples. Other sources of contamination may be collection and storage containers and chemical reagents used for preparing samples. In fact, sample contamination was responsible for erroneous reports in the earlier literature of grossly high levels of cobalt in biological specimens of unexposed persons. Therefore, blanks should always be run with the samples.

The commonly used classical methods for determining stable cobalt in biological samples are polarographic and colorimetric methods. Details about these methods are given by Saltzman and Keenan (1957). Since these older methods have interference problems and are unsuitable for determining low levels of cobalt in many biological samples, the samples are pretreated before quantification. Precipitation, chelation, chromatography, and ion-exchange are some of the methods used for this purpose. In recent years, the two single-element instrumental techniques most frequently used methods for determining cobalt are graphite furnace-atomic absorption spectrometry (GF-AAS) (also called electrothermal atomic absorption spectrometry) and differential pulse anodic stripping voltammetry (DPAVS). Multi-element techniques commonly used for cobalt determination are neutron activation analysis and inductively coupled plasma-atomic emission spectrometry (ICP-AES). Several other methods are available for determining stable cobalt in biological samples; these include x-ray fluorescence and Spark source mass spectrometry (Adeloju et al. 1985; Smith and Carson 1981).

For the *in vitro* analysis of cobalt radioisotopes in human samples, the majority of the analytical methods measure the cobalt radioisotopes directly in the samples, without the requirement for an extensive sample preparation procedure, using gamma spectrometry techniques. Of the cobalt radioisotopes that have been detected in the environment (e.g., ^{57}Co, ^{58}Co, and ^{60}Co), ^{60}Co is the most common. Consequently, most of the analytical methods that will be described in this chapter are those developed for the detection and quantitation of ^{60}Co in biological (see Table 7-2) and environmental samples (see Table 7-4).

The radiochemical analysis of ^{60}Co in urine has been used in conjunction with whole body scanning methods to assess acute and long-term body burdens of this isotope. The analysis of ^{60}Co in urine is the same as that described for a standardized method of analysis of cesium radioisotopes in urine (Gautier 1983). A urine sample of approximately 2 L is collected (either over 24 hours or before and after bedtime) and a 1-L aliquot is transferred to a Marinelli beaker for counting in a gamma-ray spectrometer (Gautier 1983). This simple procedure offers high recoveries of cobalt (98%) and the minimum detection sensitivity (100 pCi/L [3.7 Bq/L]) that is required to evaluate individuals for exposures to radioactive cobalt (Gautier 1983). Direct counting methods are also used for the analysis of cobalt radioisotopes in tissues, feces, and blood (Smith et al. 1972, Table 7-2). However, some of these methods may require sample preparation to reduce volume or increase concentration.

Accuracy of *in vivo* and *in vitro* measurements of cobalt is determined through the use of standard, certified solutions or radioactive sources with known concentrations or activities of cobalt. Certified standards for stable cobalt can be obtained through a number of commercial sources. The primary source of certified cobalt radioisotope standards is the National Institute of Standards and Technology (NIST). Gamma ray point sources for ^{60}Co (SRM 4200, 60,000 Bq [1.6 µCi] and SRM 4207, 300,000 Bq [56 µCi]) and standard solutions of ^{60}Co (SRM 4233, 600,000 Bq/g [16 µCi/g]) are available from NIST. Also, the determination of accuracy of a method often requires standard reference materials (SRMs). Unfortunately, very few biological SRMs are available. An SRM for cobalt in animal muscle is available from the International Atomic Energy Agency (IAEA), Vienna; an SRM for bovine liver (SRM-1577) is available from NIST (formerly the National Bureau of Standards) (Adeloju et al. 1985; Smith and Carson 1981).

7.2 ENVIRONMENTAL SAMPLES

There are two common approaches for measuring cobalt in the environment. Cobalt radioisotopes can either be measured directly in the field (*in situ*) using portable survey instruments or samples can be procured from the field and returned to the laboratory for quantitation. However, quantitation of the stable cobalt isotope ^{59}Co in environmental samples is generally conducted in the laboratory.

7.2.1 Field Measurements of Cobalt

In situ measurement techniques are extremely useful for the rapid characterization of radionuclide contamination in the environment, such as soils, sediments, and vegetation, or when monitoring personnel for exposure to radionuclides. The measurement of gamma-ray-emitting radionuclides, like cobalt, in the environment is conducted with portable survey instruments such as Gieger-Mueller detectors, sodium iodide scintillation detectors, and gamma-ray spectrometers. However, the use of gamma-ray spectrometers in field survey equipment is preferred for measuring cobalt in the field because of its selectivity and sensitivity. The relatively high energy and penetrability of the gamma ray that is emitted during the decay of ^{60}Co provides an advantage for assessing the level of cobalt both on and below the surface using portable field survey instruments such as the gamma-ray spectrometer. These gamma-ray spectrometers are equipped with a high purity germanium detector that is able to selectively and sensitively differentiate the 1,173 and 1,332 keV gamma rays emitted from ^{60}Co from the gamma-rays emitted from other radionuclides, for example ^{40}K or ^{137}Cs (USNRC 1997). Minimum detectable activities (MDAs) of 0.005 Bq/g (0.05 pCi/g) for ^{60}Co are routinely achieved using p-type germanium gamma-ray spectrometers with 10-minute counting times (USNRC 1997). However, counting errors can occur where the simultaneous detection of the 1,173 and 1,332 keV gamma rays produces a sum peak at 2,505 keV or a count in the continuum between the individual peaks and the sum peak (APHA 1998; USNRC 1997). These errors can be minimized by changing the geometry of the detector or the distance of the detector from the source of radioactivity. Computational methods have been derived to aid in determining the concentrations and distributions of ^{60}Co in different soil types and depths (USNRC 1997). The concentrations and distributions of ^{60}Co that have been derived from the computational analysis of the survey data are often verified by laboratory-based analyses of soil samples procured from the survey area.

7.2.2 Laboratory Analysis of Environmental Samples

Analytical methods for quantifying stable cobalt and cobalt radioisotopes in environmental samples (e.g. air, water, soil, and biota) are summarized in Tables 7-3 (^{59}Co) and 7-4 (^{60}Co). The methods that are commonly used in the analysis of stable cobalt are based on instrumental analytical techniques, such as atomic absorption spectrometry (AAS), instrumental neutron activation analysis (INAA), and mass spectrometry (MS). The analysis of ^{60}Co can be determined either as total mass or total activity, depending on the analytical technique that is used. Typically, radiochemical methods of analysis employing gamma-ray spectrometry techniques are used to quantitate ^{60}Co in environmental samples.

Analytical methods for determining stable cobalt in environmental samples are given in Table 7-3. Since cobalt exists in the particulate form in the atmosphere, it is sampled by drawing air through a metal-free filter (usually cellulose ester membrane), and the metal is quantified in the collected particles. Sample treatment prior to quantification is important for environmental samples. For example, the use of sodium carbonate for dry ashing plant materials results in poor cobalt recovery. Low-temperature ashing may be inadequate for some samples, and losses may occur during rigorous dry ashing. Wet ashing is the preferred method when sample treatment is necessary. Wet extraction with dilute nitric acid is most suitable for analyzing cobalt in dust samples. In some samples, the determination of soluble and insoluble cobalt is important, and analytical methods used to determine cobalt in filtered and unfiltered samples are available for this purpose.

As in the case of biological samples, contamination of environmental samples during sample collection, storage, and treatment should be avoided. Loss of cobalt from aqueous samples due to adsorption on storage containers should be avoided by using polyethylene or similar containers and acidifying the solution to the proper pH (Smith and Carson 1981). Because of its rapidity, accuracy, and low detection limit, GF-AAS with Zeeman background correction is the most commonly used method for quantifying cobalt in environmental samples. To meet the detection limits of the available analytical methods, preconcentration prior to quantification may be necessary for some samples (e.g., seawater). A few commonly used methods for determining cobalt in environmental samples are given in Table 7-3. Other less frequently used methods are inductively coupled plasma-mass spectrometry (ICP-MS) (Henshaw et al. 1989; McLaren et al. 1985), gas, liquid, and ion chromatography with colorimetric, electron capture, and electrochemical detection (Bond and Wallace 1984; Carvajal and Zienius 1986; Cheam and Li 1988; King and Fritz 1987; Schaller and Neeb 1987), photoacoustic spectroscopy with colorimetry (Kitamori

Table 7-3. Analytical Methods for Determining Stable Cobalt in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (workplace)	Weighed filter irradiated in a reactor	INAA	0.17 µg/m^3	No data	Haddad and Zikovsky 1985
	Sample filter digested by wet acid ashing	Flame-AAS with background correction (NIOSH method 7027)	0.4 µg/m^3	98% with 12–96 µg spiked filter	NIOSH 1984
	Sample filter digested by wet acid ashing	ICP-AES (NIOSH method 7300)	0.5 µg/m^3	95–100% with 2.5–1,000 spiked filter	NIOSH 1984
Water (low ionic strength)	Direct injection	GF-AAS with Zeeman or deuterium back-ground correction	<0.5 µg/L	93–115% at 8.5–30 µg/L	Fishman et al. 1986
Lake water	Sample complexed with 8-hydroxyquinoline absorbed on a column, desorbed and digested with acid	ICP-AES	<0.004 µg/L	No data	Nojiri et al. 1985
Rainwater	Sample preconcentrated onto polystyrene films by spray-drying	PIXE	0.08 µg/L	No data	Hansson et al. 1988
Seawater	Sample complexed with 8-hydroxyquinoline absorbed on a column, desorbed and digested with acid	GF-AAS with Zeeman back-ground correction	0.0002 µg/L	90%	Nakashima et al. 1988
Water and waste water	Direct aspiration of sample	Flame-AAS (EPA method 219.1)	0.05 mg/L	97–98% at 0.2–5.0 mg/L	EPA 1983
	Direct injection	GF-AAS with background correction (EPA method 219.2)	1 µg/L	No data	EPA 1983
Groundwater or leachate	Direct aspiration	Flame-AAS with background correction (EPA method 7200)	0.05 mg/L	97–98% at 0.2–5.0 mg/L	EPA 1986b
Groundwater or leachate	Direct injection	GF-AAS with background correction (EPA method 7201)	1 µg/L	No data	EPA 1986b

Table 7-3. Analytical Methods for Determining Stable Cobalt in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Sample digested with acid	GF-AAS with background correction	1.88 µg/L in dissolved extract	100–107% at 0.2–0.6 mg/kg (leaves, liver)	Barbera and Farre 1988
Milled Wheat	Wet ashing (HNO_3), preconcentration and chelation	ET-AAS	20 ng/L	approximately 100%	González et al. 2000

AAS = atomic absorption spectrometry; EPA = Environmental Protection Agency; ET-AAS = electrothermal atomic absorption spectrometry; GF-AAS= graphite furnace atomic absorption spectrometry; ICP-AES = inductively coupled plasma-atomic emission spectrometry; INAA = instrumental neutron activation analysis; NIOSH = National Institute for Occupational Safety and Health; PIXE = photon induced x-ray emission

Table 7-4. Analytical Methods for Determining Radioactive Cobalt in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Air	Direct count of sample collected on paper filter	γ-spectrometry with Ge/Li detector	0.001 pCi/m^3	No data	USAEC 1974a
Air	Sample filter ashed	Scintillation counter with NaI detector	No data	No data	De Franceschi et al. 1974
Drinking water	Direct count of sample	γ-spectrometry with Ge detector	<2 pCi/L	99%	APHA 1998
Drinking water	Direct count of sample	γ-spectrometry	2 pCi/L	No data	USAEC 1974b
Water	Direct count of sample	γ-spectrometry with Ge/Li detector	2 pCi/L	No data	ASTM 1999
Water	Direct count of sample	γ-spectrometry	10 pCi/L	No data	Cahill et al. 1972
Seawater	Sample concentrated using continuous-flow coprecipitation-flotation separation technique	Scintillation detector	50 fCi/L	92–95%	Hiraide et al. 1984
Sediments	Sample dried and ground	γ-spectrometry	0.04 pCi/g	No data	Cahill et al. 1972
Fish	Samples dried and ashed	γ-spectrometry	0.001 pCi/g (DW)	No data	Cushing et al. 1981
Mollusc	Samples dried and ashed	γ-spectrometry	<0.01 pCi/g	No data	De Franceschi et al. 1976

[a]1 Bq=2.7×10^{-11} Ci=27 pCi

DW = dry weight; Ge/Li = lithium drifted geranium; NaI = sodium iodide

et al. 1986), electrothermal vaporization with ICP-AES (Malinski et al. 1988) and chemiluminescence with spectrofluorimetry (Jones et al. 1989).

Analytical methods for determining cobalt radioisotopes in the environment are shown in Table 7-4. The analysis of cobalt in air is based on quantifying cobalt within aerosols or particles that become trapped on cellulose (paper) or glass fiber filters after a calibrated amount of air is passed through the filters. Since the cobalt radioisotopes do not occur naturally, but may be released as a result of nuclear weapons testing (which has been discontinued for several years), neutron-activation of specific materials (e.g., cobalt containing alloys used in piping of nuclear reactors), or a severe core damage accident in a nuclear plant, the amounts of these isotopes within the ambient environment are near or below the minimum detectable levels for these isotopes (DOE 1995). However, trace amounts of ^{60}Co can be detected in air, water, and sediments within or near nuclear weapons or fuel production facilities, nuclear reactors, and nuclear waste storage sites (DOE 1995; Boccolini et al. 1976; USAEC 1973). Analysis of cobalt radioisotopes in air filters, water, sediments, vegetation, and biota can be performed directly using gamma-ray spectrometry, or following some sample preparation (e.g., drying, ashing, or extraction) (Boccolini et al. 1976; Cahill et al. 1972; Cushing 1981; Hiraid et al. 1984; Windham and Phillips 1973).

The detection limits, accuracy, and precision of any analytical methodology are important parameters in determining the appropriateness of a method for quantifying a specific analyte at the desired level of sensitivity within a particular matrix. The Lower Limit of Detection (LLD) has been adopted to refer to the intrinsic detection capability of a measurement procedure (sampling through data reduction and reporting) to aid in determining which method is best suited for the required sample quantitation (USNRC 1984). Several factors influence the LLD, including background, size or concentration of sample, detector sensitivity and recovery of desired analyte during sample isolation and purification, level of interfering contaminants, and, particularly, counting time. Because of these variables, the LLDs between laboratories, utilizing the same or similar measurement procedures, will vary.

The accuracy of a measurement technique in determining the quantity of a particular analyte in environmental samples is greatly dependent on the availability of standard reference materials. Several SRMs for cobalt in environmental samples are also available. Some of these are coal, fly ash, diet, and orchard leaf SRMs available from NIST. The Community Bureau of Reference, European Communities offers SRMs for cobalt in sludges, and an SRM for cobalt in thin polymer films is available from NIST for x-ray fluorescence analysis in aerosol particle samples (Dzubay et al. 1988; Miller-Ihli and Wolf

1986; Schramel 1989; Smith and Carson 1981; Tinsley et al. 1983). Gamma ray point sources for ^{60}Co (SRM 4200, 60,000 Bq [1.6 µCi] and SRM 4207, 300,000 Bq [56 µCi]) and standard solutions of ^{60}Co (SRM 4233, 600,000 Bq/g [16 µCi/g]) are available from NIST.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cobalt is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cobalt.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Cobalt concentrations in blood or urine can serve as exposure indicator (Alexandersson 1988; Ichikawa et al. 1985; Scansetti et al. 1985). The available analytical methods are capable of determining the levels of cobalt in both the blood and urine of normal and occupationally exposed persons (Table 7-1). For the quantitation of cobalt radioisotopes, whole body counters can be used to assess radioactive cobalt body burdens that have occurred both from acute and chronic exposures to cobalt radioisotopes (Bhat et al. 1973; NCRP 1987). *In vitro* analytical methods are available for analyzing cobalt radioisotopes in urine, feces, and tissues obtained from normal and occupationally exposed persons (Table 7-2).

Sensitive serum protein responses were found in animals exposed to cobalt at levels below those that produce hematopoietic effects. This unique serum protein response to cobalt exposure includes an increase in alpha globulin fractions of serum proteins and associated serum neuraminic acid. Details of this effect are given in Chapters 2 and 3. If similar changes occur in humans, this measurement may provide the earliest indications of effects of cobalt exposure. The available analytical methods are capable of determining these effects of cobalt exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods with good sensitivity and specificity are available for determining cobalt in air, water, soil, and other environmental media (Table 7-3). Analytical methods for cobalt, like those for most metals, measure total metal content rather than the particular compound. Therefore, analytical methods do not generally differentiate between the parent compound and a transformation product as would be the case, for example, were cobalt oxide to be converted to cobalt sulfate. (An exception to this would be the case of radioactive decay in which the parent could be readily distinguished from the decay product.) Analytical methods with the capability of distinguishing between different cobalt species would be important an important tool for assessing the fate of cobalt compounds in the environment. However, methods for quantifying specific cobalt compounds were not found in the literature.

The levels of the parent compound or its reaction products in different environmental media can be used to assess the exposure to cobalt by humans through the inhalation of air and ingestion of food and drinking water. In the case of cobalt, a correlation between its levels in environmental media (e.g., occupational air) and in biological tissues and body fluids has been found (Alexandersson 1988; Ichikawa et al. 1985; Scansetti et al. 1985). Therefore, it is possible to estimate the total body burden of cobalt in workers exposed to airborne cobalt vapor and fumes from its concentration in workplace air.

For cobalt radioisotopes, analytical methods also exist that have good sensitivity and specificity for determining radioactive cobalt in air, water, soil, and other environmental media are available (Table 7-4). Because ^{60}Co decays to the stable element ^{60}Ni, there is no need to develop methods to detect and quantify the decay products.

7.3.2 Ongoing Studies

Two studies involving analytical techniques for cobalt was listed in the Federal Research in Progress database (FEDRIP 2002, 2004). N.J. Miller-Ihli and co-workers of the Agricultural Research Service in Beltsville, Maryland are developing single and multielement methods for the determination of trace elements of nutritional and health concern. This work will develop new/improved methods permitting direct analysis of solids by GF-AAS and ICP-MS, as well as methods for the determination of different chemical forms of these elements by coupling capillary zone electrophoresis with inductively coupled plasma mass spectrometry (ICP-MS). This research is supported by the U.S. Department of Agriculture (USDA) Agricultural Research Service. B.T. Jones of Wake Forest University in Winston-Salem, North Carolina along with C. Calloway of Winthrop College, South Carolina, are working to develop a novel, low-cost, portable instrument for the simultaneous determination of trace radioactive elements in nuclear forensic samples. The instrument to be developed is expected to provide analytical figures comparable to ICP-MS, but the instrument is much lower cost and more portable. The specific objectives of the project include determination of the analytical figures of merit for elements including cobalt, cesium, and strontium, and analysis of real samples such as soil, urban dust, water, and agricultural materials.

8. REGULATIONS AND ADVISORIES

International and national guidelines and state regulations regarding exposure to stable cobalt and its compounds are summarized in Table 8-1. The regulations regarding radioactive cobalt are summarized in Table 8-2.

Stable Cobalt. An MRL of $1x10^{-4}$ mg cobalt/m^3 has been derived for chronic-duration inhalation exposure. The MRL is based on a NOAEL of 0.0053 mg cobalt/m^3 for decreased respiratory function in exposed workers (Nemery et al. 1992). An MRL of $1x10^{-2}$ mg/kg-day has been derived for intermediate-duration oral exposure, based on a LOAEL of 1 mg/kg-day for polycythemia in human volunteers (Davis and Fields 1958). No other inhalation or oral MRLs were derived.

The EPA has not derived an RfC or RfD for cobalt and compounds. Similarly, no cancer classification has been performed by the EPA (IRIS 2000). The American Conference of Governmental Industrial Hygienists (ACGIH) has given cobalt a classification of A3, *confirmed animal carcinogen with unknown relevance to humans*, and established an 8-hour time-weighted average (TWA) of 0.02 mg/m^3 for occupational exposure (ACGIH 2000). The Occupational Safety and Health Administration (OSHA) has promulgated an 8-hour permissible exposure limit (PEL) of 0.1 mg/m^3 (OSHA 2001e), and the National Institute for Occupational Safety and Health (NIOSH) recommends an 8-hour TWA of 0.05 mg/m^3 (NIOSH 2001). IARC (2001b) reports that cobalt and cobalt compounds are *possibly carcinogenic to humans* (Group 2B), based on sufficient evidence for cobalt metal and cobalt oxides and limited evidence for cobalt chloride and cobalt sulfate.

Cobalt and its compounds are regulated by the Clean Water Effluent Guidelines for the following industrial point sources: nonferrous metal manufacturing, asbestos, timber products processing, paving and roofing, paint formulating, ink formulating, gum and wood, carbon black, and battery manufacturing (EPA 1988).

Radioactive Cobalt. No MRLs were derived for inhalation or oral exposure to radioactive cobalt. MRLs for acute and chronic exposure to ionizing radiation exist (Agency for Toxic Substances and Disease Registry 1999) and are applicable to cobalt. The EPA has not derived an RfC or RfD for radioactive

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2001b
	Cobalt and cobalt compounds[a]	Group 2B[b]	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA		ACGIH 2000
	Cobalt, elemental, and inorganic compounds (as Co)	0.02 mg/m^3	
NIOSH	REL (TWA)		NIOSH 2001
	Cobalt metal, dust, and fumes (as Co)	0.05 mg/m^3	
	IDLH		
	Cobalt metal, dust, and fumes (as Co)	20 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2001e 29CFR1910.1000 Table Z
	Cobalt metal, dust, and fumes (as Co)	0.1 mg/m^3	
	PEL (8-hour TWA) for construction industry		OSHA 2001d 29CFR1926.55
	Cobalt metal, dust, and fumes (as Co)	0.1 mg/m^3	
	PEL (8-hour TWA) for shipyard industry		OSHA 2001c 29CFR1915.1000
	Cobalt metal, dust, and fumes (as Co)	0.1 mg/m^3	
USC	HAP (cobalt compounds)		USC 2001a 42USC7412
b. Water			
EPA	NPDES permit application testing requirements; conventional and nonconventional pollutants required to be tested by existing dischargers if expected to be present		EPA 2001g 40CFR122 Appendix D Table IV
	BPT effluent limitations		EPA 2001b 40CFR415.652
	Maximum for 1 day	3x10^{-4} kg/kkg	
	Average of daily values for 30 consecutive days	1.2x10^{-4} kg/kkg	
	Groundwater monitoring		EPA 2001d 40CFR264 Appendix IX
	Suggested method	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
NATIONAL (cont.)			
c. Food			
FDA	Drug products withdrawn or removed from the market for reasons of safety or effectiveness	All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives)	FDA 2000a 21CFR216.24
	New drug status accorded through rulemaking procedures	Cobalt preparations intended for use by man	FDA 2000b 21CFR310.502 (a)(7)
	Over-the-counter drugs; recommended warning and caution statement for cobalt as a cobalt salt	Required on articles containing ≥0.5 µg per dose and ≥2 µg per 24-hour period	FDA 2000e 21CFR369.20
	Substances generally recognized as safe; trace minerals added to animal feeds	Cobalt acetate Cobalt carbonate Cobalt chloride Cobalt oxide Cobalt sulfate	FDA 2000f 21CFR582.20
	Substances prohibited from use in human food	Cobaltous salts and its derivatives	FDA 2000g 21CFR189.120
d. Other			
ACGIH	Carcinogenicity classification Cobalt, elemental, and inorganic compounds (as Co)	 A3[c]	ACGIH 2000
	BEI Cobalt in urine—end of shift at end of workweek Cobalt in blood—end of shift at end of workweek	 15 µg/L 1 µg/L	
EPA	Carcinogenicity classification RfC RfD	No data	IRIS 2000
	Toxic chemical release reporting; Community Right-to-Know; effective date	01/01/87	EPA 2001c 40CFR372.65(a)
	Hazardous waste; identification and listing	Contain ≤1 ppmv in synthesis gas fuel generated from hazardous waste	EPA 2001e 40CFR261.38 (b)(5)
	TSCA; health and safety data reporting		EPA 2001j 40CFR716.120
EPA	Municipal solid waste landfills; hazardous constituent for detection monitoring Suggested method 6010 7200 7201	 PQL 70 µg/L 500 µg/L 10 µg/L	EPA 2001f 40CFR258 Appendix I and II
	Reportable quantity (cobalt compounds)	1 pound	EPA 2001h 40CFR302.4

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
NATIONAL (cont.)			
USC	Superfund imposition of tax on cobalt	$4.45 per ton	USC 2001c 26USC4661
	Exemption of tax imposed on recycled cobalt		USC 2001b 26USC4662
STATE Regulations and Guidelines			
a. Air			
Alabama	HAP (cobalt compounds)		BNA 2001
Alaska	Air contaminant standard (TWA)		BNA 2001
	Cobalt metal, dust, and fumes	0.05 mg/m^3	
California	Airborne contaminant (cobalt metal, dust, and fumes)		BNA 2001
	HAP (cobalt compounds)		BNA 2001
	Toxic air contaminant (cobalt compounds)		CA Air Resources Board 2000
Colorado	HAP (cobalt metal, dust, and fumes)		BNA 2001
	"High-concern" pollutant (cobalt and compounds)		BNA 2001
	Reportable pollutants (cobalt metal, dust, and fumes)		CO Dept. of Public Health and Environment 2000
Connecticut	HAP—hazard limiting value (cobalt metal, dust, and fumes)		BNA 2001
	8 hours	2 µg/m^3	
	30 minutes	10 µg/m^3	
Delaware	Reportable quantities		DE Air Quality Management 2000
	Cobalt carbonyl	1 pound	
	Cobaltous sulfamate	1,000 pounds	
	Cobalt, ((2,2'-(ethane-diylbis(nitrilomethylidyne)	1 pound	
Hawaii	Air contaminant limit (PEL-TWA)		BNA 2001
	Cobalt metal, dust, and fumes	0.05 mg/m^3	
	HAP (cobalt compounds)		BNA 2001
Idaho	TAP non-carcinogenic increments		ID Dept. of Environmental Quality 2000
	Cobalt carbonyl and cobalt hydrocarbonyl (as Co)		
	OEL	1x10^{-1} mg/m^3	
	EL	7x10^{-3} pounds/hour	
	AAC (24-hour average)	5x10^{-3} mg/m^3	
	Cobalt metal, dust, and fumes		
	OEL	5x10^{-2} mg/m^3	
	EL	3.3x10^{-3} pounds/hour	
	AAC (24-hour average)	2.5x10^{-3} mg/m^3	
Illinois	Toxic air contaminant (cobalt)		IL EPA 2000a
Kansas	HAP (cobalt compounds)		KS Dept. of Health and Environment 2000

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
STATE (cont.)			
Kentucky	HAP (cobalt compounds)		BNA 2001
Louisiana	Toxic air pollutant (cobalt compounds		BNA 2001
Maine	Emissions standards	2,000 pounds	BNA 2001
Maryland	Toxic air pollutant (cobalt compounds)		BNA 2001
Michigan	High concern toxic air pollutants (cobalt compounds)		BNA 2001
Minnesota	HAP threshold (cobalt metal and cobalt carbonyl)	0.1 tons/year	BNA 2001
Missouri	HAP (cobalt compounds)		BNA 2001
Montana	Occupational air contaminant (cobalt metal, dust, and fumes)	0.1 mg/m^3	BNA 2001
Nebraska	HAP (cobalt compounds and cobalt)		BNA 2001
New Mexico	Toxic air pollutant (cobalt metal, dust, and fumes [as Co])		BNA 2001
	OEL	$1x10^{-1}$ mg/m^3	
	Emissions	$6.67x10^{-3}$ pounds/hour	
New York	Annual guideline concentrations	$5x10^{-3}$ $\mu g/m^3$	NYS Dept. of Environmental Conservation 2000
	Dangerous air contaminants (TLV) for cobalt metal, dust, and fumes	0.1 mg/m^3	BNA 2001
	HAP (cobalt compounds)		BNA 2001
	Transition limits (PEL)		BNA 2001
	Cobalt metal, dust, and fumes	0.1 mg/m^3	
	Final rule limits (TWA)		
	Cobalt metal, dust, and fumes	0.05 mg/m^3	
North Carolina	PEL-TWA (cobalt metal, dust, and fumes)	0.05 mg/m^3	BNA 2001
Ohio	TRI		Ohio EPA 2000
Oregon	Air contaminant (cobalt metal, dust, and fumes)	0.1 mg/m^3	BNA 2001
Rhode Island	HAP (cobalt compounds)		BNA 2001
South Carolina	Toxic air emissions (MAC) for cobalt compounds	0.25 $\mu g/m^3$	BNA 2001
Texas	HAP (cobalt metal, dust, and fumes)	0.1 mg/m^3	BNA 2001
Vermont	HAP (cobalt compounds)		BNA 2001
	Hazardous ambient air standards		BNA 2001
	Cobalt compounds		
	Annual average	0.12 $\mu g/m^3$	
	Averaging time	24 hours	
	Action level	$6.2x10^{-3}$ pounds/8 hours	
Washington	Class B TAP and ASIL (24-hour average)		WA Dept. of Ecology 2000
	Cobalt metal, dust and fumes	0.17 $\mu g/m^3$	
	Cobalt carbonyl and cobalt hydrocarbonyl	0.33 $\mu g/m^3$	

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
STATE (cont.)			
	Thresholds for HAPs		BNA 2001
	Cobalt carbonyl	0.1 tons/year	
	Cobalt metal, dust, and fumes	0.1 tons/year	
Wisconsin	HAP—existing sources		WI Dept. of Natural Resources 1999
	AAC <25 feet	4.08×10^{-3} pounds/hour	
	AAC ≥25 feet	1.704×10^{-2} pounds/hour	
b. Water			
Alabama	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
Arizona	Drinking water guideline	0.70 µg/L	FSTRAC 1999
Arkansas	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
California	Chemicals known to cause cancer or reproductive toxicity; date of initial appearance on the list		Cal/EPA 2000
	Cobalt metal powder		
	Cobalt[II] oxide	07/01/92	
	Cobalt sulfate heptahydrate	07/01/92 06/02/00	
Colorado	Groundwater standard (cobalt)	0.05 mg/L	BNA 2001
Delaware	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
Illinois	Groundwater quality standards for Class II	1 mg/L	IL EPA 2000b
Kentucky	Hazardous waste constituent for groundwater monitoring (cobalt)		BNA 2001
Louisiana	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
Massachusetts	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
Minnesota	Drinking water guideline	2 µg/L	FSTRAC 1995
	Groundwater protection hazardous constituent for cobalt (total)		BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
STATE (cont.)			
Missouri	Water quality standards		BNA 2001
	Livestock, wildlife watering	$1x10^3$ µg/L	
	Groundwater	$1x10^3$ µg/L	
New Mexico	Standards for groundwater of 10,000 mg/L TDS concentration or less (cobalt)	0.05 mg/L	BNA 2001
New York	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
Tennessee	Effluent limitations—daily maximum concentration (cobalt)	10 mg/L	BNA 2001
Wisconsin	Drinking water guideline	40 µg/L	FSTRAC 1999
	Groundwater standards (cobalt)		BNA 2001
	Enforcement standard	40 µg/L	
	Preventive action limit	8 µg/L	
c. Food		No data	
d. Other			
Alabama	Detection limit values for comparable fuel specification for cobalt; concentration limit	4.6 mg/kg at 10,000 BTU/pound	BNA 2001
Arizona	Soil remediation levels (cobalt)		BNA 2001
	Residential	$4.6x10^3$ mg/kg	
	Non-residential	$9.7x10^4$ mg/kg	
Arkansas	Detection limit values for comparable fuel specification for cobalt; concentration limit	4.6 mg/kg at 10,000 BTU/pound	BNA 2001
	Solid waste management (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
California	Characteristics of toxicity for cobalt and cobalt compounds		BNA 2001
	STLC	80 mg/L	
	TTLC	8,000 mg/kg (wet-weight)	
	Chemicals known to cause cancer or reproductive toxicity (cobalt metal powder); initial appearance on the list	07/01/92	BNA 2001
	Hazardous substance (cobalt, cobalt carbonyl, and cobalt hydrocarbonyl)		BNA 2001
Delaware	Detection limit values for comparable fuel specification for cobalt; concentration limit	4.6 mg/kg at 10,000 BTU/pound	BNA 2001
Florida	Toxic substance in the workplace (cobalt metal, dust, and fumes)		BNA 2001
Georgia	Soil concentration (cobalt)	20 mg/kg	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
STATE (cont.)			
Illinois	Analytical parameters and required quantitation limits for cobalt Water Soil Method	 50 µg/L 10 mg/kg 6010A	BNA 2001
Indiana	Constituent subject to assessment monitoring (cobalt [total and dissolved])		BNA 2001
Maine	Screening standards for beneficial use (cobalt)	5,875 mg/kg (dry weight)	BNA 2001
Michigan	Identification and listing of hazardous waste (cobalt)	When in the form of 100 microns or less	BNA 2001
Minnesota	Hazardous substance Cobalt metal, dust, and fumes (as Co) Cobalt carbonyl (as Co) Cobalt, elemental and inorganic compounds (as Co) Cobalt hydrocarbonyl (as Co)		BNA 2001
Missouri	Hazardous constituent (cobalt [total])		BNA 2001
New Jersey	Hazardous substance Cobalt Cobalt carbonyl Cobalt compounds		BNA 2001
New York	Occupational lung disease; hard metal disease	Cobalt	BNA 2001
Ohio	Toxic release inventory		BNA 2001
Oklahoma	Fertilizer labels and labeling; minimum percentage accepted for registration (cobalt)	$5x10^{-4}$ percent	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
Oregon	Toxic substance (cobalt)		BNA 2001
Pennsylvania	Hazardous substance (cobalt and cobalt fumes)		BNA 2001

[a]Cobalt compounds: includes cobalt(II) carbonate, cobalt(II) chloride, cobalt(II) nitrate, cobalt(II) oxide, cobalt(II,III) oxide, cobalt(III) oxide, and cobalt(II) sulfate
[b]Group 2B: possibly carcinogenic to humans
[c]A3: confirmed animal carcinogen with unknown relevance to humans

AAC = acceptable ambient concentrations; ACGIH = American Conference of Governmental Industrial Hygienists; ASIL = acceptable source impact level; BEI = biological exposure indices; BNA = Bureau of National Affairs; BPT = best practicable control technology; BTU = British thermal unit; CFR = Code of Federal Regulations; EL = emissions levels; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FSTRAC = Federal-State Toxicology and Risk Analysis Committee; HAP = hazardous air pollutant; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; MAC = maximum allowable concentration; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; STLC = soluble threshold limit concentrations; TAP = toxic air pollutant; TDS = total dissolved solids; TLV = threshold limit value; TRI = Toxic Release Inventory; TSCA = Toxic Substances Control Act; TTLC = total threshold limit concentrations; TWA = time-weighted averages; USC = United States Code

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information	Reference
INTERNATIONAL Guidelines:			
IARC	Carcinogenicity classification	Group 1 (carcinogenic to humans)	IARC 2001b
ICRP	Occupational dose limits; effective dose	20 mSv per year, averaged over defined periods of 5 years	ICRP 1991
	Annual equivalent dose		
	Lens of the eye	150 mSv	
	Skin	500 mSv	
	Hands and feet	500 mSv	
	General population dose limits; effective dose	1 mSv in a year	ICRP 1991
	Annual equivalent dose		
	Lens of eye	15 mSv	
	Skin	50 mSv	
WHO	Drinking water quality	No data	
NATIONAL Regulations and Guidelines:			
a. Air			
ACGIH	All radiation exposures must be kept as low as reasonably achievable		ACGIH 2000
	Effective dose		ACGIH 2000
	Any single year	50 mSv	
	Averaged over 5 years	20 mSv per year	
	Annual equivalent dose		
	Lens of the eye	150 mSv	
	Skin	500 mSv	
	Hands and feet	500 mSv	
	Embryo-fetus exposures once the pregnancy is known		
	Monthly equivalent dose	0.5 mSv	
	Dose to the surface of women's abdomen (lower trunk)	2 mSv for the remainder of the pregnancy	
	Intake of radionuclide	1/20 of the ALI	

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
DOE	Radiation standards			DOE 2000
	Inhalation DAC (µCi/mL)	Class Wa	Class Yb	10CFR835
	^{55}Co	$1x10^{-6}$	$1x10^{-6}$	Appendix A
	^{56}Co	$1x10^{-7}$	$8x10^{-8}$	
	^{57}Co	$1x10^{-6}$	$3x10^{-7}$	
	^{58}mCo	$4x10^{-5}$	$3x10^{-5}$	
	^{58}Co	$5x10^{-7}$	$3x10^{-7}$	
	^{60}mCo	$2x10^{-3}$	$1x10^{-3}$	
	^{60}Co	$7x10^{-8}$	$1x10^{-8}$	
	^{61}Co	$3x10^{-5}$	$2x10^{-5}$	
	^{62}mCo	$7x10^{-5}$	$7x10^{-5}$	
	Radiation standards for air immersion DACc (µCi/mL) for ^{60}mCo	1x10-3		DOE 2000 10CFR835 Appendix C
NIOSH	REL	No data		
USNRC	Effluent concentrations—air			USNRC 2001k
	^{55}Co	ALI (µCi/mL)		10CFR20
	Class Wd	$4x10^{-9}$		Appendix B
	Class Ye	$4x10^{-9}$		Table 2
	^{56}Co			
	Class Wd	$4x10^{-10}$		
	Class Ye	$3x10^{-10}$		
	^{57}Co			
	Class Wd	$4x10^{-9}$		
	Class Ye	$9x10^{-10}$		
	^{58}Co			
	Class Wd	$2x10^{-9}$		
	Class Ye	$1x10^{-9}$		
	^{58}mCo			
	Class Wd	$1x10^{-7}$		
	Class Ye	$9x10^{-8}$		
	^{60}Co			
	Class Wd	$2x10^{-10}$		
	Class Ye	$5x10^{-11}$		
	^{60}mCo			
	Class Wd	$6x10^{-6}$		
	Class Ye	$4x10^{-6}$		
	^{61}Co			
	Class Wd	$9x10^{-8}$		
	Class Ye	$8x10^{-8}$		
	^{62}mCo			
	Class Wd	$2x10^{-7}$		
	Class Ye	$2x10^{-7}$		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
USNRC	Occupational values			USNRC 2001k
	Inhalation			10CFR20
	^{55}Co	ALI (µCi)	DAC (µCi/mL)	Appendix B
	Class Wd	$3x10^{3}$	$1x10^{-6}$	Table 1
	Class Ye	$3x10^{3}$	$1x10^{-6}$	
	^{56}Co			
	Class Wd	$3x10^{2}$	$1x10^{-7}$	
	Class Ye	$2x10^{2}$	$8x10^{-8}$	
	^{57}Co			
	Class Wd	$3x10^{3}$	$1x10^{-6}$	
	Class Ye	$7x10^{2}$	$3x10^{-7}$	
	^{58}Co			
	Class Wd	$1x10^{3}$	$5x10^{-7}$	
	Class Ye	$7x10^{2}$	$3x10^{-7}$	
	^{58}mCo			
	Class Wd	$9x10^{4}$	$4x10^{-5}$	
	Class Ye	$6x10^{4}$	$3x10^{-5}$	
	^{60}Co			
	Class Wd	$2x10^{2}$	$7x10^{-8}$	
	Class Ye	$3x10^{1}$	$1x10^{-8}$	
	^{60}mCo			
	Class Wd	$4x10^{6}$	$2x10^{-3}$	
	Class Ye	$3x10^{6}$	$1x10^{-3}$	
	^{6}1Co			
	Class Wd	$6x10^{4}$	$3x10^{-5}$	
	Class Ye	$6x10^{4}$	$2x10^{-5}$	
	^{62}mCo			
	Class Wd	$2x10^{5}$	$7x10^{-5}$	
	Class Ye	$2x10^{5}$	$6x10^{-5}$	
OSHA	Safety and health regulations for construction—ionizing radiation			OSHA 2001e 29CFR1926.53
	Toxic and hazardous substances—ionizing radiation			OSHA 2001d 29CFR1910.1096
b. Water				
EPA	Drinking water standards			EPA 2000
	Beta particle and photon activity (formerly man-made radionuclides)			
	MCL	4 mrem		
	Caner risk at 10^{-4}	4 mrem/year		
	Gross alpha particle activity			
	MCL	15 pCi/L		
	Caner risk at 10^{-4}	15 pCi/L		
	Carcinogenic classification	Group A (human carcinogen)		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
USNRC	Effluent concentrations		USNRC 2001k
	Water		10CFR20
	^{55}Co	ALI (µCi/mL)	Appendix B
	Class Wd	$2x10^{-5}$	Table 2
	^{56}Co		
	Class Wd	$6x10^{-6}$	
	^{57}Co		
	Class Wd	$6x10^{-5}$	
	^{58}Co		
	Class Wd	$2x10^{-5}$	
	^{58}mCo		
	Class Wd	$8x10^{-4}$	
	^{60}Co		
	Class Wd	$3x10^{-6}$	
	^{60}mCo		
	Class Wd	$2x10^{-2}$	
	^{61}Co		
	Class Wd	$3x10^{-4}$	
	^{62}mCo		
	Class Wd	$7x10^{-4}$	
	Releases to sewers—monthly average concentration		USNRC 2001k 10CFR20
	^{55}Co	ALI (µCi/mL)	Appendix B
	Class Wd	$2x10^{-4}$	Table 3
	^{56}Co		
	Class Wd	$6x10^{-5}$	
	^{57}Co		
	Class Wd	$6x10^{-4}$	
	^{58}Co		
	Class Wd	$2x10^{-4}$	
	^{58}mCo		
	Class Wd	$8x10^{-3}$	
	^{60}Co		
	Class Wd	$3x10^{-5}$	
	^{60}mCo		
	Class Wd	$2x10^{-1}$	
	^{61}Co		
	Class Wd	$3x10^{-3}$	
	^{62}mCo		
	Class Wd	$7x10^{-3}$	
c. Food and Drug			
FDA	Ionizing radiation for the treatment of poultry feed and poultry feed ingredients (energy sources)	Ioninzing radiation is limited to gamma rays from sealed units of ^{60}CO	FDA 1999 21CFR579.40
	Requirements regarding certain radioactive drugs for ^{58}Co or ^{60}Co	Labeled cyanocobalamin for use in intestinal absorption studies	FDA 2000d 21CFR310.503(c)

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information			Reference
NATIONAL *(cont.)*					
FDA	Sources of radiation used for inspection of food, packaged food, and controlling food processing				FDA 2000c 21CFR179.21 (a)(2)
d. Other					
DOE	Values for establishing sealed radioactive source accountability and radioactive material posting and labeling requirements				DOE 2000 10CFR835 Appendix E
		Activity (µCi)			
	^{56}Co	4.0×10^{1}			
	^{57}Co	2.3×10^{2}			
	^{58}Co	1.4×10^{2}			
	^{60}Co	1.8×10^{1}			
DOT	Activity values (Ci)	A1	A2		DOT 2001a 49CFR173.435 Table
	^{55}Co	13.5	13.5		
	^{56}Co	8.11	8.11		
	^{57}Co	216	216		
	^{58}mCo	1080	1080		
	^{58}Co	27.0	27.0		
	^{60}Co	10.8	10.8		
	Superfund, reportable quantity (Ci) (pounds)				DOT 2001b 49CFR172.101 Appendix A Table 2
	^{55}Co	10			
	^{56}Co	10			
	^{57}Co	100			
	^{58}Co	10			
	^{58}mCo	1,000			
	^{60}Co	10			
	^{60}mCo	1,000			
	^{61}Co	1,000			
	^{62}mCo	1,000			
EPA	Carcinogenicity classification	No data			IRIS 2000
	RfC				
	RfD				
	Annual possession quantities for environmental compliance (Ci/year)	Gas	Liquid/ Powder	Solid	EPA 2001a 40CFR61 Appendix E Table 1
	^{56}Co	2.3×10^{-6}	2.3×10^{-3}	2.3	
	^{57}Co	1.8×10^{-2}	1.8×10^{1}	1.8×10^{4}	
	^{58}Co	2.5×10^{-6}	2.5×10^{-3}	2.5	
	^{58m}Co	2.3×10^{-6}	2.3×10^{-3}	2.3	
	^{60}Co	4.6×10^{-2}	4.6×10^{1}	4.6×10^{4}	
	^{60m}Co	7.0	7.0×10^{3}	7.0×10^{6}	
	^{61}Co	9.8×10^{-1}	9.8×10^{2}	9.8×10^{5}	

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Concentration levels for environmental compliance (Ci/m^3)		EPA 2001a 40CFR61 Appendix E Table 2
	^{56}Co	$1.8x10^{-13}$	
	^{57}Co	$1.3x10^{-12}$	
	^{58}Co	$6.7x10^{-13}$	
	^{58m}Co	$1.2x10^{-10}$	
	^{60}Co	$1.7x10^{-14}$	
	^{60m}Co	$4.3x10^{-9}$	
	^{61}Co	$4.5x10^{-9}$	
	Carcinogenicity—slope factors		EPA 2002
	Lifetime risk per pCi—ingestion		EPA 2002
	Water		
	^{57}Co	$1.04x10^{-12}$	
	^{58m}Co	$2.95x10^{-12}$	
	^{58}Co	$1.26x10^{-13}$	
	^{60}Co	$1.57x10^{-11}$	
	Lifetime risk per pCi—ingestion		EPA 2002
	Food		
	^{57}Co	$1.49x10^{-12}$	
	^{58m}Co	$4.18x10^{-12}$	
	^{58}Co	$1.83x10^{-13}$	
	60Co	$2.23x10^{-11}$	
	Lifetime risk per pCi—ingestion		EPA 2002
	Soil		
	^{57}Co	$2.78x10^{-12}$	
	^{58}mCo	$7.44x10^{-12}$	
	^{58}Co	$3.47x10^{-13}$	
	^{60}Co	$4.03x10^{-11}$	
	Lifetime risk per pCi—inhalation		EPA 2002
	^{57}Co	$2.09x10^{-12}$	
	^{58}mCo	$5.99x10^{-12}$	
	^{58}Co	$6.88x10^{-14}$	
	^{60}Co	$3.58x10^{-11}$	
	External exposure—risk/year per pCi/g soil		EPA 2002
	^{57}Co	$3.55x10^{-7}$	
	^{58}mCo	$4.48x10^{-6}$	
	^{58}Co	$1.00x10^{-12}$	
	^{60}Co	$1.24x10^{-5}$	

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
EPA	Superfund, reportable quantities (Ci) (pounds)			EPA 2001i 40CFR302.4
	^{55}Co	10		Appendix B
	^{56}Co	10		
	^{57}Co	100		
	^{58}mCo	1,000		
	^{58}Co	10		
	^{60}mCo	1,000		
	^{60}Co	10		
	^{61}Co	1,000		
	^{62}mCo	1,000		
NCRP	Occupational exposures			NCRP1993
	Effective dose limits			
	Annual	50 mSv		
	Cummulative	10 mSv x age		
	Equivalent dose annual limits			
	Lens of eye	150 mSv		
	Skin, hands, and feet	500 mSv		
	Public exposures (annual)			
	Effective dose limits, continuous or frequent exposure	1 mSv		
	Effective dose limits, infrequent exposures	5 mSv		
	Equivalent dose limits			
	Lens of eye	15 mSv		
	Skin, hands, and feet	50 mSv		
	Embryo and fetus exposures (monthly)			
	Effective dose limit	0.5 mSv		
USNRC	Activity values for radionuclides (Ci)	A1	A2	USNRC 2001a 10CFR71
	^{55}Co	13.5	13.5	
	^{56}Co	8.11	8.11	
	^{57}Co	216	216	
	^{58}mCo	1080	1080	
	^{58}Co	27.0	27.0	
	^{60}Co	10.8	10.8	
	Byproduct material listing; exempt concentrations			USNRC 2001e 10CFR30.70
	Liquid and solid concentration (μCi/mL^{2})			Schedule A
	^{57}C	$5x10^{-3}$		
	^{58}C	$1x10^{-3}$		
	^{60}C	$5x10^{-4}$		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
USNRC	Byproduct material listing (μCi)			USNRC 2001b
	^{58}mCo			10CFR30.71
	^{58}Co	10		Schedule B
	^{60}Co	10		
		1		
	Byproduct material listing (Ci)	Column If	Column IIg	USNRC 2001c
	^{58}mCo	100	1.0	10CFR33.100
	^{58}Co	1.0	0.01	Schedule A
	^{60}Co	0.1	$1x10^{-4}$	
	Items containing byproduct material listing—^{60}Co (μCi)			USNRC 2001d 10CFR30.15(a)(8)
	Electron tubes	1.0		
	Spark gap irradiators	1.0		
	Medical use—^{60}Co as a source for brachytherapy	As a sealed source in needles and applicator cells for topical, interstitial, and intracavitary treatment of cancer		USNRC 2001h 10CFR35.400
	Occupational values—oral ingestion			USNRC 2001k 10CFR20
	^{55}Co	ALI (μCi)		Appendix B
	Class Wd	$1x10^{3}$		Table 1
	^{56}Co			
	Class Wd	$5x10^{2}$		
	Class Ye	$4x10^{2}$		
	^{57}Co			
	Class Wd	$8x10^{3}$		
	Class Ye	$4x10^{3}$		
	^{58}Co			
	Class Wd	$2x10^{3}$		
	Class Ye	$1x10^{3}$		
	^{58}mCo			
	Class Wd	$6x10^{4}$		
	^{60}Co			
	Class Wd	$5x10^{2}$		
	Class Ye	$2x10^{2}$		
	^{60}mCo			
	Class Wd	$1x10^{6}$		
	St. wall	$1x10^{6}$		
	^{61}Co			
	Class Wd	$2x10^{4}$		
	Class Ye	$2x10^{4}$		
	^{62}mCo			
	Class Wd	$5x10^{4}$		
	St. wall	$4x10^{4}$		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
USNRC	Quantities of radioactive material requiring labeling (µCi)		USNRC 2001g 10CFR30 Appendix B
	^{58}mCo	10	
	^{58}Co	10	
	^{60}Co	1	
	Quantities of licensed material requiring labeling (µCi)		USNRC 2001i 10CFR20 Appendix C
	^{55}Co	100	
	^{56}Co	10	
	^{57}Co	100	
	^{58}mCo	1,000	
	^{58}Co	100	
	^{60}mCo	1,000	
	^{60}Co	1	
	^{61}Co	1,000	
	^{62}mCo	1,000	
	Quantities of radioactive materials requiring need for an emergency plan		USNRC 2001j 10CFR30.72 Schedule C
	Release fraction	0.001%	
	Quantity (Ci)	5,000	
	Radioactive waste classification		USNRC 2001l 10CFR61.55
	Class A (Ci/m3)		
	60Co	≤700	
	Reports of individual monitoring—processing or manufacturing for distribution, byproduct material in quantities exceeding		USNRC 2001f 10CFR20.2206 (a)(7)
	^{60}Co (Ci)	1.0	
STATE Regulations and Guidelines:			
a. Air			
Alabama	HAP—radionuclides		BNA 2001
California	HAP—radionuclides		BNA 2001
Hawaii	HAP—radionuclides		BNA 2001
Illinois	Toxic air contaminant—radionuclides		BNA 2001
Kansas	HAP—radionuclides		BNA 2001
Kentucky	HAP—radionuclides		BNA 2001
Minnesota	HAP—radionuclides		BNA 2001
Missouri	HAP—radionuclides		BNA 2001

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information	Reference
STATE *(cont.)*			
Nebraska	HAP—radionuclides		BNA 2001
New York	HAP—radionuclides		BNA 2001
Rhode Island	HAP—radionuclides		BNA 2001
Wyoming	HAP—radionuclides		BNA 2001

[a]Class W: refers to the approximate length of retention in the pulmonary region which is 10–100 days for this class
[b]Class Y: refers to the approximate length of retention in the pulmonary region which is greater than 100 days for this class
[c]Air immersion DAC values: based on a stochastic dose limit of 5 rems (0.05 Sv) per year or a nonstochastic (organ) dose limit of 50 rems (0.5 Sv) per year
[d]Class W: all compounds except those given for Y
[e]Class Y: oxides, hydroxides, halides, and nitrates
[f]Column I: gas concentration
[g]Column II: liquid and solid concentration

ACGIH = American Conference of Governmental Industrial Hygienists; ALI = annual limits on intake; BNA = Bureau of National Affairs; CFR = Code of Federal Regulations; DAC = derived air concentrations; DOE = Department of Energy; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; ICRP = International Commission on Radiological Protection; IRIS = Integrated Risk Information System; mSv = millisievert; NCRP = National Council on Radiation Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted averages; USNRC = U.S. Nuclear Regulatory Commission; WHO = World Health Organization

cobalt (IRIS 2000). Slope factors have been derived for exposure to cobalt radioisotopes (EPA 2002). The slope factors for ^{60}Co are 1.57×10^{-11}, 2.23×10^{-11}, and 4.03×10^{-11}/pCi for ingestion of water, food, and soil, respectively. The slope factor for inhalation exposure is 3.58×10^{-11}/pCi, and 1.24×10^{-5}/year/pCi/g soil for external exposure. The slope factors for ^{58}Co are $1.26 \times 10^{-13,}$, $1.83 \times 10^{-13,}$, and 3.47×10^{-13}/pCi for ingestion of water, food, and soil, respectively. The slope factor for inhalation exposure is 6.88×10^{-14}/pCi for inhalation exposure, and 1.00×10^{-12}/year/pCi/g soil for external exposure. The slope factors for ^{58m}Co are $2.95 \times 10^{-12,}$, $4.18 \times 10^{-12,}$, and 7.44×10^{-12}/pCi for ingestion of water, food, and soil, respectively. The slope factor for inhalation exposure is 5.99×10^{-14}/pCi for inhalation exposure, and 4.48×10^{-6}/year/pCi/g soil for external exposure. The slope factors for ^{57}Co are 1.04×10^{-12}, 1.49×10^{-12}, and 2.78×10^{-12}/pCi for ingestion of water, food, and soil, respectively. The slope factor for inhalation exposure is 2.09×10^{-12}/pCi for ingestion, and 3.55×10^{-7}/year/pCi/g soil for external exposure.

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10. GLOSSARY

Some terms in this glossary are generic and may not be used in this profile.

Absorbed Dose, Chemical—The amount of a substance that is either absorbed into the body or placed in contact with the skin. For oral or inhalation routes, this is normally the product of the intake quantity and the uptake fraction divided by the body weight and, if appropriate, the time, expressed as mg/kg for a single intake or mg/kg/day for multiple intakes. For dermal exposure, this is the amount of material applied to the skin, and is normally divided by the body mass and expressed as mg/kg.

Absorbed Dose, Radiation—The mean energy imparted to the irradiated medium, per unit mass, by ionizing radiation. Units: rad (rad), gray (Gy).

Absorbed Fraction—A term used in internal dosimetry. It is that fraction of the photon energy (emitted within a specified volume of material) which is absorbed by the volume. The absorbed fraction depends on the source distribution, the photon energy, and the size, shape and composition of the volume.

Absorption—The process by which a chemical penetrates the exchange boundaries of an organism after contact, or the process by which radiation imparts some or all of its energy to any material through which it passes.

Absorption Coefficient—Fractional absorption of the energy of an unscattered beam of x- or gamma-radiation per unit thickness (linear absorption coefficient), per unit mass (mass absorption coefficient), or per atom (atomic absorption coefficient) of absorber, due to transfer of energy to the absorber. The total absorption coefficient is the sum of individual energy absorption processes (see Compton Effect, Photoelectric Effect, and Pair Production).

Absorption Coefficient, Linear—A factor expressing the fraction of a beam of x- or gamma radiation absorbed in a unit thickness of material. In the expression $I=I_o e^{-\mu x}$, I_o is the initial intensity, I the intensity of the beam after passage through a thickness of the material x, and μ is the linear absorption coefficient.

Absorption Coefficient, Mass—The linear absorption coefficient per cm divided by the density of the absorber in grams per cubic centimeter. It is frequently expressed as μ/ρ, where μ is the linear absorption coefficient and ρ the absorber density.

Absorption Ratio, Differential—Ratio of concentration of a nuclide in a given organ or tissue to the concentration that would be obtained if the same administered quantity of this nuclide were uniformly distributed throughout the body.

Activation—The process of making a material radioactive by bombardment with neutrons or protons.

Activity—The number of radioactive nuclear transformations occurring in a material per unit time (see Curie, Becquerel). The term for activity per unit mass is specific activity.

Activity Median Aerodynamic Diameter (AMAD)—The diameter of a unit-density sphere with the same terminal settling velocity in air as that of the aerosol particle whose activity is the median for the entire size distribution of the aerosol.

Acute Exposure, Chemical—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Acute Exposure, Radiation—The absorption of a relatively large amount of radiation (or intake of a radioactive material) over a short period of time.

Acute Radiation Syndrome—The symptoms which taken together characterize a person suffering from the effects of intense radiation. The effects occur within hours or days.

***Ad libitum*—**Available in excess and freely accessible.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit surface area or per unit weight of organic carbon of a specific particle size in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—See Distribution Coefficient.

Alpha Particle—A positively charged particle ejected spontaneously from the nuclei of some radioactive elements. It is identical to a helium nucleus, i.e., 2 neutrons and two protons, with a mass number of 4 and an electrostatic charge of +2.

Alpha Track—The track of ionized atoms (pattern of ionization) left in a medium by an alpha particle that has traveled through the medium.

Annihilation (Positron-Electron)—An interaction between a positive and a negative electron in which they both disappear; their rest mass, being converted into electromagnetic radiation (called annihilation radiation) with two 0.51 MeV gamma photons emitted at an angle of 180° to each other.

Annual Limit on Intake (ALI)—The derived limit for the amount of radioactive material taken into the body of an adult worker by inhalation or ingestion in a year. It is the smaller value of intake of a given radionuclide in a year by the reference man that would result in a committed effective dose equivalent of 5 rem or a committed dose equivalent of 50 rem to any organ or tissue.

Atom—The smallest particle of an element that cannot be divided or broken up by chemical means. It consists of a central core called the *nucleus*, which contains *protons* and *neutrons* and an outer shell of *electrons*.

Atomic Mass (u)—The mass of a neutral atom of a nuclide, usually expressed in terms of "atomic mass units." The "atomic mass unit" is one-twelfth the mass of one neutral atom of carbon-12; equivalent to 1.6604×10^{-24} g.

Atomic Mass Number—See Mass Number.

Atomic Number—The number of protons in the nucleus of an atom. The "effective atomic number" is calculated from the composition and atomic numbers of a compound or mixture. An element of this atomic number would interact with photons in the same way as the compound or mixture. (Symbol: Z).

Atomic Weight—The weighted mean of the masses of the neutral isotopes of an element expressed in atomic mass units.

Attenuation—A process by which a beam from a source of radiation is reduced in intensity by absorption and scattering when passing through some material.

Attenuation Coefficient—The fractional reduction in the intensity of a beam of radiation as it passes through an absorbing medium. It may be expressed as reduction per unit distance, per unit mass thickness, or per atom, and is called the linear, mass, or atomic attenuation coefficient, respectively.

Auger Effect—The emission of an electron from the extranuclear portion of an excited atom when the atom undergoes a transition to a less excited state.

Background Radiation—The amount of radiation to which a member of the general population is exposed from natural sources, such as terrestrial radiation from naturally occurring radionuclides in the soil, cosmic radiation originating from outer space, and naturally occurring radionuclides deposited in the human body.

Becquerel (Bq)—International System of Units unit of activity and equals that quantity of radioactive material in which one transformation (disintegration) occurs per second (see Units).

Terabecquerel (TBq)—One trillion becquerel.
Gigabecquerel (GBq)—One billion becquerel.
Megabecquerel (MBq)—One million becquerel.
Kilobecquerel (kBq))—One thousand becquerel.
Millibecquerel (mBq)—One-thousandth of a becquerel.
Microbecquerel (µBq)—One-millionth of a becquerel.

Beta Particle—An electron that is emitted from the nucleus of an atom during one type of radioactive transformation. A beta particle has a mass and charge equal in magnitude to that of the electron. The charge may be either +1 or -1. Beta particles with +1 charges are called positrons (symbolized β^+), and beta particles with -1 charges are called negatrons (symbolized β^-).

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biologic Effectiveness of Radiation—See Relative Biological Effectiveness.

Biological Half-time—The time required for a biological system, such as that of a human, to eliminate by natural process half of the amount of a substance (such as a chemical substance, either stable or radioactive) that has entered it.

Biomagnification—The progressive increase in the concentration of a bioaccumulated chemical in organisms as that chemical is passed from the bottom to the top of the food web.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Body Burden, Chemical—The total amount of a chemical found in an animal or human body.

Body Burden, Radioactivity—The amount of radioactive material found in an animal or human body.

Bone Seeker—Any compound or ion which migrates in the body and preferentially deposits into bone.

Branching—The occurrence of two or more modes by which a radionuclide can undergo radioactive decay. For example, ^{214}Bi can undergo alpha or beta minus decay, ^{64}Cu can undergo beta minus, beta plus, or electron capture decay. An individual atom of a nuclide exhibiting branching disintegrates by one mode only. The fraction disintegrating by a particular mode is the "branching fraction" for that mode. The "branching ratio" is the ratio of two specified branching fractions (also called multiple disintegration).

Bremsstrahlung—X rays that are produced when a charged particle accelerates (speeds up, slows down, or changes direction) in the strong field of a nucleus.

Buildup Factor—The ratio of the radiation intensity, including both primary and scattered radiation, to the intensity of the primary (unscattered) radiation.

Cancer Effect Level (CEL)—The lowest dose of chemical or radiation in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Capture, Electron—A mode of radioactive decay involving the capture of an orbital electron by its nucleus. Capture from a particular electron shell, e.g., K or L shells, is designated as "K-electron capture" or "L-electron capture."

Capture, K-Electron—Electron capture from the K shell by the nucleus of the atom. Also loosely used to designate any orbital electron capture process.

Carcinogen—A chemical or radiation that is capable of inducing cancer.

Carcinoma—Malignant neoplasm composed of epithelial cells, regardless of their derivation.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Cataract—A clouding of the crystalline lens of the eye which obstructs the passage of light.

Ceiling Value—A concentration of a substance that should not be exceeded, even temporarily.

Charged Particle—A nuclear particle, atom, or molecule carrying a positive or negative charge.

Chronic Exposure—A long-term, continuous exposure to a chemical or radioactive material. For example, exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Collective Dose—The sum of the individual doses received in a given period of time by a specified population from exposure to a specified source of radiation. Collective dose is expressed in units such as man-rem and person-sievert.

Compton Effect—An attenuation process observed for x- or gamma radiation in which an incident photon interacts with an orbital electron of an atom to produce a recoil electron and a scattered photon whose energy is less than the incident photon.

Containment—The confinement of a chemical or radioactive substance in such a way that it is prevented from being dispersed from its container or into the environment, or is released only at a specified rate.

Contamination—Deposition of a stable or radioactive substance in any place where it is not desired.

Cosmic Rays—High-energy particulate and electromagnetic radiations that originate outside the earth's atmosphere and interact with the atmosphere to produce a shower of secondary cosmic rays.

Count (Radiation Measurements)—The external indication of a radiation-measuring device designed to enumerate ionizing events. It refers to a single detected event. The term “count rate” refers to the total number registered in a given period of time. The term is sometimes erroneously used to designate a disintegration, ionizing event, or voltage pulse.

Counter, Gas-flow Proportional (GPC)—An instrument for detecting beta particle radiation. Beta particles are detected by ionization of the counter gas which results in an electrical impulse at an anode wire.

Counter, Geiger-Mueller (GM counter)—Highly sensitive, gas-filled radiation-measuring device that detects (counts) individual photons or particulate radiation.

Counter, Scintillation—The combination of a crystal or phosphor, photomultiplier tube, and associated circuits for counting light emissions produced in the phosphors by ionizing radiation. Scintillation counters generally are more sensitive than GM counters for gamma radiation.

Counting, Cerenkov—Relatively energetic β-particles pass through a transparent medium of high refractive index and a highly-directional, bluish-white light ("Cerenkov" light) is emitted. This light is detected using liquid scintillation counting equipment.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Curie (Ci)—A unit of radioactivity. One curie equals that quantity of radioactive material in which there are 3.7×10^{10} nuclear transformations per second. The activity of 1 gram of radium is approximately 1 Ci.

Attocurie (aCi)—One-thousandth of a femtocurie (3.7×10^{-8} disintegrations per second).
Femtocurie (fCi)—One-billionth of a microcurie (3.7×10^{-5} disintegrations per second).

Megacurie (MCi)—One million curies ($3.7x10^{16}$ disintegrations per second).
Microcurie (μCi)—One-millionth of a curie ($3.7x10^{4}$ disintegrations per second).
Millicurie (mCi)—One-thousandth of a curie ($3.7x10^{7}$ disintegrations per second).
Nanocurie (nCi)—One-billionth of a curie ($3.7x10^{1}$ disintegrations per second).
Picocurie (pCi)—One-millionth of a microcurie ($3.7x10^{-2}$ disintegrations per second).

Daughter Products—See Progeny and Decay Product

Decay Chain or Decay Series—A sequence of radioactive decays (transformations) beginning with one nucleus. The initial nucleus, the parent, decays into a daughter or progeny nucleus that differs from the first by whatever particles were emitted during the decay. If further decays take place, the subsequent nuclei are also usually called daughters or progeny. Sometimes, to distinguish the sequence, the daughter of the first daughter is called the granddaughter, etc.

Decay Constant (λ)—The fraction of the number of atoms of a radioactive nuclide which decay in unit time (see Disintegration Constant).

Decay Product, Daughter Product, Progeny—A new nuclide formed as a result of radioactive decay. A nuclide resulting from the radioactive transformation of a radionuclide, formed either directly or as the result of successive transformations in a radioactive series. A decay product (daughter product or progeny) may be either radioactive or stable.

Decay, Radioactive—Transformation of the nucleus of an unstable nuclide by spontaneous emission of radiation, such as charged particles and/or photons (see Disintegration).

Delta Ray—An electron removed from an atom of a medium that is irradiated, or through which radiation passes, during the process of ionization (also called secondary electron). Delta rays cause a track of ionizations along their path.

Derived Air Concentration (DAC)—The concentration of radioactive material in air that, if breathed by the reference man for a working year of 2000 hours under conditions of light work (at a rate of 1.2 liters of air per hour), would result in an intake of one ALI (see Annual Limit on Intake).
Deterministic Effect—A health effect, the severity of which varies with the dose and for which a threshold is believed to exist (also called a non-stochastic effect).

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical or radiation prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Disintegration Constant—Synonymous with decay constant. The fraction of the number of atoms of a radioactive material that decays per unit time (see Decay Constant.)

Disintegration, Nuclear—A spontaneous nuclear transformation (radioactivity) characterized by the emission of energy and mass from the nucleus. When large numbers of nuclei are involved, the process is characterized by a definite half-life (see Transformation, Nuclear).

Distribution Coefficient (K_d)—Describes the distribution of a chemical between the solid and aqueous phase at thermodynamic equilibrium, is given as follows:

$K_d = \frac{[C]_s}{[C]_w}$, Units = (L solution)/(kg solid),

where $[C]_s$ is the concentration of the chemical associated with the solid phase in units of (mg)/(kg solid), and $[C]_w$ is the concentration of the chemical in the aqueous phase in units of (mg)/(L solution). As the magnitude of K_d decreases, the potential mobility of the chemical to groundwater systems increases and vice versa.

Dose—A general term denoting the quantity of a substance, radiation, or energy absorbed. For special purposes it must be appropriately qualified. If unqualified, it refers to radiation absorbed dose.

Absorbed Dose—The energy imparted to matter by ionizing radiation per unit mass of irradiated material at the place of interest. The unit of absorbed dose is the rad. One rad equals 100 ergs per gram. In SI units, the absorbed dose is the gray which is 1 J/kg (see Rad).

Cumulative Dose (Radiation)—The total dose resulting from repeated or continuous exposures to radiation.

Dose Assessment—An estimate of the radiation dose to an individual or a population group usually by means of predictive modeling techniques, sometimes supplemented by the results of measurement.

Dose Equivalent (DE)—A quantity used in radiation safety practice to account for the relative biological effectiveness of the several types of radiation. It expresses all radiations on a common scale for calculating the effective absorbed dose. The NRC defines it as the product of the absorbed dose, the quality factor, and all other modifying factors at the location of interest. ICRP has changed its definition to be the product of the absorbed dose and the radiation weighting factor. (The unit of dose equivalent is the rem. In SI units, the dose equivalent is the sievert, which equals 100 rem.)

Dose, Fractionation—A method of administering therapeutic radiation in which relatively small doses are given daily or at longer intervals.

Dose, Protraction—A method of administering therapeutic radiation by delivering it continuously over a relatively long period at a low dose rate.

Dose, Radiation—The amount of energy imparted to matter by ionizing radiation per unit mass of the matter, usually expressed as the unit rad, or in SI units, the gray. 100 rad = 1 gray (Gy) (see Absorbed Dose).

Committed Dose Equivalent ($H_{T,50}$)—The dose equivalent to organs or tissues of reference (T) that will be received from an intake of radioactive material by an individual during the 50 years following the intake.

Committed Effective Dose Equivalent ($H_{E,50}$)—The sum of the products of the weighting factors applicable to each of the body organs or tissues that are irradiated and the committed dose equivalent to those organs or tissues.

Effective Dose —A dose value that attempts to normalize the detriment to the body (for cancer mortality and morbidity, hereditary effects, and years of life lost) from a non-uniform exposure to

that of a uniform whole body exposure. Effective dose is calculated as the sum of products of the equivalent dose and the tissue weighting factor (w_T) for each tissue exposed. ($E = \sum D_{T,R}\ w_R\ w_{T)}$).

Effective Dose Equivalent (H_E)—This dose type is limited to internal exposures and is the sum of the products of the dose equivalent to the organ or tissue (H_T) and the weighting factors (w_T) applicable to each of the body organs or tissues that are irradiated. ($H_E = \sum w_T\ H_T$).

Equivalent Dose—A dose quantity that places the biological effect of all radiation types on a common scale for calculating tissue damage. Alpha particles, for example, are considered to cause 20 times more damage than gamma rays. Equivalent dose is calculated as the sum of products of the average absorbed dose (in gray) in an organ or tissue ($_{DT,R}$) from each type of radiation and the radiation weighting factor (w_R) for that radiation ($\sum D_{T,R}\ w_R$).

External Dose—That portion of the dose equivalent received from radiation sources outside the body.

Internal Dose—That portion of the dose equivalent received from radioactive material taken into the body.

Limit—A permissible upper bound on the radiation dose.

Maximum Permissible Dose (MPD)—The greatest dose equivalent that a person or specified part thereof shall be allowed to receive in a given period of time.

Median Lethal Dose (MLD)—Dose of radiation required to kill, within a specified period (usually 30 days), 50% of the individuals in a large group of animals or organisms. Also called the LD_{50}, or $LD_{50/30}$ if for 30 days.

Threshold Dose—The minimum absorbed dose that will produce a detectable degree of any given effect.

Tissue Dose—Absorbed dose received by tissue in the region of interest, expressed in rad (see Dose, Gray, and Rad).

Dose Rate—The amount of radiation dose delivered per unit time. Generically, the rate at which radiation dose is delivered to any material or tissue.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Dosimetry—Quantification of radiation doses to cells, tissues, organs, individuals or populations resulting from radiation exposures.

Early Effects (of radiation exposure)—Effects that appear within 60 days of an acute exposure.

Electron—A stable elementary particle having an electric charge equal to $\pm 1.60210 \times 10^{-19}$ C (Coulombs) and a rest mass equal to 9.1091×10^{-31} kg. A positron is a positively charged "electron" (see Positron).

Electron Volt—A unit of energy equivalent to the energy gained by an electron in passing through a potential difference of one volt. Larger multiple units of the electron volt are frequently used: keV for thousand or kilo electron volts; MeV for million or mega electron volts (eV). 1 eV=$1.6x10^{-12}$ erg.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Energy—Capacity for doing work. Gravitationally, "potential energy" is the energy inherent in a mass because of its spatial relation to other masses. Chemically or radiologically, “potential energy” is the energy released when a chemical reaction or radiological transformation goes to completion. "Kinetic energy" is the energy possessed by a mass because of its motion (SI unit: joules):

> **Binding Energy (Electron)—**The amount of energy that must be expended to remove an electron from an atom.
>
> **Binding Energy (Nuclear)—**The energy represented by the difference in mass between the sum of the component parts and the actual mass of the nucleus. It represents the amount of energy that must be expended to break a nucleus into its component neutrons and protons.
>
> **Excitation Energy—**The energy required to change a system from its ground state to an excited state. Each different excited state has a different excitation energy.
>
> **Ionizing Energy—**The energy required to knock an electron out of an atom. The average energy lost by electrons or beta particles in producing an ion pair in air or in soft tissue is about 34 eV.
>
> **Radiant Energy—**The energy of electromagnetic radiation, such as radio waves, visible light, x and gamma rays.

Enrichment, Isotopic—An isotopic separation process by which the relative abundances of the isotopes of a given element are altered, thus producing a form of the element that has been enriched in one or more isotopes and depleted in others. In uranium enrichment, the percentage of uranium-235 in natural uranium can be increased from 0.7% to >90% in a gaseous diffusion process based on the different thermal velocities of the constituents of natural uranium (^{234}U, ^{235}U, ^{238}U) in the molecular form UF_6.

EPA Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Equilibrium, Radioactive—In a radioactive series, the state which prevails when the ratios between the activities of two or more successive members of the series remains constant.

> **Secular Equilibrium—**If a parent element has a very much longer half-life than the daughters (so there is not appreciable change in its amount in the time interval required for later products to attain equilibrium) then, after equilibrium is reached, equal numbers of atoms of all members of

the series disintegrate in unit time. This condition is never exactly attained, but is essentially established in such a case as ^{226}Ra and its transformation series to stable ^{206}Pb. The half-life of ^{226}Ra is about 1,600 years; of ^{222}Rn, approximately 3.82 days, and of each of the subsequent members, a few minutes. After about a month, essentially the equilibrium amount of radon is present; then (and for a long time) all members of the series disintegrate the same number of atoms per unit time. At this time, the activity of the daughter is equal to the activity of the parent.

Transient Equilibrium—If the half-life of the parent is short enough so the quantity present decreases appreciably during the period under consideration, but is still longer than that of successive members of the series, a stage of equilibrium will be reached after which all members of the series decrease in activity exponentially with the period of the parent. At this time, the ratio of the parent activity to the daughter activity is constant.

Equilibrium, Electron—The condition in a radiation field where the energy of the electrons entering a volume equals the energy of the electrons leaving that volume.

Excitation—The addition of energy to a system, thereby transferring it from its ground state to an excited state. Excitation of a nucleus, an atom, or a molecule can result from absorption of photons or from inelastic collisions with other particles. The excited state of an atom is an unstable or metastable state and will return to ground state by radiation of the excess energy.

Exposure (Chemical)—Contact of an organism with a chemical or physical agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut) and available for absorption.

Exposure (Radiation)—Subjection to ionizing radiation or to a radioactive material. For example, exposure in air is a measure of the ionization produced in air by x or gamma radiation; the sum of the electric charges on all ions of one sign produced in air when all electrons liberated by photons in a volume of air are completely stopped in air (dQ), divided by the mass of the air in the volume (dm). The unit of exposure in air is the roentgen, or coulomb per kilogram (SI units). One roentgen is equal to 2.58×10^{-4} coulomb per kilogram (C/kg).

Fission, Nuclear—A nuclear transformation characterized by the splitting of a nucleus into at least two other nuclei with emission of several neutrons, accompanied by the release of a relatively large amount of energy.

Gamma Ray, Penetrating—Short wavelength electromagnetic radiation of nuclear origin.

Genetic Effect of Radiation—Inheritable change, chiefly mutations, produced by the absorption of ionizing radiation by germ cells. Genetic effects have not been observed in any human population exposed at any dose level.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Gray (Gy)—SI unit of absorbed dose, 1 J/kg. One gray equals 100 rad (see Units).

Half-life, Effective—See Half-Time, Effective.

Half-life, Radioactive—Time required for a radioactive substance to lose 50% of its activity by decay. Each radio-nuclide has a unique physical half-life. Known also as physical half-time and symbolized as T_r or T_{rad}.

Half-time, Biological—Time required for an organ, tissue, or the whole body to eliminate one-half of any absorbed substance by regular processes of elimination. This is the same for both stable and radioactive isotopes of a particular element, and is sometimes referred to as half-time, symbolized as t_{biol} or T_b.

Half-time, Effective—Time required for a radioactive element in an organ, tissue, or the whole body to be diminished 50% as a result of the combined action of radioactive decay and biological elimination, symbolized as T_e or T_{eff}.

$$\text{Effective half-time} = \frac{\text{Biological half-time} \times \text{Radioactive half-life}}{\text{Biological half-time} + \text{Radioactive half-life}}$$

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube. Literally, “in glass.”

***In Vivo*—**Occurring within the living organism. Literally, “in life.”

Intensity—Amount of energy per unit time passing through a unit area perpendicular to the line of propagation at the point in question.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Internal Conversion—Process in which a gamma ray knocks an electron out of the same atom from which the gamma ray was emitted. The ratio of the number of internal conversion electrons to the number of gamma quanta emitted in the de-excitation of the nucleus is called the "conversion ratio."

Ion—Atomic particle, atom or chemical radical bearing a net electrical charge, either negative or positive.

Ion Pair—Two particles of opposite charge, usually referring to the electron and positive atomic or molecular residue resulting after the interaction of ionizing radiation with the orbital electrons of atoms.

Ionization—The process by which a neutral atom or molecule acquires a positive or negative charge.

> **Primary Ionization—**(1) In collision theory: the ionization produced by the primary particles as contrasted to the "total ionization" which includes the "secondary ionization" produced by delta

rays. (2) In counter tubes: the total ionization produced by incident radiation without gas amplification.

Specific Ionization—Number of ion pairs per unit length of path of ionizing radiation in a medium; e.g., per centimeter of air or per micrometer of tissue.

Total Ionization—The total electric charge of one sign on the ions produced by radiation in the process of losing its kinetic energy. For a given gas, the total ionization is closely proportional to the initial ionization and is nearly independent of the nature of the ionizing radiation. It is frequently used as a measure of absorption of radiation energy.

Ionization Density—Number of ion pairs per unit volume.

Ionization Path (Track)—The trail of ion pairs produced by an ionizing particle in its passage through matter.

Ionizing Radiation—Any radiation capable of knocking electrons out of atoms and producing ions. Examples: alpha, beta, gamma and x rays, and neutrons.

Isobars—Nuclides having the same mass number but different atomic numbers.

Isomers—Nuclides having the same number of neutrons and protons but capable of existing, for a measurable time, in different quantum states with different energies and radioactive properties. Commonly the isomer of higher energy decays to one with lower energy by the process of isomeric transition.

Isotopes—Nuclides having the same number of protons in their nuclei, and hence the same atomic number, but differing in the number of neutrons, and therefore in the mass number. Identical chemical properties exist in isotopes of a particular element. The term should not be used as a synonym for nuclide because isotopes refer specifically to different nuclei of the same element.

Stable Isotope—A nonradioactive isotope of an element.

Joule—The S.I. unit for work and energy. It is equal to the work done by raising a mass of one newton through a distance of one meter (J = Nm), which corresponds to about 0.7 ft-pound.

Kerma (k)—A measure of the kinetic energy transferred from gamma rays or neutrons to a unit mass of absorbing medium in the initial collision between the radiation and the absorber atoms. The SI unit is J/kg. The special name of this unit is the rad (traditional system of units) or Gray (SI).

Labeled Compound—A compound containing one or more radioactive atoms intentionally added to its structure. By observations of radioactivity or isotopic composition, this compound or its fragments may be followed through physical, chemical, or biological processes.

Late Effects (of radiation exposure)—Effects which appear 60 days or more following an acute exposure.

$LD_{50/30}$—The dose of a chemical or radiation expected to cause 50% mortality in those exposed within 30 days. For radiation, this is about 350 rad (3.5 gray) received by humans over a short period of time.

Lethal Concentration$_{(Lo)}$ (LC_{Lo})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population within a specified time, usually 30 days.

Lethal Dose$_{(Lo)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals within a specified time, usually 30 days.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Linear Energy Transfer (LET)—A measure of the energy that a charged particle transfers to a material per unit path length.

> **Average LET—**The energy of a charged particle divided by the length of the path over which it deposits all its energy in a material. This is averaged over a number of particles.
>
> **High-LET—**Energy transfer characteristic of heavy charged particles such as protons and alpha particles where the distance between ionizing events is small on the scale of a cellular nucleus.
>
> **Low-LET—**Energy transfer characteristic of light charged particles such as electrons produced by x and gamma rays where the distance between ionizing events is large on the scale of a cellular nucleus.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lung Clearance Class (fast, F; medium, M; slow, S)—A classification scheme for inhaled material according to its rate of clearance from the pulmonary region of the lungs to the blood and the gastrointestinal tract.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Mass Numbers (A)—The number of nucleons (protons and neutrons) in the nucleus of an atom.

Minimal Risk Level—An estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mutagen—A substance that causes changes (mutations) in the genetic material in a cell. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a substance.

Neutrino (ν)—A neutral particle of infinitesimally small rest mass emitted during beta plus or beta minus decay. This particle accounts for conservation of energy in beta plus and beta minus decays. It plays no role in damage from radiation.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a substance at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Nuclear Reactor—A power plant that heats the medium (typically water) by using the energy released from the nuclear fission of uranium or plutonium isotopes instead of burning coal, oil, or natural gas. All of these sources of energy simply heat water and use the steam which is produced to turn turbines that make electricity or propel a ship.

Nucleon—Common name for a constituent particle of the nucleus. Applied to a proton or neutron.

Nuclide—A species of atom characterized by the constitution of its nucleus. The nuclear constitution is specified by the number of protons (Z), number of neutrons (N), and energy content; or, alternatively, by the atomic number (Z), mass number A(N+Z), and atomic mass. To be regarded as a distinct nuclide, the atom must be capable of existing for a measurable time. Thus, nuclear isomers are separate nuclides, whereas promptly decaying excited nuclear states and unstable intermediates in nuclear reactions are not so considered.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Pair Production—An absorption process for x- and gamma radiation in which the incident photon is absorbed in the vicinity of the nucleus of the absorbing atom, with subsequent production of an electron and positron pair (see annihilation). This reaction can only occur for incident photon energies exceeding 1.02 MeV.

Parent—Any radionuclide nuclide which, upon disintegration, yields a new nuclide (termed the progeny or daughter), either directly or as a later member of a radioactive series.

Permissible Exposure Limit (PEL)—A maximum allowable atmospheric level of a substance in workplace air averaged over an 8-hour shift.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereas the physiologically-based model compartments represent real anatomic regions of the body.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A model comprising a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Photoelectric Effect—An attenuation process observed for x and gamma radiation in which an incident photon interacts with a tightly bound inner orbital electron of an atom delivering all of its energy to knock the electron out of the atom. The incident photon disappears in the process.

Photon—A quantum of electromagnetic energy (E) whose value is the product of its frequency (ν) in hertz and Planck's constant (h). The equation is: $E = h\nu$.

Population dose—See Collective dose.

Positron—A positively charged electron.

Potential, Ionization—The energy expressed as electron volts (eV) necessary to separate one electron from an atom, resulting in the formation of an ion pair.

Power, Stopping—A measure of the ability of a material to absorb energy from an ionizing particle passing through it; the greater the stopping power, the greater the energy absorbing ability (see Linear Energy Transfer).

Progeny—The decay product or daughter products resulting after a radioactive decay or a series of radioactive decays. The progeny can also be radioactive, and the chain continues until a stable nuclide is formed.

Proton—Elementary nuclear particle with a positive electric charge equal numerically to the charge of the electron and a rest mass of 1.007 mass units.

Quality—A term describing the distribution of the energy deposited by a particle along its track; radiations that produce different densities of ionization per unit intensity are said to have different "qualities."

Quality Factor (Q)—The linear-energy-transfer-dependent factor by which absorbed doses are multiplied to obtain (for radiation protection purposes) a quantity that expresses - on a common scale for all ionizing radiation - the approximate biological effectiveness of the absorbed dose.

Type of radiation	Quality Factor
X, gamma, or beta	1
Alpha particles	20
Neutrons of unknown energy	10
High energy protons	10

Rad—The traditional unit of absorbed dose equal to 100 ergs per gram, or 0.01 joule per kilogram (0.01 Gy) in any medium (see Absorbed Dose).

Radiation—The emission and propagation of energy through space or through a material medium in the form of waves (e.g., the emission and propagation of electromagnetic waves, or of sound and elastic waves). The term radiation or radiant energy, when unqualified, usually refers to electromagnetic radiation. Such radiation commonly is classified according to frequency, as microwaves, infrared, visible (light), ultraviolet, and x and gamma rays (see Photon.) and, by extension, corpuscular emission, such as alpha and beta radiation, neutrons, or rays of mixed or unknown type, as cosmic radiation.

Radiation, Annihilation—Photons produced when an electron and a positron unite and cease to exist. The annihilation of a positron-electron pair results in the production of two photons, each of 0.51 MeV energy.

Radiation, Background—See Background Radiation.

Radiation, Characteristic (Discrete)—Radiation originating from an excited atom after removal of an electron from an atom. The wavelength of the emitted radiation is specific, depending only on the element and particular energy levels involved.

Radiation, External—Radiation from a source outside the body.

Radiation, Internal—Radiation from a source within the body (as a result of deposition of radionuclides in body tissues).

Radiation, Ionizing—Any electromagnetic or particulate radiation capable of producing ions, directly or indirectly, in its passage through matter (see Radiation).

Radiation, Monoenergetic—Radiation of a given type in which all particles or photons originate with and have the same energy.

Radiation, Scattered—Radiation which during its passage through a substance, has been deviated in direction. It may also have been modified by a decrease in energy.

Radiation, Secondary—A particle or ray that is produced when the primary radiation interacts with a material, and which has sufficient energy to produce its own ionization, such as bremsstrahlung or electrons knocked from atomic orbitals with enough energy to then produce ionization (see Delta Rays).

Radiation Weighting Factor (also called Quality Factor)—In radiation protection, a factor (1 for x-rays, gamma rays, beta particles; 20 for alpha particles) weighting the absorbed dose of radiation of a specific type and energy for its effect on tissue.

Radioactive Material—Material containing radioactive atoms.

Radioactivity—Spontaneous nuclear transformations that result in the formation of new elements. These transformations are accomplished by emission of alpha or beta particles from the nucleus or by the capture of an orbital electron. Each of these reactions may or may not be accompanied by a gamma photon.

Radioactivity, Artificial—Man-made radioactivity produced by particle bombardment or nuclear fission, as opposed to naturally occurring radioactivity.

Radioactivity, Induced—Radioactivity produced in a substance after bombardment with neutrons or other particles. The resulting activity is "natural radioactivity" if formed by nuclear reactions occurring in nature and "artificial radioactivity" if the reactions are caused by man.

Radioactivity, Natural—The property of radioactivity exhibited by more than 50 naturally occurring radionuclides.

Radioisotope—An unstable or radioactive isotope of an element that decays or disintegrates spontaneously, emitting radiation.

Radionuclide—Any radioactive isotope of any element. Approximately 5,000 natural and artificial radioisotopes have been identified.

Radiosensitivity—Relative susceptibility of cells, tissues, organs, organisms, or any living substance to the injurious action of radiation. Radiosensitivity and its antonym, radioresistance, are used comparatively, rather than absolutely.

Reference Dose (RfD)—An estimate of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to non-threshold effects such as cancer.

Relative Biological Effectiveness (RBE)—The RBE is a factor used to compare the biological effectiveness of absorbed radiation doses (i.e., rad) due to different types of ionizing radiation. More specifically, it is the experimentally determined ratio of an absorbed dose of a radiation in question to the absorbed dose of a reference radiation (typically ^{60}Co gamma rays or 200 kVp x rays) required to produce an identical biological effect in a particular experimental organism or tissue (see Quality Factor).

Rem—The traditional unit of dose equivalent that is used in the regulatory, administrative, and engineering design aspects of radiation safety practice. The dose equivalent in rem is numerically equal to the absorbed dose in rad multiplied by the quality factor (1 rem is equal to 0.01 sievert).

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Roentgen (R)—A unit of exposure (in air) to ionizing radiation. It is the amount of x or gamma rays required to produce ions carrying 1 electrostatic unit of electrical charge in 1 cubic centimeter of dry air under standard conditions. Named after William Roentgen, a German scientist who discovered x rays in 1895.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Self-Absorption—Absorption of radiation (emitted by radioactive atoms) by the material in which the atoms are located; in particular, the absorption of radiation within a sample being assayed.

Short-Term Exposure Limit (STEL)—The maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily TLV-TWA may not be exceeded.

SI Units—The International System of Units as defined by the General Conference of Weights and Measures in 1960. These units are generally based on the meter/kilogram/second units, with special quantities for radiation including the becquerel, gray, and sievert.

Sickness, Acute Radiation (Syndrome)—The complex symptoms and signs characterizing the condition resulting from excessive exposure of the whole body (or large part) to ionizing radiation. The earliest of these symptoms are nausea, fatigue, vomiting, and diarrhea, and may be followed by loss of hair (epilation), hemorrhage, inflammation of the mouth and throat, and general loss of energy. In severe cases, where the radiation dose is relatively high (over several hundred rad or several gray), death may occur within two to four weeks. Those who survive six weeks after exposure of a single high dose of radiation may generally be expected to recover.

Sievert (Sv)—The SI unit of any of the quantities expressed as dose equivalent. The dose equivalent in sieverts is equal to the absorbed dose, in gray, multiplied by the quality factor (1 sievert equals 100 rem). The sievert is also the SI unit for effective dose equivalent, which is the sum of the products of the dose equivalent to each organ or tissue and its corresponding tissue weighting factor.

Specific-Activity—Radioactivity per unit mass of a radionuclide, expressed, for example, as Ci/gram or Bq/kilogram.

Specific Energy—The actual energy per unit mass deposited per unit volume in a small target, such as the cell or cell nucleus, as the result of one or more energy-depositing events. This is a stochastic quantity as opposed to the average value over a large number of instance (i.e., the absorbed dose).

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Stochastic Effect—A health effect that occurs randomly and for which the probability of the effect occurring, rather than its severity, is assumed to be a linear function of dose without a threshold (also called a nondeterministic effect).

Stopping Power—The average rate of energy loss of a charged particle per unit thickness of a material or per unit mass of material traversed.

Surface-seeking Radionuclide—A bone-seeking internal emitter that deposits and remains on the bone surface for a long period of time, although it may eventually diffuse into the bone mineral. This contrasts with a volume seeker, which deposits more uniformly throughout the bone volume.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Target Theory (Hit Theory)—A theory explaining some biological effects of radiation on the basis that ionization, occurring in a discrete volume (the target) within the cell, directly causes a lesion which subsequently results in a physiological response to the damage at that location. One, two, or more "hits" (ionizing events within the target) may be necessary to elicit the response.

Teratogen—A chemical that causes birth defects.

Threshold Limit Value (TLV®)—The maximum concentration of a substance to which most workers can be exposed without adverse effect. TLV is a term used exclusively by the ACGIH. Other terms used to express similar concepts are the MAC (Maximum Allowable Concentration) and PEL (Permissible Exposure Limits).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Tissue Weighting Factor (W_t)—Organ- or tissue-specific factor by which the equivalent dose is multiplied to give the portion of the effective dose for that organ or tissue. Recommended values of tissue weighting factors are:

Tissue/Organ	Tissue Weighting Factor
Gonads	0.70
Bone marrow (red)	0.12
Colon	0.12
Lung	0.12
Stomach	0.12
Bladder	0.05
Breast	0.05
Liver	0.05
Esophagus	0.05
Thyroid	0.05
Skin	0.01
Bone surface	0.01
Remainder (adrenals, brain, upper large intestine, small intestine, pancreas, spleen, thymus, and uterus)	0.05

Toxic Dose (TD_{50})—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution and elimination of toxic compounds in the living organism.

Toxicosis—A diseased condition resulting from poisoning.

Transformation, Nuclear—The process of radioactive decay by which a nuclide is transformed into a different nuclide by absorbing or emitting particulate or electromagnetic radiation.

Transition, Isomeric—The process by which a nuclide decays to an isomeric nuclide (i.e., one of the same mass number and atomic number) of lower quantum energy. Isomeric transitions (often abbreviated I.T.) proceed by gamma ray and internal conversion electron emission.

Tritium—The hydrogen isotope with one proton and two neutrons in the nucleus (Symbol: ^{3}H). It is radioactive and has a physical half-life of 12.3 years.

Unattached Fraction—That fraction of the radon daughters, usually ^{218}Po and ^{214}Po, which has not yet attached to a dust particle or to water vapor. As a free atom, it has a high probability of being exhaled and not retained within the lung. It is the attached fraction which is primarily retained.

Uncertainty Factor (UF)—A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

Units, Prefixes—Many units of measure are expressed as submultiples or multiples of the primary unit (e.g., 10^{-3} curie is 1 mCi and 10^{3} becquerel is 1 kBq).

Factor	Prefix	Symbol	Factor	Prefix	Symbol
10^{-18}	atto	A	10^{3}	kilo	k
10^{-15}	femto	F	10^{6}	mega	M
10^{-12}	pico	p	10^{9}	giga	G
10^{-9}	nano	N	10^{12}	tera	T
10^{-6}	micro	M	10^{15}	peta	P
10^{-3}	milli	M	10^{18}	exa	E
10^{-2}	centi	C			

Units, Radiological—

Units	Equivalents
Becquerel* (Bq)	1 disintegration per second = 2.7×10^{-11} Ci
Curie (Ci)	3.7×10^{10} disintegrations per second = 3.7×10^{10} Bq
Gray* (Gy)	1 J/kg = 100 rad
Rad (rad)	100 erg/g = 0.01 Gy
Rem (rem)	0.01 sievert
Sievert* (Sv)	100 rem

*International Units, designated (SI)

Working Level (WL)—Any combination of short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^{5} MeV of potential alpha energy.

Working Level Month (WLM)—A unit of exposure to radon daughters corresponding to the product of the radon daughter concentration in Working Level (WL) and the exposure time in nominal months (1 nominal month = 170 hours). Inhalation of air with a concentration of 1 WL of radon daughters for 170 working hours results in an exposure of 1 WLM.

X rays—Penetrating electromagnetic radiations whose wave lengths are very much shorter than those of visible light. They are usually produced by bombarding a metallic target with fast electrons in a high vacuum. X rays (called characteristic x rays) are also produced when an orbital electron falls from a high energy level to a low energy level.

Zero-Threshold Linear Hypothesis (or No-Threshold Linear Hypothesis)—The assumption that a dose-response curve derived from data in the high dose and high dose-rate ranges may be extrapolated through the low dose and low dose range to zero, implying that, theoretically, any amount of radiation will cause some damage.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cobalt
CAS Number: 10026-24-1
Date: March 2004
Profile Status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Key to figure: 26
Species: human

Minimal Risk Level: $1x10^{-4}$ [ ] mg/kg/day [ ] ppm [x] mg/m^3

Reference:

Nemery B, Casier P, Roosels D, et al. 1992. Survey of cobalt exposure and respiratory health in diamond polishers. Am Rev Respir Dis 145:610-616.

Experimental design:

Nemery et al. (1992) conducted a cross-sectional study of cobalt exposure and respiratory effects in diamond polishers. The study group was composed of 194 polishers working in 10 different workshops. In two of these workshops (#1, 2), the workers used cast iron polishing disks almost exclusively, and in the others, they used cobalt-containing disks primarily. The number of subjects from each workshop varied from 6 to 28 and the participation rate varied from 56 to 100%. The low participation in some workshops reflects the fact that only workers who used cobalt disks were initially asked to be in the study, rather than a high refusal rate (only eight refusals were documented). More than a year after the polishing workshops were studied, an additional three workshops with workers engaged in sawing diamonds, cleaving diamonds, or drawing jewelry were studied as an unexposed control group (n=59 workers). Subjects were asked to fill out a questionnaire regarding employment history, working conditions, medical history, respiratory symptoms, and smoking habits, to give a urine sample for cobalt determination, and to undergo a clinical examination and lung function tests. Both area air samples and personal air samples were collected (always on a Thursday). Sampling for area air determinations started 2 hours after work began and continued until 1 hour before the end of the work day. Personal air samples were collected from the breathing zone of a few workers per workshop for four successive 1-hour periods. Air samples were analyzed for cobalt and iron. In addition, personal air samplers were used to sample the air 1 cm above the polishing disks. These samples were analyzed for the entire spectrum of mineral and metallic compounds. Air samples were not obtained at one of the polishing workshops (#4), but this workshop was reported to be almost identical to an adjoining workshop (#3) for which samples were obtained. Urinary cobalt levels were similar between workers in these two workshops, so exposure was considered to be similar as well. It is important to note that the study authors suggested that the available methods used for air sampling may have underestimated the exposure levels.

There was a good correlation (R=0.92) between the results of area and personal air sampling, with area air sampling reporting lower concentrations than personal air samples in all workshops except one (#9) (Nemery et al. 1992). In this workshop, personal air samples appeared to be artificially low in comparison to area air samples and urinary cobalt levels of the workers. When this workshop was excluded, there was a good correlation (R=0.85–0.88) between urinary cobalt and cobalt in the air. Based on urinary cobalt levels, the concentration of cobalt expected in personal air samples from workshop #9 was about 45 $\mu g/m^3$ (the mean value actually reported was 6 $\mu g/m^3$). The polishing workshops were divided into two groups: those with low exposure to cobalt (#1–5, n=102) and those with high exposure to

cobalt (#6–10, n=91). Mean cobalt exposure concentrations were 0.4, 1.6, and 10.2 µg/m^3 by area air sampling and 0.4, 5.3, and 15.1 µg/m^3 by personal air sampling in the control, low-exposure, and high-exposure groups, respectively. The inclusion of the apparently biased personal air samples from workshop #9 means that the reported mean cobalt exposure in the high-exposure group obtained by personal air sampling (15.1 µg/m^3) may be lower than the true value. Air concentrations of iron were highest in the two polishing workshops that used iron disks and the sawing workshop (highest value =62 µg/m^3), and were not correlated with cobalt levels. Analysis of samples taken near the disks showed the presence of cobalt, with occasional traces of copper, zinc, titanium, manganese, chromium, silicates, and silicon dioxide. No tungsten was detected. There is a possibility that some workers had previously been exposed to asbestos, since pastes containing asbestos had been used in the past to glue the diamonds onto holders. However, the degree of asbestos exposure had apparently been insufficient to produce functional impairment. The researchers considered cobalt to be the only relevant exposure. Smoking habits were similar in workers from the high-exposure, low-exposure, and control groups. Duration of exposure was not discussed.

Effects noted in study and corresponding doses:

Workers in the high-exposure group were more likely than those in the other groups to complain about respiratory symptoms; the prevalences of eye, nose, and throat irritation and cough, and the fraction of these symptoms related to work, were significantly increased in the high-exposure group (Nemery et al. 1992). Workers in the high-exposure group also had significantly reduced lung function compared to controls and low-exposure group workers, as assessed by FVC (forced vital capacity), FEV_1 (forced expiratory volume in 1 second), MMEF (forced expiratory flow between 25 and 75% of the FVC), and mean PEF (peak expiratory flow rate), although the prevalence of abnormal values did not differ significantly between exposure categories. Results in the low-exposure group did not differ from controls. Two-way analysis of variance was used to show that the effect on spirometric parameters in the high exposure group was present in both men and women. Women seemed to be affected more than men, but the interaction between exposure and sex was not significant. Smoking was found to exert a strong effect on lung function, but lung function level remained negatively correlated with exposure to cobalt, independently of smoking.

Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL
Nemery et al. (1992) established a NOAEL of 0.0053 mg cobalt/m^3 for effects on pulmonary function (decreased values upon spirometric examination).

Uncertainty Factors used in MRL derivation:

[x] 1 [ ] 3 [ ] 10 (for use of a NOAEL)
[x] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

The chronic inhalation MRL for cobalt is derived as follows:

$MRL = NOAEL_{[ADJ]} \div UF$
$MRL = 0.0013$ mg cobalt/$m^3 \div 10$
$MRL = 1x10^{-4}$ mg cobalt/m^3

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

Was a conversion used from intermittent to continuous exposure? If so, explain:

0.0053 mg cobalt/m^3 * (8 hours/24 hours) * (5 days/7 days) = 0.0013 mg cobalt/m^3 continuous exposure.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information which lend support to this MRL:

Necrosis and inflammation of the respiratory tract epithelium (larynx, trachea, bronchioles, nasal turbinates) were reported in rats exposed to 19 mg cobalt/m^3 and mice exposed to 1.9 mg cobalt/m^3 (and above) as cobalt sulfate over 16 days (NTP 1991). Exposure of rats and mice to cobalt as cobalt sulfate for 13 weeks resulted in adverse effects on all parts of the respiratory tract, with the larynx being the most sensitive part (NTP 1991). At concentrations of ≥0.11 mg cobalt/m^3, rats and mice had squamous metaplasia of the larynx. Histiocytic infiltrates in the lung were also reported at similar levels in both the rats and mice. In rats, chronic inflammation of the larynx was found at ≥0.38 mg cobalt/m^3, and more severe effects on the larynx, nose, and lung were reported at higher exposures. In mice, acute inflammation of the nose was found at ≥1.14 mg cobalt/m^3, and more severe effects on the larynx, nose, and lung were reported at higher exposures.

Exposure of rats and mice to aerosols of cobalt (as cobalt sulfate) at concentrations from 0.11 to 1.14 mg cobalt/m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice (NTP 1998). Squamous metaplasia of the larynx occurred in rats and mice at exposure concentrations of ≥0.11 mg cobalt/m^3, with severity of the lesion increasing with increased exposure concentration. Hyperplastic lesions of the nasal epithelium occurred in rats at concentrations of ≥0.11 mg cobalt/m^3, and in mice at concentrations of ≥0.38 mg cobalt/m^3. Both sexes of rats had greatly increased incidences (>90% incidence) of alveolar lesions at all exposure levels, including inflammatory changes, fibrosis, and metaplasia. Similar changes were seen in mice at all exposure levels, though the changes in mice were less severe.

Both studies by NTP (1991, 1998) failed to define a NOAEL, with the lowest concentration examined (0.11 mg/m^3) a LOAEL for a variety of respiratory effects. If an MRL were to be calculated based upon these studies, it would be as follows:

Duration adjustment: 0.11 mg cobalt/m^3 * (6 h/24 h) * (5 d/7 d) = 0.020 mg cobalt/m^3 continuous exposure.
Calculation of human equivalent concentration:
If fractional depositions in humans and animals are assumed to be equal, then:
$RDDR = V_E(animal)/S_{ET}(animal) \div V_E(human)/S_{ET}(human)$ = 0.24 m^3/day / 15 cm^2 ÷ 20 m^3/day / 200 cm^2
RDDR = 0.16
$LOAEL_{[HEC]}$ = LOAEL[ADJ] * RDDR
= 0.020 mg cobalt/m^3 * 0.16 = 0.0032 mg cobalt/m^3

To the $LOAEL_{[HEC]}$, an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation, and 10 for human variability) to derive an MRL of $1x10^{-5}$ mg/m^3. This number is an order of magnitude lower than the number derived from the Nemery et al. (1992) data, reflecting the fact that it is derived from animal data, not from a human study, and is based on a LOAEL, not a NOAEL. As the Nemery et al. (1992) study was a well-performed study in humans that defined a NOAEL and LOAEL, it was selected as the basis for derivation of the MRL.

Agency Contact (Chemical Manager): Obaid Faroon D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cobalt
CAS Number: 10026-24-1
Date: March 2004
Profile Status: Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 30
Species: human

Minimal Risk Level: $1x10^{-4}$ [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference:

Davis, J.E. and Fields, J.P. 1958. Experimental production of polycythemia in humans by administration of cobalt chloride. Proc Soc Exp Biol Med 99:493-495.

Experimental design:

Six apparently normal men, ages 20–47, were administered a daily dose of cobalt chloride, administered as a 2% solution diluted in either water or milk, for up to 22 days. Five of the six received 150 mg cobalt chloride per day for the entire exposure period, while the sixth was started on 120 mg/day and later increased to 150 mg/day. Blood samples were obtained daily from free-flowing punctures of fingertips at least 2 hours after eating, and at least 15 hours after the last dosage of cobalt. Blood was analyzed for red blood cell counts, hemoglobin percentage, leukocyte counts, reticulocyte percentages, and thrombocyte counts.

Effects noted in study and corresponding doses:

Exposure to cobalt resulted in the development of polycythemia in all six subjects, with increases in red blood cell numbers ranging from 0.5 to 1.19 million (~16–20% increase above pre-treatment levels). Polycythemic erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. Hemoglobin levels were also increased by cobalt treatment, though to a lesser extent than the erythrocyte values, with increases of 6–11% over pretreatment values. In five of the six subjects, reticulocyte levels were elevated, reaching at least twice the pre-experiment values. Thrombocyte and total leukocyte counts did not deviate significantly from pretreatment values.

Dose end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

Davis and Fields (1958) identified a LOAEL of 150 mg cobalt chloride per day for increased levels of erythrocytes in volunteers. 150 mg cobalt chloride/day corresponds to ~1 mg Co/kg/day, assuming a reference body weight of 70 kg. Available animal studies, presented below, lend support to this LOAEL, having demonstrated LOAEL values within half an order of magnitude of that identified by Davis and Fields (1958).

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [x] 10 (for use of a LOAEL)

[x] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

The intermediate oral MRL for cobalt is derived as follows:

MRL = LOAEL ÷ UF
MRL = 1 mg cobalt/kg-day ÷ 100
MRL = $1x10^{-2}$ mg cobalt/kg-day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

Was a conversion used from intermittent to continuous exposure? If so, explain: No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Other additional studies or pertinent information that lend support to this MRL:

No other studies of the effect of intermediate oral cobalt exposure on erythrocyte levels in healthy human subjects were identified in a search of the literature. Treatment of pregnant women for 90 days with 0.5–0.6 mg cobalt/kg/day as cobalt chloride did not prevent the reduction in hematocrit and hemoglobin levels often found during pregnancy (Holly 1955). However, treatment of anephric patients (with resulting anemia) with 0.16–1.0 mg cobalt/kg/day daily as cobalt chloride for 3–32 weeks resulted in increased levels of circulating erythrocytes and a decreased need for transfusions (Duckham and Lee 1976b; Taylor et al. 1977). While these studies provide additional evidence that exposure to cobalt can increase erythrocyte levels in humans, the fact that the patients were anephric makes definitive interpretation of the results more difficult.

Roche and Layrisse (1956) exposed volunteers to similar levels (150 mg $CoCl_2$/day) of cobalt, and reported a reversible decrease in uptake of ^{131}I by the thyroid. The decreased uptake is believed to result from cobalt blocking the organic binding of iodine (Paley et al. 1958). This observation adds support to the choice of effect level, as a similar exposure resulted in measurable effects in volunteers, though whether the changes in iodine uptake operate through the same mechanisms as the changes in erythrocyte numbers has not been determined.

Stanley et al. (1947) exposed groups (n=4, 6 for controls) of 6 Sprague-Dawley rats to 0, 0.62, 2.5, or 10 mg cobalt/kg/day (0, 2.5, 10, or 40 mg/kg-day of $CoCl_2 \cdot 6H_2O$) in gelatin capsules for 8 weeks. Blood counts and hemoglobin levels were examined at the beginning of the experiment and at 2-week intervals. Rats exposed to 0.62 mg cobalt/kg-day showed no change in erythrocyte number. At 2.5 mg cobalt/kg-day, a progressive increase in erythrocyte number was seen, increasing up to a maximum of 17% above pretreatment values on week 6. At the highest exposure level, a progressive increase in erythrocyte numbers was seen, reaching 29% above pretreatment values at 8 weeks of exposure. Statistical analyses of the group means were not provided, and the study provided only mean values of the measurements, precluding statistical analysis. However, if a 10% change is assumed to be an effect level, exposure to 2.5 mg cobalt/kg-day was the LOAEL for this study, with a NOAEL of 0.62 mg cobalt/kg-day.

Krasovskii and Fridyland (1971) exposed groups of rats to 0, 0.05, 0.5, or 2.5 mg Co/kg/day for up to 7 months. In the 2.5 mg/kg-day group, a persistent increase in erythrocyte levels was seen. The increase was transient in the 0.5 mg/kg/day rats, and was not present in rats exposed to 0.05 mg/kg/day. However, numerical data were not presented and statistical significance was not reported.

A number of other studies in animals have reported increases in erythrocyte levels following intermediate oral administration of cobalt compounds (see the LSE table for further details of these studies). However, the majority of them have considerable methodological limitations, including examination of either very high exposure levels or only one exposure level, limited reporting of results, or limited or no statistical analysis.

Whether or not polycythemia, a condition wherein an excess of erythrocytes is produced, constitutes an adverse effect is open to interpretation. At the levels seen in the available studies, and in particular in the Davis and Fields (1958) study, the subjects would be expected to be asymptomatic. However, data on the long-term effects of elevated erythrocyte levels are not available. As such, this end point was considered an adverse effect as a health-protective assumption, and was utilized as a critical end point for MRL derivation.

Agency Contact (Chemical Manager): Obaid Faroon D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Radioactive Cobalt
CAS number: Multiple
Date:March 2004
Profile status: Final
Route: [ ] Inhalation [ ] Oral [x] External
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Species: Human

Minimal Risk Level: 4 [ ] mg/kg/day [ ] ppm [ ] mg/m^3 [x] mSv (400 mrem)

References:

Schull WJ, Otake M, Yoshimaru H. 1988. Effect on intelligence test score of prenatal exposure to ionizing radiation in Hiroshima and Nagasaki: A comparison of the T65DR and DS86 dosimetry systems. Radiation Effects Research Foundation (RERF) Technical Report No. 3-88. Hirroshima, Japan. NTIS Report Number: DE89-906462.

Burt C. 1966. The genetic determination of differences in intelligence: A study of monozygotic twins reared together and apart. Brit J Psychol 57(1&2):137-153.

Experimental design:

Schull et al. (1988) study: Schull et al. (1988) evaluated the quantitative effect of exposure to ionizing radiation on the developing fetal and embryonic human brain. The end point measured was changes in intelligence test scores. The effects on individuals exposed *in utero* to the atomic bombing of Hiroshima and Nagasaki were based on the original PE86 samples (n=1,759; data on available intelligence testing) and a clinical sample (n=1,598). The original PE86 sample included virtually all prenatally exposed individuals who received tissue-absorbed doses of 0.50 Gy or more. There were many more individuals in the dose range 0–0.49 Gy in the PE86 sample than in the clinical sample. The clinical sample does not include children prenatally exposed at distances between 2,000 and 2,999 m in Hiroshima and Nagasaki. Children exposed at greater distances or not present in the city were selected as controls. In 1955–1956, Tanaka-B (emphasis on word-sense, arithmetic abilities, and the like, which were associated with the more subtle processing of visual clues than their simple recognition and depended more on connectedness) and the Koga (emphasis on perception of spatial relationships) intelligence tests were conducted in Nagasaki and the Koga test in Hiroshima.

Burt (1966) study: This study determined differences in intelligence in monozygotic twins reared together (n=95) and apart (n=53). All tests conducted in school consisted of (1) a group test of intelligence containing both non-verbal and verbal items, (2) an individual test (the London Revision of the Terman-Binet Scale) used primarily for standardization and for doubtful cases, and (3) a set of performance tests, based on the Pitner-Paterson tests and standardization. The methods and standard remained much the same throughout the study. Some of the reasons for separation of the twins were given as follows: death of the mother (n=9), unable to bring them up properly, mother's poor health (n=12), unmarried (n=6), and economic difficulties. The children were brought up by parents or foster parents (occupation ranged from unskilled to professional). IQ scores in the study group ranged from 66 to 137. The standard deviation of the group of separated monozygotic twins was reported at 15.3 as compared to 15.0 of ordinary siblings. Twins brought up in different environments were compared with those brought up in similar circumstances.

Effects noted in study and corresponding doses:

Schull et al. (1986) study: No evidence of radiation-related effect on intelligence was observed among individuals exposed within 0–7 weeks after fertilization or in the 26th or subsequent weeks. The highest risk of radiation damage to the embryonic and fetal brain occurs 8–15-weeks after fertilization under both dosimetric systems. The regression of intelligence score on estimated DS86 uterine absorbed dose is linear with dose, and the diminution in intelligence score is 21–29 points per Gy for the 8–15-week group and 10–26 points per Gy for the 16–25-week group. The results for 8–15 weeks applies regardless whether or not the mentally retarded individuals were included. The cumulative distribution of test scores suggested a progressive shift downwards in individual scores with increasing exposure. The mean IQ scores decrease significantly and systematically with uterine or fetal tissue dose within the 8–15- and 16–25-week groups.

In summary, analysis of intelligence test scores at 10–11 years of age of individuals exposed prenatally showed that:

- There is no evidence of a radiation-related effect on intelligence scores among those individuals exposed within 0–7 weeks of fertilization or in the 26th week of gestation and beyond;
- The cumulative distribution of test scores suggests a progressive shift downwards in intelligence scores with increasing exposure to ionizing radiation (dose-response relationship).
- The most sensitive group was the 8–15 weeks exposure group. The regression in intelligence scores was found to be linear, with 1 Gy dose resulting in a 21–29 point decline in intelligence scores.
- There was no indication of groups of individuals with differing sensitivities to radiation.

Burt (1966) study: The average intelligence of the twins measured on a conventional IQ scale (SD=15) was 97.8 for the separated monozygotes, 98.1 for monozygotes brought up together, 99.3 for the dizygotes as compared with 100.2 for the siblings, and 100.0 for the population as a whole. The difference of 0.3 IQ point between the separated and unseparated identical twins is considered a NOAEL for this study.

Dose endpoint used for MRL derivation:

[x] NOAEL [ ] LOAEL 0.3 IQ point reduction in twins, between those raised together and those raised apart.

Uncertainty factors (UF) used in MRL derivation:

[x] 1 [ ] 3 [ ] 10 (for use of a NOAEL)
[x] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [x] 3 [ ] 10 (for human variability/sensitive population)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? If so, explain: No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL:

Husen (1959) reported a study involving 269 pairs of Swedish monozygotic (identical) twins where the intrapair IQ difference was 4 IQ points for a combination of twins raised together and apart. This is somewhat lower than the value of 7 IQ points for identical twins raised apart, and just larger than the range of IQ scores for Washington, DC children repetitively tested (Jacobi and Glauberman 1995).

Supporting evidence for the acute MRL is provided by Jacobi and Glauberman (1995). Children in the 1st, 3rd, and 5th grades born in Washington, DC were tested, and average IQ levels of 94.2, 97.6, and 94.6, respectively, were reported. The range of 3.4 IQ points is considered to be a LOAEL for this study, which, if used for MRL derivation, would yield an MRL of 0.004 Sv (3.4 IQ points x 1 Sv/25 IQ points ÷ 30 [10 for use of a LOAEL and 3 for a sensitive population]).

Additional supporting evidence for the acute MRL is provided by Berger et al. 1997, in a case study of accidental radiation injury to the hand. A Mexican engineer suffered an accidental injury to the hand while repairing an x-ray spectrometer. The day after the accident, his symptoms included a tingling sensation and itching in the index and middle fingers. On days 4 and 7, a "pinching" sensation, swelling, and slight erythema were observed. By day 7, the tip of his index fingers was erythematous and a large blister developed with swelling on other fingers. On day 10, examination by a physician showed that the lesions had worsened and the fingers and palms were discolored. On day 10, he was admitted to the hospital where hyperbaric oxygen therapy was administered without success. One month after the accident, the patient entered the hospital again with pain, discoloration, and desquamation of his hand. Clinical examination showed decreased circulation in the entire hand, most notably in the index and middle finger. Total white blood count decreased to 3,000/µL (normal range 4,300–10,800/µL). Cytogenic studies of peripheral blood lymphocytes revealed four dicentrics, two rings, and eight chromosomal fragments in the 300 metaphases studied. The estimated whole body dose was reported to be 0.382 Gy (38.2 rad). This dose is a potential LOAEL for acute ionizing radiation and would yield an MRL of 0.004 Sv (0.38 Sv ÷100 [10 for use of LOAEL and 10 for sensitive human population]).

The USNRC set a radiation exposure limit of 0.5 rem (50 mSv) for pregnant working women over the full gestational period (USNRC 1991). For the critical gestational period of 8–15 weeks, ATSDR believes that the conservative acute MRL of 4 mSv is consistent with the USNRC limit and could be applied to either acute (0–14-day) or intermediate (15–365-day) exposure periods.

Calculations

Given: 0.3 IQ point is a NOAEL. A 1 Sv dose results in a 25 IQ point reduction (range=21–29 points; mean=25) and provides a conversion factor from IQ prediction to radiation dose. Assume that the radiation dose and the subsequent reduction in IQ is a linear relationship.
MRL = NOAEL x CF ÷ UF
MRL = 0.3 x 1/25 ÷ 3
MRL = 0.004 Sv = 4 mSv (400 mrem)

Agency Contact (Chemical Manager): Obaid Faroon D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Radioactive Cobalt
CAS Number: Multiple
Date: March 2004
Profile Status: Final
Route: [ ] Inhalation [ ] Oral [X] External
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Species: Human

Minimal Risk Level: 1 [ ] mg/kg/day [ ] ppm [ ] mg/m^3 [X] mSv/year (100 mrem/year)

Reference: BEIR V. 1990. Health effects of exposure to low levels of ionizing radiation. Committee on the Biological Effects of Ionizing Radiations, National Research Council. National Academy Press. Washington, DC.

Experimental design: Not applicable

Effects noted in study and corresponding doses: No individual studies were identified that could be used to base a chronic-duration external exposure MRL that did not result in a cancer-producing end point. However, two sources of information were identified that did provide doses of ionizing radiation that have not been reported to be associated with detrimental effects (NOAELs). These sources provide estimates of background levels of primarily natural sources of ionizing radiation that have not been implicated in producing cancerous or noncancerous toxicological endpoints. BEIR V states that the average annual effective dose to the U.S. population is 3.6 mSv/year. A total annual effective dose equivalent of 3.6 mSv (360 mrem)/year to members of the U.S. population is obtained mainly by naturally occurring radiation from external sources, medical uses of radiation, and radiation from consumer products. The largest contribution (82%) is from natural sources, two-thirds of which is from naturally occurring radon and its decay products. Specific sources of this radiation are demonstrated in Table A-1.

The annual dose of 3.6 mSv per year has not been associated with adverse health effects or increases in the incidences of any type of cancers in humans or other animals.

Dose and end point used for MRL derivation: 3.6 mSv/year

[X] NOAEL [ ] LOAEL 3.6 mSv/year

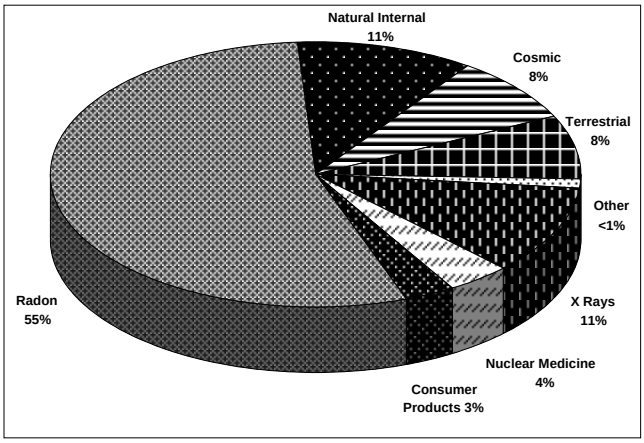
Uncertainty Factors used in MRL derivation:

[X] 1 [ ] 3 [ ] 10 (for use of a NOAEL)
[X] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [X] 3 [ ] 10 (for human variability)

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

Table A-1. Average Annual Effective Dose Equivalent from Ionizing Radiation to a Member of the U.S. Population[a]

	Effective dose equivalent	
Source	mSv	Percent of total dose
Natural		
Radon[b]	2.0	55
Cosmic	0.27	8.0
Terrestrial	0.28	8.0
Internal	0.39	11
Total natural	3.0	82
Artificial		
Medical		
X-ray	0.39	11
Nuclear	0.14	4.0
Consumer products	0.10	3.0
Other		
Occupational	<0.01	<0.3
Nuclear fuel cycle	<0.01	<0.03
Fallout	<0.01	<0.03
Miscellaneous[c]	<0.01	<0.03
Total artificial	0.63	18
Total natural and artificial	3.6	100



[a]Adapted from BEIR V, Table 1-3 , page 18.
[b]Dose equivalent to bronchi from radon daughter products
[c]DOE facilities, smelter, transportation, etc.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information which lend support to this MRL: ICRP has developed recommended dose limits for occupational and public exposure to ionizing radiation sources. The ICRP recommends limiting public exposure to 1 mSv/year (100 mrem/year), but does note that values at high altitudes above sea level and in some geological areas can sometimes be twice that value (≥2 mSv). In Annex C of ICRP 60, the commission provides data that suggests increasing the dose from 1 mSv to 5 mSv results in a very small, but detectable, increase in age-specific human mortality rate. ICRP states that the value of 1 mSv/year was chosen over the 5 mSv value because 5 mSv/year (500 mrem/year) causes this increase in age specific mortality rate, and 1 mSv/year (100 mrem/year) is typical of the annual effective dose from background, less radon (ICRP 1991). The 1 mSv estimate may underestimate the annual exposure to external sources of ionizing radiation to the U.S. population, as it does not include radiation from radon. Conversely, the 5 mSv estimate may be high, in that increases in mortality rate been reported. The most useful estimate appears to be the BEIR V estimate of 3.6 mSv, in that it accounts for an annual exposure to radon, is specific to the U.S. population, has not been associated with increases mortality, and it falls short of the 5 mSv value associated with small increases in human mortality.

Calculations:

$MRL = NOAEL_{(ADJ)} \div UF$
MRL = 3.6 mSv/year ÷ 3
MRL = 1.20 mSv/year
MRL = 1.0 mSv/year =100 mrem/year above background

Agency Contact (Chemical Manager): Obaid Faroon D.V.M., Ph.D.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.10, "Interactions with Other Substances," and Section 3.11, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.5, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38r is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

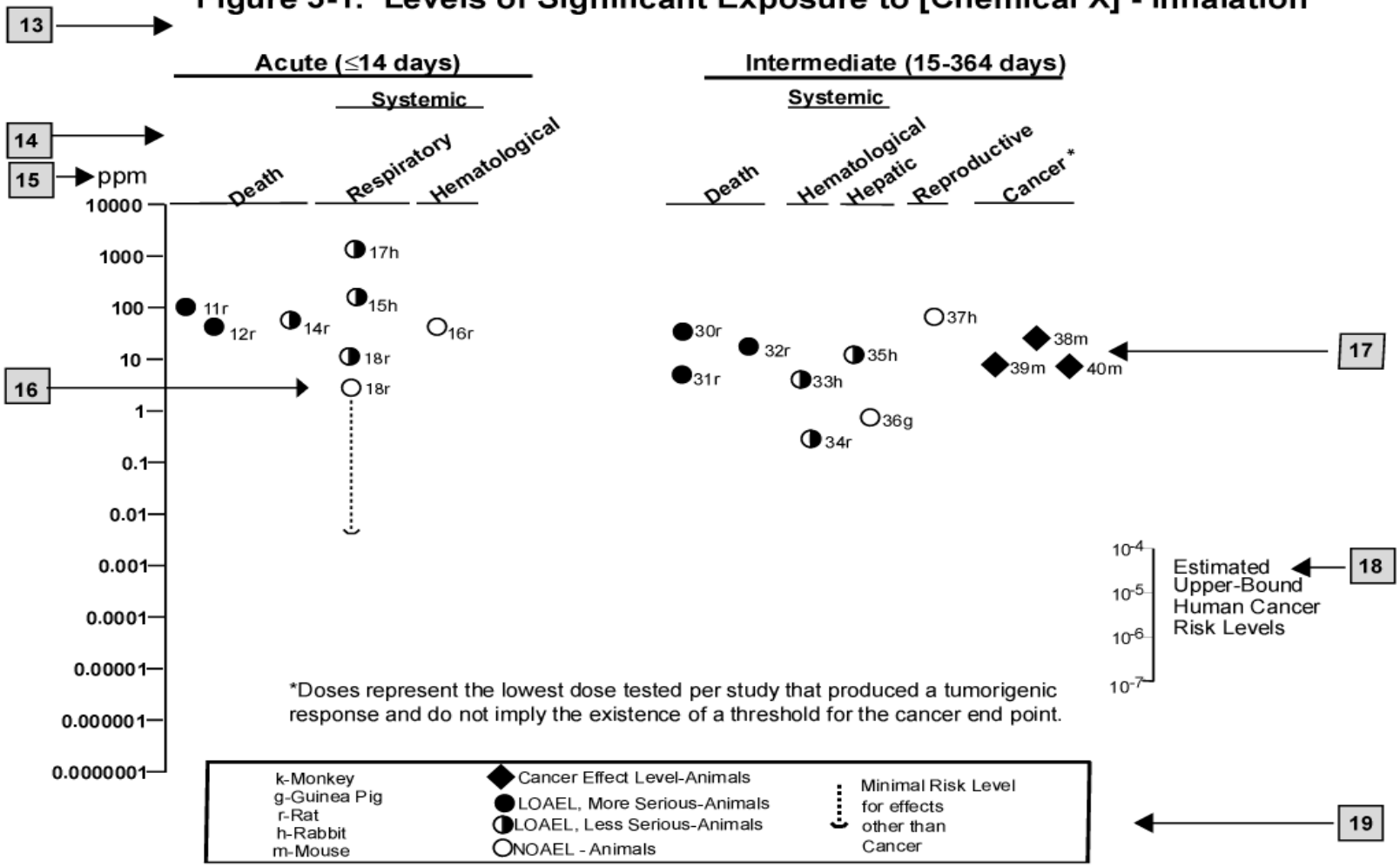
1 → **TABLE 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer						11	
						↓	
38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → a The number corresponds to entries in Figure 3-1.
b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5x10-3 ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

Some terms are generic and may not be used in this profile.

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALI	annual limit on intake
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DAC	derived air concentration
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense

DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid

MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration

OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	United States Nuclear Regulatory Commission
VOC	volatile organic compound

WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. OVERVIEW OF BASIC RADIATION PHYSICS, CHEMISTRY, AND BIOLOGY

Understanding the basic concepts in radiation physics, chemistry, and biology is important to the evaluation and interpretation of radiation-induced adverse health effects and to the derivation of radiation protection principles. This appendix presents a brief overview of the areas of radiation physics, chemistry, and biology and is based to a large extent on the reviews of Mettler and Moseley (1985), Hobbs and McClellan (1986), Eichholz (1982), Hendee (1973), Cember (1996), and Early et al. (1979).

D.1 RADIONUCLIDES AND RADIOACTIVITY

The substances we call elements are composed of atoms. Atoms in turn are made up of neutrons, protons and electrons: neutrons and protons in the nucleus and electrons in a cloud of orbits around the nucleus. Nuclide is the general term referring to any nucleus along with its orbital electrons. The nuclide is characterized by the composition of its nucleus and hence by the number of protons and neutrons in the nucleus. All atoms of an element have the same number of protons (this is given by the atomic number) but may have different numbers of neutrons (this is reflected by the atomic mass numbers or atomic weight of the element). Atoms with different atomic mass but the same atomic numbers are referred to as isotopes of an element.

The numerical combination of protons and neutrons in most nuclides is such that the nucleus is quantum mechanically stable and the atom is said to be stable, i.e., not radioactive; however, if there are too few or too many neutrons, the nucleus is unstable and the atom is said to be radioactive. Unstable nuclides undergo radioactive transformation, a process in which a neutron or proton converts into the other and a beta particle is emitted, or else an alpha particle is emitted. Each type of decay is typically accompanied by the emission of gamma rays. These unstable atoms are called radionuclides; their emissions are called ionizing radiation; and the whole property is called radioactivity. Transformation or decay results in the formation of new nuclides some of which may themselves be radionuclides, while others are stable nuclides. This series of transformations is called the decay chain of the radionuclide. The first radionuclide in the chain is called the parent; the subsequent products of the transformation are called progeny, daughters, or decay products.

In general there are two classifications of radioactivity and radionuclides: natural and artificial (man-made). Naturally-occurring radioactive materials (NORMs) exist in nature and no additional energy is necessary to place them in an unstable state. Natural radioactivity is the property of some naturally occurring, usually heavy elements, that are heavier than lead. Radionuclides, such as radium and uranium, primarily emit alpha particles. Some lighter elements such as carbon-14 and tritium (hydrogen-3) primarily emit beta particles as they transform to a more stable atom. Natural radioactive atoms heavier than lead cannot attain a stable nucleus heavier than lead. Everyone is exposed to background radiation from naturally-occurring radionuclides throughout life. This background radiation is the major source of radiation exposure to man and arises from several sources. The natural background exposures are frequently used as a standard of comparison for exposures to various artificial sources of ionizing radiation.

Artificial radioactive atoms are produced either as a by-product of fission of uranium or plutonium atoms in a nuclear reactor or by bombarding stable atoms with particles, such as neutrons or protons, directed at the stable atoms with high velocity. These artificially produced radioactive elements usually decay by emission of particles, such as positive or negative beta particles and one or more high energy photons (gamma rays). Unstable (radioactive) atoms of any element can be produced.

Both naturally occurring and artificial radioisotopes find application in medicine, industrial products, and consumer products. Some specific radioisotopes, called fall-out, are still found in the environment as a result of nuclear weapons use or testing.

D.2 RADIOACTIVE DECAY

D.2.1 Principles of Radioactive Decay

The stability of an atom is the result of the balance of the forces of the various components of the nucleus. An atom that is unstable (radionuclide) will release energy (decay) in various ways and transform to stable atoms or to other radioactive species called daughters, often with the release of ionizing radiation. If there are either too many or too few neutrons for a given number of protons, the resulting nucleus may undergo transformation. For some elements, a chain of daughter decay products may be produced until stable atoms are formed. Radionuclides can be characterized by the type and energy of the radiation emitted, the rate of decay, and the mode of decay. The mode of decay indicates how a parent compound undergoes transformation. Radiations considered here are primarily of nuclear origin, i.e., they arise from nuclear excitation, usually caused by the capture of charged or uncharged nucleons by a nucleus, or by the radioactive decay or transformation of an unstable nuclide. The type of radiation may be categorized as charged or uncharged particles, protons, and fission products) or electromagnetic radiation (gamma rays and x rays). Table D-1 summarizes the basic characteristics of the more common types of radiation encountered.

D.2.2 Half-Life and Activity

For any given radionuclide, the rate of decay is a first-order process that is constant, regardless of the radioactive atoms present and is characteristic for each radionuclide. The process of decay is a series of random events; temperature, pressure, or chemical combinations do not effect the rate of decay. While it may not be possible to predict exactly which atom is going to undergo transformation at any given time, it is possible to predict, on average, the fraction of the radioactive atoms that will transform during any interval of time.

The *activity* is a measure of the quantity of radioactive material. For these radioactive materials it is customary to describe the activity as the number of disintegrations (transformations) per unit time. The unit of activity is the curie (Ci), which was originally related to the activity of one gram of radium, but is now defined as that quantity of radioactive material in which there are:

1 curie (Ci) = 3.7×10^{10} disintegrations (transformations)/second (dps) or 2.22×10^{12} disintegrations (transformations)/minute (dpm).

The SI unit of activity is the becquerel (Bq); 1 Bq = that quantity of radioactive material in which there is 1 transformation/second. Since activity is proportional to the number of atoms of the radioactive material, the quantity of any radioactive material is usually expressed in curies, regardless of its purity or concentration. The transformation of radioactive nuclei is a random process, and the number of transformations is directly proportional to the number of radioactive atoms present. For any pure radioactive substance, the rate of decay is usually described by its radiological half-life, T_R, i.e., the time it takes for a specified source material to decay to half its initial activity. The specific activity is the activity of a radionuclide per mass of that radionuclide. If properly qualified, it can refer to activity per unit mass of related materials, such as the element itself or a chemical compound labeled with the radionuclide. The higher the specific activity of a radioisotope, the faster it is decaying.

The activity of a radionuclide at time t may be calculated by:

$$A = A_o e^{-0.693t/Trad}$$

where A is the activity in dps or curies or becquerels, A_o is the activity at time zero, t is the time at which measured, and T_{rad} is the radiological half-life of the radionuclide (T_{rad} and t must be in the same units of time). The time when the activity of a sample of radioactivity becomes one-half its original value is the radioactive half-life and is expressed in any suitable unit of time.

Table D-1. Characteristics of Nuclear Radiations

Radiation	Rest mass[a]	Charge	Typical energy range	Path length[b]		Comments
				Air	Solid	
Alpha (α)	4.00 amu	+2	4–10 MeV	5–10 cm	25–80 μm	Identical to ionized He nucleus
Negatron (β^-)	$5.48x10^{-4}$ amu; 0.51 MeV	–1	0–4 MeV	0–10 m	0–1 cm	Identical to electron
Positron (β^+)	$5.48x10^{-4}$ amu; 0.51 MeV	+1	0-4 MeV	0–10 m	0–1 cm	Identical to electron except for sign of charge
Neutron	1.0086 amu; 939.55 MeV	0	0–15 MeV	b	b	Free half-life: 16 min
X ray (e.m. photon)	–	0	5 keV–100 keV	b	b	Photon from transition of an electron between atomic orbits
Gamma (ɣ) (e.m. photon)	–	0	10 keV–3 MeV	b	b	Photon from nuclear transformation

[a] The rest mass (in amu) has an energy equivalent in MeV that is obtained using the equation $E=mc^2$, where 1 amu = 932 MeV.
[b] Path lengths are not applicable to x- and gamma rays since their intensities decrease exponentially; path lengths in solid tissue are variable, depending on particle energy, electron density of material, and other factors.

amu = atomic mass unit; e.m. = electromagnetic; MeV = Megaelectron Volts

The specific activity is a measure of activity, and is defined as the activity of a radionuclide per mass of that radionuclide. This activity is usually expressed in curies per gram and may be calculated by

$$\text{curies/gram} = 1.3x10^8 / (T_{rad})\ (\text{atomic weight}) \quad \text{or}$$

$$[3.577 \times 10^5 \times \text{mass(g)}] / [T_{rad} \times \text{atomic weight}]$$

where T_{rad} is the radiological half-life in days.

In the case of radioactive materials contained in living organisms, an additional consideration is made for the reduction in observed activity due to regular processes of elimination of the respective chemical or biochemical substance from the organism. This introduces a rate constant called the biological half-life (T_{biol}) which is the time required for biological processes to eliminate one-half of the activity. This time is virtually the same for both stable and radioactive isotopes of any given element.

Under such conditions the time required for a radioactive element to be halved as a result of the combined action of radioactive decay and biological elimination is the effective clearance half-time:

$$T_{eff} = (T_{biol} \times T_{rad}) / (T_{biol} + T_{rad}).$$

Table D-2 presents representative effective half-lives of particular interest.

Table D-2. Half-Lives of Some Radionuclides in Adult Body Organs

		Half-life[a]		
Radionuclide	Critical organ	Physical	Biological	Effective
Uranium 238	Kidney	4,460,000,000 y	4 d	4 d
Hydrogen 3[b] (Tritium)	Whole body	12.3 y	10 d	10 d
Iodine 131	Thyroid	8 d	80 d	7.3 d
Strontium 90	Bone	28 y	50 y	18 y
Plutonium 239	Bone surface	24,400 y	50 y	50 y
	Lung	24,400 y	500 d	474 d
Cobalt 60	Whole body	5.3 y	99.5 d	95 d
Iron 55	Spleen	2.7 y	600 d	388 d
Iron 59	Spleen	45.1 d	600 d	42 d
Manganese 54	Liver	303 d	25 d	23 d
Cesium 137	Whole body	30 y	70 d	70 d

[a]d = days, y = years
[b]Mixed in body water as tritiated water

D.2.3 Interaction of Radiation with Matter

Both ionizing and nonionizing radiation will interact with materials; that is, radiation will lose kinetic energy to any solid, liquid or gas through which it passes by a variety of mechanisms. The transfer of energy to a medium by either electromagnetic or particulate radiation may be sufficient to cause formation of ions. This process is called ionization. Compared to other types of radiation that may be absorbed, such as ultraviolet radiation, ionizing radiation deposits a relatively large amount of energy into a small volume.

The method by which incident radiation interacts with the medium to cause ionization may be direct or indirect. Electromagnetic radiations (x rays and gamma photons) are indirectly ionizing; that is, they give up their energy in various interactions with cellular molecules, and the energy is then utilized to produce a fast-moving charged particle such as an electron. It is the electron that then may react with a target molecule. This particle is called a “primary ionizing particle. Charged particles, in contrast, strike the tissue or medium and directly react with target molecules, such as oxygen or water. These particulate radiations are directly ionizing radiations. Examples of directly ionizing particles include alpha and beta particles. Indirectly ionizing radiations are always more penetrating than directly ionizing particulate radiations.

Mass, charge, and velocity of a particle, as well as the electron density of the material with which it interacts, all affect the rate at which ionization occurs. The higher the charge of the particle and the lower the velocity, the greater the propensity to cause ionization. Heavy, highly charged particles, such as alpha particles, lose energy rapidly with distance and, therefore, do not penetrate deeply. The result of these

interaction processes is a gradual slowing down of any incident particle until it is brought to rest or "stopped" at the end of its range.

D.2.4 Characteristics of Emitted Radiation

D.2.4.1 Alpha Emission. In alpha emission, an alpha particle consisting of two protons and two neutrons is emitted with a resulting decrease in the atomic mass number by four and reduction of the atomic number of two, thereby changing the parent to a different element. The alpha particle is identical to a helium nucleus consisting of two neutrons and two protons. It results from the radioactive decay of some heavy elements such as uranium, plutonium, radium, thorium, and radon. The alpha particles emitted by a given radionuclide have the same energy and intensity combination. Most of the alpha particles that are likely to be found have energies in the range of about 4 to 8 MeV, depending on the isotope from which they came.

The alpha particle has an electrical charge of +2. Because of this double positive charge and their size, alpha particles have great ionizing power and, thus, lose their kinetic energy quickly. This results in very little penetrating power. In fact, an alpha particle cannot penetrate a sheet of paper. The range of an alpha particle (the distance the charged particle travels from the point of origin to its resting point) is about 4 cm in air, which decreases considerably to a few micrometers in tissue. These properties cause alpha emitters to be hazardous only if there is internal contamination (i.e., if the radionuclide is inside the body).

D.2.4.2 Beta Emission. A beta particle (β) is a high-velocity electron ejected from a disintegrating nucleus. The particle may be either a negatively charged electron, termed a negatron (β-) or a positively charged electron, termed a positron (β+). Although the precise definition of "beta emission" refers to both β- and β+, common usage of the term generally applies only to the negative particle, as distinguished from the positron emission, which refers to the β+ particle.

D.2.4.2.1 Beta Negative Emission. Beta particle (β-) emission is another process by which a radionuclide, with a neutron excess achieves stability. Beta particle emission decreases the number of neutrons by one and increases the number of protons by one, while the atomic mass number remains unchanged.[1] This transformation results in the formation of a different element. The energy spectrum of beta particle emission ranges from a certain maximum down to zero with the mean energy of the spectrum being about one-third of the maximum. The range of betas is much less in tissue than in air. Beta negative emitting radionuclides can cause injury to the skin and superficial body tissues, but mostly present an internal contamination hazard.

D.2.4.2.2 Positron Emission. In cases in which there are too many protons in the nucleus, positron emission may occur. In this case a proton may be thought of as being converted into a neutron, and a positron (β+) is emitted.1 This increases the number of neutrons by one, decreases the number of protons by one, and again leaves the atomic mass number unchanged. The gamma radiation resulting from the annihilation (see glossary) of the positron makes all positron emitting isotopes more of an external radiation hazard than pure β emitters of equal energy.

D.2.4.2.3 Gamma Emission. Radioactive decay by alpha, beta, or positron emission, or electron capture often leaves some of the energy resulting from these changes in the nucleus. As a result, the nucleus is raised to an excited level. None of these excited nuclei can remain in this high-energy state. Nuclei release this energy returning to ground state or to the lowest possible stable energy level. The energy released is in the form of gamma radiation (high energy photons) and has an energy equal to the change in the energy state of the nucleus. Gamma and x rays behave similarly but differ in their origin;

[1] Neutrinos also accompany negative beta particles and positron emissions

gamma emissions originate in the nucleus while x rays originate in the orbital electron structure or from rapidly changing the velocity of an electron (e.g., as occurs when shielding high energy beta particles or stopping the electron beam in an x ray tube).

D.3 ESTIMATION OF ENERGY DEPOSITION IN HUMAN TISSUES

Two forms of potential radiation exposures can result: internal and external. The term exposure denotes physical interaction of the radiation emitted from the radioactive material with cells and tissues of the human body. An exposure can be "acute" or "chronic" depending on how long an individual or organ is exposed to the radiation. Internal exposures occur when radionuclides, which have entered the body (e.g., through the inhalation, ingestion, or dermal pathways), undergo radioactive decay resulting in the deposition of energy to internal organs. External exposures occur when radiation enters the body directly from sources located outside the body, such as radiation emitters from radionuclides on ground surfaces, dissolved in water, or dispersed in the air. In general, external exposures are from material emitting gamma radiation, which readily penetrate the skin and internal organs. Beta and alpha radiation from external sources are far less penetrating and deposit their energy primarily on the skin's outer layer. Consequently, their contribution to the absorbed dose of the total body dose, compared to that deposited by gamma rays, may be negligible.

Characterizing the radiation dose to persons as a result of exposure to radiation is a complex issue. It is difficult to: (1) measure internally the amount of energy actually transferred to an organic material and to correlate any observed effects with this energy deposition; and (2) account for and predict secondary processes, such as collision effects or biologically triggered effects, that are an indirect consequence of the primary interaction event.

D.3.1 Dose/Exposure Units

D.3.1.1 Roentgen. The roentgen (R) is a unit of x or gamma-ray exposure and is a measured by the amount of ionization caused in air by gamma or x radiation. One roentgen produces 2.58×10^{-4} coulomb per kilogram of air. In the case of gamma radiation, over the commonly encountered range of photon energy, the energy deposition in tissue for a dose of 1 R is about 0.0096 joules (J) /kg of tissue.

D.3.1.2 Absorbed Dose and Absorbed Dose Rate. The absorbed dose is defined as the energy imparted by radiation to a unit mass of the tissue or organ. The unit of absorbed dose is the rad; 1 rad = 100 erg/gram = 0.01 J/kg in any medium. An exposure of 1 R results in a dose to soft tissue of approximately 0.01 J/kg. The SI unit is the gray which is equivalent to 100 rad or 1 J/kg. Internal and external exposures from radiation sources are not usually instantaneous but are distributed over extended periods of time. The resulting rate of change of the absorbed dose to a small volume of mass is referred to as the absorbed dose rate in units of rad/unit time.

D.3.1.3 Working Levels and Working Level Months. Working level (WL) is a measure of the atmospheric concentration of radon and its short-lived progeny. One WL is defined as any combination of short-lived radon daughters (through polonium-214), per liter of air, that will result in the emission of 1.3×10^5 MeV of alpha energy. An activity concentration of 100 pCi radon-222/L of air, in equilibrium with its daughters, corresponds approximately to a potential alpha-energy concentration of 1 WL. The WL unit can also be used for thoron daughters. In this case, 1.3×10^5 MeV of alpha energy (1 WL) is released by the thoron daughters in equilibrium with 7.5 pCi thoron/L. The potential alpha energy exposure of miners is commonly expressed in the unit Working Level Month (WLM). One WLM corresponds to exposure to a concentration of 1 WL for the reference period of 170 hours, or more generally

WLM = concentration (WL) x exposure time (months) (one “month” = 170 working hours).

D.3.2 Dosimetry Models

Dosimetry models are used to estimate the dose from internally deposited to radioactive substances. The models for internal dosimetry consider the amount of radionuclides entering the body, the factors affecting their movement or transport through the body, distribution and retention of radionuclides in the body, and the energy deposited in organs and tissues from the radiation that is emitted during spontaneous decay processes. The dose pattern for radioactive materials in the body may be strongly influenced by the route of entry of the material. For industrial workers, inhalation of radioactive particles with pulmonary deposition and puncture wounds with subcutaneous deposition have been the most frequent. The general population has been exposed via ingestion and inhalation of low levels of naturally occurring radionuclides as well as radionuclides from nuclear weapons testing.

The models for external dosimetry consider only the photon doses (and neutron doses, where applicable) to organs of individuals who are immersed in air or are exposed to a contaminated object.

D.3.2.1 Ingestion. Ingestion of radioactive materials is most likely to occur from contaminated foodstuffs or water or eventual ingestion of inhaled compounds initially deposited in the lung. Ingestion of radioactive material may result in toxic effects as a result of either absorption of the radionuclide or irradiation of the gastrointestinal tract during passage through the tract, or a combination of both. The fraction of a radioactive material absorbed from the gastrointestinal tract is variable, depending on the specific element, the physical and chemical form of the material ingested, and the diet, as well as some other metabolic and physiological factors. The absorption of some elements is influenced by age, usually with higher absorption in the very young.

D.3.2.2 Inhalation. The inhalation route of exposure has long been recognized as being a major portal of entry for both nonradioactive and radioactive materials. The deposition of particles within the lung is largely dependent upon the size of the particles being inhaled. After the particle is deposited, the retention will depend upon the physical and chemical properties of the dust and the physiological status of the lung. The retention of the particle in the lung depends on the location of deposition, in addition to the physical and chemical properties of the particles. The converse of pulmonary retention is pulmonary clearance. There are three distinct mechanisms of clearance which operate simultaneously. Ciliary clearance acts only in the upper respiratory tract. The second and third mechanisms act mainly in the deep respiratory tract. These are phagocytosis and absorption. Phagocytosis is the engulfing of foreign bodies by alveolar macrophages and their subsequent removal either up the ciliary "escalator" or by entrance into the lymphatic system. Some inhaled soluble particles are absorbed into the blood and translocated to other organs and tissues.

D.3.3 Internal Emitters

An internal emitter is a radionuclide that is inside the body. The absorbed dose from internally deposited radionuclide depends on the energy absorbed per unit mass by the irradiated tissue. For a radionuclide distributed uniformly throughout an infinitely large medium, the concentration of absorbed energy must be equal to the concentration of energy emitted by the radionuclide. An infinitely large medium may be approximated by a tissue mass whose dimensions exceed the range of the particle. All alpha and most beta radiation will be absorbed in the organ (or tissue) of reference. Gamma-emitting radionuclide emissions are penetrating radiation, and a substantial fraction of gamma energy may be absorbed in tissue. The dose to an organ or tissue is a function of the effective retention half-time, the energy released in the tissue, the amount of radioactivity initially introduced, and the mass of the organ or tissue.

D.4 BIOLOGICAL EFFECTS OF RADIATION

When biological material is exposed to ionizing radiation, a chain of cellular events occurs as the ionizing particle passes through the biological material. A number of theories have been proposed to describe the interaction of radiation with biologically important molecules in cells and to explain the resulting damage to biological systems from those interactions. Many factors may modify the response of a living organism to a given dose of radiation. Factors related to the exposure include the dose rate, the energy of the radiation, and the temporal pattern of the exposure. Biological considerations include factors such as species, age, sex, and the portion of the body exposed. Several excellent reviews of the biological effects of radiation have been published, and the reader is referred to these for a more in-depth discussion (Brodsky 1996; Hobbs and McClellan 1986; ICRP 1984; Mettler and Moseley 1985; Rubin and Casarett 1968).

D.4.1 Radiation Effects at the Cellular Level

According to Mettler and Moseley (1985), at acute doses up to 10 rad (100 mGy), single strand breaks in DNA may be produced. These single strand breaks may be repaired rapidly. With doses in the range of 50–500 rad (0.5–5 Gy), irreparable double-stranded DNA breaks are likely, resulting in cellular reproductive death after one or more divisions of the irradiated parent cell. At large doses of radiation, usually greater than 500 rad (5 Gy), direct cell death before division (interphase death) may occur from the direct interaction of free-radicals with essential cellular macromolecules. Morphological changes at the cellular level, the severity of which are dose-dependent, may also be observed.

The sensitivity of various cell types varies. According to the Bergonie-Tribondeau law, the sensitivity of cell lines is directly proportional to their mitotic rate and inversely proportional to the degree of differentiation (Mettler and Moseley 1985). Rubin and Casarett (1968) devised a classification system that categorized cells according to type, function, and mitotic activity. The categories range from the most sensitive type, "vegetative intermitotic cells", found in the stem cells of the bone marrow and the gastrointestinal tract, to the least sensitive cell type, "fixed postmitotic cells," found in striated muscles or long-lived neural tissues.

Cellular changes may result in cell death, which if extensive, may produce irreversible damage to an organ or tissue or may result in the death of the individual. If the cell recovers, altered metabolism and function may still occur, which may be repaired or may result in the manifestation of clinical symptoms. These changes may also be expressed at a later time as tumors or cellular mutations, which may result in abnormal tissue.

D.4.2 Radiation Effects at the Organ Level

In most organs and tissues the injury and the underlying mechanism for that injury are complex and may involve a combination of events. The extent and severity of this tissue injury are dependent upon the radiosensitivity of the various cell types in that organ system. Rubin and Casarett (1968) describe and schematically display the events following radiation in several organ system types. These include: a rapid renewal system, such as the gastrointestinal mucosa; a slow renewal system, such as the pulmonary epithelium; and a nonrenewal system, such as neural or muscle tissue. In the rapid renewal system, organ injury results from the direct destruction of highly radiosensitive cells, such as the stem cells in the bone marrow. Injury may also result from constriction of the microcirculation and from edema and inflammation of the basement membrane, designated as the histohematic barrier, which may progress to fibrosis. In slow renewal and nonrenewal systems, the radiation may have little effect on the parenchymal cells, but ultimate parenchymal atrophy and death over several months result from fibrosis and occlusion of the microcirculation.

D.4.3 Low Level Radiation Effects

Cancer is the major latent harmful effect produced by ionizing radiation and the one that most people exposed to radiation are concerned about. The ability of alpha, beta, and gamma radiation to produce cancer in virtually every tissue and organ in laboratory animals has been well-demonstrated. The development of cancer is not an immediate effect. Radiation-induced leukemia has the shortest latent period at about 2 years, while other radiation induced cancers, such as osteosarcoma, have latent periods greater than 20 years. The mechanism by which cancer is induced in living cells is complex and is a topic of intense study. Exposure to ionizing radiation can produce cancer at any site within the body; however, some sites appear to be more common than others, such as the breast, lung, stomach, and thyroid.

DNA is the major target molecule during exposure to ionizing radiation. Other macromolecules, such as lipids and proteins, are also at risk of damage when exposed to ionizing radiation. The genotoxicity of ionizing radiation is an area of intense study, as damage to the DNA is ultimately responsible for many of the adverse toxicological effects ascribed to ionizing radiation, including cancer. Damage to genetic material is basic to developmental or teratogenic effects, as well. However, for effects other than cancer, there is little evidence of human effects at low levels of exposure.

D.5 UNITS IN RADIATION PROTECTION AND REGULATION

D.5.1 Dose Equivalent (or Equivalent Dose)

Dose equivalent (as measured in rem or sievert) is a special radiation protection quantity that is used for administrative and radiation safety purposes to express the absorbed dose in a manner which considers the difference in biological effectiveness of various kinds of ionizing radiation. ICRP (1990) changed this term to equivalent dose, but it has not yet been adopted by the USNRC or DOE.

The USNRC defines the dose equivalent, H, as the product of the absorbed dose, D, and the quality factor, Q, at the point of interest in biological tissue. This relationship is expressed as $H = D \times Q$. The dose equivalent concept is applicable only to doses that are not great enough to produce biomedical effects.

The quality factor or radiation weighting factor is a dimensionless quantity that depends in part on the stopping power for charged particles, and it accounts for the differences in biological effectiveness found among the types of radiation. Originally relative biological effectiveness (RBE) was used rather than Q to define the quantity, rem, which was of use in risk assessment. The generally accepted values for quality factors and radiation weighting factors for various radiation types are provided in Table D-3. The dose equivalent rate is the time rate of change of the dose equivalent to organs and tissues and is expressed as rem/unit time or sievert/unit time.

Table D-3. Quality Factors (Q) and Absorbed Dose Equivalencies

Type of radiation	Quality factor (Q)	Radiation weighting factor (w_r)*
X, gamma, or beta radiation	1	1
Alpha particles, multiple-charged particles, fission fragments and heavy particles of unknown charge	20	0.05
Neutrons (other than thermal >> 100 keV to 2 MeV), protons, alpha particles, charged particles of unknown energy	10	20
Neutrons of unknown energy	10	
High-energy protons	10	0.1
Thermal neutrons		5

*Absorbed dose in rad equal to 1 rem or the absorbed dose in gray equal to 1 sievert.

Source: USNRC. 2004. Standards for the protection against radiation, table 1004(b).1. 10 CFR 20.1004. U.S. Nuclear Regulatory Commission, Washington, D.C. NCRP 1993

D.5.2 Relative Biological Effectiveness

RBE is used to denote the experimentally determined ratio of the absorbed dose from one radiation type to the absorbed dose of a reference radiation required to produce an identical biologic effect under the same conditions. Gamma rays from cobalt-60 and 200–250 kVp x-rays have been used as reference standards. The term RBE has been widely used in experimental radiobiology, and the term quality factor (or radiation weighting factor) used in calculations of dose equivalents for radiation safety purposes (ICRP 1977; NCRP 1971; UNSCEAR 1982). Any RBE value applies only to a specific biological end point, in a specific exposure, under specific conditions to a specific species. There are no generally applicable values of RBE since RBEs are specific to a given exposure scenario.

D.5.3 Effective Dose Equivalent (or Effective Dose)

The absorbed dose is usually defined as the mean energy imparted per unit mass to an organ or tissue. This represents a simplification of the actual problem. Normally when an individual ingests or inhales a radionuclide or is exposed to external radiation that enters the body (gamma), the dose is not uniform throughout the whole body. The simplifying assumption is that the detriment will be the same whether the body is uniformly or non-uniformly irradiated. In an attempt to compare detriment from absorbed dose of a limited portion of the body with the detriment from total body dose, the ICRP (1977) has derived a concept of effective dose equivalent. ICRP (1990) changed this term to effective dose, but it has not yet been adopted by the USNRC or DOE.

The effective dose equivalent, H_E, is

$$H_E = (\text{the sum of}) \; W_t \, H_t$$

where H_t is the dose equivalent (or equivalent dose) in the tissue t, W_t is the tissue weighting factor in that tissue, which represents the estimated proportion of the stochastic risk resulting from tissue, t, to the stochastic risk when the whole body is uniformly irradiated for occupational exposures under certain conditions (ICRP 1977). Tissue weighting factors for selected tissues are listed in Table D-4.

D.5.4 SI Units

The ICRU (1980), ICRP (1984), and NCRP (1985) now recommend that the rad, roentgen, curie, and rem be replaced by the SI units: gray (Gy), Coulomb per kilogram (C/kg), Becquerel (Bq), and sievert (Sv), respectively. The relationship between the customary units and the international system of units (SI) for radiological quantities is shown in Table D-5.

Table D-4. Tissue Weighting Factors for Calculating Effective Dose Equivalent and Effective Dose for Selected Tissues

	Tissue weighting factor	
Tissue	NCRP115/ ICRP60	USNRC/ICRP26
Bladder	0.05	–
Bone marrow	0.12	0.12
Bone surface	0.01	0.03
Breast	0.05	0.15
Colon	0.12	–
Esophagus	0.05	–
Gonads	0.20	0.25
Liver	0.05	–
Lung	0.12	0.12
Skin	0.01	–
Stomach	0.12	–
Thyroid	0.05	0.03
Remainder	0.05	0.30
Total	1.00	1.00

ICRP60 = International Commission on Radiological Protection, 1990 Recommendations of the ICRP
NCRP115 = National Council on Radiation Protection and Measurements. 1993. Risk Estimates for Radiation Protection, Report 115. Bethesda, Maryland
USNRC = Nuclear Regulatory Commission, Title 10, Code of Federal Regulations, Part 20

Table D-5. Comparison of Common and SI Units for Radiation Quantities

Quantity	Customary units	Definition	SI units	Definition
Activity (A)	curie (Ci)	3.7×10^{10} transformations s^{-1}	becquerel (Bq)	s^{-1}
Absorbed dose (D)	rad	10^{-2} Jkg^{-1}	gray (Gy)	Jkg^{-1}
Absorbed dose rate ($\dot{D}$)	rad per second (rad s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	gray per second (Gy s^{-1})	Jkg^{-1} s^{-1}
Dose equivalent (H)	rem	10^{-2} Jkg^{-1}	sievert (Sv)	Jkg^{-1}
Dose equivalent rate ($\dot{H}$)	rem per second (rem s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	sievert per second (Sv s^{-1})	Jkg^{-1} s^{-1}
Effective dose	rem	10^{-2} Jkg^{-1}	Sievert (Sv)	Jkg^{-1}
Equivalent dose (H)	rem	10^{-2} Jkg^{-1}	Sievert (Sv)	Jkg^{-1}
Linear energy transfer (LET)	kiloelectron volts per micrometer (keV μm^{-1})	1.602×10^{-10} Jm^{-1}	kiloelectron volts per micrometer (keV μm^{-1})	1.602×10^{-10} Jm^{-1}

Jkg^{-1} = Joules per kilogram; $Jkg^{-1}s^{-1}$ = Joules per kilogram per second; Jm^{-1} = Joules per meter; s^{-1} = per second

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TOXICOLOGICAL PROFILE FOR COPPER

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2004

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Copper, Draft for Public Comment was released in September 2002. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE,
Mailstop F-32
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

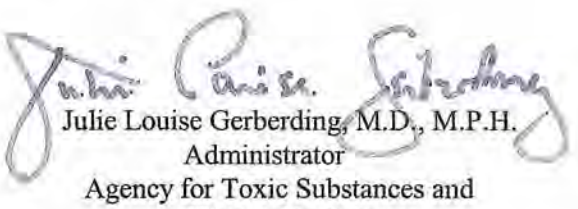
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 7, 2003 (68 FR 63098) . For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792) and October 25, 2001 (66 FR 54014). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

> ***NOTE***: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	How Can (Chemical X) Affect Children?
Section 1.7	How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7	Children's Susceptibility
Section 6.6	Exposures of Children

Other Sections of Interest:

Section 3.8	Biomarkers of Exposure and Effect
Section 3.11	Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (770) 488-4178
E-mail: atsdric@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposure*s—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for copper (September 2002 profile). The panel consisted of the following members:

1. Dr. Jonathan H. Freedman, Center for Environmental Genomes, Duke University, Durham, North Carolina;

2. Dr. Paul Mushak, PB Associates, Durham, North Carolina; and

3. Dr. Robert B. Ruckner, School of Medicine, Department of Nutrition, University of California at Davis, Davis, California.

4. Dr. Edward Massaro, U.S. Environmental Protection Agency, Reproductive Toxicology Facility, Durham, North Carolina

These experts collectively have knowledge of copper's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about copper and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Copper has been found in at least 906 of the 1,647 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which copper is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it and your body is able to absorb it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to copper, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex and other genetic traits, diet, family traits, lifestyle, and state of health, including pregnancy and developmental stage of embryo/fetus.

1.1 WHAT IS COPPER?

Copper is a reddish metal that occurs naturally in rock, soil, water, sediment, and, at low levels, air. Its average concentration in the earth's crust is about 50 parts copper per million parts soil (ppm) or, stated another way, 50 grams of copper per 1,000,000 grams of soil (1.8 ounces or 0.11 pounds of copper per 2,200 pounds of soil). Copper also occurs naturally in all plants and animals. It is an essential element for all known living organisms including humans and other

animals at low levels of intake. At much higher levels, toxic effects can occur. The term copper in this profile not only refers to copper metal, but also to compounds of copper that may be in the environment.

Metallic copper can be easily molded or shaped. The reddish color of this element is most commonly seen in the U.S. penny, electrical wiring, and some water pipes. It is also found in many mixtures of metals, called alloys, such as brass and bronze. Many compounds (substances formed by joining two or more chemicals) of copper exist. These include naturally occurring minerals as well as manufactured chemicals. The most commonly used compound of copper is copper sulfate. Many copper compounds can be recognized by their blue-green color.

Copper is extensively mined and processed in the United States and is primarily used as the metal or alloy in the manufacture of wire, sheet metal, pipe, and other metal products. Copper compounds are most commonly used in agriculture to treat plant diseases, like mildew, or for water treatment and as preservatives for wood, leather, and fabrics. For more information on the properties and uses of copper, please see Chapters 4 and 5.

1.2 WHAT HAPPENS TO COPPER WHEN IT ENTERS THE ENVIRONMENT?

Copper can enter the environment through releases from the mining of copper and other metals, and from factories that make or use copper metal or copper compounds. Copper can also enter the environment through waste dumps, domestic waste water, combustion of fossil fuels and wastes, wood production, phosphate fertilizer production, and natural sources (for example, windblown dust, from native soils, volcanoes, decaying vegetation, forest fires, and sea spray). Therefore, copper is widespread in the environment. About 1,400,000,000 pounds (640,000,000,000 grams) of copper were released into the environment by industries in 2000. Copper is often found near mines, smelters, industrial settings, landfills, and waste disposal sites.

When copper is released into soil, it can become strongly attached to the organic material and other components (e.g., clay, sand, etc.) in the top layers of soil and may not move very far when it is released. When copper and copper compounds are released into water, the copper that

dissolves can be carried in surface waters either in the form of copper compounds or as free copper or, more likely, copper bound to particles suspended in the water. Even though copper binds strongly to suspended particles and sediments, there is evidence to suggest that some water-soluble copper compounds do enter groundwater. Copper that enters water eventually collects in the sediments of rivers, lakes, and estuaries. Copper is carried on particles emitted from smelters and ore processing plants, and is then carried back to earth through gravity or in rain or snow. Copper is also carried into the air on windblown metallurgical dust. Indoor release of copper comes mainly from combustion processes (for example, kerosene heaters).

Elemental copper does not break down in the environment. Copper can be found in plants and animals, and at high concentrations in filter feeders such as mussels and oysters. Copper is also found in a range of concentrations in many foods and beverages that we eat and drink, including drinking water. You will find additional information on the fate of copper in the environment in Chapters 5 and 6.

1.3 HOW MIGHT I BE EXPOSED TO COPPER?

Copper is common in the environment. You may be exposed to copper by breathing air, drinking water, eating food, and by skin contact with soil, water and other copper-containing substances. Most copper compounds found in air, water, sediment, soil and rock are strongly attached to dust and dirt or imbedded in minerals. You can take copper into your body upon ingestion of water or soil that contains copper or by inhalation of copper-containing dust. Some copper in the environment is less tightly bound to soil or particles in water and may be soluble enough in water to be taken up by plants and animals. In the general population, soluble copper compounds (those that dissolve in water), which are most commonly used in agriculture, are more likely to threaten your health. When soluble copper compounds are released into lakes and rivers, they generally become attached to particles in the water within approximately 1 day. This could lessen your exposure to copper in water, depending on how strongly the copper is bound to the particles and how much of the particles settle into lake and river sediments. However, fine particles have an enormous surface area and can remain suspended for prolonged periods of

time. Therefore, at high fine particle concentrations, both exposure and uptake can be considerable even under conditions of tight copper binding to the suspended particulates.

The concentration of copper in air ranges from a few nanograms (1 nanogram equals 1/1,000,000,000 of a gram or 4/100,000,000,000 of an ounce) in a cubic meter of air (ng/m^3) to about 200 ng/m^3. A cubic meter (m^3) is approximately 25% larger than a cubic yard. Near smelters, which process copper ore into metal, concentrations may reach 5,000 ng/m^3. You may breathe high levels of copper-containing dust if you live or work near copper mines or processing facilities.

You may be exposed to levels of soluble copper in your drinking water that are above the acceptable drinking water standard of 1,300 parts copper per billion parts of water (ppb), especially if your water is corrosive and you have copper plumbing and brass water fixtures. The average concentration of copper in tap water ranges from 20 to 75 ppb. However, many households have copper concentrations of over 1,000 ppb. That is more than 1 milligram per liter of water. This is because copper is dissolved from copper pipes and brass faucets when the water sits in the pipes overnight. After the water is allowed to run for 15–30 seconds, the concentration of copper in the water decreases below the acceptable drinking water standard.

The concentration of copper in lakes and rivers ranges from 0.5 to 1,000 ppb with an average concentration of 10 ppb. The average copper concentration in groundwater (5 ppb) is similar to that in lakes and rivers; however, monitoring data indicate that some groundwater contains levels of copper (up to 2,783 ppb) that are well above the standard of 1,300 ppb for drinking water. This copper is generally bound to particles in the water. Lakes and reservoirs recently treated with copper compounds to control algae or receive cooling water from a power plant can have high concentrations of dissolved copper. Once in natural water, much of this copper soon attaches to particles or convert to other forms that can settle into sediments. This can limit exposure to copper unless the sediments are stirred; for example, by the resuspension and swallowing of sediments by swimmers in recreational waters.

Garden products containing copper that are used to control certain plant diseases are also a potential source of exposure through contact with skin or if they are accidentally swallowed. For example, you can find copper compounds in some fungicides.

Soil generally contains between 2 and 250 ppm copper, although concentrations close to 17,000 ppm have been found near copper and brass production facilities. High concentrations of copper may be found in soil because dust from these industries settles out of the air, or wastes from mining and other copper industries are disposed of on the soil. Another common source of copper in soil results from spreading sludge from sewage treatment plants. This copper generally stays strongly attached to the surface layer of soil. You may be exposed to this copper by skin contact. Children may also be exposed to this copper by hand to mouth contact and eating the contaminated dirt and dust.

Food naturally contains copper. You eat and drink about 1 milligram (1/1,000 of a gram or 4/100,000 ounces) of copper every day.

While some hazardous waste sites on the NPL contain high levels of copper, we do not always know how high it is above natural levels. We also do not know what form it is in at most of these sites. However, evidence suggests that most copper at these sites is strongly attached to soil.

You may be exposed to copper in the workplace. If you work in the industry of mining copper or processing the ore, you are exposed to copper by breathing copper-containing dust or by skin contact. If you grind or weld copper metal, you may breathe high levels of copper dust and fumes. Occupational exposure to forms of copper that are soluble or not strongly attached to dust or dirt would most commonly occur in agriculture, water treatment, and industries such as electroplating, where soluble copper compounds are used. Exposure to copper in air in the workplace is regulated and is set to be below concentrations that can be harmful to you.

For more information on the potential for exposure to copper, please refer to Chapter 6.

1.4 HOW CAN COPPER ENTER AND LEAVE MY BODY?

Copper can enter your body when you drink water or eat food, soil, or other substances that contain copper. Copper can also enter your body if you breathe air or dust containing copper. Copper may enter the lungs of workers exposed to copper dust or fumes.

Copper rapidly enters the bloodstream and is distributed throughout the body after you eat or drink it. Certain substances in foods eaten with copper can affect the amount of copper that enters the bloodstream from the gastrointestinal tract. Your body is very good at blocking high levels of copper from entering the bloodstream. We do not know how much copper enters the body through the lungs or skin. Copper then leaves your body in feces and urine, mostly in feces. It takes several days for copper to leave your body. Generally, the amount of copper in your body remains constant (the amount that enters your body equals the amount that leaves). More information on how copper enters and leaves the body is presented in Chapter 3.

1.5 HOW CAN COPPER AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

Copper is essential for good health. However, exposure to higher doses can be harmful. Long-term exposure to copper dust can irritate your nose, mouth, and eyes, and cause headaches, dizziness, nausea, and diarrhea. If you drink water that contains higher than normal levels of

copper, you may experience nausea, vomiting, stomach cramps, or diarrhea. Intentionally high intakes of copper can cause liver and kidney damage and even death. We do not know if copper can cause cancer in humans. EPA does not classify copper as a human carcinogen because there are no adequate human or animal cancer studies.

More detailed information on the health effects of copper in animals and humans can be found in Chapter 3.

1.6 HOW CAN COPPER AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Exposure to high levels of copper will result in the same types of effects in children and adults. We do not know if these effects would occur at the same dose level in children and adults. Studies in animals suggest that children may have more severe effects than adults; we do not know if this would also be true in humans. There is a very small percentage of infants and children who are unusually sensitive to copper. We do not know if copper can cause birth defects or other developmental effects in humans. Studies in animals suggest that ingestion of high levels of copper may cause a decrease in fetal growth.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO COPPER?

The greatest potential source of copper exposure is through drinking water, especially in water that is first drawn in the morning after sitting in copper piping and brass faucets overnight. To reduce copper in drinking water, run the water for at least 15–30 seconds before using it. Additionally, if there is concern about the concentration of copper in drinking water exceeding the minimum value of 1,300 ppb, families should have their water tested.

If your doctor finds that you have been exposed to substantial amounts of copper, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO COPPER?

Copper is normally found in all tissues of the body, blood, urine, feces, hair, and nails. High levels of copper in the blood, urine, hair, and nails can show that you have been exposed to higher than normal levels of copper. Tests to measure copper levels in the body are not usually available at a doctor's office because they require special equipment, but the doctor can send samples to a specialty laboratory. Although these tests can show that you have been exposed to higher than normal copper levels, they can not be used to predict the extent of exposure or potential health effects. More detailed information on the measurement of copper is provided in Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans.

Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for copper include the following:

The EPA has determined that drinking water should not contain more than 1.3 mg copper per liter of water (1.3 mg/L). The EPA has also developed regulations on the amount of copper that industry is allowed to release.

The OSHA has set a limit of 0.1 milligrams/cubic meter (mg/m^3) for copper fumes (vapor generated from heating copper) and 1.0 mg/m^3 for copper dusts (fine metallic copper particles) and mists (aerosols of soluble copper) in workroom air to protect workers during an 8-hour work shift (40-hour workweek).

The Food and Nutrition Board of the Institute of Medicine has developed recommended dietary allowances (RDAs) of 340 micrograms (µg) of copper per day for children aged 1–3 years, 440 µg/day for children aged 4–8 years, 700 µg/day for children aged 9–13 years, 890 µg/day for children aged 14–18 years, and 900 µg/day for adults. This provides enough copper to maintain health. Further information on regulations and guidelines pertaining to copper is provided in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mail at atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO COPPER IN THE UNITED STATES

Copper is a metallic element that occurs naturally as the free metal, or associated with other elements in compounds that comprise various minerals. Most copper compounds occur in +1 Cu(I) and +2 Cu(II) valence states. Copper is primarily used as a metal or an alloy (e.g., brass, bronze, gun metal). Copper sulfate is used as a fungicide, algicide, and nutritional supplement. Copper particulates are released into the atmosphere by windblown dust; volcanic eruptions; and anthropogenic sources, primarily copper smelters and ore processing facilities. Copper particles in the atmosphere will settle out or be removed by precipitation, but can be resuspended into the atmosphere in the form of dust. The mean concentration of copper in ambient air in the United States ranges from 5 to 200 ng/m^3. Copper is released into waterways by natural weathering of soil and rocks, disturbances of soil, or anthropogenic sources (e.g., effluent from sewage treatment plants). Copper concentrations in drinking water vary widely as a result of variations in pH and hardness of the water supply; the levels range from a few ppbs to 10 ppm. The mean concentration of copper in soil in the United States ranges from 5 to 70 mg/kg. The estimated daily intake of copper from food is 1.0–1.3 mg/day for adults (0.014–0.019 mg/kg/day).

The general population is exposed to copper through inhalation, consumption of food and water, and dermal contact with air, water, and soil that contains copper. The primary source of copper intake is the diet; however, the amount of copper in the diet usually does not exceed the average dietary requirements (RDAs) for copper. Drinking water is the primary source of excess copper. Populations living near sources of copper emissions, such as copper smelters and refineries and workers in these and other industries may also be exposed to high levels of copper in dust by inhalation. Copper concentrations in soils near copper emission sources could be sufficiently high to result in significantly high intakes of copper in young children who ingest soil. For example, copper concentrations of 2,480–6,912 ppm have been measured near copper smelters. These levels of copper in soils would result in the intake of 0.74–2.1 mg copper per day in a child ingesting 300 mg of soil. Copper has been identified in at least 906 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA NPL.

2.2 SUMMARY OF HEALTH EFFECTS

Copper is an essential nutrient that is incorporated into a number of metalloenzymes involved in hemoglobin formation, drug/xenobiotic metabolism, carbohydrate metabolism, catecholamine biosynthesis, the cross-linking of collagen, elastin, and hair keratin, and the antioxidant defense mechanism. Copper-dependent enzymes, such as cytochrome c oxidase, superoxide dismutase, ferroxidases, monoamine oxidase, and dopamine β-monooxygenase, function to reduce activated oxygen species or molecular oxygen. Symptoms associated with copper deficiency in humans include normocytic, hypochromic anemia, leukopenia, and osteoporosis; copper deficiency is rarely observed in the U.S. general population. In the United States, the median intake of copper from food is 0.93–1.3 mg/day for adults (0.013–0.019 mg Cu/kg body weight/day using a 70-kg reference body weight). A recommended dietary allowance (RDA) of 0.9 mg/day (0.013 mg/kg/day) has recently been established.

Copper is readily absorbed from the stomach and small intestine. After nutritional requirements are met, there are several mechanisms that prevent copper overload. Excess copper absorbed into gastrointestinal mucosal cells induces the synthesis of and binds to the metal binding protein metallothionein. This bound copper is excreted when the cell is sloughed off. Copper that eludes binding to intestinal metallothionen is transported to the liver. It is stored in the liver bound to liver metallothionen, from which it is ultimately released into bile and excreted in the feces. Although copper homeostasis plays an important role in the prevention of copper toxicity, exposure to excessive levels of copper can result in a number of adverse health effects including liver and kidney damage, anemia, immunotoxicity, and developmental toxicity. Many of these effects are consistent with oxidative damage to membranes or macromolecules. Copper can bind to the sulfhydryl groups of several enzymes, such as glucose-6-phosphatase and glutathione reductase, thus interfering with their protection of cells from free radical damage.

One of the most commonly reported adverse health effect of copper is gastrointestinal distress. Nausea, vomiting, and/or abdominal pain have been reported, usually occurring shortly after drinking a copper sulfate solution, beverages that were stored in a copper or untinned brass container, or first draw water (water that sat in the pipe overnight). The observed effects are not usually persistent and gastrointestinal effects have not been linked with other health effects. Animal studies have also reported gastrointestinal effects (hyperplasia of forestomach mucosa) following ingestion of copper sulfate in the diet. Copper is also irritating to the respiratory tract. Coughing, sneezing, runny nose, pulmonary fibrosis, and increased vascularity of the nasal mucosa have been reported in workers exposed to copper dust.

The liver is also a sensitive target of toxicity. Liver damage (necrosis, fibrosis, abnormal biomarkers of liver damage) have been reported in individuals ingesting lethal doses of copper sulfate. Liver effects have also been observed in individuals diagnosed with Wilson's disease, Indian childhood cirrhosis, or idiopathic copper toxicosis (which includes Tyrollean infantile cirrhosis). These syndromes are genetic disorders that result in an accumulation of copper in the liver; the latter two syndromes are associated with excessive copper exposure. Inflammation, necrosis, and altered serum markers of liver damage have been observed in rats fed diets with copper sulfate levels that are at least 100 times higher than the nutritional requirement. Damage to the proximal convoluted tubules of the kidney has also been observed in rats. The liver and kidney effects usually occur at similar dose levels; however, the latency period for the kidney effects is longer than for the liver effects.

There is some evidence from animal studies to suggest that exposure to airborne copper or high levels of copper in drinking water can damage the immune system. Impaired cell-mediated and humoral-mediated immune function have been observed in mice. Studies in rats, mice, and mink suggest that exposure to high levels of copper in the diet can result in decreased embryo and fetal growth.

The carcinogenicity of copper has not been adequately studied. An increase in cancer risk has been found among copper smelters; however, the increased risk has been attributed to concomitant exposure to arsenic. Increased lung and stomach cancer risks have also been found in copper miners. However, a high occurrence of smoking and exposure to radioactivity, silica, iron, and arsenic obscure the association of copper exposure with carcinogenesis. Animal studies have not found increased cancer risks in orally exposed rats or mice. The IARC has classified the pesticide, copper 8-hydroxyquinoline, in Group 3, unclassifiable as to carcinogenicity in humans and EPA has classified copper in Group D, not classifiable as to human carcinogenicity

A more detailed discussion of the critical targets of copper toxicity, the gastrointestinal tract and the liver, follows.

Gastrointestinal Effects. The available human and animal data suggest that the gastrointestinal tract is a sensitive target of toxicity. There are numerous reports of nausea, vomiting, and/or abdominal pain in humans ingesting beverages contaminated with copper or water containing copper sulfate. These symptoms typically occur shortly after ingestion and are not persistent. The results of three single exposure studies suggest that the threshold for gastrointestinal symptoms is between 4 and 6 ppm, which is equivalent to doses of 0.11 mg/kg and 0.017–0.018 mg Cu/kg. Nausea, vomiting, and/or abdominal

pain also appear to be the most sensitive end point following repeated exposure to copper in drinking water. These symptoms were reported by adults drinking water containing ≥3 ppm copper as copper sulfate (0.0731 mg Cu/kg/day) for 1–2 weeks or 4 ppm copper as copper sulfate (0.091 mg Cu/kg/day) for 2 months. Similar gastrointestinal effects were observed in adults ingesting copper oxide in drinking water. Although gastrointestinal irritation may play a role in the observed gastrointestinal effects, data from ferrets and monkeys suggest that vagal afferent fibers and 5-HT_3 and 5-HT_4 receptors are involved in copper-induced emesis.

Hepatic Effects. In humans, copper-induced hepatic damage is dependent on several factors including genetics, age, and copper intake. Liver damage is rarely reported in adults; the few reported cases of liver damage (centrilobular necrosis, jaundice, and increased aspartate aminotransferase activity) have been associated with intentional ingestion of a lethal dose of copper sulfate. In infants and children, reported liver effects are usually manifested in one of three syndromes: Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis. Wilson's disease is an autosomal recessive genetic disorder associated with impaired copper metabolism. Dietary exposure to higher than normal levels of copper does not appear to be necessary for the manifestation of liver damage. Some heterozygous carriers of Wilson's disease also have elevated hepatic levels of copper and increased urinary excretion, although adverse health effects have not been reported in these individuals. There is evidence that Indian childhood cirrhosis and idiopathic copper toxicosis are also caused by a genetic defect that is transmitted in an autosomal recessive mode. However, unlike Wilson's disease, manifestation of the disease is associated with exposure to unusually high levels of dietary copper from milk stored in copper or brass containers or from drinking water. The clinical age of onset is usually between 6 months and 5 years, and the observed liver effects include pericellular fibrosis, abnormal biochemical markers of liver damage (e.g., increased serum aspartate aminotransferase and alkaline phosphatase activities and serum bilirubin levels), and very high levels of copper in the liver. In general, the potential hepatotoxicity of copper has not been extensively investigated in healthy humans. No effect levels of 0.14–0.17 and 0.315 mg Cu/kg/day for liver effects in adults and infants (3–12 months of age), respectively, had been reported in intermediate-duration studies (2–9 months); these studies used serum chemistry biomarkers (e.g., alanine aminotransferase, aspartate aminotransferase) to assess liver damage. Two community survey studies also found no evidence of liver damage in infants living in households with 0.8 ppm copper in drinking water. The results of the three studies involving infants should be interpreted cautiously due to the high drop out rate, small number of subjects examined for possible liver damage, and the dismissal of anomalous findings as secondary to infection rather than possibly indicative of copper toxicity.

Adverse liver effects have been observed in rats exposed to dietary copper levels that were more than 100 times higher than the nutritional requirement. The liver effects included inflammation, necrosis, and abnormal serum chemistry markers of liver damage. Rats appear to develop a tolerance to copper doses of 180–<550 mg Cu/kg/day. Tolerance is defined as "the ability to endure the continued or increasing administration of a toxicant and the capacity to exhibit less response to a test dose than previous." As the levels of hepatic copper increase, so does the severity of the damage until peak copper levels are reached. After about 3–5 weeks of exposure, the copper levels begin to decline and are maintained at a steady level for the remainder of the exposure period. When the hepatic levels decline, regeneration of hepatic tissue is observed, and continued exposure or exposure to higher doses does not result in more tissue damage. The decline in hepatic copper levels and regeneration of damaged tissue occurs early at higher doses. At doses >550 mg Cu/kg/day, the liver becomes permanently overloaded and chronic hepatitis develops.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for copper. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Inhalation MRLs

The available data on the toxicity of inhaled copper were considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs. Data on the inhaled toxicity of copper in humans following acute-duration exposure are limited to a report of workers developing metal fume fever while cutting brass pipe with an electric cutting tool in a poorly ventilated area (Armstrong et al. 1983); exposure levels were not reported. Respiratory effects and impaired immune function have been observed in mice following a single 3-hour exposure to 3.3 mg Cu/m^3 as copper sulfate or repeated exposure (3 hours/day, 5 days/week for 1–2 weeks) to 0.12–0.13 mg Cu/m^3 as copper sulfate (Drummond et al. 1986). The Drummond et al. (1986) study was not selected as the basis of an acute-duration inhalation MRL because a small number of animals was tested (four per group) and a limited number of end points (respiratory tract and immune function) were examined. Intermediate-duration data are limited to studies by Johansson et al. (1983, 1984), which did not find any histological alterations in the lungs or functional or morphological alterations in alveolar macrophages of rabbits exposed to copper chloride. As with the acute-duration data, the limited number of end points examined precludes deriving an intermediate-duration inhalation MRL. The chronic-duration database for copper consists of two occupational exposure studies reporting respiratory (Askergren and Mellgren 1975; Suciu et al. 1981) and gastrointestinal (Suciu et al. 1981) irritation, hepatic effects (Suciu et al. 1981), and possible neurological and reproductive effects (Suciu et al. 1981). Chronic-duration inhalation MRLs cannot be derived from these studies due to poor exposure characterization and/or lack of controls.

Oral MRLs

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure (1–14 days) to copper.

The available human and animal acute-duration studies strongly suggest that the gastrointestinal tract is the most sensitive target of copper toxicity. Numerous studies and case reports have reported nausea, vomiting, and/or abdominal pain in humans immediately following ingestion of copper-contaminated water or other beverages (Araya et al. 2001, 2003a, 2003b, 2003c; Chuttani et al. 1965; Gotteland et al. 2001; Knobeloch et al. 1994; Nicholas and Brist 1968; Olivares et al. 2001; Pizarro et al. 1999, 2001; Spitalny et al. 1984). In human studies involving a single exposure to copper following an overnight fast, adverse gastrointestinal effects (nausea, vomiting, abdominal pain, and/or diarrhea) have been observed at doses of 0.011–0.03 mg Cu/kg (Araya et al. 2001, 2003a, 2003c; Gotteland et al. 2001; Olivares et al. 2001). Under these experimental conditions, the apparent threshold appears to fall between 0.011 and

0.017 mg Cu/kg (Araya et al. 2001, 2003a; Olivares et al. 2001). Slightly higher thresholds for gastrointestinal symptoms were observed in two acute-duration repeated exposure studies in which subjects used a copper-containing water as their primary source of drinking water for 1 or 2 weeks (Pizarro et al. 1999, 2001). In the 2-week study, 60 women were given copper sulfate containing water to be used for drinking and cooking purposes. No significant alterations in serum biomarkers of liver damage (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase) were observed in the subjects at the end of the study. An increased occurrence of nausea, vomiting, and/or abdominal pain was observed when the women were exposed to 3 ppm copper as copper sulfate (0.0731 mg Cu/kg/day) (Pizarro et al. 1999); no significant increases in the incidence of gastrointestinal symptoms were noted at 1 ppm (0.0272 mg Cu/kg/day). Nausea, vomiting, and/or abdominal pain were also reported by women ingesting water containing 5 ppm (0.096 mg Cu/kg/day) as copper sulfate or copper oxide for 1 week (Pizarro et al. 2001). Animal studies support the identification of the gastrointestinal tract as a sensitive target of toxicity. Hyperplasia of the forestomach mucosa was observed in rats exposed to 44 mg Cu/kg/day as copper sulfate in the diet (NTP 1993) and in mice exposed to 197 mg Cu/kg/day as copper sulfate in the diet (NTP 1993). At higher doses, liver and kidney damage have been observed (Haywood 1980; Haywood and Comerford 1980; Haywood et al. 1985b; NTP 1993).

The Pizarro et al. (1999) 2-week study was selected as the basis of the acute-duration oral MRL for copper. This study identified no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values of 0.0272 and 0.0731 mg Cu/kg/day for increases in the incidence of nausea, vomiting, and/or abdominal pain. Although the LOAEL values identified in the single exposure studies (Araya et al. 2001, 2003; Olivares et al. 2001) are slightly lower than the than the NOAEL identified in the Pizarro et al. (1999) study, the Pizarro et al. (1999) study was selected as the critical study because it is a longer-duration study and it more closely mimics an exposure scenario of a population drinking copper-contaminated drinking water. The NOAEL was divided by an uncertainty factor of 3 (to account for human variability) to yield an acute-duration oral MRL of 0.01 mg Cu/kg/day. The observed gastrointestinal effects were probably due to direct contact; thus, only a partial uncertainty factor of 3 was used to account for human variability because toxicokinetic differences among individuals should not affect sensitivity. The acute-duration MRL is intended to protect against the health effects associated with exposure to copper-contaminated drinking water; it assumes that the affected population will have a normal intake of copper from the diet.

- An MRL of 0.01 mg/kg/day has been derived for intermediate-duration oral exposure (15–365 days) to copper.

There are limited data on the intermediate-duration toxicity of copper in humans. Araya et al. (2003b) exposed groups of 327–355 adults to <0.01 (control group), 2, 4, or 6 ppm copper sulfate in water for 2 months. The subjects prepared the copper sulfate solution to be used at home by mixing a stock copper sulfate solution with tap water; this solution was used for drinking water and preparing beverages and soups. Exposure to copper sulfate resulted in increases in the occurrence of gastrointestinal symptoms; the incidence was significantly higher than controls at 6 ppm when the data were analyzed using the chi-square test with Bonferroni correction and at 4 ppm when the Bonferroni correction was not used. Only one test was used to assess whether exposure to copper results in adverse gastrointestinal effects (reported symptoms); thus, the Bonferroni correction is not needed for this end point. Therefore, the 4 ppm concentration is identified as the LOAEL and the 2 ppm concentration as the NOAEL. The study authors reported copper intakes for 48–49 subjects per group who provided blood samples; no information on selection criteria were provided. The copper intakes were 0, 0.042, 0.091, and 0.17 mg Cu/kg/day for the control, 2, 4, and 6 ppm groups, respectively. The dietary intake of copper was not measured in this study; however, Araya et al. (2003b) noted that copper intake found in a survey of other community residents was 0.9 mg Cu/day. No significant alterations in copper status or liver function (as assessed by serum alanine aminotransferase, asparatate aminotransferase, and γ-glutamyl transferase activities) were observed in a subset of subjects from each group. In a study by Pratt et al. (1985), a group of seven adults were administered 10 mg Cu/day (0.14 mg Cu/kg/day) as copper gluconate in a capsule for 12 weeks. No significant alterations in serum markers of liver damage (cholesterol and triglyceride levels and serum aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transferase, and lactate dehydrogenase activities) were found. Similarly, no alterations in total bilirubin or serum alanine aminotransferase, aspartate aminotransferase, or γ-glutamyl transferase activities were observed in infants exposed to 0.315 mg Cu/kg/day for 9 months (Olivares et al. 1998). Zietz et al. (2003a, 2003b) also did not find evidence of liver damage in infants living in households with water concentrations of 0.8 ppm and higher. The Pratt et al. (1985), Olivares et al. (1998), and Zietz et al. (2003a, 2003b) studies did not report significant alterations in the occurrence of gastrointestinal disturbances and the study design did not include symptoms questionnaires, although the high dropout rate observed in the Olivares et al. (1998) study may have been related to gastrointestinal effects. Severe liver damage (pericellular fibrosis and increased serum aminotransferase and alkaline phosphatase activities) has been observed in children with a genetic susceptibility to high levels of copper in the liver. The liver was a critical target of toxicity in rats exposed to very high levels of copper in diet (greater than 100 times the nutritional requirement), Inflammation, necrosis, and increased alanine and aspartate aminotransferases activities have been

reported in rats at exposure levels of 16 mg Cu/kg/day as copper sulfate in the diet (Haywood 1980, 1985; Haywood and Comerford 1980; Haywood and Loughran 1985; Haywood et al. 1985a; NTP 1993). No liver effects where observed at 8 mg Cu/kg/day (NTP 1993). Histological alterations in stomach, indicative of irritation (hyperplasia of the squamous mucosa on the limiting ridge separating the forestomach from the glandular stomach), have also been observed in rats and mice exposed to 33 or 267 mg Cu/kg/day, respectively, as copper sulfate in the diet for 13 weeks (NTP 1993).

An intermediate-duration oral MRL of 0.01 mg Cu/kg/day was derived for copper based on gastrointestinal effects using the data from the Araya et al. (2003b) study. This study identified NOAEL and LOAEL values of 0.042 and 0.091 mg Cu/kg/day, respectively; these copper doses were in excess of normal dietary intake. The NOAEL was divided by an uncertainty factor of 3 (to account for human variability) to yield an intermediate-duration oral MRL of 0.01 mg Cu/kg/day. As with the acute-duration MRL, the intermediate-duration MRL is intended to protect against exposure to excess copper in drinking water and assumes a normal copper dietary intake.

The database on the chronic oral toxicity of copper is inadequate for derivation of a MRL. Massie and Aiello (1984) reported a 15% decrease in the lifespan in mice exposed to 4.2 mg Cu/kg/day as copper gluconate in drinking water.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of copper. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which

major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

No studies were located regarding death of humans or animals following inhalation exposure to copper.

3.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, musculoskeletal, renal, dermal, or body weight effects in humans or animals following inhalation exposure to copper.

Respiratory, gastrointestinal, hematological, hepatic, endocrine, and ocular effects were observed in humans. Respiratory effects have also been observed in animals exposed to copper sulfate aerosols.

Respiratory Effects. In humans, copper is a respiratory irritant. Workers exposed to copper dust report a number of symptoms that are suggestive of respiratory irritation, including coughing, sneezing, thoracic pain, and runny nose (Askergren and Mellgren 1975; Suciu et al. 1981). In the Suciu et al. (1981) study of 75–100 workers involved in sieving copper, lung radiographs revealed linear pulmonary fibrosis, and in some cases, nodulation. During the first year of operation, the workers were exposed to 434 mg Cu/m^3; the exposure levels declined each year, and by year 3, the levels were 111 mg Cu/m^3. In

sheet metal workers exposed to patina dust (copper-hydroxide-nitrate, copper-hydroxide-sulfate, copper silicate, copper oxide), 6 of the 11 examined workers had increased vascularity and superficial epistatic vessels in the nasal mucosa (Askergren and Mellgren 1975); no exposure levels were reported.

Copper is considered the etiologic agent in the occupational disease referred to as "vineyard sprayer's lung". This disease, which is observed in vineyard workers spraying an antimildew agent containing 1–2.5% copper sulfate neutralized with hydrated lime, was first described in humans by Cortez Pimentel and Marques (1969). In most cases, published information on this disease comes from case reports (Cortez Pimentel and Marques 1969; Cortez Pimentel and Menezes 1975; Stark 1981; Villar 1974; Villar and Nogueira 1980) with no concentration-response information. Common findings (obtained by alveolar lavage and biopsy) include intraalveolar desquamation of macrophages, formation of histiocytic and noncaseating granulomas containing inclusions of copper, and healing of lesions in the form of fibrohyaline nodules, very similar to those found in silicosis (Cortez Pimentel and Marques 1969; Plamenac et al. 1985). Higher incidences of abnormal columnar cells, squamous metaplasia without atypia, copper containing macrophages, eosinophilia, and respiratory spirals were found in the sputa of smoking and nonsmoking vineyard sprayers, as compared to rural workers from the same geographic region who did not work in the vineyards (Plamenac et al. 1985).

The potential of copper to induce respiratory effects has been tested in mice, hamsters, and rabbits. Decreased cilia beating was observed in Syrian-Golden hamsters exposed to 3.3 mg Cu/m^3 as copper sulfate for 3 hours (Drummond et al. 1986); this effect was not observed in similarly exposed CD-1 mice. Repeated exposure resulted in alveolar thickening in CD-1 mice exposed to 0.12 mg Cu/m^3 as copper sulfate for 3 hours/day, 5 days/week for 1–2 weeks (Drummond et al. 1986); the severity of the effect increased with the duration of exposure. In rabbits (strain not reported) exposed to 0.6 mg Cu/m^3 as copper chloride for 6 hours/day, 5 days/week for 4–6 weeks, the only histological alteration in the lungs was a slight increase in alveolar type II cell volume density (Johansson et al. 1984); this effect was not considered adverse. No functional or morphological alterations were observed in the alveolar macrophages of similarly exposed rabbits (Johansson et al. 1983).

Gastrointestinal Effects. In workers involved in grinding and sieving copper dust, anorexia, nausea, and occasional diarrhea were reported (Suciu et al. 1981); exposure levels ranged from 111 to 434 mg Cu/m^3 over a 3-year period. It is likely that the observed gastrointestinal effects were due to oral exposure to copper. Ingestion probably resulted from mucocilliary clearance of copper particles deposited in the nasopharyngeal and tracheobronchial regions of the respiratory tract.

No studies were located regarding gastrointestinal effects in animals following inhalation exposure to copper.

Hematological Effects. Decreased hemoglobin and erythrocyte levels have been observed in workers exposed to airborne copper levels of 0.64–1.05 mg/m^3. Results of hair analysis reveal that the workers were also exposed to iron, lead, and cadmium (Finelli et al. 1981).

No studies were located regarding hematological effects in animals following inhalation exposure to copper.

Hepatic Effects. Hepatomegaly was observed in workers involved in grinding and sieving copper dust (Suciu et al. 1981); the exposure levels ranged from 111 to 434 mg Cu/m^3.

No studies were located regarding hepatic effects in animals following inhalation exposure to copper.

Endocrine Effects. Seven cases of enlargement of the sella turcica, nonsecretive hypophyseal adenoma, accompanied by obesity, arterial hypertension, and "red facies" were observed in a group of 100 workers exposed to 111–434 mg Cu/m^3 as copper dust (Suciu et al. 1981). The study authors noted that there was a possibility that the clinical manifestations of hypophyseal adenoma or of Cushing's syndrome may have been the result of a disturbance of copper metabolism. The significance of this effect and its relationship to copper exposure cannot be determined.

Ocular Effects. Eye irritation has been reported by workers exposed to copper dust (Askergren and Mellgren 1975). The irritation is likely due to direct contact with the copper rather than a systemic effect resulting from inhalation exposure.

Other Systemic Effects. A few studies have reported metal fume fever, a 24–48-hour illness characterized by chills, fever, aching muscles, dryness in the mouth and throat, and headache, in workers exposed to copper dust or fumes (Armstrong et al. 1983; Gleason 1968). Gleason (1968) reported airborne copper dust concentrations of 0.075–0.12 mg/m^3. It has been suggested that other metals present in the workplace may have been the causative agent for the metal fume fever, rather than copper. This is supported by the small number of reports of metal fume fever despite the extensive use of copper in many industries (Borak et al. 2000).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following inhalation exposure to copper.

An acute exposure study in mice reported an impaired immune response following exposure to copper sulfate and a bacterial challenge (Drummond et al. 1986). Increased mortality and decreased survival time were observed in CD-1 mice challenged by an aerosol of *Streptococcus zooepidemicus* following 0.56 mg Cu/m^3 for 3 hours or 0.13 mg Cu/m^3 for 3 hours/day, 5 days/week for 2 weeks. Decreased bactericidal activity of alveolar macrophages was also observed in mice exposed to 3.3 mg Cu/m^3 for 3 hours or 0.12 mg Cu/m^3 for 3 hours/day, 5 days/week for 2 weeks following exposure to an aerosol of *Klebsiella pneumonia*.

These LOAEL values for immunological effects are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Only one study examining neurological effects was located. Headache, vertigo, and drowsiness were reported in factory workers exposed to 111–434 mg/m^3 copper dust (Suciu et al. 1981).

3.2.1.5 Reproductive Effects

Sexual impotence was reported in 16% of workers (75–100 workers examined) exposed to 111–434 mg/m^3 copper dust during grinding and sieving operations (Suciu et al. 1981). The significance of this finding is difficult to assess because a control group was not used.

No studies were located regarding reproductive effects in animals following inhalation exposure to copper.

Table 3-1 Levels of Significant Exposure to Copper - Inhalation

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m^3)	LOAEL				Reference Chemical Form
					Less Serious (mg/m^3)		Serious (mg/m^3)		
	ACUTE EXPOSURE								
	Systemic								
1	Mouse	3 hr	Resp	3.3					Drummond et al. 1986
2	Mouse	1-2 wk 5d/wk 3hr/d	Resp		0.12	(alveoli thickening)			Drummond et al. 1986
3	Hamster	3 hr	Resp	1.21	3.3	(decr cilia beating frequency)			Drummond et al. 1986
4	Hamster	1-2 wk 5d/wk 3hr/d	Resp	0.13					Drummond et al. 1986
	Immuno/ Lymphoret								
5	Mouse	1-2 wk 5d/wk 3hr/d			0.12	(decr bactericidal activity)	0.13	(decr mean survival time)	Drummond et al. 1986
6	Mouse	3 hr			3.3	(decr bactericidal activity)	0.56	(decr mean survival time)	Drummond et al. 1986

Table 3-1 Levels of Significant Exposure to Copper - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL			Reference Chemical Form
					Less Serious (mg/m³)		Serious (mg/m³)	
	INTERMEDIATE EXPOSURE							
	Systemic							
7	Rabbit (NS)	1 mo 5d/wk 6hr/d	Resp	0.6 M				Johansson et al. 1983 copper chloride
8	Rabbit (NS)	4-6 wk 5d/wk 6hr/d	Resp	0.6 M				Johansson et al. 1984 copper chloride
	CHRONIC EXPOSURE							
	Systemic							
9	Human	8 hr/d, 5 d/wk	Hemato		0.64	(decr hemoglobin and erythrocyte levels)		Finelli et al. 1981 NS

aThe number corresponds to entries in Figure 3-1.

d = day(s); decr = decreased; hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; (NS) = not specified; Resp = respiratory;wk = week(s); yr = year(s)

Figure 3-1. Levels of Significant Exposure to Copper- Inhalation

Acute (≤14 days)

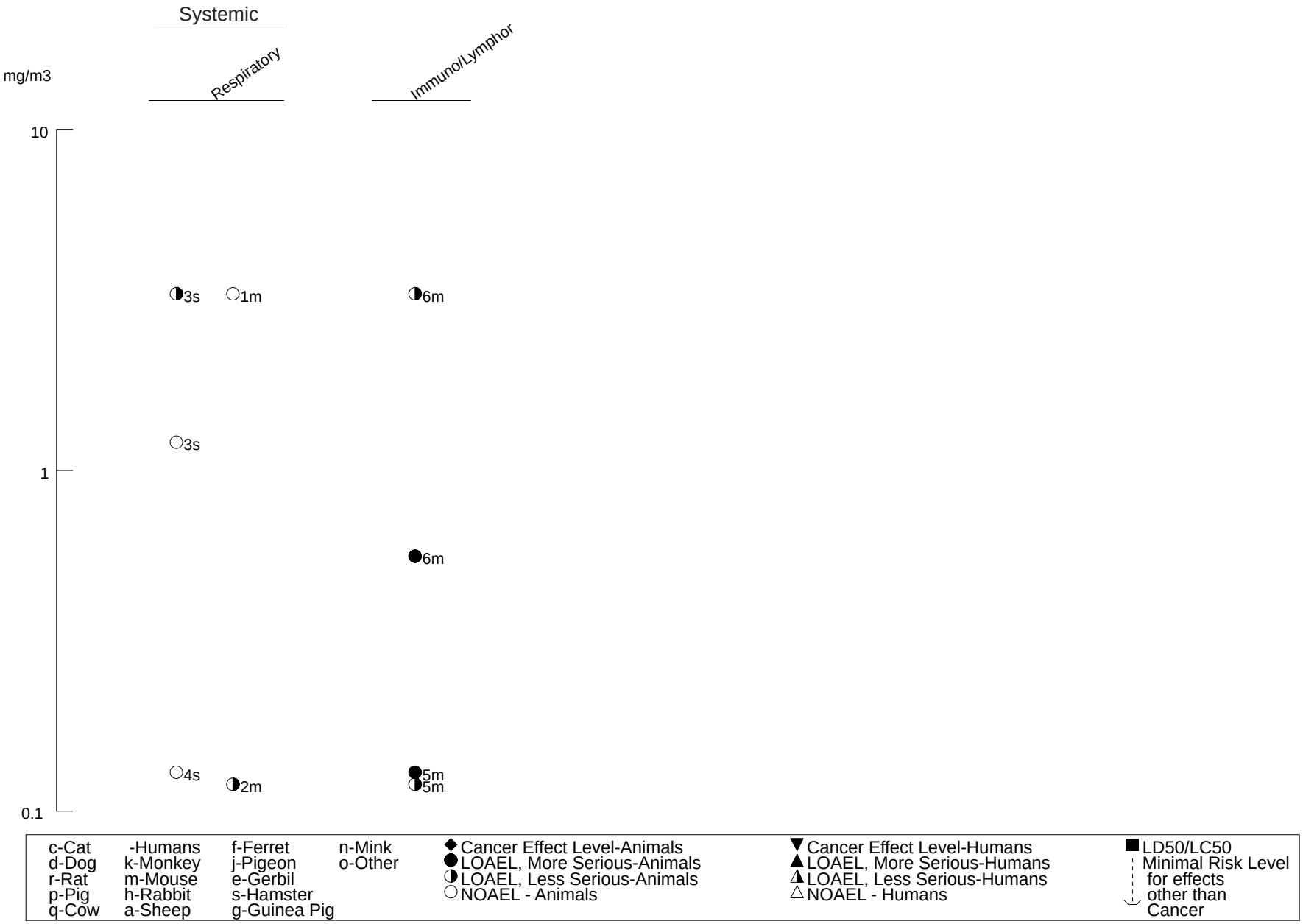


Figure 3-1. Levels of Significant Exposure to Copper- Inhalation (*Continued*)

Intermediate (15-364 days)

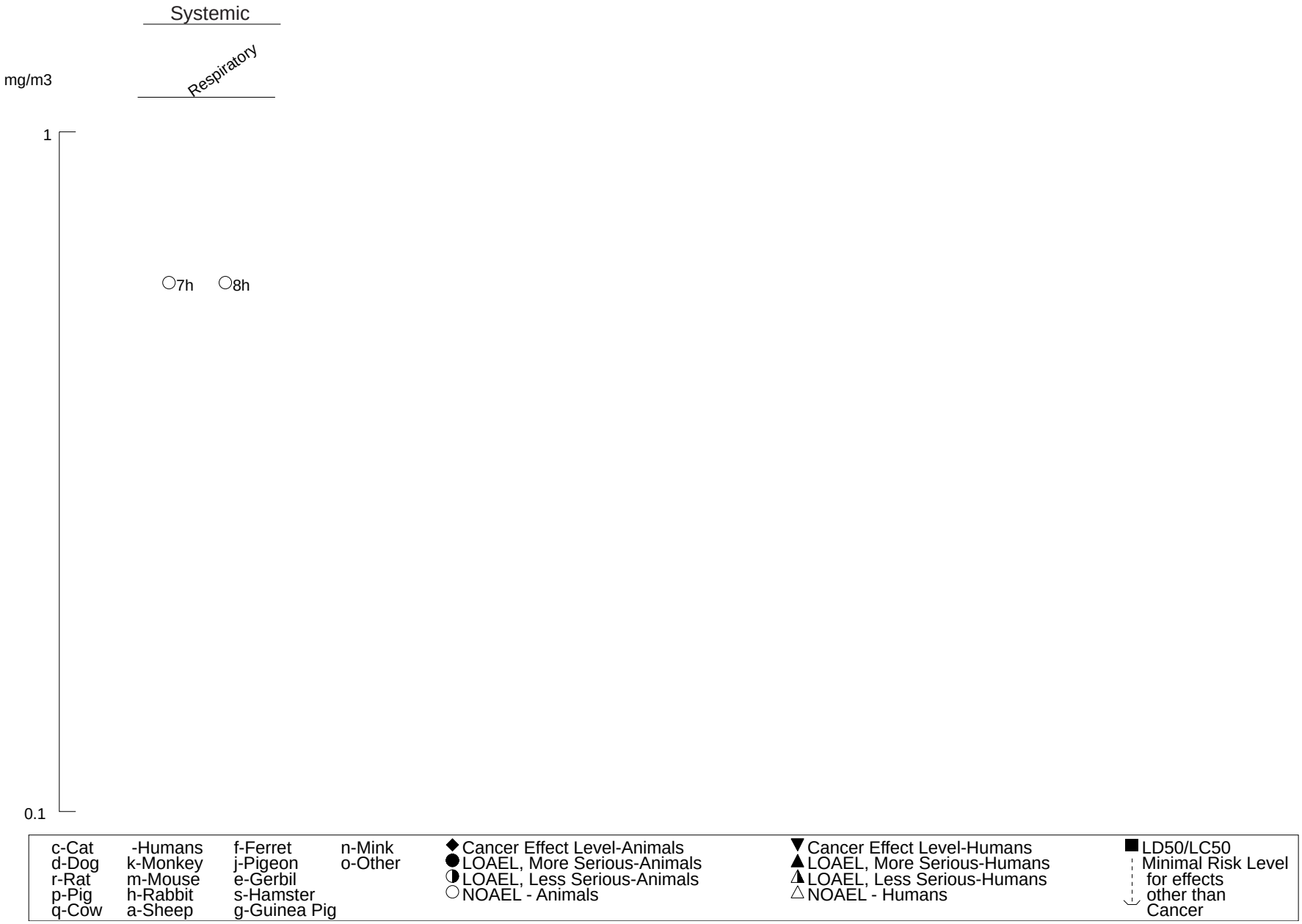
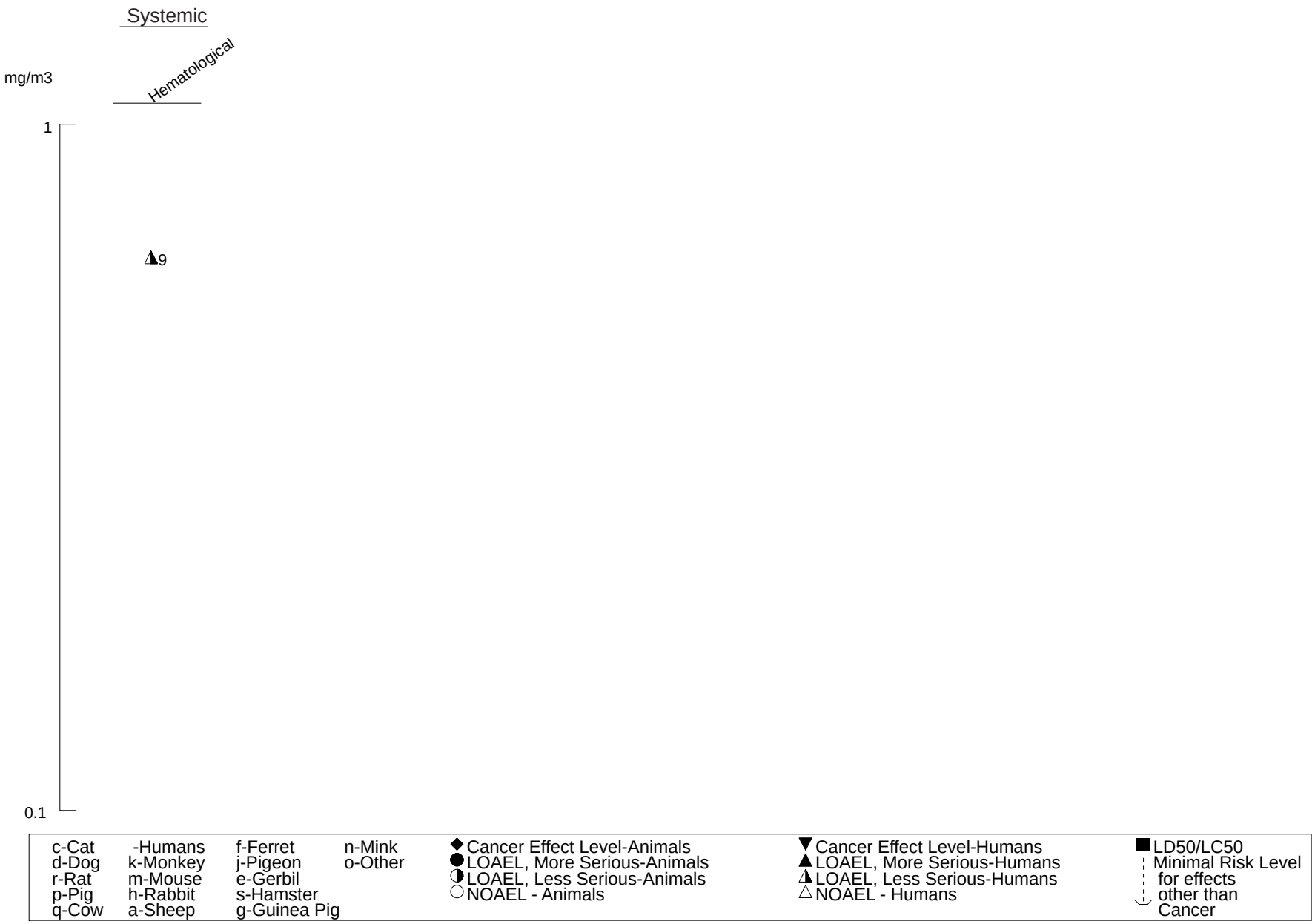


Figure 3-1. Levels of Significant Exposure to Copper- Inhalation (*Continued*)

Chronic (≥365 days)



3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans and animals following inhalation exposure to copper.

3.2.1.7 Cancer

There are limited data for humans and no data for animals on the carcinogenicity of inhaled copper. Although a number of studies have examined cancer risk among copper smelters, these papers are not discussed because the cancer risk has been attributed to exposure to arsenic rather than to copper. In a study of over 6,700 male workers at a Chinese copper mine, significant increases in the risk of cancer (all sites combined) (standardized mortality ratio [SMR] =123; 95% confidence interval [CI] =109–139), stomach cancer (SMR=131; 95% CI=105–161), and lung cancer (SMR=147; 95% CI=112–189) were observed (Chen et al. 1993). The cancer risk increased with increasing duration of employment and time since first exposure and was also higher in workers employed in the 1950s when there was a dramatic increase in production, dry drilling methods were used, and there was poor underground ventilation. Radon and radon daughters were detected in the underground mines; between 1960 and 1990, radioactivity levels of 1.29×10^{-11} Ci/L were measured. To assess the relative contribution of radon and radon daughters to the lung cancer risk, the workers were divided into two groups: underground miners and workers involved in drilling (presumably above ground). Increases in lung cancer risk were observed in both groups, thus suggesting that exposure to radioactivity was not the primary source of increased cancer risk. The copper ore also contained silica, iron, manganese, arsenic, titanium, and sulfur. The study authors noted that the arsenic level in the copper was relatively low (0.061%) and did not likely contribute to the lung cancer risk; however, the lung cancer risk from exposure to silica and iron could not be ruled out. A significant increase in the risk of silicosis was observed in the miners. In a 7-year follow-up of this cohort (Chen et al. 1995), the risk of all sites of cancer (SMR=129; 95% CI=117–142), stomach cancer (SMR=141; 95% CI=116–169), and lung cancer (SMR=152; 95% CI=123–187) were still significantly elevated. This study also conducted a smoking survey and found that a higher percentage of the miners were smokers (71.7%) than in the control population of local residents (64.3%); this increased smoking rate, along with exposure to radioactivity, silica, iron, and arsenic may have contributed to the increased cancer risk.

3.2.2 Oral Exposure

3.2.2.1 Death

A number of deaths have been reported in individuals intentionally ingesting large doses of copper sulfate (Chuttani et al. 1965). Thirteen of 53 individuals died after ingesting 6–637 mg/kg copper; because the amount of copper sulfate was self-reported, the estimated doses may be inaccurate. The deaths were attributed to shock and hepatic and/or renal complications. Deaths, probably due to central nervous system depression and hepatic and renal failure, have also been reported in individuals ingesting "spiritual green water", which contains ≥100 mg copper sulfate/L (Akintonwa et al. 1989).

Increased mortality was observed in rats fed a diet containing 4,000 ppm of copper (133 mg Cu/kg/day) for 1 week. Anorexia, possibly the result of taste aversion, contributed to the deaths (Boyden et al. 1938). Weanling rats exposed to 300 mg Cu/kg/day as Cu(II) in the diet (6,000 ppm) died after 2 weeks (Haywood 1985). The deaths were attributed to extensive centrilobular necrosis.

Lifetime exposure to 42.5 mg Cu/kg/day as copper gluconate in drinking water resulted in a 12.8% reduction of the maximal lifespan (from 986 to 874 days) in mice (Massie and Aiello 1984).

The doses associated with deaths in the Haywood (1985) and Massie and Aiello (1984) studies are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding endocrine, dermal, ocular, or metabolic effects in humans or animals following oral exposure to copper.

The highest NOAEL values and all reliable LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. Data on the potential of copper to induce respiratory effects are limited to the NTP (1993) study that found no histological alterations in the lungs of rats exposed to 285 or 134 mg Cu/kg/day as copper sulfate in the diet for 14 or 90 days, respectively, or in mice exposed to 717 or 814 mg Cu/kg/day for 14 or 90 days.

Table 3-2 Levels of Significant Exposure to Copper - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Wistar)	2-15 wk (F)				550 M (increased mortality)	Haywood 1985 NS
2	Rat (Fischer- 344)	14 d (W)				31 F (100% mortality)	NTP 1993 copper sulfate
3	Mouse (B6C3F1)	14 d (W)				62 M (increased mortality)	NTP 1993 copper sulfate
	Systemic						
4	Human	once (W)	Gastro	0.011	0.017 (nausea, vomiting, diarrhea, or abdominal pain)		Araya et al. 2001 copper sulfate
5	Human	once (W)	Gastro	0.012 F	0.018 F (nausea)		Araya et al. 2003a copper sulfate
6	Human	once (W)	Gastro		0.046 (nausea, delayed gastric emptying)		Araya et al. 2003c copper sulfate
7	Human	once (W)	Gastro		0.03 (nausea and vomiting)		Gotteland et al. 2001 copper sulfate

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
8	Human	once (W)	Gastro		6 (vomiting)		Karlsson and Noren 1965 copper sulfate
9	Human	once (W)	Gastro		0.08 M (vomiting, diarrhea)		Nicholas and Brist 1968 NS
10	Human	once (W)	Gastro	0.0057	0.011 (nausea)		Olivares et al. 2001 copper sulfate
11	Human	2 wks (W)	Gastro	0.0272 F[b]	0.0731 F (abdominal pain, nausea, and/or vomiting)		Pizarro et al. 1999 copper sulfate
12	Human	1 wk (W)	Gastro		0.096 F (nausea, vomiting, and/or abdominal pain)		Pizarro et al. 2001 copper sulfate and copper oxide
13	Rat (NS)	1-2 wk (F)	Hepatic		300 M (parenchymal cell hypertrophy)		Haywood 1980 copper sulfate
			Renal	300 M			

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
14	Rat (NS)	1-2 wk (F)	Hepatic		300 M (increased alanine aminotransferase activity)		Haywood and Comerford 1980 copper sulfate
15	Rat (Wistar)	1-2 wk (F)	Hepatic		450 M (hepatocellular necrosis)		Haywood et al. 1985a NS
			Renal		450 M (copper-containing droplets and granules in proximal tubule cells)		
16	Rat (Wistar)	2 wk (F)	Renal		200 M (droplets in proximal tubule lumen)		Haywood et al. 1985b NS

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
17	Rat (Fischer- 344)	14 d (W)	Resp	29 M			NTP 1993 copper sulfate
			Cardio	29 M			
			Gastro	29 M			
			Hepatic	29 M			
			Renal		10 M (protein droplets in epithelial cells of proximal tubule)		
			Bd Wt	26 F			

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
18	Rat (Fischer- 344)	14 d (F)	Resp	285 F			NTP 1993 copper sulfate
			Cardio	285 F			
			Gastro	23 F	44 F (hyperplasia of forestomach mucosa)		
			Hemato	93 F	196 F (depletion of hematopoietic cells in bone marrow)		
			Hepatic	92 M	198 M (inflammation)		
			Renal	46 M	92 M (increased protein droplets in cortical tubules)		
			Bd Wt	93 F	196 F (18% decrease in body weight gain)		

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
19	Mouse (B6C3F1)	14 d (W)	Resp	24 M			NTP 1993 copper sulfate
			Cardio	24 M			
			Gastro	24 M			
			Hepatic	24 M			
			Renal	24 M			
			Bd Wt	24 M			

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
20	Mouse (B6C3F1)	14 d (F)	Resp	717 M			NTP 1993 copper sulfate
			Cardio	717 M			
			Gastro	92 M	197 M (hyperplasia of forestomach mucosa)		
			Hepatic	717 M			
			Renal	717 M			
			Bd Wt	717 M			
	INTERMEDIATE EXPOSURE						
	Systemic						
21	Human	daily 2 months (W)	Gastro	0.042[c]	0.091 (gastrointestinal symptoms)		Araya et al. 2003b copper sulfate
			Hepatic	0.17			

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
22	Human	9 months (W)	Gastro	0.319			Olivares et al. 1998 copper sulfate
			Hepatic	0.319			
			Bd Wt	0.319			
23	Human	12 wks (C)	Gastro	0.14			Pratt et al. 1985 copper gluconate
			Hemato	0.14			
			Hepatic	0.14			
24	Rat (Fischer- 344)	3 mo (F)	Hepatic	66 M	89 M (increased number of necroinflammatory foci in the liver)		Aburto et al. 2001b copper sulfate
			Bd Wt	114 M	140 M (15% decreased in terminal body weight)		

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
25	Rat (Sprague-Dawley)	30-58 d (F)	Hepatic	20 F			Cristofori et al. 1992 NS
			Renal	20 F			
26	Rat (Sprague-Dawley)	90 d (W)	Hepatic		8 M (increased aspartate aminotransferase activity)		Epstein et al. 1982 copper acetate
			Bd Wt	8 M			
27	Rat (Fischer- 344)	18 wks (F)	Hepatic		150 M (inflammation and increased serum enzyme activity in adult rats)		Fuentealba et al. 2000 copper sulfate
					120 M (inflammation, necrosis, and increases serum enzyme levels in young rats)		
28	Rat (NS)	3-15 wk (F)	Hepatic		180 M (necrosis)		Haywood 1980 copper sulfate
			Renal		180 M (cytoplasmic droplets and desquamation of epithelial cells in proximal tubules)		

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
29	Rat (Wistar)	2-15 wk (F)	Hepatic		280 M (inflammation, necrosis)	550 M (chronic hepatitis)	Haywood 1985 NS
			Renal		280 M (degeneration of proximal tubule cells)		
			Bd Wt			550 M (weight loss)	
						280 M (50% decrease in body weight gain)	
30	Rat (NS)	3-15 wk (F)	Hepatic		180 M (increased alanine aminotransferase activity)		Haywood and Comerford 1980 copper sulfate
31	Rat (Wistar)	15 wk (F)	Hepatic		320 M (necrosis)	640 M (chronic hepatitis)	Haywood and Loughran 1985 copper sulfate
			Bd Wt			640 M (weight loss)	
						320 M (50% decrease in body weight gain)	

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
32	Rat (Wistar)	4-14 wks (F)	Hepatic		280 M (hepatocellular necrosis)		Haywood et al. 1985a NS
			Renal		280 M (tubular cell necrosis)		
33	Rat (Wistar)	4-15 wk (F)	Renal		200 M (reversible degeneration and necrosis of tubule cells)		Haywood et al. 1985b NS
34	Rat (NS)	30 d (G)	Hemato		100 M (decreased erythrocyte and hemoglobin levels)		Kumar and Sharma 1987 copper sulfate
			Hepatic		100 M (increased glucose, cholesterol, bilirubin, serum enzymes, and decreased total protein levels)		
			Renal		100 M (increased BUN levels)		
35	Rat (Wistar)	15 wks (F)	Cardio		14 M (increased blood pressure)		Liu and Medeiros 1986 copper carbonate

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
36	Rat (Holtzman)	21 wks (F)	Musc/skel	120 M			Llewellyn et al. 1985 copper acetate
			Bd Wt		120 (23% decrease in body weight gain)		

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
37	Rat (Fischer- 344)	13 wk (F)	Resp	134 F			NTP 1993 copper sulfate
			Cardio	134 F			
			Gastro	16 M	33 M (squamous mucosa hyperplasia of forestomach)		
			Hemato	33 M	66 M (decreases in hematocrit, hemoglobin, reticulocytes, mean cell volume, and mean cell hemoglobin levels and increases in platelet levels)		
			Hepatic	8 M	66 M (chronic active inflammation with focal necrosis)		
					16 M (increases serum alanine aminotransferase)		
			Renal	9 F	17 F (increased BUN)	134 F (tubular degeneration)	
			Bd Wt	66 M	140 M (24% decrease in body weight gain)		

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rat (NS)	20 d (G)	Hemato		100 M (decreases in erythrocyte, hemoglobin, and hematocrit levels)		Rana and Kumar 1980 copper sulfate
			Hepatic		100 M (hepatocellular necrosis)		
			Renal		100 M (tubular cell necrosis)		
39	Mouse (B6C3F1)	13 wk (F)	Resp	814 M			NTP 1993 copper sulfate
			Cardio	814 M			
			Gastro	126 F	267 F (hyperplasia of forestomach mucosa)		
			Hepatic	814 M			
			Renal	814 M			
			Bd Wt	187 M	398 M (12% decrease in body weight gain)		

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
40	Pig (Hampshire)	54 d (F)	Hemato	11	24 (decreased hemoglobin levels)		Kline et al. 1971 copper sulfate
			Bd Wt	11	24 (decreased body weight gain)		
41	Pig (NS)	49 d (F)	Hemato		36 F (decreased hemoglobin levels)		Suttle and Mills 1966a copper carbonate
			Hepatic		36 F (increased asparate aminotransferase activity)		
42	Pig (NS)	6 wks (F)	Hemato		35 F (decreased hemoglobin level)		Suttle and Mills 1966a copper carbonate
			Hepatic		35 F (increased aspartate aminotransferase activity)		
	Immuno/ Lymphoret						
43	Mouse (C57BL/6N)	8 wks (W)			24 (impaired immune function)		Pocino et al. 1990 copper sulfate
44	Mouse (C57BL/6N)	3-5 or 8-10 wks (W)			13 (altered cell-mediated and humoral immunity)		Pocino et al. 1991 copper sulfate

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Neurological						
45	Rat (Sprague-Dawley)	11 mo (W)			36 F (decreased 3,4-dihydroxyphenylacetic acid levels in corpus striatum)		DeVries et al. 1986 copper sulfate
46	Rat (NS)	30 d (F)		23			Murthy et al. 1981 copper sulfate
	Reproductive						
47	Rat (Fischer- 344)	13 wk (F)		66 M 68 F			NTP 1993 copper sulfate
48	Mouse (B6C3F1)	13 wk (F)		398 M 536 F			NTP 1993 copper sulfate
49	Mink (dark mink)	153 or 367 d (F)		12			Aulerich et al. 1982 copper sulfate

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Developmental						
50	Rat (Wistar)	60-73 d (W)			130 (delayed growth and development)		Haddad et al. 1991 copper acetate
51	Mouse (C57BL/6N)	1 mo + gd 0-19 (F)		138 F	208 (decreased mean litter size and fetal body weights)		Lecyk 1980 copper sulfate
52	Other (dark mink)	153 or 367 d (F)		13			Aulerich et al. 1982 copper sulfate
	CHRONIC EXPOSURE						
	Death						
53	Mouse (C57BL/6N)	850 d (W)				4.2 (14.7% decrease in lifespan)	Massie and Aiello 1984 copper gluconate
	Systemic						
54	Mouse (C57BL/6N)	850 d (W)	Bd Wt	42 M			Massie and Aiello 1984 copper gluconate

a The number corresponds to entries in Figure 3-2.

b Used to derive an acute-duration oral minimal risk level (MRL) of 0.01 mg Cu/kg/day; the NOAEL was divided by an uncertainty factor of 3 to account for human variability.

c Used to derive an intermediate-duration minimal risk level (MRL) of 0.01 mg Cu/kg/day; the NOAEL divided by an uncertainty factor of 3 to account for human variability.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; G = gavage; Gastro = gastrointestinal; gd = gestational day; Gn pig = guinea pig; hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; occup = occupational; NS = not specified; Resp = respiratory; (W) = drinking water; wk = week(s)

Figure 3-2. Levels of Significant Exposure to Copper - Oral

Acute (≤14 days)

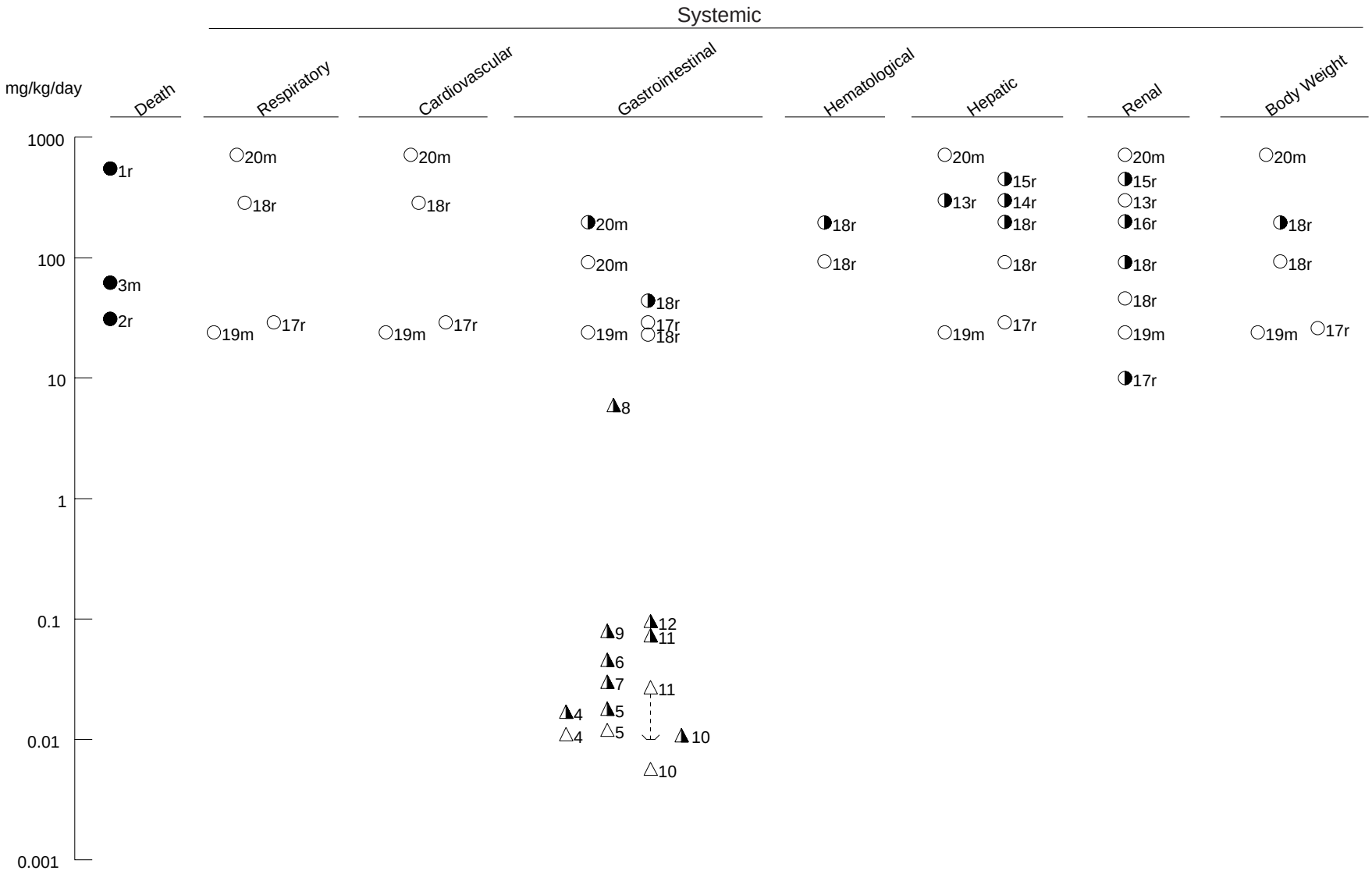


Figure 3-2. Levels of Significant Exposure to Copper - Oral (*Continued*)

Intermediate (15-364 days)

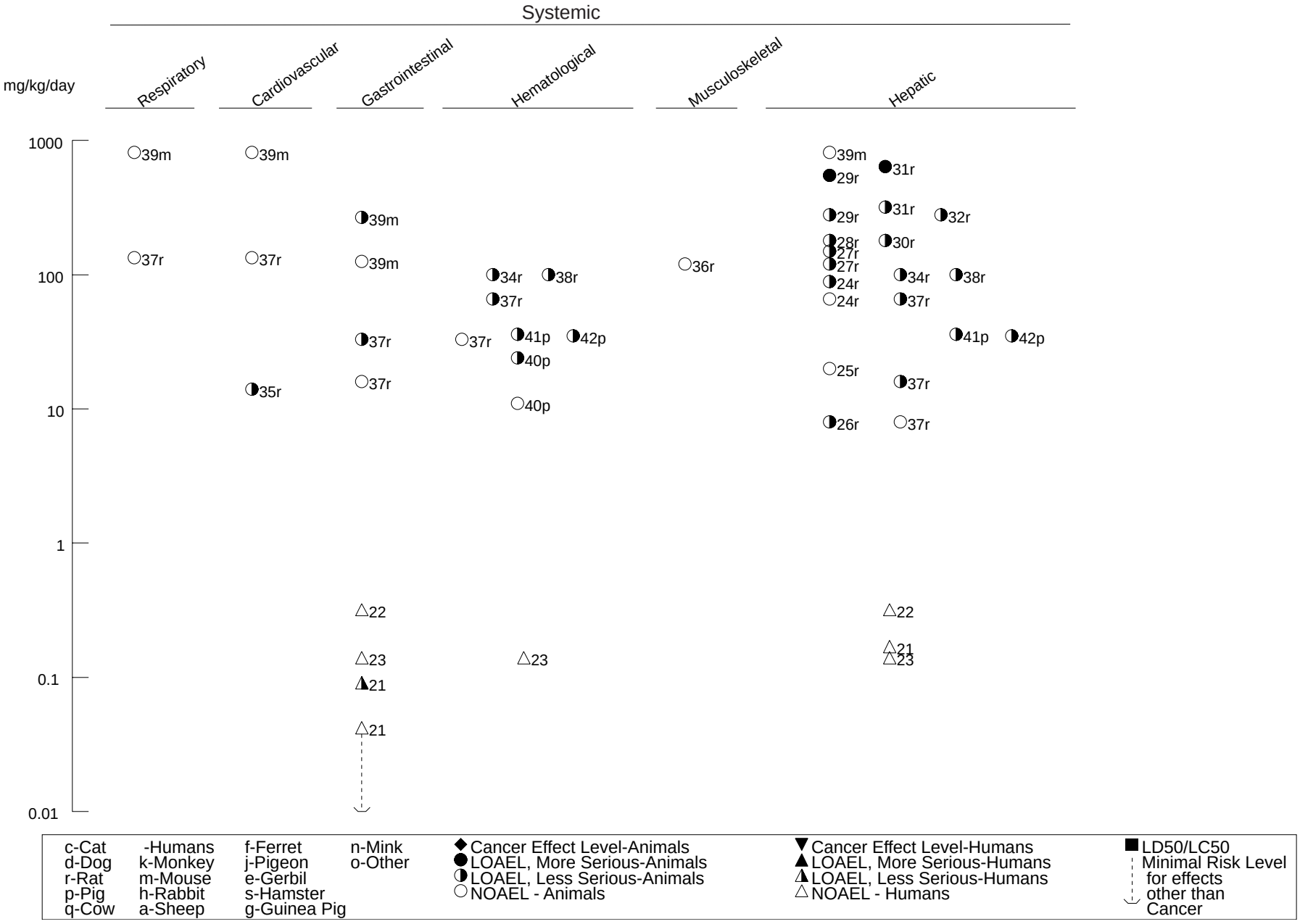


Figure 3-2. Levels of Significant Exposure to Copper - Oral (*Continued*)

Intermediate (15-364 days)

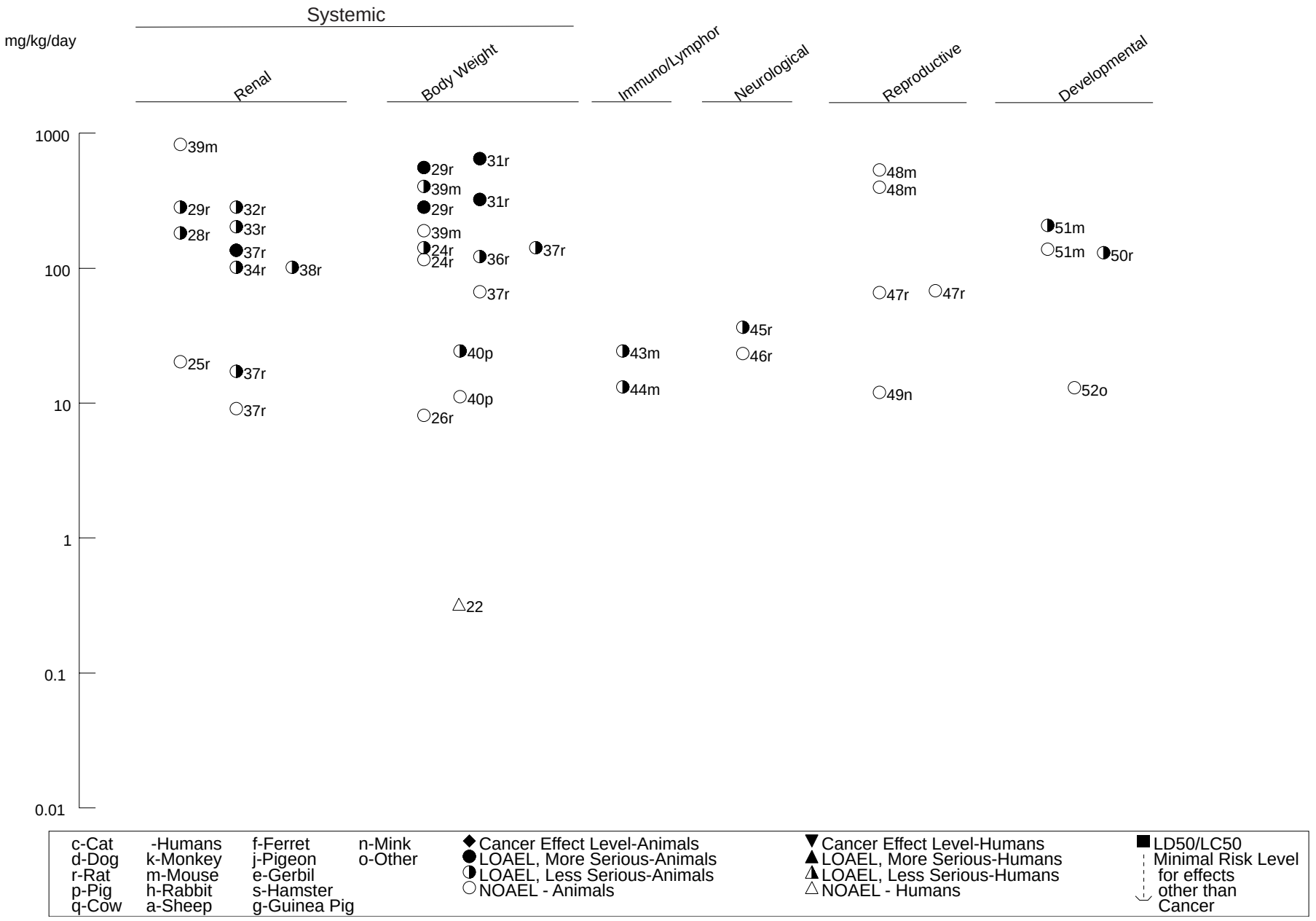
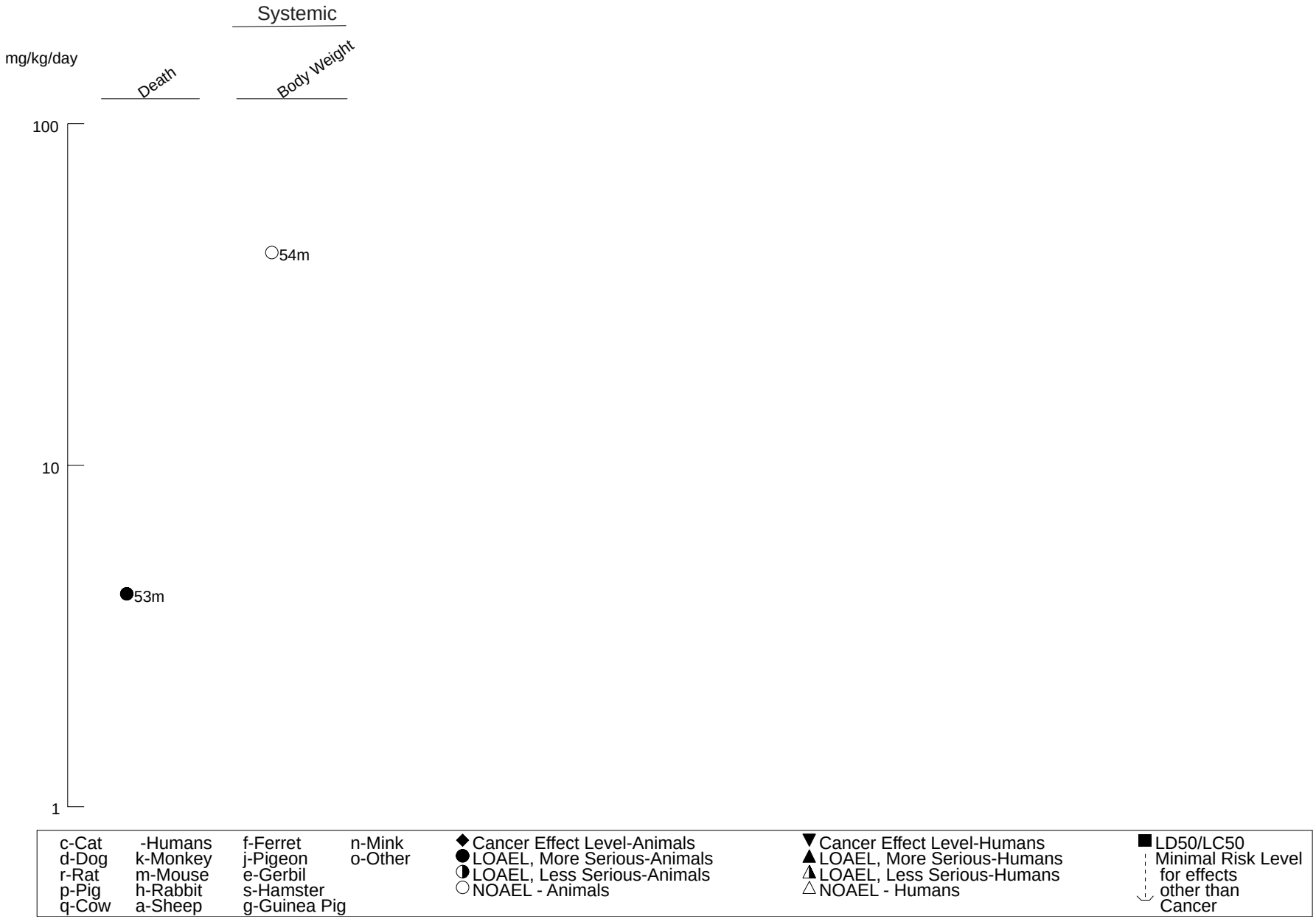


Figure 3-2. Levels of Significant Exposure to Copper - Oral (*Continued*)

Chronic (≥365 days)



Cardiovascular Effects. Several human studies have examined the possible relationship between increased serum copper levels and an increased risk of coronary heart disease. Although a number of studies have found increased risk of coronary heart disease deaths with increasing serum copper levels (Ford 2000), a number of studies have not found a relationship. However, whether copper directly affects atherosclerosis or is a marker of inflammation associated with atherosclerosis remains to be established.

There are limited data on the toxicity of copper to the cardiovascular system. A significant increase in systolic blood pressure was observed in rats exposed to 14 mg Cu/kg/day as copper carbonate in the diet for 15 weeks (Liu and Mederios 1986). No histological alterations were observed in the hearts of rats or mice exposed to 285 or 717 mg Cu/kg/day, respectively, for 14 days or 134 or 814 mg Cu/kg/day for 90 days (NTP 1993).

Gastrointestinal Effects. There are numerous reports of acute gastrointestinal effects in humans after ingestion of large amounts of copper in drinking water or beverages. The most prevalent effects are nausea and vomiting, which typically occur shortly after ingestion and are not persistent (Araya et al. 2001, 2003a, 2003b, 2003c; Chuttani et al. 1965; Eife et al. 1999; Gill and Bhagat 1999; Gotteland et al. 2001; Holleran 1981; Jantsch et al. 1984, 1985; Karlsson and Noren 1965; Knobeloch et al. 1994, 1998; Nicholas and Brist 1968; Olivares et al. 2001; Pizarro et al. 1999, 2001; Semple et al. 1960; Spitalny et al. 1984; Walsh et al. 1977). Abdominal pain and diarrhea have also been reported, but their incidence is typically much lower than nausea and vomiting. Although most of the data on gastrointestinal effects in humans come from case reports of accidental exposure from contaminated beverages with limited information on exposure levels, several recently conducted studies were designed to identify the threshold for gastrointestinal effects. These experiments typically involve adults ingesting a single dose of copper sulfate following an overnight fast (Araya et al. 2001, 2003a, 2003b; Gotteland et al. 2001; Olivares et al. 2001). Olivares et al. (2001) identified the lowest LOAEL for gastrointestinal effects; a significant increase in the incidence of nausea was observed at 4 ppm copper (0.01 mg Cu/kg) and higher. At 6 ppm, a significant increase in the incidence of vomiting was also observed. Administering the copper sulfate in an orange-flavored drink increased the threshold for nausea to 8 ppm (0.022 mg Cu/kg) (Olivares et al. 2001). In two multinational studies conducted by Araya and associates (Araya et al. 2001, 2003a), NOAEL and LOAEL values of 4 and 6 ppm (0.042 and 0.091 mg Cu/kg), respectively, were identified for nausea. Araya et al. (2003a) determined that both the copper concentration and the total copper dose are important variables in predicting a response; as the concentration and dose increase, the probability of eliciting nausea increases.

Similar thresholds for effects were observed in repeated exposure studies (Araya et al. 2003c; Pizarro et al. 1999, 2001). Abdominal pain, nausea, and/or vomiting were observed in women drinking water containing 5 ppm (0.096 mg Cu/kg) copper sulfate or copper oxide for 1 week (Pizarro et al. 2001). The occurrence of gastrointestinal effects (excluding diarrhea) was not significantly different in subjects ingesting copper sulfate and those ingesting copper oxide. In a 2-week exposure study by Pizarro et al. (1999), significant increases in the incidence of gastrointestinal symptoms were observed in subjects exposed to 3 or 5 ppm (0.0731 and 0.124 mg Cu/kg/day), but not to 1 ppm (0.0272 mg Cu/kg/day). The incidences of nausea, vomiting, and/or abdominal pain were 5, 2, 17, and 15% in the control, 1, 3, and 5 ppm groups, respectively. In a similarly designed study, Araya et al. (2003b) examined the occurrence of gastrointestinal symptoms in adults exposed to copper sulfate for 2 months. The incidences of gastrointestinal symptoms were 11.7, 15.3, 18.3, and 19.7% in the control, 2, 4, and 6 ppm groups, respectively. As analyzed using the chi-square test with Bonferroni correction, the incidence was significantly elevated in the 6 ppm (0.17 mg Cu/kg/day) group; if the Bonferroni correction was not used, the incidence was significantly elevated in the 4 ppm (0.091 mg Cu/kg/day) group. A case report by Spitalny et al. (1984) also examined the effects of repeated exposure to copper. Recurrent, acute symptoms, including nausea, vomiting, and abdominal pain, were reported by three of four family members shortly after drinking juice, coffee, or water in the morning. The effects disappeared when the family switched to bottled water. An early morning water sample contained 7.8 ppm copper. A study by Buchanan et al. (1991) also examined individuals with elevated levels of copper in household water. The occurrence of vomiting and nausea with abdominal pain was not significantly different among residents with a first-draw water sample of 3 ppm or higher, as compared to controls with less than 1.3 ppm copper in first-draw sample. The investigators noted that in a case-control study of this population, all of the cases reported that none of the subjects obtained their water immediately from the tap, but most (70%) only let it run for less than 1 minute. The study found that copper content in the tap water used for drinking averaged 14% of first draw samples.

Most of the available human studies examined the relationship between copper exposure and the manifestation of symptoms of gastrointestinal irritation; Gotteland et al. (2001) and Araya et al. (2003c) also looked at physiological alterations. Gotteland et al. (2001) found significant increases in gastric permeability to sucrose following the bolus ingestion of 10 ppm copper as copper sulfate (0.03 mg Cu/kg); no alterations in intestinal permeability to lactulose/mannitol were found. The increased gastric permeability was independent of gastrointestinal symptoms. A significant delay in decreasing the stomach’s antral area was found during the first hour after bolus ingestion of 10 ppm copper as copper

sulfate (0.046 mg Cu/kg) (Arayaet et al. 2003c). This change in antral area is suggestive of a delay in gastric emptying. As with gastric permeability, this effect was independent of gastrointestinal symptoms.

Gastrointestinal effects have also been reported in animal studies. Hyperplasia with hyperkeratosis of the squamous mucosa on the limiting ridge separating the forestomach from the glandular stomach was observed in rats and mice exposed to 44 and 197 mg Cu/kg/day, respectively, as copper sulfate in the diet for 14 days or 33 and 267 mg Cu/kg/day, respectively, as copper sulfate in the diet for 13 weeks (NTP 1990a). No gastrointestinal effects were observed in rats and mice exposed to 23 or 92 mg Cu/kg/day for 14 days or in rats and mice exposed to 16 or 126 mg Cu/kg/day 13 weeks. Additionally, no gastrointestinal effects were observed in rats and mice exposed to 29 or 24 mg Cu/kg/day as copper sulfate in drinking water (NTP 1990a).

Hematological Effects. There are limited data on the effect of copper on the human hematological system. Acute hemolytic anemia was observed in an 18-month-old child 2 days after he drank a solution containing approximately 3 g of copper sulfate (Walsh et al. 1977). Acute intravascular hemolysis was also reported in 5 of 125 individuals intentionally ingesting a large dose of copper sulfate (Ahasan et al. 1994). No alterations in hematocrit level or mean corpuscular volume were observed in individuals ingesting 0.14 mg Cu/kg/day as copper gluconate in a capsule for 12 weeks (Pratt et al. 1985).

Information on the hematological effects in animals associated with exposure to high levels of copper is also limited to several studies that measured hemoglobin and hematocrit values. Decreased hemoglobin and hematocrit values were observed in rats exposed to ≥66 mg Cu/kg/day (Kumar and Sharma 1987; NTP 1993; Rana and Kumar 1980) for 20–90 days and in pigs exposed to ≥24 mg Cu/kg/day for 48–54 days (Kline et al. 1971; Suttle and Mills 1966a, 1966b). Depletion of hematopoietic cells in the bone marrow was observed in rats exposed to 196 mg Cu/kg/day as copper sulfate in the diet for 14 days (NTP 1993). Contrary to these findings, Liu and Medeiros (1986) observed an increase in hemoglobin levels and no change in hematocrit levels in rats fed a diet containing 14 mg Cu/kg/day as copper carbonate for 20 weeks.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following oral exposure to copper.

Equivocal results on the effects of copper on the musculoskeletal system have been found. Depressed skeletal growth has been observed in rats administered 100 mg Cu/kg/day via gavage; tail length was used

to assess skeletal growth (Rana and Kumar 1980). Using radiographic data, no qualitative or quantitative differences were observed in bones of rats exposed to 120 mg Cu/kg/day as copper acetate in the diet for 21 weeks (Llewellyn et al. 1985). The different outcomes may reflect the different methods used to assess skeletal growth.

Hepatic Effects. With the exception of several defined syndromes—Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis—liver effects are rarely reported in humans, although this has not been extensively investigated. In a compilation of case reports of individuals intentionally ingesting copper sulfate, jaundice was reported in 11 of 53 individuals (Chuttani et al. 1965). Centrilobular necrosis, biliary stasis, elevated serum bilirubin level and aspartate aminotransferase activity, and elevated bile salts in the urine were found in five of the individuals with jaundice. Jaundice (Akintonwa et al. 1989), centrilobular congestion (Lamont and Duflou 1988), and acute hepatotoxicity (Ahasan et al. 1994) have also been reported in case reports of lethal ingestion of copper sulfate. O'Donohue et al. (1993) reported a case of an adult with jaundice and hepatomegaly following a 3-year exposure to copper supplements. For 2 years, the individual ingested 30 mg/day followed by 1 year of 60 mg/day. In a study of seven adults receiving capsules containing 0.14 mg Cu/kg/day as copper gluconate, no significant alterations in serum aspartate aminotransferase, alkaline phosphatase, serum gamma glutamyl transferase, or lactate dehydrogenase activities were found (Pratt et al. 1985). No alterations in biomarkers of liver damage (serum aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase) were observed in adults exposed to 0.17 mg Cu/kg/day as copper sulfate in drinking water for 2 months (Araya et al. 2003b).

Several studies have examined liver function in infants exposed to elevated levels of copper in drinking water. A no adverse effect level for liver effects was identified in a study of infants (3 months of age at study initiation) exposed to 0.315 mg Cu/kg/day as copper sulfate in drinking water for 9 months (Olivares et al. 1998). No alterations in total bilirubin levels or serum alanine aminotranferase, aspartate aminotransferase, or gamma-glutamyl transferase activities were found. A higher percentage of copper-exposed infants (30.4%) were withdrawn from the study, as compared to the control group (11.1%). The reasons for being withdrawn from the study were blood sampling refusal (eight infants in the copper group and two infants in the control group), protocol transgression (four infants in the copper group and no infants in the control group), and change of address (five infants in the copper group and one infant in the control group). Two recent surveys of infants exposed to 0.8 mg Cu/L in household water did not find significant alterations in serum parameters of liver function or alterations in liver ultrasound imaging tests (Zietz et al. 2003a, 2003b).

There is strong evidence to suggest that Wilson's disease, Indian childhood cirrhosis, and possible idiopathic copper toxicosis are caused by an increased genetic susceptibility to copper toxicity.

Wilson's Disease. Wilson's disease is an autosomal recessive genetic disorder with a worldwide occurrence of 1 in 30,000 to 1 in 100,000 depending on the population (Llanos and Mercer 2002; Scheinberg and Sternlieb 1996). It is characterized by high levels of copper in the liver and low levels of serum ceruloplasmin. The accumulation of copper in the liver is due to a genetic defect in one of the Cu-ATPases (ATP7B), resulting in impaired biliary excretion of copper. One of the early manifestations of the disease, typically at 8–12 years of age, is liver damage. Three types of liver damage are seen—cirrhosis, chronic active hepatitis, and fulminant hepatic failure. It is unlikely that the manifestation of Wilson's disease is related to exposure to high levels of copper; high levels of hepatic copper have been observed in affected individuals consuming average copper intakes (Scheinberg and Sternlieb 1996).

Indian Childhood Cirrhosis (ICC). ICC is a type of cirrhosis typically seen in infants and young children (6 months to 5 years of age with a mean of 18 months) living in rural areas of the Indian subcontinent. Other features include high rates of parental consanguinity and up to 22% of siblings affected (Pandit and Bhave 1996; Tanner 1998). Two of the most discriminatory features of ICC are coarse, dark brown orcein staining (representing copper) and intralobular pericellular fibrosis (Pandit and Bhave 1996). Liver copper levels ranging from 790 to 6,654 µg/g dry weight (mean of 939 µg/g) were found in 53 children diagnosed with ICC, as compared to levels of 8–118 µg/g (mean 42–45 µg/g) in 12 controls aged 6 months to >1 year (Bhave et al. 1982); interpretation of these study results is limited by the small number of controls and the lack of detail on the control group.

In a study of 100 children with ICC and 100 age-, sex-, and caste-matched controls, it was determined that ICC was attributable to the early introduction of cow or buffalo milk feeds contaminated with copper from brass vessels, which were used to store and heat the milk (Bhave et al. 1987). Although a cause and effect relationship between high copper intake and ICC has not been firmly established, there is strong evidence to support an association. In another study in which the parents of 100 children with ICC were advised to use aluminum or stainless steel vessels for preparing infant milk feeds, only 1 of 86 younger siblings of the children with ICC developed ICC (this child was known to have received copper-contaminated milk) as compared to 30 of 125 older siblings (Tanner 1998).

Idiopathic Copper Toxicosis (ICT). Although there are limited data on ICT, it is also believed to be caused by an autosomal-recessive inherited defect in copper metabolism and excess dietary copper

(Müller et al. 1998; Wijmenga 2002). In the literature, ICT is also referred to as Indian childhood cirrhosis-like liver disease, copper-associated liver disease in childhood, and Tyrollean infantile cirrhosis. In the last 25 years, there have been <200 cases of ICT reported in a number of countries including Australia, Austria, Germany, Ireland, Italy, Kuwait, Mexico, United Kingdom, and United States. With the exception of a study of ICT in 138 children living in Tyrol Austria (Müller et al. 1996), most papers describe the clinical course of 1–4 children. Compiling the data from these studies, Müller et al. (1998) found a number of patterns: (1) the age of onset of clinical symptoms occurs before the age of 2 years (infantile onset) or before the age of 5 years (late onset), although onset as late as 10 years has also been observed; (2) rapid progression and death within 2 weeks to 11 months; (3) very high copper levels in the liver, 190–3,360 µg/g dry weight (normal is <50 µg/g); (4) abnormal biochemical markers of liver damage such as aminotransferases, alkaline phosphatase, bilirubin, albumin, and prothrombin time; and (5) marked panlobular and pericellular fibrosis associated with an usually mild inflammatory infiltrate, ballooning degeneration of hepatocytes, and an abundance of Mallory bodies. The high levels of copper in the liver, the identification of environmental copper exposure, and the similarity of the clinical presentation and histopathology with ICC suggest that copper is the causative agent. As with ICC, an increased genetic susceptibility to copper toxicity has been suggested. A genealogic investigation conducted by Müller et al. (1996) provided suggestive evidence that the disease is transmitted in an autosomal recessive mode.

The hepatotoxicity of copper in animals has been described and investigated in a number of acute- and intermediate-duration oral exposure studies. The majority of these studies used rats; a small number of studies used pigs and mice. In addition to these studies, there are a number of studies in animals with similar genetic defects as Wilson's disease, including Long Evans Cinnamon (LEC) rats and Bennington terrier dogs. The results of these studies were not considered relevant to healthy humans and will not be discussed. The earliest symptoms of hepatotoxicity in rats orally exposed to copper are increases in serum chemistry enzymes, particularly alanine aminotransferase and asparate aminotransferase (Epstein et al. 1982; Fuentealba et al. 2000; Haywood 1980; Haywood and Comerford 1980; Kumar and Sharma 1987; NTP 1993; Sugawara et al. 1995). Continued exposure or exposure to higher concentrations can result in inflammation, parenchymal cell hypertrophy, and hepatocellular necrosis (Aburto et al. 2001b; Fuentealba et al. 2000; Haywood 1980, 1985; Haywood and Loughran 1985; Haywood et al. 1985a; NTP 1993). At very high doses, chronic hepatitis (Haywood 1985; Haywood and Loughran 1985) has also been observed.

Studies in rats provide information on the dose-response relationships as a function of exposure duration. The highest NOAEL and lowest LOAEL for liver effects in acutely exposed rats are 92 and 198 mg Cu/kg/day, respectively, administered as copper sulfate in the diet for 14 days (NTP 1993). Chronic inflammation was observed at the LOAEL; a LOAEL for serum chemistry changes was not identified in the available acute exposure studies because the only study testing low doses (NTP 1993) did not assess this parameter. The threshold for hepatoxicity in rats following intermediate-duration exposure appears to be between 8 - 16 mg Cu/kg/day. NTP (1993) found a significant increase in serum alanine aminotransferase activity in Fischer 344 rats exposed to 16 mg Cu/kg/day as copper sulfate in the diet for 13 weeks; no effects were observed at 8 mg Cu/kg/day. However, Epstein et al. (1982) found a significant increase in asparate aminotransferase in Sprague-Dawley rats exposed to 8 mg Cu/kg/day as copper sulfate in drinking water for 90 days; differences in the exposure route and rat strain may have contributed to these differences. Histological damage (chronic active inflammation and focal hepatocellular necrosis) has been observed at 66 mg Cu/kg/day (administered as copper sulfate in the diet for 90 days) and higher (NTP 1993). Severe hepatic damage (chronic hepatitis) has been observed in rats exposed to >550 mg Cu/kg/day as copper sulfate in the diet for 15 weeks (Haywood 1985; Haywood and Loughran 1985).

The available rat hepatoxocity data, along with toxicokinetic data, suggest that there are three phases of copper toxicity in the rat. In the first phase, copper levels increase in the liver, with minimal to no damage to hepatic tissues. As the hepatic copper levels increase, inflammation and necrosis occur. Thereafter, the copper levels in the liver begin to decrease and the parenchymal tissue begins to regenerate. At this point, the animal develops a tolerance to copper. Haywood et al. (1985a) speculated that the tolerance resulted from a shift in the liver from copper storage and biliary excretion to copper transport and renal clearance. Tolerance appears to protect the animals from subsequent liver toxicity. For example, no adverse liver effects were observed in rats exposed to 640 mg Cu/kg/day as copper sulfate in the diet when this exposure was preceded by a 15-week exposure to 320 mg Cu/kg/day as copper sulfate in the diet. This is in contrast to the severe hepatocellular necrosis that was observed in animals exposed to a control diet for 15 weeks followed by a 3-week exposure to 640 mg Cu/kg/day (Haywood and Loughran 1985). The time course of each phase of liver toxicity appears to be dose-related. At higher doses, the onset of the necrosis and regeneration occurred earlier as compared to lower doses. Additionally, there appears to be an upper limit of copper intake, which would induce copper tolerance; doses that exceed this level would result in permanent damage to the liver. Dietary exposure of rats to ≥550 mg Cu/kg/day as copper sulfate for 15 weeks resulted in chronic hepatitis with no evidence of regeneration of parenchymal tissue (Haywood and Loughran 1985).

There are limited experimental data on the hepatoxocity of copper in other animal species. Pigs fed a diet providing 35–36 mg Cu/kg/day for 7 weeks had a significant increase in aspartate aminotransferase activities (Suttle and Mills 1966a, 1966b). It appears that rats and pigs are equally sensitive to high levels of copper in the diet or drinking water. In contrast, mice do not appear to be as sensitive to the hepatic toxicity of copper as rats. No hepatic effects were observed in mice exposed to 814 mg Cu/kg/day for 13 weeks as compared to rats, which exhibited an increase in alanine aminotransferase activity at 16 mg Cu/kg/day and chronic active inflammation at 66 mg Cu/kg/day (NTP 1993).

Renal Effects. There is limited information on the renal toxicity of copper in humans. Congestion of the glomeruli and denudation of tubular cells were observed in four individuals consuming a single lethal dose of copper sulfate (Chuttani et al. 1965). Acute renal failure was reported in 5 of 125 individuals intentionally ingesting large doses of copper sulfate (Ahasan et al. 1994). Hematuria, glycosuria, cylindruria, and proteinuria, indicative of renal tubular damage, were observed in a child who drank a solution containing approximately 3 g of copper sulfate (Walsh et al. 1977).

A number of animal studies confirm that the kidney is a target of copper toxicity. Renal toxicity as a result of copper loading follows a specific time course (Haywood 1980, 1985; Haywood et al. 1985a, 1985b). No treatment-related effects were observed in rats exposed to 300 mg Cu/kg/day as copper sulfate in the diet for 1–2 weeks (Haywood 1980). However, eosinophilic droplets were observed in the epithelial cell cytoplasm of the proximal convoluted tubules in rats exposed to 450 mg Cu/kg/day for 2 weeks (Haywood et al. 1985a). The number of eosinophilic droplets increased with increasing duration (Haywood 1980, 1985). Exposure to 100–280 mg Cu/kg/day for 3–5 weeks resulted in necrosis and degeneration of proximal tubule cells (Haywood 1985; Haywood et al. 1985a, 1985b; Rana and Kumar 1980). After 9 weeks, extensive desquamation of the epithelial cells of the proximal convoluted tubules was evident in rats exposed to 180 mg Cu/kg/day (Haywood 1980). Complete regeneration of the proximal tubules was observed after 15 weeks of copper treatment in rats exposed to 180–280 mg Cu/kg/day (Haywood 1980, 1985; Haywood et al. 1985a, 1985b). In contrast to the Haywood and associates studies, a 13-week study by NTP (1993) did not find evidence of regeneration of renal tissue. An increase in protein droplets in epithelial cell cytoplasm and the lumen of the proximal convoluted tubules was observed in rats exposed to 10 or 92 mg Cu/kg/day as copper sulfate in drinking water or diet, respectively, for 2 weeks or to 33 mg Cu/kg/day as copper sulfate in the diet for 13 weeks. At 134 mg Cu/kg/day, karyomegaly and tubule cell degeneration were also observed. Additional renal effects observed in the intermediate-duration study included an increase in serum urea nitrogen levels in females exposed to ≥17 mg Cu/kg/day, increased urinary glucose output in males exposed to ≥66 mg

Cu/kg/day, and increased urinary aspartate aminotransferase and N-acetyl-β-glucosaminidase activities in male and female rats exposed to 140 or 134 mg Cu/kg/day, respectively. The NTP (1993) study identified a NOAEL of 9 mg Cu/kg/day. No effects were observed in mice fed a diet for 13 weeks which provided 814 mg Cu kg/day as copper sulfate (NTP 1993).

Body Weight Effects. No studies were located regarding body weight effects in humans following oral exposure to copper.

Dietary exposure studies have reported 12–24% decreases in body weight gain in rats following exposure to 120–140 mg Cu/kg/day for 2–15 weeks (Llewellyn 1985; NTP 1993), in mice following exposure to 398 mg Cu/kg/day for 13 weeks (NTP 1993), or in pigs (magnitude of decreased weight gain not reported) following exposure to 24 mg Cu/kg/day for 54 days (Kline et al. 1971). No effect levels of 66 (NTP 1993), 187 (NTP 1993), and 11 mg Cu/kg/day (Kline et al. 1971) have been reported in rats, mice, and pigs, respectively; Epstein et al. (1982) also reported no adverse effects on body weight gain in rats exposed to 8 mg Cu/kg/day in drinking water. More severe decreases in body weight gain and weight loss have also been reported (Haywood 1985; Haywood and Loughran 1985); the weight loss was reported at lethal concentrations. Only one study examined the effect of copper on body weight gain following chronic-duration exposure (lifetime exposure beginning at 58 days of age); this study found no biologically significant effect in mice exposed to 42 mg Cu/kg/day as copper gluconate in drinking water (Massie and Aiello 1984).

3.2.2.3 Immunological and Lymphoreticular Effects

Information on the immunotoxicity of copper following oral exposure is limited to two drinking water studies in which mice were exposed to several concentrations of copper sulfate for 8 weeks (Pocino et al. 1990) or copper chloride for 3–5 or 8–10 weeks (Pocino et al. 1991). In these studies, groups of mice underwent several tests to assess immune function: *in vitro* lymphoproliferative responses to *Escherichia coli* lipopolysaccharide (LPS), and concanavalin A (Con A), induction and evaluation of antibody response to sheep red blood cells, evaluation of autoantibody production, and induction and elicitation of delayed-type hypersensitivity response (only tested in the Pocino et al. 1991 study). At the lowest dose tested (13 mg Cu/kg/day as copper chloride), impaired cellular (proliferative response to LPS) and humoral (autoantibody production) immunity were observed. Impaired performance on the remaining immune function tests were observed at ≥26 mg Cu/kg/day as copper chloride (Pocino et al. 1991) or

≥24 mg Cu/kg/day as copper sulfate (Pocino et al. 1990). The LOAEL values from these studies are presented in Table 3-2 and Figure 3-2.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to copper.

No effects on spontaneous motor activity (assessed using an actophometer), learning ability (assessed using a pole climbing chamber), or relearning capacity and memory (assessed using a Y-maze) were observed in rats fed a diet containing 23 mg Cu/kg/day as copper sulfate (Murthy et al. 1981). This study found no alterations in brain dopamine or norepinephrine levels. De Vries et al. (1986) also did not find significant alterations in corpus striatial dopamine levels in rats exposed to 36 mg Cu/kg/day as copper sulfate in drinking water for 11 months. However, a 25% decrease in a dopamine metabolite, 3,4-di-hydroxyphenylacetic acid, was found in the corpus striatum.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to copper.

Reproductive performance, as assessed by the length of gestation, number of kits whelped, and average kit weight, was not adversely affected in minks fed a diet containing 12 mg Cu/kg/day as copper sulfate (Aulerich et al. 1982). No other oral exposure studies examined reproductive function. The intermediate-duration study by NTP (1993) did not find any histological alterations or alterations in sperm morphology or vaginal cytology in male and female rats exposed to 66 and 68 mg Cu/kg/day, respectively, or in male and female mice exposed to 398 and 536 mg Cu/kg/day, respectively. The NOAEL values for reproductive effects are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects of humans following oral exposure to copper.

There are limited data on the developmental toxicity of copper in experimental animals. Delayed growth and development were observed in the offspring of rats exposed to 130 mg Cu/kg/day as copper sulfate in

the diet for 7 weeks prior to mating and during gestation (Haddad et al. 1991). In 11.5-day-old embryos, significant decreases in mean somite number, crown-rump length, and yolk sac diameter were observed. In 21.5-day-old fetuses and newborns, delayed ossification was observed in the cervical and cauda vertebrae, sternum, metacarpals, forelimb phalanges, metatarsals, and hindlimb phalanges. Exposure of mouse dams to a higher dose, 208 mg Cu/kg/day as copper sulfate in the diet, resulted in decreased mean litter size and decreased fetal body weights; the statistical significance of these effects is not known (Lecyk 1980). No statistically significant alterations in newborn mortality or body weight were observed in the offspring of mink exposed to 13 mg Cu/kg/day as copper sulfate in the diet (Aulerich et al. 1982). There was a trend toward increased kit mortality between birth and 4 weeks of age in the offspring of mink exposed to 6 or 13 mg Cu/kg/day. The incidences were 12, 9, 19, 38, and 32% in the 1, 6, 3, 6, and 13 mg Cu/kg/day groups, respectively; the statistical significance of this effect was not reported. The NOAEL values and all reliable LOAEL values for developmental effects in each species are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to copper.

Several oral studies have examined the carcinogenicity of copper compounds in animals. These studies did not find increases in the occurrence of tumors in mice exposed to 86 mg Cu/kg/day as the pesticide, copper 8-hydroxyquinoline (BRL 1968), liver tumors in rats exposed to 130 mg Cu/kg/day as copper acetate (Kamamoto et al. 1973), or large intestine tumors in rats exposed to 9 mg Cu/kg/day as an unspecified copper compound (Greene et al. 1987). These studies are limited in scope and it can not be determined whether the maximum threshold dose (MTD) was achieved. An increased occurrence of hepatocellular carcinomas has been reported in Long-Evans Cinnamon rats (Sawaki et al. 1994), an animal model for Wilson's disease. However, liver cancer has not been reported in individuals with Wilson's disease; thus the significance of this finding in not known.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans and animals following dermal exposure to copper.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, or body weight effects in humans or animals following dermal exposure to copper.

Hematological Effects. Hemolytic anemia was observed in a severely burned and debilitated child in whom copper sulfate crystals were being applied to granulation tissue. Increased serum and urine copper levels were observed (Holtzman et al. 1966). Because the skin was severely damaged, this study cannot be used to predict the dermal toxicity of copper following exposure to intact skin. No studies were located regarding hematological effects in animals following dermal exposure to copper.

Ocular Effects. Eye irritation has been reported by factory workers exposed to copper dust (Askergren and Mellgren 1975). No studies were located regarding ocular effects in animals following exposure to copper.

3.2.3.3 Immunological and Lymphoreticular Effects

In some individuals, exposure to copper metal produces pruritic dermatitis. Saltzer and Wilson (1968) reported a case of a woman who had recurrent pruritus on her ring finger and wrist caused by copper metal in her ring and wristwatch. Allergic contact dermatitis has been observed in individuals following a patch test using a copper penny and/or a copper sulfate solution (Barranco 1972; Saltzer and Wilson 1968).

No studies were located regarding the following health effects in humans and/or animals after dermal exposure to copper:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

Cardiovascular Effects. A dramatic decrease in pulse pressure and heart rate was observed in New Zealand white rabbits infused with 2.5 mg Cu/kg as copper sulfate with an infusion pump in the femoral vein for 10–15 minutes (Rhee and Dunlap 1990). Systolic and diastolic pressure initially increased, then rapidly decreased.

Reproductive Effects. Intraperitoneal exposure to 0.95 or 1.4 mg Cu/kg/day for 26 days resulted in significant decreases in testes, seminal vesicle, and ventral prostate weights and in plasma testosterone levels in Wistar rats (Chattopadhyay et al. 1999); decreases in testicular Δ5-3β-hydroxysteroid dehydrogenases and 17β-hydroxysteroid dehydrogenase activities were also observed at 1.4 mg Cu/kg/day. An in vitro study (Holland and White 1988) demonstrated that cupric ions and cuprous ions decrease human spermatozoa motility.

Cancer. Several studies have examined the carcinogenicity of copper compounds following parenteral administration. No significant alterations in tumor incidence were observed in male Wistar rats receiving subcutaneous injections of 2 mg Cu/kg/day as copper acetate (Yamane et al. 1984), in male and female F344 rats receiving intramuscular injections of 0.25 or 0.41 mg Cu/kg/day as finely ground copper (Furst 1971), or in Wistar rats receiving 150 mg Cu/kg as copper oxide, 150 mg Cu/kg as copper sulfide, or 70 mg Cu/kg as copper sulfate (Gilman 1962). An increase in the occurrence of renal cell carcinoma was observed in male Wistar rats receiving 3–5 mg Cu/kg as cupric nitrilotriacetate 5 days/week for 12 weeks (Toyokuni et al. 1996); cupric nitrilotriacetate is a chelated compound of copper that is water soluble. A study by BRL (1968) found a slight, but statistically significant, increase in the incidence of reticulum cell sarcomas in mice 18 months after receiving a single subcutaneous injection of copper 8-hydroxyquinoline; the significance of this finding is not known.

3.3 GENOTOXICITY

No studies were located regarding genotoxicity in humans after inhalation, oral, or dermal exposure to copper or its compounds. Several studies have assessed the genotoxicity of copper sulfate following oral or parenteral exposure; the results of these *in vivo* genotoxicity studies are summarized in Table 3-3. Significant increases in the occurrence of micronuclei and chromosomal aberrations have been observed in chick bone marrow cells and erythrocytes (Bhunya and Jena 1996) and mouse bone marrow cells (Agarwal et al. 1990; Bhunya and Pati 1987). A study by Tinswell and Ashby (1990) did not find

Table 3-3. Genotoxicity of Copper *In Vivo*

Species (test system)	End point	Results	Reference	Compound
Drosophila melanogaster (injection into larvae)	Recessive lethals	+	Law 1938	Copper sulfate
White Leghorn chick bone marrow cells (intraperitoneal injection and oral exposure)	Chromosomal aberrations	+	Bhunya and Jena 1996	Copper sulfate
White Leghorn chick bone marrow cells (intraperitoneal injection and oral exposure)	Micronuclei	+	Bhunya and Jena 1996	Copper sulfate
White Leghorn chick erythrocytes (intraperitoneal injection and oral exposure)	Micronuclei	+	Bhunya and Jena 1996	Copper sulfate
Inbred Swiss mice bone marrow cells (intraperitoneal and/or subcutaneous injection)	Chromosomal aberrations	+	Bhunya and Pati 1987	Copper sulfate
Inbred Swiss mice bone marrow cells (intraperitoneal and/or subcutaneous injection)	Micronuclei	+	Bhunya and Pati 1987	Copper sulfate
Inbred Swiss mice (intraperitoneal injection)	Sperm abnormalities	+	Bhunya and Pati 1987	Copper sulfate
CBA mice bone marrow cells (intraperitoneal injection)	Micronuclei	–	Tinwell and Ashby 1990	Copper sulfate
Swiss mice (intraperitoneal injection)	Chromosomal aberrations	+	Agarwal et al. 1990	Copper sulfate

+ = positive results; – = negative results

increases in the number of micronuclei in mouse bone marrow cells. Increases in the occurrence of recessive lethals (Law 1938) and sperm abnormalities (Bhunya and Pati 1987) have also been observed in Drosophila and mice, respectively.

Several studies copper sulfate and copper chloride genotoxicity did not find significant increases in the occurrence of reverse mutations in *Salmonella typhimurium* (Marzin and Phi 1985; Tso and Fung 1981; Wong 1988) or *Saccharomyces cerevisiae* (Singh 1983). In contrast, Demerec et al. (1951) found an increased occurrence of reverse mutations in *Escherichia coli*. Positive results have been found in studies testing for DNA damage. Errors in DNA synthesis by viral DNA polymerase (Sirover and Loeb 1976), a reduction in DNA synthesis (Garrett and Lewtas 1983; Sirover and Loeb 1976), and an increase in the occurrence of DNA strand breaks (Sideris et al. 1988; Sina et al. 1983) have been observed. The increase in sister chromatid exchange in Chinese hamster cells (Sideris et al. 1988) is consistent with the clastogenic effects observed in *in vivo* assays. The results of these studies are summarized and are presented in Table 3-4.

3.4 TOXICOKINETICS

Physiologically normal levels of copper in the body are held constant by alterations in the rate and amount of copper absorption, compartmental distribution, and excretion.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption following inhalation exposure of humans to copper. There are limited data on copper absorption in animals. Copper oxide was observed in alveolar capillaries 3 hours after albino rats were exposed to a welding dust aerosol generated from pure copper wires (no additional exposure information was provided) (Batsura 1969). The half-time of copper sulfate in the lungs was estimated to be 7.5 hours after intratracheal instillation of 20 µg copper per Wistar rat (Hirano et al. 1990).

Table 3-4. Genotoxicity of Copper *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Prokaryotic organisms:					
Salmonella typhimurium TA102	Reverse mutation	NT	–	Marzin and Phi 1985	Copper sulfate
S. typhimurium TA98, TA102, TA1535, TA1537	Reverse mutation	–	–	Wong 1988	Copper chloride
S. typhimurium TA100	Reverse mutation	NT	–	Tso and Fung 1981	Copper chloride
Escherichia coli	Reverse mutation	NT	+	Demerec et al. 1951	Copper sulfate
Avian myeloblastosis virus, DNA polymerase	Errors in DNA synthesis	NT	+	Sirover and Loeb 1976	Copper chloride
Bacillus subtilis	rec assay	NT	–	Nishioka 1975	Copper chloride
Eukaryotic organisms:					
Fungi:					
Saccharomyces cerevisiae	Reverse mutation	NT	–	Singh 1983	Copper sulfate
S. cerevisiae	Recombination	NT	–	Sora et al. 1986	Copper sulfate
Mammalian cells:					
Chinese hamster ovary cells	DNA synthesis	NT	+	Garrett and Lewtas 1983	Copper chloride
Rat hepatocytes	DNA strand breaks	NT	+	Sina et al. 1983	Copper sulfate
Chinese hamster V79 cells	DNA strand breaks	NT	+	Sideris et al. 1988	Copper nitrate
Chinese hamster V79 cells	Sister chromatid exchange	NT	+	Sideris et al. 1988	Copper nitrate

+ = positive results; – = negative results; DNA = deoxyribonucleic acid; NT = not tested

3.4.1.2 Oral Exposure

Copper is absorbed from the stomach and small intestine; there appear to be species differences in the site of maximal absorption. The site of maximal copper absorption is not known for humans, but it is assumed to be the stomach and duodenum because of the rapid appearance of ^{64}Cu in the plasma after oral administration (Bearn and Kunkel 1955). In rats, copper is primarily absorbed from the duodenum, and to a lesser extent from the stomach (Van Campen and Mitchell 1965); in Golden hamsters, copper is primarily absorbed from the lower small intestine (25–35 cm from the pylorus) (Crampton et al. 1965).

Copper is absorbed from the gastrointestinal tract as ionic copper or bound to amino acids. Absorption of the latter apparently involves at least two kinetically distinguishable processes. The first mechanism transports copper from the mucosal side of the intestine to the serosal side. Only a small fraction of the ingested copper is transported via this mechanism (Crampton et al. 1965; Gitlan et al. 1960). The second mechanism of copper absorption involves the delivery of copper to the absorptive surface, mucosal uptake and binding to metallothionein or another intestinal binding protein (Evans and LeBlanc 1976). The copper bound to metallothionein can be slowly released to the blood (Marceau et al. 1970) or is excreted when the mucosal cell is sloughed off.

A number of human studies have examined the oral absorption of ^{64}Cu; the average absorption efficiencies ranged from 24 to 60% in presumably healthy adults (Jacob et al. 1987; Johnson et al. 1988b; Strickland et al. 1972; Turnlund et al. 1982, 1983, 1985, 1988a; 1988b; 1989; Weber et al. 1969).

Numerous factors may affect copper absorption. These factors include: the amount of copper in the diet (Farrer and Mistilis 1967; Strickland et al. 1972; Turnland et al. 1989), competition with other metals, including zinc, iron, and cadmium (Davies and Campbell 1977; Hall et al. 1979; Haschke et al. 1986; Hoogenraad et al. 1979; Prasad et al. 1978; Turnland et al. 1988a) and age (Varada et al. 1993). The absorption of copper appears to be inversely related to the amount of copper in the gastrointestinal tract (Strickland et al. 1972; Turnland et al. 1989). In a study of 11 young men administered various copper doses in food over a period of 42–98 days, absorption efficiencies of 55–56, 36, and 12% were found at doses of 0.785, 1.68, and 7.53 mg/day, respectively (Turnland et al. 1989). In humans, the amount of stored copper does not appear to influence copper absorption (Strickland et al. 1972). In rats, the absorption of copper appears to be inversely related to the amount of cadmium in the diet (Davies and Campbell 1977). A significant decrease in copper absorption was observed when the copper:cadmium

ratio was 1:4. The amount of copper retained in the intestinal mucosal cells was also inversely related to cadmium dietary concentration. In addition, increased levels of zinc in the diet result in decreased in copper absorption in humans and rats (Hall et al. 1979; Hoogenraad et al. 1979; Prasad et al. 1978). Turnland et al. (1988a) found that diets low in zinc (below the dietary requirement) decreased copper absorption in humans; 48.1% of radiolabeled copper was absorbed when the diet contained 1.3 mg copper and 16.5 mg zinc (dietary requirement is 15 mg zinc), and 37.2–38.5% of radiolabelled copper was absorbed when the diet contained 1.3 mg copper and 5.5 mg zinc. A decrease in copper absorption has been observed in infants with high intakes of iron (Haschke et al. 1986). Apparently conflicting results have been reported on the effect of ascorbic acid on copper absorption in humans. Based on a decrease in serum ceruloplasmin levels, Finley and Cerklewski (1983) concluded that a diet high in ascorbic acid resulted in a decrease in copper status. In a study by Jacob et al. (1987), copper absorption was not affected by a high ascorbic acid intake. A decrease in serum ceruloplasmin activity was also found; however, the amount of ceruloplasmin protein was not affected.

Studies in humans and animals provide suggestive evidence of age-related changes in copper absorption. Varada et al. (1993) found that copper absorption was linear and nonsaturable in suckling (16 days of age) and weanling (21–22 days of age) rats. In contrast, copper absorption was saturable in adolescent rats (6 weeks of age). The levels of copper retained in the intestine were greater in the suckling rats than in the weanling or adolescent rats. However, the increased retention was not related to increased metallothionen levels; the levels of metallothionen (after zinc induction) were higher in the adolescent rats compared to the younger rats. A linear relationship between copper intake and retention was also found in a balance study of infants (aged 2–16 weeks) (Dörner et al. 1989). Olivares et al. (2002) did not find significant differences in copper absorption between 1-month-old and 3-month-old infants. The relatively small range of doses used in this study does not allow for a determination of whether copper absorption is saturable in infants. Several studies of adults did not find differences in copper absorption between male and female adults aged 20–83 years (Johnson et al. 1992) or between elderly men (65–74 years) and young men (22–30 years) (Turnland et al. 1982, 1988b).

Human studies did not find that increased levels of fiber (α-cellulose or phytate) (Turnland et al. 1985) or ascorbic acid (Turnland et al. 1987) significantly altered copper absorption. However, a study in rats found an increase in fecal excretion of copper (and a decrease in apparent absorption) in rats fed a high fiber (potato fiber or sugar beet pulp) diet (Gralak et al. 1996). The administration of copper in infant formula or in a solution high in fulvic acid did not appear to influence copper uptake from the intestinal lumen into the intestinal mucosa of suckling rats, as compared to copper in drinking water (Lind and

Glynn 1999). However, the absorption rate of copper into the circulatory system was decreased when administered in the infant formula or fulvic acid solutions. Gender does not appear to influence copper absorption. Johnson et al. (1992) found that women aged 20–59 years absorbed more copper (66.1–74.1%) than similarly aged men (62.0–69.2%); however, when net copper absorption was normalized by body weight, no sex-related differences in absorption were found. No sex-related differences in net copper absorption were found in older (60–83 years) men and women.

3.4.1.3 Dermal Exposure

The available *in vivo* data do not provide information on the rate and extent of absorption through intact skin following dermal exposure of humans or animals to copper. Following a copper azide explosion that yielded metallic copper and nitrogen fumes, a small increase in serum copper levels was found in the affected worker (Bentur et al. 1988). Similarly, animal studies demonstrate that copper can pass through dermal barriers when applied with an appropriate vehicle, (e.g., salicylic acid or phenylbutazone) (Beveridge et al. 1984; Walker et al. 1977). *In vitro* studies suggest that copper is poorly absorbed through intact skin. Less than 6% of copper deposited on *ex vivo* human skin samples was absorbed (Pirot et al. 1996a, 1996b); copper chloride was absorbed to a higher extent than copper sulfate (Pirot et al. 1996a).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding the rate and extent of distribution of copper following inhalation exposure of humans or animals.

3.4.2.2 Oral Exposure

Following ingestion of copper, copper levels in the blood rapidly rise. The copper is predominantly bound to albumin. There is some evidence that albumin plays a passive role in copper transport, carrying a large portion of the exchangeable copper in the circulation and releasing this to other carriers for actual cell-specific uptake. There is also evidence that transcuprein is another plasma protein carrier (Weiss and Linder 1985). Thus, dietary copper is transported to, and enters, the liver and kidney. Copper then reemerges into the plasma bound to the ceruloplasmin. Ceruloplasmin, which tightly binds six or seven

copper atoms (Musci et al. 1993; Saenko et al. 1994), is the most abundant copper protein in the plasma; 60–95% of the plasma copper is bound to ceruloplasmin (Harris 1993). Copper is transported from the liver to other tissues via ceruloplasmin. Ceruloplasmin does not enter the cell (Percival and Harris 1990). Copper, probably as Cu(I) rather than Cu(II) (Dameron and Harris 1989; Percival and Harris 1989), enters the cell via a carrier-mediated process. The membrane-bound copper transporting adenosine triphosphatase (Cu-ATPase), which selectively binds copper ions, transports copper ions into and out of cells (Harris et al. 1998). In most organs and tissues, copper turnover is biphasic (Levenson and Janghorbani 1994). In the plasma, the half-lives of the first and second components were 2.5 and 69 days, respectively. It is likely that the first order component is ceruloplasmin associated copper. The respective calculated copper half-lives for other tissues are 3.9 and 21 days for the liver, 5.4 and 35 days for the kidney, and 23 and 662 days for the heart; copper turnover in the brain appears to be monophasic with a half-life of 457 days.

3.4.2.3 Dermal Exposure

No studies were located regarding the rate and extent of distribution of copper following dermal exposure of humans or animals to copper.

3.4.3 Metabolism

The metabolism of copper consists mainly of its transfer to and from various organic ligands, most notably sulfhydryl and imidazole groups on amino acids and proteins. Several specific binding proteins for copper have been identified that are important in the uptake, storage, and release of copper from tissues.

In the liver and other tissues, copper is stored bound to metallothionein and amino acids and in association with copper-dependent enzymes. Several studies have shown that copper exposure induces metallothionein synthesis (Mercer et al. 1981; Wake and Mercer 1985). Increased levels of metallothionein may be associated with resistance to copper toxicity in pigs (Mehra and Bremner 1984). Ceruloplasmin is synthesized in the liver. Copper is incorporated into the molecule, and it is released from the liver. Copper exposure has also been shown to induce ceruloplasmin biosynthesis (Evans et al. 1970b; Haywood and Comerford 1980).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies were located regarding the rate and extent of excretion of copper following inhalation exposure of humans or animals.

3.4.4.2 Oral Exposure

Bile is the major pathway for the excretion of copper. After the oral administration of radioactive copper as copper acetate in healthy humans, 72% was excreted in the feces (Bush et al. 1955). A considerable fraction of fecal copper is of endogenous biliary origin. The remainder of the fecal copper is derived from unabsorbed copper and copper from desquamated mucosal cells. Copper in bile is associated with low molecular weight copper binding components as well as macromolecular binding species (Gollan and Dellar 1973). Reabsorption of biliary copper is negligible (Farrer and Mistilis 1967).

Normally, 0.5–3.0% of daily copper intake is excreted into the urine (Cartwright and Wintrobe 1964).

3.4.4.3 Dermal Exposure

No studies were located regarding the rate and extent of excretion of copper following dermal exposure of humans or animals to copper.

3.4.4.4 Other Routes of Exposure

Biliary excretion of copper following intravenous administration does not increase proportionally with dosage, suggesting that the hepatobiliary transport of copper is saturable (Gregus and Klaassen 1986). Thus, at high copper intakes, urinary copper excretion increases (Gitlan et al. 1960).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological

processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

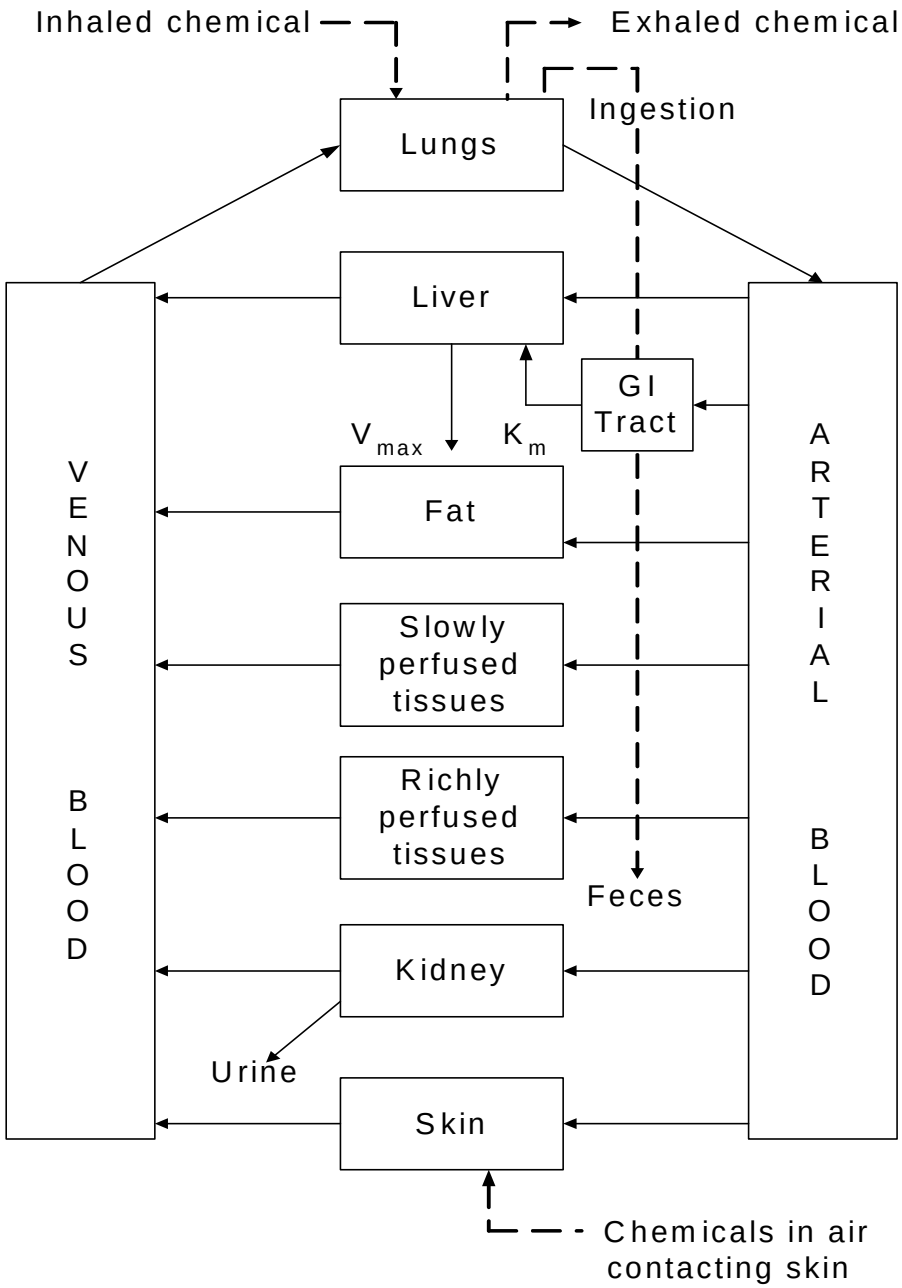
A PBPK model for copper has not been identified.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Copper is an essential element required for the normal functioning of more than 30 enzymes. The ability of copper to cycle between an oxidized state, Cu(II), and reduced state, Cu(I), is used by cuproenzymes involved in redox reactions. However, it is this property of copper that is also potentially toxic because the transitions between Cu(II) and Cu(I) can result in the generation of superoxide radicals and hydroxyl radicals (Camakaris et al. 1999). Under most circumstances, a number of homeostatic mechanisms maintain a physiologically essential concentration of copper. Copper homeostasis involves regulation of absorption, cellular uptake, intracellular transport, sequestration/storage, cellular efflux, and excretion from the body. Turnland et al. (1989) demonstrated that copper absorption from the gastrointestinal tract is inversely proportional to dietary intake; as dietary copper increases, absorption efficiency decreases. At dietary concentrations of 0.785, 1.68, and 7.53 mg/day (the recommended dietary allowance [RDA] for copper is 0.900 mg/day), 56, 36, and 12%, respectively, of the radiolabelled copper was absorbed. How the absorption of copper is regulated is not fully understood. *In vitro* studies provide evidence that copper uptake into intestinal cells appears to be saturable (Arredondo et al. 2000). This study also provides suggestive evidence that copper uptake into the intestinal cell and efflux are influenced by intracellular copper concentrations. There is evidence that copper diffuses across the intestinal cell membrane; however, it is unlikely that this is the only absorption mechanism. It is possible that recently identified copper transporters (hCtr1 and hCtr2) play a role in the regulation of copper uptake. The Menkes protein (MNK), a copper-translocating P-type ATPase, may be involved in the transport of copper across the basolateral membrane of intestinal cells (Pena et al. 1999). MNK protein is involved the delivery of copper to copper-dependent enzymes and the efflux of copper from the cell. The export of

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan et al. 1994

copper via the MNK protein appears to be regulated by intracellular copper concentration. Exposure to copper produces a conformational change in the MNK protein resulting in the formation of a copper cluster, which allows access to the phosphorylation site that upon phosphorylation, initiates copper translocation (Dameron and Harrison 1998). Once copper is released from the intestinal cells, it is transported bound to albumin and histidine to the liver via the portal circulation. Once in the hepatic cells, copper complexes with small cytoplasmic proteins known as copper chaperones. These copper chaperones are involved in intracellular distribution of copper ions. In the liver, another P-type ATPase, Wilson protein (WND), delivers copper to ceruloplasmin, which is then released to the blood for distribution to other tissues and organs. Under conditions of elevated copper, WND is involved in the release of copper at the canalicular membrane with ensuing biliary excretion of copper. The liver plays a critical role in copper homeostasis as both the storage site for this metal and as part of the physiologic route for excretion through the biliary system. The molecular mechanisms determining biliary copper excretion are becoming clearer due to the better understanding of genetic defects, such as Wilson's disease. Specifically, the Wilson protein localized to the trans-Golgi network of hepatocytes not only delivers copper to ceruloplasmin, but also is essential for biliary copper excretion. Recently, other proteins have also been identified that interact with Wilson protein and appear to be equally important in the process of biliary copper excretion (Tao et al. 2003).

3.5.2 Mechanisms of Toxicity

Although a number of studies have investigated the mechanisms of copper hepatotoxicity in rats, it is not known whether rats would be a good model for human liver toxicity unrelated to a genetic defect in copper metabolism. Lysosomes serve an important role in hepatic copper metabolism. Excess copper is sequestered within hepatocyte lysosomes where it is complexed with metallothionein. However, this protective mechanism is saturable and liver lesions can develop above the saturation limit. In copper loaded rats, lysosomes become enlarged and more fragile with decreased membrane fluidity (Myers et al. 1993). The results of the Haywood et al. (1985a) study do not suggest that liver damage is due to rupturing of lysosomes because lysosomal instability precedes and is not synchronous with liver damage. It is speculated that saturation of the lysosomes results in an accumulation of copper in the nucleus and subsequent nuclear damage (Fuentealba and Haywood 1988; Fuentealba et al. 1989; Haywood et al. 1985a). The mechanism by which copper accumulates in the nucleus and the mechanisms by which it provokes injury are not clear. It has been suggested that excess copper results in oxidative damage, including lipid peroxidation. Increases in the level of thiobarbituric acid reactive substance (TBARS), a measure of lipid peroxidation, have been found in copper-loaded rats (Myers et al. 1993; Sokol et al.

1993). However, a study by Aburto et al. (2001b) did not find significant alterations in the levels of malaondialdehyde, a lipid peroxidation by product, prompting the study authors to postulate that lipid peroxidation does not play a major role in copper toxicity although it may occur as a terminal event as a consequence of cell injury. Sokol et al. (1990, 1993) suggested that oxidant injury to hepatocyte mitochondria may be one of the initiating factors in hepatocellular damage. Numerous studies have shown that rats can develop tolerance to high levels of copper. After 3–5 weeks of copper loading resulting in tissue damage, the copper levels in the liver begin to decline and the tissue begins to regenerate (Haywood and Loughran 1985). It is believed that the mechanism involved in tolerance development is the increased synthesis of metallothionein (Evering et al. 1991a, 1991b; Freedman and Peisach 1989).

Studies in monkeys, dogs, and ferrets provide strong evidence that copper-induced emesis results from stimulation of the vagus nerve. Abdominal vagotomy resulted in a dramatic decrease in the occurrence of emesis in dogs (Fukui et al. 1994) and ferrets (Makale and King 1992) orally exposed to copper sulfate and in monkeys receiving oral or intravenous injections of copper sulfate (Fukui et al. 1993). In monkeys, administration of compounds that block 5-HT_3 receptors also resulted in a decrease in emesis following oral or intravenous administration of copper sulfate (Fukui et al. 1993). In contrast, 5-HT_3 blockers did not affect the occurrence of emesis in dogs (Fukui et al. 1994) or ferrets (Bhandari and Andrew 1991) receiving an oral dose of copper sulfate, but compounds that block 5-HT_4 receptors did inhibit copper-induced vomiting. Fukui et al. (1994) suggested that copper sulfate caused gastrointestinal irritation that resulted in the release of 5-HT and evoked emesis by activation of abdominal visceral afferents through 5-HT_4 receptors.

3.5.3 Animal-to-Human Extrapolations

The toxicity of copper has been assessed in a number of experimental animal species, and sensitivity to copper toxicity is highly species dependent. Ruminants are more susceptible than nonruminant species. NTP (1993) demonstrated that rats are much more sensitive than mice to the hepatotoxicity of copper. In rats, dietary exposure to 16 mg Cu/kg/day for 13 weeks resulted in an increase in alanine aminotransferase activity; chronic active liver inflammation was observed at 66 mg Cu/kg/day. In contrast, no evidence of liver damage was observed in mice exposed to 814 mg Cu/kg/day for 13 weeks.

Most of the experimental data on the toxicity of copper come from studies in which rats were used; however, the relevance of this species to human toxicity has not been fully evaluated. The dietary

requirement for copper in rats is 5 mg Cu/kg diet (NRC 1995); a commonly used diet for rats (AIN76, AIN 93G, AIN93M) has a cupric carbonate concentration of 300 mg/kg diet (160 mg Cu/kg diet). An intermediate-duration exposure to approximately 250 mg Cu/kg diet resulted in mild liver effects (increased serum alanine aminotransferase) (NTP 1993). It is unlikely that humans would tolerate prolonged exposure to a copper dose that is 50 times higher than the dietary requirement (0.65 mg Cu/kg/day); gastrointestinal disturbances were observed in women ingesting 0.0731 mg Cu/kg/day in drinking water (Pizarro et al. 1999). Thus, the applicability of these animal data to humans is not known.

The Long-Evans Cinnamon rat is often used as a model for Wilson's disease. This rat strain shares many characteristics with Wilson's disease: accumulation of liver copper, decreased serum copper and ceruloplasmin levels, and impaired biliary excretion of copper (Sugawara et al. 1991, 1992, 1994; Suzuki et al. 1995).

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others believe that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics include the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial,

scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992). However, in the case of ambient human exposures, the validity of these possibilities has yet to be established conclusively.

There is no evidence that copper interferes with the normal function of the neuroendocrine axis.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects to humans from exposures during the period from conception to maturity at 18 years of age, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any direct or indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Potentially relevant animal and *in vitro* models are also discussed.

Children should not be considered small adults. They may differ from adults in their exposures and in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children may differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life at which particular structures and/or functions will be most sensitive to perturbation. Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Also, the distribution of xenobiotics may be different; for example, infants

have a larger proportion of their bodies as extracellular water, their brains and livers are proportionately larger, and the composition and quality of their lipid depots differ from those of adults (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form and/or in detoxification. There may also be differences in excretion, particularly in newborns who have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). In addition, children and adults may differ in their capacity to repair damage from chemical insults. In general, children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to the development of cancer.

Certain characteristics of the developing human may increase exposure or susceptibility to certain toxicants, whereas others may decrease susceptibility to the same toxicant. For example, although infants breathe more air per kilogram of body weight than adults, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Copper is an essential element required for normal growth and development and for a variety of metabolic functions including iron metabolism, cross-linking of connective tissue, and lipid metabolism. Signs of copper deficiency in infants and children include anemia that is unresponsive to iron supplementation, neutropenia, bone abnormalities, and hypopigmentation of the hair (Cordano 1998; Danks 1988).

Exposure to excess levels of copper has been associated with adverse health effects in infants and children. There is an extensive body of literature on two syndromes that have been associated with exposure to high levels of copper, Indian childhood cirrhosis and idiopathic copper toxicosis. Both are characterized by severe liver damage in infants and children (<5 years of age). In the case of Indian childhood cirrhosis, excessive copper exposure has been traced to the use of brass or copper containers for storage and heating of milk. Doses as high as 0.930 mg/kg/day have been estimated; this dose is

approximately 30 times higher than the dietary requirement for copper (Tanner 1998). Idiopathic copper toxicosis (also referred to as non-Indian childhood cirrhosis) has also been linked to exposure to high levels of copper in drinking water and/or the use of copper utensils (Wijemenga 2002). A common finding in both syndromes is the early dietary introduction of non-mother's milk and/or formula. Genealogical investigations provide suggestive evidence that both syndromes are transmitted in an autosomal recessive mode. However, the mechanism of action has not been identified. It is possible that the genetic defect results in reduced copper efflux from the liver. Very high levels of copper have been detected in the livers of affected infants; copper levels ranging from 790 to 6,654 µg/g dry weight (mean of 939 µg/g) have been reported in infants diagnosed with Indian childhood cirrhosis (levels in control infants ranged from 8 to 118 µg/g (Bhave et al. 1982). Support for the genetic component comes from the finding that decreasing copper exposure levels dramatically decreases the occurrence of Indian childhood cirrhosis (Tanner 1998). Additionally, no alterations in serum biomarkers of liver damage (alanine aminotransferase activity, aspartate aminotransferase activity, gamma glutamyl transferase activity, and total bilirubin levels) were observed in infants ingesting water containing 2 mg/L copper (0.319 mg/kg/day) (Olivares et al. 1998) or infants living in households with tap water copper levels of 0.8 mg/L (Zietz et al. 2003a, 2003b). Together, these data suggest that exposure to copper levels exceeding the copper metabolic capacity of certain individuals with a genetic defect is the causative agent for severe liver damage.

Another adverse health effect that has been reported in infants and children is gastrointestinal upset. This effect, which is one of the most commonly reported adverse health effect in adults, is manifested in nausea, vomiting, abdominal pain, and/or diarrhea. Symptoms usually occur shortly after ingesting a copper-contaminated beverage or drinking water containing a high level of copper. In most of the reports of gastrointestinal upset in children (Gill and Bhagat 1999; Karlsson and Noren 1965; Knobeloch et al. 1994; Spitalny et al. 1984; Walsh et al. 1977), no reliable information on copper concentration or dose was reported. In one report where school-age children ingested a beverage stored in an old urn, the concentration of copper in the beverage was estimated to be 300 mg/L (Gill and Bhagat 1999). Another study reported vomiting in infants ingesting a single dose of 7.5 mg/L copper sulfate (Karlsson and Noren 1965). Knobeloch et al. (1994) noted that children appear to be more sensitive to the gastrointestinal effects of copper than adults. This statement was based on two surveys of residents with elevated copper levels in the drinking water. In the first survey, it appears that children who were described as "unusually irritable" or had recurrent headaches were categorized as having gastrointestinal upset. In the second survey, mothers were asked to recall the frequency of gastrointestinal effects for all family members. A significantly higher percentage of children, as compared to adults, were reported to have gastrointestinal

effects. It is difficult to determine what role recall bias had in the results and how well the mothers knew of symptoms of gastrointestinal upset in the adult members of the household. The available data are inconclusive to assess accurately whether there is an age-related difference in the gastrointestinal toxicity of copper.

The potential age-related differences in the toxicity of copper has been assessed in rats exposed to 120 mg Cu/kg/day as copper sulfate in the diet for 12 weeks (Fuentealba et al. 2000). The observed liver effects were more severe in young rats (exposed *in utero*, during lactation, and for 12 weeks post weaning) as compared to the effects observed in adult rats. The copper levels in the liver were also higher in the young rats (1,553–1,635 versus 472–534 µg/g). The doses used in this study are very high, 1,000 times higher than the rat dietary requirement of 0.15–0.30 mg/kg/day (AIN 1977). It is not known if increased liver sensitivity would also occur at lower copper doses. Although these data are suggestive that children may be more sensitive to the hepatotoxicity of high doses of copper, uncertainty in the use of rats as a model for human toxicity limits the extrapolation of these study results to humans.

Several studies have investigated the potential developmental toxicity of dietary copper sulfate; the results suggest that *in utero* exposure to copper can result in delays in growth and development in the offspring of rats exposed to 130 mg Cu/kg/day (Haddad et al. 1991) and mice exposed to 208 mg Cu/kg/day (Lecyk 1980). No developmental effects were observed in the offspring of mink exposed to 13 mg Cu/kg/day (Aulerich et al. 1982).

There is concern that toxicokinetic differences between infants and adults may result in increased sensitivity in infants. During the second half of pregnancy, particularly in the third trimester, the fetus accumulates copper at a rate of 50 g/kg/day (Widdowson et al. 1974). Approximately half of the copper in the fetus is stored in the liver, mostly bound to metallothionen. Additionally, the rate of transfer of copper from the liver to the bile or blood is decreased due to the immaturity of the liver. The magnitude of the amount of copper in the fetal liver is similar to levels observed in Wilson’s disease; however, the fetal/neonatal liver tolerates these high concentrations (Olivares et al. 2000). After birth, the copper levels in the liver steadily decrease from about 51 µg/g at birth to 5.7 µg/g at 6–14 months of age (Klein et al. 1991; Olivares et al. 2000).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to copper are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by copper are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that may result in an increase in absorbed dose, a decrease in the dose-level required for biological effectiveness, or a target tissue response. Biomarkers of susceptibility are discussed in Section 3.10 “Populations that are Unusually Susceptible.”

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Copper

Copper levels can readily be measured in tissues, body fluids, and excreta. Depending on the dose and exposure duration, inhalation and/or oral exposure to copper can result in increased levels of copper in serum, urine, hair, and liver. Increased whole blood and serum copper levels have been reported in humans following intentional ingestion of a single dose of 1–30 g of copper as copper sulfate (Chuttani et al. 1965). The serum and whole blood levels of copper ranged from 239 to 346 and from 383 to 684 µg/100 mL, respectively; the serum and whole blood levels in non-exposed individuals were 151.6 and 217 µg/100 mL, respectively. Following chronic inhalation exposure to 111–464 mg Cu/m^3 copper dust, plasma serum levels of >200 µg/100 mL were observed in 16% of factory workers exposed to copper dust (Suciu et al. 1981). However, increased serum copper levels may only be reflective of recent exposure. Chuttani et al. (1965) observed that serum ionic copper rapidly diminished to normal levels following an acute bolus dose.

A relationship between blood copper levels and the severity of symptoms has not been established. Among individuals intentionally ingesting a single dose of copper sulfate (1–30 g), Chuttani et al. (1965) noted that there did not appear to be any difference between serum copper levels in individuals only exhibiting gastrointestinal effects and those with more severe symptoms (jaundice, renal manifestations, or shock). In contrast, whole blood copper levels were much higher in the individuals with severe symptoms (798 µg/100 mL) compared to those with mild symptoms (287 µg/100 mL).

Copper levels in hair and nails can also be used to assess copper exposure. In a study of preschool children, the levels of copper in hair and toenail samples were log-normally distributed (Wilhelm et al. 1991). The geometric mean concentrations of copper in hair and toenails were 10.6 µg/g (range of 5.4–20.7 µg/g) and 7.5 µg/g (range of 3.0–18.6 µg/g), respectively. Based on a hair growth rate of 10 mm per month, the copper levels in the first 2 cm proximal to the scalp would represent copper intake over 2 months (Hopps 1977). In contrast, toenail samples would represent copper intake over 12–18 months, based on a toenail growth rate of 1 mm/month (Fleckman 1985). Increased hair copper levels have been reported in workers exposed to 0.64–1.05 mg/m^3 of an unspecified copper compound; the concentration of copper in the hair was 705.7 µg/g, as compared to a 8.9 µg/g concentration in non-exposed workers (Finelli et al. 1981), and increased hair and fingernail copper levels were observed in children with Indian childhood cirrhosis (Sharda and Bhandari 1984).

3.8.2 Biomarkers Used to Characterize Effects Caused by Copper

The harmful health effects of copper occur over a wide range of copper intakes from too little copper in the diet to excessive copper exposure.

Low Intakes of Copper. The nutritional requirements of copper and the health effects associated with copper deficiency have been reviewed by numerous authors (Gallagher 1979; Mason 1979; O'Dell 1984). Copper deficiency is rarely observed in humans; the existence of covert copper deficiency among segments of the population is unknown. The limited data available on human health effects of inadequate copper intakes are derived mostly from case reports of severely malnourished children, patients maintained by total parenteral nutrition without copper, and children with Menkes' disease (a genetic disorder resulting in impaired copper absorption). Copper deficiency is characterized by hypochromic anemia, abnormalities of connective tissues, and central nervous system disorders. Sudden death associated with spontaneous rupture of a major blood vessel or the heart itself has been observed in some animal species.

The manifestations of copper deficiency are related to a decrease in several of the copper-containing metalloenzymes. The most severe biochemical alteration is decreased cytochrome oxidase activity; this is manifested as poor growth, anemia, and central nervous system effects. The decreased oxidative metabolism associated with decreased cytochrome oxidase results in poor growth in infants, weight loss, and emaciation. The hypochromatic anemia observed during copper deficiency is not distinguishable from iron deficiency anemia; however, it is not responsive to iron administration. A decrease in protoheme synthesis, a result of decreased cytochrome oxidase, has also been observed. As with anemia, the central nervous system effects, primarily the result of hypomyelination, are associated with low activity levels of cytochrome oxidase; the decreased synthesis of phospholipids observed in copper deficiency may also contribute to the development of central nervous system effects. In addition to the decrease in cytochrome oxidase, a decrease in lysyl oxidase is also observed. Lysyl oxidase is involved in the formation of cross-links in collagen and elastin. Depending on the species, this impairment results in bone disorders, a defective cardiovascular system, or abnormal lung structure.

Exposure to Excess Levels of Copper. No copper-specific biomarkers of effects have yet been identified. The most notable sign of toxicity in humans ingesting a beverage or water containing copper is gastrointestinal distress. Symptoms (typically nausea, vomiting, and abdominal pain) usually occur shortly after ingesting the contaminated beverage. The liver is another sensitive target of copper toxicity. Alterations in a number of serum enzymes have been observed in humans and animals with copper-

induced liver damage (Chuttani et al. 1965; Epstein et al. 1982; Haywood 1980; Haywood and Comerford 1980; Müller et al. 1998; NTP 1993; Sugawara et al. 1995). The affected serum enzymes include serum aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Increases in serum bilirubin levels have also been observed in humans. Animal studies demonstrate that the rise in serum enzyme activities are the first evidence of liver damage. However, alterations in serum enzyme levels are not unique to copper-induced liver damage.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Numerous studies have demonstrated the interaction between copper and several other metals. Dietary zinc strongly affects copper absorption. A diet high in zinc can result in copper deficiency. Reductions in erythrocyte superoxide dismutase, indicative of marginal copper deficiency, have been found in studies of women ingesting zinc supplements (50 mg zinc/day) for 10 weeks (Yadrick et al. 1989) and men ingesting 50 mg zinc/day for 6 weeks (Fisher et al. 1984). The exact mechanism of the zinc-copper interaction is not known. However, increased dietary zinc results in induction of metallothionein synthesis in the intestine and metallothionein has a greater binding capacity for copper than for zinc. Thus, the dietary copper is sequestered in the intestinal mucosal cell and eventually is excreted in the feces when the mucosal cell is sloughed off (Hall et al. 1979; Whanger and Weswig 1971). Because exposure to excess dietary zinc results in decreased copper absorption, it is often used as a treatment for Wilson's disease (Brewer et al. 1993). An oral/intraperitoneal study in mice provides some evidence that zinc and copper may interact at sites other than the intestine. In this study on the influence of zinc on mitigating the immunotoxicity of copper, mice were exposed to copper sulfate in the drinking water for 8 weeks and received an intraperitoneal injection of zinc sulfate once a week (Pocino et al. 1990). Decreases in the magnitude of the proliferative response to con A or LPS and the antibody response to sheep red blood cells were observed in the copper-exposed mice, but not the mice receiving copper and zinc. However, zinc did not modify the increased production of auto-antibodies reactive with bromelain-treated mouse red blood cells.

Several other divalent cations compete with copper for intestinal absorption. Exposure to dietary cadmium (Evans et al. 1970a), ferrous iron (Wapnir et al. 1993; Yu et al. 1994), and stannous tin (Pekelharing et al. 1994; Wapnir et al. 1993) can result in decreased copper absorption. In the case of cadmium, the decrease is related cadmium induction of metallothionein and the binding of copper to it. Tetrathiomolybdate is used for the treatment of Wilson's disease (Brewer 1995) and excessive dietary molybdenum can also result in decreased uptakes and, therefore, copper utilization and toxicity. Two

mechanisms of action of tetrathiomolybdate have been proposed: it reacts with copper-metallothionein to form a soluble complex which is excreted (Ogra et al. 1996) and it can complex with nonceruloplasmin plasma copper, preventing its cellular absorption (Brewer 1995).

Because selenide is a strong reducing agent (Frost 1972), it has been postulated that selenium may play a role in detoxifying copper. Aburto et al. (2001a, 2001b) examined the possible interaction between copper and selenium. Selenium did not influence the hepatotoxicity of copper in rats fed diets with excess levels of copper and inadequate, adequate, or excess levels of dietary selenium. Hepatic copper levels and histological alterations were not significantly different in rats receiving a high copper/high selenium diet as compared to rats receiving a high copper/adequate selenium diet.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to copper than will most persons exposed to the same level of copper in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). Whatever the basis of the increased susceptibility may be, the result is reduced detoxification or excretion of copper or compromised functioning of organs affected by copper. Populations at greater risk due to unusually high exposure to copper are discussed in Section 6.7, Populations with Potentially High Exposures.

A number of populations of individuals unusually susceptible to copper toxicity have been identified. The increased susceptibility to copper toxicity is associated with genetic defects that impair copper homeostatic mechanisms. Wilson's disease, also referred to as hepatolenticular degeneration, is an autosomal recessive disorder with a worldwide incidence of 1 in 30,000 (Scheinberg and Sternlieb 1996). The primary genetic defect in Wilson's disease is in ATP7B, which encodes a P-type ATPase (Wilson protein), which delivers copper to ceruloplasmin. The genetic defect results in impaired biliary excretion of copper and an accumulation of copper in the liver. As described by Brewer and Yuzbasiyan-Gurkan (1992), the progression of the disease begins with an accumulation of copper in the liver, damage to the liver, and subclinical liver cirrhosis. Over time, the individual will develop hepatic, neurological, and psychiatric symptoms. The hepatic effects are characterized by jaundice, hypoalbuminemia, ascites, coagulation defects, hyperammonemia, hepatic encephalopathy, and/or liver failure; in the cases of massive liver failure, large amounts of copper are released from the liver resulting in hemolytic anemia. Neurological symptoms include tremors and other movement disorders and speech abnormalities. Psychiatric and behavioral symptoms are often found in individuals also manifesting neurological other

symptoms. The psychiatric symptoms include reduced performance in school or work, inability to cope, depression, very labile moods ranging from mania to depression, sexual exhibitionism, and frank psychosis. Individuals with Wilson's disease have low serum ceruloplasmin levels, elevated urinary copper levels, and elevated liver copper levels; Kayser-Fleischer rings, which result from corneal copper deposits, are also detected in individuals with Wilson's disease. Individuals who are heterozygotes for Wilson's disease may also be unusually susceptible to the toxicity of copper. Increases in urinary copper and hepatic concentrations and decreased copper incorporation into ceruloplasmin have been observed in heterozygotes. These findings may suggest that long-term exposure to elevated levels of copper may result in copper overload. Although the incidence of heterozygotes is not known, NAS (2000) estimates that 1 in 40,000 individuals (approximately 1% of the U.S. population) may be heterozygotes for Wilson's disease.

Indian childhood cirrhosis (ICC) and idiopathic copper toxicosis (ICT) are two syndromes that result in severe, often fatal, liver cirrhosis in infants and young children. Although the basis of the defect has not been firmly established, it is believed to be due to an inherited autosomal recessive defect in copper metabolism aggravated by high copper intake (Bhave et al. 1982, 1987; Müller et al. 1996, 1998). ICC occurs in infants and children living in rural areas of the Indian subcontinent who are introduced early to cow or buffalo milk that is stored or heated in brass or copper vessels. Copper is believed to be the causative agent because the milk has very high copper levels, very high copper levels are found in the liver, and replacing the brass or copper vessels with aluminum or stainless steel vessels eliminates the occurrence of ICC in siblings of ICC affected children (Bhave et al. 1982; Tanner 1998). A high degree of parental consanguinity, the occurrence of ICC in children, but not the parents, and the fact that 22% of siblings affected suggest an autosomal recessive component to the disease (Pandit and Bhave 1996; Tanner 1998). For ICT, which includes Tyrolean infantile cirrhosis, sources of high copper exposure have been identified. For the 138 cases of ICT in children living in the Tyrolean region of Austria, the source of the copper was the use of a water/unpasteurized cow's milk mixture that was heated in a copper pot (Müller et al. 1996). For the other cases of ICT that have been identified in a number of countries, the source of the excess copper intake was drinking water (Müller et al. 1998). The similarity of ICT to ICC has prompted investigators to suggest that ICT may also be due to an autosomal recessive genetic defect in copper metabolism and excessive copper intake at a very young age. A genealogical investigation by Müller et al. (1996) provides supportive evidence for a genetic basis of the disease.

It has been postulated that individuals with a deficiency of the enzyme glucose-6-phosphate dehydrogenase would be susceptible to the toxic effects of oxidative stressors such as copper (Calabrese

and Moore 1979; Chugh and Sakhuja 1979). This has not been supported by epidemiological or experimental data. In the blood, most of the copper is bound to ceruloplasmin. With the exception of ingestion of a very large dose of copper salts, the levels of nonceruloplasmin bound copper remain low following copper exposure. Thus, it is unlikely that this relatively small change in free copper would alter the survival of glucose-6-phosphate dehydrogenase deficient red cells.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to copper. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to copper. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to copper:

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. Second edition. Baltimore, MD: Williams & Wilkins, 1554-1556.

Goldfrank LR, Flomenbaum FE, Lewin NA, et al., eds. 1998. Goldfrank's toxicologic emergencies. Sixth edition. Stamford, CT: Appleton & Lange, 1339-1340.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical management of poisoning and drug overdose. Third edition. Philadelphia, PA: WB Saunders, 165.

3.11.1 Reducing Peak Absorption Following Exposure

Following ingestion of copper or copper compounds, milk or water should be given immediately after ingestion and/or prior to vomiting. Because of the strong emetic properties of copper and copper compounds, vomiting usually occurs shortly after ingestion. Induction of vomiting and gastric lavage are contraindicated following ingestion of caustic copper salts, such as copper sulfate. Gastric lavage may be indicated after ingestion of noncorrosive copper compounds (HSDB 2002).

For individuals with Wilson's disease, the administration of a diet high in zinc is used as a maintenance treatment (Brewer et al. 1989). The zinc interferes with copper absorption by inducing intestinal metallothionein resulting in increased copper sequestration (Brewer et al. 1992).

3.11.2 Reducing Body Burden

A number of methods have been employed to reduce copper body burden. These methods range from the use of chelating agents to increases in dietary levels of zinc and molybdenum. Gao et al. (1989) tested the *in vitro* effectiveness of five chelating agents using human serum albumin. The agents (in order of decreasing effectiveness) were ethylenediaminotetraacetate (EDTA), diethylene triaminopentaacetate, ethylene glycol-*bis*-(aminoethylether)-tetraacetate, nitrilotriacetate, and iminodiacetate. The *in vivo* effectiveness of these agents has not been established. D-penicillamine is often used to decrease the elevated levels of hepatic copper in individuals with Wilson's disease (Walshe 1996; Walshe and Yealland 1993) and idiopathic childhood cirrhosis (Rodeck et al. 1999). However, a number of potential side effects have been associated with penicillamine treatment (Brewer and Yuzbasiyan-Gurkan 1992). A variety of other chelating agents have been tested in copper loaded rats. Tetraethylenepentamine pentahydrochloride (TETREN) was more effective in increasing urinary excretion of copper than 1,4,7,11-tetraazaundecane tetrahydrochloride (TAUD) or penicillamine, which were equally effective (Domingo et al. 2000). TETREN did not result in a decrease in copper levels in the liver, although a significant decrease in kidney copper levels was observed. In contrast, TAUD and penicillamine reduced the levels of copper in the liver. None of the three chelating agents affected the amount of copper excreted into the feces.

The known interaction between copper and molybdenum have been used to treat individuals with Wilson's disease. The administration of tetrathiomolybdate to individuals with neurological or psychiatric symptoms associated with Wilson's disease has resulted in an improvement or reversal of symptoms (Brewer 1995). In blood plasma, tetrathiomolybdate complexes with nonceruloplasmin plasma copper, preventing its cellular absorption. Studies in Long-Evans Cinnamon rats, a model for Wilson's disease, and sheep have found that administration of tetrathiomolybdate results in a dramatic decrease in the levels of copper in the liver (Humphries et al. 1988; Kumaratilake and Howell 1989; Ogra et al. 1996) and decreased liver damage (Humphries et al. 1988). Tetrathiomolybdate also reacts with copper bound to metallothionein resulting in a soluble copper-tetrathiomolybdate complex (Ogra et al. 1996). The addition of molybdenum to a high sulfur, low copper diet can result in a decrease in liver and plasma copper levels in copper loaded sheep (van Ryssen 1994).

Although zinc is used in the treatment of Wilson's disease to decrease the absorption of copper, zinc does not appear to be effective in reducing the copper body burden. No alterations in hepatic copper levels were observed in sheep administered a low copper, high zinc diet (van Ryssen 1994). A reduction in hepatic copper levels has been observed in dogs administered a high zinc diet (Brewer et al. 1992);

however, it is believed that the reduction was secondary to the induction of copper deficiency and the mobilization of copper from the liver (van Ryssen 1994).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

There are limited data on methods for interfering with the mechanisms of action of copper. An *in vitro* study suggested that lazaroids (21-aminosteroids) may have a protective effect against copper-induced erythrocyte lipid peroxidation (Fernandes et al. 1992). Oxidative damage to the erythrocyte membrane may be the cause of the hemolysis observed following exposure to very high doses of copper.

3.12 ADEQUACY OF THE DATABASE

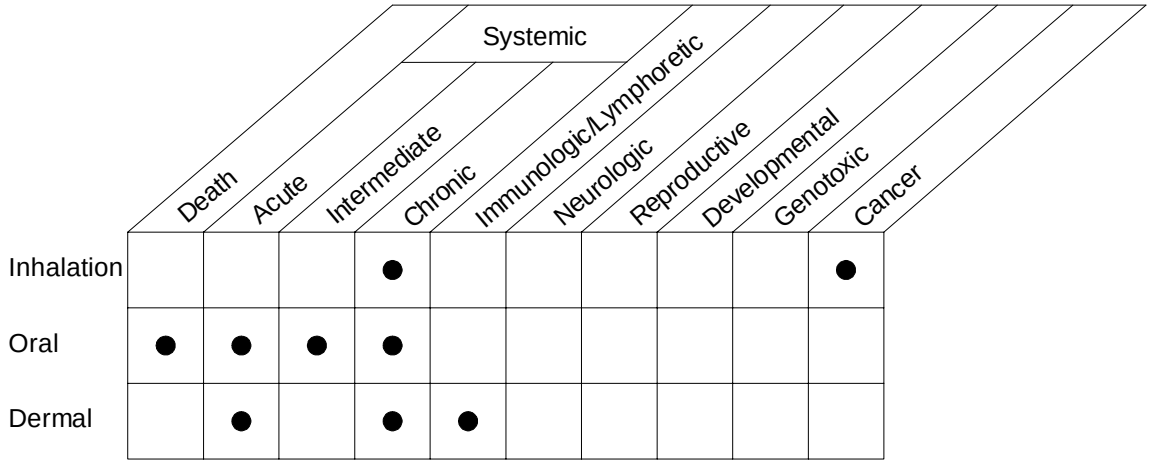
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of copper is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of copper.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

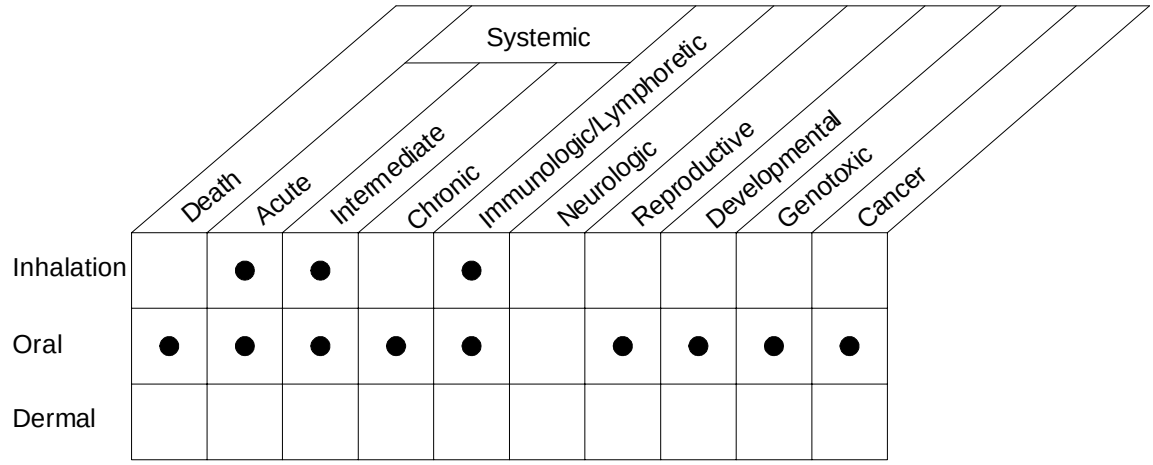
3.12.1 Existing Information on Health Effects of Copper

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to copper are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of copper. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data

Figure 3-4. Existing Information on Health Effects of Copper



Human



Animal

● Existing Studies

need." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments.

Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

The toxicity of inhaled copper has been investigated in a couple of occupational exposure studies. These studies examined a limited number of systemic end points, and exposure is poorly characterized. There are numerous reports and studies on the toxicity of ingested copper in humans. Most of the reports and studies focused on the gastrointestinal effects following acute exposure to copper in drinking water or other beverages. Data on other health effects in humans comes from individuals with Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis. These diseases/syndromes are the result of genetic defect(s) resulting in impaired copper kinetics; the latter two syndromes are also associated with exposure to high levels of copper in drinking water or milk (due to storage of milk in brass vessels). These studies provide information on potential targets of toxicity, primarily the liver.

Information on the dermal toxicity of copper is limited to reports of contact dermatitis in individuals and eye irritation in workers exposed to copper dust.

As with the human database, there are limited data on the toxicity of inhaled copper in animals. The available studies have primarily focused on potential respiratory effects. There is a more extensive database on the toxicity of ingested copper in animals. These studies have found a number of systemic effects, including gastrointestinal, hepatic, and renal effects following acute, intermediate, and chronic exposure. Immunological and developmental effects have also been reported in animal studies. Several studies have also examined potential neurological and reproductive targets, but have not found effects. Carcinogenic effects were not found in several animal studies; however, the studies are limited in scope and tested low doses. No animal studies examining the dermal toxicity of copper were identified.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. No data were located regarding health effects after acute inhalation exposure to copper in humans. Animal data are limited to information from studies in mice and hamsters conducted by Drummond et al. (1986). Respiratory tract irritation and impaired immune function were

observed. This study was not selected as the basis for an acute-duration inhalation MRL because it only examined a limited number of end points, and the liver and kidney, which are targets following oral exposure, were not examined; in addition, the animals were only exposed for 3 hours/day. Additional inhalation studies are needed to identify the critical targets of toxicity and to establish concentration-response relationships for copper. The most commonly reported effect in humans acutely exposed to copper is gastrointestinal upset. The reported symptoms include nausea, vomiting, abdominal pain, and diarrhea (Chutanni et al. 1965; Gill and Bhagat 1999; Gotteland et al. 2001; Nicholas and Brist 1968; Olivares et al. 2001; Pizarro et al. 1999, 2001; Semple et al. 1960; Walsh et al. 1977). Hepatic and renal effects have also been seen in individuals ingesting lethal doses of copper sulfate (Chuttani et al. 1965). Animal studies support the identification of the gastrointestinal tract, liver, and kidneys as sensitive targets of copper toxicity. Hyperplasia of the forestomach has been observed in rats and mice exposed to copper sulfate in the diet for 14 days (NTP 1993). Hepatic effects ranging from increases in alanine aminotransferase activity to hepatocellular necrosis and renal effects (protein droplets in proximal tubules) have been observed in rats exposed to fairly high doses of copper sulfate in the diet (Haywood 1980; Haywood and Comerford 1980; Haywood et al. 1985b; NTP 1993). Decreases in body weight gain have also been observed in rats (NTP 1993). The acute-duration oral database was considered adequate for derivation of an MRL. The MRL was based on gastrointestinal upset in women ingesting drinking water containing copper sulfate for 2 weeks (Pizarro et al. 1999). There are limited data on the dermal toxicity of copper. Pruritic dermatitis and allergic contact dermatitis have been reported in humans exposed to copper. No animal studies were identified. These data provide suggestive evidence that copper may be irritative to the skin; additional dermal studies are needed to determine whether copper exposure will also result in systemic effects.

Intermediate-Duration Exposure. No studies were located regarding health effects in humans after intermediate-duration inhalation. Only one animal inhalation exposure study was located. This study did not find any adverse histological alterations in the lungs or functional alterations in alveolar macrophages of rabbits exposed to copper chloride (Johansson et al. 1983, 1984). Because the lungs were the only tissues examined, these studies were not considered suitable for derivation of an intermediate-duration inhalation MRL for copper. Additional studies are needed to identify the critical targets of toxicity and establish concentration-response relationships for inhaled copper. Three experimental human studies and two community-based studies have examined the oral toxicity of copper in healthy humans. The primary focus of these studies was examination of the potential of low doses of copper to induce hepatic effects in adults (Araya et al. 2003b; Pratt et al. 1985) or infants (Olivares et al. 1998; Zietz et al. 2003a, 2003b); no adverse effects were found. The Araya et al. (2003b) study also assessed the potential for gastrointestinal

effects in adults and found significant increases in the incidence of effects as a function of dose/duration. A number of animal studies have reported adverse liver and kidney effects following intermediate-duration oral exposure to copper compounds (Epstein et al. 1982; Fuentealba et al. 2000; Haywood 1980, 1985; Haywood and Comerford 1980; Haywood and Loughran 1985; Haywood et al. 1985a, 1985b; Kumar and Sharma 1987; NTP 1993). The observed liver and kidney effects demonstrated dose- and duration-response relationships. The studies by Haywood and associates demonstrate that rats can develop a tolerance to copper following repeated oral exposure. Studies in other animal species are needed to determine if this phenomenon is unique to rats or is observed in other species as well. Other systemic effects that have been reported in animals include hyperplasia of the forestomach mucosa (NTP 1993), decreased erythrocyte and hemoglobin levels (Kumar and Sharma 1987; Rana and Kumar 1980; Suttle and Mills 1966a), and decreased body weight gain or weight loss (Haywood 1985; Haywood and Loughran 1985; Kline et al. 1971; Llewellyn 1985; NTP 1993). For the most part, these studies involved dietary exposure of rats to copper sulfate; additional studies in other species would be useful for identifying a model for human toxicity. The Araya et al. (2003b) human study was used as the basis of an intermediate-duration oral MRL for copper. No data on the dermal toxicity of copper following intermediate-duration exposure were identified. Studies are needed to identify the critical targets of copper toxicity following dermal exposure.

Chronic-Duration Exposure and Cancer. Systemic effects such as nausea (Suciu et al. 1981), hepatomegaly (Suciu et al. 1981), decreased hemoglobin and erythrocyte levels (Finelli et al. 1981), and respiratory irritation (Askergren and Mellgren 1975; Suciu et al. 1981) have been observed in workers exposed to copper dust. The mild gastrointestinal effects observed in some workers were attributed to swallowing airborne copper dust (Suciu et al. 1981). The poor characterization and/or the lack of controls preclude deriving a chronic-duration inhalation MRL based on the occupational exposure studies. Additional studies are needed to identify the critical targets of toxicity of inhaled copper. There are numerous reports of severe health effects in infants and children ingesting copper-contaminated milk or water containing high levels of copper (Müller et al. 1996, 1998; Pandit and Bhave 1996; Tanner 1998). Indian childhood cirrhosis and idiopathic copper toxicosis are characterized by severe liver cirrhosis occurring before the age of 5 years. There is suggestive evidence that both of these syndromes are related to increased dietary intake of copper in conjunction with increased genetic susceptibility. Nausea, vomiting, and abdominal pain were reported by members of a family with very high levels of copper in the drinking water (Spitalny et al. 1984). The animal database on the oral toxicity of copper following chronic-duration exposure is limited to one study (Massie and Aiello 1984) that found a decrease in lifespan and no effect on body weight gain in mice exposed to copper gluconate for 850 days. No other

end points of toxicity were examined in this study. The database was considered inadequate for derivation of a chronic-duration oral MRL. Additionally, studies that examine a variety of end points are needed to identify the critical targets of toxicity and establish dose-response relationships. Information on the dermal toxicity of copper is limited to a report of ocular irritation in workers exposed to copper dust (Askergren and Mellgren 1975). Additional dermal toxicity studies are needed to identify the critical targets of toxicity following dermal exposure.

Data on the carcinogenicity of copper in humans are limited to a study of copper miners (Chen et al. 1993) and a follow-up to this study (Chen et al. 1995). Increased risk of cancer, stomach cancer, and lung cancer were observed. Because the workers were also exposed to radon and radon daughters, silica, iron, titanium, sulfur, and arsenic, a causal relationship between copper and increased cancer risk can not be established. No studies examining the association between copper ingestion and cancer risk in humans were identified. Several animal studies have examined the carcinogenic potential of ingested copper (BRL 1968; Greene et al. 1987; Kamamoto et al. 1973). These studies are limited in scope, the studies by Green et al. (1987) and Kamamoto et al. (1973) only examined one potential target, and tested fairly low doses of copper. No dermal carcinogenicity studies in humans or animals were identified. Additional studies by the inhalation, oral, and dermal routes are needed to assess the carcinogenic potential of copper in humans.

Genotoxicity. No data on the genotoxicity of copper in humans were located; studies of workers or individuals accidentally exposed to high levels of copper would provide value information on its genotoxic potential in humans. The available genotoxicity data suggest that copper is a clastogenic agent (Agarwal et al. 1990; Bhunya and Jena 1996; Bhunya and Pati 1987; Sideris et al. 1988). However, mixed results have been found in point mutation assays (Demerec et al. 1951; Marzin and Phi 1985; Singh 1983; Tso and Fung 1981; Wong 1988). Additional studies are needed to assess copper's potential to induce point mutations. Several studies have also shown that exposure to copper can result in DNA damage (Garrett and Lewtas 1983; Sideris et al. 1988; Sina et al. 1983).

Reproductive Toxicity. There are no human studies and two animal studies that examined the potential of copper to induce reproductive effects. These studies did not find any adverse alterations in reproductive performance in mink (Aulerich et al. 1982), sperm morphology in rats and mice (NTP 1993), or vaginal cytology in rats or mice (NTP 1993). The NTP (1993) study also did not find histological alterations in reproductive tissues. Multigeneration or continuous breeding studies would provide information on the reproductive effects of copper in animals, which may be used to assess possible reproductive effects in humans exposed to high levels of copper.

Developmental Toxicity. Developmental studies by the oral route in rats (Haddad et al. 1991) and mice (Lecyk 1980) have shown that high copper intakes can result in impaired growth. The developmental toxicity of copper in humans has not been adequately investigated. No data were located regarding developmental effects of copper after inhalation or dermal exposures in humans or animals. Further studies in other animal species would provide valuable information on the potential of copper to adversely affect development. Such information might be relevant to humans.

Immunotoxicity. There are limited data on the immunotoxic potential of copper and its compounds. Reports on humans developing dermatitis after dermal exposure to copper (Barranco 1972; Saltzer and Wilson 1968) suggest that copper is an allergen. This is supported by a report of a woman developing dermatitis after insertion of a copper IUD (Barranco 1972). Immunological effects also have been observed in mice (Drummond et al. 1986) following acute inhalation exposure to copper sulfate. In addition, impaired immune function has been observed in mice exposed to copper chloride (Pocino et al. 1991) or copper sulfate (Pocino et al. 1990) in drinking water. Intermediate-duration studies concentrating on immunologic effects in different species would be useful for establishing dose-response relationships and assessing whether there are species differences. More studies in humans and animals that examine the immune response to copper exposure and the mechanisms involved therein would be useful.

Neurotoxicity. Neurological impairment has been observed in factory workers exposed to copper dust. No effects on neurobehavioral performance were observed in rats exposed to copper in the diet (Murthy et al. 1981). However, this study did find alterations in the levels of a dopamine metabolite, suggesting that copper may adversely affect the nervous system. Additional studies are needed to further investigate the neurotoxic potential of copper; these studies should assess the potential of copper to perturb dopaminergic pathways and related functions.

Epidemiological and Human Dosimetry Studies. Several studies have examined the toxicity of inhaled copper in workers (Askergren and Mellgren 1975; Finelli et al. 1981; Suciu et al. 1981). These studies have primarily focused on the respiratory tract, although health examinations revealed other adverse effects (e.g., hepatomegaly). Chen et al. (1993, 1995) examined the carcinogenic potential of inhaled copper. In general, these studies are limited by poor exposure characterization, co-exposure to several toxic and/or carcinogenic compounds (e.g., arsenic, cadmium, radon, lead), and limited number of end points examined. Occupational exposure studies examining populations of workers exposed to

copper and with minimal exposure to other metals would be useful in assessing the toxicity of inhaled copper. These studies should examine a wide variety of end points, particularly the gastrointestinal tract, liver, and kidneys, which are targets of toxicity following oral exposure.

There are numerous reports of accidental or intentional ingestion of copper. The most commonly reported effect in these studies is gastrointestinal upset. There have also been several experimental studies designed to identify a no effect level for gastrointestinal upset following short-term (2 weeks or less) exposure to copper in drinking water (Olivares et al. 2001; Pizarro et al. 1999, 2001). There are several subpopulations of individuals exposed to higher than normal levels of copper; these groups include communities with higher than normal levels of copper in drinking water and individuals ingesting higher than normal levels of copper in the form of supplements. Studies of these groups that involved examination for a variety of potential effects (including gastrointestinal, hepatic, and renal effects, which have been shown to be sensitive end points in animal studies) could provide useful information on the toxicity of copper in otherwise healthy humans. In addition, if the study group included both children and adults, these data could address the issue of age-related differences in toxicity.

Biomarkers of Exposure and Effect.

Exposure. Copper levels can be measured in tissues, body fluids, and excreta. Whole blood, serum, and urine copper levels have been established in healthy individuals. It has been demonstrated that copper levels in the body increase with increased exposure after acute poisoning. Similarly, increased copper levels were observed in workers after occupational exposure. Serum and urine copper levels, plasma ceruloplasmin levels, and clinical manifestations are specific indicators of copper status. It is doubtful that a single “specific” biomarker of intoxication resulting from exposure to a specific metal will be found. In any case, elevated tissue copper levels should be a sufficient indicator of exposure and the possibility of intoxication.

Effect. There are no specific biomarkers for copper toxicity. Individuals with Wilson's disease are usually diagnosed by examining serum and urine copper levels, plasma ceruloplasmin levels, and clinical manifestations. However, the relationship between serum and urine levels of copper and health effects are not known. Studies examining the possible correlation between blood levels or excreta levels of copper with effects would facilitate medical surveillance leading to early detection and possible treatment.

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism, and excretion of copper administered orally have been studied in animals and, to some

extent, in humans. Furthermore, alterations in copper absorption, distribution, and excretion have been studied in deficiency and toxicity states. Despite the information on copper absorption, there is very little information on differences between absorption rates of the various Cu(II) compounds and differences between the bioavailability of copper from food and water.

Several studies have shown that ingested or implanted metallic copper results in increased serum copper levels and liver toxicity (Keller and Kaminski 1984; Yelin et al. 1987). Studies on the release of copper ions from both ingested and implanted metallic copper would be useful.

There is very limited information on copper absorption following inhalation exposure, and data on the absorption of copper through the skin are limited. Further studies in animals on the rate and extent of copper absorption following exposure from both the inhalation route and the dermal route would more fully characterize copper toxicokinetics in animals and by extrapolation in humans.

There is evidence that animals develop a tolerance to continued high doses of copper; more information on the mechanism(s) involved might be useful to establish if humans also could develop tolerance, as well as to provide insight for the development of more effective and efficient treatment of copper toxicity.

Comparative Toxicokinetics. The metabolism of copper has been studied in rats, pigs, hamsters, and humans. However, there are no comparative studies on the effects of high copper intakes on the distribution of copper in the body or the development of tolerance to continued high intakes of copper. Furthermore, the animal species that might serve as the best model for extrapolating results to humans is not known.

Methods for Reducing Toxic Effects. Methods for reducing the toxic effects of copper have primarily focused on reducing body burdens. Many of these methods have been designed for individuals with Wilson's disease; however, it is likely that these would also be effective in other instances of copper intoxication. D-penicillamine (Rodeck et al. 1999; Walshe 1996; Walshe and Yealland 1993) is the most commonly used palliative agent for Wilson's disease; however, it has a number of potentially deleterious side effects. Studies in animals suggest that TETREN and TAUD may also be effective chelating agents (Domingo et al. 2000). Other treatment methods include administration of tetrathiomolybdate (Humphries et al. 1988; Kumaratilake and Howell 1989; Ogra et al. 1996), diets high in molybdenum and sulfur (van Ryssen 1994), and diets high in zinc (Brewer et al. 1992; van Ryssen 1994). Further studies

are needed to identify treatments that would interfere with copper's mechanism of toxicity and reduce body burden with minimal side effects.

Children's Susceptibility. There are some data on the toxicity of copper in infants and children. Severe liver damage has been reported in infants and children. These effects are typically clustered in geographically regions and have been grouped into two syndromes: Indian childhood cirrhosis and idiopathic copper toxicosis. Both of these syndromes are associated with elevated copper intakes and early dietary introduction of milk and/or formula, and are believed to have a genetic component. Very high levels of copper are found in the livers of affected children, suggesting that the mechanism of action is related to impaired copper efflux. Additional studies are needed to determine the mechanism of toxicity and to ascertain copper's role in the observed effects. Information that would provide a better understanding of copper absorption and excretion in early infancy and homeostatic mechanisms in infants would also provide valuable documentation on these syndromes and their relationship to copper.

Child health data needs relating to exposure are discussed in Section 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies pertaining to copper have been identified and are shown in Table 3-5 (FEDRIP 2003).

Table 3-5. Ongoing Studies on Copper

Investigator	Affiliation	Research description	Sponsor
Turnland JR	Agricultural Research Service, Davis, California	Influence of high copper intake on copper homeostasis and mineral metabolism	USDA
Kelvay LM	Agricultural Research Service, Grand Forks, North Dakota	Determination of a no effect level for copper	USDA
Reeves PG	Agricultural Research Service, Grand Forks, North Dakota	Correlation between sperm motility and copper status in humans and animals	USDA
Harris ED	Texas A & M University	Copper metabolism and homeostasis in humans and animals	CSREES TEX
Thiele DJ	University of Michigan at Ann Arbor	Copper homeostasis	NIGMS
Culotta VC	John Hopkins University	Intracellular pathways of copper trafficking	NIEHS
Gitlin JD	Washington University	Copper chaperones	NIDDKD

CSREES TEX = Cooperative State Research Education and Extension Service, Texas; NIDDKD = National Institute of Diabetes and Digestive and Kidney Disease; NIEHS = National Institute of Environmental Health and Science; NIGMS = National Institute of General Medical Sciences; USDA = U.S. Department of Agriculture

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Copper is the first element of Group IB of the periodic table and displays four oxidation states: Cu(O), Cu(I), Cu(II), and Cu(III). Along with silver and gold, it is classified as a noble metal and, like them, can be found in nature in the elemental form. Copper's unique chemical and physical properties have made it one of the most important metals. These properties include high thermal conductivity, high electrical conductivity, malleability, low corrosion, alloying ability, and pleasing appearance. Properties of metallic copper such as electrical conductivity and fabricability vary markedly with purity. Standard classifications have been defined according to processing method. For example, ASTM B5-74 is >99.90% pure and is the accepted basic standard for electrolyte copper wire bars, etc. (Tuddenham and Dougall 1978). Data on the chemical identity of copper are shown in Table 4-1. Data on the chemical identity of copper sulfate, the most important commercial compound of copper, are shown in Table 4-2.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Copper is positioned below hydrogen in the electromotive-force series, so it will not displace hydrogen ions from dilute acid. Accordingly, copper will not dissolve in acid unless an oxidizing agent is present. Therefore, while it readily dissolves in nitric and hot concentrated sulfuric acid, it only dissolves slowly in hydrochloric and dilute sulfuric acid, and then only when exposed to the atmosphere (Hawley 1981). It is also attacked by acetic acid and other organic acids. When exposed to moist air, a characteristic green layer of the basic copper carbonate slowly forms (Windholz 1983). This tightly adherent coating protects the underlying metal from further attack and is also prized for its appearance. Copper dissolves in ammonia in the presence of air, forming the cupric ammonium complex ion $Cu(NH_3)_4^{2+}$ (Cotton and Wilkinson 1980).

Cu(I) or the cuprous ion disproportionates rapidly (<1 second) in aqueous solution to form Cu(II) and Cu(0) (Cotton and Wilkinson 1980). The only Cu(I) compounds that are stable in water are extremely insoluble ones such as CuCl. It has been shown that Cu(I) complexes may be formed in seawater by photochemical processes and may persist for several hours (Moffett and Zika 1987). Cuprous compounds are generally colorless.

Table 4-1. Chemical Identity of Copper

Characteristic	Information	Reference
Chemical name	Copper	
Synonym(s)	Not reported	
Registered trade names(s)	Not reported	
Chemical formula	Cu	HSDB 2004
Chemical structure	Face-centered cubic	Budavari 2001
Identification numbers:		
CAS registry	7440-50-8	HSDB 2004
NIOSH RTECS	GL5324000	HSDB 2004
EPA hazardous waste	Not reported	
OHM/TADS	Not reported	
DOT/UN/NA/IMCO shipping	Not reported	
HSDB	1622	HSDB 2004
NCI	Not reported	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Chemical Identity of Copper Sulfate

Characteristic	Information	Reference
Chemical name	Copper sulfate	
Synonym(s)	Cupric sulfate; blue stone; blue vitriol; cupric sulphate; Roman vitriol; Salzburg vitriol; blue copperas; copper(II) sulfate	Budavari 2001; Hawley 1997; HSDB 2004
Registered trade names(s)	Not reported	
Chemical formula	CuO_4S	Budavari 2001
Chemical structure	$CuSO_4$	Budavari 2001
Identification numbers:		
CAS registry	7758-98-7	HSDB 2004
NIOSH RTECS	GL8800000	HSDB 2004
EPA hazardous waste	Not reported	
OHM/TADS	Not reported	
DOT/UN/NA/IMCO shipping	Not reported	
HSDB	916	HSDB 2004
NCI	Not reported	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Cu(II) or the cupric ion is the most important oxidation state of copper. Cu(II) is the oxidation state of copper generally encountered in water (Cotton and Wilkinson 1980). Cupric ions are coordinated with six water molecules in solution; the arrangement of the water molecules is distorted in that there are four molecules bound closely to the copper in a planar array while the other two are more loosely bound in polar position (Cotton and Wilkinson 1980). Addition of ligands such as NH_3 to the solution will successively displace only the four planar water molecules. Most cupric compounds and complexes are blue or green in color. They are frequently soluble in water.

When Cu(II) is introduced into the environment, the cupric ion typically binds to inorganic and organic materials contained within water, soil, and sediments. In water, Cu(II) binds to dissolved organics (e.g., humic or fulvic acids). The Cu(II) ion forms stable complexes with $-NH_2$, -SH and, to a lesser extent, -OH groups of these organic acids. Cu(II) will also bind to inorganic and organic components in sediments and soils with varying affinities. For example, Cu(II) binds strongly to hydrous manganese and iron oxides in clay and to humic acids in organic matter, but much less strongly to aluminosilicates in sand. As in water, the binding affinities of Cu(II) with inorganic and organic matter in sediments and soils is dependent on pH, the oxidation-reduction potential in the local environment, and the presence of competing metal ions and inorganic anions.

Cu(III) is strongly oxidizing and only occurs in a few compounds (Kust 1978). At this time, none of these compounds are industrially important or environmentally significant.

Data on the physical and chemical properties of copper and copper sulfate are shown in Table 4-3.

Table 4-3. Physical and Chemical Properties of Copper and Copper Sulfate

Property	Copper	Copper sulfate
Molecular weight	63.546[a]	159.61[a]
Color	Reddish[b]	Blue crystals, white dehydrated[b]
Physical state	Solid[b]	Solid[b]
Melting point	1,083[c]	Decomposes at 560[a]
Boiling point	2,595[c]	No data
Specific gravity (20/4 °C)	8.94[c]	3.60[a] 2.286 (pentahydrate)[a]
Odor	No data	None[d]
Odor threshold		
Air	No data	No data
Water	No data	No data
Taste	No data	No data
Taste threshold	No data	No data
pK_a		
Solubility:		
Water	Insoluble[e]	32.0g/100g (20 °C)[f]
Organic solvent(s)		Soluble in methanol, slightly soluble in ethanol[b]
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure:	1 (1,628 °C)[g]	No data
Henry's law constant at 25 °C	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors at 25 °C ppm to mg/m^3	Since these substances exist in the atmosphere in the particulate state, the concentration is expressed as mg/m^3.	
Explosive limits	No data	No data

[a]Lide 2000
[b]Lewis 1997
[c]Budavari et al. 2001
[d]Meister et al. 2001
[e]Stewart and Lassiter 2001
[f]Dean 1985
[g]Lewis 2000

pK_a = The dissociation constant of the conjugate acid

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Copper occurs naturally in many minerals, such as cuprite (Cu_2O), malachite ($CuCO3{\cdot}Cu(OH)_2$), azurite ($2CuCO_3{\cdot}Cu(OH)_2$), chalcopyrite ($CuFeS_2$), chalcocite (Cu_2S), and bornite (Cu_5FeS_4). It also occurs uncombined as the metal (Tuddenham and Dougall 1979; Weast 1980). The copper content of ore deposits ranges from 0.5 to 5% by weight, whereas in igneous rock copper content ranges from 0.0005 to 0.011% (Duby 1980; Weant 1985). The three most important sources of copper are chalcocite, chalcopyrite, and malachite (Weant 1985). The major U.S. deposits are porphyry, indicating that they are of hydrothermal origin and are uniformly distributed in fractures or veins.

The United States is the world's second leading copper producer. The country produced 148 million metric tons of mined ore in 2001, with an average copper content of 0.48% (USGS 2001). Mine production of recoverable copper in the United States totaled 1,340,000 metric tons in 2001, an estimated 10% of world production behind Chile, which accounted for 35%. Copper was mined in six states in 2001, with Arizona accounting for 67% of U.S. copper production, followed by Utah (13%), New Mexico (13%) and Nevada (1%). There were 23 copper-producing mines in 2001, down from 27 in 2000. Thirteen of these are copper mines accounting for 99% of production in the United States. The remaining mines yielded copper as a by-product of gold, lead, silver, or zinc mining. Of the 13 largest mines, 10 were in Arizona, 2 were in New Mexico, and 1 was in Utah. Production, processing and use of copper and copper compounds in the United States, listed by state, are given in Tables 5-1 and 5-2, respectively.

After mining, most of the ore is crushed and concentrated to a material containing 15–35% copper using flotation. The remaining copper is obtained by first leaching the ore or tailings and then concentrating the leachate by applying solvent extraction or ion exchange (Butterman 1982).

Most primary copper is produced from its sulfide ore by matte smelting, an operation yielding a molten sulfide of copper and iron, called matte, which is further oxidized in a conversion step to yield metallic copper. The conversion operation takes place in two stages. In the first, slag-forming stage, FeS is oxidized to iron oxides, which combine with a silica flux to form a slag. In the second, copper-producing stage, CuS_2 is oxidized to form sulfur dioxide and metallic copper. The product of the conversion

Table 5-1. Facilities that Produce, Process, or Use Copper

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	2	10,000	99,999	12
AL	47	100	49,999,999	1, 2, 3, 5, 7, 8, 9, 11, 12, 13
AR	45	1,000	49,999,999	1, 2, 3, 4, 7, 8, 9, 12, 13, 14
AZ	26	0	999,999,999	1, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
CA	153	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
CO	14	1,000	499,999,999	2, 3, 4, 7, 8, 11, 12, 14
CT	54	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11
FL	28	1,000	9,999,999	2, 3, 4, 6, 7, 8, 9, 10, 11, 12
GA	58	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
HI	2	1,000	9,999	12
IA	31	1,000	99,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12
ID	3	10,000	999,999	1, 3, 8, 9, 12
IL	150	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14
IN	148	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	23	100	9,999,999	2, 3, 4, 6, 7, 8, 9, 11, 12, 14
KY	69	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
LA	10	100	9,999,999	2, 6, 8, 10, 12, 13, 14
MA	59	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
MD	7	1,000	999,999	1, 2, 4, 5, 7, 8, 9
ME	10	10,000	9,999,999	2, 3, 8
MI	133	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
MN	49	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	73	100	499,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12
MS	33	100	9,999,999	4, 7, 8, 9, 12
MT	1	1,000	9,999	6, 11
NC	72	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12
ND	2	10,000	99,999	7, 8
NE	18	1,000	9,999,999	1, 3, 5, 7, 8, 9, 11, 12, 13
NH	19	100	49,999,999	2, 3, 4, 7, 8, 9
NJ	36	1,000	49,999,999	1, 2, 3, 4, 6, 7, 8, 9, 11, 12
NM	7	1,000	9,999,999	2, 3, 8, 12
NV	6	1,000	99,999	7, 8, 11, 12
NY	100	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
OH	204	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	51	100	99,999,999	1, 2, 3, 4, 7, 8, 9, 11, 12, 13
OR	23	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
PA	207	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
PR	22	1,000	9,999,999	1, 2, 3, 8, 11
RI	28	1,000	9,999,999	2, 3, 4, 6, 7, 8, 9, 12

Table 5-1. Facilities that Produce, Process, or Use Copper

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
SC	53	100	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14
SD	11	1,000	49,999,999	1, 5, 7, 8, 12, 14
TN	75	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
TX	102	100	99,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 14
UT	10	1,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 11, 12
VA	42	1,000	9,999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13, 14
VT	4	1,000	99,999	2, 3, 4, 6, 8, 9
WA	24	1,000	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	148	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14
WV	12	1,000	9,999,999	2, 3, 6, 7, 8, 12
WY	4	0	99,999	1, 4, 9, 10, 12

Source: TRI01 2003

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation component
9. Article component
10. Repackaging
11. Chemical processing aid
12. Manufacturing aid
13. Ancillary/Other uses
14. Process impurity

Table 5-2. Facilities that Produce, Process, or Use Copper Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	5	10,000	9,999,999	1, 2, 3, 4, 5, 7, 10, 12, 13, 14
AL	37	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
AR	26	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
AZ	27	1,000	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
CA	74	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	7	100	99,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
CT	24	1,000	999,999,999	1, 3, 5, 6, 7, 8, 9, 10, 11, 12
DC	1	1,000	9,999	12
DE	5	1,000	99,999	1, 2, 3, 5, 7, 9, 12, 13
FL	36	100	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
GA	36	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IA	26	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	8	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10
IL	92	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	72	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	11	0	999,999	1, 3, 5, 7, 8, 9, 10, 11, 12, 13
KY	39	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
LA	26	0	99,999,999	1, 2, 3, 4, 5, 7, 8, 10, 11, 12, 13
MA	25	100	9,999,999	1, 3, 4, 5, 6, 7, 8, 10, 11, 12
MD	10	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
ME	5	100	999,999	1, 3, 5, 7, 8, 11, 13
MI	52	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MN	29	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	34	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	14	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13
MT	9	1,000	99,999,999	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14
NC	48	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	8	100	99,999	1, 5, 7, 9, 12, 13, 14
NE	10	10,000	99,999,999	1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
NH	12	100	9,999,999	1, 3, 5, 6, 7, 8, 9, 11, 12, 13
NJ	24	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
NM	8	1,000	99,999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
NV	17	100	10,000,000,000	1, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
NY	30	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	83	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	14	100	999,999	1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14
OR	16	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
PA	92	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	3	1,000	99,999	7, 10

Table 5-2. Facilities that Produce, Process, or Use Copper Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
RI	12	100	999,999	1, 2, 3, 4, 7, 8, 10, 12
SC	31	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
SD	2	1,000	999,999	1, 3, 5, 6, 10, 13
TN	47	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
TX	89	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	14	1,000	10,000,000,000	1, 3, 4, 5, 6, 7, 8, 9, 12, 13
VA	36	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WA	13	1,000	999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	35	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	17	1,000	999,999	1, 3, 4, 5, 7, 8, 9, 12, 13, 14
WY	4	100	999,999	1, 5, 9, 12, 13

Source: TRI01 2003

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation component
9. Article component
10. Repackaging
11. Chemical processing aid
12. Manufacturing aid
13. Ancillary/Other uses
14. Process impurity

operation is blister copper, which is 98.5–99.5% copper. Concentrated leachate from low-grade ore is subject to electrowinning, which electrolyzes aqueous sulfate solutions, or to cementation, which displaces copper from solution by a more active metal such as iron (Duby 1980). Further purification is obtained by electrolytic refining. For more details on copper mining, ore processing, smelting, and refining, see Duby (1980) and EPA (1980b).

Production of copper in the United States includes not only the processing of both domestic and foreign ores, but also the recovery of scrap. Scrap is a significant part of the U.S. copper supply. Scrap refers to both 'old scrap' (metal that has been used) and 'new scrap' (generated during fabrication). In 1999, smelting was performed in the United States by four primary smelters and two secondary smelters with a combined capacity of 1,750,000 metric tons per year (USGS 2000). Together, they produced 1,290,000 metric tons of copper from both domestic and foreign ores and scrap in 1999 (USGS 2001). In 2000, smelting was performed in the United States by four primary smelters and one secondary smelter with a combined capacity of 1,180,000 metric tons per year. Production of copper from U.S. smelters in 2000 was reported to be 1,000,000 metric tons, down from 1,290,000 metric tons in 1999 (USGS 2001). During 2000, 23 refineries operating with a combined capacity of 2,400,000 tons, produced 1,587,000 metric tons of copper from domestic and foreign ores. An additional 208,000 metric tons of copper was produced from new and old scrap for a combined total refinery production in the United States of 1,790,000 tons (USGS 2001). This level of refinery production was down from a level of 2,120,000 metric tons in 1999 (USGS 2001). Production of secondary copper and copper-alloys amounted to 1,490,000 metric tons in both 1999 and 2000 (USGS 2000). Apparent consumption for 2000 was 3,130,000 metric tons (USGS 2001). This includes domestic refined copper production, net imports of refined copper, copper recovered from old scrap, and stock adjustments. These alloys, primarily brass and bronze, contain approximately 60–>90% copper.

Most industrially important copper compounds are made starting with copper metal. Copper sulfate, the most commercially important copper compound, was produced by at least six companies in plants in Casa Grande, Arizona; Sewaren and Oak Bridge, New Jersey; El Paso and Garland, Texas; Sante Fe Springs, California; Union, Illinois; Copperhill, Tennessee; and Sumter, South Carolina (Jolly and Edelstein 1987).

Copper sulfate also is produced as a by-product of copper production by ore-leaching with sulfuric acid. Production of copper sulfate increased by 29% from 1996 to 2000, standing at 55,500 metric tons in 2000

(USGS 2000). However, in 2001, production of copper sulfate decreased slightly to 55,200 metric tons (USGS 2001). Recent production figures for other copper compounds were not located.

5.2 IMPORT/EXPORT

In 2000, 1,340,000 million tons of unmanufactured copper and 1,060,000 metric tons of refined copper were imported (USGS 2001). Peru, Canada, and Chile were the principal sources of imported refined copper. The quantity of imported unmanufactured copper increased by 93% since 1994; the increase was almost entirely in the importation of refined powder, as opposed to ore concentrate, blister copper, or scrap (USGS 1994, 2001). Imports of copper sulfate amounted to 4,650 metric tons and were primarily obtained from Australia and Mexico (USGS 2001).

In 2000, 483,000 metric tons of copper were exported, of which 19% was refined copper (USGS 2000). In 2001, exports dropped to 379,000 metric tons with a large decrease in exports of refined copper (from 93,600 metric tins in 2000 to 22,500 metric tons in 2001); exports of unalloyed copper scrap increased from 228,000 metric tons in 2000 to 262,000 metric tons in 2001 (USGS 2001).

5.3 USE

Copper is one of the most important metals because of its durability, ductility, malleability, and electrical and thermal conductivity. It is used primarily as the metal or in alloys. Its alloys, including brass, bronze, gun metal, and Monel metal, are important commodities. All current American coins are copper alloys. A small percentage of copper production goes into the manufacture of copper compounds, primarily copper sulfate.

The Copper Development Association's 2000 estimates of the end-use distribution of copper and copper-alloy products by the industrial sector were: construction, 39%; electrical and electrical products, 28%; transportation equipment, 11%; industrial machinery and equipment, 11%; and consumer and general products, 11% (USGS 2002). The top 10 markets for copper and copper-alloy during 1986 were, in order of importance: plumbing, building wire, telecommunications, power utilities, in-plant equipment, air conditioning, automotive electrical, automotive nonelectrical, business electronics, and industrial valves and fittings (Jolly and Edelstein 1987).

Copper sulfate was the only copper compound for which end-use distribution data were available; these data addressed only domestic producers. Sixty-five percent of production went into agricultural use, 28% for industrial uses such as metal finishing, mineral froth flotation and wood preservatives, and 7% for water treatment.

In agriculture, copper compounds are used as fungicides and to prepare copper fungicidal products, algicides for reservoirs and streams and nutritional supplements in animal feed and fertilizers. Industrial applications of copper sulfate include use as an activator in froth flotation of sulfide ores, production of chromated copper arsenate wood preservatives, electroplating, azo dye manufacture, mordant for textile dyes, petroleum refining and in the manufacture of other copper compounds such as copper hydroxide and copper carbonate (Mannsville Chemical Products 1984).

Copper compounds are applied as fungicides to foliage, seed, wood, fabric, and leather to protect against blight, downy mildew and rust. The 1982 consumption of copper-containing fungicides was 2.8 million pounds (Mannsville Chemical Products 1984). The major copper compound used for this purpose was the basic copper sulfate (1.8 million pounds). Other important fungicidal compounds were copper hydroxide, copper ammonium carbonate, copper oxychloride and copper oxychloride sulfate. The major target crops of copper-containing fungicides are citrus fruits, peanuts, deciduous fruits (other than apples), potatoes, vegetables and other field crops. Copper compounds are also used as algicides, insecticides and repellents. Products containing copper compounds frequently contain other chemicals and may be sold under various trade names. Formulation may be in wettable powders or aqueous solutions.

5.4 DISPOSAL

It is estimated that 60% of copper in scrap is recycled (Tuddenham and Dougall 1978). In 1986, ~40% of the copper produced came from this source (Jolly and Edelstein 1987). Copper-containing wastes can be concentrated using ion exchange, reverse osmosis, or evaporation, and then reclaimed by electrolysis (HSDB 2002). Copper and copper compounds not recycled are disposed of in landfills or released into waste water. Methods of copper containing sludge disposal from waste water treatment facilities include landfilling, landspreading, incineration or ocean disposal.

In case of a solid copper sulfate spill on land, the solids should be protected from rain and fire-fighting water by covering the material with plastic sheeting (HSDB 2002). In the event of a water spill, the

copper sulfate should be neutralized with crushed limestone, slaked lime, or sodium bicarbonate, and the solidified masses should be removed.

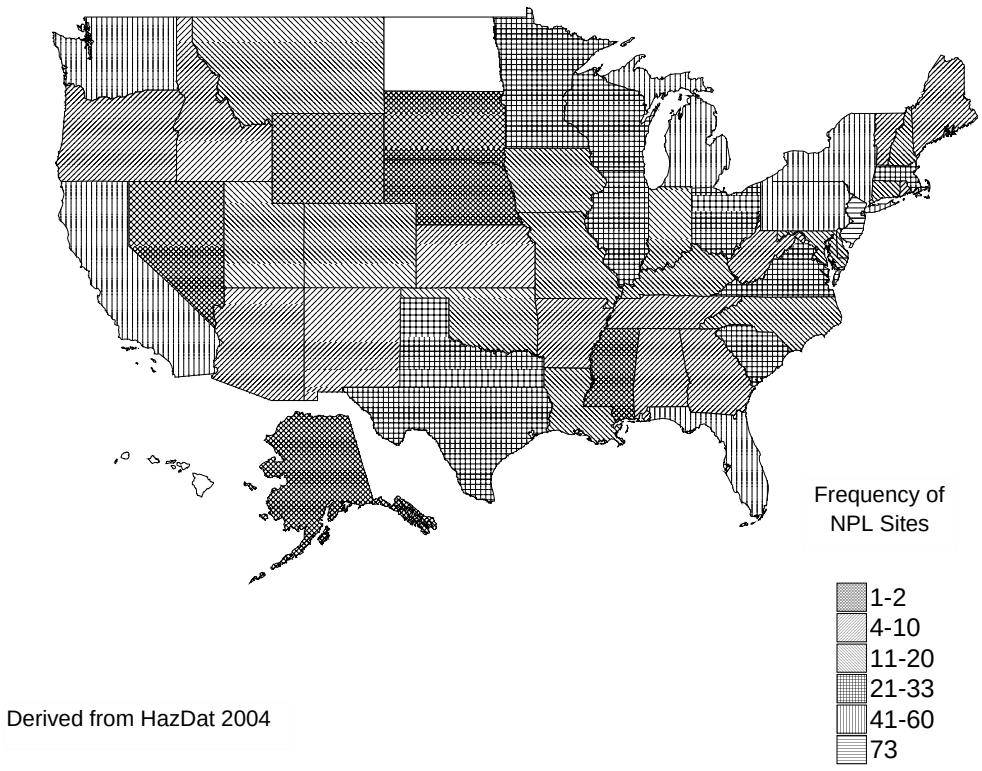
6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Copper has been identified in at least 906 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for copper is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 895 are located within the United States, 2 are located in the Territory of Guam, 8 are located in the Commonwealth of Puerto Rico, and 1 is located in the U.S. Virgin Islands (the sites in the Territory of Guam, the Commonwealth of Puerto Rico, and the U.S. Virgin Islands are not shown).

Copper and its compounds are naturally present in the earth's crust. Natural discharges to air and water, such as windblown dust, volcanic eruptions, etc., may be significant. Therefore, it is important to consider the copper concentrations within a specific environment, geographical region, or human population study site that has been minimally affected by anthropogenic sources of copper in order to accurately assess the contribution of an anthropogenic activity to human exposures to copper. In air, the mean copper concentrations in the atmosphere range between 5 and 200 ng/m^3 in rural and urban locations. Airborne copper is associated with particulates that are obtained from suspended soils, combustion sources, the manufacture or processing of copper-containing materials, or mine tailings. The median concentration of copper in natural water (e.g., rivers, lakes, and oceans) is 4–10 ppb. It is predominantly in the Cu(II) state. Most of it is complexed or tightly bound to organic matter. Little is present in the free (hydrated) or readily exchangeable form. The combined processes of complexation, adsorption, and precipitation control the level of free Cu(II). The chemical conditions in most natural water are such that, even at relatively high copper concentrations, these processes will reduce the free Cu(II) concentration to extremely low values. The mean concentration of copper in soil ranges from 5 to 70 mg/kg and is higher in soils near smelters, mining operations, and combustion sources. Sediment is an important sink and reservoir for copper. In relatively clean sediment such as those found in some of the bays and estuaries along the New England Coast, the copper concentration is <50 ppm; polluted sediment may contain several thousand ppm of copper. The form of copper in the sediment also will be site-specific. In aerobic sediments, copper is bound mainly to organics (humic substances) and iron oxides. However, in some cases, copper is predominantly associated with carbonates. In anaerobic sediments, Cu(II) will be reduced to Cu(I) and insoluble cuprous salts will be formed.

Figure 6-1. Frequency of NPL Sites with Copper Contamination



The largest release of copper to the environment by anthropogenic activities is by far to land. The major sources of release are mining operations, agriculture, sludge from publicly-owned treatment works (POTWs) and municipal and industrial solid waste. Mining and milling contribute the most waste. Copper is released to water as a result of natural weathering of soil and discharges from industries and sewage treatment plants. Copper compounds may also be intentionally applied to water to kill algae.

Copper associated with particulate matter is emitted into the air naturally from windblown dust, volcanoes, and anthropogenic sources, the largest of which are being primary copper smelters and ore processing facilities. The concentration of copper in emissions from copper smelters has been found to range between 7 and 137.8 ng/m^3 (Hutchinson 1979; Romo-Kröger et al. 1994).

In the general population, the highest exposures to copper come from drinking water and food. Of special concern is copper that gets into drinking water from water distribution systems (both from the water treatment plant and in the home). When a system has not been flushed after a period of disuse, the concentration of copper in tap water may exceed 1.3 ppm, the EPA drinking water limit. The estimated intakes of copper in the general population are 0.15 mg/day from drinking water, and approximately 2 mg/day from food. The dietary intake of copper can be increased from the regular consumption of certain foods, such as shellfish, organ meats (e.g., liver and kidney), legumes, and nuts. However, except for shellfish, where an additional intake of 2–150 mg/day is possible for those individuals who regularly consume shellfish, these other sources of higher copper intake are not expected to increase the total daily intake of copper beyond the recommended limit of 10–12 mg/day for adults (WHO 1996). In comparison to intake of copper through ingestion of water and food, the intake of copper through inhalation of copper in dust is much less significant at an estimated rate of 0.1–4.0 µg copper/day. Contact with available copper also may result from the use of copper fungicides and algicides.

Many workers are exposed to copper in agriculture, industries connected with copper production, metal plating, and other industries. Little information is available concerning the forms of copper to which workers are exposed.

At this time, copper has been identified in 906 out of 1,647 NPL hazardous waste sites in the United States (HazDat 2004). The frequency of these sites within the United States is noted in Figure 6-1. Based on the available data, people living close to NPL sites may be at greater risk for exposure to copper than the general population with respect to inhalation of airborne particulates from the NPL sites, ingestion of

contaminated water or soil, and/or uptake of copper into fruits and vegetables raised in gardens of residents living near NPL sites. People living near copper smelters and refineries and workers in these and other industries may be exposed to high levels of dust-borne copper by both inhalation and ingestion routes. For example, ingestion of 300 mg of soils near copper smelters by children could result in the intake as high as 0.74–2.1 mg copper per day, based on measurements of copper concentrations in these soils of 2,480–6,912 mg/kg.

6.2 RELEASES TO THE ENVIRONMENT

Industrial manufacturers, processors, and users of copper and copper compounds are required to report the quantities of this substance released to environmental media annually (EPA 1988d). The data compiled in the Toxics Release Inventory (TRI01 2003) are for releases in 2001 to air, water, soil, and transfer of copper and copper compounds for offsite disposal. These data are summarized in Tables 6-1 (copper) and 6-2 (copper compounds). Total releases (rounded to three significant digits) of copper into the environment in 2001 were approximately 11,100,000 pounds (approximately 5,050 metric tons) (TRI01 2003), of which approximately 821,000 pounds (373 metric tons), or 7.4% of the total, were released to air. Another 46,600 pounds (21 metric tons) or approximately 0.4% of the total, were released into water, 0.5% (53,800 pounds, 24 metric tons) was injected underground, and 91.9% (10,200,000 pounds, 4,360 metric tons) was released to land. Total releases (rounded to three significant digits) of copper compounds to the environment in 2001 were approximately 1,000,000,000 pounds (approximately 455,000 metric tons) (TRI01 2003) of which approximately 1,420,000 pounds (645 metric tons), or 0.1% of the total, were released to air. Another 418,000 pounds (190 metric tons), or approximately 0.04% of the total, were released into water, 0.09% (894,000 pounds or 406 metric tons) was injected underground, and 99.8% (998,000,000 pounds or 454,000 metric tons) was released to land. The TRI data should be used with caution because only certain types of facilities are required to report them (i.e., this is not an exhaustive list).

Industrial releases are only a fraction of the total environmental releases of copper and copper compounds. Other sources of copper release into the environment originate from domestic waste water, combustion processes, wood production, phosphate fertilizer production, and natural sources (e.g., wind blown dust, volcanoes, decaying vegetation, forest fires, sea spray, etc.) (Georgopoulos et al. 2001;

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Copper[a]

State[c]	Number of facilities	Reported amounts released in pounds per year[b]						
		Air[d]	Water	Underground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
AK	2	0	No data	0	27,324	27,324	0	27,324
AL	51	11,825	1,321	0	14,906	28,052	47,708	75,760
AR	48	5,951	573	0	143,970	150,494	231,861	382,355
AZ	30	978	48	0	227,993	229,019	9,094	238,113
CA	168	9,745	908	0	2,608,971	2,619,624	171,791	2,791,415
CO	18	472	16	0	125,387	125,875	15,991	141,866
CT	63	10,662	904	0	5	11,571	47,415	58,985
FL	35	832	303	51,262	158,561	210,958	40,092	251,050
GA	72	4,473	575	0	135,127	140,175	30,052	170,227
HI	2	0	No data	0	117,010	117,010	0	117,010
IA	39	3,050	566	0	250	3,866	35,144	39,010
ID	5	120	5	0	450,820	450,945	4,000	454,945
IL	160	46,380	4,623	0	1,601,420	1,652,423	658,745	2,311,168
IN	161	42,775	1,239	0	369,664	413,678	2,223,563	2,637,241
KS	24	2,535	251	0	297,190	299,976	24,566	324,542
KY	73	18,633	390	0	269,927	288,950	179,301	468,251
LA	15	126,947	710	2,200	2,426	132,283	690	132,973
MA	69	2,530	77	0	0	2,607	64,821	67,427
MD	12	250	10	0	250	510	89,168	89,678
ME	11	106	321	0	500	927	9,034	9,961
MI	142	35,480	685	0	849	37,014	161,721	198,735
MN	50	16,129	10	0	5	16,144	825,881	842,025
MO	79	9,204	671	0	52,581	62,456	409,753	472,209
MS	35	2,350	657	0	520	3,527	56,712	60,239
MT	1	161	No data	0	1,030,000	1,030,161	No data	1,030,161
NC	83	7,965	1,076	0	193,576	202,617	107,899	310,516
ND	3	23	5	0	0	28	339	367
NE	19	3,638	5	0	47,005	50,648	7,628	58,276
NH	22	1,005	25	0	0	1,030	37,543	38,573
NJ	46	15,584	165	5	22,973	38,727	12,291	51,018
NM	7	500	No data	0	118,680	119,180	23,453	142,633
NV	6	905	No data	0	500	1,405	5,201	6,606
NY	104	11,484	14,198	0	114,462	140,144	894,995	1,035,138
OH	251	55,122	5,424	0	606,137	666,683	481,776	1,148,459
OK	64	8,712	303	0	80,952	89,967	29,726	119,693
OR	23	771	9	0	81,984	82,764	1,495	84,259
PA	222	85,511	2,913	0	43,546	131,970	343,353	475,324

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Copper[a]

State[c]	Number of facilities	Reported amounts released in pounds per year[b]						
		Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
PR	21	15,944	5	0	0	15,949	9,247	25,196
RI	33	5,093	5	0	0	5,098	22,759	27,857
SC	55	10,018	875	0	76,761	87,654	59,678	147,332
SD	10	4,885	No data	0	750	5,635	280	5,915
TN	89	165,328	567	0	206	166,101	87,117	253,218
TX	117	26,388	4,006	369	574,322	605,085	178,081	783,166
UT	12	1,179	56	0	46,085	47,320	298	47,618
VA	46	21,649	694	5	239,776	262,124	210,846	472,970
VT	5	0	No data	0	250	250	1,025	1,275
WA	28	474	633	0	166,530	167,637	150,773	318,410
WI	159	25,741	617	0	26,845	53,203	257,886	311,089
WV	12	1,951	116	5	30,759	32,831	8,102	40,933
WY	5	381	0	0	60,882	61,263	75	61,338
Total	2,807	821,838	46,559	53,846	10,168,637	11,090,881	8,268,966	19,359,847

Source: TRI01 2003

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]The sum of fugitive and stack releases are included in releases to air by a given facility.
[e]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[f]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Copper Compounds[a]

State[c]	Number of facilities	Reported amounts released in pounds per year[b]						
		Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
AK	6	475	57	670,000	5,193,578	5,864,110	750	5,864,860
AL	66	27,363	28,896	0	2,315,767	2,372,026	66,409	2,438,435
AR	60	17,082	3,277	0	86,510	106,869	173,666	280,535
AZ	27	135,813	584	0	451,467,272	451,603,669	76,083	451,679,752
CA	92	5,374	878	0	111,029	117,281	166,771	284,053
CO	15	720	15,810	0	115,190	131,720	61,086	192,806
CT	24	2,072	635	0	0	2,707	354,565	357,272
DC	1	0	0	0	4,600	4,600	0	4,600
DE	9	3,203	9,196	0	25,029	37,428	30,509	67,937
FL	54	85,273	22,720	0	648,038	756,031	169,746	925,777
GA	69	14,994	48,943	0	776,472	840,409	369,367	1,209,776
IA	52	15,425	3,386	0	156,575	175,386	152,607	327,993
ID	11	1,305	800	0	424,736	426,841	272	427,113
IL	114	46,746	5,233	0	503,051	555,030	1,021,024	1,576,054
IN	88	52,013	20,411	250	1,098,611	1,171,285	1,044,431	2,215,716
KS	20	3,774	0	0	247,277	251,051	112,520	363,571
KY	49	37,298	40,320	0	889,385	967,003	529,758	1,496,761
LA	33	5,626	17,074	7	274,009	296,716	156,664	453,380
MA	27	720	39	0	3	762	104,579	105,341
MD	19	7,471	8,993	0	20,391	36,855	163,428	200,283
ME	5	2,200	485	0	0	2,685	37,187	39,872
MI	68	60,059	14,850	0	643,734	718,643	511,519	1,230,162
MN	46	9,598	882	0	281,020	291,500	2,115,492	2,406,992
MO	55	20,270	2,900	0	4,658,137	4,681,307	248,752	4,930,059
MS	35	45,892	279	12,000	22,708	80,879	54,015	134,894
MT	10	12,595	10	47,757	3,385,422	3,445,784	32,403	3,478,187
NC	88	21,656	15,299	0	758,429	795,384	124,485	919,869
ND	8	632	11,877	0	138,516	151,025	124,852	275,877
NE	21	1,999	155	0	207,272	209,426	21,672	231,098
NH	13	561	12	0	0	573	28,554	29,127
NJ	30	1,187	5,754	0	18,117	25,058	1,869,339	1,894,397
NM	10	11,839	4,005	0	55,651,587	55,667,431	43,010	55,710,441
NV	18	2,034	160	1	27,004,822	27,007,017	3,067	27,010,084
NY	35	9,816	9,830	1	52,320	71,967	161,344	233,311
OH	105	14,459	17,520	8,100	1,158,856	1,198,935	1,555,185	2,754,120
OK	23	2,466	5,082	662	212,835	221,045	48,189	269,234
OR	25	2,160	1,021	0	216,646	219,827	19,130	238,957

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Copper Compounds[a]

		Reported amounts released in pounds per year[b]						
State[c]	Number of facilities	Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
PA	115	484,099	14,493	0	371,008	869,600	3,121,602	3,991,202
PR	7	44	265	0	0	309	0	309
RI	13	253	608	0	108	969	2,927	3,896
SC	53	32,578	2,664	0	203,101	238,343	309,623	547,966
SD	5	6,150	1,340	0	88,000	95,490	18	95,508
TN	60	17,676	20,876	0	11,178,079	11,216,631	336,292	11,552,923
TX	124	99,287	12,731	155,405	1,302,462	1,569,885	849,639	2,419,524
UT	18	63,960	2,860	0	424,682,491	424,749,311	36,408	424,785,719
VA	50	10,518	19,707	0	390,234	420,459	184,428	604,887
WA	23	6,200	756	0	212,242	219,198	35,097	254,295
WI	56	7,319	13,315	0	59,775	80,409	221,765	302,174
WV	18	4,390	11,557	0	769,830	785,777	199,314	985,091
WY	5	1,470	118	0	235,587	237,175	46,668	283,843
Total	1,978	1,416,114	418,663	894,183	998,260,861	1,000,989,821	17,096,211	1,018,086,032

Source: TRI01 2003

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]The sum of fugitive and stack releases are included in releases to air by a given facility.
[e]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[f]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

Harrison 1998). Quantitative information on release of copper to specific environmental media is discussed below. A summary of copper concentrations in environmental media is provided in Table 6-3.

6.2.1 Air

Copper is emitted into the air from both natural and anthropogenic sources. Since copper is a component of the earth's crust, the earth's crust is the primary natural source of copper. Windblown dust has an estimated mean worldwide emission of 0.9–15x10^6 kg/year of copper into the atmosphere (WHO 1998). Other natural sources of copper emitted into air (in terms of estimated ranges of worldwide emissions) are forest fires (0.1–7.5x10^6 kg/year), volcanoes (0.9–18x10^6 kg/year), biogenic processes (0.1–6.4x10^6 kg/year), and sea spray (0.2–6.9x10^6 kg/year) (WHO 1998). Based on these data, the mean total non-crustal sources of copper emitted into the atmosphere is 1.3–38.8x10^6 kg/year. Anthropogenic emission sources include nonferrous metal production, wood production, iron and steel production, waste incineration, industrial applications, coal combustion, nonferrous metal mining, oil and gasoline combustion, and phosphate fertilizer manufacture. It is estimated that only 0.04% of copper released to the environment is released into the air (Perwak et al. 1980). Global atmospheric anthropogenic and natural emissions of copper have been estimated to be 35x10^6 and 28x10^6 kg/year, respectively (Giusti et al. 1993; Nriagu 1989; Nriagu and Pacyna 1988). The estimates for the anthropogenic and natural emissions are based on the sum of copper emissions from various sources as shown in Tables 6-4 and 6-5, respectively.

The EPA conducted a detailed study of the total amount of copper emitted into the atmosphere (Weant 1985). The sources of emissions and the estimated quantities of copper emitted in 10^6 kg/year are: primary copper smelters, 0.043–6; copper and iron ore processing, 0.480–0.660; iron and steel production, 0.112–0.240; combustion sources, 0.045–0.360; municipal incinerators, 0.0033–0.270; secondary copper smelters, 0.160; copper sulfate production, 0.045; gray iron foundries, 0.079; primary lead smelting, 0.0055–0.065; primary zinc smelting, 0.024–0.340; ferroalloy production, 0.0019–0.0032; brass and bronze production, 0.0018–0.036; and carbon black production, 0.013. Using the ranges of copper emitted from these sources, it is estimated that U.S. copper emissions into air are 0.9424–7.974(x10^6) kg per annum. Daily stack emission rates have been reported for three coal-burning power plants on a kg/day/1,000 megawatt basis (Quee Hee et al. 1982); they are 0.3–0.7 and 2.00 kg/day/1,000 megawatt for those using low-sulfur western coal and high-sulfur eastern coal, respectively. This amounts to annual emission rates of 110–260 and 730 kg/1,000 megawatt, respectively. In another report, emission of copper into air from a 650 megawatt electrical power plant,

Table 6-3. Summary of Copper Concentrations in Environmental Media[a]

Environmental media		Concentration	Units
Atmosphere			
Aerosol		0.1–382	ppt
Hydrosphere—water			
Coastal	Dissolved	0.06–4.3	ppb
	Total	0.5–13.8	ppb
	Suspended solids	0.6–370,000	ppm
Estuarine	Dissolved	0.02–4.7	ppb
	Total	1.2–71.6	ppb
	Suspended solids	0.38–72	ppm
Ocean	Dissolved	Not detected–10	ppb
	Total	0.04–10	ppb
	Suspended solids	0.01–2.8	ppm
Lake	Dissolved	0.1–15.6	ppb
	Total	0.1–15.6	ppb
River	Dissolved	0.18–3,000	ppb
	Total	0.5–5,800	ppb
Groundwater	Dissolved	0.003–70	ppb
	Total	1–1,160	ppb
Drinking water	Total	0.3–1,352	ppb
Hydrosphere—sediments			
Coastal	Particulate	0.03–3,789	ppm
	Interstitial water	25.5–32.7	ppb
Estuarine	Particulate	0.3–2,985	ppm
	Interstitial water	0.3–100	ppb
Ocean	Particulate	3.1–648	ppb
	Interstitial water	22–45	ppm
Lake	Particulate	0.4–796	ppm
	Interstitial water	45.6–52	ppb
River	Particulate	5.3–4,570	ppm
Pedosphere			
Soil	Total	0.01–3,138	ppm
	Organic	293–7,634	ppm
Dust	Total	2.9–76	ppm

[a]As reported in the Copper Sourcebook 1998 (Harrison 1998), covering the years 1993–1996.

Source: Georgopoulos et al. 2001

Table 6-4. Global Emissions of Copper from Natural Sources ($x10^6$ kg/year)

	Median	Range
Wind-borne particulates	8.0	0.9–15
Marine spray—seasalt and surface organic microlayers	4.0	0.25–7.7
Volcanoes	9.4	0.9–18
Forest fires	3.8	0.1–7.5
Biogenic—continental particulates and volatiles	2.9	0.11–5.6
Total emissions	28	2.3–54

Source: Nriagu 1989

Table 6-5. Global Emissions of Copper from Anthropogenic Sources ($x10^6$ kg/year)

	Median	Range
Coal combustion	5.15	2.3–8.0
Oil combustion	1.86	0.42–3.3
Pyrometallurgical	23.5	15–32
Secondary nonferrous metal production	0.115	0.06–0.17
Steel and iron manufacturing	1.47	0.14–2.8
Refuse incineration	1.5	1.0–2.0
Phosphate fertilizers	0.415	0.14–0.69
Wood combustion	0.9	0.60–1.2
Total emissions	35	20–51

Source: Nriagu and Pacyna 1988

burning bituminous coal, was estimated at 213 kg/year, based on a summary of reportable TRI releases (Rubin 1999).

Emission factors in grams of copper released to the atmosphere per ton of product have been estimated for various industries (Nriagu and Pacyna 1988). These factors would enable estimation of an industry's copper emissions from its production volume. Missing from these emission estimates is fugitive dust arising from drilling, blasting, loading, and transporting operations associated with copper mining. The only control for reducing fugitive dust is the manual use of water sprays (EPA 1980b). The highest concentrations of copper in atmospheric particulate matter were obtained from mining activities, primary and secondary production, and industrial manufacturing (Table 6-6).

Romo-Kröger et al. (1994) were able to show, through the use of radioactive tracers and cluster analysis of interelemental correlations, that Cu, S, Zn, and As measured near a copper smelter in Chile were derived from the plant and not from the surrounding soil. The concentration of copper in air near the plant decreased from 66 ng/m^3 (fine particles) and 131 ng/m^3 (coarse particles) to 22 ng/m^3 (fine particles) and 50 ng/m^3 (coarse particles) during a period of inactivity at the plant, clearly demonstrating the contribution of plant emissions to copper levels in the surrounding area.

The amount of copper and other pollutants in fugitive dust originating from copper production sites, such as from smelter bag houses, or waste sites, is of some concern. In one study, the amount of airborne copper and other heavy metals deposited near a large refuse dump that received municipal and industrial waste and sewage sludge was determined by first measuring the amount of the metal accumulated in moss bags suspended 1–3 meters above the ground. The deposition rate was then determined from the amount of copper in the moss bags accumulated over the summer of 1985 and compared with that for an agricultural control area. The mean copper deposition rates in the two areas were about the same, 0.55 mg/kg-month (range of 0.04–1.6 mg/kg-month) over the refuse dump and 0.51 mg/kg-month (range of 0.26–0.76 mg/kg-month) in the control area (Lodenius and Braunschweiler 1986).

In a study of automobile exhaust emitted from light duty vehicles conducted in Denver, Colorado, it has been shown that this source of copper emission makes a small local contribution to copper in air. The amount of copper emitted in the exhaust from automobiles powered by regular gasoline has been measured to be 0.001–0.003 mg/mile driven using the Urban Dynamometer Driving Schedule (UDDS) of the Federal Test Schedule (FTS) during the summer of 1996 and the winter of 1997 (Cadle et al. 1999).

Table 6-6. Concentrations of Copper in Particulate Matter (<10 µm) Generated from Various Sources[a]

Source	Copper concentration (percent, w/w)
Metal mining	6.17[b]
Secondary metal production	4.6[b]
Primary metal production	3.50[b]
Industrial manufacturing	2.16[b]
Steel production	0.55[b]
Gray iron foundries	0.19[b]
Steel foundry, general	0.17[b]
Solid waste	0.09[b]
Food and agriculture	0.05[b]
Chemical manufacturing	0.03[b]
Petroleum industry	0.03[b]
Gasoline vehicle exhaust	0.05[c]
Paved road dust	0.0162[c]
Construction dust	0.0102[c]
Landfill dust	0.0102[c]
Unpaved road dust	0.0087[c]
Agricultural lands, dust	0.0067[c]
Diesel vehicle exhaust	0.003[c]

[a]Values obtained from CEIDARS 2000
[b]Data obtained from USEPA Speciate 3.0; Shareef, G.S; Radian, September, 1987
[c]Data obtained from KVB Literature Search

Diesel powered vehicles were also studied and found to emit 0.005–0.039 mg of copper per mile driven for vehicles using #2 diesel fuel.

Only in a few cases has the form of copper released into the air been determined. Copper released into the atmosphere will be in particulate matter in the elemental form or in the form of an oxide, sulfate, or carbonate. Because copper smelters co-emit SO_X gases, copper is expected to be released largely as the sulfate in particulate matter from these facilities. Combustion processes are reported to release copper into the atmosphere as the oxide, elemental copper, and adsorbed copper. Cupric oxide has been identified in emissions from steel manufacturing and in fly ash from oil-fired power plants and open-hearth steel mills (Graedel 1978; Perwak et al. 1980). Copper associated with fine particles (<1 μm) tends to result from combustion, while that associated with large particles (>10 μm) is likely to originate from wind blown soil and dust (Schroeder et al. 1987).

Copper was detected in air at 39 of the 906 NPL hazardous waste sites where copper has been detected in environmental media (HazDat 2004). Copper was detected in offsite air samples at concentrations ranging from 0.02 to 10 μg/m^3 (median concentration of 0.38 μg/m^3) (HazDat 2002). These copper concentrations in air are generally above the annual atmospheric concentrations of 0.005–0.2 μg/m^3 (EPA 1987a).

6.2.2 Water

Much of the copper that enters environmental waters will be associated with particulate matter. Copper is a natural constituent of soil and will be transported into streams and waterways in runoff either due to natural weathering or anthropogenic soil disturbances. Sixty-eight percent of releases of copper to water is estimated to derive from these processes. Copper sulfate use represents 13% of releases to water and urban runoff contributes 2% (Perwak et al. 1980). In the absence of specific industrial sources, runoff is the major factor contributing to elevated copper levels in river water (Nolte 1988). In the EPA-sponsored National Urban Runoff Program, in which 86 samples of runoff from 19 cities throughout the United States were analyzed, copper was found in 96% of samples, at concentrations of 1–100 μg/L (ppb) with a geometric mean of 18.7 μg/L (Cole et al. 1984). This mean concentration of copper in runoff water is higher than the geometric mean concentration of 4.2 ppb for copper in surface water based on measurements in EPA's STORET database (Eckel and Jacob 1988). Of the 71 priority pollutants analyzed, copper, along with lead and zinc, was the most frequently detected.

Giusti et al. (1993) provided estimates of global anthropogenic and natural copper inputs into oceans that are derived from two sources, atmospheric deposition and riverine input. Atmospheric input has been estimated at 14–45x10^6 kg/year for copper in a dissolved form (e.g., rainwater) and 2–7x10^6 kg/year for copper in a particulate form (e.g., aerosols). Riverine input is estimated to be 10x10^6 kg/year as dissolved copper and 1,500x10^6 kg/year as copper bound to particulates.

Domestic waste water is the major anthropogenic source of copper in waterways (Isaac et al. 1997; Nriagu and Pacyna 1988). Studies in Cincinnati and St. Louis showed discharges of copper into sewer systems from residential areas to be significant, with an average loading of 42 mg/person/day (Perwak et al. 1980). In a more comprehensive review, Jenkins and Russell (1994) reported a range of average copper loadings derived from residential and some small industrial contributions of 2.8–83 mg/person/day. Concentrations of copper in influents to 239 waste water treatment plants (12,351 observations) were 0.0001–36.5 ppm, and the median value was ~0.4 ppm (Minear et al. 1981). Copper is not entirely removed in POTWs, and releases from these facilities contribute ~8% of all copper released to water (Perwak et al. 1980). Inputs into the Narraganset Bay, Rhode Island, in decreasing order of importance, are sewage effluent, rivers, urban runoff, and atmospheric fallout (Mills and Quinn 1984; Santschi et al. 1984). Ninety percent of both dissolved and particulate copper was from the effluent of sewage treatment plants that discharged into the Providence River.

While some copper is removed from the waste stream by sewage treatment facilities, considerable copper remains in the effluent and is released into receiving waters (EPA 1981; Perwak et al. 1980). Because removal efficiencies for copper from waste streams tend to remain constant rather than proportional to influent copper concentrations, increases in copper concentrations in POTW influent streams will also result in increased copper concentrations in the effluent streams (Isaac et al. 1997). The copper in domestic waste water has been found to make up a substantial fraction of the copper found in POTW influent in the waste water systems of four Massachusetts municipalities. The range of removal efficiencies reported for pilot and full scale plants suggests that removal depends strongly on plant operation or influent characteristics.

A source of copper released into waterways is from urban storm water runoff. Copper in storm water runoff originates from the sidings and roofs of buildings, various emissions from automobiles, and wet and dry depositional processes (Davis et al. 2001). Concentrations of between 1 and 100 µg/L of copper in storm water runoff have been measured (Georgopoulos et al. 2001). Storm water runoff normally contributes approximately 2% to the total copper released to waterways. In contrast, copper in runoff that

is obtained from the natural weathering of soil or is release from disturbed soils contributes 68% of the copper released to waterways (Georgopoulos et al. 2001).

The best data on typical POTWs using secondary treatment show that 55–90% of copper is removed in these plants with a median and mean removal efficiency of 82% (Perwak et al. 1980). By contrast, those plants using only primary treatment had a 37% median removal efficiency. A more recent study focused on heavy metal removal in three POTWs that received primarily municipal sewage and used activated sludge as a secondary treatment. The study looked at removals in both the primary and secondary treatment stage. The mean removals of soluble copper and total copper after secondary treatment were 49–82 and 83–90%, respectively. The average copper concentration in the final effluent was 17–102 ppb, which would amount to an output of between 0.58 and 3.47 kg of copper into receiving waters per day, based on an effluent volume of 34,000 cubic meters (9 million gallons) per day (Aulenbach et al. 1987; Stephenson and Lester 1987).

Overflow outfalls within combined sewer systems (e.g., combination of domestic and industrial waste water plus storm water) are the primary sources of copper pollutants entering estuaries and other coastal areas of the United States (Crawford et al. 1995; Georgopoulos et al. 2001; Huh 1996; Iannuzzi et al. 1997). For example, Crawford et al. (1995) compiled a summary of the sources of various metals and other contaminants into the Newark Bay estuary. The mass loadings of copper into the estuary as a function of source are (in kg/day): municipal treatment systems, 103.4; industry direct discharge, 8.82; combined sewer overflows, 48.0; storm-water runoff, 62.2; tributary flow, 39.1 and discharges from the Passaic Valley Commission and Middlesex County Sewerage Authority, 126.5.

Discharges to water from active mining and milling are small and most of the western operations do not release any water because water is a scarce resource and is recycled (Perwak et al. 1980). Discharges from electroplating operations are either made directly to the water environment or indirectly via POTWs. Runoff from abandoned mines is estimated to contribute 314 metric tons annually to surface water (Perwak et al. 1980). These discharges are primarily insoluble silicates and sulfides and readily settle out into stream, river, or lake beds. Releases from manufactured products containing copper may be substantial, but are difficult to predict. Corrosion of copper in plumbing or construction may result in direct discharges or runoff into waterways. Copper and brass production releases relatively little copper to water.

Waste water generated from copper mining operations comes from seepage, runoff from tailing piles, or utility water used for mine operation. The amount of waste water generated ranges from 0–300 L water/metric ton of ore mined for open pit copper mines and 8–4,000 L water/metric ton of ore mined underground (EPA 1980b). Copper concentrations in waste water from a selected open pit and underground copper mine were 1.05 and 0.87 ppm, respectively. Data regarding copper concentrations in waste water associated with selected concentrating, smelting, and refining operations can be found in EPA (1980b). Drainage from mining operations and abandoned mines has been shown to have an effect on copper content in local surface waters (see Table 6-7) with concentrations as high as 69,000 ppb being measured (Rösner 1998).

Results of an EPA industrial effluent survey show that mean and maximum levels of copper in treated waste water from six industries exceeded 1 and 10 ppm, respectively (EPA 1981). These industries and their mean and maximum discharges in ppm are: inorganic chemicals manufacturing (<1.6, 18); aluminum forming (<160, 2,200); porcelain enameling (1.3, 8.8); gum and wood chemicals (1.4, 3.0); nonferrous metals manufacturing (1.4, 27.0) and paint and ink formulation (<l.0, 60.0). Emission factors in nanograms of copper released per L of water outflow have been estimated for various industries. These factors would enable estimation of an industry's copper releases if the discharge volumes were known (Nriagu and Pacyna 1988).

Effluents from power plants that use copper alloys in the heat exchangers of their cooling systems discharge copper into receiving waters (Harrison and Bishop 1984). The largest discharges occur after start-up and decrease rapidly thereafter. At the Diablo Canyon Nuclear Power Station, a very high start-up discharge containing 7,700 ppb of copper fell to 67 ppb after 24 hours (Harrison et al. 1980). During normal operation at two nuclear power stations $6.5x10^6$ cubic meters (1,700 million gallons) of seawater per day is used as cooling water for these facilities and discharged into the ocean with copper levels in the effluent ranging between 0.6 and 3.3 ppb (Harrison et al. 1980). This amounts to a total output of copper in the discharged seawater of 3.9–42 kg per day or 1,400–15,000 kg/annum from these two power plants. Except for after start-up of the cooling system, most of the soluble copper (that which passes through a 0.45 µm filter) discharged was in bound forms (Harrison et al. 1980). During normal operation, <20% of the copper released was in the <1,000 molecular weight fraction, which contains the more available copper species.

Copper sulfate is added directly to lakes, reservoirs, and ponds for controlling algae. However, the copper concentration in the water column generally returns to pretreatment levels within a few days

Table 6-7. Concentrations of Copper in Water

Sample type/ source	Location	Concentration (ppb) Range (mean) [median]	Comments	Reference
Drinking water				
Private wells	Nova Scotia, four communities	40–200	at tap, running water	Maessen et al. 1985
		130–2,450, 53% of samples >1,000 ppm	at tap, standing water	
Private wells	New Bedford, Massachusetts	(330)	at tap, running water	Yannoni and Piorkowski 1995
Not specified	Seattle, Washington	(160)	running water	Maessen et al. 1985
		(450), 24% of samples >1,000 ppm	standing water	
River water	Canada (National Survey)	≤5–530 [≤5]	raw water	Meranger et al. 1979
		≤5–100 [≤5]	treated water	
		≤5–220 [20]	distributed water	
Lake water	Canada (National Survey)	≤5–80 [≤5]	raw water	Meranger et al. 1979
		≤5–100 [≤5]	treated water	
		≤5–560 [40]	distributed water	
Well water	Canada (National Survey)	≤5–110 [≤5]	raw water	Meranger et al. 1979
		≤5–70 [≤5]	treated water	
		10–260 [75]	distributed water	
School drinking water	New Jersey	BD–10,200[a]	first draw	Murphy 1993
		BD–7,800	10-minute flush	
		BD–8,500	mid-day, first draw	
Municipal water supply	Berlin, Germany	0.009–4.2 (0.561)	at tap, running water	Zietz et al. 2003a
Municipal water supply	Lower Saxony, Germany	<0.1–6.40 (0.183)	at tap, standing water	Zietz et al. 2003b
		<0.1–3.00 (0.106)	at tap, running water	
Groundwater				
Representative sample	New Jersey	[5.0]	1,063 samples, 90th percentile 64.0 ppb, maximum 2,783 ppb, groundwater may or may not be used for drinking water	Page 1981
Shallow monitoring well	Denver, Colorado	<1–14 [2]	30 monitoring wells, 22 with PVC casings and 8 with metal casings; samples obtained after purging well 20 minutes	Bruce and McMahon 1996
Surface water				
U.S. Geological Survey stations	United States	(4.2) [4.0]	53,862 occurrences	Eckel and Jacob 1988

Table 6-7. Concentrations of Copper in Water

Sample type/ source	Location	Concentration (ppb) Range (mean) [median]	Comments	Reference
Representative sample	New Jersey	[3.0]	590 samples, 90th percentile 9.0 ppb, maximum 261 ppb	Page 1981
Surface, marine	East Arctic Ocean	(0.126)	26 locations 0.5–1 m depth	Mart and Nurnberg 1984
Surface, marine	Atlantic Ocean	0.0572–0.0210	20 sites, 2 cruises, 0–1 m depth	Yeats 1988
Pond	Massachusetts	<10–105	Low in summer, high in winter	Kimball 1973
Lakes	Canada	1–8 (2)	Acid sensitive lakes	Reed and Henningson 1984
Lakes	Great Lakes	629–834 (756)	Lake Superior	Nriagu et al. 1996
		703–1,061 (870)	Lake Erie	
		540–1,098 (830)	Lake Ontario	
	Representative samples, nearby to acidic mine drainage	32-1,200 (736)	12 samples taken from streams and ponds near abandoned coal mines in Indiana	Allen et al. 1996
	Representative samples from copper mining areas in Arizona	100–69,000 [1,200]	Samples obtained from the Cerbat Mountains mining area; 15 surface water sites with 14 sites downstream from old tailings and adits	Rösner 1998

[a]BD = below detection limit

PVC = Polyvinyl chloride

(Effler et al. 1980; Perwak et al. 1980). The reduction in dissolved copper during this period was accompanied by an increase in particulate copper (e.g., sorption to algae or other organic matter, which settles into the sediments of these bodies of water). The copper in the settled particulates is in equilibrium with the water column, which greatly favors copper in a bound state.

A potential source of copper release into waterways is leachate from municipal landfills. Copper concentrations in leachate obtained from waste sites have been found to vary widely. For example, copper concentrations in leachate from municipal landfills have been found to range from 0.005 to 1,110 ppm (Christensen et al. 1994; Perwak et al. 1980; Roy 1994). Although copper was measured in these leachates, its origin may not be from copper contained within the waste site, but from the surrounding soils. Cyr et al. (1987) reported that leachate from three municipal landfills in New Brunswick, Canada, did not contain copper concentrations significantly above those in control samples representing the surrounding soil types. Therefore, the emissions of copper from landfills into leachates should be made relative to the contribution of copper from surrounding soils, as determined from appropriately selected control samples.

Copper can enter surface waters as a result of agricultural runoff. For example, estimated loading rates of copper into surface water from irrigation water runoff near the Stillwater National Wildlife Refuge ranged from 0.307 to 8.34 mg/hour, depending on what period of the irrigation season samples were taken (Kilbride et al. 1998). The highest loading rates were obtained during the middle period (August through mid-September) of the irrigation season. The copper in the runoff water was found to be predominantly bound to drift material in the water (e.g., algae, vascular plants, invertebrates, vertebrates, and detritial material).

Copper was detected in groundwater and surface water at 558 and 308 of the 906 NPL hazardous waste sites, respectively, where copper has been detected in environmental media (HazDat 2004). Copper was detected at concentrations ranging from 0.006 to 5.6 ppm (median concentration of 0.103 ppm) in offsite groundwater and 0.00025–590 ppm (median concentration of 0.0282 ppm) in offsite surface water (HazDat 2002).

6.2.3 Soil

An estimated 97% of copper released from all sources into the environment is primarily released to land (Perwak et al. 1980). These include primarily tailings and overburdens from copper mines and tailings

from mills. The copper in tailings represents the portion of copper that could not be recovered from the ore and is generally in the form of insoluble sulfides or silicates (Perwak et al. 1980). These wastes accumulate in mining states. Other releases to land include sludge from POTWs, municipal refuse, waste from electroplating, iron and steel producers, and discarded copper products (e.g., plumbing, wiring) that are not recycled. The copper content of municipal solid waste is ~0.16%. Much of this waste is landfilled directly or is in the form of residues following incineration. Emission factors in milligrams of copper released per gram of solid waste have been estimated for various industries. These factors would enable estimation of an industry's copper releases in terms of total quantity of solid waste discharged. Sludge from sewage treatment plants is a major source of copper released to land (Nriagu and Pacyna 1988). Agricultural products are believed to constitute 2% of the copper released to soil (Perwak et al. 1980). However, even though the largest releases of copper are to land, uptake of copper in human populations through ingestion of copper in soil are expected to be minimal in comparison to the primary route of exposure through the ingestion of drinking water (see Section 6.5).

Copper was detected in soil and sediment (e.g., lakes, streams, ponds, etc.) at 528 and 338 of the 906 NPL hazardous waste sites, respectively, where copper has been detected in environmental media (HazDat 2004). Copper was detected at concentrations ranging from 0.01 to 182,000 ppm (median concentration of 0.103 ppm) in offsite soils and 0.022–14,000 ppm (median concentration of 43 ppm) in offsite sediments (HazDat 2002).

6.3 ENVIRONMENTAL FATE

When considering the environmental fate of a metal, it is not always possible to clearly separate the processes related to the transport and partitioning of a metal, its compounds, and complexes from those related to transformation and degradation of these metal species. Because of analytical limitations, investigators do not often identify the form of a metal present in the environment. A change in the transport or partitioning of a metal may result from the transformation of the metal from one form to another. For example, complexation of a metal with small organic compounds may result in enhanced mobility, while formation of a less-soluble sulfide would decrease its mobility in water or soil. Adsorption may be the result of strong bonds being formed (transformation) as well as weak ones. Characterizing weak and strong adsorption is dependent on the analytical method that is used and care should be exercised when comparing results from different studies. Deposition and general adsorption of copper are discussed in Section 6.3.1. Speciation, compound formation, and oxidation-reduction are examined in Section 6.3.2.

6.3.1 Transport and Partitioning

6.3.1.1 Ambient Air

Copper is released to the atmosphere in the form of particulate matter or adsorbed to particulate matter. It is removed by gravitational settling (bulk deposition), dry deposition (inertial impaction characterized by a deposition velocity), in-cloud scavenging (attachment of particles by droplets within clouds), and washout (collision and capture of particles by falling raindrops below clouds) (Schroeder et al. 1987). The removal rate and distance traveled from the source will depend on a number of factors, including source characteristics, particle size, turbulence, and wind velocity.

Gravitational settling governs the removal of large particles with mass median aerodynamic (MMA) diameters of >5 μm, whereas smaller particles are removed by the other forms of dry and wet deposition. The importance of wet to dry deposition generally increases with decreasing particle size. The scavenging ratio (ratio of the copper concentration in precipitation [ppm] to its air concentration [$\mu g/m^3$]) for large particles displays a seasonal dependence that reflects more effective scavenging by snow than by rain (Chan et al. 1986). Copper from combustion sources is associated with sub-micron particles. These particles remain in the troposphere for an estimated 7–30 days. In that time, some copper may be carried far from its source (Perwak et al. 1980).

Rates of metal deposition (e.g., depositional fluxes) vary between dry and wet depositional processes and show spatial variability. Dry depositional fluxes of copper tend to decrease between highly urbanized area such as Chicago, Illinois with an average depositional rate of 0.06 mg/m^2/day, to less urbanized areas such as South Haven, Michigan with rate of 0.007 mg/m^2/day or areas with minimal anthropogenic activity such as Lake Michigan (between 6 and 10 km off shore) with a rate of 0.01 mg/m^2/day (Paode et al. 1998). Estimated copper deposition rates in urban areas are 0.119 and 0.164 kg per hectare per year (kg/ha/year) or 0.0326 and 0.0449 mg/m^2/day for dry and wet deposition, respectively (Schroeder et al. 1987). Bulk deposition reportedly ranges from 0.002–3.01 kg/ha/year or 0.0005–0.825 mg/m^2/day (Golomb et al. 1997; Landing et al. 1995; Schroeder et al. 1987). For rural areas, the range of bulk deposition reportedly is 0.018–0.5 kg/ha/year or 0.0049–0.14 mg/m^2/day, and wet deposition is 0.033 kg/ha/year or 0.009 mg/m^2/day. The washout ratio is 114,000–612,000 ($\mu g/m^3$ rain)/($\mu g/m^3$ air) or, expressed on a mass basis, 140–751 (μg/kg rain)/(μg/kg air). In southern Ontario, Canada, where the average concentration of copper in rain was 1.57 ppb during 1982, 1.36 mg of copper was deposited annually per square meter, or 13.6 kg/ha, as a result of wet deposition (Chan et al. 1986). For central and

northern Ontario, the mean concentrations of copper in rain were 1.36 and 1.58 ppb, respectively, and the annual wet depositions averaged in both instances 1.13 mg/m^2 or 11.3 kg/ha.

For the majority of time, the concentration in air of toxic trace elements, like copper, in a study conducted by Sweet et al. (1993) approached levels measured at a rural site (Bondville, Illinois). These rural levels of airborne copper represented regional background levels in urban study sites with only episodic increases, depending on wind speed and direction and location relative to local point sources. In one urban study site (East St. Louis), smelters are the primary source of copper. Copper depositional fluxes follow an exponential decay as one transitions from urban to rural settings (Sweet et al. 1993). Soil is not the major source of copper in cities or nearby rural soils, but is the predominant source for copper in the atmosphere over more remote areas (Fergusson and Stewart 1992). Sources of copper in urban areas include coal combustion, soil, tire wear, and automobile emissions (Kim and Fergusson 1994). Copper emission from combustion processes is typically associated with fine particles; however, there can be instances where the highest concentrations of copper are measured in coarse particles obtained from paved and unpaved roads and industries (Paode et al. 1998).

Estimated depositional velocities for fine particles (<2.5 µm) and coarse particles (2.5–10 µm) in urban (Chicago) and rural (Kankalee, Illinois) areas have been made (Pirrone and Keeler 1993). These are: urban, 0.25–0.46 cm/second and rural, 0.18–0.25 in (rural) Kankalee, Illinois for fine particles; and urban, 1.47–2.93 cm/second and rural, 0.87–1.71 cm/second for coarse particles. The differences in velocities are due to higher surface roughness and wind velocities in Chicago.

Copper concentrations in particulates formed in a controlled study of waste oil combustion are (in µg/g): 687±11 (10 µm), 575±8 (50 µm), 552±12 (100 µm), 568±9 (300 µm), and 489±8 (500 µm). Approximately 25% of copper is in the 10 µm fraction and ~18% is in each of the larger fractions (e.g., 50, 100, 300, and 500 µm) (Nerín et al. 1999).

6.3.1.2 Ambient Waters

The average concentrations of copper in Lakes Superior, Erie, and Ontario are 760, 870, and 830 ng/L, respectively (Georgopoulos et al. 2001; Nriagu et al. 1996). These values were derived from measurements taken from 11, 11, and 9 nearshore and offshore sampling sites at different points in the water column up to depths of 251, 55, and 145 meters for Lakes Superior, Erie, and Ontario, respectively (Nriagu et al. 1996). In Lake Ontario, the highest copper concentrations were found at nearshore

sampling sites neighboring Buffalo, New York (887–1,051 ng/L), Rochester, New York (1,041–1,098 ng/L), and Kingston, Ontario (921–1,026 ng/L). The lowest concentrations of copper in Lake Ontario were measured in an offshore sampling site (540–710 ng/L) that was approximately 40 km from the Buffalo sampling site.

The atmospheric input of copper into the Great Lakes is substantial, 330–1,470 ng/m^2/year, which amounts to a total deposition of 8.00–35.6x10^{13} ng/year. This input of copper accounts for 60–80% of the anthropogenic input into Lake Superior and 20–70% into Lakes Erie and Ontario (Georgopoulos et al. 2001; Nriagu et al. 1996). The mean residency times of copper in sediments are estimated to be 15 years in Lake Erie and 101 years in Lake Superior.

Much of the copper discharged into waterways is in particulate matter and settles out. In the water column and in sediments, copper adsorbs to organic matter, hydrous iron and manganese oxides, and clay. In the water column, a significant fraction of the copper is adsorbed within the first hour of introduction, and in most cases, equilibrium is obtained within 24 hours (Harrison and Bishop 1984). In fact, most of the copper in POTW effluent and surface runoff is already in the form of complexes (Sedlak et al. 1997). Copper in waste water discharged into Back River leading into Chesapeake Bay, Maryland, contained 53 ppb of copper, of which 36 ppb (based on weight) were in the form of settleable solids (Helz et al. 1975). The concentration of copper rapidly decreased downstream of the outfall so that 2–3 km from the outfall, the copper concentration had fallen to 7 ppb. The concentration of copper in sediment 2–3 km downstream from the outfall was about a factor of 10 higher than in uncontaminated areas (e.g., Rappahannock River). Based on their data and the results from other studies, Helz et al. (1975) estimated a total of 200 metric tons of copper entered the Cheasapeake Bay from the effluent discharged from waste treatment plants.

Copper binds primarily to organic matter in estuarine sediment, unless the sediment is low in organic matter content. A study evaluated the importance of the absorption properties of different nonlithogenic components of aerobic estuarine sediment to copper binding by determining copper's adsorptivity to model components (phases) in artificial seawater (Davies-Colley et al. 1984). The phases included hydrous iron and manganese oxides, clay, aluminosilicates, and organic matter. The binding affinities varied by over a factor of 10,000 and were in the following order: hydrous manganese oxide > organic matter > hydrous iron oxide > aluminosilicates > clay (montmorillonite). The partition coefficients at pH 7 for the more strongly bound phases (manganese oxide, iron oxide, and estuarine humic material), were 6,300, 1,300, and 2,500, respectively. The affinity increased somewhat with pH; but did not vary

appreciably when the salinity was reduced from 35 to 5%. Considering the compositional characteristics of estuarine sediment in terms of binding capacity, the results indicate that copper binds predominantly to organic matter (humic material) and iron oxides. Manganese oxide contributes only 1% to the binding because of its generally low concentration in sediment; the other phases are usually unimportant. These findings concur with results of selective extraction experiments (Badri and Aston 1983) and studies of the association of copper with humic material (Raspor et al. 1984).

6.3.1.3 Ambient Soils

Most copper deposited on soil from the atmosphere, agricultural use, and solid waste and sludge disposal will be adsorbed with greater concentrations of copper measured in the upper 5–10 centimeters of soil in comparison to lower soil depths, except in sandy soils where the lability of bound copper is greater (Breslin 1999; Giusquiani et al. 1992; Hutchinson 1979; Luncan-Bouché et al. 1997; Keller and Védy 1994; Levy et al. 1992; Perwak et al. 1980). Copper's movement in soil is determined by a host of physical and chemical interactions of copper with the soil components. In general, copper will adsorb to organic matter, carbonate minerals, clay minerals, or hydrous iron and manganese oxides (EPA 1979; Fuhrer 1986; Janssen et al. 1997; Petruzzelli 1997; Tyler and McBride 1982). Sandy soils with low pH have the greatest potential for leaching. In a laboratory study, Luncan-Bouché et al. (1997) have shown that between 55 and 85% of copper bound to sand (with no other soil components added) is remobilized upon reduction of the pH from 9 to 4. In most temperate soils, the pH, organic matter, concentrations of metal oxyhydroxides and ionic strength of the soil solutions are the key factors affecting adsorption (Elliot et al 1986; Fuhrer 1986; Gerritse and Van Driel 1984; Janssen et al. 1997; Rieuwerts et al. 1998; Tyler and McBride 1982). The ionic strength and pH of the soil solution affect the surface charge of soils and thereby influence ionic interaction (Rieuwerts et al. 1998). Soil microorganisms also affect the absorption of copper in soils due to the uptake and assimilation of the metal by these microorganisms (Rieuwerts et al. 1998). However, it is not known how the rate of uptake and absorption capacity of the microorganisms for copper compares with the binding capacity and affinities of copper by organic matter in soils, such as humic and fulvic acids. When the amount of organic matter is low, the mineral content or Fe, Mn, and Al oxides become important in determining the adsorption of copper. Fuhrer (1986) reported that, in oxidized estuarine sediment, adsorption of copper is dominated both by amorphous iron oxide and humic material.

Copper binds strongly to soils with high organic content (14–34% organic matter, dry weight) and the distribution of copper in the soil solution is less affected by changes in pH (within the range of pHs

normally encountered in the environment) than other metals are (Gerritse and Van Driel 1984). In a laboratory study of competitive adsorption and leaching of metals in soil columns of widely different characteristics, copper eluted in a 0.01 M $CaCl_2$ leaching solution much more slowly and in much lower quantities than Zn, Cd, and Ni from a low-pH and a high-pH mineral soils and not at all from peat soil, which contained the greatest amount of organic matter (Tyler and McBride 1982). Elliot et al. (1986) investigated at pH-dependent adsorption of the divalent transition metal cations Cd, Cu, Pb, and Zn in two mineral soils (silty clay loam, 0.5 g/kg organic dry weight, and sandy clay, 1.6 g/kg organic) and two soils containing considerable organic matter (loamy sand, 20.5 g/kg organic, and silt loam, 42.5 g/kg organic). Adsorption increased with pH, and Cu and Pb were much more strongly retained than Cd and Zn. Reduction in absorptivity after removal of the organic matter demonstrated the importance of organic matter in binding copper. In a study of clay soils, Wu et al. (1999) observed preferential copper binding to organic matter, but found higher binding affinities to fine (<0.2 μm) clay fractions once the organic matter had been removed.

To determine the factors affecting copper solubility in soil, Hermann and Neumann-Mahlkau (1985) performed a study in the industrial Ruhr district of West Germany, which has a high groundwater table (10–80 cm from the surface) and a history of heavy metal pollution. Groundwater samples were taken from six locations and two soil horizons, an upper oxidizing loam, and a lower reducing loam. Total copper concentrations were high in the upper soil horizons and low in the lower horizons. Copper showed a pronounced solubility only in the oxidizing environment. In the reducing environment, solubility was low, possibly due to the formation of sulfides.

The form of copper at polluted and unpolluted sites may affect its leachability, particularly by acid rain. The leaching of heavy metals by simulated acid rain (pH 2.8–4.2) was measured by applying this rainwater to columns containing humus layers obtained from sites in a Swedish spruce forest both near to and far from a brass mill (Strain et al. 1984). Leaching of copper increased considerably when water with a pH <3.4 was applied to soil from polluted sites. Acid rain produced from SO_X emitted from smelters may increase the leachability of copper in areas affected by smelter stack emissions. The mobility of copper from soils was also found to increase following the introduction of 10–100 mM sodium chloride or calcium magnesium acetate deicing salts into soil (Amrhein et al. 1992). The concentration of sodium chloride or calcium magnesium acetate used in the study approximate those in runoff water produced from the melting of snow along salted roadways.

Since, in the range of 0.01–1.97 mg of copper per liter of water, 25–75% of copper entering POTWs is removed in sludge, much of which is disposed of by spreading on land, it is important to ascertain whether copper in sludge is apt to leach into soil. Where it stands, this does not appear to be the case and leachate collected from the sludge-amended soil contained <12 ppb of copper (Perwak et al. 1980). In laboratory experiments, three sludges containing 51, 66, and 951 ppm (dry weight) of copper were applied to the top of soil columns containing four coastal plain soils. These soils, Sassafras loamy sand, Woodstown sandy loam, Evesboro loamy sand, and Matapeake silt loam, had similar pHs, 5.1–5.8, and contained 0.9, 1.4, 1.6, and 3.5% organic matter (dry weight), respectively. The sludge containing 51 ppm copper was loaded on the soil columns at amounts that approximated field loadings of between 0 and 90 metric tons per hectare; the sludges containing 66 and 951 ppm copper were loaded in amounts that approximated field loadings of between 0 and 180 metric tons per hectare. The columns were subsequently leached with distilled water at a flow rate of 2.5 cm/day for a total column application of 25.4 cm of water. Only small amounts (<0.01–0.87 ppm) of copper were found in the leachate (Ritter and Eastburn 1978). This suggests that hazardous amounts of copper leach only slowly into groundwater from sludge, even from sandy soils. In another study, soil cores taken after sewage sludge were applied to grassland for 4 years showed that 74 and 80% of copper remained in the top 5 cm of a sandy loam and calcareous loam soil (Davis et al. 1988). Similar studies have also shown that copper is typically confined to the upper 5–10 cm of sludge-amended agricultural soils (Breslin 1999; Giusquiani et al. 1992). In soils receiving long-term, heavy applications of sludge, high copper concentrations (471 mg/kg in comparison to 19.1 mg/kg in unamended control soils) were reported to depths of up to 25 cm (Richards et al. 1998). The mobility of copper into soil from sludge was found to be determined mainly by the amount of soil organic carbon and soil surface area (Domergue and Védy 1992; Gao et al. 1997). In addition, soils amended by sludge with low metal content were found to have increased sorption for copper due to the increased binding capacity provided by the “low metal” organics in the sludge (Petruzzelli et al. 1994).

Similarly, copper remains in the surface layer when it is applied to soil as a liquid. Secondary sewage effluent spiked with 0.83 ppm of copper was applied weekly to four different soils. After 1 year of treatment, the concentration of copper in the surface horizons increased greatly: 50–76% of the applied copper was found in the upper 2.5 cm and 91–138% was found in the upper 12.7 cm (Brown et al. 1983). In a study of accumulation and movement of metal in sludge-amended soils, field plots received massive amounts of sewage over a period of 6 years. Two sludges (one containing industrial waste), with average copper contents of 0.29 and 23 ppm were incorporated into the top 20 cm of soil in the spring. Barley was grown and, after harvest, core samples of soil were taken down to 1 m. Some movement of copper

into the 22.5–25 cm layer of soil was observed, but little, if any, below this zone. However, at this depth, the copper is still within the root zone of many important food crops and, therefore, is available for uptake into these plants. Also, the availability of the copper in soil, as determined by its extractability with diethylenetriamine pentaacetic acid (DTPA) and nitrate, remained constant over a 4-year period at all depths. From the results of other work, the major portion of the copper (40–74%) is expected to be associated with the organic, Fe-Mn-oxide and carbonate fractions of most soils (Ma and Rao 1997).

6.3.1.4 Bioconcentration and Biomagnification

The bioconcentration factor (BCF) of copper in fish obtained in field studies is 10–667, indicating a low potential for bioconcentration (Perwak et al. 1980). The BCF is higher in mollusks, such as oysters, and squid where it may reach 30,000 and $2.1x10^7$, respectively, (Perwak et al. 1980) and may present a major dietary source of copper that could be of concern for those individuals who regularly consume oysters, clams, or squid. Due to the fact that molluscs are filter feeders and copper concentrations are higher in particulates than in water, this is to be expected. On the other hand, there are limited data suggesting that there is little biomagnification of copper in the aquatic food chain (Perwak et al. 1980). For example, a study was conducted with white suckers and bullheads, both bottom-feeding fish, in two acidic Adirondack, New York, lakes (Heit and Klusek 1985). These lakes were known to have received elevated loadings of copper; but the suckers and bullhead had average copper levels of only 0.85 and 1.2 ppm (dry weight) in their muscle tissue. The biomagnification ratio (the concentration of copper in fish compared to that in their potential food sources on a wet weight/wet weight basis) was <l, indicating no biomagnification in the food chain. Similarly, the copper content of muscle tissue of fish from copper-contaminated lakes near Sudbury, Ontario, did not differ significantly from that of the same fish species in lakes far from this source (Bradley and Morris 1986).

No evidence of bioaccumulation was obtained from a study of pollutant concentrations in the muscle and livers of 10 mammal species in Donana National Park in Spain (Hernandez et al. 1985). The park is impacted by organochlorine compounds and heavy metals emitted from anthropogenic activities that surround the park. For example, the Guadalquivir River that flows through the park first flows through a major mining region in addition to a large urban area and industrial areas, carrying with it contaminants acquired from these sites. The animal species in the study were classified into three categories (herbivorous, omnivorous, and carnivorous) to ascertain if the pollutants were showing biomagnification in higher trophic levels of animals. No evidence of copper biomagnification in the food chain was observed. Likewise, in a study of a food web in a beech tree forest in Northern Germany, there was no

evidence of biomagnification in tertiary consumers (e.g., vole, shrew, and mouse) compared to secondary consumers (e.g., earthworm, snail, beetle, and isopod) (Scharenberg and Ebeling 1996). A study of heavy metals in cottontail rabbits on mined land treated with sewage sludge showed that, while the concentration of copper in surface soil was 130% higher than in a control area, the elevation was relatively little in foliar samples and no significant increase in copper was observed in rabbit muscle, femur, kidney, or liver. Apparently, copper was not bioaccumulating in the food chain of the rabbit (Dressler et al. 1986).

At the lowest levels of the food chain, there is little evidence of copper bioaccumulation. In a study of copper uptake in earthworms as a function of copper concentration (6–320 mg/kg dry weight) in sludge amended soils, a bioconcentration factor of <1 (0.67) was obtained (Neuhauser et al. 1995). In another example, a study of earthworms and soil from 20 diverse sites in Maryland, Pennsylvania, and Virginia, copper concentrations in earthworms showed a poor correlation with that in soil (Beyer and Cromartie 1987). These results are consistent with the results of another study that also showed no clear correlation between copper concentrations in earthworm tissues and two soils that were heavily contaminated with heavy metals (copper concentrations of 242 and 815 mg/kg dry weight) (Marinussen et al. 1997). However, there is some evidence in one study for bioconcentration of copper at low copper concentrations in soil. Even though Scharenberg and Ebeling (1996) showed that there was no evidence for biomagnification of copper in a forest food web, their results did show that the total concentrations of copper in the secondary (18.3–192.0 mg/kg dry weight) and tertiary consumers (9.9–17.4 mg/kg dry weight) were higher than the concentrations of the metal in the dominant vegetation (5.3–10.9 mg/kg dry weight) and soil (1.8–5.8 mg/kg dry weight) in the ecosystem.

Diks and Allen (1983) added copper to four sediment/water systems and studied the distribution of copper among five geochemical phases, namely, absorbed/exchangeable, carbonate, easily reducible (Mn-oxides and amorphous Fe-oxides), organic, and moderately reducible (hydrous Fe-oxides). The investigators then attempted to correlate the concentration in each phase with the copper uptake by tubificid worms. Only copper extracted from the manganese oxide/easily-reducible phase correlated with the copper content of worms at the 95% confidence level. This result suggests that the redox potential and pH in the gut of the worm is such that manganese oxide coatings are dissolved. The copper in the dissolved manganese oxide phase is now soluble and available for uptake by other organisms.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Few data are available regarding the chemical forms of copper in the atmosphere and their transformations. In the absence of specific information, it is generally assumed that metals of anthropogenic origin, especially those from combustion sources, exist in the atmosphere as oxides because metallic species are readily attacked by atmospheric oxidants. As these oxides age, sulfatization may occur, but only when SO_X gases are present in the atmosphere in sufficient amount. For example, in Arizona, atmospheric copper oxide levels derived from copper smelters was strongly correlated with co-emitted sulfur (Schroeder et al. 1987).

In fog water, Cu(II) is reduced to Cu(I) by sulfite, which becomes enhanced by the fact that sulfite is also a ligand of and binds to Cu(I) (Xue et al. 1991). Concentrations of Cu(I) in fog water ranged between 0.1 and 1 µM or, respectively, 4 and >90% of copper in the Cu(I) state. The reduction of Cu(II) to Cu(I) is pH dependent and occurs rapidly at pHs>6 (Xue et al. 1991).

6.3.2.2 Water

The Cu(I) ion is unstable in aqueous solution, tending to disproportionate to Cu(II) and copper metal unless a stabilizing ligand is present (EPA 1979; Kust 1978). The only cuprous compounds stable in water are insoluble ones such as Cu_2S, CuCN, and CuF. Therefore, human exposures to copper will predominately be in the form of Cu(II). Copper in its Cu(II) state forms coordination compounds or complexes with both inorganic and organic ligands. Ammonia and chloride ions are examples of species that form stable ligands with copper. Copper also forms stable complexes with organic ligands such as humic acids, binding to $-NH_2$ and -SH groups and, to a lesser extent, with -OH groups. Natural waters contain varying amounts of inorganic and organic species. This affects the complexing and binding capacity of the water and the types of complexes formed. In seawater, organic matter is generally the most important complexing agent (Coale and Bruland 1988). In water, the formation of ligands may affect other physicochemical processes such as adsorption, precipitation, and oxidation-reduction (EPA 1979). More specific information on the transformation and degradation of copper in its cupric [Cu(II)] and cuprous [Cu(I)] states is given below.

At the pH values and carbonate concentrations characteristic of fresh surface waters, most dissolved Cu(II) exists as carbonate complexes rather than as free (hydrated) cupric ions (Stiff 1971).

Based on the results of a theoretical model, the major species of soluble copper found in freshwater, seawater, and a 50:50 combination of the freashwater and seawater over a pH range of 6.5–7.5 is Cu^{2+}, $Cu(HCO_3)^+$, and $Cu(OH)_2$ (Long and Angino 1977).

The concentration of dissolved copper depends on factors such as pH, the oxidation-reduction potential of the water and the presence of competing cations (Ca^{2+}, Fe^{2+}, Mg^{2+}, etc.), salts (OH^-, S^{2-}, PO_4^{3-}, CO_3^{2-}), and anions of insoluble cupric-organic and -inorganic complexing agents. If the combination of a particular anion with copper forms an insoluble salt, precipitation of that salt will occur. The most significant precipitate formed in fresh surface waters is malachite ($Cu_2[OH]_2CO_3$) (Sylva 1976). Other important precipitates are $Cu(OH)_2$ (and ultimately CuO) and azurite ($Cu_3[OH]_2[CO_3]_2$). In anaerobic waters, Cu_2S, Cu_2O, and metallic copper forms and settles out (EPA 1979). The combined processes of complexation, adsorption, and precipitation control the level of free Cu(II) in water. The chemical conditions in most natural water are such that, even at relatively high copper concentrations, these processes will reduce the free Cu(II) concentration to extremely low values.

As a result of the aforementioned physico-chemical processes, copper in water may be dissolved or associated with colloidal or particulate matter. Copper in particulate form includes precipitates, insoluble organic complexes, and copper adsorbed to clay and other mineral solids. In a survey of nine rivers in the United Kingdom, 43–88% of the copper was in the particulate fraction (Stiff 1971). A study using suspended solids from the Flint River in Michigan found that the fraction of adsorbed copper increased sharply with pH, reaching a maximum at a pH of 5.5–7.5 (McIlroy et al. 1986).

The soluble fraction of copper in water is usually defined as that which will pass through a 0.45 μm filter. It includes free copper and soluble complexes as well as fine particulates and colloids. The soluble fraction may be divided according to the lability (e.g., the relative ability of the copper to dissociate from the bound form to the free ion) of the copper forms in the water. Categories range from the very labile (e.g., free metal ion, ion pairs, inorganic or organic complexes) to slowly or nonlabile (e.g., colloidally bound to inorganic colloidal phases of other metals such as $Fe(OH)_3$ or FeOOH, or bound to high molecular weight organic material) metal (Tan et al. 1988). For example, in a typical study, 18–70% of dissolved copper in river water was labile and 13–30% was slowly labile (Tan et al. 1988). Various techniques may be used to classify the lability of different fractions of soluble copper; these techniques include solvent extraction, ion-specific electrodes, ion exchange, ultrafiltration, electrochemical methods such as anodic stripping voltammetry, and gel filtration chromatography (Harrison and Bishop 1984).

The resulting classification depends on the specific procedure employed. Therefore, a comparison of the results of different researchers should be done in general terms

The nature of copper's association with inorganic and organic ligands will vary depending on the pH, copper concentration, concentration of competing ligands, binding capacity of the ligands, and hardness or salinity of the water (Breault et al. 1996; Cao et al. 1995; Gardner and Ravenscroft 1991; Giusti et al. 1993; Lores and Pennock 1998; Town and Filella 2000). In river water from the northwestern United States that had a relatively high pH (7.0–8.5) and alkalinity (24–219 ppm as $CaCO_3$), inorganic species like CO_3^{2-} and OH^- were the most important ligands at high copper concentrations (McCrady and Chapman 1979). However, other species such as organic compounds were important at low copper concentrations. On the other hand, copper in samples from surface water of lakes and rivers in southern Maine with a relatively low pH (4.6–6.3) and alkalinity (1–30 ppm as $CaCO_3$) was largely associated with organic matter (Giesy et al. 1978). The binding of copper to dissolved organics was found to be dependent on the specific organic chemical species (e.g., fulvic acid) and their concentrations in the surface water, the number of available binding sites per fulvic acid carbon, and the hardness of the water (Breault et al. 1996). Increasing water hardness results in deceased fulvic acid binding sites. This effect is due more to the depression of the solubility of high molecular weight fulvic acid in the presence of Ca and Mg ions than to competition of these ions with copper for fulvic acid binding sites. Increasing pH from 8 to 6 resulted in a 7-fold increase in the binding constant for Cu(II) with humic acid (Cao et al. 1995).

The extent to which copper binds to inorganic and organic ligands can be altered by materials carried in runoff. For example, after a period of rain in southeastern New Hampshire, inorganic constituents contributed more to copper binding in lakes and rivers than did dissolved organic matter (Truitt and Weber 1981). A green precipitate, confirmed to be malachite ($Cu_2[OH]_2CO_3$) was formed in river water in Exeter. This water had the highest pH (7.4) and alkalinity (43.5 mg/L as $CaCO_3$) than six other surface waters (e.g., three rivers, two reservoirs, a pond, and a swamp) with pH and alkalinity values of 5.7–7.4 and 1.7–41 mg/L, respectively. A computer simulation of the copper species in water of a pond and water obtained from an artesian well that fed the pond predicted that 98% of the copper in the artesian well water would exist as the free copper ion (Cu^{+2}), whereas 88 and 63% of the copper in pond water would be bound to organics in the spring and fall, respectively (Giesy et al. 1983). These estimates were based on experimentally determined binding capacities of the organic matter in the two water sources and stability constants for the copper-organic matter complexes.

Seawater samples obtained in a transect of the uppermost Narragansett Bay in August 1980 were analyzed for dissolved, particulate and organically bound copper to investigate the geochemistry of copper-organic complexes (Mills and Quinn 1984). Narragansett Bay is a partly mixed estuary in Massachusetts and Rhode Island that receives organic matter and metals from rivers, municipal and industrial effluents and from runoff. The Fields Point waste treatment facility accounts for 90% of the copper input into the bay through the Providence River with dissolved copper representing 60% of the total copper input. The concentrations of dissolved and organic copper ranged from 16.4 and 2.3 µg/kg, respectively, in the Providence River to 0.23 and 0.12 µg/kg, respectively, in Rhode Island Sound. Particulate copper concentrations in Narragansett bay ranged from 2.42 to 0.06 µg/kg and generally comprised 40% of the total copper in the bay. Analysis of the data indicated that ~75% of the dissolved copper that enters the bay from the Providence River is removed within the bay.

Organic ligands may contain a variety of binding sites, and the strength of the resulting copper complexes will vary accordingly. Over 99.7% of the total dissolved copper in ocean surface water from the northeast Pacific was associated with organic ligands (Coale and Bruland 1988). The dominant organic complex, limited to surface water, was a strong ligand of biological origin. A second, weaker class of organic ligand was of geologic origin. An independent study showed the copper binds to humic material at a number of sites. The binding strength of the sites varied by two orders of magnitude (Giesy et al. 1986). The humic material in this study was derived from nine surface waters in the southeastern United States. Soluble copper in water discharged from a nuclear power station was primarily complexed with organic matter in the 1,000–100,000 molecular weight range (Harrison et al. 1980). Ten to 75% of the discharged copper was in particulate form.

The bioavailability of Cu(I) has been difficult to access due to its thermodynamic instability in the environment (Xue et al. 1991). Cu(I) is a reactive reducing agent, and its concentrations in the environment will be determined both by its reaction with oxygen and other oxidants in the aqueous environment to form Cu(II) and its rate of production through the reaction of Cu(II) with reducing agents (Sharma and Millero 1988). Investigators have shown the presence of Cu(I) in seawater, which is thought to occur through the reduction of Cu(II) to Cu(I) by photochemical processes (Moffett and Zika 1987; Xue et al. 1991). The detection of Cu(I) in seawater is likely the result of the stabilization of Cu(I) through complex formation with chloride ions. Cu(II)-organic complexes absorb radiation at wavelengths >290 nm and can undergo charge transfer reactions where the Cu(II) is reduced and a ligand is oxidized. Photochemically-generated reducing agents such as O_2^- and H_2O_2 in the surface water of oceans and

possibly other natural waters (e.g., lakes) may contribute to the reduction of Cu(II) to Cu(I) in these waters (Moffett and Zika 1987; Sharma and Millero 1988).

Experiments performed in synthetic seawater and water from Biscayne Bay, Florida, showed that in the reduction of Cu(II) to Cu(I), the rate was first-order in Cl^- and second-order in H_2O_2 (Sharma and Zika 1987). The chloride ion is thought to be required for stabilizing Cu(I) by forming the copper complex $CuClOH^-$, although experimental evidence suggests that the reduction of Cu(II) may also occur through the formation of a complex between Cu(II) and HO_2^-. Experiments have shown that as much as 15% of copper in surface seawater exists as Cu(I). Photochemical reduction by sunlight increases the percentage of free Cu(I). The photochemical reduction mechanism is supported by the observation that the Cu(I) concentration is highest in the surface layer of seawater and that the hydrogen peroxide concentration increases in parallel to that of Cu(I) (Moffett and Zika 1987). In addition, the percentage of free Cu(I) is highest on the surface.

Once Cu(I) is formed, its lifetime is determined by its rate of oxidation to Cu(II). After Biscayne Bay water was exposed to sunlight for 5 hours, the Cu(I) formed was oxidized to Cu(II). The half-life of Cu(I) was 12 hours. Primarily, dissolved oxygen is responsible for this oxidative reaction. Since the oxidation of Cu(I) by O_2 in distilled water occurs in <6 minutes, Cu(I) in seawater apparently is stabilized by the formation of complexes. In the presence of humic acids, the oxidation of Cu(I) occurs very rapidly. In coastal water off the Everglades in Florida, no Cu(I) was detected. This is due to the binding of Cu(II) in organic complexes and the high concentration of radical oxidants in the water. Sharma and Millero (1988) measured the rate of Cu(I) oxidation in seawater as a function of pH, temperature and salinity. The rate of reaction increased with pH and temperature, and decreased with increasing ionic strength (or salinity). The results suggested that the rates are controlled by Mg^{2+}, Ca^{2+}, Cl^- and HCO_3^- through their involvement in complex formation and ligand exchange.

6.3.2.3 Sediment and Soil

The adsorption of copper to soil and sediment was discussed in Section 6.3.1 under transport and partitioning, even though adsorption may really be complexation and transformation. Understanding the transport and fate of copper and its compounds in soils and sediments is important because these compartments tend to be large reservoirs of copper and could have an impact on human exposures to copper. Copper concentrations in drinking water obtained from groundwater can be affected by the leaching of copper from soil. Reservoir sediments have been shown to be sources of copper in drinking

water (Georgopoulos et al. 2001). Although much of the copper is bound to inorganic or organic matrices in soils and sediments, there is the potential for release of copper into pore water within soils and sediments depending on the extractability of the copper and soil conditions. There is evidence to suggest that copper binding in soil is correlated with pH, cation exchange capacity, the organic content of the soil, the presence of manganese and iron oxides and even the presence of inorganic carbon such as carbonates (Petruzzelli 1997; Rieuwerts et al. 1998). At pHs above 5, absorption of copper from pore water on to soil components becomes a significant process, whereas at pHs below 5, copper largely remains in pore water and is therefore mobile in soil (Perwak et al. 1980). However, broad generalizations about the lability of copper in soils are not possible since the situation will differ among different soil types and environmental conditions. More specific information on the lability (e.g., extractability) of copper from differing soils and conditions is given below.

The form of copper in soil is determined by measuring the extractability of the copper with different solvents. Extractability is a function of the nature of the soil and the form of copper deposited in the soil. If a relatively labile form of copper is applied, binding to inorganic and organic ligands may occur, as well as other transformations. On the other hand, if a mineral form is deposited, it would be unavailable for binding. The capacity of soil to remove copper and the nature of the bound copper were evaluated by incubating 70 ppm of copper with 5 g samples of soil for 6 days (King 1988). Twenty-one samples of soils (10 mineral and 3 organic) from the southeastern United States were included in the study. Some soil samples were taken from the subsoil as well as the surface. The amount of adsorbed copper ranged from 36 to 100%, of which 13–100% was nonexchangeable when extracted with KCl. Removal of copper from solution was much higher with surface soils than with subsurface sandy soils; 95–100% of the copper was removed by five of the mineral surface soils and all three organic soils. The percentage of copper that was nonexchangeable was relatively high in all but some of the acid subsoils. While the fraction of exchangeable copper was not dependent on pH in surface soils, 96% of the variation in exchangeability was correlated with pH in subsoils. The soil/water partition coefficient for copper was >64 for mineral soils and >273 for organic soils. Of the eight heavy metals in the study, only Pb and Sb had higher partition coefficients than copper. Most of the copper in Columbia River estuary sediment and soil was correlated with inorganic carbon (e.g., carbonate), but not with the amount of extractable Fe or the organic carbon content of the sediment (Fuhrer 1986).

The amount of ammonium acetate- and DTPA-extractable copper in wetland soil/sediment resulting from atmospheric deposition from smelters in Sudbury, Ontario, showed the same pattern as total copper, despite random variations in soil pH, redox potential and organic carbon (Taylor and Crowder 1983).

Therefore, in this case, soil characteristics were not the dominant factors determining extractability and availability, but rather the form of copper that was deposited. The median concentrations of total copper, ammonium acetate-extractable copper, and DTPA-extractable copper at 25 sample sites were 371, 49, and 98 ppm, respectively.

In another study of copper partitioning in nine different contaminated soils, sequential extractions were used to operationally define six soil fractions in decreasing order of copper availability: water soluble > exchangeable > carbonate > Fe-Mn oxide > organic > residual (Ma and Rao 1997). The results of this study showed that the distribution of copper in these six soil fractions differed depending on the total copper concentration in the soil. As the copper concentration increased above 240 mg/kg, between 69 and 74.4% of the total copper was found in the water soluble, carbonate, Fe-Mn oxide, and organic fractions. In relatively uncontaminated soils (<240 mg/kg copper), between 97.6 and 99.6% of the copper was found to be associated with the residual fraction.

Within the estuarine environment, anaerobic sediments are known to be the main reservoir of trace metals. Under anaerobic conditions, cupric salts will reduce to cuprous salts. The precipitation of cupric sulfide and the formation of copper bisulfide and/or polysulfide complexes determine copper's behavior in these sediments (Davies-Colley et al. 1985). In the more common case where the free sulfide concentration is low due to the controlling coexistence of iron oxide and sulfide, anaerobic sediment acts as a sink for copper, that is, the copper is removed from water and held in the sediment as an insoluble cuprous sulfide. However, in the unusual situation where the free sulfide concentration is high, soluble cuprous sulfide complexes may form, and the copper concentration in sediment pore water may then be high.

In sediment, copper is generally associated with mineral matter or tightly bound to organic material (Kennish 1998). As is common when a metal is associated with organic matter, copper generally is associated with fine, as opposed to coarse, sediment. Badri and Aston (1984) studied the association of heavy metals in three estuarine sediments with different geochemical phases. The phases were identified by their extractability with different chemicals and termed easily or freely leachable and exchangeable; oxidizable-organic (bound to organic matter); acid-reducible (Mn and Fe oxides and possibly carbonates); and resistant (lithogenic). In the three sediments, the nonlithogenic fraction accounted for ~14–18% of the total copper and the easily exchangeable component was 5% of the total copper. In addition, the compositional associations of copper in sediment samples taken from western Lake Ontario were analyzed employing a series of sequential extractions (Poulton et al. 1988). The mean and standard

deviation percentages of copper in the various fractions were: exchangeable, 0 (0); carbonate, 0.1 (0.3); iron or manganese oxide-bound, 0.2 (0.3); organic-bound, 40 (11); and residual, 60 (8). Another study found that 10–20% of the copper in Lake Ontario sediment samples was bound to humic acids, with virtually all of the copper bound to organic matter (Nriagu and Coker 1980). The concentration of copper associated with humic acids was 21–40 times greater than in the sediment as a whole.

6.3.2.4 Other Media

Copper is an essential nutrient in plant metabolism. Therefore, uptake of copper from soil in plants through the roots is a natural and necessary process, a process that is actively regulated by the plant (Clemens 2001). The uptake of copper into plants is dependent on the concentration and bioavailability of copper in soils. The bioavailability of copper is determined largely by the equilibrium between copper bound to soil components and copper in soil solution. As noted in the discussion of copper binding in soils (Section 6.3.1.3), this is determined by copper concentrations in soil, soil type, soil components, pH, oxidation-reduction potential in the soil, and concentrations of other cations and anions in the soil, etc. (Rieuwerts et al. 1998). Other factors include root surface area, plant genotype, stage of plant growth, weather conditions, interaction with other nutrients in the soil and the water table (Gupta 1979). Liming is another factor that affects copper uptake. For example, liming acidic soils has been shown to increase copper uptake in hay, but to decrease copper uptake in wheat (Gupta 1979). However, the effect that liming has on increasing soil pH does not appear to be the overriding mechanism behind the changes in copper uptake in plants, even though there is evidence that the addition of lime to soil to increase the pH to 7 or 8 reduces copper availability to some plants (Perwak 1980). This is evidenced by the fact that changes in pH (5.4–8.0) have been found to have little effect on copper concentrations in plant tissues (Gupta 1979).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Human exposure to copper in air comes from both natural and anthropogenic sources. For the general population, exposures to copper concentrations in air average between 5 and 200 ng/m^3. The concentrations of copper in air can be higher in the proximity of major sources such as smelters, mining operations, and combustion sources (e.g., power plants, incinerators, automobiles, etc.). The results of

several studies in which concentrations of copper in air were reported and described below and are summarized in Table 6-8.

According to the EPA's National Air Surveillance Network report for the years 1977, 1978, and 1979, median copper concentrations were 133, 138, and 96 ng/m^3, respectively, for urban samples and 120, 179, and 76 ng/m^3 for nonurban samples, respectively (Evans et al. 1984). In this study, 10,769 urban and 1,402 nonurban air samples collected for 24 hours were analyzed. For 1977, 1978, and 1979, 1% of urban samples exceeded 1,156, 975, and 843 ng/m^3, respectively, and 1% of nonurban samples exceeded 1,065, 1,396, and 645 ng/m^3, respectively. The maximum urban and nonurban copper concentrations reported were 4,625 and 4,003 ng/m^3, respectively. Davies and Bennett (1985) reported average atmospheric copper concentrations of 5–50 ng/m^3 in rural areas and 20–200 ng/m^3 in urban locations. The concentrations in rural areas are considerably lower than those reported in the EPA survey. Data from many urban locations in the United States show concentrations of copper associated with particulate matter ranging from 3 to 5,140 ng/m^3 (Schroeder et al. 1987). Remote and rural areas have concentrations of 0.029–12 and 3–280 ng/m^3, respectively. The levels reported by Schroeder et al. (1987) are consistent with those obtained in a study of airborne trace elements in national parks (Davidson et al. 1985). In the Smokey Mountain National Park, the copper concentration in air was 1.6 ng/m^3, while in the Olympic National Park, where several locations were monitored, 3.3–6.7 ng/m^3 of copper was measured in the atmosphere. The lower copper concentrations found in Smokey Mountain Park compared with those in the Olympic National Park have been attributed to greater vegetative cover and higher moisture in the former and larger amounts of exposed rock and soil in the latter. Average copper crustal enrichment factors (the concentration of copper in air compared with the average concentration in the earth's crust) were 31 and 76, respectively.

As part of the Airborne Toxic Element and Organic Substances (ATEOS) project for determining patterns of toxic elements in different settings, three urban areas (Camden, Elizabeth, and Newark) and one rural site (Ringwood) in New Jersey were studied during two summers and winters between 1981 and 1983 (Lioy et al. 1987). Each site was sampled every 24 hours for 39 consecutive days. As an example, the geometric mean copper concentrations in the summer of 1983 were 16.0, 21.0, 21.0, and 6.0 ng/m^3 for Camden, Elizabeth, Newark, and Ringwood, respectively. In the winter of 1983, the mean copper concentrations were slightly higher with values of 21.0, 36.0, 33.0, and 63.0 ng/m^3, respectively. The levels of copper measured in these industrial urban areas are considerably higher than the mean values reported in the National Air Surveillance survey where arithmetic means of 0.201 and 0.259 ng/m^3 for copper in air were obtained in1978 and 1979, respectively (Evans et al. 1984). Summer and winter

Table 6-8. Concentrations of Copper in Air

Date/sample	Location	Concentration[a] (ng/m^3) (mean) [median]	Comments	Reference
1977, urban	United States	[133], 433_{90}, $1{,}156_{99}$ (207.5), $3{,}296_{max}$	4,648 samples, National Survey	EPA 1984
1978, urban	United States	[138], 430_{90}, 975_{99} (200.8), $4{,}625_{max}$	3,615 samples, National Survey	EPA 1984
1979, urban	United States	[96], 363_{90}, 519_{99} (259.3), $1{,}627_{max}$	2,507 samples, National Survey	EPA 1984
1977, nonurban	United States	[120], 450_{90}, $1{,}065_{99}$ (193.2), $16{,}706_{max}$	709 samples, National Survey	EPA 1984
1978, nonurban	United States	[179], 607_{90}, $1{,}396_{99}$ (265.7), $1{,}396_{max}$	458 samples, National Survey	EPA 1984
1977, nonurban	United States	[76], 322_{90}, 645_{99} (141.7), $4{,}003_{max}$	235 samples, National Survey	EPA 1984
Urban		20–200, [50]	Representative values	Davies and Bennett 1985
Rural		5–50, [20]		
Remote		0.29–12	Values from literature survey	Schroeder et al. 1987
Rural		3–280		
Urban	Canada	17–500		
Urban	United States	3–5,140		
Urban	Europe	13–2,760		
Urban	Other	2.0–6,810		
1979, remote	Smokey Mountain National Park	(1.6)	Above canopy, crustal enrichment factor 31	Davidson et al. 1985
1980, remote	Olympic National Park	3.3–6.7, (5.6)	Crustal enrichment factor 76	Davidson et al. 1985
1981, 1982, summer	Camden, New Jersey	16.0–18.0[b], 100.0_{max}	Seasonal variations noted; three urban areas and one rural area.	Lioy et al. 1987
	Elizabeth, New Jersey	21.0–29.0, 120.0_{max}		
	Newark, New Jersey	25.0–33.0, 131.0_{max}		
	Ringwood, New Jersey	13.0–63.0, 77.0_{max}		
1982, 1983, winter	Camden, New Jersey	17.0–21.0, 231.0_{max}		
	Elizabeth, New Jersey	28.0–36.0, 493.0_{max}		
	Newark, New Jersey	21.0–27.0, 380.0_{max}		
	Ringwood, New Jersey	6.0–18.0, 29.0_{max}		

[a]Percentile level and maximum indicated as subscripts.
[b]Concentrations in Lioy et al. (1987) are geometric means, unless otherwise noted.

maxima in the four ATEOS study areas were: 100.0 and 131.0 ng/m^3 in Camden, 231.0 and 493.0 ng/m^3 in Elizabeth, 131.0 and 380.0 ng/m^3 in Newark, and 77.0 and 29.0 ng/m^3 in Ringwood, respectively. Copper follows the same pattern as other heavy metals, in that increased copper levels are present in winter in urban areas and in summer in rural areas. No explanation for this pattern has been offered.

Anderson et al. (1988) performed a study of the atmospheric aerosols collected at a site in Chandler, Arizona, over a 12-day period in February and March 1982. Several major copper smelters are located ~120 km to the southeast, which were upwind of the sampling site during approximately 50% of the study period. Particles containing >0.5% Cu were termed 'Cu-bearing' particles; 5.6% of the fine (0.4 to ~2 μm) particles collected were in this category. The most abundant type of Cu-bearing particle, representing 74% of the total, was associated with sulfur. However, the analysis was not able to specify the form of sulfur present. These particles were often associated with Zn, Fe, Pb, As, and Ca. Sixteen percent of the Cu-bearing particles were associated with silicon and 4% were associated with chloride. The concentration of Cu-S particles was highest when the surface and upper level winds were from the southeast to the east, and reached a maximum 1–2 days after the winds began to blow. Therefore, the smelters to the southeast appear to be the probable source. The particles associated with silicon and chlorine did not show any apparent correlation with wind and were either from a diffuse regional source or a local source.

Mine waste dump sites are a source of airborne copper carried in dust (Table 6-9). Particle size distribution and the concentration of copper in particle size ranges differ depending on the mine waste site (Mullins and Norman 1994). For example, the mean concentrations (ppm, w/w) of copper in dust (<10 μm particle size range) collected at four mine waste dump sites in Butte, Montana, were 3,370 (Gray Rock), 1,950 (Corra), 1,960 (Late Acquisition), and 2,570 (Railroad Bed).

Mean concentration ranges of copper in remote (any area of lowest copper concentration such as the Antarctic or Arctic) and rural (any site that represents a regional background that is not directly influenced by local anthropogenic emissions) precipitation ranges were 0.013–1.83 and 0.68–1.5 ppb, respectively, based on a weight per unit volume basis (Barrie et al. 1987). Although an earlier survey referred to by these investigators (Galloway et al. 1982) yielded much higher values, 0.060 and 5.4 ppb, these were ascribed to sample contamination. The mean concentration of copper in rain reported in an extensive study in southern Ontario, Canada, was 1.57 (0.36 standard deviation) ppb during 1982 (Chan et al. 1986). These concentrations showed little spatial variability. Concentration of copper

Table 6-9. Particle Size Distributions and Total Copper Concentrations in Dust Collected at Four Mine Waste Pump Sites in Butte, Montana

Site	Particle size (µm)	Percent in total dust collected	Concentration of copper (ppm, w/w)
Corra	4.7–10	76.6±4.8	1,550
	1.1–4.7	20.9±0.63	3,110
	<1.1	1.9±0.14	4,900
Gray rock	4.7–1.0	84.5±0.93	3,240
	1.1–4.7	13.6±0.82	4,120
	<1.1	1.9±0.14	4,370
Railroad bed	4.7–10	61.5±1.06	2,580
	1.1–4.7	31.3±0.96	2,850
	<1.1	7.2±0.26	1,400
Late acquisition	4.7–10	70.3±1.36	1,560
	1.1–4.7	25.0±1.18	2,730
	<1.1	4.7±0.44	3,330

Source: Mullins and Norman 1994

in cloud water over Olympic Peninsula in Washington State has been measured at 1.7±1.6 µg/L (air-equivalent mean concentration of 0.5 ng/m^3) (Vong et al. 1997).

The concentration of copper in rain samples taken within 2–15 km downwind of the Claremont, New Hampshire, municipal waste incinerator was found to range from 0.11 to 2.12 µg/L with a mean concentration of 0.87 µg/L. The total mean deposition rate of airborne copper from rain was measured to be 4.0 µg/m^2/day for the eight sampling sites used in the study (Feng et al. 2000). However, copper deposition from automobile emissions, as measured by the concentration of copper in snow, did not vary significantly as a function of distance (15–150 meters) from an expressway in Montreal, Canada. Mean concentrations of copper in the snow (expressed as mg/L [and standard deviations]) were measured as 0.051 (0.073), 0.065 (0.127), 0.034 (0.027), and 0.044 (0.051) at 15, 20, 15, and 150 meters, respectively (Loranger et al. 1996).

Airborne concentrations of copper in the indoor atmosphere within homes located in Suffolk and Onondaga counties in New York average between 8 and 12 ng/m^3 (Koutrakis et al. 1992). The concentration was significantly affected by the use of kerosene heaters, which were found to emit copper into the indoor air at a rate of 15,630 ng/hour (Koutrakis et al. 1992).

Elevated levels of copper in fog water have been observed 3 km downwind from a refuse incinerator in Switzerland (Johnson et al. 1987). High concentrations of copper were associated with low pH. The maximum concentration, 673 ppb, occurred at pH 1.94; levels >127 ppb were associated with pH values <3.6. Copper(II) concentrations in fog water from the central valley of California ranged from 1.7 to 388 ppb (Miller et al. 1987). The source of the copper was not investigated. The highest values were recorded just as the fog was dissipating.

6.4.2 Water

Copper is widely distributed in water since it is a naturally occurring element. Copper levels in surface water range from 0.5–1,000 ppb, with a median of 10 ppb; seawater contains <1–5 ppb (Davies and Bennett 1985; Mart and Nurnberg 1984; Page 1981; Perwak et al. 1980; Yeats 1988). The results of several studies in which copper was detected in drinking water, groundwater, and surface water are described in this section and summarized in Table 6-7. The information in Table 6-7 demonstrates that copper concentrations in drinking water can vary widely (≤5–10,200 ppb) and can exceed the action limits of 1,300 ppb that have been set for copper in drinking water (EPA 1991). The table also

emphasizes the importance of running tap water before using it and the need to control corrosion of piping in water distribution systems.

Copper concentrations in drinking water vary widely as a result of variations in pH, hardness of the water supply and copper released from the water distribution system (Davies and Bennett 1985; Yannoni and Piorkowski 1995). Copper concentrations in drinking water range from a few ppb to 10 ppm. A Canadian national survey of copper and other metals in drinking water was conducted from November 1976 to January 1977 (Meranger et al. 1979). Supplies from 70 municipalities representing 38% of the Canadian population were included in the survey, including 50 derived from river or lake water and 20 derived from groundwater. Unfiltered raw, treated and distributed drinking waters were analyzed. Whether the water was derived from river, lake, or well water did not significantly affect the copper concentration in the raw water. Only in a few supplies did copper levels in raw water exceed 20 ppb and only one of these was derived from groundwater. The results in groundwater contrast with those of Page (1981) in New Jersey, in which over 100 wells contained copper levels in excess of 64 ppb. However, that study included groundwater that was a source of drinking water, in addition to groundwater that was not. The copper concentration in Canadian treated water was generally ~10 ppb (Meranger et al. 1979). In 20% of the samples, the copper level in distributed water was significantly higher than the treated water. The increase was greater in areas where the water was soft and corrosive, thus enhancing leaching of copper from the distribution system.

Elevated concentrations of copper in drinking water can result as a consequence of leaching processes that occur in water distribution systems. A study of 1,000 water samples from random households in Ohio found that ~30% contained copper levels >1 ppm (Strain et al. 1984). The highest copper level in the study was 18 ppm. In a study of private water wells in four communities in Nova Scotia, Maessen et al. (1985) found that the concentrations of copper increased in water that remained in the distribution system overnight, indicating that copper was mobilized from the distribution system. Whereas the level of copper in running water was generally very low, that in the standing water was variable and exceeded 1.0 ppm in 53% of the homes. Similar results were reported for U.S. cities (Maessen et al. 1985; Schock and Neff 1988; Strain et al. 1984). In a study in Seattle, Washington, the mean copper concentrations in running and standing water were 0.16 and 0.45 ppm, respectively, and 24% of the standing water samples exceeded 1.0 ppm (Maessen et al. 1985). The difference in copper level between standing and flushed systems became evident at pH 7 and increased with decreasing pH (Strain et al. 1984). Copper levels in school drinking water were found to differ by 3-fold between first draw and 10-minute flush water samples, irrespective of the corrosiveness of the water (Murphy 1993). However, the concentration of

copper in both first draw and 10-minute flush samples decreased by approximately 10-fold as the corrosiveness of the water decreased. Increasing pH in water distribution lines has been found to result in an overall decrease in metal concentrations. For example, increasing the pH of water from 7.5 to 8.5 in distribution lines decreased copper concentration by 50% (Yannoni and Piorkowski 1995).

In homes with copper piping, the mean concentration of copper in tap water has been shown to decline with the age of the home. In a sampling of tap water of 2,619 households in Berlin, Germany, that are supplied with municipal drinking water, the mean concentration of copper decreased from 0.77 ppm in homes with stated ages of 0–<5 years to 0.23 ppm in homes with stated ages of 35–<40 years (Zietz et al. 2003a). In another study of 1,619 homes in Lower Saxony, Germany, the mean concentration of copper in first draw tap water decreased from 0.37 ppm in homes with stated ages of 0–<5 years to 0.05 ppm in homes with stated ages of 35–<40 years (Zietz et al. 2003b). These decreases of copper concentration with age were attributed to a buildup of a surface layer on the piping that reduced corrosion. However, in these same two studies, it was found that the concentration of copper in tap water began to increase with increasing age in homes with stated ages of >45 years. This increase in copper concentration was attributed to the increased probability of repair or partial placement (or unknown total replacement) of piping in these homes.

In a study of groundwaters and surface waters throughout New Jersey in which >1,000 wells and 600 surface sites were sampled, the median copper levels in groundwater and surface water were 5.0 and 3.0 ppb, respectively (Page 1981). The respective 90^{th} percentile and maximum levels were 64.0 and 2,783.0 ppb for groundwater and 9.0 and 261.0 ppb for surface water. The pattern of contamination in surface water correlates with light hydrocarbons, while that in groundwater correlates with heavy metals. This suggests that the sources of contamination of surface water and groundwater are different. The nature of the sites with elevated levels of copper was not indicated.

The geometric mean (standard deviation) and median concentration of dissolved copper in surface water based on 53,862 occurrences in EPA's STORET database are 4.2 (2.71) and 4.0 ppb, respectively (Eckel and Jacob 1988). Higher concentrations tend to be found in New England, the western Gulf and the lower Colorado River (Perwak et al. 1980). The finding of high concentrations of copper species in minor river basins reported in EPA's STORET database in 1978 revealed that sources of copper in the Gila, Coeur D'Alene, and Sacramento River Basins appear to be primarily mining activities, especially abandoned sites (Perwak et al. 1980). Generally, the high concentrations (>120 µg/L) were generally observed at localized stations and correlated with low pH of the surface water. However, in another study concerning

75 Canadian headwater lakes sensitive to acid rain, copper values were relatively low (1–8 ppb range, 2 ppb mean) regardless of pH or alkalinity (Reed and Henningson 1984).

Copper concentrations were measured in surface water obtained from sampling sites in the Spearfish Creek, Whitewood Creek, and Bear Butte Creek watersheds. These watersheds are affected by water leaching from tailings and acid-mine drainage from gold mining operations in the Black Hills of South Dakota. Copper concentrations of <0.24–28 µg/L were measured in surface water, whereas concentrations in sediments were much higher, ranging from 7.8 to 159 mg/kg (May et al. 2001).

In a survey of sources of copper in storm water, measurements of copper concentrations in storm water samples were taken from various urban locations in Birmingham, Alabama. Copper concentrations were generally low in filtered samples (dissolved copper), ranging between 1.4 and 20 µg/L; but were much higher in unfiltered samples (copper bound to particulate matter) with mean values (in µg/L) of 110 (roof areas), 116 (parking areas), 280 (street runoff), 135 (vehicle service areas), 81 (landscaped areas), 50 (urban creeks), and 43 (retention ponds) (Pitt et al. 1995).

As a result of improvements in controlling the quality of discharges from municipal and industrial waste water treatment plants mandated in the Clean Water Act, copper concentrations have been declining in surface waters. For example, median copper concentrations in the Hudson River estuary have fallen 36–56% between the mid-1970s and the mid-1990s (Sañudo-Wilhelmy and Gill 1999).

The copper concentration in some bodies of water evidently varies with season. In a study of a small pond in Massachusetts from April of 1971 to March 1972, the concentration of copper was found to vary, decreasing during the spring and early summer to lows of <10–30 ppm in early August and then increasing when the pond was under the cover of ice to a maximum values of 80–105 ppb in late January and early February (Kimball 1973). Similar seasonal variations were noted in the epilimnion of the offshore waters of the Great Lakes (Nriagu et al. 1996). In both examples, the cycling in copper concentrations is thought to be a response to biological need and copper uptake during the growing season and its subsequent release from seasonal die-off and decay of biota.

Copper concentrations in seawater usually are in the 1–5 ppb range (Perwak et al. 1980). Copper levels are overall lower in the Pacific Ocean than in the Atlantic Ocean and higher near the continental shelf than in the open ocean. Copper concentrations in surface water at a depth of 1 meter transected on a cruise from Nova Scotia to the Sargasso sea ranged from 57.2 to 210 parts per trillion (ppt) (Yeats 1988).

The mean value in surface water sampled at a depth of 1 meter of the eastern Arctic Ocean was 93 ppt (Mart and Nurnberg 1984). As noted in a review by Kennish (1998), concentrations of copper in estuarine and coastal waters in the United States were 0.3–3.8 and 0.1–2.5 ppb, respectively.

6.4.3 Sediment and Soil

Copper occurs naturally at levels of ~50 ppm in the earth's crust, which includes soil and parent rock (Perwak et al. 1980). In the United States, copper concentrations in differing soil types can vary over a large range (1–300 mg/kg, dry weight); but the mean values are relatively similar (14–41 mg/kg, dry weight) as a function of soil type (Table 6-10) and land resource region (Table 6-11) (Chen et al. 1999; Fuhrer 1986). These copper levels are similar to those given in a review of soil copper concentrations that reported a median concentration of 30 ppm (dry weight) and a range of 2–250 ppm (Davies and Bennett 1985). In other studies of copper concentrations in U.S. soils, the mean copper concentrations are within the range of 14–41 mg/kg. In the work of Ma et al. (1997), the mean concentration of copper in soils of the United States was determined to be 30 mg/kg, whereas the copper concentration in agricultural surface soils in the United States that had not received an application of sludges from municipal waste treatment plants was found to be 18 mg/kg. In Florida surface soils, the geometric mean of copper concentration in 40 different soil types was 4.10 mg/kg, with a range of 1.89–10.7 mg/kg (Ma et al. 1997). Chen et al. (1999) reported copper concentrations in Florida soils ranging from 0.1 to 318 mg/kg with a geometric mean of 2.21±3.15 mg/kg (arithmetic mean of 6.10±22.1 mg/kg). These investigators also reported geometric means of 24.0 mg/kg in California soils and 17 mg/kg in U.S. soils. In agriculturally productive soils, copper ranges from 1 to 50 ppm, while in soil derived from mineralized parent material the copper levels may be much higher (NRC 1977; Perwak et al. 1980).

Copper concentrations in soil may be much higher in the vicinity of a source of copper emissions, such as a mining operation or smelter. Concentrations in the top 5 cm of soil near the boundary of a secondary copper smelter were 2,480±585 ppm (Davies and Bennett 1985). Maximum wetland soil/sediment copper concentrations were 6,912 ppm in the immediate vicinity of a Sudbury, Ontario, smelter but the concentration decreased logarithmically with increasing distance from the smelter (Taylor and Crowder 1983). The observation that the copper concentrations were highest in soils within 1–2 km from the smelter and decreased exponentially with increasing distance from the plant suggests that copper in the soil from the study area was primarily derived from particulate emissions from the smelter.

Table 6-10. Concentration of Copper in Surface Soils of the United States (in ppm-Dry Weight [dw], Equivalent to mg/kg-dw)

Soil	Range	Mean
Sandy soils and lithosols on sandstones	1–70	14
Light loamy soils	3–70	25
Loess and soils on silt deposits	7–100	25
Clay and clay loamy soils	7–70	29
Alluvial soils	5–50	27
Soils over granites and gneisses	7–70	24
Soils over volcanic rocks	10–150	41
Soils over limestones and calcareous rocks	7–70	21
Soils on glacial till and drift	15–50	21
Light desert soils	5–100	24
Silty prairie soils	10–50	20
Chernozems and dark prairie soils	10–70	27
Organic light soils	1–100	15
Forest soils	7–150	17
Various soils	3–300	26

Source: EPA 1995

Table 6-11. Geometric Means of Selected Soil Elements and Associated Soil Parameters in U.S. Surface Soils by Land Resource Regions

Land resource region	mg/kg dry soil
Mineral soils	
Northwestern specialty	34.3
Northwestern wheat	23.2
California subtropical	43.4
Western range and irrigated	26.8
Rocky Mountain	19.1
Northern Great Plains	20.2
Western Great Plains	16.3
Central Great Plains	12.6
Southwest Plateau	10.0
Southwest Prairie	4.9
Northern lake states	15.4
Lake states	18.2
Central feed grains	19.7
East and central farming	8.0
Mississippi Delta	21.1
South Atlantic and Gulf slope	6.3
Northeastern forage	34.0
Northern Atlantic slope	13.5
Atlantic and Gulf coast	7.6
Florida subtropical	31.9
All mineral soils	15.6
Histosols	
Northern lake states	59.6
Lake states	84.7
Northeastern forage	149.0
Florida subtropical	94.3
All histosols	86.9

Source: Holmgren et al. 1993

Copper and its compounds were found at 906 of 1,647 hazardous waste sites on the NPL of highest priority sites for possible remedial action (HazDat 2002). Since copper is commonly found in soil, it should occur at all sites. In past work, data analysis of metal concentrations measured in soil from hazardous waste sites taken from the 1980–1983 Contract Laboratory Program (CLP) Analytical Results Data Base (CARD) was conducted to ascertain whether elemental concentrations at hazardous waste sites were elevated above that which normally would be expected in soil of similar composition and derivation. Of the 1,307 samples in CARD, 10.5 and 7.3% had copper concentrations exceeding the number normally expected in soil at the 95 and 99% confidence intervals, respectively (Eckel and Langley 1988).

In a study in which the copper concentrations of 340 soil samples collected from diverse land-use situations, the average copper concentrations reported were 25 ppm in agricultural land, 50 ppm in suburban/residential land, 100 ppm in mixed industrial/residential land, and 175 ppm in industrial/inner urban areas (Haines 1984). From an analysis of the spatial distribution of the copper concentrations in soils where lowest copper soil concentrations are observed for rural (agricultural) soils and highest in soils obtained from industrialized urban areas, it was concluded that most of the contamination was a result of airborne deposition from industrial sources.

The concentration of copper in soils and sediments was assessed as part of the National Water-Quality Assessment Program (Rice 1999). The median concentrations of copper at 541 sites throughout the conterminous United States ranged from 5 to 70 µg/g (dry weight). At nonurban indicator sites, the median concentrations ranged from 13 to 47 µg/g. The same study derived an average crustal abundance of copper of 60 µg/g.

Sediment is an important sink and reservoir for copper. In areas where there is no known input of copper obtained from anthropogenic sources, sediment generally contains <50 ppm copper. The level can reach several thousand ppm in polluted areas (Harrison and Bishop 1984). The mean copper level in surficial sediment of Penobscot Bay, Maine, was 14.1 ppm (dry weight), while that in estuaries or bays in other New England locations ranged from 4.4 to 57.7 ppm (Larsen et al. 1983b). Levels reflect anthropogenic input as well as the mineral content of the regional bedrock. Copper levels in sediment from 24 sites along the New Jersey coast ranged from <1.0 to 202 ppm, with a mean value of 66 ppm (Renwick and Edenborn 1983). The texture of the sediment varied from 94% clay to 100% sand, and the copper level was correlated negatively with the percentage of sand in the sediment.

Surficial sediment in lakes in the Sudbury region of northeastern Ontario, where several smelters operate, decreased rapidly with increasing distance from the smelters (Bradley and Morris 1986). Three lakes, 10 km from the Sudbury smelters, contained copper concentrations in sediment approaching 2,000 ppm dry weight, over 100 times the concentration in a lake selected as a baseline lake 180 km away.

An analysis of the Coastal Sediment Database (COSED) showed that 73% of coastal waterways had copper concentrations below 42 µg/g; 25% had copper concentrations between 42 and 210 µg/g; and 2% were above 210 µg/g. These higher concentrations are associated with locations of high ship traffic, industrial activity, and relatively poor water flushing (Daskalakis and O'Connor 1995). In coastal areas receiving persistently high influxes of contaminants, high concentrations of copper (151 ppm) have been measured to sediments to depths of 54 cm (Bopp et al. 1993). Combined sewer outflows can also contribute significantly to the copper content in sediments. For example, mean (arithmetic) copper concentrations of 180, 208, 280, and 284 mg/kg were measured in sediment samples obtained near four sewer outflows in the lower Passaic River, New Jersey (Iannuzzi et al. 1997). In Jamaica Bay, New York, copper concentrations in sediments were 151–406 ppm, with a concentration of 151 ppm in sediment core samples obtained at a depth of 52–54 cm (Bopp et al. 1993). The highest concentrations were found in the middle depths (16–44 cm) ranging from 280 to 406 ppm during a period where untreated industrial effluents and sewage outflows were allowed to enter the bay. However, copper concentrations in surface sediments (0–2 cm) where measured at 208 ppm. The decrease in copper concentration in the surface sediments suggests that efforts to reduce metal contaminants from sewage outflows have been making an impact on the copper concentrations in receiving waters and their sediments.

6.4.4 Other Environmental Media

In addition to the ingestion of drinking water, the consumption of food is the other primary route for copper intake in the general population. Several studies of copper content in a variety of foods have been conducted as part of the FDA's Total Diet Survey and are described in this section. These data have been used to estimate the average intakes of copper in the human diet within various age groups. For example, in the 25–30-year-old age group, copper intake has been estimated to be 0.93 mg/day for women and 1.24 mg/day for men (Pennington 1983). The levels of copper in other food sources such as mollusks, fish, and agricultural plants have been measured and the results summarized in this section. One highlight in the data is the potential for high dietary intakes of copper for those individuals who regularly consume of mollusks where the daily intake of copper could increase by 5.7–136 mg/day in comparison to the

general population (see Section 6.5). Other media covered in this section are human tissues, cigarette smoke, industrial and municipal waste streams, and agricultural products.

The FDA Total Diet Survey has provided copper concentration in various foods, examples of which are given in Table 6-12 (FDA 2001). The highest concentrations of copper were found in liver, in some oat and bran cereals, in some legumes and nuts, and in raw avocadoes and mushrooms. Coleman et al. (1992) reported copper concentrations in the edible tissues of livestock and poultry with the highest mean concentrations (ppm) found in liver (cow 43.7; lamb 89.8; chicken 4.60; turkey 7.14), followed by kidney (cow 8.15; lamb 5.39; chicken 3.07; turkey 3.68), and muscle (cow 1.41; lamb 1.47; chicken 0.67; turkey 0.83) (Coleman et al. 1992).

More recent measurements of copper concentrations in 265 foods analyzed from 1991 to 1996 and from 1991 to 1999 have been obtained from the FDA Total Diet Study (Capar and Cummingham 2000; FDA 2000). The copper contents of selected foods provided in the most recent FDA Total Diet Study (FDA 2000) are similar to those obtained from the 1982–1984 FDA study. The contribution of food groups to copper intake varies depending on the age group (Pennington and Schoen 1996). For example, animal flesh only contributes to 18% of the copper intake for a 2-year-old child, but contributes to 38% of the copper intake for a 60–65-year-old male. The results of a 1994–1996 Continuing Survey of Food Intakes (CSFII) found that the daily intakes of copper for men and women ages ≥60 years old are 1.3 and 1.0 mg/day, respectively (Ma and Betts 2000). In a separate study by Ellis et al. (1997), copper intake for male and female African-Americans ages 21–65 years old was determined to be 1.0 mg/day for both sexes.

Daily intakes of copper and other essential minerals were estimated for eight age-sex groups of the United States population as part of the FDA's Total Diet Study (Pennington et al. 1986). By analyzing the mean mineral content of samples of 234 foods obtained in 24 cities from mid-1982 to mid-1984 and by using previously determined daily intakes of each food as determined from data obtained from the National Food Consumption Survey (1977–1978) and the Second National Health and Nutrition Examination Survey (1976–1980) (Pennington 1983), the daily mineral intake for the age-sex groups was determined. The copper intakes in mg/day of the eight age-sex groups were: 6–11-month-old infant, 0.47; 2-year-old child, 0.58; 14–16-year-old girl, 0.77; 14–16- year-old boy, 1.18; 25–30-year-old woman, 0.93; 25–30-year-old man, 1.24; 60–65-year-old woman, 0.86; and 60–65-year-old man, 1.17. All values were low in terms of the estimated safe and adequate daily dietary intake of this nutrient. The food item with the highest copper level was beef/calf liver (61 ppm).

Table 6-12. Copper Content of Selected Foods (mg/kg)[a]

Food description	Mean	SD[b]	Food description	Mean	SD[b]
Breads			green pepper, raw	0.7	0.3
bagel, plain	1.3	0.2	iceberg lettuce, raw	0.2	0.2
cracked wheat bread	1.8	0.2	lima beans, immature, frozen, boiled	1.5	0.2
English muffin, plain, toasted	1.3	0.1	mixed vegetables, frozen, boiled	0.6	0.2
graham crackers	1.5	0.3	mushrooms, raw	2.4	0.6
rye bread	1.5	0.2	okra, fresh/frozen, boiled	0.8	0.3
saltine crackers	1.4	0.1	onion, mature, raw	0.4	0.1
white bread	1.1	0.2	peas, mature, dry, boiled	2.3	0.3
white roll	1.3	0.2	spinach, fresh/frozen, boiled	0.8	0.3
whole wheat bread	2.3	0.3	summer squash, fresh/frozen, boiled	0.5	0.1
			sweet potato, fresh, baked	1.4	0.4
Cereal, rice, and pasta			tomato, red, raw	0.5	0.2
corn flakes	0.5	0.1	tomato sauce, plain, bottled	1.2	0.4
crisped rice cereal	2.0	0.2	tomato, stewed, canned	0.7	0.2
egg noodles, boiled	1.0	0.2	turnip, fresh/frozen, boiled	0	0.1
granola cereal	3.0	0.4	white potato, baked with skin	1.0	0.4
macaroni, boiled	0.9	0.1	white potato, boiled without skin	0.6	0.2
oatmeal, quick (1–3 minutes), cooked	0.7	0.1	winter squash, fresh/frozen, baked, mashed	0.6	0.2
oatring cereal	3.3	0.4			
raisin bran cereal	4.4	0.4	**Fruits**		
shredded wheat cereal	3.7	0.5	apple, red, raw	0.2	0.2
wheat cereal, farina, quick (1–3 minutes), cooked	0.3	0.3	applesauce, bottled	0.2	0.1
white rice, cooked	0.7	0.1	apricot, raw	0.8	0.3
			avocado, raw	2.2	0.6
Vegetables			banana, raw	1.1	0.2
asparagus, fresh/frozen, boiled	1.0	0.2	cantaloupe, raw	0.3	0.1
beets, fresh/frozen, boiled	0.7	0.2	fruit cocktail, canned in heavy syrup	0.5	0.1
black olives	1.4	0.4	grapefruit, raw	0.3	0.1
broccoli, fresh/frozen, boiled	0.2	0.1	grapes, red/green, seedless, raw	1.1	0.6
Brussels sprouts, fresh/frozen, boiled	0.4	0.1	orange, raw	0.4	0.1
cabbage, fresh, boiled	0	0	peach, canned in light/medium syrup	0.3	0.2
carrot, fresh, boiled	0.3	0.2	peach, raw	0.7	0.2
cauliflower, fresh/frozen, boiled	0	0	pear, canned in light syrup	0.4	0.1
celery	0	0.1	pear, raw	0.8	0.1
collards, fresh/frozen, boiled	0.5	0.4	pineapple, canned in juice	0.5	0.1
corn, fresh/frozen, boiled	0.3	0.2	plums, raw	0.6	0.1
cream style corn, canned	0.1	0.2	prunes, dried	2.9	0.3
cucumber, raw	0.2	0.2	raisins, dried	3.3	0.4
eggplant, fresh, boiled	0.5	0.2	strawberries, raw	0.5	0.3
green beans, fresh/frozen, boiled	0.5	0.3	watermelon, raw	00.4	0.1
green peas, fresh/frozen, boiled	1.0	0.2			

Table 6-12. Copper Content of Selected Foods (mg/kg)[a]

Food description	Mean	SD[b]	Food description	Mean	SD[b]
Fruit juices			pork roast, baked	0.8	0.1
apple juice, bottled	0	0.1	pork sausage, pan-cooked	0.8	0.1
grape juice, bottled	0	0.1	quarter-pound hamburger on bun, fast-food	0.9	0.1
grapefruit juice, from frozen concentrate	0.3	0.1	salami, sliced	1.0	0.2
orange juice, from frozen concentrate	0.3	0.1	salmon, steaks or filets, fresh or frozen, baked	0.5	0.1
pineapple juice from frozen concentrate	0.4	0.1	shrimp, boiled	2.3	0.6
prune juice	0.1	0.1	tuna, canned in oil	0.5	0.1
tomato juice, bottle	0.6	0.1	turkey breast, roasted	0.4	0.1
			veal cutlet, pan-cooked	1.0	0.3
Dairy products					
American, processed cheese	0.1	0.2	**Legumes, nuts, and nut products**		
cheddar cheese	0.3	0.2	kidney beans, dry, boiled	2.7	0.5
chocolate milk, fluid	0.3	0.2	mixed nuts, no peanuts, dry roasted	15.5	2.6
cottage cheese, 4% milkfat	0	0	peanut butter, smooth	5.2	0.6
cream cheese	0	0	peanuts, dry roasted	5.8	0.6
eggs, boiled/fried	0.6	0.1	pinto beans, dry, boiled	2.4	0.2
eggs, scrambled	0.5	0.1	pork and beans, canned	1.8	0.2
half & half	0	0			
lowfat (2%) milk, fluid	0	0	**Fats, oils, condiments, snacks, and sweets**		
skim milk	0	0	butter, regular (salted)	0	0
sour cream	0	0	corn chips	1.0	0.2
Swiss cheese	0.4	0.4	fruit flavor sherbet	0	0.1
whole milk	0	0	gelatin dessert, any flavor	0	0
			honey	0	0
Meat, poultry, and seafood			jelly, any flavor	0	0.1
beef chuck roast, baked	1.0	0.1	margarine, stick, regular (salted)	0	0
beef steak, loin, pan-cooked	1.0	0.2	mayonnaise, regular, bottled	0	0
bologna, sliced	0.4	0.2	olive/safflower oil	0	0
chicken breast, roasted	0.3	0.1	popcorn, popped in oil	1.7	0.4
chicken, fried (breast, leg, and thigh)	0.7	0.1	potato chips	2.8	0.8
frankfurters, beef, boiled	0.4	0.1	pretzels, hard, salted, any shape	1.6	0.2
ground beef, pan-cooked	0.8	0.1	vanilla ice cream	0.06	0.24
haddock, pan-cooked	0.06	0.13	white sugar, granulated	0	0
ham, baked	0.6	0.2			
ham luncheon meat, sliced	0.5	0.1	**Beverages**		
lamb chop, pan-cooked	1.4	0.2	coffee, from ground	0	0
liver, beef, fried	123	57	cola carbonated beverage	0	0
pork bacon, pan-cooked	1.2	0.4	tea, from tea bag	0	0
pork chop, pan-cooked	0.8	0.2			

[a]Source: FDA 2000
[b]SD = Standard Deviation

A baseline value for the copper content of mother's milk was determined by a survey of literature values. Based on the data obtained from 28 study sets, a baseline copper concentration of 331 ppb was determined from a range of values of 197–751 ppb and a median of 290 ppb (Iyengar and Woittiez 1988). In a separate study of 11 lactating women, it was found that the variability in the copper content of mother's milk was primarily subject-related. The copper concentration in milk declined moderately, from 0.43 µg/mL between 1 and 3 months postpartum to 0.24 µg/mL between 10 and 12 months postpartum (Vaughan et al. 1979). In a study of 82 lactating women, the copper concentration in breast milk ranged between 0.8 and 1.1 ppm and remained relatively constant in individual women over the first 7 days postpartum (Arnaud and Favier 1995).

The concentrations of copper in the soft tissue in mussels and oysters collected as part of the U.S. Mussel Watch Program in 1976–1978 were 4–10 ppm (dry weight) for mussels and 25–600 ppm for oysters (Goldberg 1986). Copper concentrations in mussels collected from 11 sites near Monterey Bay, California, were 4.63–8.93 ppm (dry weight) (Martin and Castle 1984). Perwak et al. (1980) reported similar results for mussels (3.9–8.5 ppm) and for clams (8.4–171 ppm). Recent measurements of copper concentrations in zebra and quagga mussels taken from Lakes Erie and Ontario in 1997 ranged from 21 to 41 ppm (dry weight) (Rutzke et al. 2000). In the National Oceanic and Atmospheric Administration (NOAA) Mussel Watch Project, copper concentrations were quantified in mollusks (*M. edulis, M. californianus, C. virginica,* and *Ostrea equestris*) from 113 sites around the United States in 1993 and compared to copper concentrations measured in mollusks taken from the same site in the EPA2 Mussel Watch Program, 1976–1978 (Lauenstein and Daskalakis 1998). The results of the comparison indicate that the decreasing and increasing trends in copper concentrations in mollusks were approximately equal among the sites, except in California, where increasing trends were noted at five sites.

As a part of the National Contaminant Biomonitoring Program of the U.S. Fish and Wildlife Service, eight species of freshwater fish were collected at 112 stations in the United States in 1978–1979 and 1980–1981 (Lowe et al. 1985). The geometric mean concentrations of copper in ppm (wet weight, whole fish) for these two periods were 0.86 and 0.68, respectively; the 85th percentiles were 1.14 and 0.90, respectively, and the ranges were 0.29–38.75 and 0.25–24.10, respectively. The highest concentration, 38.75 and 24.10 ppm, during both collecting periods was in white perch from the Susquehanna River and the second highest concentration, 19.3 ppm, was found in white perch from the Delaware River near Trenton, New Jersey. However, copper concentrations in common carp and white catfish collected from the same station at the same time were 0.76 and 1.35 ppm, respectively.

In bluefin tuna caught in the northwest Atlantic off Newfoundland, the mean copper concentration in muscle tissue has been measured at 1.0 ppm (dry weight) (Hellou et al. 1992a). In cod caught off the coast of Newfoundland, mean copper concentrations of <1.2–1.5 µg/g (dry weight) in muscle and 5–10 ppm (dry weight) in liver have been determined (Hellou et al. 1992b).

Copper residues in muscle of 268 fish specimens from 17 species were analyzed over a 5-year period in several surface water systems in eastern Tennessee (Blevins and Pancorbo 1986). The mean residue levels in the muscle of different species of fish from nine stations ranged from 0.12–0.86 ppm (wet weight). Maximum levels ranged from 0.14 to 2.2 ppm.

Concentrations of copper in three species of fish living in storm treatment ponds have been compared to copper concentrations in controls collected from surrounding surface waters near Orlando, Florida (Campbell 1994). In bluegill sunfish collected from storm water ponds, the mean whole body copper concentrations were 6.37 and 2.08 mg/kg wet weight, respectively, and were significantly higher than the mean concentrations of copper, 0.879 and 1.07 mg/kg wet weight, respectively, measured in controls collected in natural lakes or ponds. However, in largemouth bass, the mean copper concentrations in fish collected from storm water ponds and controls did not significantly differ, with values of 3.81 and 4.71 mg/kg wet weight, respectively.

Respective mean and median copper concentrations of 127 samples of finfish from Chesapeake Bay and its tributaries were 1.66 and 0.36 ppm in 1978, and 1.85 and 0.61 ppm in 1979 (Eisenberg and Topping 1986). In striped bass taken from Turkey Point in the bay, copper levels were below the detection limit of the study (<0.1 µg/g) in muscle, but were higher in liver tissue ranging from 0.86 to 23.5 µg/g. In gonad tissue obtained from tissue from a different site on the bay, there was also an increase in the mean copper concentration in this tissue (4.25 µg/g) as compared to muscle (0.76 µg/g). The copper content of muscle tissue of several species of fish collected from metal-contaminated lakes near Sudbury, Ontario, ranged from 0.5 to 1.4 ppm (dry weight). No major pattern in variation was evident among species or among the study lakes (Bradley and Morris 1986). The copper concentration in the livers, however, ranged from 5 to 185 ppm (dry weight) and differed significantly among species and among lakes. Unlike muscle tissue, liver tissue is a good indicator of copper availability, although the data indicate that there are other factor(s) that influence the availability and bioaccumulation of copper in these fish.

The copper concentrations in the liver of lake trout and grayling taken from four fresh water lakes in Alaska did not correlate well with the concentrations of copper in the sediments of these lakes (Allen-Gil et al. 1997). Lake trout were found to have statistically significant higher burdens of copper in their livers than grayling, and the concentrations of copper in the livers of trout varied considerably depending on the lake from which they were collected. The species and site differences in copper concentrations in fish livers have been attributed to differences in diet, (grayling consume mainly insects, whereas trout consume a mix of snails, insects and small fish) and time spent at various depths of the water column.

Although the concentrations of copper in plants vary widely, they usually range from 1 to 50 ppm (dry weight) (Davies and Bennett 1985) and from 1 to 143 ppm (dry weight) in edible plants (Perwak et al. 1980). Concentration ratios of copper in plants relative to soil (concentration factors or CF) demonstrate that copper uptake differs significantly between plants. For example, CF values have been found to vary from 0.02 (onion), 0.13 (celery), 0.21 (lettuce), and 0.30 (potato) to 2 (grapes), 4.5 (alfalfa), and 6.8 (grass) (Pinochet et al. 1999). Concentration factors in rice were found to vary among soil types (0.59–3.58) with copper concentrations in rice ranging from 1.7 to 5.1 µg/g (Herawati et al. 2000). Copper concentrations in rice grain have been found to increase significantly from 1.4 to 15.5 µg/g when copper concentrations in waste water irrigated soils increased from 17.0 mg/kg (wet weight) to 101.2 mg/kg (wet weight) (Cao and Hu 2000).

Studies of copper in human tissues suggest that copper content in a 70 kg adult ranges from 50–70 mg (Davies and Bennett 1985). Wise and Zeisler (1984) reported an average copper concentration of 10 ppm in the human liver in 36 samples. Despite the wide variation in copper concentrations in the environment, the copper concentration in the liver only varied by a factor of 2–3.5. Copper concentrations in human tissues are given in Table 6-13 (Georgopoulos et al. 2001). The concentration of copper in blood is not expected to be predictive of the total body burden of copper: Saltzman et al. (1990) found that the correlation between copper concentrations measured in blood and total body burden was poor (r=0.54).

The mean copper content of tobacco in Finnish cigarettes was 24.7 ppm, with a standard deviation of 10.8 ppm (Mussalo-Rauhamaa et al. 1986). However, only 0.2% of this copper passes into mainstream smoke. This translates to a daily exposure of approximately 1 µg of copper in a pack of 20 cigarettes.

In an EPA-sponsored study conducted to determine the metal concentration in sewage sludge (Feiler et al. 1980), copper concentrations in primary sludge at seven POTWs were reported to be 3.0–77.4 ppm, with

Table 6-13. Copper Content of Human Tissues and Body Fluids

Tissue	Mean content (µg/g dry weight)	
	Normal	Wilson's disease
Adrenal	7.4	17.6
Aorta	6.7	—
Bone	4.2	—
Brain	—	—
Caudate nucleus	—	212
Cerebellum	—	261
Frontal lobe cortex	—	118
Globus pallidus	—	255
Putamen	—	314
Cornea	—	92.9
Erythrocytes (per 100 mL packed red blood cells)	23.1	—
Hair	89.1	—
Heart	16.5	12.7
Kidney	14.9	96.2
Leukocytes (per 109 cells)	0.9	—
Liver	25.5	584
Lung	9.5	15.5
Muscle	5.4	25.9
Nail	18.1	—
Ovary	8.1	5.2
Pancreas	7.4	4.2
Placenta	13.5	—
Prostate	6.5	—
Skin	2	5.2
Spleen	6.8	5.6
Stomach and intestines	12.6	22.9
Thymus	6.7	—
Thyroid	6.1	—
Uterus	8.4	—
Aqueous humor	12.4	—
Bile (common duct)	1,050	173
Cerebrospinal fluid	27.8	—
Gastric juice	28.1	—
Pancreatic juice	28.4	—
Plasma, Wilson's disease		—
Saliva	50	—

Table 6-13. Copper Content of Human Tissues and Body Fluids

Tissue	Mean content (µg/g dry weight)	
	Normal	Wilson's disease
Serum		
Female	120	—
Male	109	—
Newborn	36	—
Sweat		
Female	148	—
Male	55	—
Tissue		
Synovial fluid	21	—
Urine (24-hour)	18	—

Source: Georgopoulos et al. 2001; Scheinberg 1979; Sternlieb and Scheinberg 1977

a median concentration of 20.5 ppm. The plant with the highest copper concentrations received wastes from plating industries, foundries, and coking plants. In a comprehensive survey of heavy metals in sewage sludge, 30 sludges from 23 American cities were analyzed (Mumma et al. 1984). The copper concentration in the sludges ranged from 126 to 7,729 ppm (dry weight), with a median value of 991 ppm. Gutenmann et al. (1994) report similar concentrations (217–793 ppm, dry weight) in sewage sludge obtained from 16 major cities in the United States. The proposed limit for copper in sludge spread on agricultural land is 1,000 ppm (Mumma et al. 1984). For comparison, the concentration of copper in cow's manure is ~5 ppm (Mumma et al. 1984).

In municipal solid waste compost obtained from nine sites in the United States, a mean copper concentration of 281 mg/kg (dry weight) was obtained with range of 36.4–424 mg/kg (He et al. 1995). Lisk et al. (1992) reported copper concentrations in composts formed from yard waste ranging from 22.7 to 327 ppm, from sewage sludge ranging from 432 to 1,019 ppm and from municipal solid waste ranging from 191 to 1,143 ppm.

Copper concentrations in waste from the combustion of municipal solid waste and other combustion processes have been reported. Copper in incinerator bottom ash and fly ash has been measured at mean concentrations of 1,700 and 1,000 mg/kg, respectively (Goldin et al. 1992). Buchholz and Landberger (1995) report concentrations of copper of 390–530 µg/g in fly ash, 1,560–2,110 µg/g in bottom ash, and 1,140–1,540 µg/g in combined ash. In sewage sludge incineration process steams, copper concentrations were 4,561 mg/kg in sludge cake, 3,465 mg/kg in bottom ash, 3,707 mg/kg in cyclone ash, 3,684 mg/kg in scrubber particulate matter, and 6,666 mg/kg in stack particulate matter (Balogh 1996). In fossil fuel wastes, copper concentrations of 33–2,200 mg/kg in fly ash, 4–930 mg/kg in bottom ash, 6–340 mg/kg in flue gas desulfurization sludge, 10–130,000 mg/kg oil ash, and 2–190 mg/kg in coal have been obtained (Eary et al. 1990).

Agricultural sources of copper contamination in soils has been summarized by EPA (1995) and are shown in Table 6-14. Concentrations of copper in fertilizers, soil amendments and other agricultural materials have been measured by Raven and Loeppert (1997). The materials and mean concentrations: urea (<0.6 µg/g), ammonium nitrate (<0.6 µg/g), ammonium sulfate (<0.6 µg/g), ammonium phosphate (<2–41.8 µg/g), potassium chloride (<2–3.5 µg/g), potassium-magnesium-sulfate (1.4–5 µg/g), North Carolina rock phosphate (9.6 µg/g), calcite (2.3 µg/g), corn leaves (9.4 µg/g), manure (17.5 µg/g), and austinite (300 µg/g).

Table 6-14. Agricultural Sources of Copper Contamination in Soils

Source	Concentration (ppm dry weight)[a]
Sewage sludges	50–3,300
Phosphate fertilizers	1–300
Limestones	2–125
Nitrogen fertilizers	<1–15
Manure	2–60
Pesticides (percent)	12–50

Source: EPA 1995

[a]Equivalent to mg/kg-dry weight

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Due to the ubiquitousness of copper in the environment and the general occurrence of copper in airborne particulates, exposure to copper through inhalation is commonplace. Estimates of atmospheric copper concentrations from different source categories (e.g., smelters, ore processing, steel production, and combustion) yielded a maximum annual concentration of 30 μg/m^3 (EPA 1987a). If a person is assumed to inhale 20 m^3 of air/day, this would amount to an average daily intake of 600 μg of copper. For the reported range of annual atmospheric copper concentrations, 5–200 ng/m^3 (EPA 1987a), the average daily intake by inhalation, would range from 0.1 to 4.0 μg. At the maximum reported ambient air concentration, 100 μg/m^3 for a 24-hour period at a location within one-half mile of a major source (EPA 1987a), the average daily intake would rise to 2,000 μg. These estimates assume that all of the copper is attached to particles of inhalable size, which is usually not the case. The average daily dietary intake of copper from food is ~2 mg/day. The dietary intake of copper is expected to be above this average for those individuals who regularly consume organ meats (e.g., liver and kidney), nuts, seeds (including cocoa powder), legumes, and bran and germ portions of grains; these intakes are not expected to exceed the maximum recommended limits of 10–12 mg/day (WHO 1996). Those individuals who regularly consume oysters or clams may increase their dietary intake of copper by 2–150 mg/day when consuming 250 g of edible tissue per day, based on copper concentrations of 25–600 and 8.4–171 ppm in oysters and clams, respectively (Goldberg 1986; Perwak et al. 1980). Assuming a median copper concentration in drinking water of 75 μg/L, the average daily copper exposure from consumption of 2 L of water per day is 0.15 mg. However, many people may have high levels of copper in their tap water that have been acquired during transport through the water distribution system. If the system is not permitted to flush out, average intakes from water may be >2 mg/day. It is less likely that high dermal exposures will result from bathing in this tap water because the distribution system will flush itself out as the water is drawn. The total exposure of copper for the average person from all sources (e.g., air, drinking water, and food) is estimated to be 2.75 mg/day.

A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that potentially 505,982 workers, including 42,557 women, were occupationally exposed to copper in the United States (NIOSH 1988). The NOES estimate is provisional because all of the data for trade name products that may contain copper have not been analyzed. Of the potential exposures, 1,073 are to pure copper, while in the other cases, the molecular form of copper was unspecified. Additionally, according to the NOES, 125,045 workers, including 38,075 women, were potentially exposed to copper sulfate

(NIOSH 1988). The NOES was based on field surveys of 4,490 facilities and was designed as a nationwide survey based on a statistically valid sample of virtually all workplace environments in the United States where eight or more persons are employed in all standard industrial codes (SIC) except mining and agriculture. The exclusion of mining and agriculture is significant for estimating exposure to copper since there is a high potential for exposure in these industries. Current occupational exposure limits for copper fume are 0.2 and 1 mg/m^3 for dust and mists (Frazier and Hage 1998).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

With respect to inhalation, exposures of children to copper are not expected to be very different from those of the rest of the general population. However, exposure of copper through oral routes may differ, due to differences in the consumption of various food groups between children and adults and ingestion of dust and soils. The dietary copper intake for infants who receive the major portion of their nutritional requirements from breast milk is likely to be different from infants whose nutritional needs are either supplemented or entirely received through the consumption of formula. Estimates of copper intake from inhalation and ingestion in children in the United States are limited. From the work of Pennington et al. (1986), the copper intakes for a 6–11-month-old infant and a 2-year-old child were estimated to be 0.47 and 0.58 mg/day, values which are lower than the adult intake of ~1 mg/day. However, one study has provided estimated inhalation and ingestion exposures of copper for children in India (Raghunath et al. 1997). In this work, concentrations of copper in particulates in air were measured at 0.01–0.26 µg/m^3. Based on these measurements, estimated inhalation exposures of children to copper were calculated to be

0.1–3.2 µg/day. In this same work, exposures to copper through ingestion were estimated to be between 684–1,732 µg/day.

Exposures of children to copper are likely to increase in areas where copper concentrations in air are expected to be high, such as mining sites, waste dump sites, smelters, and foundries. For example, copper burdens in children living near a lead smelter, as measured by copper concentration in teeth, increased with decreasing distance from the smelter (Blanuša et al. 1990). Children are also at risk for increased copper intake through consumption of drinking water where leaching of copper from the distribution system has occurred (Murphy 1993; Yannoni and Piorkowski 1995). This route of copper exposure can be minimized through the flushing of drinking water supply lines or increasing the pH of the water in the distribution system.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In discussing exposure to copper, the important question is whether individuals are exposed to readily available copper, which in general, means free (hydrated) Cu(II) and perhaps some weakly complexed or adsorbed forms of copper. The data indicate that copper in natural water, sediment, and soil mainly exists in bound form. Even so, the free form of copper can be released readily from ingested materials, for example a child's sampling of soil, following exposure to the low pHs encountered in the stomach (Pizarro et al. 2001). Potential for high uptake copper in the general population may exist where people consume large amounts of tap water that has picked up copper from the distribution system, or already has a high copper background due to natural or anthropogenic activities (e.g., close proximity to mining activities or mine drainage). Leaching of copper from water distribution systems is likely to occur where the water is soft and not allowed to run to flush out the system. In such cases, the concentration of copper frequently exceeds 1 ppm, a large fraction of the copper may be in the form of free cupric ion, and uptake will result by ingestion and, perhaps, dermal contact. Soluble cupric salts are used extensively in agriculture and in water treatment. Workers engaged in the formulation and application of these chemicals and industrial workers, such as those in the plating industry, may come into dermal contact with these chemicals. Exposure to high levels of free Cu(II) may occur, for example, from swimming in water that has been recently treated with a copper-containing algicide.

Based on the available data, people living close to NPL sites may be at greater risk for exposure to copper than the general population. In this case, exposure can occur through inhalation of airborne particulates from the NPL sites, ingestion of water from private wells which are in close proximity to the sites,

ingestion of contaminated soil, and/or uptake of copper into fruits and vegetables raised in gardens of residents living near NPL sites.

People living near copper smelters and refineries and workers in these and other industries may be exposed to high levels of dust-borne copper by both inhalation and ingestion. In some industries, workers may be exposed to fumes or very fine dust that may be more hazardous than coarse-grained dust, because it can be inhaled more deeply into the lung, thereby evading the mucocilliary escalator.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of the ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to pursue assessment of the adequacy of the available information on the health effects of copper. Where adequate information is not available, the ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of copper.

The following categories of possible data needs have been identified by a joint team of scientists from the ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce uncertainties of regarding human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized and a refined substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. In general, the available data on the physical and chemical properties of elemental copper and copper sulfate are sufficient for estimating their environmental fate. That no numerical value is listed for the water solubility of copper in Table 4-3 is of no special significance. For inorganic salts, the solubility product coupled with stability constants for the ionic species in solution are the factors determining how much of a compound goes into solution (i.e., the concentration). The solubility products and stability constants for copper that are required for determining the copper species in natural water and their concentrations are known (Schnoor et al. 1987; Town and Filella 2000). Although no K_{oc} values are listed, copper binds very strongly to organic matter, and values for the binding constants and solubility products to humic acids are available (Schnoor et al.

1987). Similarly, there are binding constants and solubility products for other species that bind or coprecipitate with copper, such as clay minerals and iron and manganese oxides (Schnoor et al. 1987). Binding constants for copper in specific natural waters are also available (Town and Filella 2000). Other physical and chemical properties in Table 4-3 for which there is no data are not well defined for these copper compounds.

In general, experimental confirmation is required for predicting copper's fate in the environment. The factors which determine the copper species present or the material to which copper may be bound and the strength of the binding can be site specific. If the level of detail requires knowledge of, for example, the percentage of copper associated with iron oxides or that which is easily exchangeable, experimental confirmation is necessary.

Production, Import/Export, Use, Release, and Disposal. Information on the production, use, release, and disposal of copper is used for evaluating the potential for exposure of people to copper who live or work near waste sites and other sources. Copper exposure is widespread; but much of this exposure is to generally benign forms, such as metallic copper. The information available often does not distinguish between these forms and those of greater toxicological significance.

Information on the production, use, release, and disposal of metallic copper and copper sulfate is generally available. These two forms of copper account for most of the copper used. This information is tabulated by the U.S. Geological Survey every year in the Minerals Yearbook and predictions of future trends in production and use are available. Such information is not available for other copper compounds. We also know the major uses of copper and where these uses occur (e.g., the home, workplace, etc.).

According to the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The TRI contains release information for copper and copper compounds and is updated yearly.

For disposal, industrial waste copper is generally either recycled or landfilled. Data on secondary copper production (i.e., copper produced from scrap) is compiled by the U.S. Geological Survey. Effluent and disposal regulations for copper and its compounds are listed in the Clean Water Act and the Resource Conservation and Recovery Act (RCRA).

Environmental Fate. Reliable information on how copper and its compounds partition in the environment (i.e., to soil and sediment), and the type of transformations that occur in different media, is available from over 35 published studies included in this chapter. We also have data concerning its transport in the environment from over 50 reliable studies. Although information on the fate of copper in air, water, and soil is available, the fate of copper is both species- and site- specific. Information concerning the forms of copper (i.e., specific compound, to what it is bound or complexed, or, in the case of air, the particle size) or the lability of the copper in particular media is available from only a few, -yet reliable, studies. These are sufficient to identify numerous contributors to the fate of copper and its compounds; but are insufficiently comprehensive for developing accurate fate maps. In addition, studies of how fate data relate to human exposures, especially in regard to projecting copper toxicity in children, is inadequate.

Bioavailability from Environmental Media. Copper is found in food, water, ambient air, and soil. The bioavailability of copper from food and water has been investigated in animals and humans. No information on the availability of copper from air was located. Copper in air originating from smelter sites is predominantly associated with sulfur, and presumably exists as the sulfate. Copper dust from soil in general as well as around mining and smelter sites may occur in ore dust or a silicate. No information was located on the bioavailability of copper in air. Copper in soil often is bound to organic molecules. Therefore, the bioavailability of the copper from soil cannot be assessed based on bioavailability information from drinking water or food studies. Studies on the bioavailability of copper from soil and ambient air would be useful in assessing potential toxicity to people living near a hazardous waste site.

The form and lability of copper in the environment is known in only a few site-specific cases. None of these cases include hazardous waste sites. More information on the forms of copper found at industrial sites and hazardous waste sites would be useful, especially since data from the Hazardous Substances Data Bank (HSDB) indicate that concentrations of copper as high as 182,000 ppm in soil and 14,000 ppm in sediments have been measured offsite of listed NPL sites (HazDat 2002). Monitoring groundwater near industries that use highly acid, copper-containing solutions, such as electroplating, electrowinning, and ore leaching industries, is important for the protection of human populations at risk of exposure to their highly mobile and highly bioavailable copper to human risk populations.

Food Chain Bioaccumulation. Because copper occurs in different forms in the environment, its bioaccumulation is expected to vary according to site and species. Data are available on the bioconcentration of copper in aquatic organisms, plants, and animals, as well as biomagnification in food

chains. This information is useful in assessing the potential for exposure from ingesting food originating from contaminated areas. However, little information is available on the potential for intoxication from foodstuffs from apparently nonpolluted areas or where they may have accumulated toxic levels of copper through biomagnification resulting from foraging in polluted areas.

Exposure Levels in Environmental Media. Data are available regarding the concentrations of copper in environmental media, including the concentration of copper in soil at some hazardous waste sites. Since copper is naturally present in soil, trace quantitative analytical and statistical techniques can be used to determine whether the copper found at these sites is elevated above normal levels. Monitoring data are reasonably current and human intake of copper from food, water, and air can be estimated.

Exposure Levels in Humans. There are reasonably current data on levels of copper in human tissue and human milk. Although information on copper concentrations in individuals exposed within specific work settings is increasing (for example, Gerhardsson et al. 1993; Saltzman et al. 1990), none of the studies address specific U.S. populations living around hazardous waste sites. There are some quantitative data relating occupation, level and route of exposure to the form of copper to which people are exposed. There is some limited information correlating copper concentration and form to body burden in the general population. However, more information is needed for occupational and other at-risk populations.

Exposures of Children. Reasonably current data report levels of copper intake in infants and children. Information on copper intake by infants from human milk also is available. Exposure of children to copper in drinking water has been assessed and methods to decrease this exposure have been identified and implemented. However, only limited information on inhalation and ingestion is available. Some information on exposure of children to copper near mining, smelting, refining, manufacture facilities, waste sites and other hazardous sites is available; but not for U.S. populations. This information is needed to better estimate exposures of children in U.S. populations living near these facilities and sites. The use of copper concentrations in toenails and hair has been investigated as a surrogate measure of copper exposure in children and adults and more research into establishing the validity of these surrogates is underway.

Child health data needs relating to susceptibility are discussed in Section 3.12.2 Identification of Data Needs: Children’s Susceptibility.

Exposure Registries. No exposure registries for copper and its compounds were located. No subregistry has currently been established for these chemicals. They will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates epidemiological research needed to assess adverse health outcomes that may be related to the exposure to these chemicals.

6.8.2 Ongoing Studies

Ongoing studies of copper in soils, sediments and aquifers have been identified and are listed in Table 6-15. Also included in Table 6-15 are ongoing investigations of human exposures to copper.

Table 6-15. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Copper

Investigator	Affiliation	Research description	Sponsor[a]
Gardea-Torresdey J	Stanford University	Uptake of copper and lead into creosote bushes in regions with heavy metal contamination	National Center for Research Services
Naqvi SM	Southern University A&M	Bioaccumulation and biomagnification of copper in crayfish	National Institute of General Medical Sciences
Conklin MH	University of Arizona College of Pharmacy	Characterization of abandoned mine sites and mine wastes in Arizona; assess stability of these sites to emission of copper and other metals to surface waters	National Institute of Environmental Health Sciences
Sparks DL	University of Delaware	Influence of aging and competitive sorption on stabilization of metals through surface precipitates in soils	CSREES Delaware
Reeve AS	University of Maine	Use of stable isotope tracing techniques to determine the source of salts in Maine groundwater, including copper	CSREES Maine
Welch RM	Agricultural Research Service, Ithaca, New York	Study the soil chemistry, distribution, and bioavailability to crops of health-related elements (e.g., Fe, Zn, Ca, Se, Cd, B) and their movement into edible plant parts.	ARS
Ahner BA	Cornell University	Determine the nature and source of organic ligands in marine waters to better understand the cycling and bioavailability of Cu and Fe.	SAES New York
Hesterberg DL	North Carolina State University	Determine the significance of heavy-metal sulfides (and other stable chemical species) for reducing the mobility and bioavailability of potentially-toxic metals in complex clay-organic systems.	CSREES North Carolina

Table 6-15. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Copper

Hunt JR	Agricultural Research Center, Grand Forks, North Dakota	Determine how changes in the U.S. diet may affect nutritional status, with emphasis on intakes and bioavailabilities of iron, zinc, copper, and selenium	ARS
Zelazny LW	Virginia Polytechnic Institute	Determine and compare the quantity, chemical forms, and plant available levels of P, Cu, and Zn from manures treated with phytase after reacting with selected soils for various time periods	CSREES Virginia

Source: CRIS 2003; FEDRIP 2003

[a]ARS = Agricultural Research Service; CSREES = Cooperative State Research, Education, and Extension Service; SAES = State Agricultural Research Station–Multistate Research Projects

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring copper, its metabolites, and other biomarkers of exposure to and affects of copper. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Analytical methods and detection limits for copper in biological materials are given in Table 7-l. Copper in other biological materials such as hair and nails can be determined by using suitable procedures for dissolving the sample matrix and employing the same analytical techniques as with blood and tissue. These methods determine the total amount of copper in the sample. The methodology for analyzing biological material is similar to that used for environmental samples. The most commonly employed methods use atomic adsorption spectroscopy (AAS) or inductively coupled plasma-atomic emission spectroscopy (ICP-AES) (Araki et al. 1990; Lo and Araki 1989; Lopez-Artiguez et al. 1993). Differential-pulse anodic stripping voltammetry techniques have also been used to quantify copper in urine, yielding detection limits of 0.041 µg/L and an accuracy of 97% (Horng 1996).

7.2 ENVIRONMENTAL SAMPLES

Analytical methods and detection limits for copper in environmental media are given in Table 7-2. Analytical methods determine the total copper content of the samples. Determining specific copper compounds and complexes in samples is difficult. The most common methods used for environmental samples are AAS, either flame or graphite furnace, ICP-AES, and inductively coupled plasma-mass spectrometry (ICP-MS). Water and waste water samples can be analyzed for copper by EPA Test Method 200.1 (flame atomic absorption), 200.7 ICP-AES, or EPA Test Method 200.9 (temperature

Table 7-1. Analytical Methods for Determining Copper in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood or tissue	Acid digestion	Method 8005[a]; ICP-AES	1 µg/100 mL blood; 0.2 µg/g tissue	Not available	NIOSH 1987
Urine	Filter and polydithio-carbamate resin collection followed by low temperature plasma ashing or acid digestion	Method 8310[a]; ICP-AES	0.1 µg	Not available	NIOSH 1987
Tissue	HNO_3 digestion	AAS/graphite furnace	0.25 µg/g wet weight	103.1±7.7% mean recovery; 8.2±6.9% mean difference in duplicates[b]; 0.01% accuracy	Lowe et al. 1985
Toenails	HNO_3 digestion	AAS/graphite furnace	0.6 µg/g	<5% within run precision; 3.5% day-to-day precision	Wilhelm et al. 1991

[a]Simultaneous, multielemental analysis, not compound specific.
[b]Mean±1 standard deviation

AAS = atomic absorption spectrometry; ICP-AES = inductively coupled plasma-atomic emission spectroscopy

Table 7-2. Analytical Methods for Determining Copper in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Filter collection on 0.8 mμ membrane filter and acid digestion	Method 730, ICP-AES	1 μg	No bias identified	NIOSH 1987
Air	Filter collection on 0.8 mμ membrane filter and acid digestion	Method 7029, AAS	0.05 μg	No significant bias	NIOSH 1987
Water, waste water	Acidify with 1:1 HNO_3 to a pH<2	Method 220.1, AAS/direct aspiration	20 μg/L	0.9–29.7% bias between 7.5 and 332 μg/L	EPA 1983
Water, waste water	Sample solutions should contain 0.5% HNO_3	Method 220.2, AAS/furnace technique	1 μg/L	Not available	EPA 1983
Water, waste water	Filter and acidify sample	Method 200.7 CLP-M ICP-AES	6 μg/L	Not available	EMMI 1997
Water, waste water	Digestion with H_2SO_4 and HNO_3	Neocuproine, spectrometric	120 μg/L in 1 cm cell	Not available	Greenberg et al. 1985
Waste water	Adjust pH to 1.65–1.85, mix, filter	Method 200.1, flame atomic absorption	4 mg/L	Not available	EMMI 1997
Water, waste water	Filter and acidify	Method 200.7_M, ICP-AES	25 μg/L	Not available	EMMI 1997
Groundwater, surface water, and drinking water	Filter and acidify	Method 200.8, ICP-MS	20 μg/L	Not available	EMMI 1997
Marine waters	Digest in HNO_3, concentrate on iminodi-acetate chelating resin, elute with 1.25 M HNO_3	Method 200.10, ICP-MS	7 μg/L	Not available	EMMI 1997
Marine waters, estuarine waters, seawaters, and brines	Digest in HNO_3, concentrate on iminodi-acetate chelating resin, elute with 1.25 M HNO_3	Method 200.13, GFAA	5 μg/L	Not available	EMMI 1997
Soil, sediment, sludge, and solid waste	Digestion with HNO_3 and H_2O_2, reflux with dilute HCl	Method 7210, AAS	20 μg/L	As in Method 220.1	EPA 1986

Table 7-2. Analytical Methods for Determining Copper in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Closed-system digestion	AAS or ASV	0.32 µg/g (ASV), not reported (AAS)	94–100	Holak 1983
Biological tissues	HNO_3 digestion, reaction with H_2O_2	Method 200.3, ICP-MS	18 µg/L	Not available	EMMI 1997
Fish tissue (fresh edible tissue)	Dissociate tissue in tetraammonium hydroxide, acidify with HNO_3	Method 200.11, ICP-AES	18 µg/L	Not available	EMMI 1997

AAS = atomic absorption spectrometry; ASV = anodic stripping voltammetry; GFAA = graphite furnace atomic absorption; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry

stabilized graphite furnace atomic absorption spectroscopy) (EMMI 1997). These methods are suitable for groundwater and surface water as well as domestic and industrial effluents. EPA Test Method 200.8 ICP-MS or EPA Test Method 200.15 ICP-AES are suitable for analysis of groundwater, surface water, and drinking water. EPA Test Method 200.8, EPA Test Method 200.10 (on-line chelation and ICP-MS), or EPA Test Method 200.13 (chelation and graphite furnace atomic absorption spectroscopy) are suitable for marine, estuary, and brine waters. If determination of dissolved and suspended copper is required, samples should be filtered using a 0.45 µm membrane filter. Suspended solids, as well as sludge and sediment, may be analyzed by EPA Methods 200.1 and 200.13 after an initial acid digestion with HNO_3. Interference by other elements is not a problem in the analysis. However, background correction may be required when using atomic absorption spectroscopy to correct for nonspecific absorption and scattering, which may be significant at the analytical wavelength, 324.7 nm (EPA 1986). In the determination of trace metals, major concerns are contamination and loss. Contamination can be introduced from impurities in reagents and containers as well as from laboratory dust. Losses may also occur due to adsorption onto containers.

Other analytical methods used for copper analysis include x-ray fluorescence, anodic stripping voltammetry, neutron activation analysis, photon-induced x-ray emission, as well as chemical derivatization, followed by gas chromatographic or liquid chromatographic analysis. Discussion of these methods is beyond the scope of this profile. However, methodology for the determination of copper has been reviewed by Gross et al. (1987) for food, by Fox (1987) for air, by MacCarthy and Klusman (1987) for water, and Lichte et al. (1987) for geological materials.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of copper is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of copper.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce certain uncertainties of human health assessment. This definition should not be interpreted to

mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods for determining background and elevated levels of copper in biological materials are well developed, sensitive, specific, and reliable. Standardized methods are available from NIOSH and other sources. The use of copper concentrations in toenails and hair has been investigated as surrogate markers of copper exposure, with validation studies currently underway.

Effect. No specific biomarkers of copper toxicity have been determined. Until such biomarkers are determined, the methodology needed to identify them cannot be established.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining background and elevated levels of copper in environmental media are well-developed, sensitive, and selective. Water is the medium of most concern, since the form of copper generally associated with health effects is soluble copper(II). Standardized methods of analysis for copper in air, water, soil, and food are available from EPA, NIOSH, and other sources. Analytical methods measure total copper. Therefore, the methods can not specifically analyze for a parent compound and a degradation product.

7.3.2 Ongoing Studies

Ongoing studies regarding new analytical methods for measuring copper in biological materials or environmental media were located in the literature. Dr. M. Longnecker at the National Institute of Environmental Health Sciences is working to validate toenail copper concentrations as a surrogate measure of exposure to copper. Development of high-performance liquid chromatography (HPLC) and derivatization techniques for identifying natural copper chelators in marine water is being conducted at Cornell University under the guidance of Drs. B.A. Ahner and J.W. Moffett. Dr. D.L. Sparks, at the University of Delaware, is developing x-ray absorption fine structure (XAFS) and atomic force microscopy (AFS) techniques for the study of metal/metalloid reactions in soil. Dr. J.F. Tyson and

colleagues at the University of Massachusetts at Amherst are developing liquid-liquid extraction pretreatment techniques that can be interfaced with HPLC-ICP-MS instrumentation.

8. REGULATIONS AND ADVISORIES

ATSDR has derived acute- and intermediate-duration oral MRLs for copper. These MRLs are intended to protect against the health effects associated with exposure to copper-contaminated drinking water; it assumes that the affected population will have a normal intake of copper from the diet. The acute-duration oral MRL is 0.01 mg copper/kg/day. It is based on the occurrence of gastrointestinal disturbances in women ingesting 0.0731 mg Cu/kg/day in drinking water for 2 weeks; no adverse effects were observed at a drinking water dose of 0.0272 mg Cu/kg/day (Pizarro et al. 1999). To calculate an MRL, the NOAEL of 0.0272 mg Cu/kg/day was divided by an uncertainty factor of 3 to account for human variability.

An intermediate-duration oral MRL of 0.01 mg copper/kg/day was derived for copper. This MRL is based on the occurrence of gastrointestinal disturbances in men and women ingesting 0.091 mg Cu/kg/day in drinking water for 2 months; no adverse effects were observed at a drinking water dose of 0.042 mg Cu/kg/day (Araya et al. 2003b). To calculate an MRL, the NOAEL of 0.042 mg Cu/kg/day was divided by an uncertainty factor of 3 to account for human variability.

International, national, and state regulations and guidelines regarding human exposure to copper are summarized in Table 8-1.

Table 8-1. Regulations and Guidelines Applicable to Copper

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2002
	Copper 8-hydroxyquinoline	Group 3[a]	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2001
	Fume (Cu)	0.2 mg/m^3	
	Dusts and mists (as Cu)	1.0 mg/m^3	
EPA	Serious health effects form ambient air exposure (Cu)		EPA 2002b 40CFR1910.1000
NIOSH	REL (10-hour TWA)		NIOSH 2002
	Fume (as Cu)	0.1 mg/m^3	
	Dusts and mists (as Cu)	1.0 mg/m^3	
	IDLH		
	Fume, dusts, and mists (as Cu)	100 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2002c 29CFR1910.1000
	Fume (as Cu)	0.1 mg/m^3	
	Dusts and mists (as Cu)	1.0 mg/m^3	
	PEL (8-hour TWA) for construction industry		OSHA 2002b 29CFR1926.55
	Fume (as Cu)	0.1 mg/m^3	
	Dusts and mists (as Cu)	1.0 mg/m^3	
	PEL (8-hour TWA) for shipyard industry		OSHA 2002a 29CFR1915.1000
	Fume (as Cu)	0.1 mg/m^3	
	Dusts and mists (as Cu)	1.0 mg/m^3	
b. Water			
DOT	Marine pollutant (Cu metal powder and cupric sulfate)		DOT 2002 49 CFR172.101, Appendix B
EPA	Drinking water standard		EPA 2002c
	Action level (Cu)	1.3 mg/L	
	MCLG (Cu)	1.3 mg/L	EPA 2002d 40CFR141.51(b)
	Groundwater monitoring (Cu)		EPA 2002g 40CFR264, Appendix IX
	Suggested method	PQL	
	6010	60 µg/L	
	7210	200 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Copper

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Hazardous substance in accordance with Section 311(b)(2)(A) of the Clean Water Act (cupric sulfate and cupric sulfate ammoniated)		EPA 2002j 40CFR116.4
	Reportable quantity of hazardous substance designated pursuant to Section 311 of the Clean Water Act		EPA 2002k 40CFR117.3
	Cupric sulfate	10 pounds	
	Cupric sulfate, ammoniated	100 pounds	
	Secondary MCL for public water systems (Cu)	1.0 mg/L	EPA 2002e 40CFR143.3
	Toxic pollutant designated pursuant to Section 307(a)(1) of the Federal Water Pollution Control Act and is subject to effluent limitations (Cu and compounds)		EPA 2002a 40CFR401.15
	Water quality criteria (Cu)		EPA 1999
	Fresh water		
	CMC	13.0 µg/L	
	CCC	9.0 µg/L	
	Salt water		
	CMC	4.8 µg/L	
	CCC	3.1 µg/L	
	Human health for consumption of water and organism	1,300 µg/L	
	Organoleptic effect criteria	1,000 µg/L	
c. Food and Drugs			
EPA	Exemption from requirement of a tolerance in meat, milk, poultry, eggs, fish, shellfish, and irrigated crops when it results from the use as an algaecide, herbicide, and fungicide when used in accordance with good agricultural practices (Cu)		EPA 2002f 40CFR180.1021
FDA	Bottled water; allowable level (Cu)	1.0 mg/L	FDA 2001a 21CFR165.110
	Clinical chemistry test system; copper test system measures copper levels in plasma, serum, and urine	Exempt from premarket notification procedures in Subpart E of Part 807	FDA 2001b 21CFR862.1190
	Color additives exempt from certification—copper powder for use in externally applied drugs	Cu not less than 95%	FDA 2001e 21CFR73.1647

Table 8-1. Regulations and Guidelines Applicable to Copper

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
FDA	Color additives exempt from certification—copper powder for use in cosmetics		FDA 2001f 21CFR73.2647
	Direct food substance affirmed as generally recognized as safe when used as a nutrient supplement or as a processing aid (cupric sulfate)		FDA 2001c 21CFR184.1261
	Drug products containing certain active ingredients offered over-the-counter; inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses (Cu)	Weight control drug product	FDA 2001g 21CFR310.545(a)(20)
	Trace minerals added to animal feeds as nutritional dietary supplements are generally recognized as safe when added at levels consistent with good feeding practices (Cu compounds)		FDA 2001i 21CFR582.80
IOM	Recommended dietary allowance (RDA)	0.9 mg/day	IOM 2001
	Tolerable upper intake level	10 mg/day	
d. Other			
EPA	Carcinogenicity classification (Cu)	Group D[b]	IRIS 2004
	RfC	No data	
	RfD	No data	
	Reportable quantity designated as a CERCLA hazardous substance under Section 307(a) of the Clean Water Act (Cu)	5,000 pounds	EPA 2002h 40CFR302.4
	Reportable quantity designated as a CERCLA hazardous substance under Section 311(b) (4) of the Clean Water Act (cupric sulfate)	10 pounds	EPA 2002h 40CFR302.4
	Toxic chemical release reporting; community right-to-know; effective date of reporting (Cu)	01/01/87	EPA 2002i 40CFR372.65(a)
STATE			
Regulations and Guidelines			
a. Air			
Illinois	Toxic air contaminant (Cu)		BNA 2001
Louisiana	Toxic air pollutant[c]		BNA 2001
	Minimum emission rate (Cu and compounds)	25 pounds/year	

Table 8-1. Regulations and Guidelines Applicable to Copper

Agency	Description	Information	Reference
STATE *(cont.)*			
New Mexico	Toxic air pollutant		BNA 2001
	Fume (Cu)		
	OEL	0.2 mg/m^3	
	Emissions	0.0133 pounds/ hour	
	Dusts and mists (as Cu)		
	OEL	1.0 mg/m^3	
	Emissions	0.0667 pounds/ hour	
Vermont	Cu compounds		BNA 2001
	Hazardous ambient air standard	100 µg/m^3	
	Averaging time	8 hours	
	Action level	4 pounds/hour	
b. Water			
Arizona	Drinking water guideline (Cu)	1,300 µg/L	HSDB 2004
North Carolina	Groundwater quality standard (Cu)	1.0 mg/L	BNA 2001
c. Food	No data		
d. Other			
Arizona	Soil remediation levels (Cu and compounds)		BNA 2001
	Residential	2,800 mg/kg	
	Non-residential	63,000 mg/kg	
Florida	Toxic substance in the workplace (Cu fume, dust, and mist)		BNA 2001

[a]Group 3: unclassifiable as to carcinogenicity to humans
[b]Group D: not classifiable as to human carcinogenicity
[c]Class II: suspected human carcinogen and known or suspected human reproductive toxin

ACGIH = American Conference of Governmental Industrial Hygienists; BNA = Bureau of National Affairs; CERCLA = Comprehensive Environmental Response Compensation and Liability Act; CFR = Code of Federal Regulations; CCC = criterion continuous concentration; CMC = criteria maximum concentration; Cu = copper; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IOM = Institute of Occupational Medicine; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limits; PQL = practical quantitation limits; RDA = recommended dietary allowance; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit value; TWA = time-weighted average

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD10 would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration(Lo) (LC_{Lo})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose(Lo) (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose(50) (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time(50) (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose(50) (TD50)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Copper and Compounds
CAS Number:
Date: September 8, 2004
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 11
Species: Humans

Minimal Risk Level: 0.01 [X] mg copper/kg/day [ ] ppm

Reference: Pizarro F, Olivares M, Uauy R, et al. 1999. Acute gastrointestinal effects of graded levels of copper in drinking water. Environ Health Perspect 107:117-121.

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): A group of 60 healthy women (mean ages of 32.9–36.3 years) were divided into four groups. Each group consumed water containing 0, 1, 3, or 5 mg/L ionic copper as copper sulfate (0.006, 0.0272, 0.0731, and 0.124 mg Cu/kg/day) for a 2-week period with a 1-week rest between copper exposures. Each week, the subjects received a bottle containing copper sulfate solution and were asked to mix the contents of the bottle with 3 L water; this water was then used for drinking and cooking. The subjects recorded daily water consumption and any symptoms. Blood samples were collected 1 week before the study, at the end of the first 2-week exposure period, and at the end of the study; the blood was analyzed for serum copper, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase activities, and hemoglobin levels. The average copper dietary intake, based on a 24-hour dietary recall, was 1.7 mg Cu/day (0.0266 mg Cu/kg/day using an average body weight of 64 kg).

Effects noted in study and corresponding doses: No significant alterations in serum copper, ceruloplasmin, hemoglobin, or liver enzymes were observed. Twenty-one subjects reported gastrointestinal symptoms, predominantly nausea. Nine subjects reported diarrhea with or without abdominal pain, no association between copper level and diarrhea was found. Six of these episodes of diarrhea occurred during the first week of the study independent of copper concentration. Twelve subjects reported abdominal pain, nausea, and/or vomiting; the incidences were 3/60, 1/60, 10/60, and 9/60 in the control, 0.0272, 0.0731, and 0.124 mg Cu/kg/day groups, respectively. There was a significant difference between in the incidences at concentrations of ≤1 mg/L (0.0272 mg/kg/day) versus ≥3 mg/L (0.0731 mg/kg/day). No other differences between groups were found.

Dose and end point used for MRL derivation: The MRL is based on the NOAEL of 0.0272 mg Cu/kg/day for gastrointestinal effects in women ingesting copper sulfate in drinking water for 2 weeks (Pizarro et al. 1999).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a extrapolation from animals to humans
[X] 3 for human variability; a partial uncertainty factor was used because toxicokinetic differences among individuals should not affect the sensitivity of this direct contact effect.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes. Daily doses of copper from drinking water were calculated using reported daily copper intakes (0.04, 1.74, 4.68, and 7.94 mg) and the average of the mean reported body weights (64 kg).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? No

Other additional studies or pertinent information that lend support to this MRL: Numerous experimental studies and case reports support the identification of the gastrointestinal tract as the most sensitive end point of toxicity in humans acutely exposed to copper in drinking water or in contaminated beverages (Araya et al. 2001, 2003a, 2003b, 2003c; Chuttani et al. 1965; Gotteland et al. 2001; Knobeloch et al. 1994; Nicholas and Brist 1968; Olivares et al. 2001; Pizarro et al. 1999, 2001; Spitalny et al. 1984). In single exposure experiments in which subjects ingested copper sulfate in drinking water following an overnight fast, nausea, vomiting, and/or abdominal pain were reported at doses ranging from 0.011 to 0.03 mg Cu/kg/day as copper sulfate (Araya et al. 2001, 2003a, 2003c; Gotteland et al. 2001; Olivares et al. 2001). NOAEL values identified in these studies ranged from 0.0057 to 0.011 mg Cu/kg. Daily exposure to 0.096 mg Cu/kg/day as copper sulfate or copper oxide for 1 week also resulted in an increased occurrence of nausea, vomiting, and/or abdominal pain (Pizarro et al. 2001). Animal studies support the identification of the gastrointestinal tract as the most sensitive target of toxicity following acute-duration oral exposure. Hyperplasia of the forestomach mucosa was observed in rats exposed to 44 mg Cu/kg/day as copper sulfate in the diet (NTP 1993) and in mice exposed to 197 mg Cu/kg/day as copper sulfate in the diet (NTP 1993). At higher doses, liver and kidney damage have been observed (Haywood 1980; Haywood and Comerford 1980; Haywood et al. 1985b; NTP 1993).

Although the LOAEL values identified in the single exposure studies are lower than the NOAEL identified in the Pizarro et al. (1999) study, the Pizarro et al. (1999) study was selected as the critical study because it is a longer-duration study and it more closely mimics an exposure scenario of a population drinking copper-contaminated drinking water.

Agency Contact (Chemical Manager): Alfred Dorsey, DVM

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Copper and Compounds
CAS Number:
Date: September 8, 2004
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to Figure: 21
Species: Humans

Minimal Risk Level: 0.01 [X] mg copper/kg/day [ ] ppm

Reference: Araya M, Olivares M, Pizarro F, et al. 2003b. Gastrointestinal symptoms and blood indicators of copper load in apparently healthy adults undergoing controlled copper exposure. Am J Clin Nutr 77:646-650.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 327–340 men and women (mean age 32.9 years) were exposed to 0, 2, 4, or 6 mg Cu/L in drinking water for 2 months. The subjects prepared the copper sulfate solution daily using tap water and a stock copper sulfate solution. The copper solution was used for drinking and preparation of beverages and soups. The subjects completed a daily survey on gastrointestinal and other symptoms. Blood samples were analyzed for a subset of 48–49 subjects for red blood cell copper, monocyte copper, serum copper, serum ceruloplasmin, superoxide dismutase, aspartate aminotransferase, alanine amino transferases, γ-glutamyltransferase, and hemoglobin levels. Reported copper intakes from water in the subset of subjects were 0, 42.5, 92.9, and 177.9 µmol/day (0, 2.7, 5.9, and 11.3 mg/day).

Doses were calculated using reported copper intakes for the subset of subjects and a reference body weight of 65 kg. 2 ppm: 2.7 mg Cu/day x 1/65 kg = 0.042 mg Cu/kg/day; 4 ppm: 5.9 mg/day = 0.091 mg Cu/kg/day; 6 ppm: 11.3 mg/day = 0.17 mg Cu/kg/day

Effects noted in study and corresponding doses: The incidences of gastrointestinal symptoms were 11.7, 15.3, 18.3, and 19.7% in the 0, 0.042, 0.091, and 0.17 mg Cu/kg/day groups, respectively. Using a chi-square test with Bonferroni correction, the incidence of gastrointestinal symptoms was significantly increased in the 0.17 mg Cu/kg/day group. However, if the Bonferroni correction was not used, the incidence was also significantly increased in the 0.091 mg Cu/kg/day group. Only one test is used to assess whether exposure to copper results in adverse gastrointestinal effects (reported symptoms); thus, the Bonferroni correction is not needed for this end point. No significant alterations in copper status parameters or biomarkers of liver disease were observed.

Dose and end point used for MRL derivation: The MRL is based on the NOAEL of 0.042 mg Cu/kg/day for gastrointestinal effects in men and women ingesting copper sulfate in drinking water for 2 months.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a extrapolation from animals to humans

[X] 3 for human variability; a partial uncertainty factor was used because toxicokinetic differences among individuals should not affect the sensitivity of this direct contact effect

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes. Daily doses were calculated using reported daily copper intakes (2.7, 5.9, and 11.3 mg) and a reference body weight of 65 kg.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? No

Other additional studies or pertinent information that lend support to this MRL: There are limited data on the intermediate-duration toxicity of copper in humans. The Araya et al. (2003b) is the only human study located that examined the gastrointestinal tract following intermediate-duration exposure to copper. A number of acute-duration studies (Araya et al. 2001, 2003a, 2003c; Gotteland et al. 2001; Nicholas and Brist 1968; Olivares et al. 2001) support the identification of the gastrointestinal tract as the sensitive target of toxicity in humans. An intermediate-duration study by Pratt et al. (1985) did not find alterations in serum biomarkers of liver damage (cholesterol and triglyceride levels and aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transferase, and lactate dehydrogenase activities) in seven adults administered 10 mg Cu/day (0.14 mg Cu/kg/day) as copper gluconate in a capsule for 12 weeks. Three intermediate-duration studies in infants also found no significant evidence of liver damage (Olivares et al. 1998; Zietz et al. 2003a, 2003b).

Numerous animal studies have examined the toxicity of copper following intermediate-duration oral exposure (Epstein et al. 1982; Fuentealba et al. 2000; Haywood 1980, 1985; Haywood and Comerford 1980; Haywood and Loughran 1985; Haywood et al. 1985a, 1985b; Kumar and Sharma 1987; NTP 1993; Rana and Kumar 1980). Most of these studies have focused on the liver and kidneys, with adverse effect levels of at least 100 times higher than the adverse effect level for gastrointestinal effects in humans. Gastrointestinal tract alterations were observed in rats and mice. Hyperplasia of the squamous mucosa on the limiting ridge separating the forestomach from the glandular stomach was observed in rats and mice exposed to 33 or 267 mg Cu/kg/day, respectively, as copper sulfate in the diet for 13 weeks (NTP 1993).

Agency Contact (Chemical Manager): Alfred Dorsey, DVM

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered

in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the

extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

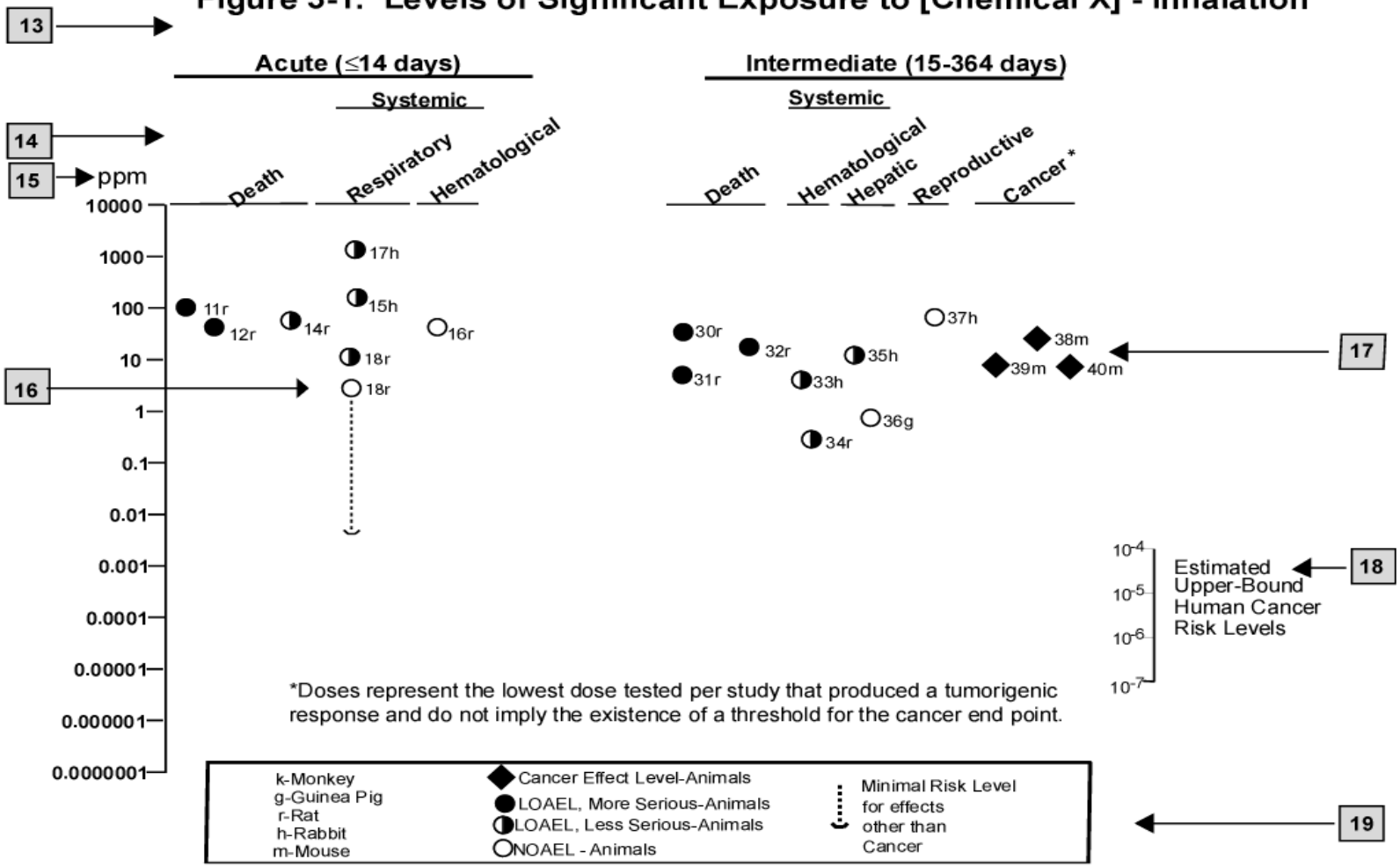
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/NA/IMCO	Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. INDEX

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TOXICOLOGICAL PROFILE FOR HEPTACHLOR and HEPTACHLOR EPOXIDE

Prepared by:

Syracuse Research Corporation
Under Contract No. 200-2004-09793

Prepared for:

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

November 2007

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Heptachlor/Heptachlor Epoxide, Draft for Public Comment was released in September 2005. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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Agency for Toxic Substances and
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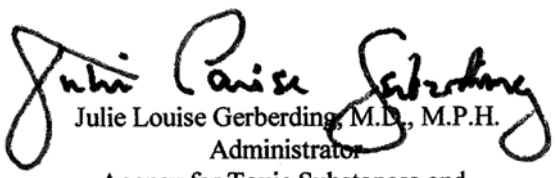

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The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014); and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for heptachlor and heptachlor epoxide. The panel consisted of the following members:

1. Richard Dickerson, Ph.D., DABT, Department of Pharmacology and Neuroscience and Department of Environmental Toxicology, Texas Tech University Health Sciences Center, Lubbock, TX;

2. Sam Kacew, Ph.D., Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada; and

3. James Klaunig, Ph.D., Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, IN.

These experts collectively have knowledge of heptachlor and heptachlor epoxide's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about heptachlor and heptachlor epoxide and the effects of exposure to them.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Heptachlor has been found in at least 210 of the 1,684 current or former NPL sites. Heptachlor epoxide has been found in at least 200 NPL sites. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that heptachlor and heptachlor epoxide may be found in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to these substances may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to heptachlor or heptachlor epoxide, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Heptachlor is a manufactured chemical that was used in the past for killing insects in homes, in buildings, and on food crops. It has not been used for these purposes since 1988. There are no natural sources of heptachlor or heptachlor epoxide. Trade names for heptachlor include Heptagran®, Heptamul®, Heptagranox®, Heptamak®, Basaklor®, Drinox®, Soleptax®, Gold Crest H-60®, Termide®, and Velsicol 104®. Heptachlor is both a breakdown product and a component of the pesticide chlordane (approximately 10% by weight). Pure heptachlor is a white powder.

Technical-grade heptachlor is a tan powder and has a lower level of purity than pure heptachlor. Technical-grade heptachlor was the form of heptachlor used most often as a pesticide. Heptachlor smells somewhat like camphor. Heptachlor does not burn easily and does not explode. It does not dissolve easily in water.

Like pure heptachlor, heptachlor epoxide is a white powder that does not explode easily. It was not manufactured and was not used as an insecticide like heptachlor. Bacteria and animals break down heptachlor to form heptachlor epoxide. This profile describes these two chemicals together because about 20% of heptachlor is changed within hours into heptachlor epoxide in the environment and in your body.

You might find heptachlor or heptachlor epoxide in the soil or air of homes treated for termites, dissolved in surface water or groundwater, or in the air near hazardous waste sites. You might also find heptachlor or its byproduct, heptachlor epoxide, in plants and animals near hazardous waste sites. Heptachlor can no longer be used to kill insects on crops or in homes and buildings. However, heptachlor is still approved by EPA for killing fire ants in buried power transformers, although it is unclear whether or not it is still being used for this purpose in the United States. More information on the chemical and physical properties of heptachlor and heptachlor epoxide is found in Chapter 4 of this document. More information on the production and use of heptachlor is found in Chapter 5.

1.2 WHAT HAPPENS TO HEPTACHLOR AND HEPTACHLOR EPOXIDE WHEN THEY ENTER THE ENVIRONMENT?

From 1953 to 1974, heptachlor entered the soil and surface water when farmers used it to kill insects in seed grains and on crops. It also entered the air and soil when homeowners and professional insect exterminators used it to kill termites. Today, heptachlor is no longer used by homeowners to kill termites or other insects. However, exterminators can still use existing stocks of heptachlor to kill fire ants in underground power transformers.

Heptachlor and heptachlor epoxide can enter the air, soil, groundwater, and surface water from leaks at hazardous waste sites or landfills. Heptachlor sticks to soil very strongly and evaporates

slowly into the air. Heptachlor does not dissolve easily in water. Heptachlor epoxide dissolves more easily in water than heptachlor does and evaporates slowly from water. Like heptachlor, heptachlor epoxide sticks to soil.

Both heptachlor and heptachlor epoxide can travel long distances in the wind from places where they are released, such as treated fields or manufacturing sites. In soil and water, heptachlor is changed by bacteria into the more harmful substance, heptachlor epoxide, or into other less harmful substances. Plants can absorb heptachlor through their roots from the soil. Heptachlor in the air can be deposited on plant leaves and enter the plant from contaminated soil.

Animals that eat plants containing heptachlor can also absorb it. Animals can also change heptachlor to heptachlor epoxide in their bodies. Heptachlor epoxide breaks down very slowly in the environment. It can stay in soil and water for many years. Both heptachlor and heptachlor epoxide build up in fish and in cattle. People store heptachlor epoxide in their fatty tissue. Some studies show that heptachlor epoxide can still be measured in fatty tissue 3 years after a person is exposed to it.

Most of the breakdown products of heptachlor are thought to be less harmful than heptachlor itself. However, in laboratory animals, heptachlor epoxide is more harmful than heptachlor. For more information on heptachlor and heptachlor epoxide in the environment, see Chapters 5 and 6.

1.3 HOW MIGHT I BE EXPOSED TO HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Exposure to heptachlor and heptachlor epoxide most commonly occurs when you eat food contaminated with those chemicals. Contaminated foods might include fish, shellfish (such as clams), dairy products, meat, and poultry. Children and toddlers drink large amounts of milk and may have greater exposure if the milk is contaminated with heptachlor or heptachlor epoxide. Infants can be exposed to these compounds from drinking breastmilk or cow's milk.

Exposure can also occur when you drink water, breathe air, or touch contaminated soil at hazardous waste sites that contain heptachlor or heptachlor epoxide. People whose homes have been treated with heptachlor to kill termites can be exposed by breathing heptachlor in the air. After heptachlor is changed to heptachlor epoxide in the soil, it can get into the air. People who breathe this air will be exposed to heptachlor epoxide. Workers who use heptachlor to kill fire ants are exposed if they breathe in the heptachlor or get it on their skin.

Background levels of a substance are levels found in the environment that cannot be traced to a specific source. Information on background levels of heptachlor and heptachlor epoxide in the air was not found. In one survey, the background levels of heptachlor in drinking water and groundwater in the United States ranged from 20 to 800 parts of heptachlor in one trillion parts of water (ppt). Heptachlor was found in less than 2% of U.S. groundwater samples that are known to be contaminated from pesticide application. The average level of heptachlor in the contaminated groundwater samples was 800 ppt. No information was found for levels of heptachlor epoxide in groundwater or drinking water. Heptachlor epoxide has been found in surface water (river, lakes) at levels between 0.1 and 10 parts of heptachlor epoxide in one billion parts of water (ppb, 1 ppb is 1 thousand times more than 1 ppt).

Heptachlor and heptachlor epoxide stick to sediment and soil. Sediment in stream beds is likely to contain a lot of the heptachlor that enters the water. Heptachlor and heptachlor epoxide were found in less than 0.7 and 1.8% of river bed sediments that were tested from 2003 to 2005. Contaminated fish and shellfish have been found to contain 2–750 ppb heptachlor and 0.1–480 ppb heptachlor epoxide. Heptachlor epoxide has been found in human milk samples at levels ranging from 0.13 to 128 ppb. See Chapter 6 for more information on how you might be exposed to heptachlor and heptachlor epoxide.

1.4 HOW CAN HEPTACHLOR AND HEPTACHLOR EPOXIDE ENTER AND LEAVE MY BODY?

When you breathe air containing heptachlor or heptachlor epoxide, both can enter your bloodstream through your lungs. It is not known how fast these compounds enter and remain in the bloodstream. Both heptachlor and heptachlor epoxide can also enter your body through your

stomach after you eat food or drink water or milk containing them. Most of the heptachlor that is swallowed passes through your stomach into your blood. It can also enter your body through your skin. Heptachlor and heptachlor epoxide can pass directly from a mother's blood to an unborn baby through the placenta. It can also pass from the mother to an infant through breast milk.

Once inside your body, heptachlor is changed to heptachlor epoxide and other related chemicals. Most of the heptachlor, heptachlor epoxide, and other breakdown products leave your body in the feces within a few days after exposure. Some breakdown products can also leave in the urine. Some heptachlor and heptachlor epoxide are stored in your body fat for long periods after exposure has occurred. The heptachlor and heptachlor epoxide that have been stored in fat leave your body much more slowly. Chapter 3 contains more information on how heptachlor and heptachlor epoxide can enter and leave the body.

1.5 HOW CAN HEPTACHLOR AND HEPTACHLOR EPOXIDE AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

People can begin to smell heptachlor or heptachlor epoxide at around 0.3 milligrams in a cubic meter of air (0.3 mg/m^3). No reliable studies in humans were found that show whether harmful health effects occur as a result of breathing heptachlor or heptachlor epoxide. No animal studies

examining the harmful effects resulting from breathing air that contains heptachlor or heptachlor epoxide were found.

In addition, no reliable human studies were found that show whether harmful effects occur from eating contaminated foods or by drinking liquids contaminated with heptachlor or heptachlor epoxide. Studies have shown a number of harmful health effects when animals were fed heptachlor or heptachlor epoxide. These effects were more harmful when the exposure levels were high or when exposure lasted many weeks. The effects observed in animals include damage to the liver, excitability, and decreases in fertility.

Animals fed heptachlor throughout their lifetime had more liver tumors than animals that ate food without heptachlor. EPA and the International Agency for Research on Cancer have classified heptachlor as a possible human carcinogen. EPA also considers heptachlor epoxide as a possible human carcinogen.

Chapter 3 contains more information on the adverse health effects of heptachlor and heptachlor epoxide.

1.6 HOW CAN HEPTACHLOR AND HEPTACHLOR EPOXIDE AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Some studies in animals suggest that young animals exposed during gestation and infancy may be very sensitive to heptachlor and heptachlor epoxide. Changes in nervous system and immune function were found in these animals. There is some evidence that similar effects may occur in humans, but a study that found some changes in performance on some tests that measure nervous system function is not conclusive and exposure to other chemicals cannot be ruled out. Exposure to higher doses of heptachlor in animals can also result in decreases in body weight and death in animal newborn babies.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO HEPTACHLOR AND HEPTACHLOR EPOXIDE?

If your doctor finds that you have been exposed to substantial amounts of heptachlor and heptachlor epoxide, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

Heptachlor is no longer used in the United States except to control fire ants; therefore, exposure should be limited. Before the use of heptachlor was cancelled in 1988, it was used on various agricultural crops, in homes for the treatment of termites, and in power lines for fire ant control. However, because of the persistence of both heptachlor and heptachlor epoxide, exposure to the general population can occur from contaminated water, soil, and air. People who live in homes where heptachlor was used for termite control or on farms where heptachlor was used on crops may have a higher risk of exposure through contaminated crops, soil, water, and air. To avoid exposure from contaminated soil, you should discourage your children from eating or playing with dirt near home or barn foundations. Make sure they wash their hands frequently and before eating. Discourage children from putting their hands in their mouths or other hand-to-mouth activities.

Heptachlor and heptachlor epoxide are also persistent in food and milk. Eating fish from contaminated water can increase exposure to heptachlor. Avoid eating fish from contaminated water. Local fishing advisories can tell you if the water is contaminated.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Laboratory tests can detect heptachlor and heptachlor epoxide in blood, fat, breast milk, and body tissues after exposure to high levels of these chemicals. These tests are not commonly available at your doctor's office. Most often, the test for heptachlor epoxide is used because heptachlor is quickly changed into heptachlor epoxide in your body. Blood samples are used most often because they are easy to collect. These tests are specific for heptachlor and heptachlor epoxide. However, heptachlor is both a breakdown product and a component of

chlordane, another pesticide. So if heptachlor and heptachlor epoxide are measured in the blood, the actual exposure could have been to chlordane. Methods for measuring heptachlor and heptachlor epoxide in body fat are more precise and can detect lower levels than tests that measure levels in blood. If heptachlor or heptachlor epoxide is found in your blood or fat, it is not possible to tell when you were exposed to these chemicals or if harmful health effects will occur. See Chapters 3 and 7 for more information on detecting these chemicals in the environment or in human tissues.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as “not-to-exceed” levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for heptachlor and heptachlor epoxide include the following:

For exposures of up to 10 days, EPA recommends that a child weighing 22 pounds or less not drink water containing more than 0.01 mg heptachlor or heptachlor epoxide per liter of water (0.01 mg/L or 0.01 ppm). EPA requires that drinking water should not contain more than 0.0004 mg/L (0.0004 ppm) heptachlor and 0.0002 mg/L (0.0002 ppm) of heptachlor epoxide.

FDA controls the amount of heptachlor and heptachlor epoxide on raw food crops and on edible seafood. The limit for most food crops is 0.01 parts heptachlor per million parts food (0.01 ppm). The limit in milk is 0.1 parts heptachlor per million parts of milk fat. The limit on edible seafood is 0.3 ppm.

OSHA has set a limit of 0.5 mg/m^3 for heptachlor in workplace air over an 8-hour workday for a 40-hour workweek. For more information on standards and guidelines for heptachlor and heptachlor epoxide, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfilesTM CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO HEPTACHLOR AND HEPTACHLOR EPOXIDE IN THE UNITED STATES

Heptachlor is a polychlorinated cyclodiene insecticide that was extensively used prior to 1970 to kill termites, ants, and soil insects in seed grains and on crops. In 1983, the manufacturers voluntarily cancelled its registered uses, with the exception of termite and fire ant control. Currently, the only permitted use of heptachlor is for fire ant control in buried power transformers; however, there are no actively registered pesticides containing heptachlor as an active ingredient. Heptachlor epoxide is the primary degradation product of heptachlor. Heptachlor epoxide is more persistent in the environment than heptachlor and biomagnifies in the terrestrial food chain. Although the use of heptachlor is restricted, exposure to the general population can occur through the ingestion of contaminated food, inhalation of vapors from contaminated soil and water, and dermal contact with contaminated soil and water. The food classes most likely to contain residues are milk and other dairy products, vegetables, meat, fish, and poultry.

2.2 SUMMARY OF HEALTH EFFECTS

There are limited data on the toxicity of heptachlor or heptachlor epoxide following inhalation or dermal exposure. Most of the available information on the toxicity of heptachlor comes from oral exposure studies in laboratory animals, although some human data have been identified. Oral exposure of laboratory animals to heptachlor results in a variety of adverse effects including liver effects, neurological effects, reproductive system dysfunction, and developmental effects. Although there are very few studies involving exposure to heptachlor epoxide, it is likely that the effects resulting from heptachlor exposure are due to its metabolism to heptachlor epoxide. Several human studies have examined the possible relationship between increased serum levels of heptachlor or heptachlor epoxide and adverse health outcomes. Most of these studies involved exposure to a variety of organochlorine pesticides and the observed effects cannot be ascribed to heptachlor. Additionally, a small number of studies have examined populations consuming milk products from cows fed heptachlor-contaminated feed. In these types of studies, there is a greater degree of certainty in attributing the observed effects to heptachlor exposure.

In mature animals, liver and neurological effects appear to have similar thresholds of toxicity. Acute- or intermediate-duration exposure of rats or mice to 5–10 mg/kg/day has resulted in a variety of liver effects

including increases in serum alanine aminotransferase activity, necrosis, hepatocytomegaly, hepatitis, and increased liver weights. These studies suggest that the severity of the hepatic lesions is related to the duration of exposure. No alterations in serum liver enzyme activity levels or hepatocytomegaly incidence were observed in individuals exposed to heptachlor and heptachlor metabolites in contaminated milk products. Neurological alterations indicative of excitability and increased arousal were observed in rats exposed to 7 mg/kg/day for an acute duration and mink exposed to 1.7 or 6.2 mg/kg/day for an intermediate duration. At higher doses (17 mg/kg/day), mice exhibited difficult standing, walking, and righting. Seizures have also been observed in mink prior to death.

The reproductive system may be a more sensitive target of heptachlor toxicity than the liver or nervous system. A decrease in fertility and an increase in resorptions were observed in female rats acutely exposed to 1.8 mg/kg/day. Exposure of males to 0.65 mg/kg/day for 70 days resulted in decreased epididymal sperm count and increased resorptions when the males were mated with untreated females. In contrast, two acute studies involving exposure to 10 mg/kg/day heptachlor, 8 mg/kg/day heptachlor epoxide, or 15 mg/kg heptachlor/ heptachlor epoxide mixture did not find dominant lethal effects. Reduced fertility has also been observed in mice exposed to 8.4 mg/kg/day.

The available data provide suggestive evidence that the developing organism is the most sensitive target of heptachlor toxicity. Increases in pup mortality have been observed at doses of 5.0 mg/kg/day and higher in rats and at 1.7 mg/kg/day in mink; these doses were also associated with serious maternal toxicity. Decreases in pup body weight have also been observed at 4.5 mg/kg/day and higher. Heptachlor does not appear to increase the occurrence of anomalies or malformations. Perinatal and postnatal exposure adversely affected the development of the nervous and immune systems; the lowest-observed-adverse-effect level (LOAEL) for these effects is 0.03 mg/kg/day. No adverse effects were observed in the developing reproductive system. Studies of a population exposed to heptachlor-contaminated milk products found similar effects to those reported in animals. The risk of fetal or neonatal deaths, low birth weight infants, or major congenital malformations was not significantly altered. However, alterations in neurobehavioral performance were found when the children of women exposed to contaminated milk products reached high school. In particular, abstract concept formation, visual perception, and motor planning were adversely affected.

The carcinogenicity of heptachlor and heptachlor epoxide has been evaluated in a number of human studies. In general, these studies have examined possible associations between heptachlor and/or heptachlor epoxide tissue levels or a surrogate of heptachlor exposure and the prevalence of cancer.

Mixed results have been reported across tumor types and within tumor types. Interpretation of the studies is limited by the lack of information on heptachlor exposure, variables that may affect organochlorine levels (including diet and body mass index), and possible concomitant exposure to other chemicals. Increases in the incidence of hepatocellular carcinoma were observed in mice exposed to 2.4 mg/kg/day heptachlor and higher for 2 years, but not in rats exposed to 2.6 mg/kg/day and higher. The EPA has classified heptachlor and heptachlor epoxide in group B2 (probable human carcinogen) and the International Agency for Research on Cancer (IARC) considers heptachlor as possibly carcinogenic to humans (Group 2b). EPA has derived an oral slope factor of 4.5 per (mg/kg)/day for heptachlor and 9.1 per (mg/kg)/day for heptachlor epoxide. These slope factors correspond to drinking water unit risk levels of $1.3x10^{-4}$ and $2.6x10^{-4}$ per (µg/L), respectively.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for heptachlor. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990b), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

Data on the toxicity of heptachlor or heptachlor epoxide following inhalation exposure are limited to several mortality studies of pesticide applicators or manufacturers (Blair et al. 1983; MacMahon et al.

1988; Shindell and Associates 1981; Wang and MacMahon 1979a) and a case control study examining the possible association between organochlorine pesticide exposure and aplastic anemia (Wang and Grufferman 1981). No significant associations were found. Interpretation of the results are limited by co-exposure to other organochlorine pesticides and lack of monitoring data. No inhalation exposure animal studies were identified.

The available inhalation data are considered inadequate for the development of MRLs for heptachlor and heptachlor epoxide.

Oral MRLs

Heptachlor.

- An MRL of 0.0006 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to heptachlor.

A number of studies have examined the toxicity of heptachlor following acute-duration oral exposure; many of the toxicity studies are limited by the lack of statistical analysis and poor reporting of the observed effects, including incidence data. Despite the limitations in the studies, the acute database does identify several targets of toxicity including the liver, nervous system, reproductive capacity, and the developing offspring. Although some other adverse health effects have been reported, they have not been replicated in other studies or were observed at lethal doses. The most sensitive effect following acute-duration exposure appears to be a decrease in fertility and an increase in resorptions observed in female rats administered via gavage 1.8 mg/kg/day heptachlor in groundnut oil for 14 days prior to mating (Amita Rani and Krishnakumari 1995). Gestational exposure to 4.5 or 6.8 mg/kg/day resulted in decreases in pup body weight (Narotsky and Kavlock 1995; Narotsky et al. 1995); a decrease in pup righting reflex was also observed at 4.2 mg/kg/day (Purkerson-Parker et al. 2001b). At twice these dose levels, an increase in pup mortality was observed (Narotsky et al. 1995; Purkerson-Parker et al. 2001b). Liver effects were observed at doses similar to those resulting in developmental effects. Increases in serum alanine aminotransferase and aldolase activity levels, hepatocytomegaly, and minimal monocellular necrosis were observed in rats administered 7 mg/kg/day heptachlor in oil for 14 days (Berman et al. 1995; Krampl 1971). Exposure to 7 mg/kg/day also resulted in excitability and increased arousal in rats administered heptachlor in oil via gavage for 1 or 14 days (Moser et al. 1995).

The lowest LOAEL identified in the acute-duration oral database is 1.8 mg/kg/day for reduced fertility and an increase in resorptions in female rats (Amita Rani and Krishnakumari 1995). In this study, groups of 30 female CFT-Wistar rats received gavage doses of heptachlor in groundnut oil for 14 days (presumably 7 days/week). The total administered doses were 25 and 50 mg/kg body weight and the daily doses were 1.8 and 3.6 mg/kg/day. A vehicle control group was also used. After 14 days of exposure, the animals were mated with unexposed male rats. A significant decrease in the number of pregnant females (56.3 and 44.4%) and increase in the number of resorptions (18.90 and 11.40%) were observed in both groups of heptachlor-exposed rats. Significant decreases in estradiol-17beta and progesterone levels were also observed in the 1.8 mg/kg/day group. No alterations in the number of implantations were observed. The investigators noted that focal necrosis was observed in the liver; however, they did not note at which dose level and no incidence data were provided. This LOAEL of 1.8 mg/kg/day was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from rats to humans, and 10 for human variability) and a modifying factor of 3 to account for the use of a serious end point, resulting in an acute-duration oral MRL of 0.0006 mg/kg/day.

- An MRL of 0.0001 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to heptachlor.

Intermediate-duration oral exposure studies have identified a number of targets of heptachlor toxicity including the liver, nervous system, reproductive system, and the developing offspring. Other less documented effects have also been observed. In the absence of maternal toxicity, heptachlor is not associated with alterations in pup mortality or body weight gain (Lawson and Luderer 2004; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001). Additionally, gestational exposure does not appear to result in significant alterations in the occurrence of anomalies or abnormalities (Narotsky et al. 1995; Smialowicz et al. 2001) or the development of the reproductive system (Lawson and Luderer 2004; Smialowicz et al. 2001). *In utero* exposure followed by postnatal exposure (until postnatal day 42) did not alter reproductive function (Smialowicz et al. 2001), but did adversely affect neurobehavioral performance (Moser et al. 2001) and immune function (Smialowicz et al. 2001). The neurological effects included impaired spatial memory at 0.03 mg/kg/day and higher, impaired spatial learning at 0.3 or 3 mg/kg/day, and decreased righting reflex (Moser et al. 2001; Purkerson-Parker et al. 2001b) and increased open field activity (Moser et al. 2001) at 3 mg/kg/day. When the exposure was terminated at postnatal day 21, rather than postnatal day 42, spatial memory and learning were not adversely affected (Moser et al. 2001). The difference in results may have been due to higher heptachlor epoxide body burden in rats exposed to postnatal day 42, testing at different ages, or exposure may have occurred during a critical window of vulnerability. The effects observed in rats are consistent with those observed

in humans. Impaired performance on several neurobehavioral tests, including abstract concept formation, visual perception, and motor planning, was observed in high school students presumably prenatally exposed to heptachlor from contaminated milk products (Baker et al. 2004b). Alterations in immune function were also observed in the rats exposed until postnatal day 42. At 0.03 mg/kg/day and higher, suppression of the immune response to sheep red blood cells was observed (Smialowicz et al. 2001). A reduction in the percentage of B lymphocytes was also observed in the spleen of rats exposed to 3 mg/kg/day. Other tests of immune function were not significantly altered.

The liver effects observed in rats or mice exposed to heptachlor in the diet include increased liver weights (Izushi and Ogata 1990; Pelikan 1971), increased serum alanine aminotransferase activity levels (Izushi and Ogata 1990), steatosis (Pelikan 1971), and hepatitis and necrosis (Akay and Alp 1981). The lowest LOAEL values for these effects range from 5 to 8.4 mg/kg/day. Neurological signs such as hyperexcitability, seizures, and difficulty standing, walking, and righting were observed at similar dose levels; LOAELs ranged from 1.7 to 17 mg/kg/day (Akay and Alp 1981; Aulerich et al. 1990; Crum et al. 1993). Decreases in epididymal sperm count were observed in rats administered 0.65 mg/kg/day heptachlor in groundnut oil for 70 days (Amita Rani and Krishnakumari 1995). This dose also resulted in increased resorptions when the exposed males were mated with unexposed females. Reduced fertility was observed in all mice exposed to 8.4 mg/kg/day heptachlor for 10 weeks (Akay and Alp 1981).

The intermediate-duration oral MRL for heptachlor is based on the results of the study reported by Moser et al. (2001) and Smialowicz et al. (2001), which found alterations in development of the nervous and immune systems. In this study, groups of 15–20 pregnant Sprague Dawley rats were administered via gavage 0, 0.03, 0.3, or 3 mg/kg/day heptachlor in corn oil on gestational day 12 through postnatal day 7; pups were also exposed from postnatal day 7 to 21 or 42. The liver, kidneys, adrenals, thymus, spleen, ovaries, uterus/vagina, testes, epididymides, seminal vesicles/coagulating glands, and ventral and dorsolateral prostate were histologically examined in the offspring on postnatal day 46. Neurological (functional observational battery tests, motor activity, passive avoidance tests learning and memory, and Morris water maze test to assess spatial and working memory) and immunological (splenic lymphoproliferative responses to T cell mitogens, and to allogeneic cells in a mixed lymphocyte reaction, primary immunoglobulin M (IgM) antibody response to sheep red blood cells, examination of splenic lymphocytes subpopulations, and delayed-type and contact hypersensitivity) function tests were performed on the offspring exposed until postnatal day 42; neurological function tests were also performed on offspring exposed until postnatal day 21. Reproductive assessment included evaluation of vaginal opening (index of female puberty) and prepuce separation (index of male puberty) beginning at

postnatal days 25 and 35, respectively. The offspring were mated with an untreated mate and the dams were allowed to rear the first litter to postnatal day 10. The results of the neurobehavioral assessment were reported by Moser et al. (2001); the remaining results were reported by Smialowicz et al. (2001).

No significant alterations in maternal body weight, number of dams delivering litters, litter size, or pup survival were observed. Additionally, no alterations in pup growth rates, age at eye opening, anogenital distance, or age at vaginal opening or preputial separation were observed. A significant decrease in pup body weight at postnatal day 1 was observed at 3 mg/kg/day; this effect was not observed at postnatal days 7, 14, or 21. No consistent, statistically significant alterations in offspring body weights were observed at post natal days 21, 28, 35, or 42. Significant alterations in absolute and relative liver weights were observed in males and females exposed to 3 mg/kg/day; increases in absolute and relative ovary weights were also observed at 3 mg/kg/day. No histological alterations were observed in the examined tissues. No alterations in fertility were observed in the adult males and females mated to untreated partners, and no effects on soft tissue or gross body structure of the offspring (F_2 generation) were observed. No alterations in sperm count or sperm motility were observed.

A dose-related, statistically significant suppression of primary IgM antibody response to sheep red blood cells (sRBC) was found in male offspring, but not females. The primary IgM response to sRBCs was reduced in 21-week-old males exposed to 0.3 mg/kg/day. A second immunization with sRBCs administered 4 weeks later resulted in a significant reduction in IgG antibody response in males administered 0.03, 0.3, or 3 mg/kg/day heptachlor; no response was seen in females. A decrease in the $OX12^{+}OX19^{-}$ (i.e., B/plasma cells) population was also found in the spleen of males exposed to 3 mg/kg/day. No alterations in the following immunological parameters assessed at 8 weeks of age were found: lymphoid organ weights, splenic NK cell activity, splenic cellularity or cell viability, and lymphoproliferative responses of splenic lymphocytes to T-cell mitogens ConA and phytohemagglutinin (PHA) or to allogenic cells in the mixed lymphocyte reaction. The results of this portion of the study suggest that exposure to heptachlor adversely affects the development of the immune system.

Righting was significantly delayed in the female offspring of rats exposed to 3 mg/kg/day heptachlor; no significant alterations were observed in the male offspring. The investigators suggested that this was due to a delay in the ontogeny of righting rather than an inability to perform the task. The following significant alterations in the functional observation battery (FOB) and motor activity tests were found in the offspring dosed until postnatal day 21: increased open field activity in 3 mg/kg/day males, non-dose-related increased activity in figure-eight chambers in females (significant only in 0.03 mg/kg/day group),

and faster decline in habituation of activity in 3 mg/kg/day males. Alterations in the offspring dosed until postnatal day 42 included: increased levels of urination in males in the 0.03 and 0.3 mg/kg/day groups, increased landing foot splay in males in the 0.03 mg/kg/day group, and removal reactivity in males and females in the 0.03 mg/kg/day group. No alterations in the passive avoidance test were observed in the offspring exposed until postnatal day 21; in those exposed until postnatal day 42, an increase in the number of nose pokes was observed in all groups of females. No significant alterations in performance on the water maze test were found in the offspring exposed until postnatal day 21. In those exposed until postnatal day 42, increases in latency to find the platform were observed in males and females exposed to 3 mg/kg/day and increases in the time spent in the outer zone were found in males exposed to 0.3 or 3 mg/kg/day. In the water maze memory trial, no differences in performance were found between controls and animals exposed until postnatal day 21. Alterations in significant quadrant bias were observed in 0.03, 0.3, and 3 mg/kg/day males during the first probe test and in 0.3 and 3 mg/kg/day males and 3 mg/kg/day females in the second probe test. The study investigators noted that the heptachlor-exposed rats did not develop an efficient search strategy for locating the platform; they spent more time circling the outer zone of the tank. By the second week of the test, control rats had learned to venture into the zone where the platform was located.

The Smialowicz et al. (2001) and Moser et al. (2001) study identified a LOAEL of 0.03 mg/kg/day for developmental immunological and neurological effects. These alterations were considered to be minimally adverse and suggestive of immunotoxicity and neurotoxicity. An intermediate-duration oral MRL was calculated by dividing the minimal LOAEL of 0.03 mg/kg/day by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). The resulting MRL is 0.0001 mg/kg/day.

There is a limited publicly available database on the chronic oral toxicity of heptachlor. In a multigeneration study conducted by Mestitzova (1967), decreases in litter size, increased postnatal mortality, and increased occurrence of lens cataracts (observed in F_0, F_1, and F_2 generations) were observed at a heptachlor dose of 6 mg/kg/day. Because the only reliable chronic-duration study identified a serious LOAEL at the lowest dose tested, a chronic-duration MRL was not derived for heptachlor.

Heptachlor Epoxide. Publicly available data on the toxicity of heptachlor epoxide are limited to an LD_{50} study (Podowski et al. 1979), and a dominant lethal study (Epstein et al. 1972). Neither of these studies is suitable for derivation of MRLs for heptachlor epoxide.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of heptachlor and heptachlor epoxide. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of heptachlor and heptachlor epoxide are indicated in Table 3-1 and Figure 3-1.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Limited information exists regarding exposure to heptachlor or heptachlor epoxide and mortality. One of the four reports available studied pesticide manufacturers (Wang and MacMahon 1979b), whereas the other three examined pesticide applicators (Blair et al. 1983; MacMahon et al. 1988; Shindell and Associates 1981; Wang and MacMahon 1979a). Exposure data were not available in any of these studies and none of them provided specific information for heptachlor or heptachlor epoxide. An occupational mortality study on workers employed in the manufacture of heptachlor and other chlorinated hydrocarbon pesticides for at least 3 months between 1952 and 1979 revealed no pattern of disease or medical condition that indicated that persons were at greater risk of adverse outcome than the general population (Shindell and Associates 1981). The only significant finding observed in workers employed at two facilities manufacturing chlordane or heptachlor and endrin was an excess of deaths from cerebrovascular disease, which was unrelated to duration of exposure or latency, and occurred exclusively after termination of employment (Wang and MacMahon 1979b). In professional pesticide applicators at three U.S. companies who were employed for 3 months or longer between 1967 and 1976, only deaths due to bladder cancer were significantly elevated in the applicators as a whole (Wang and MacMahon 1979a). In a separate analysis conducted for persons ever holding jobs as “termite control operators,” a group

more likely to be exposed to chlordane and heptachlor, bladder cancer was elevated in both the termite control operators and the group comprising the rest of the applicators. However, since confidence intervals were not provided, it is unknown whether this increase was statistically significant. A follow-up analysis of the same cohort extending to the end of 1984 reported that deaths due to cancer of the lung was the only outcome significantly elevated in the group as a whole (MacMahon et al. 1988). Separate analyses, as done in the earlier study, revealed that deaths due to lung cancer were not significantly elevated in the group with the highest likelihood of exposure to chlordane and heptachlor. In the last study of licensed male pesticide applicators in Florida, the standardized mortality ratio (SMR) for all causes of death was 103, but increased SMRs, although not statistically significant, were seen for leukemia, cancers of the brain, and lung cancer (Blair et al. 1983). The increased SMRs for brain and leukemia were based on small numbers. Mortality from lung cancer was related to years licensed, but could not be attributed to any specific pesticide due to lack of information on frequency and intensity of exposures. Furthermore, information on smoking was not available. In conclusion, the information available is insufficient to determine whether there is an association between exposure of workers to heptachlor or heptachlor epoxide and mortality.

No studies were located regarding death in animals after inhalation exposure to heptachlor or heptachlor epoxide.

3.2.1.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, dermal, or ocular effects in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide.

Hematological Effects. The available data on potential hematological effects following inhalation exposure to heptachlor or heptachlor epoxide are limited to a case-control study of exterminators, gardeners, and agricultural workers exposed to several organochlorine pesticides (heptachlor among them) (Wang and Grufferman 1981). No dose-dependent causal relationship between exposure to several organochlorine pesticides and deaths from aplastic anemia was found.

No studies were located regarding hematological effects in animals after inhalation exposure to heptachlor or heptachlor epoxide.

No studies were located regarding the following effects in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide:

3.2.1.3 Immunological and Lymphoreticular Effects

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

Several studies have examined the possible association between cancer and environmental and/or occupational exposure to chlordane and heptachlor (Epstein and Ozonoff 1987; MacMahon et al. 1988; Shindell and Associates 1981; Wang and MacMahon 1979a, 1979b). Several occupational cohorts showed that workers who were involved in the manufacture of chlordane and heptachlor did not have a significant increase in death from any type of cancer (MacMahon et al. 1988; Shindell and Associates 1981; Wang and MacMahon 1979a, 1979b). These occupational studies are presumed to reflect primarily inhalation exposure, with some concomitant dermal exposure. Among workers at pesticide manufacturing facilities, the SMR for bladder cancer was of borderline statistical significance (Wang and MacMahon 1979a). A follow-up study identified an increase in lung cancer, but the SMR for deaths from lung cancer in the group with the highest chance of exposure was not significant (MacMahon et al. 1988). No information on cigarette smoking was obtained from the participants. A retrospective mortality study conducted on male workers engaged in chlordane, heptachlor, and endrin manufacture for at least 3 months also showed a slight excess of lung cancer compared to the general U.S. population, but the increase was not statistically significant (Wang and MacMahon 1979b). Leukemia was associated with exposure to chlordane and heptachlor following home termiticide use (Epstein and Ozonoff 1987). An increased risk of prostate cancer was found among Hispanic farm workers potentially exposed to heptachlor (Mills and Yang 2003). Among the workers employed in counties with the highest heptachlor use, the odds ratio (adjusted for age, surrogates for exposure initiation, and duration) was 2.01 (95% confidence interval of 1.12–3.60).

It is difficult to determine from these studies whether or not exposure to heptachlor or heptachlor epoxide causes cancer. Although some studies suggest an association between exposure and cancer, other studies have not found significant associations, and there were many limitations among the studies. Limitations include the lack of quantitative exposure information, concomitant exposure to other chemicals, lack of

control measures for confounding factors, lack of information on diet, smoking habits, and liver function, and lack of complete occupational history, including other potential causal factors such as genetic disposition or immunologic disorders.

No studies were located regarding cancer in animals after inhalation exposure to heptachlor or heptachlor epoxide.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans after oral exposure to heptachlor or heptachlor epoxide.

Acute oral LD_{50} values for heptachlor in rodents (rats, mice, hamsters, and guinea pigs) and rabbits range from 40 to 2,302 mg/kg (purity ranging from unspecified to 99.9%) (Ben-Dyke et al. 1970; Berman et al. 1995; Eisler 1968; Gaines 1969; Gak et al. 1976; Lehman 1951; Podowski et al. 1979; Sperling et al. 1972; Sun 1972). The differences in the purity of the administered heptachlor may have influenced lethality. Pure heptachlor appears to be more lethal than technical-grade heptachlor (Berman et al. 1995; Podowski et al. 1979). Acute oral LD_{50} values for heptachlor epoxide in rodents (rats and mice) and rabbits range from 39 to 144 mg/kg (Eisler 1968; Podowski et al. 1979; Sperling et al. 1972).

Heptachlor can be converted to its photoisomer, photoheptachlor, in the presence of sunlight or ultraviolet light. This photolysis can take place on plant leaves. Photoheptachlor was found to be more toxic to rats than heptachlor or heptachlor epoxide; the LD_{50} for photoheptachlor was 3.8 mg/kg (Podowski et al. 1979).

The results of the non-LD_{50} studies indicate that the lethal dose decreases with duration of exposure. A single gavage dose of up to 129 mg/kg technical-grade heptachlor (73% heptachlor, 26% chlordane) did not result in mortality in rats (Berman et al. 1995). However, repeated doses of 23 or 69 mg/kg/day of technical-grade heptachlor resulted in 100% mortality after 6 or 3 doses, respectively (Berman et al. 1995; Moser et al. 1995). Increases in mortality were also observed in male rats exposed to 30 mg/kg/day and female rats exposed to 15 mg/kg/day technical-grade heptachlor (73% heptachlor, 22% chlordane, 5% nonachlor) in the diet for 6 weeks, followed by a 2-week period of observation (NCI 1977). No deaths were observed at 14 mg/kg/day in males and 7.6 mg/kg/day in females.

Similar lethal doses were observed in mice and mink exposed to heptachlor in the diet for intermediate durations. The lethal doses were 14 mg/kg/day for mice fed diets containing technical-grade heptachlor (73% heptachlor, 22% chlordane, 5% nonachlor) for 6 weeks, followed by a 2-week period of observation (NCI 1977) and 6.19 mg/kg/day for mink fed technical-grade heptachlor (72% heptachlor) for 28 days (Aulerich et al. 1990) or 1.7 mg/kg/day for 181 days (Crum et al. 1993). No alterations in mortality were observed in mice exposed to doses of 5.2 mg/kg/day or in mink at doses of 5.67 mg/kg/day. In chronic-duration studies, no statistically significant alterations in survival were observed in male or female mice exposed to 2.4 or 3.0 mg/kg/day, respectively, technical-grade heptachlor in the diet for 80 weeks (NCI 1977).

All reliable LD_{50} values and all reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, musculoskeletal, or dermal effects in humans or animals after oral exposure to heptachlor or heptachlor epoxide.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Cardiovascular Effects. The information regarding cardiovascular effects in humans associated with heptachlor and heptachlor epoxide exposure is limited to a study that found statistically higher heptachlor epoxide serum levels among individuals with moderate to severe arterosclerosis (Pines et al. 1986). This report cannot be construed as showing a causal relationship between heptachlor epoxide exposure and arteriosclerosis because no adjustments for other risk factors were made.

Animal data are limited to a study that found increases in relative heart weight (statistical significance not reported) in female rats exposed to heptachlor in the diet 5 days/week for 4 weeks (Enan et al. 1982). The investigators noted that 10 mg/kg heptachlor was added to the diet; it is not known if this is a dietary concentration or dose. The biological significance of this effect is not known, particularly since no information on body weight changes or food intake were provided and a histological examination was not performed.

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Fischer- 344)	once (GO)				230 F (LD50)	Berman et al. 1995 heptachlor	
2	Rat (Sherman)	1 d 1 x/d (GO)				100[b] M (LD50) 162 F (LD50)	Gaines 1969 heptachlor	
3	Rat (NS)	once (GO)				105 (LD50)	Gak et al. 1976 heptachlor	
4	Rat (Fischer- 344)	Gd 6-15 (GO)				12 F (38% mortality in pregnant rats)	Narotsky et al. 1995 heptachlor	
5	Rat (NS)	once				71 M (LD50)	Podowski et al. 1979 heptachlor	
6	Rat (NS)	once				60 M (LD50)	Podowski et al. 1979 heptachlor epoxide	
7	Mouse (NS)	once (GO)				70 (LD50)	Gak et al. 1976 heptachlor	
8	Hamster (NS)	once (GO)				100 (LD50)	Gak et al. 1976 heptachlor	

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
9	Rat (Fischer- 344)	14 d 1 x/d (GO)	Hepatic	2 F	7 F (hepatocytomegaly)		Berman et al. 1995 heptachlor	
10	Rat (Wistar)	once (GO)	Hepatic		60 F (increased serum ALT and aldolase levels, decreased liver ALT and aldolase levels, vacuolated cells, pyknotic nuclei)		Krampl 1971 heptachlor	
11	Rat (Wistar)	3, 7, or 14 d (GO)	Hepatic		7 F (decreased liver ALT and aldolase levels, increased serum ALT and aldolase levels; monocellular necrosis and vacuolar dystrophy)		Krampl 1971 heptachlor	
12	Rat (Wistar)	14 d (F)	Resp	5			Pelikan 1971 heptachlor	
			Cardio	5				
			Gastro		5 (slightly hyperemic stomach and intestinal wall)			
			Hepatic	5				
			Renal	5				
			Bd Wt	5				

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
13	Mouse (albino)	11 d (W)	Endocr			87 F (atrophy in adrenal cortex)	Akay et al. 1982 heptachlor	
Immuno/ Lymphoret								
14	Rat (Fischer- 344)	once (GO)		69 F	129 F (necrotic lymphocytes in spleen and thymus)		Berman et al. 1995 heptachlor	Limited to examination of spleen and thymus.
15	Rat (Fischer- 344)	14 d 1 x/d (GO)		69 F			Berman et al. 1995 heptachlor	Limited to examination of spleen and thymus.
16	Rat (Wistar)	14 d (F)		5			Pelikan 1971 heptachlor	Limited to examination of spleen.
Neurological								
17	Rat (Fischer- 344)	once (GO)			7 F (excitability)		Moser et al. 1995 heptachlor	
18	Rat (Fischer- 344)	14 d 1 x/d (GO)		2 F	7 F (increased arousal)		Moser et al. 1995 heptachlor	
Reproductive								
19	Rat (Wistar)	14 d (GO)				1.8[c] F (decreased fertility; increased resorptions)	Amita Rani and Krishnakumari 1995 heptachlor	
20	Mouse (CD-1)	1 d 1 x/d (G)		15 M			Arnold et al. 1977 heptachlor	

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Mouse (ICR)	5 d (G)		8 M			Epstein et al. 1972 heptachlor epoxide	
22	Mouse (ICR)	5 d (G)		10 M			Epstein et al. 1972 heptachlor	
Developmental								
23	Rat (Fischer- 344)	Gd 6-19 (GO)			4.5 (decreased pup body weight at pnd 6)		Narotsky and Kavlock 1995 heptachlor	
24	Rat (Fischer- 344)	Gd 6-15 (GO)		5.1 F	6.8 F (decreased pup body weight)	9 F (pup mortality)	Narotsky et al. 1995 heptachlor	
25	Rat (Sprague-Dawley)	Gd 10-21 (GO)			4.2 F (decreased righting reflex in pups)	8.4 F (decreased pup survival)	Purkerson-Parker et al. 2001b heptachlor	
INTERMEDIATE EXPOSURE								
Death								
26	Rat (Osborne-Mendel)	6 wk (F)				30 M (2/5 male rats died) 15 F[b] (4/5 female rats died)	NCI 1977 heptachlor	
27	Mouse (B6C3F1)	6 wk (F)				14 M (5/5 males died)	NCI 1977 heptachlor	
28	Mink (NS)	28 d (F)				6.2 M (3/8 died)	Aulerich et al. 1990 heptachlor	

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Mink (NS)	181 d (F)				1.7 F (67% mortality)	Crum et al. 1993 heptachlor	
Systemic								
30	Rat (albino)	21 d (G)	Endocr	1 M			Akhtar et al. 1996 heptachlor	Measured thyroid hormone levels.
			Bd Wt	1 M				
31	Rat (Wistar)	28 d (F)	Resp	5			Pelikan 1971 heptachlor	
			Cardio	5				
			Gastro		5 (thin mucous secretion covering the stomach and intestine mucosa)			
			Hepatic		5 (steatosis, 21-23% increased relative liver weight)			
			Renal	5				
			Bd Wt	5				

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
32	Mouse (NS)	10 wk (F)	Hepatic		9.3 (hepatitis, necrosis, granuloma, congestion)		Akay and Alp 1981 heptachlor	No incidence data or statistical analysis reported.
			Renal		37 (granuloma)			
			Bd Wt		9.3 (unspecified decrease in body weight)			
33	Mouse (albino)	26 d (W)	Endocr			87 F (lipid accumulation and extensive degeneration and fibrosis in adrenal cortex)	Akay et al. 1982 heptachlor	
34	Mouse (DDY)	180 d ad lib (W)	Hepatic		6.9 M (increased serum ALT activity levels and liver weight)		Izushi and Ogata 1990 heptachlor	No histological examination.
			Bd Wt	6.9 M				
			Metab	6.9 M				
35	Mouse (DDY)	92 d 2 x/wk (GO)	Hepatic		10 M (increased serum ALT, alkaline phosphatase, and triglyceride levels, liver triglyceride levels, and liver weight)		Izushi and Ogata 1990 heptachlor	No histological examination.
			Bd Wt	10 M				
			Metab	10 M				

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Mink (NS)	28 d (F)	Bd Wt	3.1 M	5.7 M (22% decrease in body weight)		Aulerich et al. 1990 heptachlor	
Immuno/ Lymphoret								
37	Rat (Wistar)	28 d (F)		5			Pelikan 1971 heptachlor	Limited to examination of spleen.
38	Mouse (NS)	10 wk (F)		19	37 (splenic fibrosis)		Akay and Alp 1981 heptachlor	No incidence data or statistical analysis reported.
39	Mink (NS)	28 d (F)		5.7 M	6.2 M (49% decrease in spleen/brain weight)		Aulerich et al. 1990 heptachlor	
Neurological								
40	Mouse (NS)	10 wk (F)		9.3		19 F (difficulty standing, walking, and righting)	Akay and Alp 1981 heptachlor	
41	Mink (NS)	28 d (F)		5.7 M	6.2 M (clinical signs of hyperexcitability and incoordination)		Aulerich et al. 1990 heptachlor	
42	Mink (NS)	181 d (F)		1 F		1.7 F (hyperexcitability and seizures)	Crum et al. 1993 heptachlor	

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
43	Rat (Wistar)	70 d (GO)			0.65 M (decreased epididymal sperm count)	0.65 M (increased resorptions)	Amita Rani and Krishnakumari 1995 heptachlor	
44	Mouse (NS)	10 wk (F)				9.3 (100% infertility)	Akay and Alp 1981 heptachlor	
45	Mink (NS)	181 d (F)		1.7 F			Crum et al. 1993 heptachlor	Sperm motility or morphology.
Developmental								
46	Rat (Sprague-Dawley)	daily Gd 8-21, Ld 0-21 (GO)				5 F (increased pup mortality and decreased birth weights)	Lawson and Luderer 2004 heptachlor	
47	Rat (Sprague-Dawley)	Gd 12- pnd 7; pups exposed from pnd 7-21 or pnd 7-42 (GO)			0.03 (impaired spatial memory)		Moser et al. 2001 heptachlor	
48	Rat (Sprague-Dawley)	Gd 10- Ld 7; pups exposed on days 7-21 or 42 (GO)		0.3	3 (decrease in righting reflex)	8.4 (decreased pup survival)	Purkerson-Parker et al. 2001b heptachlor	
49	Rat (Sprague-Dawley)	Gd 12- pnd 71; pups exposed to day 42 (GO)			0.03[d] (suppression of immune response to sheep RBC in offspring)		Smialowicz et al. 2001 heptachlor	

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
50	Mink (NS)	181 d (F)		1		1.7	(increased stillbirths and decreased kit survival)	Crum et al. 1993 heptachlor	
CHRONIC EXPOSURE									
Cancer									
51	Mouse (B6C3F1)	80 wk (F)				2.4 M	(hepatocellular carcinoma)	NCI 1977 heptachlor	

a The number corresponds to entries in Figure 3-1.

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive an acute oral minimal risk level (MRL) of 0.0006 mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and a modifying factor of 3 for the use of a serious endpoint.

d Used to derive an intermediate oral minimal risk level (MRL) of 0.0001 mg/kg/day; dose divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

ALT = alanine aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; NOAEL = no-observed-adverse-effect level; NS = not specified; pnd = post-natal day; RBC = red blood cell(s); Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s)

Figure 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral

Acute (≤14 days)

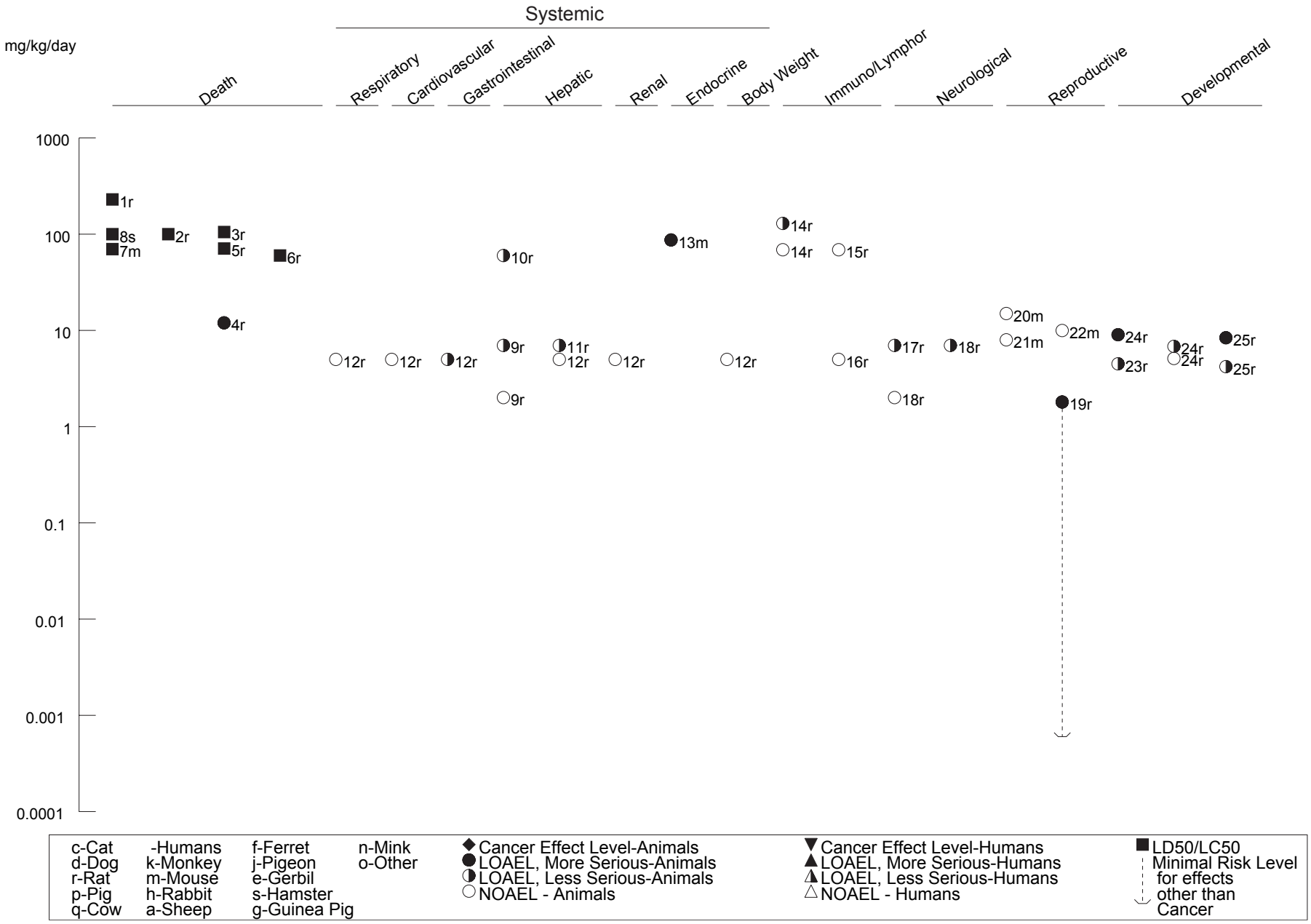


Figure 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral *(Continued)*

Intermediate (15-364 days)

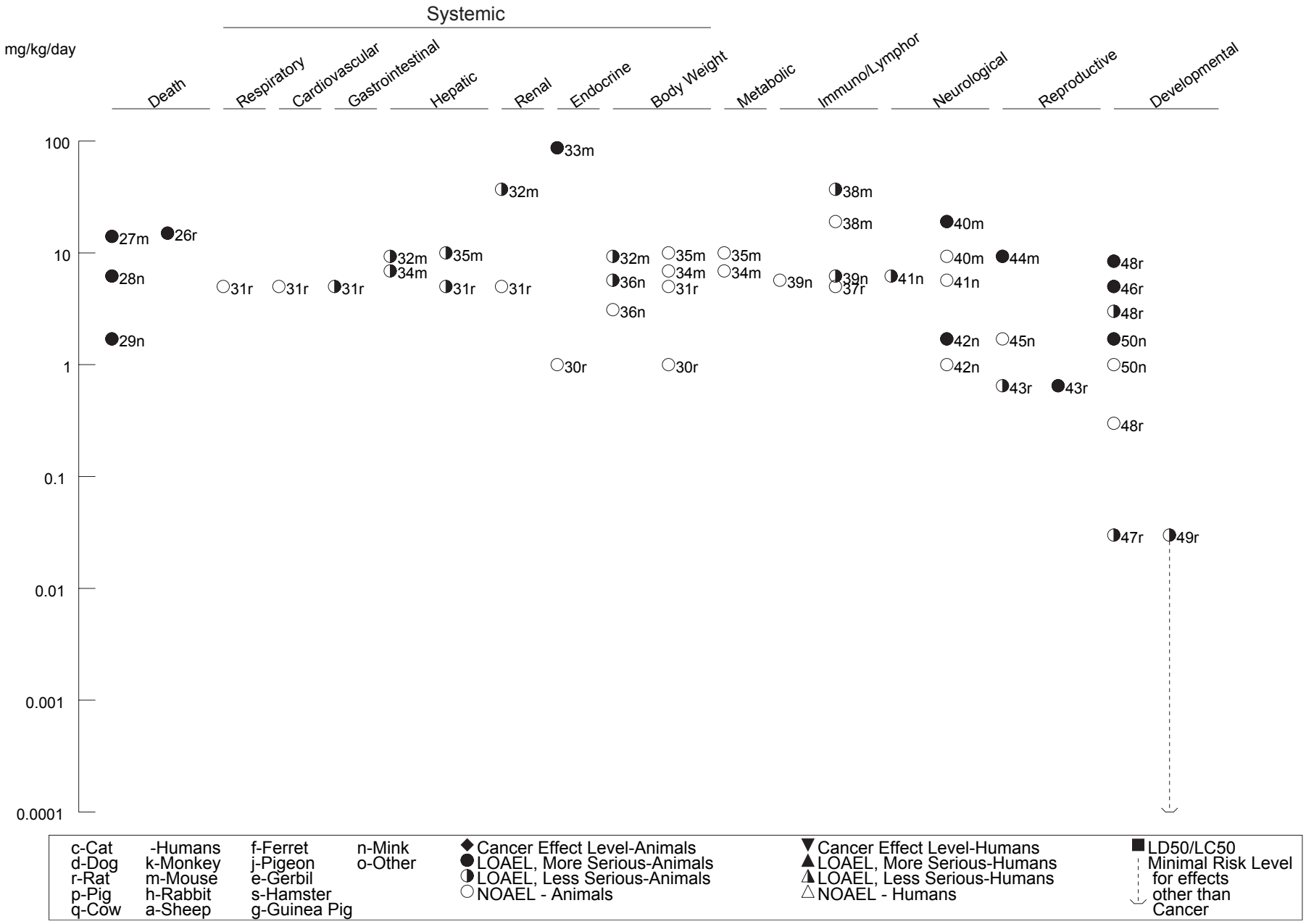
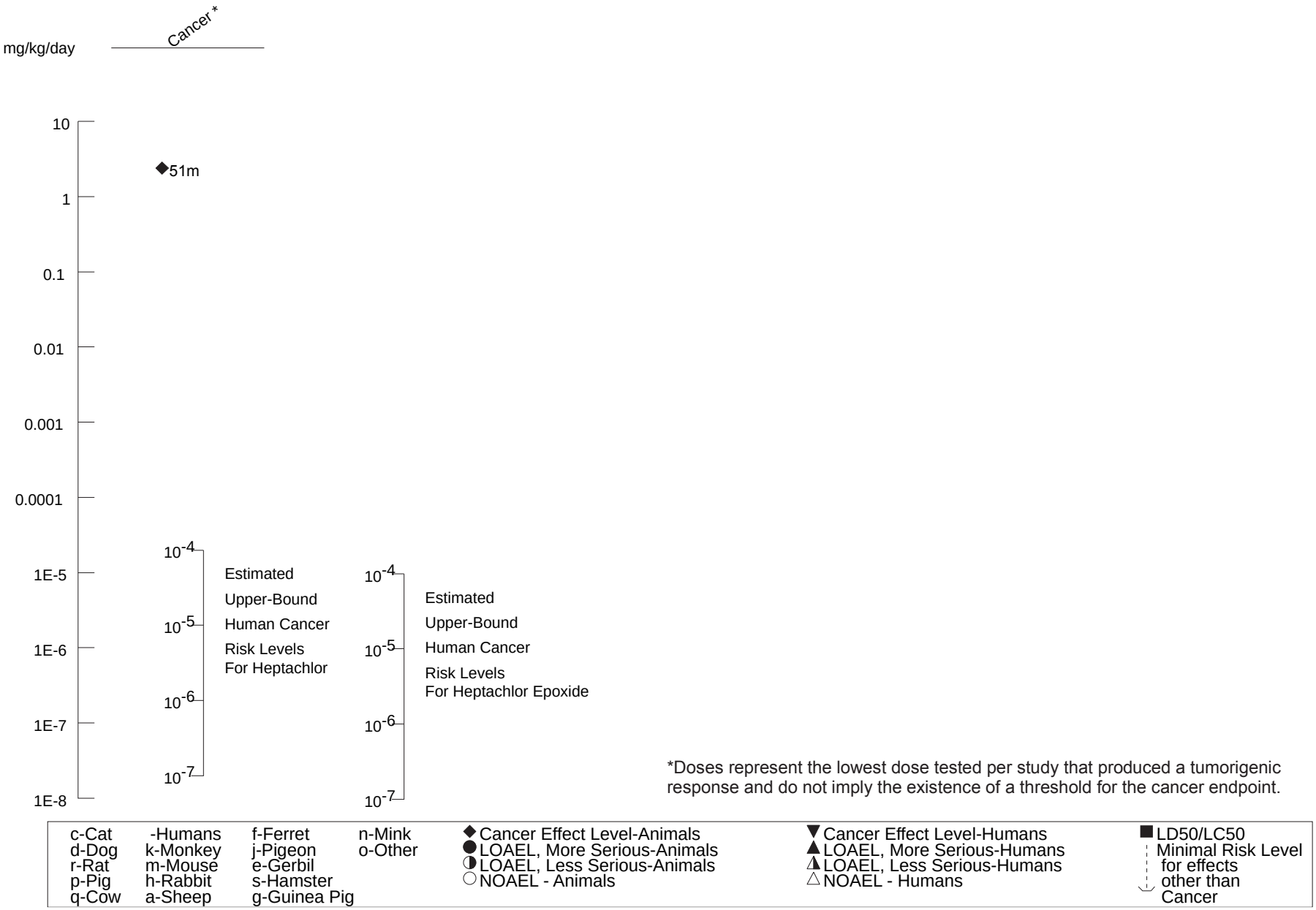


Figure 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral *(Continued)*

Chronic (≥365 days)



Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to heptachlor or heptachlor epoxide. Gross necropsy showed that the stomach and intestinal walls were slightly hyperemic in rats exposed to 5 mg/kg/day of heptachlor in the diet for 14 days (Pelikan 1971); after 28 days of exposure, the mucosa of the stomach and intestine was covered by a thin mucus secretion. No histological alterations were observed in gastrointestinal tissues at either duration. Ulceration and bloody mucus were observed in the stomachs of mink exposed to 1.7 or 3.1 mg/kg/day heptachlor in the diet for 181 days (Crum et al. 1993). These doses were also associated with mortality and pronounced neurological effects; the investigators also noted that the animals stopped eating 1–2 weeks prior to death.

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to heptachlor or heptachlor epoxide; one animal study examining hematological end points was identified. A statistically significant increase in total leukocyte levels was observed in rats exposed to heptachlor in the diet for 1, 7, or 28 days (Enan et al. 1982). No alterations in erythrocyte levels were found. As noted previously, it is not known if the reported concentration of 10 mg/kg is a dietary concentration or dose.

Hepatic Effects. Very limited information is available regarding hepatic effects of heptachlor or heptachlor epoxide in humans. Evaluation of individuals exposed for an unspecified period of time to contaminated raw milk products from cattle fed heptachlor-contaminated feed revealed significantly elevated serum levels of heptachlor metabolites relative to national background levels from National Health and Nutrition Examination Survey (NHANES) II and to levels monitored in unexposed reference subjects (Stehr-Green et al. 1986, 1988). Compared to the reference subjects, no significant alterations in serum liver enzyme activity levels were found, and no hepatomegaly was detected by clinical examination. This information is insufficient to draw any meaningful conclusion regarding liver effects of heptachlor in humans.

A number of animal studies have reported liver effects following oral exposure to heptachlor. Although collectively, the studies indicate that the liver is a target of toxicity, interpretation of many of the individual studies is limited by the lack of statistical analysis and the incomplete descriptions of the observed effects (including incidence data). No histological alterations and a small increase (15–17%) in relative liver weight were observed in rats exposed to 5 mg/kg/day in the diet for 14 days (Pelikan 1971). In another acute exposure study, hepatocytomegaly was observed at 7 mg/kg/day in rats administered

heptachlor in corn oil via gavage for 14 days (Berman et al. 1995). Monocellular necrosis and vacuolar dystrophy (statistical significance not reported) were observed in rats administered 7 mg/kg/day heptachlor in corn oil for 3, 7, or 14 days (Krampl 1971); decreases in liver alanine aminotransferase and aldolase activity levels and increases in serum alanine aminotransferase and aldolase activity levels were also observed at this dose level. A single dose of 60 mg/kg heptachlor resulted in similar enzyme activity changes (Krampl 1971); minimal evidence of single monocellular necrosis with inflammatory reaction, vacuolated cells, and pyknotic nuclei were observed 72 hours after dosing. The investigator noted that the histological alterations paralleled the time course for the enzyme changes.

At longer durations, the severity of the liver effects appeared to increase. Steatosis was observed in rats exposed to 5 mg/kg/day in the diet for 28 days (Pelikan 1971) and hepatitis, necrosis, granuloma, and congestion were observed in mice fed diets containing 9.3 mg/kg/day heptachlor for 10 weeks (Akay and Alp 1981). As with acute exposure, intermediate exposure to heptachlor also resulted in alterations in serum enzyme levels; increases in serum aldolase, alanine aminotransferase, and alkaline phosphatase activity levels were observed at 6.9 mg/kg/day and higher (Izushi and Ogata 1990; Krampl 1971). Additionally, increases in serum and hepatic triglyceride levels were observed in mice administered 10 mg/kg heptachlor in olive oil twice weekly (2.9 mg/kg/day) for 92 days (Izushi and Ogata 1990), but not in mice fed 6.9 mg/kg/day in the diet for 180 days (Izushi and Ogata 1990). Liver effects have also been observed in non-rodent experimental animals. Ultrastructural changes indicative of liver cell damage were observed in a small number of pigs administered 2 mg/kg/day “heptachlorine” in the diet for 78 days (Dvorak and Halacka 1975; Halacka et al. 1974); no histological alterations were observed. Fatty liver was reported in mink exposed to 6.2 mg/kg/day heptachlor in the diet for 28 days (Aulerich et al. 1990) or 1.7 mg/kg/day in the diet for 181 days (Crum et al. 1993). In both studies, these doses were associated with increased mortality. One chronic exposure study reported no clear effects on liver function (BSP clearance) in rats exposed to 6 mg/kg/day for 18 months (Mestitzova 1967).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to heptachlor or heptachlor epoxide. Several studies have examined the potential of heptachlor to induce renal effects in animals. No histological alterations were observed in the kidneys from rats exposed to 5 mg/kg/day heptachlor in the diet for 14 or 28 days (Pelikan 1971) or from rats exposed to 6 mg/kg/day for 18 months (Mestitzova 1967). Increased blood urea levels were observed after 7 or 28 days in rats exposed to 10 mg/kg heptachlor in the diet (Enan et al. 1982); an increase and decrease in relative kidney weight were observed after 7 or 28 days, respectively. As noted previously, interpretation of the results of this study is limited by the poor reporting of the dose. Granulomas were observed in the kidneys of mice

that received 37 mg heptachlor/day for 10 weeks (Akay and Alp 1981); however, no incidence data or statistical analysis was reported, limiting the interpretation of the results. A significant decrease in kidney-to-brain-weight ratio and granulation and discoloration of kidneys were reported in minks fed 6.2 mg/kg/day of heptachlor daily for 28 days (Aulerich et al. 1990); the incidence of kidney damage was not reported.

Endocrine Effects. There is limited information on the potential of heptachlor to induce endocrine effects. Cortical atrophy and slight hypertrophy in the zona glomerulosa of the adrenal gland was observed in mice exposed to 87 mg/kg/day for 11 days (Akay et al. 1982). When the exposure was continued for 26 days, heavy lipid accumulation, congestion, cell degeneration, and extensive fibrosis were observed in the adrenal cortex (Akay et al. 1982). The interpretation of these findings is limited by the poor reporting of the study and the lack of incidence data. One other study examined endocrine end points; no alterations in thyroxine, triiodothyronine, or thyroid stimulating hormone levels were observed in rats administered 1 mg/kg/day via gavage for 21 days (Akhtar et al. 1996).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to heptachlor or heptachlor epoxide. Lens cataracts were observed in 22% of adult rats exposed to 6 mg/kg/day heptachlor in the diet for 4.5–9.5 months; cataracts were not observed in the controls (Mestitzova 1967). As discussed in the developmental toxicity section, cataracts were also observed in the F_1 and F_2 offspring. Other studies have not reported this finding among adults, although no studies were specifically designed to assess this end point. Additionally, Narotsky and Kavlock (1995) did not find increases in cataracts in the offspring of rats administered up to 6 mg/kg/day heptachlor via gavage on gestational days 6–19.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to heptachlor or heptachlor epoxide. The available animal data do not suggest that oral exposure to heptachlor adversely affects body weight gain in the absence of decreases in food consumption. No alterations in body weight were observed in rats or mice exposed daily to doses as high as 1 and 6.9 mg/kg/day, respectively, for intermediate durations (Akhtar et al. 1996; Izushi and Ogata 1990) or mice administered 10 mg/kg 2 times/week for 92 days (Izushi and Ogata 1990). Decreases in body weight gain were observed in mink exposed to heptachlor in the diet at doses of 5.7 mg/kg/day for 28 days (Aulerich et al. 1990) or 1.7 mg/kg/day for 181 days, which included pregnancy and lactation periods (Crum et al. 1993); significant decreases in food consumption were observed in both studies.

Metabolic Effects. No studies were located regarding metabolic effects in humans after oral exposure to heptachlor or heptachlor epoxide. Studies in animals suggest that exposure to heptachlor may disrupt carbohydrate metabolism. Significant decreases in liver glycogen levels, increases in liver and kidney gluconeogenic enzymes, and increases in blood glucose levels were observed in rats administered a single dose of 200 mg/kg heptachlor (Kacew and Singhal 1973). Decreases in liver glycogen levels and increases in blood glucose were also observed in rats exposed to 10 mg/kg for 1, 7, or 28 days (Enan et al. 1982). The investigators noted that 10 mg/kg was added to the diet; it is not known if this is the dietary concentration (dose would be approximately 0.9 mg/kg/day) or dose. No alterations in blood glucose levels were observed in mice administered 6.9 mg/kg/day heptachlor in the diet for 180 days or 10 mg/kg via gavage 2 times/week (Izushi and Ogata 1990).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to heptachlor or heptachlor epoxide.

No studies were located that specifically investigated the effects on the immune system of oral exposure to heptachlor or heptachlor epoxide in adult animals. However, several studies have found alterations in the lymphoreticular system. Necrotic lymphocytes were observed in the spleen and thymus of rats administered a single dose of 129 mg/kg heptachlor via gavage (Berman et al. 1995); the investigators noted that the effect may have been secondary to generalized toxicity. Fibrosis was observed in the spleens of mice exposed to 37 mg/kg/day heptachlor in the diet for 10 weeks (Akay and Alp 1981). Enlarged and hyperemic spleens were observed in rats exposed to 5 mg/kg/day heptachlor in the diet for 14 or 28 days (Pelikan 1971); however, no apparent alterations in relative spleen weight or histological alterations were observed and the gross changes were not considered to be biologically significant. A decrease in spleen-to-brain-weight ratio was reported in minks receiving 6.2 mg/kg/day heptachlor in the diet for 28 days (Aulerich et al. 1990); this dose was also associated with mortality, weight loss, and decreased food consumption.

The highest LOAEL values for lymphoreticular effects in each species following intermediate exposure are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to heptachlor or heptachlor epoxide.

Several studies in animals have reported adverse neurological effects shortly after exposure to heptachlor. At lethal doses, tremors and convulsions were observed in rats (Lehman 1951). Hyperexcitability, incoordination, and seizures were also observed in mink exposed to lethal doses (1.7 or 6.2 mg/kg/day) for intermediate durations (Aulerich et al. 1990; Crum et al. 1993). At nonlethal doses, alterations in a number of functional observational battery tests indicative of excitability were observed in rats following a single dose or 14 doses of 7 mg/kg (Moser et al. 1995); the excitability changes included increased arousal and reactivity to removal from the home cage and handling. The persistence of the effect was directly related to dose level. Decreases in motor activity and hunched posture in the home cage was observed 4 hours after a single dose of 129 mg/kg (Moser et al. 1995). Another study conducted by this group (Moser et al. 2003) found decreases in motor activity, increases in forelimb and hindlimb grip strength, handling reactivity and arousal, gait abnormalities, tremors, and piloerection in rats receiving gavage doses of 1–14 mg/kg/day for 10 days; a LOAEL cannot be identified from this study because the investigators did not provide data for individual end points or dose levels. Similar to the effects noted in the Moser studies, Akay and Alp (1981) reported difficulty in standing, walking, and righting in mice exposed to 19 mg/kg/day heptachlor in the diet for 10 weeks. In addition to these effects observed in mature animals, adverse neurological effects have been observed in the offspring of rats exposed to heptachlor during gestation, lactation, and postnatally; these studies are discussed in Section 3.2.2.6.

Statistically significant changes in electroencephalogram (EEG) patterns were reported in mature female rats administered heptachlor in the diet at levels of 1 and 5 mg/kg/day for three generations (Formanek et al. 1976). Interpretation of these findings is difficult because details of the dosing, the procedures used, and conditions of the rats were not described.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species following intermediate exposure are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.5 Reproductive Effects

Significantly higher levels of heptachlor epoxide were detected in the sera of a group of women identified through hospital records with premature delivery than in the sera of a control group with normal delivery

(Wassermann et al. 1982). However, sera levels of 8 of the 10 organochlorine pesticides for which analytical data were obtained were all significantly higher in the premature delivery group. In addition, route, duration, and level of exposure information was not reported. Heptachlor epoxide has been detected in stillborn infant brain, adrenal, lung, heart, liver, kidneys, spleen, and adipose tissue, indicating transplacental transfer of heptachlor or heptachlor epoxide (Curley et al. 1969). These studies also reported the presence of polychlorinated biphenyls (PCBs), lindane, and dieldrin in the samples. It is difficult to assess the causal relationship between adverse reproductive outcome in humans and exposure to heptachlor and heptachlor epoxide due to lack of control for confounding factors such as smoking and concomitant exposure to other pesticides and lack of completeness of report data. No adverse effects on reproduction (no decrease in fertility, no increase in fetal or neonatal deaths) were reported by Le Marchand et al. (1986) among women of child-bearing age following ingestion of heptachlor-containing milk in excess of 0.1 ppm for 27–29 months.

A number of animal studies have demonstrated that exposure to heptachlor can result in decreased fertility and increased pregnancy losses. Impaired fertility was reported in female rats administered via gavage 0.65 mg/kg/day heptachlor in groundnut oil for 14 days prior to mating (Amita Rani and Krishnakumari 1995) and male and female rats fed 0.25 mg/kg/day heptachlor for 60 days (Green 1970); 100% infertility was observed in mice fed 9.3 mg/kg/day heptachlor for 10 weeks (Akay and Alp 1981). No effect on fertility was observed in male mice administered via gavage 10 mg/kg/day heptachlor or 8 mg/kg/day heptachlor epoxide for 5 days (Epstein et al. 1972) or a single dose of 15 mg/kg heptachlor:heptachlor epoxide (25%:75%) (Arnold et al. 1977).

Significant increases in resorptions were observed in male and female rats receiving gavage doses of 0.65 or 1.8 mg/kg/day, respectively, heptachlor for 70 or 14 days, respectively, prior to mating to control animals (Amita Rani and Krishnakumari 1995) and male and female rats fed 0.25 mg/kg/day heptachlor for 60 days prior to mating and throughout gestation (Green 1970). An increase in the incidence of stillbirths was observed in mink fed a diet containing 1.7 mg/kg/day heptachlor for 42 days prior to mating and throughout gestation (Crum et al. 1993). Similarly, a decrease in litter size was observed in rats exposed to 6 mg/kg/day heptachlor in the diet for an unspecified portion of an 18-month study (Mestitzova 1967). No alterations in preimplantation losses or early fetal deaths were observed in control females mated to males administered via gavage 10 mg/kg/day heptachlor or 8 mg/kg/day heptachlor epoxide for 5 days (Epstein et al. 1972) or a single dose of 15 mg/kg/day heptachlor:heptachlor epoxide mixture (Arnold et al. 1977).

Other reproductive alterations include a decrease in epididymal sperm count in rats administered gavage doses of 0.65 mg/kg/day heptachlor for 70 days (Amita Rani and Krishnakumari 1995) and decreases in estradiol-17β and progesterone levels in rats gavaged with 1.8 mg/kg/day for 14 days (Amita Rani and Krishnakumari 1995). Vaginal bleeding was reported in some rats exposed to 2.0 or 4.0 mg/kg/day technical-grade heptachlor for 80 weeks (NCI 1977); however, the incidence and statistical significance were not reported.

All reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

Several studies have examined potential developmental effects in the children of women exposed to elevated levels of heptachlor or heptachlor epoxide. Between 1980 and 1982, the commercial supply of cow's milk for the Hawaiian island of Oahu was contaminated with heptachlor epoxide; the source of exposure was treated pineapple plants that were used as cattle feed. Cow milk fat levels of heptachlor measured in Hawaii during this time ranged from 0.12 to 5.00 ppm (EPA's action level is 0.1 ppm); in a prior analysis (1978–1980), the levels were comparable to the rest of the United States. Using hospital records, Le Marchand et al. (1986) examined a possible association between heptachlor epoxide exposure and birth defects. No increase in fetal or neonatal deaths or incidence of low birth weight infants were found in this study cohort. Of the 23 categories of major congenital malformations evaluated, 22 were found to be decreased in the study population when compared with cohorts from the other Hawaiian islands and from the U.S. general population for the same time period. One type of malformation (anomalies of the abdominal wall) was found to be slightly increased in the study cohort during the period of known exposure compared with the control cohorts. However, the baseline data for this type of malformation were not available prior to study initiation, and birth defects may be underreported. It was, therefore, not possible to document the temporal change in the incidence of this type of malformation. Since women who might not have consumed the contaminated milk were included in the study group, positive findings may have been diluted as a result of misclassification bias. A subsequent study of high school students born on Oahu and likely prenatally exposed to heptachlor epoxide was conducted by Baker et al. (2004b; available as an abstract). As compared to high school students living on Oahu since first grade (but not born on Oahu), an association between gestational exposure to heptachlor epoxide and lower neurobehavioral performance was found. In particular, impaired performance was found on tests of abstract concept formation, visual perception, and motor planning; this group also had more reported

behavioral problems. No significant associations between school-based performance measures, such as grade point average, and gestational heptachlor epoxide exposure were found.

Two studies examined possible associations between maternal heptachlor epoxide levels and early childhood development (Hertz-Picciotto et al. 2004) or birth weight (Gladen et al. 2003). An association between maternal serum heptachlor epoxide levels and their children's performance on a test of nonverbal perceptual reasoning was found in San Francisco residents. However, inclusion of PCBs in the model severely reduced the magnitude of the association (Hertz-Picciotto et al. 2004; only available as an abstract). The investigators concluded that the cognitive deficits were probably due to co-exposure to other compounds. Gladen et al. (2003) found no significant association between breast milk levels of heptachlor epoxide (taken 4–5 days after birth) and birth weight among residents of two cities in Ukraine.

Several animal studies have examined the potential developmental toxicity of heptachlor. *In utero* exposure to heptachlor doses of 5.0 mg/kg and higher has resulted in pup mortality (Lawson and Luderer 2004; Narotsky et al. 1995; Purkerson-Parker et al. 2001b). These doses are also associated with significant maternal toxicity such as mortality, convulsions, and/or weight loss; however, at 5.0 mg/kg/day, increased pup mortality was also observed in dams without overt signs of toxicity (Lawson and Luderer 2004).

Gestational exposure to lower doses results in decreases in pup body weight. The threshold for this effect appears to be around 4–5 mg/kg/day (Lawson and Luderer 2004; Narotsky and Kavlock 1995; Narotsky et al. 1995). No alterations in pup body weight were observed at 3 mg/kg/day (Moser et al. 2001; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001). Exposure to heptachlor does not appear to result increased frequency of anomalies or abnormalities (Narotsky et al. 1995; Smialowicz et al. 2001). Additionally, heptachlor does not appear to impair the development of the reproductive system. No delays in vaginal opening or prepuce separation (indices of female and male puberty respectively) were observed in the offspring of rats administered via gavage to 3 mg/kg/day heptachlor on gestational day 12 through postnatal day 21 (Smialowicz et al. 2001) or 5 mg/kg/day on gestational days 8–21 and lactational days 1–21 (Lawson and Luderer 2004). Additionally, continued exposure of the offspring until postnatal day 42 and subsequent mating with untreated animals did not result in adverse reproductive or developmental outcomes (Smialowicz et al. 2001).

Developmental studies have found neurological and immunological effects in offspring. Gestational, lactational, and offspring exposure until postnatal day 21 or 42 to 3 mg/kg/day heptachlor resulted in

significant delays in righting reflex, likely due to a delay in the ontogeny of righting rather than an inability to perform the task (Moser et al. 2001; Purkerson-Parker et al. 2001b). No alterations in motor activity ontogeny were observed (Moser et al. 2001; Purkerson-Parker et al. 2001b). Some alterations in functional observation battery tests were observed in rats exposed to heptachlor during gestation, lactation, and postnatally until day 21 or 42 (Moser et al. 2001). Many of these alterations were only significant at the lowest dose tested (0.03 mg/kg/day). In water maze tests, exposure to 0.03 mg/kg/day heptachlor and higher resulted in slowed acquisition of a spatial task and impaired recall (Moser et al. 2001). This was observed in rats exposed *in utero*, during lactation, and until postnatal day 42, but not in rats exposed until postnatal day 21.

Smialowicz et al. (2001) found a significant suppression of the immune response to sheep red blood cells in rats exposed to 0.03 mg/kg/day *in utero*, during lactation, and postnatally until day 42 of age. No significant alterations in the response to T-cell mitogens or in delayed-type and contact hypersensitivity were observed. A decrease in $OX12^{+}OX19^{-}$ splenic populations was observed at 3.0 mg/kg/day.

The reliable LOAEL values for developmental effects in rats following intermediate and chronic exposure are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

There is limited information on the carcinogenicity of heptachlor or heptachlor epoxide in humans following oral exposure; several studies have examined the possible association between heptachlor epoxide tissue levels and cancer risk. Interpretation of the studies is limited by the lack of information on heptachlor exposure (including the route of exposure), variables that may affect organochlorine levels (including diet and body mass index), and possible concomitant exposure to other chemicals. No significant associations were found for endometrial cancer in women in the United States (Sturgeon et al. 1998) or breast cancer in Norwegian women (Ward et al. 2000). Another study found a significant association between heptachlor epoxide levels in breast tissue and the prevalence of breast cancer (Cassidy et al. 2005). Two case control studies examined the possible association between heptachlor epoxide levels and non-Hodgkin's lymphoma. One study found a significant association among individuals with the highest heptachlor epoxide adipose levels (odds ratio of 3.41, 95% confidence interval of 1.89–6.16) (Quintana et al. 2004), whereas the other study did not found a significant association between serum heptachlor epoxide levels and non-Hodgkin's lymphoma (Cantor et al. 2003).

Animal studies provide some evidence for the carcinogenicity of heptachlor. Significant increases in the incidence of hepatocellular carcinoma were observed in male and female mice exposed to time-weighted average (TWA) doses of 2.4 or 3.0 mg/kg/day, respectively, technical-grade heptachlor (72% heptachlor, 20% chlordane) in the diet for 80 weeks. Although increases in liver tumors were also observed at a lower dose (0.8 mg/kg/day for males and 1.2 mg/kg/day for females), the incidence was not significantly different than controls (NCI 1977). No significant increases in neoplastic tumor incidence were observed in male or female rats similarly exposed to technical-grade heptachlor TWA doses of 3.9 or 2.6 mg/kg/day, respectively (NCI 1977). Although a statistically significant increase in the incidence of follicular cell neoplasms (adenomas and carcinomas) was observed in the thyroid of female rats fed a TWA dose of 2.0 mg/kg/day technical-grade heptachlor for 80 weeks, the study investigators did not judge the alterations to be sufficient to clearly indicate a carcinogenic effect in the thyroid gland (NCI 1977). No other significant alterations were observed in the rats (NCI 1977). The Cancer Effect Level (CEL) in mice from chronic exposure to heptachlor is recorded in Table 3-1 and plotted in Figure 3-1.

The positive carcinogenicity findings of the mouse NCI (1977) study is supported by evidence that heptachlor is a tumor promoter. Dietary administration of ≥0.65 mg/kg/day heptachlor (97.6% purity) for 25 weeks promoted the development of hepatocellular foci and hepatocellular neoplasms in male mice previously initiated with 3.8 mg/kg/day diethylnitrosamine in drinking water for 14 weeks (Williams and Numoto 1984).

EPA has classified heptachlor and heptachlor epoxide in Group B2 (probable human carcinogen) (IRIS 2006). EPA has derived an oral slope factor of 4.5 per (mg/kg)/day for heptachlor and 9.1 per (mg/kg)/day for heptachlor epoxide. The doses corresponding to cancer risk levels ranging from 10^{-4} to 10^{-7} are $2.0x10^{-5}$–$2.0x10^{-8}$ mg/kg/day for heptachlor and $1.0x10^{-5}$–$1.0x10^{-8}$ mg/kg/day for heptachlor epoxide as indicated in Figure 3-1. The oral cancer potency factor is a plausible upper-bound estimate of the lifetime probability of an individual developing cancer as a result of oral exposure per unit intake of the chemical. The International Agency for Research on Cancer (IARC) has classified heptachlor and heptachlor epoxide as Group 2b chemicals (possibly carcinogenic to humans) (IARC 2001).

3.2.3 Dermal Exposure

There is very little information on dermal exposures in either humans or animals. Most occupational exposures to heptachlor and heptachlor epoxide are assumed to be some combination of inhalation and

dermal exposure, but there are no data to quantify the relative contribution of each route. The occupational studies on pesticide workers are discussed in Section 3.2.1.

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to heptachlor or heptachlor epoxide.

For heptachlor dissolved in xylene and administered once, Gaines (1969) reported dermal LD_{50} values in Sherman rats of 195 mg/kg (males) and 250 mg/kg (females).

3.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans or animals after dermal exposure to heptachlor or heptachlor epoxide.

No studies were located regarding the following health effects in humans or animals after dermal exposure to heptachlor or heptachlor epoxide:

3.2.3.3 Immunological and Lymphoreticular Effects
3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.3 GENOTOXICITY

There are limited mammalian *in vivo* data on the genotoxicity of heptachlor or heptachlor epoxide. Heptachlor, heptachlor epoxide, and a mixture of heptachlor and heptachlor epoxide (25:75) were found to be negative in *in vivo* dominant lethal studies in the germ-line cells of male Charles River or Swiss mice (Arnold et al. 1977; Epstein et al. 1972).

Several *in vitro* studies have examined the genotoxicity of heptachlor or heptachlor epoxide (Table 3-2). The available weight of evidence suggests that neither compound alters the frequency of gene mutations in prokaryotic organisms (Glatt et al. 1983; Marshall et al. 1976; NTP 1987; Probst et al. 1981; Zeiger et

Table 3-2. Genotoxicity of Heptachlor and Heptachlor Epoxide In Vitro

Species (test system)	End point	Results		Chemical form	Reference
		With activation	Without activation		
Prokaryotic organisms:					
Salmonella typhimurium (histidine reversion)	Gene mutation	−	−	Heptachlor	Zeiger et al. 1987
S. typhimurium (Ames assay)	Gene mutation	−	−	Heptachlor	Marshall et al. 1976; NTP 1987
S. typhimurium (Ames assay)	Gene mutation	−	−	Heptachlor epoxide	Marshall et al. 1976; NTP 1987
S. typhimurium (Ames assay)	Gene mutation	+	−	Heptachlor	Gentile et al. 1982
S. typhimurium (modified Ames assay)	Gene mutation	−	−	Heptachlor	Probst et al. 1981
S. typhimurium (modified Ames assay)	Gene mutation	−	−	Heptachlor epoxide	Glatt et al. 1983
Escherichia coli (modified Ames assay)	Gene mutation	−	−	Heptachlor	Probst et al. 1981
S. typhimurium (disc assay)	DNA damage	No data	−	Heptachlor	Rashid and Mumma 1986
E. coli (DNA repair assay)	DNA damage	No data	−	Heptachlor	Rashid and Mumma 1986
Eukaryotic organisms:					
Fungi:					
Saccharomyces cerevisiae (*ade*, *trp* loci assay)	Gene conversion	−	−	Heptachlor	Gentile et al. 1982
Aspergillus nidulans (strain 35/liquid medium)	Gene mutation	No data	−	Heptachlor epoxide	Crebelli et al. 1986
A. nidulans (strain P1/liquid medium)	Chromosome malsegregation	No data	−	Heptachlor epoxide	Crebelli et al. 1986
Mammaliam cells:					
Mouse (L5178Y tk^+/tk^- lymphoma cell forward mutation assay)	Gene mutation	No data	+	Heptachlor	McGregor et al. 1988
Rat (ARL-HGPRT assay)	Gene mutation	−	NA	Heptachlor	Telang et al. 1982
Chinese hamster (ovary cells)	Chromosomal aberrations	+	−	Heptachlor	NTP 1987
Chinese hamster (ovary cells)	Sister chromatid exchange	+	+	Heptachlor	NTP 1987

Table 3-2. Genotoxicity of Heptachlor and Heptachlor Epoxide In Vitro

Species (test system)	End point	Results		Chemical form	Reference
		With activation	Without activation		
Rat (primary hepatocytes)	Unscheduled DNA synthesis	−	NA	Heptachlor	Probst et al. 1981; Maslansky and Williams 1981
Mouse (primary hepatocyte)	Unscheduled DNA synthesis	−	NA	Heptachlor	Maslansky and Williams 1981
Syrian hamster (primary hepatocytes)	Unscheduled DNA synthesis	−	NA	Heptachlor	Maslansky and Williams 1981
Human (SV-40 transformed fibroblasts)	Unscheduled DNA synthesis	+	−	Heptachlor	Ahmed et al. 1977
Human (SV-40 transformed fibroblasts)	Unscheduled DNA synthesis	+	−	Heptachlor epoxide	Ahmed et al. 1977

− = negative result; + = positive result; *ade* = adenine; ARL = adult rat liver epithelial cell line; DNA = deoxyribonucleic acid; HGPRT = hypoxanthine-guanine phosphoribosyl transferase; NA = not applicable; tk = thymidine kinase locus; *trp* = tryptophan

al. 1987). Heptachlor without metabolic activation caused gene mutations in mouse lymphoma cells but not in adult rat liver cells (McGregor et al. 1988; Telang et al. 1982). No alterations in gene conversion were observed in *Saccharomyces cerevisiae* following heptachlor exposure with and without activation (Gentile et al. 1982); heptachlor epoxide was also negative for gene mutation in *Aspergillus nidulans* (Crebelli et al. 1986).

Heptachlor did not cause DNA damage in *Salmonella typhimurium* or *Escherichia coli* in the absence of metabolic activators (Rashid and Mumma 1986). Heptachlor was negative for unscheduled DNA synthesis (UDS) in rat, mouse, and hamster (Maslansky and Williams 1981; Probst et al. 1981). In contrast, an increase in UDS was observed in human SV-40 transformed fibroblasts after exposure to heptachlor and heptachlor epoxide in the presence of metabolic activators (Ahmed et al. 1977).

Heptachlor epoxide did not alter the occurrence of chromosome malsegregration in *A. nidulans* (Crebelli et al. 1986). Chromosomal alterations were observed in mammalian cells. Chromosomal aberrations were observed in Chinese hamster ovary cells following exposure to heptachlor with metabolic activation and sister chromatid exchange was observed both with and without metabolic activation (NTP 1987). Refer to Table 3-2 for a summary of the results of these *in vitro* studies.

Several studies were located involving heptachlor genotoxicity in plants. A positive response was noted for the waxy gene mutation in maize (*Zea mays*) following exposure to heptachlor *in situ* (Gentile et al. 1982). A micronucleus test in *Tradescantia* produced a significant positive dose-related response at 1.88 ppm heptachlor, suggesting that heptachlor has clastogenic potential in plants (Sandhu et al. 1989). Early separation during metaphase, condensation, stickiness, and chromatin bridges were observed after heptachlor treatment on mitotic chromosomes in *Lens culinaris*, *Lens esculenta*, *Pisum sativum*, and *Pisum arvense* (Jain and Sarbhoy 1987a). Chromosomal abnormalities such as stickiness, non-orientation during metaphase I, fragments, multivalents, and bridges were also observed in meiotic chromosomes after heptachlor treatment (Jain and Sarbhoy 1987b). These studies by Jain and Sarbhoy report no statistical comparisons with which to interpret the results; therefore, it is difficult to evaluate the significance of their research. Even though these plant studies suggest that heptachlor is potentially genotoxic, the applicability to mammalian genotoxicity remains questionable.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding absorption in humans after inhalation exposure to heptachlor or heptachlor epoxide. One animal study provides suggestive evidence of absorption following inhalation exposure to heptachlor epoxide (Arthur et al. 1975). Elevated levels of heptachlor epoxide were found in the fat (0.039 versus 0.016 ppm in controls) of rabbits housed outdoors in an area of pesticide use; the air concentrations of DDT, dieldrin, and heptachlor epoxide were 649.6, 4.59, and 1.86 ng/m^3, respectively.

3.4.1.2 Oral Exposure

No information on the extent of oral absorption of heptachlor or heptachlor epoxide in humans was identified. Qualitative evidence of absorption was found in a study of families consuming dairy products contaminated with heptachlor epoxide (Stehr-Green et al. 1988). Higher serum heptachlor epoxide levels were detected in the family members compared to an unexposed population (0.84 versus 0.50 ppb).

Heptachlor is absorbed from the gastrointestinal tract of rats (Radomski and Davidow 1953; Tashiro and Matsumura 1978) and cattle (Harradine and McDougall 1986) as indicated by the presence of heptachlor and/or its metabolites in serum, fat, liver, kidneys, and muscle (Radomski and Davidow 1953). Based on available toxicity data (Podowski et al. 1979), it is assumed that heptachlor epoxide is also absorbed via the gastrointestinal tract. One study provides suggestive evidence that at least 50% of an orally administered dose of heptachlor is absorbed by rats (Tashiro and Matsumura 1978). Ten days after administration of a single dose, 6% of the radioactivity from radiolabeled (^{14}C) heptachlor was found in the urine and 60% was detected in the feces (primarily present as heptachlor metabolites).

3.4.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal exposure to heptachlor or heptachlor epoxide.

Heptachlor is absorbed through the skin following topical application as indicated by its dermal toxicity in rats (Gaines 1969), but quantitative data are not available. However, the data should be interpreted

cautiously because heptachlor epoxide ingestion was not prevented by restraining the animals or removing excess heptachlor from the skin.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution of heptachlor or heptachlor epoxide in humans or animals following inhalation exposure.

3.4.2.2 Oral Exposure

No human studies were located regarding the distribution of heptachlor and its metabolites after oral exposure. A number of monitoring studies found elevated levels of heptachlor epoxide in fat, serum, liver, and brain. It is not known if the elevated levels of heptachlor epoxide were the result of heptachlor or heptachlor epoxide exposure or chlordane exposure (heptachlor epoxide is a minor metabolite of chlordane) (Adeshina and Todd 1990; Barquet et al. 1981; Burns 1974; Greer et al. 1980; Klemmer et al. 1977; Polishuk et al. 1977b; Radomski et al. 1968; Stehr-Green et al. 1988; Wassermann et al. 1974).

Heptachlor epoxide was measured in a strip of skin, fat, and subcutaneous tissue from 68 children who died in the perinatal period and ranged from not detected (nondetectable) to 0.563 ppm (mean, 0.173 ppm) (Zavon et al. 1969). In 10 other stillborn infants, heptachlor epoxide levels measured in various tissues were as follows: brain (nondetectable), lung (0.17±0.07 ppm), adipose (0.32±0.10 ppm), spleen (0.35±0.08 ppm), liver (0.68±0.50 ppm), kidneys (0.70±0.28 ppm), adrenals (0.73±0.27 ppm), and heart (0.80±0.30 ppm) (Curley et al. 1969). Selby et al. (1969) reported a placenta/maternal blood concentration ratio for heptachlor epoxide of 5.8. In another study, the following heptachlor epoxide levels were measured in extracted lipids from mothers and newborn infants: maternal adipose tissue (0.28±0.31 ppm), maternal blood (0.28±0.46 ppm), uterine muscle (0.49±0.51 ppm), newborn blood (1.00±0.95 ppm), placenta (0.50±0.40 ppm), and amniotic fluid (0.67±1.16 ppm) (Polishuk et al. 1977a). These data provide evidence of transplacental transfer to the fetus.

Animal studies regarding heptachlor and heptachlor epoxide distribution in body tissues are limited. Analysis of body fat from 20 adult female rats fed heptachlor in their diet at a level of 35 ppm for 3 months revealed a high concentration of heptachlor epoxide but not heptachlor (Radomski and Davidow 1953). Further analysis showed that accumulation of heptachlor epoxide was directly related to the dose

of heptachlor given. Examination of other tissues in addition to adipose tissue showed that fat had the highest concentrations of heptachlor epoxide; markedly lower amounts were found in liver, kidneys, and muscle, and none was found in the brain. In a parallel study, three dogs were also examined. Doses of 1 mg/kg/day for 12–18 months produced the same distribution pattern as in rats, but the livers of dogs contained more heptachlor epoxide than the kidneys and muscle tissue. Levels in all tissues were higher in female dogs than in males.

The rate of heptachlor epoxide accumulation in, and elimination from, fat was determined in rats fed diets containing 30 ppm heptachlor for 12 weeks, then fed untreated diets for 12 more weeks (Radomski and Davidow 1953). Interim sacrifices at various times during treatment showed that the residue in the fat of males reached a plateau at approximately 2–8 weeks. Thereafter, the levels decreased and were below the detection limit by the end of week 6 post-dosing. In females, the heptachlor epoxide level in fat was much higher than males by the second week and throughout the remainder of the study. By the end of the 8th week post-dosing, the heptachlor epoxide level was below the detection limit in females. No estimates of elimination half-lives from fat were provided.

Heptachlor and heptachlor epoxide residues were found in the fat (≥0.16 and ≥18.25 ppm, respectively), liver (≥0.08 and ≥2.11 ppm, respectively), and muscle (0 and ≥0.03 ppm, respectively) of pigs fed 2 mg/kg/day heptachlorine (purity unspecified) for 78 days (Halacka et al. 1974). When pigs were fed 5 mg/kg/day, the levels of heptachlor and heptachlor epoxide were higher: 0.37 and 25.82 ppm, respectively, in the fat; 0.23 and 4.94 ppm, respectively, in liver; and 0 and 0.7 ppm, respectively, in muscle.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to heptachlor or heptachlor epoxide.

3.4.3 Metabolism

No studies were located regarding metabolism of heptachlor or heptachlor epoxide in humans exposed to these pesticides. However, information is available regarding *in vivo* metabolism in rats and *in vitro* metabolism by human and rat liver microsomes.

Ten days after male rats were administered a single oral dose of ^{14}C-heptachlor by gavage in corn oil, about 72% of the radioactivity was eliminated in the feces in the form of metabolites and 26% as parent compound. The major fecal metabolites were heptachlor epoxide (13.1% of total ^{14}C compounds), 1-exo-hydroxychlordene (19.5%), 1-exo-hydroxy-2,3-exo-epoxychlordene (17.5%), and 1,2-dihydroxydihydro-chlordene (3.5%), as well as two unidentified products (Tashiro and Matsumura 1978). The proposed metabolic scheme for heptachlor is presented in Figure 3-2.

Tashiro and Matsumura (1978) also conducted experiments to compare *in vitro* metabolism of ^{14}C-heptachlor in microsomal preparations from human livers and rat livers. The primary metabolites produced by in both preparations were heptachlor epoxide, 1-exo-hydroxychlordene, 1-exo-hydroxy-2,3-exo-epoxychlordene, and 1,2-dihydroxydihydrochlordane. However, the levels of heptachlor epoxide were 4 times higher in the rat microsomal preparations than in the humans; 85.8% of the radiolabel was in the form of heptachlor epoxide in rat microsomes compared to 20.4% for human microsomes. These *in vivo* and *in vitro* data suggest that the ratio of heptachlor to heptachlor epoxide stored in adipose tissue would be higher in humans than rats (Tashiro and Matsumura 1978).

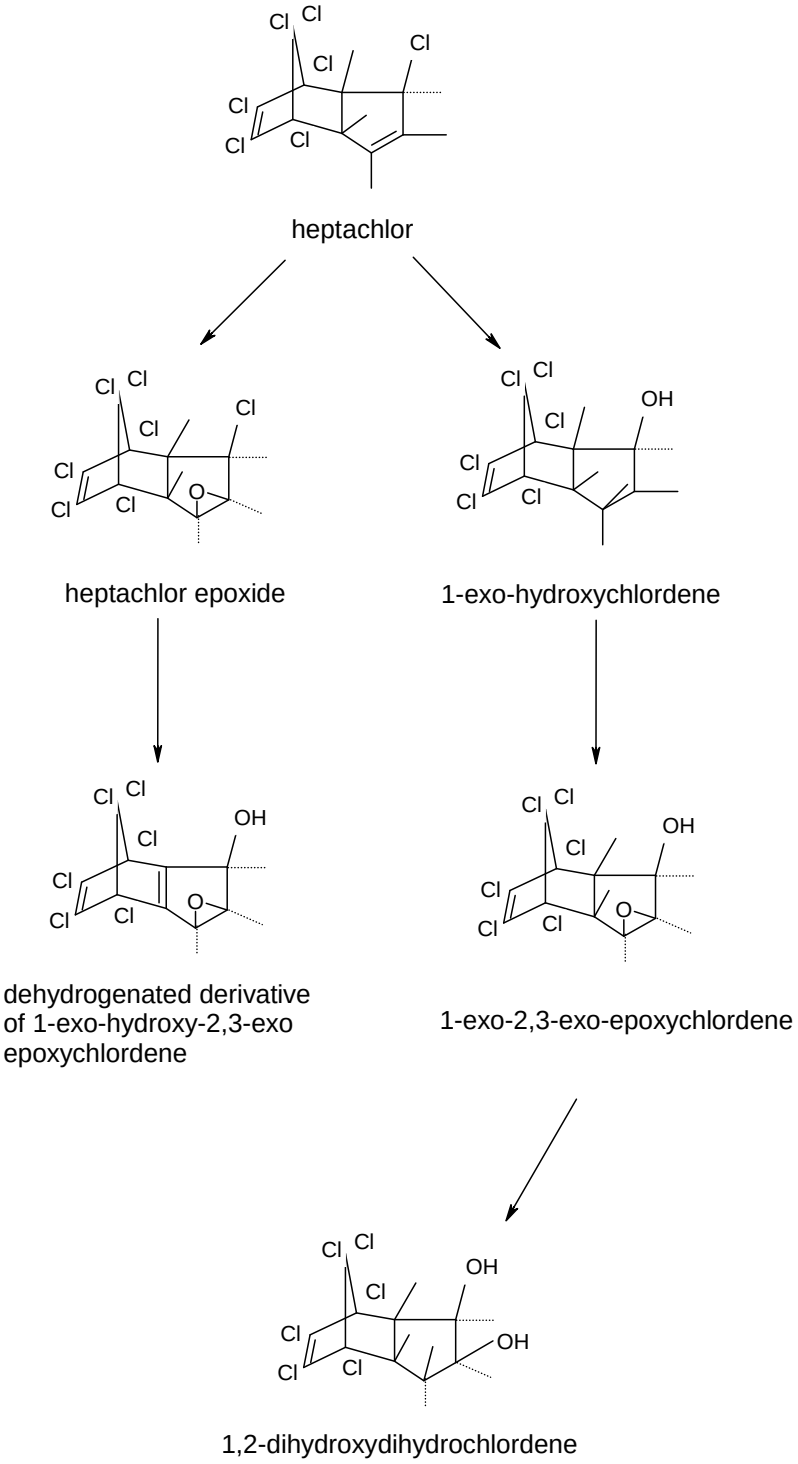
Heptachlor also is a metabolic product of chlordane. Both heptachlor and heptachlor epoxide are active inducers of microsomal epoxidation (Gillett and Chan 1968). In male Wistar rats fed a diet containing 5 ppm heptachlor or heptachlor epoxide for 10 days, the latter was much more effective in inducing epoxidation of aldrin than heptachlor (Gillett and Chan 1968). The minimally effective dietary concentration for inducing significant epoxidation was estimated to be between 1 and 5 ppm for both compounds (Gillett and Chan 1968). Heptachlor epoxide is considered more toxic than its parent compound and, like heptachlor, is primarily stored in adipose tissue (Barquet et al. 1981; Burns 1974; Greer et al. 1980; Harradine and McDougall 1986).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide. Based on the data from oral studies, heptachlor is expected to be excreted primarily in the form of metabolites and also as unchanged parent compound.

Figure 3-2. Metabolic Scheme for Heptachlor in Rats



Source: adapted from Tashiro and Matsumura (1978)

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to heptachlor or heptachlor epoxide.

Due to their relatively high lipid solubility, heptachlor and heptachlor epoxide can accumulate in breast milk. For example, heptachlor and heptachlor epoxide were measured in 51 samples of human milk at average concentrations of 0.0027 and 0.019 ppm, respectively, from women with unknown exposure histories (Jonsson et al. 1977). Heptachlor epoxide was found in 24% of the samples, and heptachlor was found in 6%. Other investigators have reported the presence of heptachlor epoxide in human milk at concentrations ranging from not detected to 0.46 ppm (Kroger 1972; Larsen et al. 1971; Mussalo-Rauhamaa et al. 1988; Polishuk et al. 1977b; Ritcey et al. 1972; Savage et al. 1981; Takei et al. 1983). These findings suggest a potential for transfer to the nursing infant (see also Sections 3.5.1 and 6.5).

In a study in cows, the concentration of heptachlor epoxide in cow's milk reached a maximum within 3–7 days after the cows began grazing 18 hours/day on pastures immediately following treatment of the grasses with heptachlor and declined steadily thereafter. The level of heptachlor epoxide in the milk reached a concentration of 0.22 ppm (Gannon and Decker 1960).

The elimination of a single oral gavage dose of ^{14}C-heptachlor in male rats showed that most of the radioactivity was eliminated in the feces (Tashiro and Matsumura 1978). One day after dosing, 36% of the dose had been eliminated, and by day 10, approximately 62% had been eliminated in the feces. Elimination of the radioactive label in urine accounted for only 6% of the total dose in 10 days. Approximately 26.2% of the total radioactivity recovered from the feces was the parent compound and the remainder was in the form of metabolites.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to heptachlor or heptachlor epoxide. Based on the data from oral studies, heptachlor is expected to be excreted primarily in the form of metabolites and also as unchanged parent compound.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for

many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for heptachlor and heptachlor epoxide exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK models were identified for heptachlor or heptachlor epoxide.

3.5 MECHANISMS OF ACTION

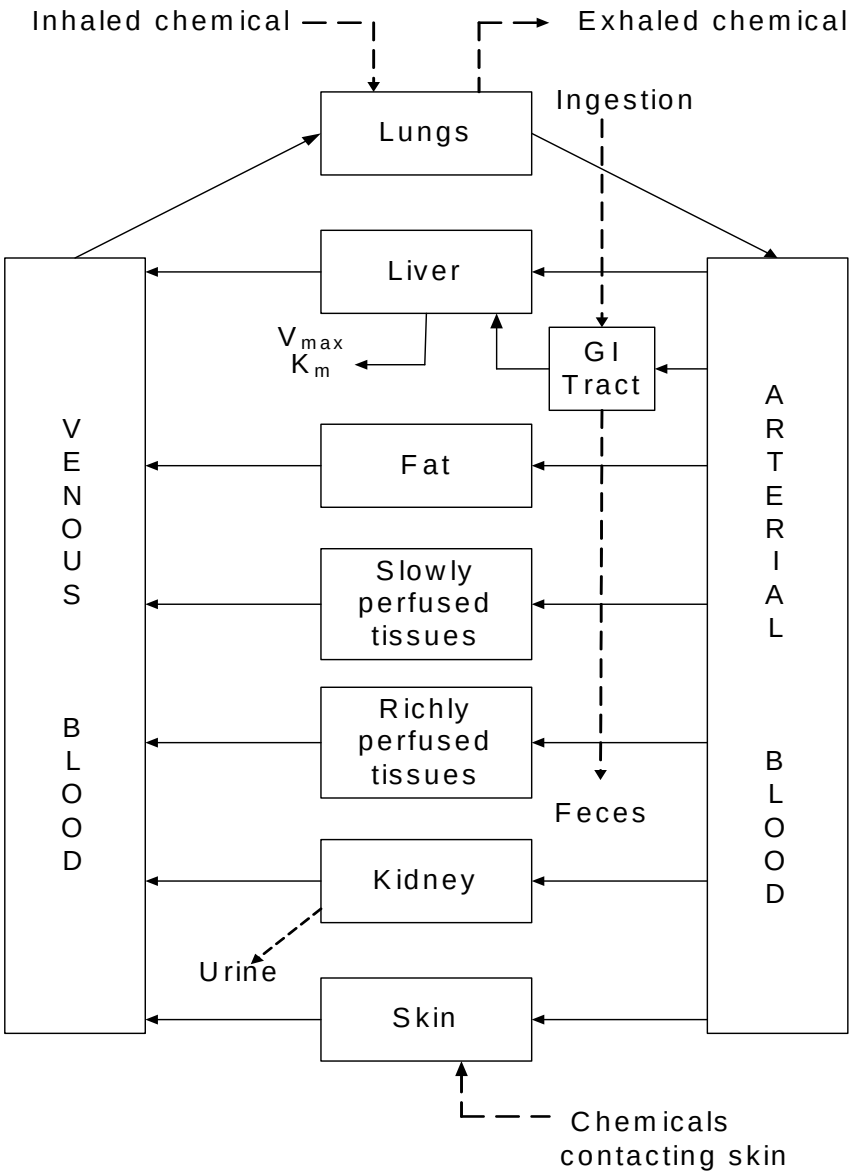
3.5.1 Pharmacokinetic Mechanisms

There is limited information on the toxicokinetics of heptachlor. No dermal toxicokinetic data were located. Heptachlor is absorbed via the lungs and digestive tract, although the site and mechanism of absorption are not known. Heptachlor is metabolized to heptachlor epoxide and is stored in the body as the parent compound and as this metabolite. Heptachlor and heptachlor epoxide are highly lipid soluble and are stored in adipose tissue; both compounds can also accumulate in breast milk. Heptachlor is primarily excreted in the feces as heptachlor epoxide.

3.5.2 Mechanisms of Toxicity

The available data suggest that the developing nervous system is the most sensitive target of heptachlor toxicity. Impaired spatial memory was observed in rats exposed to 0.03 mg/kg/day heptachlor during gestation and from postnatal day 7–42 (Moser et al. 2001). The cause of these alterions is not known. Moser et al. (2001) noted that heptachlor and other cyclodiene insecticides have a high affinity for $GABA_A$ (gamma-amino butyric acid) receptors and can alter the expression of the $GABA_A$ receptor

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

during development. In the Moser et al. (2001) study, alterations in $GABA_A$ binding sites were observed in the brainstem of female rats, but not in the cortex. However, no alterations in the functional response of the GABA receptor binding were observed. This study does not address whether the heptachlor-induced alterations in $GABA_A$ receptors and the observed neurobehavioral alterations are related.

3.5.3 Animal-to-Human Extrapolations

There are limited available data with which to compare humans and other animal species. The absorption and distribution properties of heptachlor and heptachlor epoxide appear to be the same in both humans and animals. For the most part, the human toxicity data do not allow for quantitative or qualitative comparisons with the available animal data; an exception is the neurodevelopmental toxicity data. Impaired performance on tests of abstract concept formation, visual perception, and motor planning was observed in adolescents exposed during gestation to heptachlor and/or heptachlor epoxide (Baker et al. 2004b). In rats exposed during gestation and for the first 42 postnatal days, impaired spatial memory and learning were observed (Moser et al. 2001). These data provide some qualitative support for extrapolating the rat data for human risk assessment.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate terminology to describe such effects remains controversial. The terminology endocrine disruptors, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning endocrine disruptors. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as hormonally active agents. The terminology endocrine modulators has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens

(Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to heptachlor or heptachlor epoxide. An animal study examining the impact of in utero and lactational exposure to heptachlor on the development of the reproductive system (Smialowicz et al. 2001) did not find alterations in vaginal opening, prepuce separation, or adverse reproductive or developmental outcomes when exposed offspring were mated with controls. Additionally, no *in vitro* studies were located regarding endocrine disruption of heptachlor or heptachlor epoxide.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are

critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There are suggestive data indicating that children, particularly children exposed *in utero* and during infancy may be unusually susceptible to the toxicity of heptachlor. Although no studies comparing the toxicity of heptachlor in adults and children were identified, there is a possibility that very young children may exhibit particular susceptibility to hepatic effects because of the immaturity of the hepatic microsomal system. Heptachlor is bioactivated to produce heptachlor epoxide, which is more toxic than

heptachlor. Pre-adolescent children have a greater rate of glutathione turnover, and they are expected to be more susceptible to heptachlor epoxide-induced toxicity. Their susceptibility would probably depend upon their ability to detoxify heptachlor epoxide. However, Harbison (1975) observed that heptachlor was less toxic in newborn rats than in adult rats. Newborn rats pretreated with phenobarbital were more sensitive to the effects of heptachlor than those not pretreated. Thus, the ability to metabolize and bioactivate heptachlor correlates with its toxicity in the newborn.

Several developmental toxicity studies have identified the developing organisms as a sensitive subpopulation. Heptachlor exposure does not appear to increase the risk of malformations in humans (Le Marchand et al. 1986) or animals (Narotsky et al. 1995; Smialowicz et al. 2001), although increases in pup mortality (Narotsky et al. 1995; Purkerson-Parker et al. 2001b) and decreases in pup body weight (Narotsky and Kavlock 1995; Narotsky et al. 1995) have been observed in animal studies. There is some indication that the developing nervous system may be unusually susceptible to the toxicity of heptachlor. A study of high school students exposed to heptachlor epoxide *in utero* and during early childhood found impaired performance on tests of abstract concept formation, visual perception, and motor planning (Baker et al. 2004b). Delays in the righting reflex, slowed acquisition of a spatial task, and impaired recall were observed in rat offspring exposed during gestation, lactation, and postnatally (Moser et al. 2001; Purkerson-Parker et al. 2001b). The impaired learning and memory was the basis of the intermediate-duration oral MRL. In addition to the neurological effects, suppression of the immune response to sheep red blood cells was observed at the same dose level as the impaired learning and memory (Smialowicz et al. 2001).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and

interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to heptachlor and heptachlor epoxide are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by heptachlor and heptachlor epoxide are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Heptachlor and Heptachlor Epoxide

Heptachlor and heptachlor epoxide can be measured in blood, adipose tissue, breast milk, and urine. The analytical methods available can be used to determine whether exposure has occurred, but the results cannot tell whether adverse health effects will occur. The presence of heptachlor epoxide may reflect an exposure to heptachlor or possibly chlordane since heptachlor epoxide is a metabolite of both these pesticides. However, in the absence of stable chlordane residues (e.g., nonachlor and oxychlordane), the heptachlor epoxide would most likely have been derived from heptachlor.

Detection of heptachlor or heptachlor epoxide in the body may indicate either recent or past exposure. Heptachlor epoxide has a long half-life, particularly in adipose tissue because it is very lipophilic and can remain dissolved in adipose tissue for months to years. An example of this can be found in a report in which analysis of human adipose tissue samples obtained during autopsy between 1987 and 1988 from residents of North Texas showed that tissue levels of heptachlor epoxide in subjects from the above geographical region had not significantly decreased since 1970 (Adeshina and Todd 1990). However, heptachlor epoxide is eventually mobilized into the blood and subsequently to the liver for further breakdown. Blood levels of heptachlor epoxide are often taken to indicate a more recent exposure.

As indicated in Section 3.4.4.2, due to their relatively high lipid solubility, heptachlor and heptachlor epoxide can accumulate in breast milk fat. Heptachlor and heptachlor epoxide were measured in 51 samples of human milk at average concentrations of 0.0027 and 0.019 ppm, respectively, from women with unknown exposure histories (Jonsson et al. 1977). Heptachlor epoxide was found in 24% of the samples, and heptachlor was found in 6%. Other investigators have reported the presence of heptachlor epoxide in human milk at concentrations ranging from not detected to 0.46 ppm (Kroger 1972; Polishuk et al. 1977b; Savage et al. 1981; Takei et al. 1983). These findings suggest a potential for transfer to the nursing infant (see also Sections 3.5.1 and 6.5). Other studies that have reported levels of heptachlor or heptachlor epoxide in humans' breast milk include Larsen et al. (1971), Ritcey et al. (1972), and Mussalo-Rauhamaa et al. (1988).

No studies were found correlating levels to which humans were exposed with actual body burdens.

3.8.2 Biomarkers Used to Characterize Effects Caused by Heptachlor and Heptachlor Epoxide

No clinical conditions due to specific exposure to heptachlor or heptachlor epoxide are known. The neurological and hepatic effects seen from exposure to heptachlor and heptachlor epoxide are typical of exposure to other chlorinated pesticides.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Dietary administration of heptachlor (97.6% purity) at 0.65 or 1.3 mg/kg/day in diet for 25 weeks promoted the development of hepatocellular foci and hepatocellular neoplasms in male B6C3F_1 mice previously initiated with 3.8 mg/kg/day diethylnitrosamine given in the drinking water for 14 weeks (Williams and Numoto 1984).

Nutritional factors may influence the toxicity of pesticides. Research in this area has primarily focused on the role of dietary proteins, particularly sulfur-containing amino acids, trace minerals, and vitamins A, C, D, and E. Studies in rats show that inadequate dietary protein enhances the toxicity of most pesticides but decreases, or fails to affect, the toxicity of a few. The results of these studies have shown that at one-seventh or less normal dietary protein, the hepatic toxicity of heptachlor is diminished as evidenced by fewer enzyme changes (Boyd 1969; Shakman 1974). The lower-protein diets may decrease metabolism of heptachlor to heptachlor epoxide.

Male weanling rats were fed a 5, 20, or 40% casein diet for 10 days and then given heptachlor intraperitoneally. The animals receiving the 5% casein diet showed a 3-fold tolerance to heptachlor toxicity, but the toxicity of heptachlor epoxide was not affected (Weatherholtz et al. 1969). This was probably due to inability of weanling rats to metabolically convert heptachlor to the more toxic heptachlor epoxide. This fact is further supported by the observation that changes in protein percentage in diet did not affect the toxicity of heptachlor epoxide itself.

Walter Reed-Wistar and Charles River male adult rats were exposed to oral doses of turpentine or to turpentine vapors, which consisted of α- and β-pinene. These exposures were followed by oral administration of heptachlor epoxide or of one of three pesticides, paraoxon, heptachlor, or parathion, or by an intraperitoneal injection of hexobarbital. The studies revealed that pretreatment with turpentine reduced hexobarbital sleeping time, reduced the parathion LD_{50}, and increased the heptachlor LD_{50}. The paraoxon and heptachlor epoxide LD_{50} values were unchanged. α-Pinene and β-pinene vaporized from turpentine had no effect on either hexobarbital sleeping time or parathion, paraoxon, or heptachlor epoxide mortality but did increase the heptachlor LD_{50} (Sperling et al. 1972). The authors speculated that increases in hepatic microsomal enzyme activity are responsible for these differences.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to heptachlor and heptachlor epoxide than will most persons exposed to the same level of heptachlor and heptachlor epoxide in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of heptachlor and heptachlor epoxide, or compromised function of organs affected by heptachlor and heptachlor epoxide. Populations who are at greater risk due to their unusually high

exposure to heptachlor and heptachlor epoxide are discussed in Section 6.7, Populations with Potentially High Exposures.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to heptachlor and heptachlor epoxide. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to heptachlor and heptachlor epoxide. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to heptachlor and heptachlor epoxide:

Ellenhorn MJ. 1997. Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1614-1631.

EPA. 1999. Recognition and management of pesticide poisonings. 5th. Washington, DC: U.S. Environmental Protection Agency. EPA735R98003. PB99149551.

Goldfrank L, Flomenbaum N, Lewin N, et al. 2002. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: McGraw-Hill, 1366-1378.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to heptachlor or heptachlor epoxide can occur by inhalation, oral, or dermal contact. Treatment of exposure to these substances is primarily supportive. Following a significant inhalation exposure, the patient is removed from the source to fresh air. Treatment may include administering oxygen and, if needed, maintaining ventilation with artificial respiration (Bronstein and Currance 1988; HSDB 2007a). General recommendations for reducing absorption of heptachlor following acute dermal exposure have included removal of contaminated clothing followed by washing the skin and hair with soap and water, (HSDB 2007a; Morgan 1989). Since leather absorbs pesticides, it has been recommended that leather not be worn while using heptachlor or heptachlor epoxide, and that any leather contaminated with these substances be discarded (HSDB 2007a). Oils have not been recommended as dermal cleansing agents because they could increase absorption (Haddad and Winchester 1990). If the eyes have been exposed, they are flushed with water (Bronstein and Currance 1988; HSDB 2007a). Treatment for ingestion of this substance may require gastric emptying by gastric lavage (Haddad and Winchester 1990) and administration of activated charcoal and cathartic (Haddad and Winchester 1990; HSDB 2007a; Morgan 1989). Heptachlor may be present with a hydrocarbon vehicle, which could result

in aspiration pneumonitis following the induction of emesis. Therefore, emesis may not be indicated. Some sources do not recommend the use of emetics (Bronstein and Currance 1988), although others do under some circumstances (HSDB 2007a; Morgan 1989). Treatments such as emesis and lavage may be most appropriate following ingestion of large quantities; it is unlikely that the types of exposure likely to occur at hazardous waste sites would require such measures. Treatment with milk, cream, or other substances containing vegetable or animal fats, which enhance absorption of chlorinated hydrocarbons, has not been recommended (Haddad and Winchester 1990; Morgan 1989). If seizures occur, diazepam administration, followed if necessary by additional anticonvulsant medicines such as phenytoin, pentobarbital, thiopental, or succinylcholine, may be recommended (Bronstein and Currance 1988; HSDB 2007a; Morgan 1989). As adrenergic amines, such as epinephrine, may further increase myocardial irritability and produce refractory ventricular arrhythmias, their use has not been recommended (Bronstein and Currance 1988; Haddad and Winchester 1990; HSDB 2007a; Morgan 1989).

3.11.2 Reducing Body Burden

Heptachlor is rapidly metabolized by the body, mostly to heptachlor epoxide. Most of the metabolites are rapidly excreted in the feces, with the adipose tissue serving as the major storage depot for the remainder. From the fat, heptachlor epoxide can be slowly released into the bloodstream for further metabolism and excretion. Cholestyramine resin may accelerate the biliary-gastrointestinal excretion of the more slowly eliminated organochlorine compounds, and its use has been suggested (Morgan 1989). Because of the lipophilicity of heptachlor and heptachlor epoxide, dialysis and exchange transfusion are thought to be ineffective (HSDB 2007a).

Because heptachlor epoxide is lipophilic, it is likely that the loss of adipose tissue, as may occur during fasting, will mobilize the stored compound and increase the rate of its elimination. However, this mobilization is also likely to temporarily increase the blood levels of heptachlor epoxide. Hence, any possible benefits due to a reduced body burden accompanying fat reduction would need to be balanced against potential harmful results due to the expected temporary increase in blood levels.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Since the metabolized form of heptachlor, heptachlor epoxide, is the most toxic, it may be possible to reduce the toxic effects of heptachlor by inhibiting the enzyme catalyzing this conversion. This is the same enzyme that catalyzes the epoxidation of aldrin to dieldrin (Gillett and Chan 1968). Further

research into the specificity of this enzyme, drugs that could inhibit the enzyme, and any side effects of these drugs could help to determine the feasibility of such a treatment strategy.

In the central nervous system, symptoms observed in animals following exposure include tremors, convulsions, ataxia, and changes in EEG patterns (Formanek et al. 1976). These central nervous system symptoms could be due either to (1) inhibition of the Na^+/K^+ ATPase or the Ca^+/Mg^+ ATPase activity, which can then interfere with nerve action or release of neurotransmitters (Yamaguchi et al. 1979) and/or (2) inhibition of the function of the receptor for GABA (Yamaguchi et al. 1980). In support of the latter possibility, another study showed that heptachlor epoxide inhibited the GABA-stimulated chloride uptake in the coxal muscle of the American cockroach and directly competed against [^{3}H]a-dihydropierotoxinin for binding in the rat brain synaptosomes. These results indicate that some of the nerve excitation symptoms that insecticides cause are probably due to their interaction with the picrotoxin binding site of the GABA receptor (Matsumura and Ghiasuddin 1983). A more detailed understanding of the mechanism of heptachlor/heptachlor epoxide action on the central nervous system may lead to new approaches for reducing the toxic effects.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of heptachlor and heptachlor epoxide is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of heptachlor and heptachlor epoxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

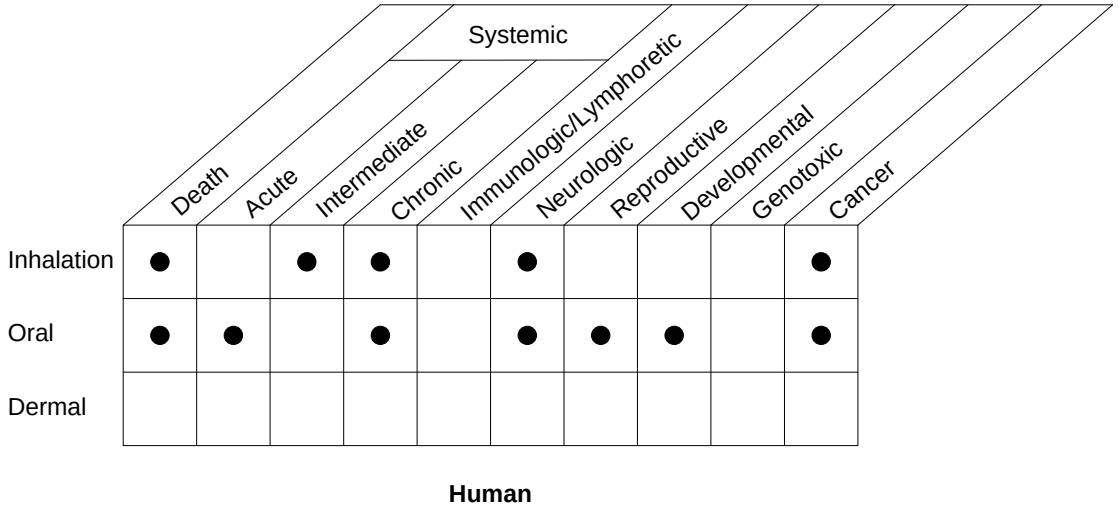
3.12.1 Existing Information on Health Effects of Heptachlor and Heptachlor Epoxide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to heptachlor and heptachlor epoxide are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of heptachlor and heptachlor epoxide. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

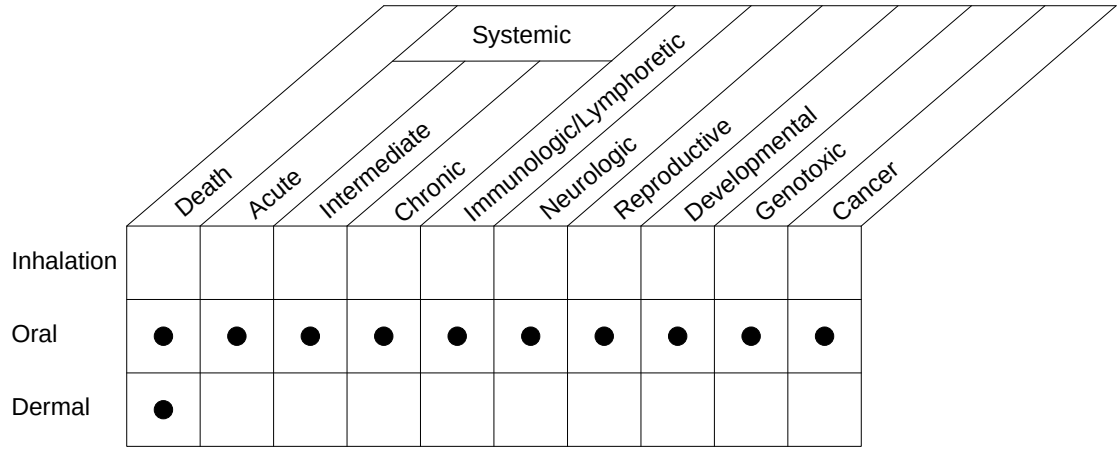
Most of the data located concerning the health effects of heptachlor and heptachlor epoxide in humans come from case reports and occupational epidemiology studies of workers engaged either in the manufacture or application of pesticides. There is some information on people who have consumed heptachlor-contaminated food or dairy products, but no adverse health effects have been related to these exposures. The occupational studies involve exposures that are predominantly inhalation with contributions from dermal exposure, whereas all the animal studies were conducted using oral or intraperitoneal exposures. The occupational and case reports provide no quantitation of dose or duration of exposure, which makes it impossible to determine with any precision the effect levels for humans. There are no data that indicate that heptachlor or heptachlor epoxide are carcinogenic to humans. However, human studies are limited by the long latency period of carcinogenesis and by ascertainment and follow-up biases.

The animal studies for oral exposure to heptachlor and heptachlor epoxide are almost all limited to some extent by the number of doses used, the lack of appropriate statistics, or the small number or lack of controls. No information was located regarding the health effects of inhalation or dermal exposure, with the exception of a dermal LD_{50} in rats. Exposure of the general population via the inhalation and dermal routes may result from contaminated soil or vapors from treated houses. Some exposures from contaminated soil or water may occur in populations located near hazardous waste sites in which these chemicals have been stored or from food grown in contaminated soil.

Figure 3-4. Existing Information on Health Effects of Heptachlor and Heptachlor Epoxide



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are no studies that have evaluated the acute toxicity of heptachlor or heptachlor epoxide following inhalation exposure; thus, acute-duration inhalation MRLs were not derived. A number of studies have evaluated the toxicity of heptachlor following acute oral exposure. The results of these studies suggest several sensitive targets of toxicity including the liver, nervous system, reproductive system, and the developing organism (Amita Rani and Krishnakumari 1995; Berman et al. 1995; Krampl 1971; Narotsky and Kavlock 1995; Narotsky et al. 1995; Purkerson-Parker et al. 2001b). The available data suggest that the most sensitive effect is impaired fertility observed in female rats administered heptachlor for 14 days prior to mating (Amita Rani and Krishnakumari 1995); this end point was used to derive an acute-duration oral MRL. Additional studies that examined a variety of systemic, neurological, reproductive, and developmental end points are needed to support the identification of critical effect and to establish dose-response relationships. Although there are limited toxicokinetic and mechanistic data for heptachlor, it is likely that its toxicity is not route-specific. The identified target organs would likely be the same for oral, inhalation, and dermal exposure; however, it is not possible to predict threshold concentrations. Toxicokinetic studies, which would allow for route-to-route extrapolation, and inhalation and dermal toxicity studies would be useful for confirming whether the toxicity of heptachlor is independent of route of exposure.

The available acute-duration studies for heptachlor epoxide are limited to oral lethality and dominant lethal studies (Epstein et al. 1972; Podowski et al. 1979). The toxicity of heptachlor is likely due to heptachlor epoxide; thus, the targets of toxicity are likely to be the same as those observed following heptachlor exposure. However, the toxic thresholds are likely to be different. Studies are needed to establish dose-response relationships and to confirm whether the targets of toxicity are the same as those identified for heptachlor.

Intermediate-Duration Exposure. The targets of toxicity of heptachlor following intermediate-duration oral exposure appear to be the same as those identified following acute-duration oral exposure and include the liver, nervous system, reproductive system, and the developing organism (Akay and Alp 1981; Amita Rani and Krishnakumari 1995; Aulerich et al. 1990; Crum et al. 1993; Izushi and Ogata 1990; Moser et al. 2001; NCI 1977; Pelikan 1971; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001). Of these targets, the developing organism appears to be the most sensitive (Moser et al. 2001; Smialowicz et al. 2001). Impaired development of the nervous and immune systems have been observed

in rats exposed to heptachlor *in utero*, during lactation, and from postnatal day 7 through 42; a NOAEL has not been identified for these end points. The intermediate-duration oral MRL for heptachlor was based on these developmental effects. The potential systemic toxicity of heptachlor has not been adequately assessed; although several studies have evaluated systemic end points (Akay and Alp 1981; Akay et al. 1982; Akhtar et al. 1996; Izushi and Ogata 1990; Pelikan 1971), many of these studies were poorly reported or examined a limited number of end points. Studies examining a variety of systemic end points would be useful for identifying target tissues and establishing dose-response relationships. No intermediate-duration inhalation or dermal studies were identified. As discussed in the Acute-Duration Exposure section, it is likely that the targets of toxicity would be the same for inhalation, oral, and dermal exposure; however, toxicokinetic data are not available to confirm this conjecture. Inhalation and dermal exposure studies are needed.

No publicly available studies on the intermediate-duration toxicity of heptachlor epoxide were identified. A 60-day dog study, which was submitted to EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) identifies the liver as a critical target of toxicity (IRIS 2006). It is likely that the targets of heptachlor epoxide toxicity are the same as those for heptachlor. Additional studies, particularly those examining the development of the nervous and immune systems are needed to identify targets of toxicity and establish dose-response relationships.

Chronic-Duration Exposure and Cancer. There are no data on chronic oral exposures in humans. There are occupational studies of workers engaged in the manufacture of heptachlor in which the exposures are presumed to be predominantly inhalation with contributions from the dermal route. No adverse health effects have been identified in these cohorts that could be positively associated with heptachlor exposure (Infante et al. 1978; MacMahon et al. 1988; Stehr-Green et al. 1988). There is a limited publicly available database on the chronic oral toxicity of heptachlor. The database is limited to a multigeneration study (Mestitzova 1967), which reported increased postnatal mortality at the lowest dose tested, and a study examining a limited number of noncancer end points (NCI 1977); thus, the database was not considered adequate for derivation of a chronic duration oral MRL. A 2-year study submitted to EPA under FIFRA identified the liver as a critical target of toxicity (IRIS 2006). This finding is consistent with the available intermediate-duration studies. However, intermediate-duration studies have also identified the nervous system, reproductive system, and the developing organism as targets of toxicity. Additional studies are needed to identify the most sensitive target following chronic duration exposure and to establish dose-response relationships; these studies would be useful for deriving an oral

MRL. Inhalation and dermal studies are also needed; these studies in animals would be useful for determining whether the target organ is the same across routes of exposure.

As with the other durations of exposure, limited publicly available data were located for heptachlor epoxide. A study submitted to EPA under FIFRA identified the liver as the most sensitive target of toxicity (IRIS 2006). Additional studies are needed that could be used to derive inhalation and oral MRLs for heptachlor epoxide and to establish the targets of toxicity for dermal exposure.

There are occupational mortality studies that have collected data appropriate for determining whether those engaged in the manufacture or application of heptachlor are at increased risk for dying of cancer. These studies have not shown an increased risk of cancer mortality (Infante et al. 1978; MacMahon et al. 1988). Occupational studies that collected cancer incidence data, rather than just mortality data, would be useful for further exploration of this issue. Carcinogenicity studies have been identified for rats and mice (NCI 1977). These data show increases in tumorigenesis following exposure to heptachlor. Chronic studies of inhalation exposure in relation to oncogenesis in animals might be useful for determining mechanism of action and the consistency of effect across routes of exposure. There are no toxicokinetic data that indicate that there will be route-specific differences.

Genotoxicity. Information on the *in vivo* genotoxic effects of heptachlor or heptachlor epoxide is limited to dominant lethality assays with negative results (Arnold et al. 1977; Epstein et al. 1972). More case reports and epidemiology studies are needed to properly evaluate genotoxic effects in humans exposed to heptachlor or heptachlor epoxide. The results of *in vitro* studies suggest that neither compound alters the frequency of gene mutations (Crebelli et al. 1986; Gentile et al. 1982; Glatt et al. 1983; Marshall et al. 1976; NTP 1987; Probst et al. 1981; Zeiger et al. 1987), and that heptachlor does not induce DNA damage in bacteria (Rashid and Mumma 1986) or rodents (Maslansky and Williams 1981; Probst et al. 1981). Alterations were observed in assays of unscheduled DNA synthesis in human fibroblasts (Ahmed et al. 1977) and chromosomal alterations in Chinese hamster ovary cells (NTP 1987). *In vivo* animal research into the effects of heptachlor and heptachlor epoxide on sister chromatid exchange, chromosomal aberrations and anomalies, DNA adduct formation, gene mutation, and other genotoxic parameters would be helpful in assessing the genotoxic potential of heptachlor and heptachlor epoxide.

Reproductive Toxicity. Although a couple of studies have attempted to establish an association between heptachlor epoxide blood levels and premature delivery or stillbirth among women presumably

exposed via ingestion (Curley et al. 1969; Wassermann et al. 1982), elevated levels of other compounds (particularly PCBs, lindane, and dieldrin) limit the interpretation of the results. Animal studies have found impaired fertility and pregnancy losses following oral exposure to heptachlor (Akay and Alp 1981; Amita Rani and Krishnakumari 1995; Green 1970; Mestitzova 1967). The mechanism of the reproductive toxicity has not been elucidated; the available data suggest that both males and females may be affected. Additional studies are needed to identify NOAELs for reproductive effects, confirm the observed results, and identify the critical targets within the reproductive system.

Developmental Toxicity. Several studies have examined the potential developmental toxicity of heptachlor or heptachlor epoxide. These studies examined potential effects in the children of women exposed to heptachlor and heptachlor epoxide in contaminated cow's milk (Baker et al. 2004b; Le Marchand et al. 1986) or examined the possible association between maternal heptachlor epoxide levels and developmental effects (Gladen et al. 2003; Hertz-Picciotto et al. 2004). Several animal studies have also examined developmental toxicity (Lawson and Luderer 2004; Moser et al. 2001; Narotsky and Kavlock 1995; Narotsky et al. 1995; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001). The finding of impaired development of the nervous and immune systems was used as the basis of the intermediate-duration oral MRL for heptachlor. This study (Moser et al. 2001; Smialowicz et al. 2001) did not identify a NOAEL for these effects, additional studies would be useful for more clearly defining the threshold of toxicity. Impaired spatial memory was observed at the lowest dose tested among the offspring exposed until postnatal day 42, but not in rats exposed until postnatal day 21 (Moser et al. 2001); studies that would address the cause of the conflicting results would also be useful.

Immunotoxicity. No studies were located that specifically addressed immune function parameters following heptachlor or heptachlor epoxide exposure, although several studies have reported alterations in the lymphoreticular system (e.g., fibrosis in spleen, and increased size of spleen; decreased relative spleen weight) (Akay and Alp 1981; Aulerich et al. 1990; Pelikan 1971). A developmental toxicity study found suppression of the immune response in rats orally exposed *in utero*, during lactation, and postnatally until day 42 (Smialowicz et al. 2001). It is not known if these effects would also occur in mature animals. A study involving a battery of immune function tests would be useful for establishing whether heptachlor or heptachlor epoxide is toxic to the immune system.

Neurotoxicity. No human data on the neurotoxicity of heptachlor or heptachlor epoxide were identified. No data exist describing neurologic effects in animals following inhalation or dermal exposure of any duration. Several studies have demonstrated that exposure to heptachlor can result in neurological

effects, in particular, excitability and decreased motor activity (Akay and Alp 1981; Aulerich et al. 1990; Crum et al. 1993; Moser et al. 1995, 2003). As discussed in the Developmental Toxicity section, exposure to heptachlor (and presumably heptachlor epoxide) can result in impaired learning and memory; studies are needed to evaluate whether exposure of mature animals to heptachlor or heptachlor epoxide can also result in impaired learning and memory.

Epidemiological and Human Dosimetry Studies. The existing epidemiological studies are primarily of occupational cohorts (Blair et al. 1983; MacMahon et al. 1988; Shindell and Associates 1981; Wang and MacMahon 1979a), case reports of health effects seen in groups exposed to contaminated milk (Baker et al. 2004b; Chadduck et al. 1987; Le Marchand et al. 1986; Stehr-Green et al. 1986, 1988), or studies examining the possible association between elevated heptachlor/heptachlor epoxide blood levels and adverse health effects (Cantor et al. 2003; Cassidy et al. 2005; Curley et al. 1969; Gladen et al. 2003; Hertz-Picciotto et al. 2004; Pines et al. 1986; Quintana et al. 2004; Sturgeon et al. 1998; Wang and Grufferman 1981; Ward et al. 2000; Wassermann et al. 1982). These studies have generally not included good quantitation of the exposure to heptachlor or heptachlor epoxide. In many cases, it is not possible to determine the exact identity of the contaminants involved. Although use of this compound has been discontinued, exposure could nevertheless occur through food grown in contaminated soil, through contact with pesticides applied to homes and other structures, or from hazardous waste sites. Analytical methods are available to determine exposure to heptachlor or heptachlor epoxide (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968). However, no information is available that correlates levels of heptachlor epoxide in tissue with either level or duration of exposure. Occupational exposure levels are likely to be high enough to enable distinction from background levels. However, many epidemiological studies examining outcomes of exposure are limited by the accuracy of determining the exposure status of those individuals who show adverse health effects and those who show none. The precision and reliability of categorizing exposed individuals and non-exposed individuals contribute significantly to the statistical power of a study and greatly assist in accurate estimation of an increased risk. If data on exposure parameters are sparse or show very wide variation, it is difficult to determine what constitutes an exposure. More data on the correlation of tissue levels to exposure parameters would be useful for increasing the power of epidemiological studies to measure statistically significant associations between heptachlor exposure and health effects in cohorts from both occupational and contaminated community environments. Additionally epidemiology studies should focus on critical end points identified in animal studies including developmental toxicity (including neurological and immunological end points), liver effects, and cancer.

Biomarkers of Exposure and Effect.

Exposure. Exposure to heptachlor and heptachlor epoxide is currently measured by determining the level of these chemicals in the blood or adipose tissue in living organisms (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968). This measure is specific for both heptachlor and heptachlor epoxide. Heptachlor epoxide is also a metabolite of chlordane, and thus its presence is not specific for exposure to heptachlor alone. However, in the absence of stable chlordane residues (e.g., nonachlor and oxychlordane), the heptachlor epoxide would most likely have been derived from heptachlor. Because heptachlor is believed to be converted rapidly in the body to heptachlor epoxide, it is impossible to determine whether the exposure was to one or the other of these two compounds. Heptachlor and heptachlor epoxide accumulate in adipose tissue and are released slowly over long periods of time. Therefore, it is not possible to accurately identify whether the exposure was recent or what the duration of exposure was. However, the ratio of heptachlor epoxide to heptachlor increases over time and therefore may be used as a biomarker of possible exposure to heptachlor. The sensitivity of the methods for identifying these compounds in human tissue appears to be only sufficient to measure background levels of heptachlor epoxide in the population. Additional biomarkers of exposure to heptachlor would be helpful at this time.

Effect. There is no clinical disease state unique to heptachlor. A major problem in developing a biomarker of effect for heptachlor or heptachlor epoxide is that human exposures to these compounds have occurred concomitantly with exposures to other chemicals, and it is difficult to attribute the health effects to heptachlor or heptachlor epoxide alone. More data that quantify the biological effects as well as data that distinguish heptachlor and heptachlor epoxide exposures from those of other chemicals would be useful for developing biomarkers of effect for population monitoring. Biomarkers that could indicate the length of time since exposure would also be useful.

Absorption, Distribution, Metabolism, and Excretion. There are very few data available to assess the relative rates of pharmacokinetic parameters with respect to route of exposure for either heptachlor or heptachlor epoxide. There are no human or animal inhalation or dermal studies on absorption, distribution, metabolism, or excretion. The only human data on metabolism come from *in vitro* studies using liver microsomes that indicate that, qualitatively, human microsomes metabolize heptachlor to the same end products as do rat microsomes (Tashiro and Matsumura 1978). Oral exposure in members of farm families led to elevated serum levels of heptachlor metabolites (Stehr-Green et al. 1986), indicating that the compound is absorbed through the gastrointestinal tract. Animal studies also

suggest that uptake occurs through the gastrointestinal tract following oral dosing; excretion of these doses occurs primarily through the bile duct into the feces (Tashiro and Matsumura 1978). Lethality data suggest that heptachlor can be absorbed through the skin (Gaines 1969), but there are no data on absorption, distribution, metabolism, or excretion of dermally absorbed doses. Heptachlor epoxide is more toxic than heptachlor and has a longer half-life. Additional absorption, distribution, metabolism, and excretion data would be useful in order to gain a thorough understanding of the pharmacokinetic parameters of heptachlor and heptachlor epoxide.

Comparative Toxicokinetics. There are limited available data with which to compare humans and other animal species. Although human toxicity data are available (Baker et al. 2004b; Blair et al. 1983; Cantor et al. 2003; Cassidy et al. 2005; Chadduck et al. 1987; Curley et al. 1969; Gladen et al. 2003; Hertz-Picciotto et al. 2004; Le Marchand et al. 1986; MacMahon et al. 1988; Pines et al. 1986; Quintana et al. 2004; Shindell and Associates 1981; Stehr-Green et al. 1986, 1988; Sturgeon et al. 1998; Wang and Grufferman 1981; Wang and MacMahon 1979a; Ward et al. 2000; Wassermann et al. 1982), the results of these studies are difficult to compare with the animal studies (Akay and Alp 1981; Amita Rani and Krishnakumari 1995; Aulerich et al. 1990; Berman et al. 1995; Crum et al. 1993; Izushi and Ogata 1990; Krampl 1971; Moser et al. 2001; Narotsky and Kavlock 1995; Narotsky et al. 1995; NCI 1977; Pelikan 1971; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001) because the exposure was not well characterized in the human studies and often involved exposure to multiple chemicals. As discussed in the previous section, there are limited data on the toxicokinetics of heptachlor and heptachlor epoxide. With the exception of human monitoring studies examining the levels of heptachlor/heptachlor epoxide in various tissues (Adeshina and Todd 1990; Barquet et al. 1981; Burns 1974; Greer et al. 1980; Klemmer et al. 1977; Polishuk et al. 1977b; Radomski et al. 1968; Stehr-Green et al. 1988; Wassermann et al. 1974), the available toxicokinetic data are in animals. Thus, direct comparisons between humans and animals can not be made. An *in vitro* comparative study found that the metabolites produced in humans and rats are identical, but the amounts differ (Tashiro and Matsumura 1978). Moreover, the rate of metabolism is not similar in both species. Thus, the rat may not be an appropriate metabolic model for humans. Additional studies, particularly *in vivo* studies, are needed to support these findings and identify the most appropriate animal model. There is a lack of information regarding kinetic changes after prolonged exposure. This kind of information would be useful because most exposures in the general population (e.g., from contaminated food or improperly applied pesticides) are likely to be long-term and low-dose.

Methods for Reducing Toxic Effects. The mechanism by which heptachlor and heptachlor epoxide are absorbed from the gastrointestinal tract is unknown. Current methods for reducing absorption

from the gastrointestinal tract involve removing these chemicals from the site of absorption (Haddad and Winchester 1990; HSDB 2007a; Morgan 1989). Additional studies examining the method of absorption would provide valuable information for developing methods that can interfere with gastrointestinal absorption. Numerous studies have examined the distribution of heptachlor and heptachlor epoxide (Barquet et al. 1981; Burns 1974; Curley et al. 1969; Greer et al. 1980; Jonsson et al. 1977; Polishuk et al. 1977b; Radomski et al. 1968). Additional studies on distribution are not necessary at this time. No established methods exist for reducing body burden of heptachlor and heptachlor epoxide. However, available information suggests that removal of these compounds via biliary-gastrointestinal excretion can be accelerated (Morgan 1989). Reducing enterohepatic recirculation before these chemicals partition to tissues may be effective (Haddad and Winchester 1990; HSDB 2007a). Thus, studies examining the effectiveness of repeated doses of activated charcoal or cholestyramine in reducing body burden would be useful. Adipose tissue serves as a major storage repository for both heptachlor and heptachlor epoxide (Barquet et al. 1981; Burns 1974; Greer et al. 1980; Harradine and McDougall 1986). Losing fat can mobilize the stored compound and increase the rate of its elimination. However, it may temporarily increase the blood levels of heptachlor epoxide. Studies that would examine the benefits of reducing body burden with accompanying fat reduction while balancing against harmful effects from temporary increase in blood level would be useful. Since heptachlor undergoes epoxidation to produce heptachlor epoxide which is more toxic than the parent compound, studies examining drugs that would inhibit the enzyme catalyzing this conversion would be helpful. Neurotoxicity of heptachlor epoxide is believed to result, at least in part, from interference with GABA receptor function (Yamaguchi et al. 1980). The available data suggest that benzodiazepenes and barbiturates may be useful in mitigating some of the neurological symptoms of heptachlor epoxide (Bronstein and Currance 1988; HSDB 2007b; Morgan 1989). However, additional studies examining the effectiveness of GABAergic function in mitigating heptachlor epoxide's neurologic effects would be useful. The liver also appears to be a major target organ for the toxic effects of heptachlor and heptachlor epoxide in animals (Akay and Alp 1981; Krampl 1971; Pelikan 1971). An understanding of the mechanism of action in the liver may identify new approaches for reducing the toxic effects.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are suggestive data indicating that children, particularly children exposed *in utero* and during infancy, may be unusually susceptible to the toxicity of heptachlor. A study in adolescents exposed to

heptachlor and heptachlor epoxide during gestation found significant alterations in neurobehavioral function (Baker et al. 2004b). Similarly, alterations in neurobehavioral function were observed in rats exposed during gestation through postnatal day 42 (Moser et al. 2001). Because neurobehavioral performance has not been investigated in adults, it is difficult to determine whether children are more susceptible to the neurotoxicity of heptachlor than adults. Additionally, no studies have investigated whether there are age-specific differences in the toxicokinetic properties of heptachlor or heptachlor epoxide. Additional studies are needed to evaluate potential age-related differences in the toxicity of heptachlor and heptachlor epoxide.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Patrick Wong at the University of California at Davis is investigating ligand-independent endocrine disruption by several pesticides include heptachlor epoxide. Ongoing research by D.E. Wooley, also at the University of California at Davis, is investigating the neurotoxic effects and mechanisms of action of environmental toxicants including heptachlor following acute and chronic exposure.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of heptachlor and heptachlor epoxide is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of heptachlor and heptachlor epoxide is located in Table 4-2.

Table 4-1. Chemical Identity of Heptachlor and Heptachlor Epoxide[a]

Characteristic	Heptachlor	Heptachlor epoxide
Synonym(s)	3-Chlorochlordene; 1,4,5,6,7,8,8a-hepta-chloro-3a,4,7,7a-tetrahydro-4,7-methanoindene; 1,4,5,6,7,8,8-heptachloro-3A,4,5,5a tetrahydro; alpha-dicylcopentadiene, 3,4,5,6,8,8a heptachloro, and others	Epoxyheptachlor; 1,4,5,6,7,8,8a-hepta-chloro-2,3-epoxy-3a,4,7,7a-tetra-hydro-4,7-methanoindene; 4,7-methanoindan, 1,4,5,6,7,8, 8-heptachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-; 2,5-methano-2h-indeno (1,2-b)oxirene, 2,3,4,5,6,7, 7-heptachloro-1a,1b, 5,5a,6,6a-hexahydro-, (1aalpha,1bbeta,2alpha,5alpha, 5abeta,6beta,6aalpha)-
Registered trade name(s)	Basaklor; Gold Crest H-60; Termide; Heptagran; Heptagranox; Heptamak; Heptamul; Soleptax; Velsicol 104	Velsicol 53-CS-17
Chemical formula	$C_{10}H_5Cl_7$	$C_{10}H_5Cl_7O$
Chemical structure		
Identification numbers:		
CAS registry	76-44-8	1024-57-3
NIOSH RTECS	PC0700000	
EPA hazardous waste	P059	D031
OHM/TADS	7216526	833300216
DOT/UN/NA/IMDG shipping	UN 2761, UN2782, UN 2995, UN2996, IMO 3.0, IMO 6.1	UN 2761, UN2782, UN 2995, UN2996, IMO 3.0, IMO 6.1
HSDB	554	6182
NCI	C00180	

[a]All information obtained from HSDB 2007a for heptachlor or HSDB 2007b for heptachlor epoxide unless otherwise noted.

CAS = Chemical Abstracts Services; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Heptachlor and Heptachlor Epoxide[a]

Property	Heptachlor	Heptachlor epoxide
Molecular weight	373.32	389.40
Color	White (pure); tan (technical grade)[b]	White[b]
Physical state	Crystalline solid	Crystalline solid[b]
Melting point	95–96 °C (pure); 46–74 °C (technical grade)[c]	160–161.5 °C
Boiling point	145 °C	No data
Specific Gravity:		
at 9 °C	1.57	No data
Odor	Camphor-like	No data
Odor threshold:		
Water	No data	No data
Air	0.3 mg/m^3	0.3 mg/m^3
Solubility:		
Water at 25 °C	0.05 mg/L[d]	0.275 mg/L[d]
Organic solvent(s)	Soluble in most organic solvents	Soluble in most organic solvents[b]
Partition coefficients:		
Log K_{ow}	6.10	5.40
Log K_{oc}	4.34[e]	3.34–4.37[f]
Vapor pressure		
	3x10^{-4} mmHg[g] at 20 °C	1.95x10^{-5} mmHg at 30 °C[h]
	3x10^{-4} mmHg at 25 °C	No data
Henry's law constant:		
at 25 °C	2.94x10^{-4} atm-m^3/mol	3.2x10^{-5} atm-m^3/mol
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	Highly flammable	Non-combustible
Conversion factors	1 ppm=15.27 mg/m^3 at 25 °C, 1 atm	1 ppm=15.93 mg/m^3 at 25 °C, 1 atm
Explosive limits	Non-combustible	Containers may explode when heated

[a]All information obtained from HSDB 2007a for heptachlor or HSDB 2007b for heptachlor epoxide unless otherwise noted
[b]IARC 1974
[c]Worthing and Walker 1987
[d]EPA 1987
[e]Chapman 1989
[f]Estimated from Lyman et al. 1982
[g]ACGIH 1986
[h]Nash 1983

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Heptachlor was first registered for use in the United States as an insecticide in 1952 and commercial production began the following year (EPA 1986a). Nearly all registered uses of heptachlor were canceled in 1974 by EPA because of its potential cancer risk and its persistence and bioaccumulation throughout the food chain (EPA 1986a). The sale of heptachlor was voluntarily canceled in 1987 by its sole U.S. manufacturer, the Velsicol Chemical Corporation. The sale, distribution, and shipment of existing stocks of all canceled chlordane and heptachlor products were prohibited in the United States as of April 1988 (EPA 1990a; SRI 1990). Heptachlor is a constituent of technical-grade chlordane, approximately 10% by weight (HSDB 2007a). Heptachlor epoxide is an oxidation product of heptachlor and of chlordane; it is not produced commercially in the United States (IARC 1979).

Crown chemical company, the last company in the United States reported to have manufactured heptachlor, transferred its registry to Wood Protection Products, Inc. on October 8, 1985. Since 1985, heptachlor use in the United States has been limited to treatment of fire ants in power transformers. All other heptachlor uses have been banned in the United States.

Table 5-1 summarizes the facilities in the United States that manufacture or process heptachlor. It also lists the maximum amounts of heptachlor that are allowed at these sites and the end uses of the heptachlor. This information is based on the release data reported to the Toxics Release Inventory (TRI) in 2004 (TRI04 2006). The majority of facilities that reported heptachlor release in 2004 were hazardous waste treatment plants that processed heptachlor for safe disposal.

Heptachlor is produced commercially by the free-radical chlorination of chlordene in benzene containing 0.5–5.0% of fuller's earth. The reaction is run for up to 8 hours. The chlordene starting material is prepared by the Diels-Alder condensation of hexachlorocyclopentadiene with cyclopentadiene (Sittig 1980). Technical-grade heptachlor usually consists of 72% heptachlor and 28% impurities such as *trans*-chlordane, *cis*-chlordane, and nonachlor (HSDB 2007a).

The U.S. International Trade Commission (USITC) did not report the domestic production volume of heptachlor separately for the years 1981–1985 (USITC 1982b, 1983b, 1984b, 1985, 1986). Only yearly totals were reported for all cyclic insecticides. The USITC reports production volume data only for

Table 5-1. Facilities that Produce, Process, or Use Heptachlor

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	3	0	99,999	7, 12
CA	1	0	99	12
FL	1	10,000	99,999	7
GA	1	1,000	9,999	7
IL	3	0	9,999	12
KY	2	100	9,999	12
LA	2	0	9,999	12
MI	1	0	99	12
MS	1	0	99	12
NE	2	100	9,999	12
NJ	2	0	9,999	12
NV	1	100	999	2, 3, 12
OH	3	100	99,999	12
OR	2	100	9,999	12
PA	1	0	99	12
SC	1	100,000	999,999	12
TN	4	10,000	999,999	1, 4, 7
TX	5	0	999,999	12
UT	3	0	9,999	12

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI04 2006 (Data are from 2004)

chemicals for which three or more manufacturers report volumes that exceed certain minimum output levels.

5.2 IMPORT/EXPORT

The USITC did not report separate import data for heptachlor for the years 1981, 1982, or 1983 (USITC 1982a, 1983a, 1984a). The sale, distribution, and shipment of existing stocks of all canceled heptachlor products were prohibited by EPA in 1988 (EPA 1990a). According to the USITC, heptachlor has not been imported into the United States from 1986 to 2007 (USITC 2007).

No information was located regarding the exportation of heptachlor or heptachlor epoxide.

5.3 USE

Heptachlor is a persistent insecticide that kills insects by both ingestion and dermal contact. It is nonphytotoxic at insecticidal concentrations (Worthing and Walker 1987). Heptachlor was used extensively from 1953 to 1974 as a soil and seed treatment to protect corn, small grains, and sorghum from pests. It was used to control ants, cutworms, maggots, termites, thrips, weevils, and wireworms in both cultivated and uncultivated soils. Heptachlor was also used nonagriculturally during this time period to control termites and household insects (EPA 1986a; Worthing and Walker 1987).

EPA proposed cancellation of nearly all registered uses of heptachlor in 1974 because of its potential cancer risk and its persistence and bioaccumulation throughout the food chain. The few agricultural uses that were not canceled in 1974, treatment of field corn, seed (for corn, wheat, oats, barley, rye, and sorghum), citrus, pineapple, and narcissus bulbs, were phased out gradually over a 5-year period ending on July 1, 1983 (EPA 1986a). By April 1988, heptachlor could no longer be used for the underground control of termites. That same year, EPA prohibited the sale, distribution, and shipment of existing stocks of all canceled chlordane and heptachlor products. Subsequently, virtually all uses of heptachlor products were voluntarily canceled by the registrant, Velsicol Chemical Corporation (EPA 1990a). The only current use of heptachlor is in the treatment of fire ants in underground power transformers. This use was specifically exempted from EPA's suspension and cancellation actions because it was believed to result in insignificant exposure and, consequently, insignificant risk. It is unclear whether or not this exempted use is currently supported since Velsicol voluntarily chose not to renew their registration for technical-grade heptachlor in 1999 (EPA 1999a). A search of the National Pesticide Information Retrieval System, which

lists all of the labels for currently registered pesticides, produced no active labels for heptachlor (NPIRS 2007).

5.4 DISPOSAL

Heptachlor and heptachlor epoxide are Resource Conservation and Recovery Act (RCRA) hazardous wastes and hazardous constituents (EPA 1986b); as such, they must be disposed of in secure landfills in compliance with all federal, state, and local regulations. They may also be incinerated at 1,500 °F for 0.5 seconds for primary combustion and at 3,200 °F for 1 second for secondary combustion, with adequate scrubbing of incinerator exhaust and disposal of ash (Sittig 1985).

6. POTENTIAL FOR HUMAN EXPOSURE

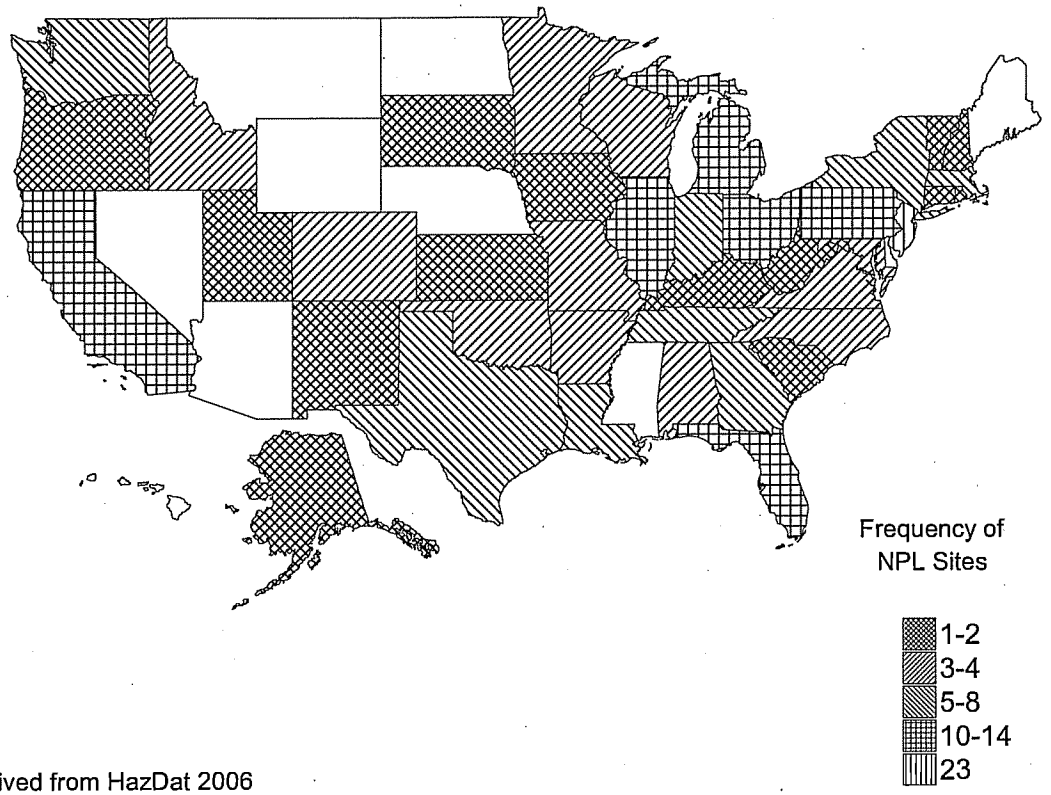
6.1 OVERVIEW

Heptachlor and heptachlor epoxide have been identified in at least 210 and 200 of the 1,684 hazardous waste sites, respectively, that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2006). However, the number of sites evaluated for heptachlor is not known. The frequency of these sites can be seen in Figure 6-1 and 6-2, respectively. Of these sites for heptachlor, 207 are located within the United States, 2 are located in the Commonwealth of Puerto Rico (not shown), and 1 is located in the Virgin Islands. For heptachlor epoxide, 195 of these sites are located within the United States, 2 are located in Guam, 2 are located in the Commonwealth of Puerto Rico, and 1 is located in the Virgin Islands.

Heptachlor was used extensively until the 1970s as a broad-spectrum insecticide on a wide variety of agricultural crops, with the major use on corn. It also had nonagricultural uses including seed treatment, home and garden uses, and termite control. In 1974, EPA proposed cancellation of nearly all registered uses of heptachlor except termite and fire ant control and dipping of roots or tops of nonfood plants, a use that was subsequently voluntarily canceled by the registrant in 1983 (EPA 1986a). In 1988, the sale, distribution, and shipment of existing stocks of all heptachlor products were prohibited in the United States with an exemption for the use of fire ant control. As of April 1988, heptachlor could no longer be used for the underground control of termites. Currently, the only commercial use of heptachlor still permitted in the United States is fire ant control in underground power transformers (EPA 1990a); however, in 1999, the sole manufacturer of heptachlor chose not to renew its registration with the EPA (EPA 1999a). As of April 2007, there were no active pesticide labels containing heptachlor (NPIRS 2007). Therefore, it is unclear whether heptachlor is still available in the United States.

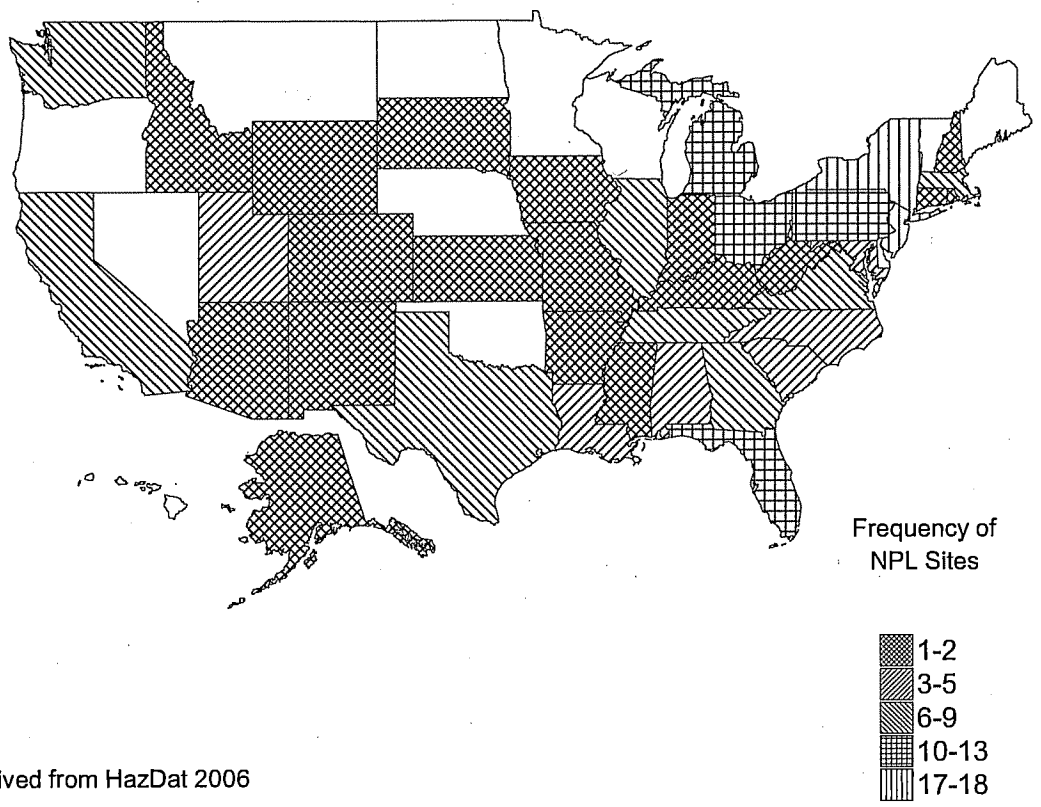
Heptachlor is converted to heptachlor epoxide and other degradation products in the environment. Heptachlor epoxide degrades more slowly and, as a result, is more persistent than heptachlor. Heptachlor epoxide has been found in food crops grown in soils treated with heptachlor many years before. Both heptachlor and heptachlor epoxide adsorb strongly to sediments, and both are bioconcentrated in aquatic and terrestrial organisms. Biomagnification of heptachlor and heptachlor epoxide in aquatic food chains is significant. Because heptachlor is readily metabolized to heptachlor epoxide by higher trophic level organisms, biomagnification of heptachlor itself is not significant. Because of the more persistent nature of heptachlor epoxide and its lipophilicity, biomagnification of heptachlor epoxide in terrestrial food chains is significant.

Figure 6-1. Frequency of NPL Sites with Heptachlor Contamination



Derived from HazDat 2006

Figure 6-2. Frequency of NPL Sites with Heptachlor Epoxide Contamination



Derived from HazDat 2006

In the past (prior to 1974), exposure of humans to heptachlor and heptachlor epoxide was directly related to the application of heptachlor as an insecticide. However, because of the persistence and bioaccumulation of heptachlor and heptachlor epoxide, exposure of the general population can occur through ingestion of contaminated food (especially cow or human milk), inhalation of vapors from contaminated soil and water, or direct contact with residual heptachlor from pesticide application. People whose homes have been treated may continue to be exposed to these chemicals in the air over long periods. Occupational exposure can occur in the manufacture of the chemical or from use of heptachlor to control fire ants. The most likely routes of exposure at hazardous waste sites are unknown. Heptachlor has been found infrequently in soil and groundwater at hazardous waste sites. Children who eat contaminated soil or people who obtain tap water from wells located near hazardous waste sites might be exposed to heptachlor. Further, since both compounds can volatilize from soil, people living near hazardous waste sites may be exposed to the compounds in the air. People whose homes have been professionally treated for termites, either by spraying or subsurface injection, may continue to be exposed to heptachlor and possibly to its transformation product, heptachlor epoxide, in the indoor air over long periods. Releases can also occur from the use of existing stocks in the possession of homeowners (EPA 1990a).

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005f). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005f).

6.2.1 Air

Estimated releases of 2 pounds of heptachlor and heptachlor epoxide to the atmosphere from 14 domestic manufacturing and processing facilities in 2004, accounted for <0.1% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases are summarized in Table 6-1.

6.2.2 Water

Estimated releases of 9 pounds of heptachlor and heptachlor epoxide to surface water from 14 domestic manufacturing and processing facilities in 2004, accounted for about 0.3% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases are summarized in Table 6-1. These releases were predominantly from hazardous waste disposal agencies (TRI04 2006).

Heptachlor and heptachlor epoxide may enter surface water and groundwater in runoff from contaminated soils or in discharges of waste water from production facilities.

6.2.3 Soil

Estimated releases of 3,140 pounds of heptachlor and heptachlor epoxide to soils from 14 domestic manufacturing and processing facilities in 2004, accounted for >99% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases are summarized in Table 6-1. These releases were predominantly from hazardous waste disposal agencies (TRI04 2006).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Heptachlor has a low vapor pressure ($3.0x10^{-4}$ mmHg at 25 °C) and low water solubility (0.056 mg/L) (EPA 1987; Jury et al. 1987). The experimental value for the Henry's law constant is $1.48x10^{-3}$ suggesting that heptachlor partitions somewhat rapidly to the atmosphere from surface water and that volatilization is significant (EPA 1987; Lyman et al. 1982). Heptachlor is also subject to long-range transport and wet deposition.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Heptachlor[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	2	0	No data	No data	0	0	0	0	0
LA	1	0	No data	No data	7	0	7	0	7
NE	1	0	No data	No data	0	0	0	0	0
NJ	1	0	9	No data	7	0	16	0	16
NV	1	0	No data	No data	162	0	162	0	162
OH	2	1	0	No data	1	0	1	1	2
OR	1	0	No data	No data	2,962	0	2,962	0	2,962
PA	1	0	No data	No data	0	0	0	0	0
TX	3	0	0	No data	0	0	0	0	0
UT	1	0	No data	No data	0	0	0	0	0
Total	14	2	9	No data	3,140	0	3,149	1	3,150

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

The log soil organic carbon adsorption coefficient (log K_{oc}) for heptachlor was estimated to be 4.34 (Chapman 1989). The log K_{oc} value indicates a very high sorption tendency, suggesting that it will adsorb strongly to soil and is not likely to leach into groundwater in most cases (Chapman 1989). The leaching potential at 15 cm (concentration in soil water/concentration in soil) for heptachlor is 0.06, and the volatilization potential at 15 cm (concentration in soil air/concentration in soil) determined in laboratory studies is $5.5x10^{-3}$, again suggesting that heptachlor is unlikely to leach appreciably in soil but has some volatilization potential (McLean et al. 1988). These are important properties since heptachlor can remain deep in soil for years. The organic matter content of the soil is another factor affecting mobility. Heptachlor is less likely to leach from soil with a high organic matter content. When released into water, it adsorbs strongly to suspended and bottom sediment.

Volatilization from soil particles to the atmosphere is possible (McLean et al. 1988). Volatilization is an important mechanism of transport of heptachlor from land surfaces (Jury et al. 1987). When heptachlor was applied to orchard grass, approximately 90% was lost in 7 days. When it was applied to moist soil surfaces, 50% was lost in 6 days. When it was applied to dry soil surface, 14–40% was lost in approximately 2 days (50 hours). Volatilization was much less—only 7% in 167 days—when incorporated to a shallow depth of 7.5 cm (Jury et al. 1987). Temperature and humidity affect the persistence of heptachlor and total heptachlor (heptachlor plus heptachlor epoxide) in soil (Shivankar and Kavadia 1989). An increase in temperature resulted in a decrease in the volatilization half-lives of heptachlor and total heptachlor. For example, at 18±1 °C (90±5% relative humidity [RH]) and 35±1 °C (90±5% RH), the half-lives of heptachlor (6 ppm) were 44.8 days and 38 days, respectively. Persistence of heptachlor and total heptachlor was found to be greater at higher humidity, irrespective of temperature. At the combination of higher temperature (25±1 °C) and low humidity (55±5% RH), faster dissipation of heptachlor occurred (half-life=24.67 days). At lower temperatures (18±1 °C) and low humidity (55±5% RH), greater persistence of heptachlor was found (40.67 days). Half-lives of total heptachlor (6 ppm) were longer because of the more persistent nature of heptachlor epoxide (Shivankar and Kavadia 1989).

The logarithm of the *n*-octanol/water partition coefficient (log K_{ow}) is a useful preliminary indicator of bioconcentration potential of a compound. The log K_{ow} for heptachlor is 5.44 (Chapman 1989; MacKay 1982), suggesting a high potential for bioaccumulation and biomagnification in the aquatic food chain. The bioconcentration factors (BCFs) for heptachlor were 10,630 in Asiatic clam fat (*Corbicula*

manilensis), 2,570 in soft clams (*Mya arenaria*), and 8,511 in oysters (*Crassostrea virginica*) (Hawker and Connell 1986).

Heptachlor epoxide is soluble in water at a concentration of 0.275 mg/L (EPA 1987). The experimental value for Henry's law constant is $3.2x10^{-5}$ (EPA 1987), suggesting that heptachlor epoxide partitions slowly to the atmosphere from surface water (Lyman et al. 1982). Based on regression equations, the log K_{oc} for heptachlor epoxide was estimated to range between 3.34 and 4.37 (Lyman et al. 1982). These log K_{oc} values suggest a high sorption tendency, meaning that this compound is not mobile in soil and has a low potential to leach. The organic matter content of soil affects the mobility of heptachlor epoxide. Heptachlor epoxide is less likely to leach from soil with a high organic matter content. If released into water, it adsorbs strongly to suspended and bottom sediments.

The log K_{ow} for heptachlor epoxide is 5.40 (MacKay 1982), indicating a high potential for bioconcentration and biomagnification in the aquatic food chain. Estimated BCFs for heptachlor epoxide are 1,698 in mussels (*Mytilus edulis*), 851 in oysters (*C. virginica*) (Hawker and Connell 1986; Geyer et al. 1982), and 2,330 in Asiatic clam fat (*C. manilensis*) (Hartley and Johnston 1983). The bioconcentration potentials of heptachlor and heptachlor epoxide differ, with the more polar epoxide being concentrated to a lesser degree than the parent compound (Hartley and Johnston 1983). Biomagnification of heptachlor and heptachlor epoxide in aquatic food chains is significant. Because heptachlor is readily metabolized to heptachlor epoxide by higher trophic level organisms, biomagnification of heptachlor itself is not significant. Because of the more persistent nature of heptachlor epoxide and its lipophilicity, biomagnification of heptachlor epoxide in terrestrial food chains is significant.

Heptachlor and heptachlor epoxide are subject to long-range transport and removal from the atmosphere by wet deposition. Snowpack samples were collected at 12 sites in the Northwest Territories, Canada, in the winter of 1985–1986. Heptachlor epoxide was present in 20 of 21 samples at a mean concentration of 0.18 ng/L ($1.8x10^{-4}$ ppb) with reported concentrations ranging from 0.02 to 0.41 ng/L (from $2x10^{-5}$ to $4.1x10^{-4}$ ppb). Heptachlor epoxide was present in both the Bering and Chukchi Seas in 1993 at mean concentrations of 2.4 and 2.8 ng/m^3, respectively (Macdonald et al. 2000).

Heptachlor and heptachlor epoxide are also taken up by plants (translocated into plants by absorption through the roots). Loamy soils were treated with heptachlor at a total of 25 pounds per 5-inch acre over a 5-year period (1958–1962) (Lichtenstein et al. 1970). The commercial formulation of heptachlor used also contained γ-chlordane and nonachlor. Insecticide residues were absorbed by crops grown in these

soils, with carrots absorbing the largest amounts. Although residue levels in soils increased up to 1962, the residue concentrations in both carrots and potatoes peaked during the 1960 growing season. During that year, the concentration of total heptachlor in carrots was 1,900 ppb. Residue levels of total heptachlor on potatoes never exceeded 540–510 ppb (1960–1962). Apparently, a threshold had been reached beyond which the content of insecticidal residues remained constant in these two crops. When insecticide residue levels in soil started to decline (1963), both carrots and potatoes also contained proportionally smaller amounts of residue. In the fall of 1968, residues of total heptachlor were found in the following crops: carrots, 413 ppb (92% heptachlor epoxide); potatoes, 70 ppb (98% heptachlor epoxide); beets, 60 ppb (100% heptachlor epoxide); radishes, 140 ppb (100% heptachlor epoxide); and cucumbers, 90 ppb (95% heptachlor epoxide) (Lichtenstein et al. 1970). Despite being banned in Argentina, trace amounts of heptachlor and heptachlor epoxide (<10 ng/g dry weight) were found in organically grown tomato plants that had never been sprayed with any pesticide outside of Buenos Aires (Gonzalez et al. 2003). Heptachlor epoxide was detected in spruce and pine trees of western Canada and the concentration of heptachlor in these trees seemed to increase as the altitude increased (Davidson et al. 2003).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Heptachlor may undergo direct photolysis in sunlight and is also susceptible to photosensitized reactions (Graham et al. 1973; Ivie et al. 1972). Heptachlor epoxide is converted to intermediate and final photoproducts when exposed to sunlight or ultraviolet light on the surface of plants (Podowski et al. 1979). About 40–50% conversion occurred in 4 hours on bean leaves treated with rotenone, an insecticide, acting as a photosensitizer. No detectable photoproducts (photoheptachlor epoxide) were formed in the absence of rotenone. The photolysis products were ketones. The intermediate photoproduct possesses a reduced toxicity in mice as compared to heptachlor epoxide, and it is completely nontoxic to houseflies. The final photoproduct is more toxic to flies and mice than the parent heptachlor epoxide (Ivie et al. 1972). The photoisomers of heptachlor epoxide are not expected to form in appreciable amounts in the environment unless a potent photosensitizer is present (Ivie et al. 1972). The photolysis of heptachlor epoxide as a solid (pressed) disk, as a powder, and as 0.5% heptachlor epoxide in a potassium bromide (a photosensitizer) disk was studied. The physical nature of the sample and the intensity of illumination affected the rate of photolysis. After 121 hours of exposure to sunlight in July, 93, 98, and 0% heptachlor epoxide remained in the solid disk, powder, and potassium bromide disk, respectively. When a powdered sample of heptachlor epoxide was irradiated on a rooftop of an

unspecified location from January through mid-September, degradation was almost negligible until May, then increased through July, reaching a maximum decomposition rate of 1% per day at the end of July. By the end of the experiment (8.5 months), 39% of the original sample had decomposed (Graham et al. 1973).

6.3.2.2 Water

Heptachlor is hydrolyzed in surface water and distilled water to 1-hydroxychlordene and heptachlor epoxide. When heptachlor was added to a sample of river water maintained at room temperature and exposed to sunlight, only 25% remained after 1 week, and no heptachlor remained after the second week. The 75% loss of heptachlor after 1 week corresponds to a half-life of 3.5 days. It was observed that an equilibrium exists at the end of 4 weeks between 1-hydroxychlordene and heptachlor epoxide, so that approximately 60% of the converted heptachlor remained as 1-hydroxychlordene and 40% was converted to the epoxide. When heptachlor epoxide was added to a sample of river water (pH 7.3–8) and to distilled water, it remained unchanged for 8 weeks. A half-life of at least 4 years was calculated for heptachlor epoxide (Eichelberger and Lichtenberg 1971).

When a ^{14}C-heptachlor-treated model aquatic ecosystem was examined for transformation of heptachlor in water, the relative amounts of various transformation products in water were determined as the percentage of the total ^{14}C label in the water sample. Heptachlor was found to decrease from 100% to approximately 10% of total ^{14}C material in 1 day (Lu et al. 1975). After 1 day, 1-hydroxychlordene epoxide was present as 50% of the total ^{14}C, rose to 70% on day 3, and then remained constant until day 13 of the experiment. The heptachlor hydrolysis product, 1-hydroxychlordene, reached a maximum of 10% of the total ^{14}C at day 1 and decreased thereafter. A relatively small proportion of heptachlor epoxide was formed. Heptachlor epoxide was never found to be >10% of the total ^{14}C in the water sample. The authors concluded that the major pathway of heptachlor in aquatic systems is rapid abiotic hydrolysis of heptachlor to 1-hydroxychlordene followed by metabolism to 1-hydroxychlordene epoxide (Lu et al. 1975).

Heptachlor is metabolized by the freshwater microcrustacean, *Daphnia magna*, to heptachlor epoxide or 1-hydroxychlordene. 1-Hydroxychlordene is then converted to 1-ketochlordene, 1-hydroxy2,3-epoxy-chlordene, and their glucosides, sulfates, and other conjugates (Feroz et al. 1990).

6.3.2.3 Sediment and Soil

Incubations of heptachlor with a mixed culture of soil microorganisms for 12 weeks showed slow conversion of heptachlor to chlordene, 1-exohydroxychlordene, heptachlor epoxide, and chlordene epoxide. A mixed culture of soil microorganisms, obtained from a sandy loamy soil, degraded heptachlor epoxide to the less toxic 1-exohydroxychlordene at a rate of 1% per week during the 12-week test period (Miles et al. 1971).

Soil samples that contained heptachlor were taken from five locations selected to represent typical soil types and rainfall patterns in portions of the United States. The samples were taken from places where subterranean termites were a major problem and where heptachlor was applied for treatment (Carter and Stringer 1970). Residues were found in the soil 1, 2, and 3 years after application of heptachlor. Relatively high values for 1-hydroxychlordene, representing approximately 60% of the insecticide in the soil, were obtained from extracts of a Quincy loamy fine sand from Oregon 2 years after application. Significant amounts of 1-hydroxychlordene were also found in extracts of Lakeland sand from Florida. Generally, heptachlor epoxide represented only a small fraction of the insecticide present in the soils (Carter and Stringer 1970). Because the distribution and penetration of heptachlor were uneven, there were large variations in concentration in the soils and therefore, no general trends were recognized (Carter and Stringer 1970).

Loamy soils treated with heptachlor at 25 pounds per 5-inch acre, over a 5-year period from 1958 through 1962, contained about 5% of the applied dosages in the fall of 1968, primarily in the form of heptachlor epoxide. In addition to γ-chlordane and nonachlor, which were present in the original heptachlor formulation, two toxic metabolites (heptachlor epoxide and α-chlordane) as well as three unidentified compounds were detected, thus indicating the breakdown in soils of heptachlor and related compounds (Lichtenstein et al.1970).

Experiments with thick anaerobically digested waste water sludge at 35°C showed that heptachlor was converted to an extractable degradation product that was more persistent than the initial heptachlor. About a 50% loss of heptachlor epoxide was found in anaerobic thick sludge after approximately 60 days. No information was given as to the identity of the product. No heptachlor epoxide loss occurred in aerobic dilute sludge, and only slight heptachlor epoxide loss occurred in anaerobic dilute sludge (Hill and McCarty 1967).

6.3.2.4 Other Media

Heptachlor was reported to degrade up to 45% after 3 weeks of composting. Heptachlor and heptachlor epoxide were found in concentrations of 8.5–26 and <3.8 μg/kg of municipal solid waste, respectively. Concentrations of biosolid and municipal solid waste compost were recorded at levels <0.23 and <0.63 μg/kg for heptachlor and heptachlor epoxide, respectively (Buyuksonmez et al. 2000).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to heptachlor and heptachlor epoxide depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of heptachlor and heptachlor epoxide in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on heptachlor and heptachlor epoxide levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring heptachlor and heptachlor epoxide in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Indoor air levels of heptachlor were measured in various homes in Bloomington, Indiana, that had been professionally treated with a termiticide either by spraying or subsurface injection. Heptachlor was detected at concentrations ranging from 1.1 to 110 ng/m^3 (0.0001–0.007 ppb) (Anderson and Hites 1989). Three houses in North Carolina were treated with a termiticide containing both chlordane (0.5%) and heptachlor (0.25%). Immediately after treatment, the average ambient air level of heptachlor was 1.41 ± 0.64 μg/m^3 (0.092 ppb). At 12 months post-treatment, the heptachlor level in the air was 1.00 ± 0.70 μg/m^3 (0.065 ppb) (Wright and Leidy 1982). Heptachlor was detected at levels ranging from 1.64 to 13.2 ppb in workplace air in 1977 at the Velsicol Chemical Corporation plant in Tennessee that manufactured heptachlor (Netzel 1981). No heptachlor epoxide levels in air were detected (Netzel 1981). A study of nine households selected on the basis of high pesticide usage in an urban-suburban area in the southeastern United States found outdoor air levels of heptachlor ranging from not detectable (0.0006 ppb) to 0.003 ppb, with a mean of 0.001 ppb (Lewis et al. 1986). Heptachlor was found in seven of nine households at levels in indoor air ranging from not detectable to 0.02 ppb, with a mean of 0.006 ppb (Lewis et al. 1986). Air samples taken from Corpus Christi, Texas in 1998 had a mean heptachlor concentration of 0.04 ng/m^3 (Park et al. 2002). Heptachlor was measured in Alabama air from

January to October 1996. Heptachlor was found in concentrations ranging from 20 to 50 pg/m^3 with the highest concentrations in the summer months and the lowest concentrations in April and May. No heptachlor was detected in October (Jantunen et al. 2000). Heptachlor and heptachlor epoxide were also detected in air in Galveston, Texas in concentrations ranging from 6.1 to 77.2 and from not detected to 30.4 pg/m^3, respectively (Park et al. 2001).

Since heptachlor was used for termite control, monitoring the levels of heptachlor when applied in a home is of interest. In a study of 19 homes where heptachlor was used in the treatment of subterranean termite control, a mean concentration of 5 μg/m^3 was observed during treatment. After 24 hours, the concentration of heptachlor decreased to about 2 μg/m^3. However, even after 180 days, heptachlor levels remained around 2 μg/m^3, which was much higher than the 0.5 μg/m^3 mean from before treatment. Concentrations of heptachlor were highest in the basement of these homes with mean concentrations of 9 and 2 μg/m^3 during treatment and after 180 days, respectively (Kamble et al. 1992).

6.4.2 Water

A statewide survey (December 1985–February 1986) was conducted in Kansas to determine the degree and extent of pesticide contamination of drinking water from approximately 100 private farmstead wells. Heptachlor was detected in 1% of the wells tested at a concentration range of 0.023–0.026 ppb with an average concentration of 0.025 ppb (detection limit=0.02 ppb) (Steichen et al. 1988).

Heptachlor was included in EPA's Pesticides in Groundwater Database for 17 states and was found in 6 states: Illinois, Indiana, Missouri, New Jersey, South Carolina, and Virginia. Concentrations of heptachlor in groundwater from these six states ranged from $6.6x10^{-5}$ to 0.052 ppb (EPA 1992). Heptachlor epoxide was included in EPA's Pesticides in Groundwater Database for 16 states and was found in 7 states: Alabama, Illinois, Indiana, Kansas, Massachusetts, South Carolina, and Virginia. Concentrations of heptachlor in groundwater from these seven states ranged from a trace to 0.014 ppb (EPA 1992).

Heptachlor and heptachlor epoxide were detected in water column samples at different depths in Lake Pontchartrain in New Orleans, Louisiana. Heptachlor was detected in the 1.5-m ebb- and flood-tide samples and in the 10-m flood-tide samples at concentrations of 0.6, 9.1, and 9.3 ppt, respectively. Heptachlor epoxide was detected in the 1.5-m ebb- and flood-tide samples and in the 10-m flood-tide sample at concentrations of 2, 3.9, or 2.5 ppt, respectively (McFall et al. 1985).

Findings from the Nationwide Urban Runoff Program priority pollutant samples collected in 1982 showed that heptachlor and heptachlor epoxide were detected at a concentration of 0.1 ppb for both compounds (Cole et al. 1984). Heptachlor and heptachlor epoxide were detected in 5 and 1%, respectively, of the 86 urban storm water runoff samples taken from 15 cities.

Despite being banned in 1988, heptachlor and heptachlor epoxide are still found in the water. Heptachlor was found in concentrations ranging from 180 to 22 ng/sample of lower Missouri River water (Petty et al. 1995). Heptachlor epoxide was found in samples taken from the Mississippi Delta in May and July of 1997 at concentrations of about 10 ng/g (Zimmerman et al. 2000). Heptachlor was found in 7% of the influent and 10% of the effluent of 84 New York City municipal waste water samples. Concentrations were 0.021–0.35 and 0.02–0.447 ng/L, respectively, for the years 1989–1993. Heptachlor epoxide was found in 1% the influent and 2% of the effluent out of 84 New York City municipal waste water samples in concentrations of 0.012 and 0.018–0.03 µg/L, respectively, for the years 1989–1993 (Stubin et al. 1996). Heptachlor epoxide was found in 11 out of 242 groundwater samples taken from areas near golf courses in concentrations lower than the maximum contaminant level (MCL), 0.16 µg/L (Cohen et al. 1999).

Analysis of rain samples demonstrates how heptachlor can be deposited at sites where it was not applied. Heptachlor epoxide was detected in rain samples at concentrations ranging from 0.03 to 1 ppt at four widely separated sites in Canada from May to October in 1984. The sites are representative of overlake and shoreline locations (Strachan 1988). Snowpack samples representing snow accumulation for the winter of 1985–1986 were collected at a total of 12 widely distributed sites throughout the Northwest Territories, Canada, during the spring of 1986. Heptachlor epoxide was detected at 11 of the 12 sites at concentrations ranging from 0.2 to 0.41 ng/L ($2x10^{-4}$–$4x10^{-4}$ ppb). The only reasonable source for these compounds is long-range atmospheric transport and deposition (Gregor and Gummer 1989). Heptachlor was detected in wet precipitation samples (rain/snow) from Lake Erie at a volume-weighted mean concentration (based on the total volume collected over the 12-month period) of 0.1 ng/L ($1x10^{-5}$ ppb) (Chan and Perkins 1989). Heptachlor epoxide was detected at volume-weighted mean concentrations of 0.05 ng/L ($5x10^{-5}$ ppb), 0.24 ng/L ($2.4x10^{-4}$ ppb), and 0.02 ng/L ($2x10^{-5}$ ppb) in wet precipitation samples from Lake Superior, Lake Erie, and Lake Ontario, respectively (Chan and Perkins 1989). Heptachlor and Heptachlor epoxide were detected in rain water near Galveston Bay, Texas in concentrations ranging as high as 139.7 and 155.7 pg/L, respectively (Park et al. 2001). Heptachlor epoxide was found in two of eight samples of rain water from horticultural areas in Denmark and in two of eight background areas in

Denmark at concentrations of above the detection limit (0.011), 0.002, 0.005, and 0.002 μg/L, respectively (Hamers et al. 2001). In January 1997, heptachlor was found in rain water in farm, urban, and Oakdale samples in Iowa at concentrations of 0.016, 0.011, and 0.0073 μg/L, respectively (Hochstedler et al. 2000).

Data maintained in the STORET database for 2003–2005 included heptachlor and heptachlor epoxide concentrations in industrial. Heptachlor was reported in 53% of the 804 water samples taken around the country in concentrations ranging from 1 μg/L to below quantification limits. Heptachlor epoxide was reported in 49% of the 809 water samples taken around the country in concentrations ranging from 1 μg/L to below quantification limits (EPA 2007).

6.4.3 Sediment and Soil

Data from the 1971 National Soils Monitoring Program at 1,486 sampling sites in 37 states showed that heptachlor was detected in 4.9% of the samples from cropland soils at concentrations ranging from 10 to 1,370 ppb. Heptachlor epoxide was detected in 6.9% of the samples at concentrations ranging from 100 to 430 ppb (Carey et al. 1978). A survey of agricultural soils (pasture soils) in the New South Wales North Coast region in Australia (1983–1984) showed soils contaminated with organochlorine residues. Heptachlor levels in the pasture soils generally averaged <100 ppb. Heptachlor epoxide residues were quantitatively higher. Heptachlor and heptachlor epoxide were generally highest in the top 22.5 cm of soil (McDougall et al. 1987). Heptachlor epoxide was detected in 17 out of 822 soil samples at 10 out of 49 agricultural sites in Illinois with a mean concentration of 17 μg/kg. In the same study, heptachlor was detected in 26 soil samples from 14 different sites with a mean concentration of 50 μg/kg (Krapac et al. 1995). Heptachlor was found in 3 out of 39 samples of Alabama soil with a geometric mean concentration of 0.037 ng/g. In the same study, heptachlor epoxide was found in 12 of the 26 soil samples with a geometric mean concentration of 0.099 ng/g (Harner et al. 1999).

Heptachlor epoxide was detected in grab and core samples of southern Lake Michigan sediments (period of sampling, 1969–1970) at trace levels up to 0.7 ppb (Leland et al. 1973). The U.S. Geological Survey investigated the sediment quality of the upper Rockaway River in New Jersey. Sediment samples were collected from seven stations along the upper Rockaway River. Stations 1 and 2 drain primarily forested areas of the upper Rockaway basin. Stations 3–7 drain an area consisting primarily of residential, commercial, and industrial land usage, including six NPL sites. Concentrations of heptachlor epoxide

were <0.1 ppb for stations 1 and 2. Heptachlor epoxide concentrations ranged from <0.1 to 10 ppb for stations 3–7 (Smith et al. 1987).

Heptachlor and heptachlor epoxide were monitored at six different sites in the sediment of San Pablo Bay, California. Heptachlor was not detected in four of the samples, while the other two samples contained 2.14 and 1.63 µg/kg of heptachlor. Heptachlor epoxide concentrations were below detection levels for all six samples (Baum et al. 2001). Heptachlor was found in the sediment of Casco Bay, Washington in concentrations ranging from 0.04 to 0.13 ppb (Kennicutt et al. 1994).

Heptachlor, which may have been applied to the World Trade Center for termite control, was detected in concentrations too low to quantify in the dust that settled across lower Manhattan after September 11, 2001 (Offenberg et al. 2003).

Heptachlor and heptachlor epoxide have been monitored in all 50 states and parts of Canada by the United States Geological Society (USGS). Heptachlor was detected in sediment at 9 out of 1,148 sites in 49 major hydrological basins at a maximum concentration of 8.3 µg/kg (USGS 2003); these data were collected from 1992 to 2001. In the same monitoring study, heptachlor epoxide was detected at 20 of the 1,148 sites, at a maximum concentration of 19.7 µg/kg. Data maintained in the STORET database for 2003–2005 included heptachlor and heptachlor epoxide concentrations in industrial effluent and ambient water. Heptachlor epoxide was reported in 4 of the 176 sediment samples taken with a maximum concentration of 0.621 µg/kg. Heptachlor was not reported in any of the 186 sites reporting data from 2003 to 2005 (EPA 2007).

6.4.4 Other Environmental Media

Heptachlor and heptachlor epoxide have been detected in several aquatic species. Heptachlor was measured in shrimp collected from the Calcasieu River/Lake Complex in Louisiana at concentrations ranging from 10 to 750 ppb (Murray and Beck 1990). A survey of organic compound concentrations in whole body tissues of the Asiatic clam, *C. manilensis*, was conducted on the Apalachicola River in northwest Florida in 1979–1980 as part of the Apalachicola River Quality Assessment. Heptachlor epoxide was detected in the whole body tissue of the clam at concentrations ranging from <0.1 to 0.6 ppb, with a median concentration of 0.3 ppb (Elder and Mattraw 1984).

Composite whole fish samples taken from tributary rivers around the Great Lakes in 1980–1981 had heptachlor levels of <0.002 mg/kg (<2 ppb) at all sites except the Ashtabula River where a maximum concentration of 0.30 mg/kg (300 ppb) occurred. Heptachlor epoxide was detected at concentrations ranging from 0.003 to 0.48 mg/kg (3–480 ppb) (DeVault 1985). Freshwater fish collected in 1984 for the National Contaminant Biomonitoring Program run by the U.S. Fish and Wildlife Service contained a geometric mean residue concentration of total heptachlor (heptachlor epoxide plus traces of heptachlor) of 0.01 ppm (wet weight). Heptachlor residues in fish were present in 49.1% of the collection stations (n=112) located at major rivers throughout the United States, including Alaska and Hawaii. Concentrations of heptachlor epoxide in whole fish samples remained highest in Hawaii and in the Midwest, especially in Lake Michigan and in the Mississippi, Missouri, Ohio, and Illinois Rivers (Schmitt et al. 1990).

Average residue levels of total heptachlor detected in Illinois soybeans in 1980 (6.6 ppb) showed an increase from 1974 levels (5.3 ppb), even though the usage of heptachlor declined during that period (MacMonegle et al. 1984). Heptachlor residues above maximum residue limits were reported in Australian beef in 1987. Upon removing the animals from contaminated pastures, the proportion of samples of beef with residue levels above the permitted limits decreased from 0.42% in 1986–1987 to 0.22% in 1987–1988 (Corrigan and Seneviratna 1989). In an earlier study, heptachlor epoxide levels in cow's milk reached a maximum of 0.22 ppm within 3–7 days after the animals had grazed on pastures immediately following treatment of the grasses with heptachlor (Gannon and Decker 1960).

Heptachlor concentrations in pork and beef have decreased from 1974 to 1996. In 1974–1984, heptachlor was detected in beef and pork in concentrations of 0.1–54 and 11.2–970 ppb, respectively. By 1988, heptachlor was not detected in beef and was detected in 33% of the pork samples studied in concentrations ranging from 1 to 8 ppb with no other detections in pork after 1988. Heptachlor epoxide was detected in concentrations of 1.9–2.9 and 0.5–5.9 ppb in pork and beef, respectively, during studies from 1974 to 1984. During the years 1985–1988, heptachlor epoxide was not detected in pork, but was detected in 35% of beef samples at concentrations ranging from 19 to 27 ppb. Heptachlor epoxide was still found in 3% of pork samples and 12% of beef samples taken from 1993 to 1996 (Cantoni and Comi 1997).

Monitoring data collected by the USGS from 1992 to 2001 at 1,148 sites in 49 U.S. major hydrological basins indicated that heptachlor and heptachlor epoxide were infrequently detected in fish (USGS 2003).

Heptachlor was detected in fish at 3 sites at a maximum concentration of 12 µg/kg and heptachlor epoxide was detected in fish at 88 sites at a maximum concentration of 270 µg/kg (USGS 2003).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is primarily exposed to heptachlor and heptachlor epoxide through diet. The food classes most likely to contain residues are milk and other dairy products, vegetables, meat, fish, and poultry. In the FDA Total Diet Study conducted between 1981 and 1982, levels of chemicals in the diet were determined by analyzing samples from retail markets in 13 cities throughout the continental United States. These samples represent the typical 14-day diet. Approximately 120 individual food items, including drinking water, were collected for each market basket sample; the infant diet consisted of about 50 of these foods, and the toddler diet included 110. The average daily intake of heptachlor epoxide for infants was estimated to be 0.01 µg/kg/day. The 1981–1982 average daily intake of heptachlor epoxide for toddlers was reported to be 0.009 µg/kg/day. Whole milk, with an average concentration of 0.1 ppb, contributed the highest daily intake of heptachlor epoxide for both toddlers and infants (Gartrell et al. 1986b). In the FDA Total Diet Study conducted between 1982 and 1984, analyses were performed of 234 items depicting the diets of eight population groups with members ranging in age from infants to elderly adults. The data represent eight food collections in regional metropolitan areas during the 2-year period. Toddlers (2 years old) had the highest daily intake of heptachlor epoxide (6.1 ng/kg/day). Infants had a daily intake of heptachlor epoxide of 2.7 ng/kg/day. Daily intake from whole milk was not included in this study. Adults had heptachlor epoxide intakes that ranged from 1.5 ng/kg/day (60–65-year-old females) to 2.8 ng/kg/day (14–16-year-old males). Heptachlor epoxide was found in 8% of the food samples analyzed between 1982 and 1984. Heptachlor intake was <0.1 ng/kg/day for all age/gender groups. Between 1980 and 1982–1984, daily intakes of heptachlor epoxide decreased from 19 to 3 ng/kg/day for infants, from 20 to 6 ng/kg/day for toddlers, and from 7 to 2–3 ng/kg/day for adults (Gunderson 1988). Heptachlor epoxide was found in 45 different food items from a total diet study. From this information and from questionnaires, it was estimated that heptachlor epoxide was found at a mean concentration of 0.3 µg/day in people surveyed in 1990 (MacIntosh et al. 1996).

The 1988 Acceptable Daily Intake (ADI) established by the United Nation's Food and Agriculture Organization and the World Health Organization (FAO/WHO) for total heptachlor was 0.5 µg/kg/day (FDA 1989). Total heptachlor intakes found in the Total Diet Analysis (1988) were 0.004 µg/kg/day for 6–11-month-old infants, 0.017 µg/kg/day for 14–16-year-old males, and 0.0007 µg/kg/day for 60–63-year-old females (FDA 1989).

Adipose tissue samples from various body parts of people living in northeast Louisiana, an area of heavy agriculture, were taken during pathological examination. Heptachlor epoxide levels in the individual tissue samples ranged from 20 to 790 ppb (average=239 ppb) for the 1980 study and from 60 to 220 ppb (average=159 ppb) from adipose tissue samples taken from other donors for the 1984 study (Holt et al. 1986).

Heptachlor and heptachlor epoxide have been found in human milk samples (Al-Omar et al. 1986; Fytianos et al. 1985; Larsen et al. 1971; Mes et al. 1986; Ritcey et al. 1972; Savage et al. 1981). Breast milk samples (n=210) taken from Canadian women from five different regions who had resided in Canada for at least 5 years were analyzed for chlorinated hydrocarbon contaminants as part of a monitoring program. Trends from 1967 to 1982 showed heptachlor epoxide levels decreased from a mean of 3 ppb in 1967 to a mean of <1 ppb in 1982 (maximum, 7 ppb) (Mes et al. 1986). Heptachlor epoxide was found in 62% of all samples taken in 1982 (Mes et al. 1986). Human milk samples obtained from 1,436 women residing in the United States were analyzed for chlorinated hydrocarbon insecticides. While heptachlor was recovered in <2% of the samples, heptachlor epoxide was found in 63% of the samples. The proportion of breast milk samples containing heptachlor epoxide varied significantly among the five geographic regions (66.1–128 ppb) with the southeastern states having the highest mean residual level. The reasons for higher levels of these chemicals in samples from women in the southeastern United States are not clear, but there may be several contributing factors. For example, more people in the southeast use pesticides in the home, lawn, and garden, and a larger proportion of southeastern U.S. homes have been treated with heptachlor for termite control. The mean residual level of heptachlor epoxide in breast milk for the whole United States was 91.4 ppb (Savage et al. 1981). A 5-month follow-up study of four pregnant Iraqi women without occupational exposure to organochlorine pesticides found total heptachlor levels in the placenta immediately after delivery ranging from not detectable to 28 ppb total tissue weight. Milk samples were then taken for 20 consecutive weeks. Average total heptachlor levels in the mothers' milk ranged from 15 to 68 parts per billion parts of whole milk (Al-Omar et al. 1986). There was considerable fluctuation in the residue concentrations over the 20 weeks. The authors suggest that the fluctuations could be attributed to changes in daily diet intake of residues and daily variations in milk production and fat content of the milk.

A pilot study for EPA's Non-Occupational Exposure Study was conducted in August 1985 in order to assess nonoccupational exposures to pesticides, including heptachlor, in indoor air and personal respiratory air. The study was conducted in nine households selected on the basis of high pesticide usage

in an urban-suburban area in the southeastern United States. The residents of these households were generally retired or semi-retired persons, who spent the majority of their time indoors (average=18 hours) and, consequently, do not represent the general adult population. The results showed that heptachlor was found in seven of nine households at levels in indoor air ranging from not detectable (at 0.0001 ppb) to 0.31 μg/m^3 (0.02 ppb), with a mean of 0.088 μg/m^3 (0.006 ppb). When residents wore personal monitors, operated only during periods of activity, heptachlor was detected in six of nine households at personal exposure levels of not detectable to 0.18 μg/m^3 (0.01 ppb), with a mean of 0.06 μg/m^3 (0.004 ppb). Outdoor air levels of heptachlor were lower, ranging from not detectable to 0.048 μg/m^3 (0.003 ppb), with a mean of 0.016 μg/m^3 (0.001 ppb), and were detected in five of nine households (Lewis et al. 1986).

Heptachlor has been routinely found in human breast milk as well as in animal and commercial milk products and has been studied extensively. A 25-year study of contaminants in human breast milk found that heptachlor in breast milk of Canadian mothers decreased from 3 ng/g in 1965 to 0.11 ng/g in 1992 (Craan and Haines 1998). Heptachlor has been detected in milk and umbilical cord fluid of 13.5% of the 385 mothers tested in the Arctic region of Canada with a mean concentration of 0.6 μg/L (Butler Walker et al. 2003). Termite control was associated with high heptachlor body burden as analyzed through breast milk in Australia where heptachlor epoxide was found in the breast milk of 575 of the 797 women tested in Victoria, Australia with concentration median of 0.007 mg/kg in 1997 (Sim et al. 1998). Average heptachlor epoxide levels in whole blood samples from non-occupationally exposed mothers and their newborns in Argentina were 0.23±0.29 ppb in 13 mothers and 0.06±0.01 ppb in 13 newborn infants (Radomski et al. 1971a). Heptachlor and heptachlor epoxide were found in 50 samples (51.5%) of pasteurized milk samples tested in Spain. Of the samples with heptachlor and heptachlor epoxide, eight of them contained levels that exceeded the limits stated by the European Union (Martinez et al. 1997). Heptachlor and heptachlor epoxide were found in cows' milk at concentrations of 6.5–28.5 and 8.5–34 ng/g, respectively (Armendariz et al. 2004).

In a study of non-occupationally exposed people in Jacksonville, Florida and Springfield/Chicopee, Massachusetts from 1986 to 1988, heptachlor was found in personal, outdoor, and indoor air samples. While Springfield/Chicopee did not have any samples that contained heptachlor, the concentration of heptachlor in samples from Jacksonville ranged from 0.1 to 0.8 ng/m^3 (Whitmore et al. 1994).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Infants and toddlers are exposed to higher levels (based on their greater dose to surface area [or body weight] ratio) of heptachlor epoxide in the diet (particularly from milk) than are adults. Higher exposure rates in indoor air may occur for at least 1 year in homes that have been treated for termites with heptachlor in the past. Although the most likely routes of exposure at hazardous waste sites are unknown, exposure may result from ingestion of contaminated soil near these sites particularly by children. Since both heptachlor and heptachlor epoxide volatilize from soil, inhalation exposure may also be important for persons living near hazardous waste sites. Exposure via ingestion of contaminated drinking water obtained from wells near hazardous waste sites is unlikely. Heptachlor and heptachlor epoxide are considered too lipophilic to leach to groundwater. While some samples have been found in well water, this trend is not universal. Workers involved in the manufacture of heptachlor and in the application of heptachlor for fire ant control are at risk of exposure to heptachlor. People living in the southeastern United States may be exposed to higher than background levels of heptachlor or heptachlor epoxide because of the larger proportion of southeastern U.S. homes that have been treated with heptachlor for termite control and the greater usage of pesticides in the home, lawn, and garden. Infants living in this region may be more likely to ingest heptachlor or heptachlor epoxide from maternal breast milk, although this exposure pathway is not restricted to the southeastern United States.

The average daily intake of heptachlor epoxide for infants was estimated to be 0.01 μg/kg/day. The 1981–1982 average daily intake of heptachlor epoxide for toddlers was reported to be 0.009 μg/kg/day. Whole milk, with an average concentration of 0.1 ppb, contributed the highest daily intake of heptachlor

epoxide for both toddlers and infants (Gartrell et al. 1986b). In the FDA Total Diet Study conducted between 1982 and 1984, analyses were performed of 234 items depicting the diets of eight population groups with members ranging in age from infants to elderly adults. The data represent eight food collections in regional metropolitan areas during the 2-year period. Toddlers (2 years old) had the highest daily intake of heptachlor epoxide (6.1 ng/kg/day). Infants had a daily intake of heptachlor epoxide of 2.7 ng/kg/day. The 1988 Acceptable Daily Intake (ADI) established by the United Nation's Food and Agriculture Organization and the World Health Organization (FAO/WHO) for total heptachlor was 0.5 μg/kg/day (FDA 1989). Total heptachlor intakes found in the Total Diet Analysis (1988) were 0.004 μg/kg/day for 6–11-month-old infants, 0.017 μg/kg/day for 14–16-year-old males, and 0.0007 μg/kg/day for 60–63-year-old females (FDA 1989).

Heptachlor epoxide was found in whole blood samples from nonoccupationally exposed mothers and their newborns in Argentina (Radomski et al. 1971a). The average level of heptachlor epoxide was 0.23±0.29 ppb in 13 mothers and 0.06±0.01 ppb in 13 newborn infants, although no blood samples were taken from the mothers during pregnancy (Radomski et al. 1971a).

In order to understand the exposure of children to pesticides, studies have been done to monitor pesticide levels in areas and food that are specific to children. Heptachlor was not detected in apple, pear, squash, or carrot baby food. Both organic and traditional manufacturers were studied (Moore et al. 2000). Studies of school areas along the Mexican-Texas border found heptachlor in 63% of all soil samples tested in concentrations ranging from a trace to 5 ppb (Miersma et al. 2003). Heptachlor was one of the most frequent chemicals found in a study of children's exposure to pesticides and was found in 8/9 home dust samples, 3/8 play areas, and 3/4 children's hand rinse samples (Lewis et al. 1994). In a study of pesticide exposure of children of farmworkers in Virginia and North Carolina, heptachlor was found in 10% of the floors at a mean concentration of 2 $\mu g/m^2$. Heptachlor, however, was not detected on any of the toys or hands of the children (Quandt et al. 2004).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Data concerning occupational exposure levels of heptachlor are very limited. An industrial hygiene survey conducted in 1977 at the Velsicol Chemical Corporation, Memphis, Tennessee, a plant that manufactured heptachlor, detected heptachlor in workplace air at levels ranging from 0.025 to 0.202 mg/m^3 (1.64–13.2 ppb) (Netzel 1981). Data from the National Occupational Exposure Survey

(NOES) conducted by NIOSH from 1981 to 1983 were not available for heptachlor or heptachlor epoxide.

People who worked with pesticides from 1954 to 1988, such as farmers and pest control workers, were at potentially higher risk of being exposed to heptachlor and heptachlor epoxide. People who worked in termite control before 1988 may have higher exposures to heptachlor since it was commonly used as a pesticide in the treatment of termites. High concentrations of heptachlor were found on applicators' hands and forearms with exposure rates calculated at 83 and 23 ng/cm^2/hour (Kamble et al. 1992). Heptachlor was not found in the blood of Japanese termite control workers in 1987, 1 year after chlordane, which contained heptachlor, was banned in Japan. Heptachlor epoxide, however, was found in all of the Japanese termite workers monitored from 1987 to 1990. The highest level of heptachlor epoxide was in the blood of a worker who had been working in pest control for 20 years and almost all of the workers still had heptachlor epoxide in their blood in 1990 (Jitunari et al. 1995). A study showed that farmers and their spouses in Iowa and North Carolina were exposed to heptachlor epoxide at concentration ranges of 0.21–0.55 ng/mL. With the exception of two of the spouses, everyone in the study had exposure limits of 0.21 ng/mL or greater as analyzed from serum concentrations (Brock et al. 1998).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of heptachlor and heptachlor epoxide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of heptachlor and heptachlor epoxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of heptachlor and heptachlor epoxide are sufficiently well defined to allow assessments of the environmental fate of the compounds to be made (ACGIH 1986; Chapman 1989; HSDB 2007a; MacKay 1982). Some physical and chemical properties of heptachlor epoxide that are not relevant to environmental fate are lacking. Knowledge of these properties, such as odor, flashpoint, and flammability limits, would be useful for workers involved in the manufacture, use, or clean-up of heptachlor and heptachlor epoxide.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2004, became available in May of 2006. This database is updated yearly and should provide a list of industrial production facilities and emissions.

The United States International Trade Commission (USITC) did not report separate import data for heptachlor for the years 1981, 1982, or 1983 (USITC 1982a, 1983a, 1984a). The sale, distribution, and shipment of existing stocks of all canceled heptachlor products were prohibited by EPA in 1988 (EPA 1990a). According to the USITC, no heptachlor has been imported into the United States from 1996 through 2007 (USITC 2007).

Currently, heptachlor use in the United States is limited to fire ant control in power transformers (EPA 1990a). However, because of former widespread use of heptachlor and the persistence of heptachlor epoxide, these compounds and their degradation products can still be found at low levels in indoor air, water, soil, and food. Disposal methods are well documented in the literature (EPA 1986b; Sittig 1985); however, more current information would be useful. Information on historical disposal practices would be helpful in evaluating the potential for environmental contamination. More information on the volume of heptachlor used in fire ant control would be useful in estimating potential occupational exposure.

Environmental Fate. Heptachlor and heptachlor epoxide are partitioned to the air, water, and soil (EPA 1987; Jury et al. 1987; Lichtenstein et al. 1970; Shivankar and Kavadia 1989). They are both transported in air and water and sorb to soils and sediment (Chapman 1989; MacKay 1982). They are biotransformed in soil and surface water, with biotransformation occurring faster for heptachlor than for heptachlor epoxide. Current data on the biotransformation (including half-life data) of both compounds

in surface water, surface soil, and subsurface soil would be useful in assessing the environmental persistence of these substances. Data on the toxicity of the biotransformation products of both compounds would assist in better characterizing the potential public health threat. Both heptachlor and heptachlor epoxide undergo photolysis (Graham et al. 1973; Ivie et al. 1972; Podowski et al. 1979). Data regarding the half-lives for photolysis would be helpful in determining the persistence of both compounds.

Bioavailability from Environmental Media. The limited pharmacokinetic data indicate that both compounds are absorbed following inhalation, oral, and dermal exposure (Arthur et al. 1975; Gaines 1969; Harradine and McDougall 1986). Additional information on the absorption of these compounds following inhalation and following ingestion of contaminated drinking water and soil would be useful in evaluating the relative importance of various routes of exposure to populations living in the vicinity of hazardous waste sites and those whose homes have been treated for termites with heptachlor or chlordane.

Food Chain Bioaccumulation. Heptachlor and heptachlor epoxide accumulate in aquatic and terrestrial organisms (Elder and Mattraw 1984; Murray and Beck 1990; Schmitt et al. 1990). Biomagnification of heptachlor and heptachlor epoxide in aquatic food chains is significant (Connell et al. 2002; Cullen and Connell 1994; Geyer et al. 1982; Hawker and Connell 1986). Because heptachlor is readily metabolized to heptachlor epoxide by higher trophic level organisms, biomagnification of heptachlor itself is not significant (Feroz et al. 1990). Because of the more persistent nature of heptachlor epoxide and its lipophilicity, biomagnification of heptachlor epoxide in terrestrial food chains is significant (Connell et al. 2002; Cullen and Connell 1994; Hartley and Johnston 1983). More current information regarding biomagnification of heptachlor epoxide in terrestrial food chains would be helpful in evaluating the extent of environmental contamination.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of heptachlor and heptachlor epoxide in contaminated media at hazardous waste sites are needed so that the information obtained on levels of heptachlor and heptachlor epoxide in the environment can be used in combination with the known body burden of heptachlor and heptachlor epoxide to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Heptachlor and heptachlor epoxide have been detected in indoor and outdoor air, surface water, groundwater, soil, sediment, food (Larsen et al. 1971; Lewis et al. 1986; MacIntosh et al. 1996; Park et al. 2002; USGS 2003), and fish (USGS 2003). Current monitoring data on levels of both compounds in

outdoor and indoor air and soil would be useful. Dietary intake data for the general population were located (FDA 1989; Gartrell et al. 1986b; Gunderson 1988; MacIntosh et al. 1996). Intake data for other media (air and water) are needed to estimate the risk of exposure of the general population.

Exposure Levels in Humans. Heptachlor epoxide has been detected in human blood, tissues (including adipose tissue), and breast milk (Al-Omar et al. 1986; Butler Walker et al. 2003; Craan and Haines 1998; Holt et al. 1986; Larsen et al. 1971; Savage et al. 1981). The presence of heptachlor epoxide is used as an indicator of exposure to heptachlor. Current monitoring studies of heptachlor epoxide in these tissues and fluids would be helpful in assessing the extent to which populations, particularly in the vicinity of hazardous waste sites, have been exposed to heptachlor. Reliable data regarding heptachlor levels in the elderly were not found. The elderly who may have been exposed to heptachlor have reduced capability to eliminate toxicants.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Heptachlor levels have been monitored in human breast milk as well as baby food (Moore et al. 2000). Heptachlor exposure of children at the Mexican-American border was studied as well as the exposure of children of farm workers and children whose homes were treated for termites (Lewis et al. 1994; Miersma et al. 2003; Quandt et al. 2004). Current monitoring studies of heptachlor and heptachlor epoxide in blood, fluids and tissues of children would be helpful in assessing the extent to which populations, particularly in the vicinity of hazardous waste sites, have been exposed to heptachlor.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children’s Susceptibility.

Exposure Registries. No exposure registries for heptachlor were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2006) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. The only current study pertaining to heptachlor was of the direct and indirect photolytic fate of persistent organic pollutants in Arctic surface waters. The principal investigator of this study is Yu-Ping Chin of Ohio State University. This research is funded by the National Science Foundation (NSF).

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring heptachlor and heptachlor epoxide, their metabolites, and other biomarkers of exposure and effect to heptachlor and heptachlor epoxide. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Analytical methods exist for measuring heptachlor, heptachlor epoxide, and/or their metabolites in various tissues (including adipose tissue), blood, human milk, urine, and feces. The common method used is gas chromatography (GC) coupled with electron capture detection (ECD) followed by identification using GC/mass spectrometry (MS). Since evidence indicates that heptachlor is metabolized to heptachlor epoxide in mammals, exposure to heptachlor is usually measured by determining levels of heptachlor epoxide in biological media. A summary of the detection methods used for various biological media is presented in Table 7-1.

Heptachlor and heptachlor epoxide are measured in adipose tissue, blood, and serum using GC/ECD (Adeshina and Todd 1990; Burse et al. 1990; Polishuk et al. 1977a, 1977b; Radomski et al. 1971a, 1971b) and identified by GC/MS (LeBel and Williams 1986). Sample preparation steps for adipose tissue vary but, in general, involve a lipid extraction step followed by a clean-up procedure involving gel permeation chromatography (GPC) and/or Florisil column clean-up. Using GPC with methylene chloride and cyclohexane as solvents, individual organochlorine contaminants can be separated from adipose tissue to produce extracts clean enough for direct GC analysis. Clean-up efficiency using GPC is 99.9% (LeBel and Williams 1986). The sensitivity obtained using GC/ECD is in the low-ppb range. Recoveries for heptachlor are adequate (72–87%); recoveries for heptachlor epoxide are good (84–98%). Precision is good for both (Adeshina and Todd 1990; LeBel and Williams 1986). The preparation step used for measuring heptachlor epoxide in blood and serum involves lipid extraction, clean-up with column chromatography, and elution with acetonitrile, hexane, and methylene chloride (Burse et al. 1990;

Table 7-1. Analytical Methods for Determining Heptachlor and Heptachlor Epoxide in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Adipose tissue	Lipid extraction with acetone-hexane; fractionation from fat by gel permeation chromatography; Florisil column clean-up.	GC/ECD; GC/MS	1.4 ng/g (heptachlor); 1.1 ng/g (heptachlor epoxide)	72–87% (heptachlor); 86–98% (heptachlor epoxide)	LeBel and Williams 1986
Adipose tissue	Lipid extraction with petroleum ether; concentration; clean-up on Florisil column.	GC/ECD	0.001 ppm (heptachlor epoxide)	84%	Adeshina and Todd 1990
Human liver and brain tissue	Grind liver tissue and extract with petroleum ether. Dry brain tissue and grind with petroleum ether. Centrifuge and inject.	GC/ECD	NR	NR	Radomski et al. 1968
Human tissues	Homogenize. Extract with hexane containing anhydrous sodium sulfate. Evaporate. Redissolve in hexane. Clean-up on Florisil.	GC/ECD	NR	NR	Klemmer et al. 1977
Blood	Lipid extraction with chloroform/methanol; clean-up with column chromatography; elution with acetonitrile, hexane and methylene chloride.	GC/ECD	NR	NR	Polishuk et al. 1977a, 1977b
Serum	Add methanol and extract with hexane/ethyl ether. Clean-up on Florisil column. Acid treatment and clean-up on silica gel column.	GC/ECD	NR	80–96%	Burse et al. 1990
Human milk	Homogenize with chloroform/methanol; lipid extract with petroleum ether or hexane; clean-up by column chromatography; elution with acetonitrile, hexane, and methylene chloride.	GC/ECD	NR	NR	Polishuk et al. 1977b

Table 7-1. Analytical Methods for Determining Heptachlor and Heptachlor Epoxide in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human milk	Lipid extraction with acetone-hexane. Dissolve in benzene-acetone. Clean-up on Florisil. Elute with dichloromethane-petroleum ether. Concentrate and add hexane.	GC/ECD	0.001 ppm (heptachlor epoxide)	NR	Ritcey et al. 1972
Urine and feces (heptachlor, heptachlor epoxide, and metabolites)	Extract with acetone and hexane. Combine solvents and concentrate. Mix with silicic acid and air dry. Clean-up on Florisil column and silicic acid column. Metabolites extracted into hexane for GC analysis.	GC/ECD	NR	NR	Tashiro and Matsumura 1978

ECD = electron capture detector; GC = gas chromatography; MS = mass spectrometry; NR = not reported

Polishuk et al. 1977a, 1977b). Recovery is adequate (80–96%). Precision is good (9–15%). Sensitivity was not reported (Burse et al. 1990).

GC/ECD and GC equipped with a microcoulometric detector have been used to determine heptachlor and heptachlor epoxide in a variety of human tissues, including the liver, brain, adrenals, lungs, heart, kidneys, spleen, and pancreas (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968). Details of a sample preparation method were not reported for GC equipped with a microcoulometric detector (Curley et al. 1969). Sample preparation steps for GC/ECD include homogenization, extraction with petroleum ether or hexane, usually followed by a clean-up procedure (Klemmer et al. 1977; Radomski et al. 1968). Recovery, sensitivity, and precision data were not reported (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968).

Heptachlor and heptachlor epoxide have been measured in samples of human milk using GC/ECD and GC/MS (Mussalo-Rauhamaa et al. 1988; Polishuk et al. 1977b; Ritcey et al. 1972). Sample preparation steps for milk involve homogenization with chloroform/methanol, lipid extraction with petroleum ether, hexane or acetone-hexane, clean-up by column chromatography, and elution with acetonitrile, hexane, methylene chloride, or dichloromethane-petroleum ether. Precision, accuracy, and sensitivity were not reported for most of the studies; however, one study reported a sensitivity in the low-ppb range (Ritcey et al. 1972).

Heptachlor, heptachlor epoxide, and their metabolites have been measured in urine and feces using GC/ECD (Tashiro and Matsumura 1978). Sample preparation steps involve extraction with acetone and hexane, clean-up on Florisil and silicic acid columns, and extraction of the derivatized metabolites into hexane for GLC analysis. Precision, accuracy, and sensitivity were not reported (Tashiro and Matsumura 1978).

7.2 ENVIRONMENTAL SAMPLES

Methods exist for measuring heptachlor and heptachlor epoxide in air, water, soil, and food. The most common methods are GC/ECD and GC/MS. A summary of methods for detecting heptachlor and heptachlor epoxide in various environmental samples is presented in Table 7-2.

Heptachlor is measured in indoor and outdoor air samples using GC/ECD and GC/MS (Anderson and Hites 1989; Leone et al. 2000; Lewis et al. 1986; Savage 1989). Heptachlor has also been measured in

Table 7-2. Analytical Methods for Determining Heptachlor and Heptachlor Epoxide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Outdoor air	Sample collected with low-volume sampler consisting of a constant flow pump and a cartridge containing polyurethane foam. Extract with diethylether in hexane.	GC/ECD; GC/MS	0.0006 ppb	99% (heptachlor)	Lewis et al. 1986
Indoor air	Sample collected with a polyurethane foam plug sampler. Soxhlet extraction with petroleum ether.	GC/ECD	<3 ppt	NR	Leone et al. 2000
House dust	Sample collected with high-volume surface sampler; extract with diethyl ether in hexane.	GC/ECD; GC/MS	NR	NR (heptachlor)	Roberts and Camann 1989
Water	Extract with methylene chloride.	GC/MS	NR	52–68% (heptachlor)	Alford-Stevens et al. 1988
Waste water	Extract with methylene chloride; exchange to hexane.	GC/ECD (EPA Method 8080)	0.003 µg/L (heptachlor); 0.083 µg/L (heptachlor epoxide)	69% (heptachlor); 89% (heptachlor epoxide)	EPA 1994a
Waste water	Extract with methylene chloride	GC/MS (EPA Method 8250)	1.9 µg/L (heptachlor); 2.2 µg/L (heptachlor epoxide)	87% (heptachlor); 92% (heptachlor epoxide)	EPA 1994b
Drinking water	Extract with methylene chloride; solvent exchange to methyl *tert*-butyl ether.	GC/ECD (EPA Method 508)	0.01 µg/L (heptachlor); 0.015 µg/L (heptachlor epoxide)	99% (heptachlor); 95% (heptachlor epoxide)	Lopez-Avila et al. 1990
Soil/ sediment and solid waste	Extract with methylene chloride; clean-up extract.	GC/MS (EPA Method 8250)	1.9 µg/L (heptachlor); 2.2 µg/L (heptachlor epoxide)	87% (heptachlor); 92% (heptachlor epoxide)	EPA 1994a
Foodstuff (butterfat)	Lipid extraction with automated gel permeation chromatography; direct injection.	GC/ECD	NR	100% (heptachlor epoxide)	Hopper and Griffitt 1987
Milk	Extract on solid-matrix disposable columns by means of acetonitrile-saturated light petroleum; Florisil® clean-up.	GC/ECD	NR	99% (heptachlor epoxide)	DiMuccio et al. 1988
Water and soft drink	Extracted with ethyl acetate; dried with sodium sulfate and then evaporated before taken up in methanol water solvent mixture	LC/MS/MS	NR	NR	Chandramouli et al. 2004

Table 7-2. Analytical Methods for Determining Heptachlor and Heptachlor Epoxide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Extract placed on extraction well plates loaded with sorbent; standard solutions were added before injecting onto column	SPE-GC-MS	0.01–2.5 µg/L	90–99% (heptachlor)	Li et al. 2000
Water	800 mL extracted with hexane; extract concentrated and reconstituted in toluene	GC/MS	0.5 µg/L	NR	Canadian Ministry of the Environment 2003

ECD = electron capture detector; EPA = Environmental Protection Agency; GC = gas chromatography; LC = liquid chromatograph; MS = mass spectrometry; NR = not reported; SPE = solid phase extraction

house dust (Roberts and Camann 1989). Preparation methods involve the use of a variety of air trapping samplers. Examples of these include the Greenburg-Smith impinger, Chromosorb 102, low-volume samplers, and the Millipore miniature vacuum pump with a sampling tube. The next step includes extraction with diethyl ether, acetone-hexane, or toluene (Anderson and Hites 1989; Roberts and Camann 1989). For indoor air, sensitivity is in the sub-ppt range (Leone et al. 2000). For outdoor air, precision is good (13%) and recovery is excellent (99%). Sensitivity is in the sub-ppb range (Lewis et al. 1986).

Heptachlor and heptachlor epoxide are measured in water, drinking water, waste water, soil/sediment, and solid waste using GC/ECD, GC/MS, and liquid chromatography (LC)/MS/MS (Alford-Stevens et al. 1988; Canadian Ministry of the Environment 2003; Chandramouli et al. 2004; EPA 1994a, 1994b; Lopez-Avila et al. 1990; McDougall et al. 1987; Smith et al. 1987). Preparation of water, waste water, and drinking water samples involves extraction with methylene chloride, concentration, and solvent exchange to hexane or methyl *tert*-butyl ether. Mean recovery in water for heptachlor was low (52–68%) and precision was poor (48–57%) (Alford-Stevens et al. 1988). Poor recovery and precision data were thought to be attributable to chromatographic problems in some of the participating laboratories. For drinking water (EPA Method 508), recovery was excellent for heptachlor (99%) and heptachlor epoxide (95%). Precision was excellent for both compounds (<10%). Sensitivity was in the sub-ppb range (Lopez-Avila et al. 1990). Preparation of soil/sediment or solid waste samples involves extraction with methylene chloride, methylene chloride-acetone, methylene chloride-methanol, or acetone-hexane followed by clean-up with Florisil or GPC (Alford-Stevens et al. 1988; EPA 1994a). Overall precision was adequate to poor, ranging from 19 to 47% for heptachlor. Recovery and sensitivity were not reported (Alford-Stevens et al. 1988). EPA Test Methods 8080 and 8250 for evaluating waste water, soil sediment, and solid waste report sensitivity in the low-ppb range for both heptachlor and heptachlor epoxide (EPA 1994a, 1994b). Recovery for heptachlor is adequate (69–87%) and recovery for heptachlor epoxide is good (89–92%). Precision is adequate for both methods (EPA 1994a, 1994b).

GC/ECD is the method used to detect heptachlor and heptachlor epoxide in foods (butterfat, fruits, vegetables, milk, and animal feed) (Di Muccio et al. 1988; Hopper and Griffitt 1987; Korfmacher et al. 1987; Ober et al. 1987; Santa Maria et al. 1986). Preparation methods vary for the different types of foods. The sample preparation method for butterfat involves GPC. GPC is a rapid clean-up technique for separating pesticide residues from a lipid extract. It was developed into an automated clean-up apparatus for use on a wide variety of fats and oils. The automated GPC system is reproducible and reliable. After being cleaned on GPC, most samples can be analyzed by GC without additional clean-up (Hopper and Griffitt 1987). Recovery is complete (100%), and precision is very good (<3%). Sensitivity is in the sub-

ppm range. The sample preparation for milk samples involves selective extraction on solid-matrix disposable columns by means of acetonitrile-saturated light petroleum, followed by Florisil column clean-up. Recovery is excellent (99%); precision is very good (<7%) (Di Muccio et al. 1988). Sample preparation for fruits, vegetables, and animal feed involves cyclic steam distillation extraction in hexane or isooctane with direct injection into the gas chromatograph. Recoveries for this method are very low (15–50%). This is an indication that heptachlor is not extracted quantitatively by steam distillation and is not a recommended preparation method (Ober et al. 1987; Santa Maria et al. 1986).

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of heptachlor and heptachlor epoxide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of heptachlor and heptachlor epoxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods exist for determining levels of heptachlor, heptachlor epoxide, and/or their metabolites in various tissues (including adipose tissues) (Adeshina and Todd 1990; Curley et al. 1969; Klemmer et al. 1977; LeBel and Williams 1986; Radomski et al. 1968), milk (Mussalo-Rauhamaa et al. 1988; Polishuk et al. 1977b; Ritcey et al. 1972), blood (Polishuk et al. 1977a, 1977b), serum (Burse et al. 1990), urine, and feces (Tashiro and Matsumura 1978). Methods for determining levels in adipose tissue are sensitive for measuring levels at which health effects might occur as well as background levels in the population. Methods for determining heptachlor and heptachlor epoxide in adipose tissue are relatively precise. Recovery is better for heptachlor epoxide than for heptachlor. Data on the determination of

heptachlor and heptachlor epoxide in tissues, blood, serum, milk, urine, and feces are limited as precision, recovery, and/or sensitivity data were not reported for the existing methods. More information on the precision, accuracy, and sensitivity of these methods is needed to evaluate the value of using levels of heptachlor and heptachlor epoxide as biomarkers of exposure.

Effect. There is no known effect of heptachlor or heptachlor epoxide that can be quantitatively related to exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Existing methods for determining levels of heptachlor in air are sensitive enough to measure background levels in the environment, as well as levels at which health effects might occur. Data on the determination of heptachlor and heptachlor epoxide in air (Anderson and Hites 1989; Leone et al. 2000; Lewis et al. 1986; Roberts and Camann 1989; Savage 1989), water (Alford-Stevens et al. 1988; EPA 1994a, 1994b; Lopez-Avila et al. 1990), soil (EPA 1994b; McDougall et al. 1987; Smith et al. 1987), and food (Di Muccio et al. 1988; Hopper and Griffitt 1987; Korfmacher et al. 1987; Ober et al. 1987; Santa Maria et al. 1986) are limited. Information on the accuracy, precision, and sensitivity of these methods would permit better assessment of the risk of low-level environmental exposure for these media. A preparation method for fruit and vegetable analysis that provides increased recovery would allow better assessment of the risk of dietary exposure. Research investigating the relationship between levels measured in air, water, soil, and food and observed health effects could increase our confidence in existing methods and/or indicate where improvements are needed.

7.3.2 Ongoing Studies

No ongoing studies regarding analytical methods were located for heptachlor or heptachlor epoxide.

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8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines regarding heptachlor and heptachlor epoxide in air, water, and other media are summarized in Table 8-1.

ATSDR derived an acute-duration oral MRL of 0.0006 mg/kg/day for heptachlor. This MRL was based on a LOAEL of 1.8 mg/kg/day for impaired reproductive performance in female rats mated with unexposed males (Amita Rani and Krishnakumari 1995), an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), and a modifying factor of 3 for the use of a serious end point.

ATSDR derived an intermediate-duration oral MRL of 0.0001 mg/kg/day for heptachlor. This MRL was based on a minimal LOAEL of 0.03 mg/kg/day for developmental immunological and neurological effects in rats (Moser et al. 2001; Smialowicz et al. 2001) and an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

EPA (IRIS 2005) has derived an oral reference dose (RfD) for heptachlor of $5x10^{-4}$ mg/kg/day based on NOAEL of 0.15 mg/kg/day and LOAEL of 0.25 mg/kg/day for increased liver weight in rats exposed to heptachlor for 2 years and an uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 to account for limitations in the database particularly the lack of a chronic study in a second species).

EPA (IRIS 2005) also derived an RfD of $1.3x10^{-5}$ mg/kg/day for heptachlor epoxide. This RfD is based on a LOAEL of 0.0125 mg/kg/day for increased relative liver weight identified in a dog study submitted to EPA by Dow Chemical Company and an uncertainty factor of 1,000 to account for inter and intraspecies extrapolation and because a NOAEL was not attained. The studies which serve as the basis of the RfDs for heptachlor and heptachlor epoxide were not discussed in the toxicological profile because they were submitted to EPA under FIFRA and are not publicly available.

Table 8-1. Regulations and Guidelines Applicable to Heptachlor and Heptachlor Epoxide

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2004
	Heptachlor	Group 2B[a]	
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	Guideline values have not been established[b]	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA		ACGIH 2004
	Heptachlor[c]	0.05 mg/m^3	
	Heptachlor epoxide[c]	0.05 mg/m^3	
EPA	Hazardous air pollutant		EPA 2004b 42 USC 7412
	Heptachlor	Yes	
NIOSH	REL (10-hour TWA)		NIOSH 2005
	Heptachlor[d,e]	0.5 mg/m^3	
	IDLH		
	Heptachlor	35 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2005c 29 CFR 1910.1000
	Heptachlor[f]	0.5 mg/m^3	
	PEL (8-hour TWA) for construction industry		OSHA 2005b 29 CFR 1926.55
	Heptachlor[f]	0.5 mg/m^3	
	PEL (8-hour TWA) for shipyard industry		OSHA 2005a 29 CFR 1915.1000
	Heptachlor[f]	0.5 mg/m^3	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311 of the Clean Water Act		EPA 2005a 40 CFR 116.4
	Heptachlor	Yes	
	Drinking-water health advisories		EPA 2004a
	Heptachlor		
	1-day health advisory for a 10-kg child[g]	0.01 mg/L	
	10-day health advisory for a 10-kg child[h]	0.01 mg/L	
	DWEL[i]	0.02 mg/L	
	10^{-4} Cancer risk[j]	0.0008 mg/L	

Table 8-1. Regulations and Guidelines Applicable to Heptachlor and Heptachlor Epoxide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Drinking-water health advisories		EPA 2004a
	Heptachlor epoxide		
	1-day health advisory for a 10-kg child[g]	0.01 mg/L	
	10-day health advisory for a 10-kg child[h]	No data	
	DWEL[i]	0.0004 mg/L	
	10^{-4} Cancer risk[j]	0.0004 mg/L	
	National primary drinking water regulations[k]		EPA 2002a
	Heptachlor		
	MCL	0.0004 mg/L	
	MCLG	Zero	
	Heptachlor epoxide		
	MCL	0.0002 mg/L	
	MCLG	Zero	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2005b 40 CFR 117.3
	Heptachlor	1 pound	
	Water quality criteria for human health consumption of:		EPA 2002b
	Heptachlor[l]		
	Water + organism	7.9×10^{-5}	
	Organism only	7.9×10^{-5}	
	Heptachlor epoxide[l]		
	Water + organism	3.9×10^{-5}	
	Organism only	3.9×10^{-5}	
c. Food			
FDA	Action level		FDA 2000
	Heptachlor		
	Artichokes; asparagus; Brassica (cole) leafy vegetables; bulb vegetables; cereal grains; citrus fruits; eggs; figs; fruiting vegetables; leafy vegetables; legume vegetables; peanuts; pome fruits; root and tuber vegetables; salsify tops; small fruits and berries; stone fruits; and sugarcane	0.01 ppm	
	Cottonseed, cucurbit vegetables, pineapple, and rabbit (fat basis)	0.02 ppm	
	Fish (edible portion)	0.3 ppm	
	Milk (fat basis)	0.1 ppm	

Table 8-1. Regulations and Guidelines Applicable to Heptachlor and Heptachlor Epoxide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
FDA	Bottled water		FDA 2004 21 CFR 165.110
	Heptachlor	0.0004 mg/L	
	Heptachlor epoxide	0.0002 mg/L	
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2004
	Heptachlor	A3[m]	
	Heptachlor epoxide	A3[m]	
EPA	Carcinogenicity classification		IRIS 2005
	Heptachlor	B2[n]	
	Heptachlor epoxide	B2[n]	
	RfC		
	Heptachlor	Not available at this time	
	Heptachlor epoxide	Not available at this time	
	RfD		
	Heptachlor	5.0×10^{-4} mg/kg/day	
	Heptachlor epoxide	1.3×10^{-5} mg/kg/day	
	Inhalation unit risk		
	Heptachlor	1.3×10^{-3} per ug/m^3	
	Heptachlor epoxide	2.6×10^{-3} per ug/m^3	
	Oral slope factor		
	Heptachlor	4.5 per mg/kg-day	
	Heptachlor epoxide	9.1 per mg/kg-day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2005c 40 CFR 302.4
	Heptachlor[o]		
	Reportable quantity	1 pound	
	RCRA waste number	P059	
	Heptachlor epoxide[p]		
	Reportable quantity	1 pound	
	RCRA waste number	No data	
	Effective date of toxic chemical release reporting		EPA 2005e 40 CFR 372.65
	Heptachlor	01/01/87	

Table 8-1. Regulations and Guidelines Applicable to Heptachlor and Heptachlor Epoxide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Threshold amounts for manufacturing (including importing), processing, and otherwise using such toxic chemicals		EPA 2005d 40 CFR 372.28
	Heptachlor	10 pounds	
NTP	Carcinogenicity classification	No data	NTP 2005

[a]Group 2B: possibly carcinogenic to humans
[b]Guideline values have not been established: heptachlor and heptachlor epoxide occurs in drinking water at concentrations well below those at which heptachlor epoxide toxic effects may occur.
[c]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance.
[d]Potential occupational carcinogen
[e]Skin designation: indicates the potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices and gloves, coveralls, goggles, and other appropriate equipment.
[f]Skin designation
[g]1-Day health advisory: the concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects for up to 1 day of exposure. The 1-day health advisory is normally designed to protect a 10-kg child consuming 1 liter of water per day.
[h]10-Day health advisory: the concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects for up to 10 days of exposure. The 10-day health advisory is also normally designed to protect a 10-kg child consuming 1 liter of water per day.
[i]DWEL: a lifetime exposure concentration protective of adverse, noncancer health effects that assumes all of the exposure to a contaminant is from drinking water.
[j]10^{-4} Cancer risk: the concentration of a chemical in drinking water corresponding to an excess estimated lifetime cancer risk of 1 in 10,000.
[k]Potential health effects from ingestion of water include liver damage and increased risk of cancer. The contaminant in drinking water is the residue of a banned termiticide (heptachlor) and the breakdown of heptachlor from epoxide heptachlor.
[l]This criterion is based on carcinogenicity of 10^{-6} risk.
[m]A3: not classifiable as a human carcinogen
[n]B2: probable human carcinogen
[o]Heptachlor: designated CERCLA hazardous substance pursuant to Section 311(b)(2) and 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA.
[p]Heptachlor epoxide: designated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water Act.

ACGIH = American Conference of Governmental Industrial Hygienists; CERCLA = Comprehensive Environmetnal Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DWEL = drinking-water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminat level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

10. GLOSSARY

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Heptachlor
CAS Numbers: 76-44-8
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 19
Species: Rat

Minimal Risk Level: 0.0006 [X] mg/kg/day [ ] ppm

Reference: Amita Rani BE, Krishnakumari MK. 1995. Prenatal toxicity of heptachlor in albino rats. Pharmacol Toxicol 76(2):112-114.

Experimental design: Groups of 30 female CFT-Wistar rats received gavage doses of heptachlor in groundnut oil for 14 days (presumably 7 days/week). The total administered doses were 25 and 50 mg/kg body weight; the daily doses were 1.8 and 3.6 mg/kg/day; a vehicle control group was also used. After 14 days of exposure, the animals were mated with controls.

Effect noted in study and corresponding doses: A significant decrease in the number of pregnant females (56.3 and 44.4%) and increase in the number of resorptions (18.90 and 11.40%) were observed in both groups of heptachlor-exposed rats. Significant decreases in estradiol-17beta and progesterone levels were also observed in the 1.8 mg/kg/day group. No alterations in the number of implantations were observed. The investigators noted that focal necrosis was observed in the liver; however, they did not note at which dose level and no incidence data were provided.

Dose and end point used for MRL derivation: The MRL is based on a serious LOAEL of 1.8 mg/kg/day for reproductive effects.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation: 1,000

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifying Factor used in MRL derivation: 3

[X] 3 for use of a serious end point

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Several targets of toxicity have been identified, in addition to the impaired reproductive performance observed in the Amita Rani and Krishnakumari (1995) study. These include the liver, nervous system, and developing offspring. Gestational exposure to 4.5 or 6.8 mg/kg/day resulted in decreases in pup body weight (Narotsky and Kavlock 1995; Narotsky et al. 1995) and a decrease in pup righting reflex was observed at 4.2 mg/kg/day (Purkerson-Parker et al. 2001b). At twice these dose levels, an increase in pup mortality was observed (Narotsky et al. 1995; Purkerson-Parker et al. 2001b). Liver effects were observed at doses similar to those resulting in developmental effects. Increases in serum alanine aminotransferase and aldolase activity levels, hepatocytomegaly, and minimal monocellular necrosis were observed in rats administered 7 mg/kg/day heptachlor in oil for 14 days (Berman et al. 1995; Krampl 1971). Exposure to 7 mg/kg/day also resulted in excitability and increased arousal in rats administered heptachlor in oil via gavage for 1 or 14 days (Moser et al. 1995).

Agency Contacts (Chemical Managers): Zemoria Rosemond, B.A.; G. Daniel Todd, Ph.D.; Malcolm Williams, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Heptachlor
CAS Numbers: 76-44-8
Date: June 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 49
Species: Rat

Minimal Risk Level: 0.0001 [X] mg/kg/day [ ] ppm

Reference: Smialowicz RJ, Williams WC, Copeland CB, et al. 2001. The effects of perinatal/juvenile heptachlor exposure on adult immune and reproductive system function in rats. Toxicol Sci 61(1):164-175.

Moser VC, Shafer TJ, Ward TR, et al. 2001. Neurotoxicological outcomes of perinatal heptachlor exposure in the rat. Toxicol Sci 60(2):315-326.

Experimental design: Groups of 15–20 pregnant Sprague Dawley rats were administered via gavage 0, 0.03, 0.3, or 3 mg/kg/day heptachlor in corn oil on gestational day 12 through postnatal day 7; pups were also exposed from postnatal day 7 to 21 or 42. Neurobehavorial assessment consisted of righting reflex on postnatal days 2–5, functional observational battery test, motor activity, passive avoidance test of learning and memory, and Morris water maze to assess spatial and working memory. The liver, kidneys, adrenals, thymus, spleen, ovaries, uterus/vagina, testes, epididymides, seminal vesicles/coagulating glands, and ventral and dorsolateral prostate were histologically examined in 15–17 offspring from each group on postnatal day 46. The following immunological tests were performed in the 8-week-old offspring: splenic lymphoproliferative (LP) responses to T cell mitogens (e.g., concanavalin A [ConA], phytohemagglutinin [PHA]) and to allogeneic cells in a mixed lymphocyte reaction, primary IgM antibody response to sheep red blood cells, examination of splenic lymphocytes subpopulations, and delayed-type and contact hypersensitivity. Reproductive assessment included evaluation of vaginal opening (index of female puberty) and prepuce separation (index of male puberty) beginning at postnatal days 25 and 35, respectively. The offspring were mated with an untreated mate and the dams were allowed to rear the first litter to postnatal day 10. The results of the neurobehavioral assessment were reported by Moser et al. (2001); the remaining results were reported by Smialowicz et al. (2001).

Effect noted in study and corresponding doses: No significant alterations in maternal body weight, number of dams delivering litters, litter size, or pup survival were observed. Additionally, no alterations in pup growth rates, age at eye opening, anogenital distance, or age at vaginal opening or preputial separation were observed. A significant decrease in pup body weight at postnatal day 1 was observed at 3 mg/kg/day; this effect was not observed at postnatal days 7, 14, or 21. No consistent, statistically significant alterations in offspring body weights were observed at postnatal days 21, 28, 35, or 42. Significant alterations in absolute and relative liver weights were observed in males and females exposed to 3 mg/kg/day; increases in absolute and relative ovary weights were also observed at 3 mg/kg/day. No histological alterations were observed in the examined tissues. No alterations in fertility were observed in the adult males and females mated to untreated partners, and no effects on soft tissue or gross body structure of the offspring (F_2 generation) were observed. No alterations in sperm count or sperm motility were observed.

Righting was significantly delayed in the female offspring of rats exposed to 3 mg/kg/day heptachlor; no significant alterations were observed in the male offspring. The investigators suggested that this was due to a delay in the ontogeny of righting rather than an inability to perform the task. The following significant alterations in the FOB and motor activity tests were found in the offspring dosed until postnatal day 21: increased open field activity in 3 mg/kg/day males, non-dose-related increased activity in figure-eight chambers in females (significant only in 0.03 mg/kg/day group), and faster decline in habituation of activity in 3 mg/kg/day males. Alterations in the offspring dosed until postnatal day 42 included: increased levels of urination in males in the 0.03 and 0.3 mg/kg/day groups, increased landing foot splay in males in the 0.03 mg/kg/day group, and removal reactivity in males and females in the 0.03 mg/kg/day group. No alterations in the passive avoidance test were observed in the offspring exposed until postnatal day 21; in those exposed until postnatal day 42, an increase in the number of nose pokes was observed in all groups of females. No significant alterations in performance on the water maze test were found in the offspring exposed until postnatal day 21. In those exposed until postnatal day 42, increases in latency to find the platform were observed in males and females exposed to 3 mg/kg/day and increases in the time spent in the outer zone were found in males exposed to 0.3 or 3 mg/kg/day. In the water maze memory trial, no differences in performance were found between controls and animals exposed until postnatal day 21. Alterations in significant quadrant bias were observed in 0.03, 0.3, and 3 mg/kg/day males during the first probe test and in 0.3 and 3 mg/kg/day males and 3 mg/kg/day females in the second probe test. The study investigators noted that the heptachlor-exposed rats did not develop an efficient search strategy for locating the platform; they spent more time circling the outer zone of the tank. By the second week of the test, control rats had learned to venture into the zone where the platform was located.

A dose-related, statistically significant suppression of primary IgM antibody response to sRBC was found in males, but not females. The primary IgM response to sRBCs was reduced in 21-week-old males exposed to 0.3 mg/kg/day. A second immunization with sRBCs administered 4 weeks later resulted in a significant reduction in IgG antibody response in males administered 0.03, 0.3, or 3 mg/kg/day heptachlor; no response was seen in females. A decrease in the $OX12^{+}OX19^{-}$ (i.e., B/plasma cells) population was also found in the spleen of males exposed to 3 mg/kg/day. No alterations in the following immunological parameters assessed at 8 weeks of age were found: lymphoid organ weights, splenic NK cell activity, splenic cellularity or cell viability, and lymphoproliferative responses of splenic lymphocytes to T-cell mitogens ConA and PHA or to allogenic cells in the mixed lymphocyte reaction. The results of this portion of the study suggest that exposure to heptachlor adversely affects the development of the immune system.

Dose and end point used for MRL derivation: The MRL is based on a minimal LOAEL of 0.03 mg/kg/day for developmental immunological and neurological effects. The observed alterations were considered to be minimally adverse and suggestive of immunotoxicity and neurotoxicity.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

- [X] 3 for use of a minimal LOAEL
- [X] 10 for extrapolation from animals to humans
- [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: The results of the Smialowicz et al. (2001) study suggest that exposure to heptachlor adversely affects the development of the immune system. A framework for testing a chemical's potential to induce developmental immunotoxicological effects has not been established. Based on the results of studies in mature animals (Luster et al. 1992), two panels of government, industry, and academia immunotoxicology experts (Holsapple et al. 2005; Luster et al. 2003) reached a consensus that assays measuring the response to a T-cell dependent antigen (e.g., sheep red blood cells) should be included in included in a developmental immunotoxicology protocol. In mature animals, the sheep red blood cells antibody plague-forming cell test was the most reliable single test predictor of immunotoxicity (Luster et al. 1992).

Intermediate-duration oral exposure studies have identified a number of targets of heptachlor toxicity including the liver, nervous system, reproductive system, and the developing offspring. Other less documented effects have also been observed. The developing organism appears to be the most sensitive target. In the absence of maternal toxicity, heptachlor is not associated with alterations in pup mortality or body weight gain (Lawson and Luderer 2004; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001) or alterations in the development of the reproductive system (Lawson and Luderer 2004; Smialowicz et al. 2001). In contrast, heptachlor appears to adversely affect the development of the nervous and immune systems. The observed effects include impaired spatial memory at 0.03 mg/kg/day and higher (Moser et al. 2001), impaired spatial learning at 0.3 mg/kg/day and higher (Moser et al. 2001), and decreased in righting reflex (Moser et al. 2001; Purkerson-Parker et al. 2001b) and increased open field activity (Moser et al. 2001) at 3 mg/kg/day. These effects were observed in rats exposed *in utero*, during lactation, and postnatally until day 42; spatial memory and learning were not adversely affected when the exposure was terminated at postnatal day 21 (Moser et al. 2001). The conflicting results may have resulted in the higher heptachlor epoxide body burden in rats exposed to postnatal day 42, testing at different ages, or exposure may have occurred during a critical window of vulnerability. The effects observed in rats are consistent with those observed in humans. Impaired performance on several neurobehavioral tests, including abstract concept formation, visual perception, and motor planning, was observed in high school students presumably prenatally exposed to heptachlor from contaminated milk products (Baker et al. 2004b). Alterations in immune function were also observed in the rats exposed until postnatal day 42. At 0.03 mg/kg/day and higher, suppression of the immune response to sheep red blood cells was observed (Smialowicz et al. 2001). A reduction in the percentage of B lymphocytes was also observed in the spleen of rats exposed to 3 mg/kg/day. Other tests of immune function were not significantly altered.

The liver effects observed in rats or mice exposed to heptachlor in the diet include increased liver weights (Izushi and Ogata 1990; Pelikan 1971), increased serum alanine aminotransferase levels (Izushi and Ogata 1990), steatosis (Pelikan 1971), and hepatitis and necrosis (Akay and Alp 1981). The lowest LOAEL values for these effects range from 5 to 8.4 mg/kg/day. Neurological signs such as hyperexcitability, seizures, and difficulty standing, walking, and righting were observed at similar dose levels; LOAELs ranged from 1.7 to 17 mg/kg/day (Akay and Alp 1981; Aulerich et al. 1990; Crum et al. 1993). The reproductive system appeared to be more sensitive to heptachlor toxicity. Decreases in epididymal sperm count were observed in rats administered 0.65 mg/kg/day heptachlor in groundnut oil for 70 days (Amita Rani and Krishnakumari 1995). This dose also resulted in increased resorptions when the exposed males were mated with unexposed females. Infertility was observed in all mice exposed to 8.4 mg/kg/day heptachlor for 10 weeks (Akay and Alp 1981).

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

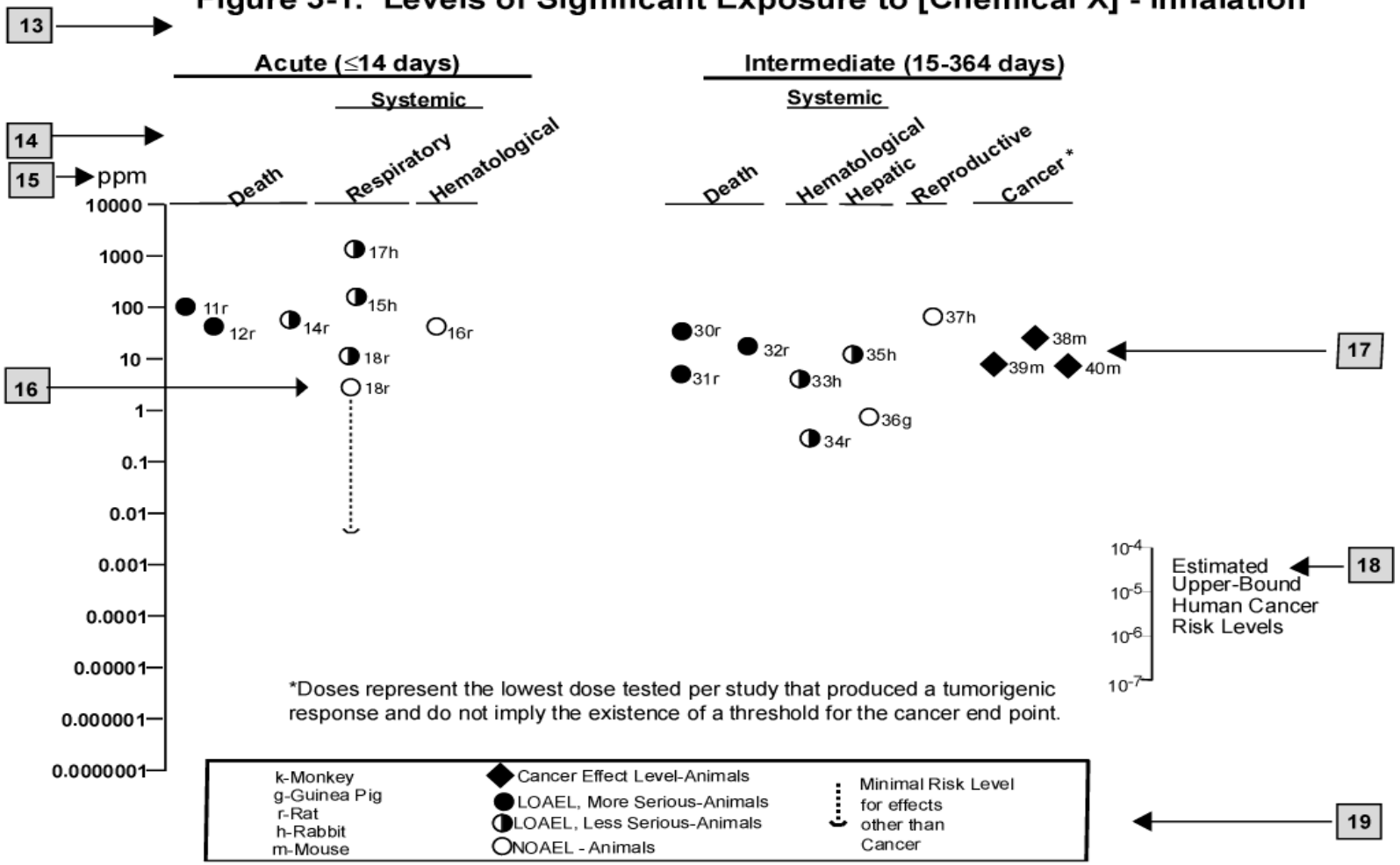
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX

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TOXICOLOGICAL PROFILE FOR LEAD

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

August 2007

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Lead, Draft for Public Comment was released in September 2005. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Howard Frumkin, M.D., Dr. P.H.
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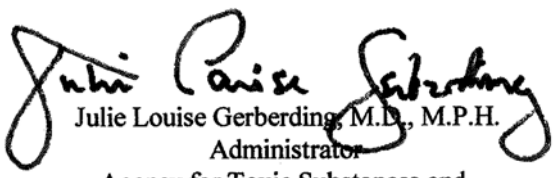
Agency for Toxic Substances and
Disease Registry



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The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014); and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone:	1-800-CDC-INFO (800-232-4636) 1-888-232-6348 (TTY)	***Fax:***	(770) 488-4178
E-mail:	cdcinfo@cdc.gov	***Internet***:	http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposure*s—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for lead. The panel consisted of the following members:

1. Philip Landrigan, M.D., Ethel H. Wise, Professor of Community and Preventive Medicine and Professor of Pediatrics, Director, Division of Environmental and Occupational Medicine, Mount Sinai School of Medicine, New York, New York;

2. Deborah Cory-Slechta, Ph.D., Director, Environmental and Occupational Health Sciences Institute, Chair, Department of Environmental and Occupational Medicine, Robert Wood Johnson Medical University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey; and

3. Howard Hu, M.D., M.P.H., Professor of Occupational and Environmental Medicine, Harvard School of Public Health, Boston, Massachusetts.

These experts collectively have knowledge of lead's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about lead and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Lead has been found in at least 1,272 of the 1,684 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which lead is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to lead, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS LEAD?

Lead is a heavy, low melting, bluish-gray metal that occurs naturally in the Earth's crust. However, it is rarely found naturally as a metal. It is usually found combined with two or more other elements to form lead compounds.

Metallic lead is resistant to corrosion (i.e., not easily attacked by air or water). When exposed to air or water, thin films of lead compounds are formed that protect the metal from further attack. Lead is easily molded and shaped. Lead can be combined with other metals to form alloys. Lead and lead alloys are commonly found in pipes, storage batteries, weights, shot and

ammunition, cable covers, and sheets used to shield us from radiation. The largest use for lead is in storage batteries in cars and other vehicles.

Lead compounds are used as a pigment in paints, dyes, and ceramic glazes and in caulk. The amount of lead used in these products has been reduced in recent years to minimize lead's harmful effect on people and animals. Tetraethyl lead and tetramethyl lead were once used in the United States as gasoline additives to increase octane rating. However, their use was phased out in the United States in the 1980s, and lead was banned for use in gasoline for motor vehicles beginning January 1, 1996. Tetraethyl lead may still be used in gasoline for off-road vehicles and airplanes. It is also still used in a number of developing countries. Lead used in ammunition, which is the largest non-battery end-use, has remained fairly constant in recent years. However, even the use of lead in bullets and shot as well as in fishing sinkers is being reduced because of its harm to the environment.

Most lead used by industry comes from mined ores ("primary") or from recycled scrap metal or batteries ("secondary"). Lead is mined in the United States, primarily in Alaska and Missouri. However, most lead today is "secondary" lead obtained from lead-acid batteries. It is reported that 97% of these batteries are recycled.

For more information on the physical and chemical properties of lead, please see Chapter 4. For more on the production and use of lead, please see Chapter 5.

1.2 WHAT HAPPENS TO LEAD WHEN IT ENTERS THE ENVIRONMENT?

Lead occurs naturally in the environment. However, most of the high levels found throughout the environment come from human activities. Environmental levels of lead have increased more than 1,000-fold over the past three centuries as a result of human activity. The greatest increase occurred between the years 1950 and 2000, and reflected increasing worldwide use of leaded gasoline. Lead can enter the environment through releases from mining lead and other metals, and from factories that make or use lead, lead alloys, or lead compounds. Lead is released into the air during burning coal, oil, or waste. Before the use of leaded gasoline was banned, most of

the lead released into the U.S. environment came from vehicle exhaust. In 1979, cars released 94.6 million kilograms (208.1 million pounds) of lead into the air in the United States. In 1989, when the use of lead was limited but not banned, cars released only 2.2 million kg (4.8 million pounds) to the air. Since EPA banned the use of leaded gasoline for highway transportation in 1996, the amount of lead released into the air has decreased further. Before the 1950s, lead was used in pesticides applied to fruit orchards. Once lead gets into the atmosphere, it may travel long distances if the lead particles are very small. Lead is removed from the air by rain and by particles falling to land or into surface water.

Sources of lead in dust and soil include lead that falls to the ground from the air, and weathering and chipping of lead-based paint from buildings, bridges, and other structures. Landfills may contain waste from lead ore mining, ammunition manufacturing, or other industrial activities such as battery production. Disposal of lead-containing products contribute to lead in municipal landfills. Past uses of lead such as its use in gasoline are a major contributor to lead in soil, and higher levels of lead in soil are found near roadways. Most of the lead in inner city soils comes from old houses with paint containing lead and previous automotive exhaust emitted when gasoline contained lead.

Once lead falls onto soil, it sticks strongly to soil particles and remains in the upper layer of soil. That is why past uses of lead such as lead in gasoline, house paint, and pesticides are so important in the amount of lead found in soil.

Small amounts of lead may enter rivers, lakes, and streams when soil particles are moved by rainwater. Small amounts of lead from lead pipe or solder may be released into water when the water is acidic or “soft”. Lead may remain stuck to soil particles or sediment in water for many years. Movement of lead from soil particles into groundwater is unlikely unless the rain falling on the soil is acidic or "soft". Movement of lead from soil will also depend on the type of lead compound and on the physical and chemical characteristics of the soil.

Sources of lead in surface water or sediment include deposits of lead-containing dust from the atmosphere, waste water from industries that handle lead (primarily iron and steel industries and lead producers), urban runoff, and mining piles.

Some lead compounds are changed into other forms of lead by sunlight, air, and water. However, elemental lead cannot be broken down.

The levels of lead may build up in plants and animals from areas where air, water, or soil are contaminated with lead. If animals eat contaminated plants or animals, most of the lead that they eat will pass through their bodies. Chapter 6 contains more information about what happens to lead in the environment.

1.3 HOW MIGHT I BE EXPOSED TO LEAD?

Lead is commonly found in soil especially near roadways, older houses, old orchards, mining areas, industrial sites, near power plants, incinerators, landfills, and hazardous waste sites. People living near hazardous waste sites may be exposed to lead and chemicals that contain lead by breathing air, drinking water, eating foods, or swallowing dust or dirt that contain lead. People may be exposed to lead by eating food or drinking water that contains lead. Drinking water in houses containing lead pipes may contain lead, especially if the water is acidic or “soft”. If one is not certain whether an older building contains lead pipes, it is best to let the water run a while before drinking it so that any lead formed in the pipes can be flushed out. People living in areas where there are old houses that have been painted with lead paint may be exposed to higher levels of lead in dust and soil. Similarly, people who live near busy highways or on old orchard land where lead arsenate pesticides were used in the past may be exposed to higher levels of lead. People may also be exposed to lead when they work in jobs where lead is used or have hobbies in which lead is used, such as making stained glass.

Foods may contain small amounts of lead. However, since lead solder is no longer used in cans, very little lead is found in food. Leafy fresh vegetables grown in lead-containing soils may have lead-containing dust on them. Lead may also enter foods if they are put into improperly glazed

pottery or ceramic dishes and from leaded-crystal glassware. Illegal whiskey made using stills that contain lead-soldered parts (such as truck radiators) may also contain lead. Cigarette smoke may also contain small amounts of lead. The amount of lead found in canned foods decreased 87% from 1980 to 1988 in the United States, which indicates that the chance of exposure to lead in canned food from lead-soldered containers has been greatly reduced. Lead-soldered cans are still used in some other nations. In the most recent studies, lead was not detectable in most foods and the average dietary intake of lead was about 1 microgram (a microgram is a millionth of a gram) per kilogram of body weight per day. Children may be exposed to lead by hand-to-mouth contact after exposure to lead-containing soil or dust.

In general, very little lead is found in lakes, rivers, or groundwater used to supply the public with drinking water. More than 99% of all publicly supplied drinking water contains less than 0.005 parts of lead per million parts of water (ppm). However, the amount of lead taken into your body through drinking water can be higher in communities with acidic water supplies. Acidic water makes it easier for the lead found in pipes, leaded solder, and brass faucets to be dissolved and to enter the water we drink. Public water treatment systems are now required to use control measures to make water less acidic. Plumbing that contains lead may be found in public drinking water systems, and in houses, apartment buildings, and public buildings that are more than 20 years old. However, as buildings age, mineral deposits form a coating on the inside of the water pipes that insulates the water from lead in the pipe or solder, thus reducing the amount of lead that can leach into the water. Since 1988, regulations require that drinking water coolers must not contain lead in parts that come into contact with drinking water.

Breathing in, or swallowing airborne dust and dirt, is another way you can be exposed to lead. In 1984, burning leaded gasoline was the single largest source of lead emissions. Very little lead in the air comes from gasoline now because EPA has banned its use in gasoline for motor vehicles. Other sources of lead in the air include releases to the air from industries involved in iron and steel production, lead-acid-battery manufacturing, and nonferrous (brass and bronze) foundries. Lead released into air may also come from burning of solid waste that contains lead, windblown dust, volcanoes, exhaust from workroom air, burning or weathering of lead-painted surfaces, fumes and exhaust from leaded gasoline, and cigarette smoke.

Skin contact with dust and dirt containing lead occurs every day. Recent data have shown that inexpensive cosmetic jewelry pieces sold to the general public may contain high levels of lead which may be transferred to the skin through routine handling. However, not much lead can get into your body through your skin.

In the home, you or your children may be exposed to lead if you take some types of home remedy medicines that contain lead compounds. Lead compounds are in some non-Western cosmetics, such as surma and kohl. Some types of hair colorants, cosmetics, and dyes contain lead acetate. Read the labels on hair coloring products, use them with caution, and keep them away from children.

People who are exposed at work are usually exposed by breathing in air that contains lead particles. Exposure to lead occurs in many jobs. People who work in lead smelting and refining industries, brass/bronze foundries, rubber products and plastics industries, soldering, steel welding and cutting operations, battery manufacturing plants, and lead compound manufacturing industries may be exposed to lead. Construction and demolition workers and people who work at municipal waste incinerators, pottery and ceramics industries, radiator repair shops, and other industries that use lead solder may also be exposed. Painters who sand or scrape old paint may be exposed to lead in dust. Between 0.5 and 1.5 million workers are exposed to lead in the workplace. In California alone, more than 200,000 workers are exposed to lead. Families of workers may be exposed to higher levels of lead when workers bring home lead dust on their work clothes.

You may also be exposed to lead in the home if you work with stained glass as a hobby, make lead fishing weights or ammunition, or if you are involved in home renovation that involves the removal of old lead-based paint. For more information on the potential for exposure to lead, please refer to Chapter 6.

1.4 HOW CAN LEAD ENTER AND LEAVE MY BODY?

Some of the lead that enters your body comes from breathing in dust or chemicals that contain lead. Once this lead gets into your lungs, it goes quickly to other parts of the body in your blood.

Larger particles that are too large to get into your lungs can be coughed up and swallowed. You may also swallow lead by eating food and drinking liquids that contain it. Most of the lead that enters your body comes through swallowing, even though very little of the amount you swallow actually enters your blood and other parts of your body. The amount that gets into your body from your stomach partially depends on when you ate your last meal. It also depends on how old you are and how well the lead particles you ate dissolved in your stomach juices. Experiments using adult volunteers showed that, for adults who had just eaten, the amount of lead that got into the blood from the stomach was only about 6% of the total amount taken in. In adults who had not eaten for a day, about 60–80% of the lead from the stomach got into their blood. In general, if adults and children swallow the same amount of lead, a bigger proportion of the amount swallowed will enter the blood in children than in adults. Children absorb about 50% of ingested lead.

Dust and soil that contain lead may get on your skin, but only a small portion of the lead will pass through your skin and enter your blood if it is not washed off. You can, however, accidentally swallow lead that is on your hands when you eat, drink, smoke, or apply cosmetics (for example, lip balm). More lead can pass through skin that has been damaged (for example, by scrapes, scratches, and wounds). The only kinds of lead compounds that easily penetrate the skin are the additives in leaded gasoline, which is no longer sold to the general public. Therefore, the general public is not likely to encounter lead that can enter through the skin.

Shortly after lead gets into your body, it travels in the blood to the "soft tissues" and organs (such as the liver, kidneys, lungs, brain, spleen, muscles, and heart). After several weeks, most of the lead moves into your bones and teeth. In adults, about 94% of the total amount of lead in the body is contained in the bones and teeth. About 73% of the lead in children’s bodies is stored in their bones. Some of the lead can stay in your bones for decades; however, some lead can leave

your bones and reenter your blood and organs under certain circumstances (e.g., during pregnancy and periods of breast feeding, after a bone is broken, and during advancing age).

Your body does not change lead into any other form. Once it is taken in and distributed to your organs, the lead that is not stored in your bones leaves your body in your urine or your feces. About 99% of the amount of lead taken into the body of an adult will leave in the waste within a couple of weeks, but only about 32% of the lead taken into the body of a child will leave in the waste. Under conditions of continued exposure, not all of the lead that enters the body will be eliminated, and this may result in accumulation of lead in body tissues, especially bone. For more information on how lead can enter and leave your body, please refer to Chapter 3.

1.5 HOW CAN LEAD AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

The effects of lead are the same whether it enters the body through breathing or swallowing. The main target for lead toxicity is the nervous system, both in adults and children. Long-term exposure of adults to lead at work has resulted in decreased performance in some tests that measure functions of the nervous system. Lead exposure may also cause weakness in fingers, wrists, or ankles. Lead exposure also causes small increases in blood pressure, particularly in middle-aged and older people. Lead exposure may also cause anemia. At high levels of exposure, lead can severely damage the brain and kidneys in adults or children and ultimately

cause death. In pregnant women, high levels of exposure to lead may cause miscarriage. High-level exposure in men can damage the organs responsible for sperm production.

We have no conclusive proof that lead causes cancer (is carcinogenic) in humans. Kidney tumors have developed in rats and mice that had been given large doses of some kind of lead compounds. The Department of Health and Human Services (DHHS) has determined that lead and lead compounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from animal studies, and the EPA has determined that lead is a probable human carcinogen. The International Agency for Research on Cancer (IARC) has determined that inorganic lead is probably carcinogenic to humans. IARC determined that organic lead compounds are not classifiable as to their carcinogenicity in humans based on inadequate evidence from studies in humans and in animals. See Chapters 2 and 3 for more information on the health effects of lead.

1.6 HOW CAN LEAD AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Studies carried out by the Centers for Disease Control and Prevention (CDC) show that the levels of lead in the blood of U.S. children have been getting lower and lower. This result is because lead is banned from gasoline, residential paint, and solder used for food cans and water pipes. However, about 310,000 U.S. children between the ages of 1 and 5 years are believed to have blood lead levels equal or greater than 10 μg/dL, the level targeted for elimination among young children in the Unites States by 2010.

Children are more vulnerable to lead poisoning than adults. Children are exposed to lead all through their lives. They can be exposed to lead in the womb if their mothers have lead in their bodies. Babies can swallow lead when they breast feed, or eat other foods, and drink water that contains lead. Babies and children can swallow and breathe lead in dirt, dust, or sand while they play on the floor or ground. These activities make it easier for children to be exposed to lead

than adults. The dirt or dust on their hands, toys, and other items may have lead particles in it. In some cases, children swallow nonfood items such as paint chips; these may contain very large amounts of lead, particularly in and around older houses that were painted with lead-based paint. The paint in these houses often chips off and mixes with dust and dirt. Some old paint contains as much as 50% lead. Also, compared with adults, a bigger proportion of the amount of lead swallowed will enter the blood in children.

Children are more sensitive to the health effects of lead than adults. No safe blood lead level in children has been determined. Lead affects children in different ways depending on how much lead a child swallows. A child who swallows large amounts of lead may develop anemia, kidney damage, colic (severe “stomach ache”), muscle weakness, and brain damage, which ultimately can kill the child. In some cases, the amount of lead in the child’s body can be lowered by giving the child certain drugs that help eliminate lead from the body. If a child swallows smaller amounts of lead, such as dust containing lead from paint, much less severe but still important effects on blood, development, and behavior may occur. In this case, recovery is likely once the child is removed from the source of lead exposure, but there is no guarantee that the child will completely avoid all long-term consequences of lead exposure. At still lower levels of exposure, lead can affect a child’s mental and physical growth. Fetuses exposed to lead in the womb, because their mothers had a lot of lead in their bodies, may be born prematurely and have lower weights at birth. Exposure in the womb, in infancy, or in early childhood also may slow mental development and cause lower intelligence later in childhood. There is evidence that these effects may persist beyond childhood.

Children with high blood lead levels do not have specific symptoms. However, health workers can find out whether a child may have been exposed to harmful levels of lead by taking a blood sample. They can also find out how much lead is in a child’s bones by taking a special type of x-ray of the finger, knee, or elbow. This type of test, however, is not routine. More information regarding children’s health and lead can be found in Section 3.5.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO LEAD?

If your doctor finds that you have been exposed to substantial amounts of lead, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

If your doctor finds that you have been exposed to substantial amounts of lead, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

The most important way families can lower exposures to lead is to know about the sources of lead in their homes and avoid exposure to these sources. Some homes or day-care facilities may have more lead in them than others. Families who live in or visit these places may be exposed to higher amounts of lead. These include homes built before 1978 that may have been painted with paint that contains lead (lead-based paint). If you are buying a home that was built before 1978, you may want to know if it contains lead based paint. Federal government regulations require a person selling a home to tell the real estate agent or person buying the home of any known lead-based hazards on the property. Adding lead to paint is no longer allowed. If your house was built before 1978, it may have been painted with lead-based paint. This lead may still be on walls, floors, ceilings, and window sills, or on the outside walls of the house. The paint may have been scraped off by a previous owner, but paint chips and lead-containing dust may still be in the yard soil. Decaying, peeling, or flaking paint can introduce lead into household dust and the area where this is occurring should be repainted. If your paint is decaying or your child has symptoms of lead poisoning, you may want to have your house tested for lead. In some states, homeowners can have the paint in their homes tested for lead by their local health departments. The National Lead Information Center (1-800-532-3394) has a listing of approved risk assessors (people who have met certain criteria and are qualified to assess the potential risks of a site) and of approved testing laboratories (for soil, paint, and dust).

Sanding surfaces painted with lead-based paint or using heat to peel the paint may cause exposure to high levels of lead. Many cases of lead poisoning have resulted from do-it-yourself

home renovations. Therefore, any renovations should be performed by a licensed contractor who will minimize exposure to household members. It is important for the area being renovated to be isolated from the rest of the house because of lead-containing dust. The federal government requires that contractors who test for or remove lead must be certified by the EPA or an EPA-approved state program. Ask to see certifications of potential contractors. Your state health department or environmental protection division should be able to identify certified contractors for you. The National Lead Abatement Council (P.O. Box 535; Olney, MD 20932; telephone 301-924-5490) can also send you a list of certified contractors.

Families can lower the possibility of children swallowing paint chips by discouraging their children from chewing or putting these painted surfaces in their mouths and making sure that they wash their hands often, especially before eating. Lead can be found in dirt and dust. Areas where levels of lead in dirt might be especially high are near old houses, highways, or old orchards. Some children have the habit of eating dirt (the term for this activity is pica). Discourage your children from eating dirt and other hand-to-mouth activity.

Non-Western folk remedies used to treat diarrhea or other ailments may contain substantial amounts of lead. Examples of these include: Alarcon, Ghasard, Alkohl, Greta, Azarcon, Liga, Bali Goli, Pay-loo-ah, Coral, and Rueda. If you give your children these substances or if you are pregnant or nursing, you may expose your children to lead. It is wise to know the ingredients of any medicines that you or your children use.

Older homes that have plumbing containing lead may have higher amounts of lead in drinking water. Inside plumbing installed before 1930 is most likely to contain high levels of lead. Copper pipes have replaced lead pipes in most residential plumbing. You cannot see, taste, or smell lead in water, and boiling your water will not get rid of lead. If you have a water-lead problem, EPA recommends that anytime water in a particular faucet has not been used for 6 hours or longer, you should flush your cold water pipes by running water until it is cold (5 seconds–2 minutes). Because lead dissolves more easily in warm water than in cold water, you should only use cold water for drinking, cooking, and preparing baby formula. You can contact your local health department or water supplier to find out about testing your water for

lead. If your water tests indicate a significant presence of lead, consult your water supplier or local health department about possible remedies.

You can bring lead home in the dust on your hands or clothes if lead is used in the place where you work. Lead dust is likely to be found in places where lead is mined or smelted, where car batteries are made or recycled, where electric cable sheathing is made, where fine crystal glass is made, or where certain types of ceramic pottery are made. Pets can also bring lead into the home in dust or dirt on their fur or feet if they spend time in places that have high levels of lead in the soil.

Swallowing of lead in house dust or soil is a very important exposure pathway for children. This problem can be reduced in many ways. Regular hand and face washing to remove lead dusts and soil, especially before meals, can lower the possibility that lead on the skin is accidentally swallowed while eating. Families can lower exposures to lead by regularly cleaning the home of dust and tracked in soil. Door mats can help lower the amount of soil that is tracked into the home; removing your shoes before entering the home will also help. Planting grass and shrubs over bare soil areas in the yard can lower contact that children and pets may have with soil and the tracking of soil into the home.

Families whose members are exposed to lead dusts at work can keep these dusts out of reach of children by showering and changing clothes before leaving work, and bagging their work clothes before they are brought into the home for cleaning. Proper ventilation and cleaning—during and after hobby activities, home or auto repair activities, and hair coloring with products that contain lead—will decrease the possibility of exposure.

Lead-containing dust may be deposited on plant surfaces and lead may be taken up in certain edible plants from the soil by the roots; therefore, home gardening may also contribute to exposure if the produce is grown in soils that have high lead concentrations. Vegetables should be well washed before eating to remove surface deposits. Certain hobbies and home or car repair activities like radiator repair can add lead to the home as well. These include soldering glass or metal, making bullets or slugs, or glazing pottery. Some types of paints and pigments that are

used as facial make-up or hair coloring contain lead. Cosmetics that contain lead include surma and kohl, which are popular in certain Asian countries. Read the labels on hair coloring products, and keep hair dyes that contain lead acetate away from children. Do not allow children to touch hair that has been colored with lead-containing dyes or any surfaces that have come into contact with these dyes because lead compounds can rub off onto their hands and be transferred to their mouths.

It is important that children have proper nutrition and eat a balanced diet of foods that supply adequate amounts of vitamins and minerals, especially calcium and iron. Good nutrition lowers the amount of swallowed lead that passes to the bloodstream and also may lower some of the toxic effects of lead.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO LEAD?

The amount of total lead in the blood can be measured to determine if exposure to lead has occurred. This test shows if you have been recently exposed to lead. Lead can be measured in teeth or bones by x-ray techniques, but these methods are not widely available. These tests show long-term exposures to lead. The primary screening method is measurement of blood lead. Exposure to lead also can be evaluated by measuring erythrocyte protoporphyrin (EP) in blood samples. EP is a part of red blood cells known to increase when the amount of lead in the blood is high. However, the EP level is not sensitive enough to identify children with elevated blood lead levels below about 25 micrograms per deciliter (μg/dL). These tests usually require special analytical equipment that is not available in a doctor's office. However, your doctor can draw blood samples and send them to appropriate laboratories for analysis. For more information on tests to measure lead in the body, see Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health

Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for lead include the following:

CDC recommends that states develop a plan to find children who may be exposed to lead and have their blood tested for lead. CDC recommends that the states test children:

- at ages 1 and 2 years;
- at ages 3–6 years if they have never been tested for lead;
- if they receive services from public assistance programs for the poor such as Medicaid or the Supplemental Food Program for Women, Infants, and Children;
- if they live in a building or frequently visit a house built before 1950;
- if they visit a home (house or apartment) built before 1978 that has been recently remodeled; and/or
- if they have a brother, sister, or playmate who has had lead poisoning.

CDC considers children to have an elevated level of lead if the amount of lead in the blood is at least 10 μg/dL. Many states or local programs provide intervention to individual children with blood lead levels equal to or greater than 10 μg/dL. Medical evaluation and environmental investigation and remediation should be done for all children with blood lead levels equal to or greater than 20 μg/dL. Medical treatment (i.e., chelation therapy) may be necessary in children if the lead concentration in blood is higher than 45 μg/dL.

EPA requires that the concentration of lead in air that the public breathes be no higher than 1.5 micrograms per cubic meter ($\mu g/m^3$) averaged over 3 months. EPA regulations no longer allow lead in gasoline. The Clean Air Act Amendments (CAAA) of 1990 banned the sale of leaded gasoline as of December 31, 1995.

Under the Lead Copper Rule (LCR), EPA requires testing of public water systems, and if more than 10% of the samples at residences contain lead levels over 0.015 milligrams per liter (mg/L), actions must be taken to lower these levels. Testing for lead in drinking water in schools is not required unless a school is regulated under a public water system. The 1988 Lead Contamination Control Act (LCCA) was created to help reduce lead in drinking water at schools and daycare centers. The LCCA created lead monitoring and reporting requirements for schools, as well as the replacement of fixtures that contain high levels of lead. However, the provisions in the LCCA are not enforceable by the federal government and individual states have the option to voluntarily comply with these provisions or create their own.

To help protect small children, the Consumer Product Safety Commission (CPSC) requires that the concentration of lead in most paints available through normal consumer channels be not more than 0.06%. The Federal Hazardous Substance Act (FHSA) bans children's products containing hazardous amounts of lead.

The Department of Housing and Urban Development (HUD) develops recommendations and regulations to prevent exposure to lead. HUD requires that federally funded housing and renovations, Public and Indian housing be tested for lead-based paint hazards and that such hazards be fixed by covering the paint or removing it. When determining whether lead-based

paint applied to interior or exterior painted surfaces of dwellings should be removed, the standard used by EPA and HUD is that paint with a lead concentration equal to or greater than 1.0 milligram per square centimeter (mg/cm^2) of surface area should be removed or otherwise treated. HUD is carrying out demonstration projects to determine the best ways of covering or removing lead-based paint in housing.

EPA has developed standards for lead-paint hazards, lead in dust, and lead in soil. To educate parents, homeowners, and tenants about lead hazards, lead poisoning prevention in the home, and the lead abatement process, EPA has published several general information pamphlets. Copies of these pamphlets can be obtained from the National Lead Information Center or from various Internet sites, including http://www.epa.gov/opptintr/lead.

OSHA regulations limit the concentration of lead in workroom air to 50 $\mu g/m^3$ for an 8-hour workday. If a worker has a blood lead level of 50 μg/dL or higher, then OSHA requires that the worker be removed from the workroom where lead exposure is occurring.

FDA includes lead on its list of poisonous and deleterious substances. FDA considers foods packaged in cans containing lead solders to be unsafe. Tin-coated lead foil has been used as a covering applied over the cork and neck areas of wine bottles for decorative purposes and to prevent insect infestations. Because it can be reasonably expected that lead could become a component of the wine, the use of such foil is also a violation of the Federal Food, Drug, and Cosmetic Act. FDA has reviewed several direct human food ingredients (i.e., food dyes) and has determined them to be “generally recognized as safe” when used in accordance with current good manufacturing practices. Some of these ingredients contain allowable lead concentrations that range from 0.1 to 10 ppm.

Please see Chapter 8 for more information on federal and state regulations and guidelines for lead.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO LEAD IN THE UNITED STATES

Lead is a naturally occurring metal found in the Earth's crust at about 15–20 mg/kg. In comparison to the two most abundant metals in the Earth, aluminum and iron, lead is a relatively uncommon metal. Lead rarely occurs in its elemental state, but rather its +2 oxidation state in various ores throughout the earth. The most important lead containing ores are galena (PbS), anglesite ($PbSO_4$), and cerussite ($PbCO_3$). The world's reserves of lead are estimated at $7.1x10^7$ tons, with over one third located in North America. Levels of lead in the environment (not contained in ore deposits) have increased over the past three centuries as a result of human activity. Human exposure to lead is common and results from the many uses of this metal due to its exceptional properties. The largest industrial use of lead today is for the production of lead batteries, largely used in the automobile industry. Other uses of lead include the production of lead alloys, use in soldering materials, shielding for x-ray machines, and in the manufacture of corrosion and acid resistant materials used in the building industry (see Chapter 5 for more details regarding lead usage).

The greatest potential for human exposure to lead arises from its previous use as an additive in gasoline, which resulted in its widespread dispersal throughout the environment, and its use as a pigment in both interior and exterior paints. Although the use of lead as a gasoline additive has been gradually phased out and completely banned by 1995 in the United States and its use in paints was banned in 1978, human exposure to lead continues because unlike organic chemicals released to the environment, lead does not degrade to other substances. Leaded paint is still prevalent in many older homes in the United States, and peeling or flaking paint contributes to indoor and outdoor dust levels. Prior to World War II, lead-arsenic compounds were used as pesticides, especially in orchards. Because lead does not degrade and is strongly absorbed to soil, the lead released from past uses still remains in the soil. Since the ban on the use of leaded gasoline took effect, lead emissions to the atmosphere have decreased significantly. According to the EPA, atmospheric emissions of lead decreased 93% over the 21-year period of 1982–2002. The atmospheric concentration of lead varies greatly, with the highest levels observed near stationary sources such as lead smelters. Levels of lead in ambient air range from about $7.6x10^{-5}$ $\mu g/m^3$ in remote areas such as Antarctica to >10 $\mu g/m^3$ near point sources. The EPA national ambient air quality standard for lead is 1.5 $\mu g/m^3$.

The amount of lead contained in pipes and plumbing fittings have been strictly regulated since 1988; however, human exposure to lead from drinking water still occurs as a consequence of leaching of lead from corroding pipes and fixtures or lead containing solder. Based on several data sets, it is estimated that <1% of the public water systems in the United States have water entering the distribution system with lead levels above 5 μg/L. Copper pipes have replaced lead pipes in most residential plumbing. Section 1417 of the Safe Drinking Water Act, which took effect in August 1998, requires that all pipes, fixtures, and solder be lead-free. However, lead-free means that solders and flux may not contain >0.2% lead, while pipes, pipe fittings, and well pumps may not contain >8% lead. The EPA requires public water distribution systems to reduce the corrosivity of water if >10% of the water samples exceed 15 μg/L of lead.

Occupational exposure to lead occurs for workers in the lead smelting and refining industries, battery manufacturing plants, steel welding or cutting operations, construction, rubber products and plastics industries, printing industries, firing ranges, radiator repair shops, and other industries requiring flame soldering of lead solder. In these occupations, the major routes of lead exposure are inhalation and ingestion of lead-bearing dusts and fumes. In the smelting and refining of lead, mean concentrations of lead in air can reach 4,470 $\mu g/m^3$; in the manufacture of storage batteries, mean airborne concentrations of lead from 50 to 5,400 $\mu g/m^3$ have been recorded; and in the breathing zone of welders of structural steel, an average lead concentration of 1,200 $\mu g/m^3$ has been found.

Certain populations may be exposed to lead from other sources. Several non-western folk medicines can contain substantial levels of lead. Lead glazing that is applied to some pottery and ceramic ware may leach lead into foods or liquids that are stored in them (see Section 6.4.5 for more information). The FDA regulates the amount of leachable lead from food containers (see Table 8-1).

Blood lead levels (PbB) in the general population of the United States have been decreasing over the past 3 decades as regulations regarding lead paint, leaded fuels, and lead-containing plumbing materials have reduced exposure. PbBs measured as a part of the National Health and Nutrition Examination Surveys (NHANES) indicated that from 1976 to 1991, the mean PbBs of the U.S. population aged from 1 to 74 years dropped 78%, from 12.8 to 2.8 μg/dL. The prevalence of PbBs ≥10 μg/dL also decreased sharply from 77.8 to 4.3%. Data from NHANES III, phase II (1991–1994) showed that 4.4% of children aged 1–5 years had PbBs ≥10 μg/dL, and the geometric mean PbBs for children 1–5 years old was 2.7 μg/dL. From the most recent sampling data conducted for 1999–2002, 1.6% of children aged 1–5 years had PbBs ≥10 μg/dL, with a geometric mean PbBs of 1.9 μg/dL (see Section 6.5 for greater

detail). The Centers for Disease Control and Prevention (CDC) action level for children ≤7 years of age is 10 μg/dL. A tiered approach is recommended for managing lead-exposed children (see Section 3.9).

Analysis of lead in whole blood is the most common and accurate method of assessing lead exposure. Erythrocyte protoporphyrin (EP) tests can also be used, but are not as sensitive at low blood lead levels (≤20 μg/dL); the screening test of choice is blood lead levels. X-ray fluorescence techniques (XRF) can be used for the determination of lead concentration in bones. Lead partitions to the bone over a lifetime of exposure; therefore, bone lead measurements are a good indicator of cumulative exposure, whereas measurements of lead in blood are more indicative of recent exposure. However, XRF is primarily used in the research area and is not widely available (see Sections 3.3 and 3.6.1 for greater detail).

2.2 SUMMARY OF HEALTH EFFECTS

An enormous amount of information is available on the health effects of lead on human health. In fact, the toxic effects of lead have been known for centuries, but the discovery in the past few decades that levels of exposure resulting in relatively low levels of lead in blood (e.g., <20 μg/dL) are associated with adverse effects in the developing organism is a matter of great concern. Most of the information gathered in modern times regarding lead toxicity comes from studies of workers from a variety of industries and from studies of adults and children in the general population. The most sensitive targets for lead toxicity are the developing nervous system, the hematological and cardiovascular systems, and the kidney. However, due to the multi-modes of action of lead in biological systems, lead could potentially affect any system or organs in the body.

Studies of lead workers suggest that long-term exposure to lead may be associated with increased mortality due to cerebrovascular disease. The same was found in a study of adults from the general population who were hospitalized for lead poisoning during childhood. Population studies suggest that there is a significant association between bone-lead levels and elevated blood pressure. Blood lead levels (PbBs) also have been associated with small elevations in blood pressure. Between the two biomarkers, bone lead appears to be the better predictor. Lead also affects kidney functions; glomerular filtration rate appears to be the function affected at the lowest PbBs. Decreased glomerular filtration rate has been consistently observed in populations with mean PbB <20 μg/dL and two studies have reported effects at PbB <10 μg/dL. Lead may alter glomerular filtration rate by several mechanisms.

2. RELEVANCE TO PUBLIC HEALTH

Lead has long been known to alter the hematological system by inhibiting the activities of several enzymes involved in heme biosynthesis. Particularly sensitive to lead action is δ-aminolevulinic acid dehydratase (ALAD). Inhibition of ALAD activity occurs over a wide range of PbBs beginning at <10 μg/dL. The anemia induced by lead is primarily the result of both inhibition of heme synthesis and shortening of erythrocyte lifespan, but lead also can induce inappropriate production of the hormone erythropoietin leading to inadequate maturation of red cell progenitors, which can contribute to the anemia.

A recent study in children 8–10 years of age suggested that lead accelerates skeletal maturation, which might predispose to osteoporosis in later life. Lead also has been associated with increased occurrence of dental caries in children and periodontal bone loss, which is consistent with delayed mineralization in teeth observed in studies in animals. Current mean PbBs in these cohorts were <5 μg/dL; however, the cross-sectional nature of the studies precluded assessment of the exposure history.

Changes in circulating levels of thyroid hormones, particularly serum thyroxine (T_4) and thyroid stimulating hormone (TSH), generally occurred in workers having mean PbB ≥40–60 μg/dL. Altered serum levels of reproductive hormones, particularly follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone have been observed at PbB ≥30–40 μg/dL. Lead also has been shown to decrease circulating levels of the active form of vitamin D, 1,25-dihydroxyvitamin D, in children with moderate to high PbB (30–60 μg/dL), but not in children with low to moderate PbB (average lifetime PbB between 4.9 and 23.6 μg/dL, geometric mean, 9.8 μg/dL). Normal levels of vitamin D are important for maintaining calcium homeostasis.

Altered immune parameters have been described in lead workers with PbB in the range of 30–70 μg/dL. Reported effects included changes in some T-cell subpopulations, response to T-cell mitogens, and reduced chemotaxis of polymorphonuclear leukocytes. Several studies of children reported significant associations between PbB and increases in serum IgE levels. IgE is the primary mediator for type-I hypersensitivity and is involved in various allergic diseases such as asthma. These findings in children along with results from studies in rodents exposed *in utero* have led some to suggest that lead may be a risk factor for childhood asthma, although a recent relatively large study (4,634 children) found that PbB was less a predictor of asthma than was race.

Exposure to high amounts of lead resulting in PbBs of 100–120 μg/dL in adults or 70–100 μg/dL in children produce encephalopathy, a general term that describes various diseases that affect brain function.

Symptoms develop following prolonged exposure and include dullness, irritability, poor attention span, epigastric pain, constipation, vomiting, convulsions, coma, and death. Lead poisoning in children can leave residual cognitive deficits that can be still detected in adulthood. Neurobehavioral effects including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, and paresthesia have been reported in lead workers with PbBs in the range of 40–80 μg/dL. Also, PbBs between 40 and 80 μg/dL have been associated with neuropsychological effects in lead workers. A recent study of lead workers reported that higher tibia lead was associated with increased prevalence and severity of white matter lesions, as assessed by brain MRI. Studies of older populations with current mean PbBs <10 μg/dL have reported associations between PbB and/or bone lead and poorer performance in neurobehavioral tests. Lead also has been shown to affect nerve conduction velocity and postural balance in workers with PbB in the range of 30–60 μg/dL. Alterations of somatosensory evoked potentials also have been reported in lead workers with mean PbBs in the range of 30–50 μg/dL.

As previously mentioned, one of the major concerns regarding lead toxicity is the cognitive and neurobehavioral deficits that are observed in children exposed to lead. Prospective studies have provided the greatest amount of information. Analyses of these and other studies suggest that an IQ decline of 1–5 points is associated with an increase in PbB of 10 μg/dL. Of special interest and concern are the results of recent studies that have reported neurobehavioral deficits in children associated with PbBs <10 μg/dL and an apparent lack of threshold down to even the lowest PbBs recorded in these studies. Lead also has caused neurobehavioral alterations in developing animals, and at PbBs similar to those reported in children. Studies in animals, particularly in monkeys, have provided key information for the interpretation of a cognitive basis for IQ changes. Studies of children also have shown associations between PbB and growth, delayed sexual maturation in girls, and decreased erythropoietin production.

Some studies of humans occupationally or environmentally exposed to lead have observed associations between PbB and abortion and preterm delivery in women and alterations in sperm and decreased fertility in men. On the other hand, there are several studies that found no significant association between lead exposure and these end points. At least for the effects in males, the threshold PbB appears to be in the range of 30–40 μg/dL. Studies have shown that lead can affect the association of protamines with DNA in sperm cells from exposed males. Lead does so by competing or reducing zinc in protamine P2 *in vivo*, which would leave sperm chromatin and DNA open to damage from other exposures.

In vitro mutagenicity studies in microorganisms have yielded mostly negative results for lead, but lead is a clastogenic agent, as shown by the induction of chromosomal aberrations, micronuclei and by sister

chromatid exchanges in peripheral blood cells from lead workers. Studies of cancer in lead workers have been inconclusive. A meta-analysis of eight major occupational studies on cancer mortality or incidence in workers with high lead exposure concluded that there is some limited evidence of increased risk of lung cancer and stomach cancer, although there might have been confounding with arsenic exposure in the study with highest relative risk of lung cancer. The results also showed a weak evidence for an association with kidney cancer and gliomas. In the only study of the general population available, there was suggestive evidence for an increase risk of cancer mortality in women, but not men, with a threshold PbB of 24 μg/dL. This study used data from the Second National Health and Nutrition Survey (NHANES II) Mortality Study. Lead has produced primarily renal tumors in rodents by a mechanism not yet elucidated. Some nongenotoxic mechanisms that have been proposed for lead-induced cancer include inhibition of DNA synthesis and repair, alterations in cell-to-cell communication, and oxidative damage.

The Department of Health and Human Services (DHHS) has determined that lead and lead compounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from animal studies. The EPA has determined that lead is a probable human carcinogen based on sufficient evidence from studies in animals and inadequate evidence in humans. The International Agency for Research on Cancer (IARC) has determined that inorganic lead is probably carcinogenic to humans based on sufficient evidence from studies in animals and limited evidence of carcinogenicity from studies in humans. IARC also determined that organic lead compounds are not classifiable as to their carcinogenicity in humans based on inadequate evidence from studies in humans and animals.

A discussion of the most sensitive end points for lead toxicity, neurodevelopmental, cardiovascular/renal, and hematological, is presented below. The reader is referred to Chapter 3, Health Effects, for information on additional effects.

Neurodevelopmental Effects. Lead can impair cognitive function in children and adults, but children are more vulnerable than adults. The increased vulnerability is due in part to the relative importance of exposure pathways (i.e., dust-to-hand-mouth) and differences in toxicokinetics (i.e., absorption of ingested lead). Although the inhalation and oral routes are the main routes of exposure for both adults and children, children are more likely to have contact with contaminated surfaces due to playing on the ground and to hand-to-mouth activities. Furthermore, children absorb a larger fraction of ingested lead than adults. However, perhaps more important is the fact that the developing nervous system is especially susceptible to lead toxicity. During brain development, lead interferes with the

trimming and pruning of synapses, migration of neurons, and neuron/glia interactions. Alterations of any of these processes may result in failure to establish appropriate connections between structures and eventually in permanently altered functions. Because different brain areas mature at different times, the final outcome of the exposure to lead during development (i.e., *in utero* vs. pediatric exposure) will vary depending on the time of exposure. This has been demonstrated in studies in animals. The time of exposure-specific response appears to have contributed to the failure to identify a "behavioral signature" of lead exposure in children. Other factors that may affect individual vulnerability are certain genetic polymorphisms, such as that for the vitamin D receptor, the lead-binding enzyme ALAD, or the APOE genotype. One important additional factor shown to influence the toxicity of lead is the characteristics of the child's rearing environment, a modifying factor. It has been argued that effect modification is a property of a true association and should be distinguished from confounding. Effect modification can explain inconsistencies in findings, and if it exists, failure to address it will lead to an error in inference. For example, if social class is an effect modifier of the association between PbB and IQ, and differs between two cohorts, the strength of the association based on these two studies will necessarily be different.

Despite the many factors that can potentially work against finding agreement among studies, the preponderance of the evidence indicates that lead exposure is associated with decrements in cognitive function. Meta-analyses conducted on cross-sectional studies or a combination of cross-sectional and prospective studies suggest that an IQ decline of 1–5 points is associated with an increase in PbB of 10 μg/dL. Most importantly, no threshold for the effects of lead on IQ has been identified. This has been confirmed by a series of recent studies in children that found significant inverse associations between cognitive function and PbBs <10 μg/dL. Moreover, these and other studies have shown that the slope of the lead effects on cognitive variables is steeper (the effect is greater) at lower than at higher PbBs (supra-linear dose-response relationship). However, there is not complete agreement on the interpretation of the lack of linearity in the dose-response relationship among the scientific community. Some have argued, based on a theoretical statistical analysis, that the supra-linear slope is a required outcome of correlations between data distributions where one is log-normally distributed and the other is normally distributed. Perhaps the strongest evidence for nonlinearity is provided by an international pooled analysis of seven prospective studies (details in Section 3.2.4). After testing several models, these investigators determined that the shape of the dose-response was nonlinear insofar as the quadratic and cubic terms for concurrent PbB were statistically significant ($p<0.001$, $p=0.003$, respectively). Additional support for the steeper slope at low PbB was provided by plotting the individual effects estimates for each of the seven cohorts, adjusted for the same covariates. The plot showed that the studies with the lowest mean PbBs had a

steeper slope compared with studies with higher PbBs. Yet further evidence for nonlinearity was presented when the data were divided at two cut-points *a priori* (maximal PbB above and below 10 μg/dL and above and below 7.5 μg/dL). The investigators then fit separate linear models to the data in each of those ranges and compared the PbB coefficients for the concurrent PbB index. The stratified analyses showed that the effects estimate for children with maximal PbB <7.5 μg/dL was significantly greater (p=0.015) than those with a maximal PbB ≥7.5 μg/dL. Similar results were seen at the cut-off point of 10 μg/dL. A reanalysis of the pooled studies found that a log-linear relationship between PbB and IQ was a better fit within the ranges of PbBs in the studies than was a linear relationship (p<0.009). Collectively, the results of the pooled analysis and of additional studies provide suggestive evidence of lead effects on cognitive functions in children at PbBs <10 μg/dL and, possibly as low as 5 μg/dL. It should be stressed, however, that the effects of lead on IQ and other neurobehavioral scores are very small compared with the effects of other factors such as parents' IQ, but is also important to stress that lead exposure, unlike most of those other factors, is highly preventable.

The other aspect that has been questioned regarding the nonlinear shape of the dose-response relationship is the apparent lack of a biological mechanism that could produce this result, and this clearly represents a data need. To explain the nonlinear shape of the dose-response, it was proposed that "the initial damage caused by lead may reflect the disruption of different biological mechanisms than the more severe effects of high exposures that result in encephalopathy or frank mental disability. This might explain why, within the range of exposures not producing overt clinical effects, an increase in PbB beyond a certain level might cause little *additional* impairment in children's cognitive function."

While measurements of IQ are convenient in that they allow comparison across populations of different demographic and cultural characteristics, and help define the extent of the public health issue, they only partially advance our understanding of the problem of lead-induced behavioral toxicity. It is important to elucidate the underlying basis of the deficits in IQ as well as the behavioral mechanisms that account for them. It was noted that "the answers are critical not only to further define neurobiological mechanisms associated with learning deficits, but also to determine behavioral or neurochemical therapeutic approaches to alleviate them." Studies in animals have provided answers to some of these questions. Studies in animals have great utility because the possibility of confounding is reduced with the controlled experimental design and genetic factors. In addition, they address specific domains of cognitive function and allow determination of critical periods of exposure. Results of behavioral tests performed primarily in rats and monkeys exposed to lead have suggested that the impaired performance is the result, at least in part, of a combination of distractibility, inability to inhibit inappropriate responding, and perseveration in

behaviors that are no longer appropriate. Evaluation of children exposed to lead with different subscales of IQ tests in conjunction with assessments of behavior on teacher's rating scales on young school-age children suggest that increased distractibility, impulsivity, short attention span, and inability to follow simple and complex sequences of directions are associated with increased lead body burden. The similarity between neurobehavioral effects in lead-exposed children and in animals, and the fact that the deficits are observed at similar PbBs should stimulate continued research to elucidate the biochemical and morphological substrates that underlie specific behaviors.

Although the decrement of IQ points in children associated with lead exposure is generally small, lead neurotoxicity may have major implications for public health when exposure is considered in terms of large populations and its preventable nature. One study quantified the economic benefits from projected improvements in worker productivity resulting from the reduction in children's exposure to lead in the United States since 1976. Based on data from NHANES (a study designed to provide national estimates of the health and nutritional status of the U.S. civilian noninstitutionalized population aged 2 months and older) and meta-analyses, it was estimated that mean PbBs declined 15.1 μg/dL between 1976 and 1999 and that IQ scores increased between 0.185 and 0.323 points for each 1 μg/dL blood lead concentration. It was further estimated that each IQ point raises worker's productivity by 1.76–2.38%, and that the economic benefit for each year's cohort of 3.8 million 2-year-old children ranges from $110 to $319 billion. In another study, using an environmentally attributable fraction model, it was estimated that the present value of economic losses in the United States attributable to lead exposure in amounts to $43.4 billion per year in each annual birth cohort. More recently, one study estimated that mild mental retardation and cardiovascular outcomes resulting from exposure to lead amounts to almost 1% of the global burden of disease, with the highest burden in developing regions.

A related and important issue is whether lead-lowering interventions, such as with chelators, are paralleled by improvement in health outcomes reportedly altered by lead. In one study, improvement in cognitive functions was related to decreases in blood lead but not to chelation treatment. In a multi-center study of 780 children, chelation therapy lowered blood lead by a mean of 4.5 μg/dL during the 6 months after initiation of treatment, but it did not improve scores on tests of cognition, behavior, or neuro-psychological function in children with PbB below 45 μg/dL. Re-analysis of these data showed that improvement in test scores was associated with greater falls in PbB only in the placebo group. A further evaluation of this cohort showed that chelation therapy lowered blood lead, but produced no benefits in cognitive, behavioral, or neuromotor end points. The conclusion of this series of studies reached by the investigators was that chelation therapy is not indicated in children with moderate blood lead levels.

Thus, it appears that lead abatement must remain the primary approach in the public health management of lead poisoning.

Cardiovascular/Renal Effects. Although lead has been shown to produce various cardiovascular and renal effects in animals, end points of greatest concern for humans at low exposures and low PbB are elevations in systemic blood pressure and decrements in glomerular filtration rate. These effects may be mechanistically related and, furthermore, can be confounders and covariables in epidemiological studies. Decrements in glomerular filtration rate may contribute to elevations in blood pressure, and elevated blood pressure may predispose people to glomerular disease.

Effects on Blood Pressure. Numerous covariables and confounders affect studies of associations between PbB and blood pressure, including, age, body mass, race, smoking, alcohol consumption, ongoing or family history of cardiovascular/renal disease, and various dietary factors. Varying approaches and breadth of inclusion of these may account for some of the disparity of results that have been reported. Including confounders in a regression model will attenuate the apparent association between lead exposure and the measured health outcome. Measurement error may also be an important factor. Blood pressure estimates based on multiple measurements or, preferably, 24-hour ambulatory measurements, are more reproducible than single measurements. Few studies have employed such techniques and, when used, have not found significant associations between PbB and blood pressure.

An additional limitation of blood lead studies, in general, is that PbB may not provide the ideal biomarker for long-term exposure to target tissues that contribute a hypertensive effect of lead. Bone lead appears to be a better predictor of lead-induced elevations in blood pressure than PbB. In a recent prospective analysis of the Normative Aging Study, higher tibial lead levels, but not PbBs, were associated with higher systolic blood pressure and abnormalities in electrocardiographic conduction.

Chronic lead exposure increases blood pressure in rats through diverse mechanisms that include alterations in neurohumoral control of peripheral vascular resistance, heart rate, and cardiac output (see Section 3.4.2). Studies conducted in animal models provide strong evidence for the plausibility of lead elevating blood pressure in humans. Meta-analyses of the epidemiological findings have found a persistent trend in the data that supports a relatively weak, but significant association. Quantitatively, this association amounts to an increase in systolic blood pressure of approximately 1 mmHg with each doubling of PbB. The results of more recent epidemiology studies indicate that the lead contribution to elevated blood pressure is more pronounced in middle age than at younger ages. A longitudinal study of

males, mean age 67 years, found positive associations between systolic blood pressure and bone lead concentrations, and increased risk of hypertension in association with increased bone lead concentration. Based on this study, an increase in patella bone lead from the midpoint of the lowest quintile (12.0 μg/g) to the highest quintile (53.0 μg/g) was associated with a 1.71-fold increase in hypertension risk (rate-ratio, 95%; confidence interval [CI], 1.08–2.71). A case-control study of women, ages >55 years, found increased risk of hypertension in association with increased bone lead concentration. In this study, an increase in patella bone lead from 6 to 31 μg/g was associated with a 1.86-fold (odds ratio [OR], 95%; CI, 1.09–3.19) increase in risk of hypertension. A large-scale cross-sectional analysis of the NHANES III data on males and females, age 40–59 years, found increasing risk for hypertension in association with increasing PbB, with higher risks in postmenopausal women than in premenopausal women. Risks of diastolic hypertension for pre- and postmenopausal women, combined, who were in the highest blood lead quartile (mean, 6.4 μg/dL; range, 3.0–31.1) was predicted to be 3.4-fold higher (OR, 95%; CI, 1.3–8.7) than that of women in the lowest quartile (mean, 1 μg/dL; range, 0.5–1.6); corresponding risks for postmenopausal women were 8.1 times greater (OR, 95%; CI, 2.6–24.7) (highest vs. lowest quartile). The results of two analyses of the NHANES III data on adult subjects provides evidence for an association between increasing PbB and increasing blood pressure that is more pronounced in blacks than whites. Lead exposures during infancy and childhood (reflected in PbB) have been associated with increased blood pressure and altered responses to acute pressor stresses in childhood. Lead poisoning in childhood has also been associated with hypertension during adulthood in the absence of clinically significant renal disease and discernable elevations in PbB.

Effects in Renal Glomerular Filtration. Classic lead nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and interstitial fibrosis and related functional deficits, including enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate. In humans, the overall dose-effect pattern suggests an increasing severity of nephrotoxicity associated with increasing PbB, with effects on glomerular filtration evident at PbBs below 10 μg/dL, enzymuria and proteinuria becoming evident above 30 μg/dL, and severe deficits in function and pathological changes occurring in association with PbB exceeding 50 μg/dL. Thus, the renal effects of greatest concern, at low exposures (i.e., low PbB), are on glomerular filtration.

The results of epidemiological studies of general populations have shown a significant effect of age on the relationship between glomerular filtration rate (assessed from creatinine clearance of serum creatinine concentration) and PbB (see Section 3.2.2. Renal Effects). Furthermore, as noted previously, hypertension can be both a confounder in studies of associations between lead exposure and creatinine

clearance as well as a covariable with lead exposure. Another important complication in the assessment of associations between lead exposure and adverse effects on glomerular filtration is the potential confounding effect of decrements in glomerular filtration rate and increased lead body burden. Lead exposure has also been associated with increases in glomerular filtration rate. This may represent a benign outcome or a potentially adverse hyperfiltration, which may contribute to subsequent adverse renal effects. Increases in glomerular filtration rate have been observed in the early phases of development of chronic renal injury in rats. When age and other covariables that might contribute to glomerular disease are factored into the dose-response analysis, decreased glomerular filtration rate has been consistently observed in populations that have average PbBs <20 μg/dL, with some studies finding effects at PbBs <10 μg/dL (see Section 3.2.2, Table 3-4). Two studies provide evidence for an effect at lead concentrations below 10 μg/dL. A longitudinal study found a significant relationship between increasing serum creatinine concentration and increasing PbB below 10 μg/dL. A cross-sectional analysis of data from the NHANES III found increased risk of chronic renal disease (defined as severely depressed glomerular filtration rate) in association with PbB <6 μg/dL. The confounding and covariable effects of hypertension are also relevant to the interpretation of the regression coefficients reported in these studies. Given the evidence for an association between lead exposure and hypertension, and that decrements in glomerular filtration rate can be a contributor to hypertension, it is possible that the reported hypertension-adjusted regression coefficients may underestimate the actual slope of the PbB relationship with serum concentration of creatinine or creatinine clearance.

Hematological Effects. The adverse hematological effects of lead are mainly the result of its perturbation of the heme biosynthesis pathway. The activity of ALAD, an enzyme occurring early in the heme synthesis pathway, is negatively correlated with PbBs between 5 and 95 μg/dL. Although inhibition of ALAD occurs at very low exposure levels, there is some controversy as to the toxicological significance of a depression in ALAD activity in the absence of a detectable effect on hemoglobin levels. Nevertheless, because the impairment of heme synthesis has a far-ranging impact not limited to the hemopoietic system, there is concern that developing organisms might be particularly susceptible.

A potential consequence of the inhibition of heme synthesis is a decreased formation of mixed function oxidases in the liver resulting in impaired metabolism of endogenous compounds, as well as impaired detoxification of xenobiotics. Mitochondrial cytochrome oxidase is another heme-requiring protein that could be affected by heme synthesis inhibition. In addition, tryptophan pyrrolase, a hepatic heme-requiring enzyme system, is inhibited via the reduction in the free hepatic heme pool. This could ultimately lead to increased levels of the neurotransmitter serotonin in the brain and increased aberrant

neurotransmission in serotonergic pathways. Inhibition of heme synthesis also results in increased levels of δ-aminolevulinic acid (ALA), which has a structure similar to that of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and therefore, interferes with GABA neurotransmission. Finally, a prospective study of children with moderate PbB (25–40 μg/dL) and hemoglobin levels within normal limits found that serum erythropoietin (EPO) was positively associated with PbB at ages 4.5 and 6.5 years, but the magnitude of the association gradually declined from 4.5 to 12 years. EPO is a glycoprotein hormone produced in the kidney that regulates both steady-state and accelerated erythrocyte production. This suggested that in nonanemic children with moderate PbB, hyperproduction of EPO is necessary to maintain normal hemoglobin concentrations. The decline in slope with age suggested that the compensatory mechanism gradually begins to fail due to direct lead-induced inhibition of EPO production or indirectly through toxic effects of lead on the kidney. Inhibition of EPO production may contribute to lead-induced anemia. Anemia occurs at PbBs of ≥20 μg/dL.

2.3 LEAD DOSE-RESPONSE RELATIONSHIPS

MRLs were not derived for lead because a clear threshold for some of the more sensitive effects in humans has not been identified. In addition, deriving an MRL would overlook the significant body of PbB literature. These data suggest that certain subtle neurobehavioral effects in children may occur at very low PbBs. In lieu of MRLs, ATSDR has developed a framework to guide decisions at lead sites. This approach utilizes site-specific exposure data to estimate internal doses as measured by PbBs (see Appendix D).

Epidemiological studies and clinical observations provide evidence for a progression of adverse health effects of lead in humans that occur in association with PbBs ranging from <10 to >60 μg/dL (Table 2-1). At the low end of the blood lead concentration range, adverse effects include delays and/or impaired development of the nervous system, delayed sexual maturation, neurobehavioral effects, increased blood pressure, depressed renal glomerular filtration rate, and inhibition of pathways in heme synthesis. Although fewer studies have examined associations between health outcomes and bone lead concentrations, recent studies provide evidence for adverse effects occurring in association with bone lead concentrations in excess of 10 μg/g (e.g., cardiovascular/renal, neurobehavioral effects).

The timing of exposure, in addition to the exposure intensity, appears to be an important variable in the exposure-response relationship for lead. Exposures that occur during pre- and postnatal development, which result in PbBs of 10 μg/dL or less, produce delays or impairments of neurological and sexual

Table 2-1. Blood and Bone Lead Concentrations Corresponding to Adverse Health Effects

Age	Effect	Blood lead[a] (µg/dL)	Bone lead[a] (⏭g/g)
Children	Depressed ALAD	<5	ND
Children	Neurodevelopmental effects	<10	ND
Children	Sexual maturation	<10	ND
Children	Depressed vitamin D	>15	ND
Children	Elevated EP	>15	ND
Children	Depressed NCV	>30	ND
Children	Depressed hemoglobin	>40	ND
Children	Colic	>60	ND
Adults (elderly)	Neurobehavioral effects	>4	>30
Adults	Depressed ALAD	<5	ND
Adults	Depressed GFR	<10	>10
Adults	Elevated blood pressure	<10	>10
Adults	Elevated EP (females)	>20	ND
Adults	Enzymuria/proteinuria	>30	ND
Adults	Peripheral neuropathy	>40	ND
Adults	Neurobehavioral effects	>40	ND
Adults	Altered thyroid hormone	>40	ND
Adults	Reduced fertility	>40	ND
Adults	Depressed hemoglobin	>50	ND

[a]Concentration range associated with effect.

ALAD = δ-aminolevulinic acid dehydratase; EP = erythrocyte protoporphyrin; GFR = glomerular filtration rate; NCV = nerve conduction velocity; ND = no data

development. Cognitive deficits, hypertension, and depressed glomerular filtration rate have been observed in older adults (>60 years and/or postmenopause) in association with PbBs <10 μg/dL. This may reflect a higher vulnerability with age and/or the effects of cumulative life-time exposures that are less evident in younger populations that have lower time-integrated exposures.

The epidemiological literature provides a basis for associating specific biomarkers (e.g., PbB, bone lead concentration) with adverse health effects. Prediction of health outcomes that might result from any given environmental exposure requires an understanding of the relationships between environmental exposure (level, frequency, duration), human physiology and behaviors that result in intake of lead (e.g., ingestion of dust, drinking water, inhalation), and lead biokinetics. Models that predict PbBs corresponding to specific exposure scenarios have been used in this context for the purpose of assessing lead health risks. Two general approaches have been explored: (1) integrated exposure-biokinetics models that simulate lead exposure, intake, absorption, tissue distribution, and excretion of lead in humans; and (2) slope factor models that predict PbB based on an empirically-derived linear parameter relating exposure level, or rate of lead absorption, to PbB. Descriptions of exposure-biokinetics and slope factor models that have been used or have potential use in assessing exposure-effect relationships in human populations are described in Section 3.3.5 and in Appendix D.

2. RELEVANCE TO PUBLIC HEALTH

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of lead. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found in Appendix C at the end of this profile.

This chapter will focus primarily on inorganic lead compounds (lead, its salts, and oxides/sulfides), the predominant forms of lead in the environment. The available data on organic (i.e., alkyl) lead compounds indicate that some of the toxic effects of alkyl lead are mediated through metabolism to inorganic lead and that during the combustion of gasoline containing alkyl lead, significant amounts of inorganic lead are released to contaminate the environment. In addition, the lead alkyl halides in automobile exhausts are quickly oxidized by sunlight and air, and do not appear to be present at hazardous waste sites in significant amounts. By far, most lead at hazardous waste sites is inorganic lead. The limited data available on alkyl lead compounds indicate that the toxicokinetic profiles and toxicological effects of these compounds are qualitatively and quantitatively different from those of inorganic lead (EPA 1985b).

The database for lead is unusual in that it contains a great deal of data concerning dose-effect relationships in humans. These data come primarily from studies of occupationally exposed groups and the general population. For the general population, exposure to lead occurs primarily via the oral route, with some contribution from the inhalation route, whereas occupational exposure is primarily by inhalation with some contribution by the oral route. Because the toxic effects of lead are the same regardless of the route of entry into the body, the profile will not attempt to separate human dose data by routes of exposure. The dose data for humans are generally expressed in terms of absorbed dose and not in terms of external exposure levels, or milligrams per kilogram per day (mg/kg/day). The most common metric of absorbed dose for lead is the concentration of lead in the blood (PbB), although other indices, such as lead in bone, hair, or teeth also are available (further information regarding these indices can be found in Section 3.3.2 and Section 3.6.1). The concentration of lead in blood reflects mainly the exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of lead in bone. Lead in bone is considered a biomarker of cumulative or long-term

exposure to lead because lead accumulates in bone over the lifetime and most of the lead body burden resides in bone. For this reason, bone lead may be a better predictor than blood lead of some health effects.

The database on effects of lead in animals is extensive and, in general, provides support for observations in human studies, with some consistency in types of effects and PbB-effect relationships. However, animal data on lead toxicity are generally considered less suitable as the basis for health effects assessments than are the human data. There is no absolutely equivalent animal model for the effects of lead on humans. In this profile, animal studies will be discussed only to the extent that they support the findings in humans.

Due to the extent of the lead database, it is impossible to cite all, or even most, of the studies on a specific topic. ATSDR acknowledges that all studies that add a new piece of information are valuable, but the relative impact on the overall picture regarding lead toxicity varies among studies. Given that the goal of Chapter 3 is to provide an overall perspective on the toxicology of lead, some sections focus on studies that have provided major contributions to the understanding of lead toxicity over those that only add a small piece of information into a very big puzzle or that only reiterate findings previously published. Health outcomes associated with internal lead doses from selected studies are presented in Table 3-1.

3.2 DISCUSSION OF HEALTH EFFECTS

3.2.1 Death

Mortality studies for workers exposed occupationally to lead as well as studies of the general population are available (see also Section 3.2.8, Cancer). Two cohorts of male lead workers, 4,519 battery plant workers and 2,300 lead production workers, all of whom had been employed for at least 1 year during the period 1946–1970, were studied for mortality from 1947 through 1980 (Cooper 1988; Cooper et al. 1985). Overall mortality and standardized mortality ratios (SMRs) were determined. From 1947 through 1972, mean PbBs were 63 µg/dL for 1,326 battery plant workers and 80 µg/dL for 537 lead production workers (PbB data were not available for many of the workers and most of the monitoring was done after 1960). For both groups, the number of observed deaths from all causes combined was significantly greater ($p<0.01$) than expected, based on national mortality rates for white males. The increased mortality rates resulted in large part from malignant neoplasms; chronic renal disease, including

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Cardiovascular [a]					
519 males, 67 years old (mean)	General population	20.3 ppm (mean tibia Pb)	Increased risk of hypertension; no significant association with PbB or patella lead	Longitudinal study (Normative Aging Study). Covariates: age and body mass index; race; family history of hypertension; education; tobacco smoking and alcohol consumption; and dietary intakes of sodium and calcium. Subjects were free from definite hypertension at baseline.	Cheng et al. 2001
667 pregnant females, 15–44 years old	General population	10.7 ppm (mean calcaneus Pb)	Hypertension; a 10 ppm increase in calcaneus Pb was associated with a 0.70 mmHg increase in systolic blood pressure and 0.54 mmHg diastolic blood pressure	Longitudinal study of pregnancy. Co-variates: age and body mass index, parity, postpartum hypertension, tobacco smoking, and education.	Rothenberg et al. 2002b
496 adults, 56 years old (mean)	Occupational	4.6 µg/dL (mean PbB at baseline) 14.7 ppm (mean tibia Pb at year 3 of study)	Increase in systolic blood pressure associated with PbB and tibia Pb	Longitudinal study. Covariates: age and body mass index; diagnosis of diabetes, arthritis, or thyroid disease; education; and blood pressure measurement interval.	Glenn et al. 2003
294 females, 61 years old (mean)	General population	17.3 ppm (mean patella Pb)	Increased risk of hypertension; no significant association with tibia Pb or PbB	Case-control study (Nurses Health Study). Covariates: age and body mass index, dietary sodium intake, and family history of hypertension.	Korrick et al. 1999

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
146 males, 67 years old (mean)	General population	24 ppm (mean tibia Pb)	Increased risk of hypertension; an increase in tibia Pb from 8 to 37 ppm associated with a 1.5 odds ratio for hypertension	Case-control study. Covariates: body mass index and family history of hypertension.	Hu et al. 1996a
13,781 males and females, >20 years old	General population	2.1–4.2 µg/dL median PbB in white and black males and females	Bordeline association between PbB and systolic BP in black males and significant association in black females; no association in whites	NHANES III analysis. Covariates: age and body mass index; hematocrit, total serum calcium, and protein concentrations; tobacco smoking; alcohol and coffee consumption; dietary calcium, potassium, and sodium intakes; diabetes; and use of antihypertensive drugs.	Den Hond et al. 2002
543 females, 50 years old (mean)	General population	6.4 µg/dL (mean PbB) 4.0–31 µg/dL (range)	Increased risk of diastolic hyper-tension	NHANES III analysis. Co-variates: race, age, and body mass index; tobacco smoking, and alcohol consumption.	Nash et al. 2003
508 males and females, 19–24 years old	General population	>10 ppm (tibia Pb)	Increase in systolic and diastolic blood pressure	Cohort follow-up study of Bunker Hill children. Covariates: gender, age, and body mass index; blood hemoglobin and serum albumin concentrations; education; tobacco smoking and alcohol consumption; current use of birth control pills; income; and current PbB.	Gerr et al. 2002

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
775 males, 68 years old (mean)	General population	22.2 ppm (mean tibia Pb)	Significant association with EKG changes and conduction defects. Less strong association with patella Pb; no association with PbB	Cross-sectional study (Normative Aging Study). Covariates: age, body mass index, diastolic blood pressure, fasting blood glucose level, alcohol consumption, and serum HDL concentration.	Cheng et al. 1998
122 children, 9 years of age	General population	1.98 µg/dL (mean PbB prenatal); 4.62 µg/dL (mean PbB at evaluation)	Higher prenatal PbB associated with higher resting systolic BP; higher childhood PbB associated with greater peripheral resistance response to stress	Covariates included in the models were: maternal age, education, IQ, SES, HOME score, health and nutrition, substance use during pregnancy, and infant and childhood characteristics.	Gump et al. 2005
Gastrointestinal					
Children	General population	60–100 µg/dL (PbB range)	Colic	Compilation of unpublished data.	NAS 1972
Hematological					
159 adults	General population and occupational	5–95 µg/dL (PbB range)	Decreased ALAD activity	Four groups of subjects were analyzed. One unexposed group and three worker groups.	Hernberg and Nikkanen 1970
579 children, 1–5 years old	Residence near lead ore smelter	PbB >20 µg/dL	Anemia	Anemia defined as hematocrit <35%. Iron status was not available.	Schwartz et al. 1990
143 children, 10–13 years old	Residence near lead smelter	5–40 µg/dL (PbB range)	Decreased ALAD activity	There was no obvious threshold for ALAD-PbB relationship. A threshold for elevation of EP was evident between 15 and 20 µg/dL PbB.	Roels and Lauwerys 1987

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Musculoskeletal					
290 children, 6–10 years old	General population	2.9 µg/dL (mean PbB)	Increased caries in urban children	No increase in caries was seen in 253 rural children (PbB, 1.7 µg/dL). Covariates: sex, race, SES, maternal smoking, parental education, and dental hygiene variables.	Gemmel et al. 2002
6,541 children 2–11 years old	General population	2.9 µg/dL (geometric mean PbB for 2–5-year-olds); 2.1 µg/dL for 6–11-year-olds)	Increasing PbB associated with increased number of dental caries in both groups	NHANES III analysis. Covariates included age, gender, race-ethnicity, poverty income ratio, exposure to tobacco smoke, geographic region, parental education, carbohydrate and calcium intake, and dental visits.	Moss et al. 1999
10,033 males and females 20–69 years old	General population	2.5 µg/dL (geometric mean PbB)	Increasing PbB associated with periodontal bone loss	NHANES III analysis. Covariates included age, gender, race/ethnicity, education, SES, age of home, smoking, and periodontal disease.	Dye et al. 2002
Renal [b]					
744 males, 64 years old (mean)	General population	8 µg/dL (mean PbB) <4–26 µg/dL (range)	Decrease in GFR; an increase in PbB of 10 µg/dL was associated with a decrease in creatinine clearance rate of 10.4 mL/minute	Cross-sectional study (Normative Aging Study). Covariates: age and body mass index; systolic and diastolic blood pressure; alcohol consumption and tobacco smoking; and analgesic or diuretic medications.	Payton et al. 1994
459 males, 57 years old (mean)	General population	10 µg/dL (mean PbB) 0.2–54 µg/dL (range)	Decrease in GFR; a 10-fold increase in PbB was associated with a significant increase in serum creatinine	Longitudinal study (Normative Aging Study). Covariates: age and body mass index; hypertension; alcohol consumption and tobacco smoking; and education.	Kim et al. 1996a

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
707 males, 62 years old (mean)	General population	6.5 µg/dL (mean PbB) 21 ppm (mean tibia Pb)	Decrease in GFR; PbB and tibia, but not patella Pb, predicted increases in serum creatinine in men with diabetes and hypertension	Prospective study (Normative Aging Study). Covariates: age and body mass index; diabetes and hypertension; alcohol consumption and tobacco smoking; and education.	Tsaih et al. 2004
4,813 males and females, >20 years old	General population	4.2 µg/dL (mean PbB)	Decrease in GFR in subjects with hypertension	NHANES III analysis. Covariates: age, gender, and body mass index; systolic blood pressure; cardiovascular disease and diabetes mellitus; alcohol consumption and cigarette smoking; and household income, marital status, and health insurance.	Muntner et al. 2003
1,981 males and females, 48 years old (mean)	General population	11 µg/dL (mean PbB), 2–72 µg/dL (range in men); 7.5 µg/dL (1.7–60 µg/dL range in women)	Decrease in GFR; a 10-fold increase in PbB associated with decrease of 10–13 mL/minute in creatinine clearance	Cross-sectional study (Cadmibel Study). Covariates: age and body mass index; urinary glutamyltransferase activity; diabetes mellitus; and analgesic or diuretic therapy.	Staessen et al. 1992
803 males and females, 18–65 years old	Occupational	32 µg/dL (mean PbB) 37 ppm (mean tibia lead)	Increasing tibia lead associated with increased serum creatinine and uric acid; increasing PbB associated with increasing BUN	Cross-sectional study of Korean workers. Associations significant only for >46-year-old workers. Covariates included age, gender, body mass index, current/former exposed status, and hypertension.	Weaver et al. (2003a, 2005a)

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Endocrinological					
75 men	Occupational	50–98 µg/dL (PbB range)	Decreased serum T_3 and T_4	No significant correlation for FT_4 and TSH in this PbB range. TSH, T3, FT4, and T4 increased in the range 8–50 µg/dL.	López et al. 2000
58 males, mean age 31.7 years	Occupational	51.9 µg/dL (mean PbB)	TSH significantly higher than in controls (mean PbB 9.5 µg/dL in controls)	Cross-sectional study. The association between PbB and TSH was independent of employment length. T3 was lower in a subgroup of 17 workers employed for 17.5 years than in those employed for 2.4 years.	Singh et al. 2000a
68 children, 11 months–7 years old	General population	2–77 µg/dL (PbB range) 25 µg/dL (mean PbB)	No effect on serum T_4 or FT_4	Covariates: sex, race, SES, and hemoglobin; 56% of the children had PbB <24 µg/dL.	Siegel et al. 1989
30 children, 1–5 years old	General population	33–120 µg/dL (PbB range)	Decreased serum Vitamin D levels	15 children with mean PbB of 18 µg/dL served as a comparison group.	Rosen et al. 1980
Immunological					
38 children, 3–6 years old	General population	PbB >10 µg/dL	Increased IgE and decreased IgG and IgM in females	35 children with PbB <10 µg/dL served as controls. No such effect was seen in males or in the combined analysis of males and females.	Sun et al. 2003
279 children, 9 months–6 years old	General population	1–45 µg/dL (PbB range)	Increased serum IgE	No other parameter of cellular or humoral immunity showed a significant association with PbB. Covariates: age, race, sex, nutrition, and SES.	Lutz et al. 1999

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Neurological					
172 children, 5 years old	General population	7.7 µg/dL (lifetime average PbB)	7.4 IQ points decline with PbB increase 1–10 µg/dL	Children tested with Stanford-Binet Intelligence Scale. Covariates: sex, birth-weight, iron status; mother's IQ, education, race, smoking, income, and HOME score.	Canfield et al. 2003
4,853 children, 6–16 years old	General population	1.9 µg/dL (geometric mean PbB)	PbB <5 µg/dL associated with decrease in arithmetic and reading skills	NHANES III (1988–1994). Covariates: sex, race, iron status, exposure to second-hand smoke, region of the United States, marital status, country, parental education, poverty index, and birth weight. Exposure history was unknown.	Lanphear et al. 2000a
237 children, 7.5 years old	General population	5.4 µg/dL (current mean PbB)	PbB associated with decrements in domains of attention, executive, function, visual-motor integration, social behavior, and motor skills	Associations were present at PbB as low as 3 µg/dL; 19 variables were controlled for in addition to alcohol and drug use.	Chiodo et al. 2004
780 children, 7 years old	General population	8 µg/dL (mean PbB at age 7)	Concurrent PbB always has the strongest association with IQ	Children had been treated for elevated PbB (20–44 µg/dL at 2 years of age and were followed until 7 years of age with serial IQ tests.	Chen et al. 2005

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
146 children, 12 and 24 months old	General population	6.1 µg/dL (mean maternal PbB during first trimester of pregnancy)	One SD (0.014 µg/dL) in first trimester plasma Pb associated with a reduction of 3.5 points in MDI score at 24 months of age	Study of women in Mexico City. Potential confounders included child's sex, PbB at 24 months, height for age and weight, and maternal age and IQ.	Hu et al. 2006
294 children, 12 and 24 months old	General population	PbB <10 µg/dL	24-month PbB inversely associated with MDI and PDI scores at 24 months; 12-month PbB associated with PDI scores at 12 months	MDI and PDI scores of the BSID II were evaluated at 12 and months. Conditions for inclusion included PbB <10 µg/dL, gestation age ≥37 weeks, and birth weight >2,000 g.	Téllez-Rojo et al. 2006
736 older adults	General population	4.5 µg/dL (mean PbB) 29.5 ppm (mean patella Pb)	Impaired cognitive test performance	Associations were found for both PbB and bone lead. Age, education, and alcohol intake were included in regression models.	Wright et al. 2003c

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Reproductive					
74 adult men	Occupational	46.3 µg/dL (mean PbB)	Decreased fertility	Wife's variables controlled for included parity, time since previous birth, age, birth cohort, employment status, and education. Husband's variables included smoking, alcohol intake, education, and parameters reflecting exposure intensity and duration.	Gennart et al. 1992b
251 men	Occupational	10–40 µg/dL (PbB range)	Weak evidence of decreased fertility	Only couples with one pregnancy were included in study. Association existed only with younger maternal age (<30 years).	Sallmén et al. 2000b
98 men	Occupational	36.7 µg/dL (mean PbB)	Significantly higher alterations in sperm density, motility, viability, and indicators of prostate function than in a reference group	Cross-sectional study. Reference group consisted of 51 men with mean PbB of 10.3 µg/dL. Exposed and controls were comparable in age, smoking status, and alcohol consumption.	Telisman et al. 2000
121 women	General population	≥5.1 µg/dL (cord blood PbB)	Increased pre-term births	The effect was evident only among primiparous, but not multiparous women.	Torres-Sánchez et al. 1999
Developmental					
329 infants, 1 month old	General population	5.6 µg/dL (mean infant PbB at 1 month) 15.3 ppm (maternal patella Pb)	Infant PbB at 1 month and maternal patella bone inversely associated with weight gain	Infant age, sex, breast feeding practices, and infant health were included in regression models. Maternal variables: age, parity, maternal anthropometry, education, and hospital of recruitment.	Sanín et al. 2001

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
233 infants, 1 month old	General population	7.0 µg/dL (mean cord blood Pb) 14.1 ppm (maternal patella Pb)	Cord PbB associated with low birth length; patella lead associated with low head circumference	Variables included in models were maternal height, calf circumference, smoking, parity, reproductive history, age and education, hospital of delivery, infant sex, and gestational age.	Hernández-Avila et al. 2002
4,391 children, 1–7 years old	General population	1–72 µg/dL (PbB range)	Decrease of 1.57 cm in stature and 0.52 cm in head circumference per 10 µg/dL increase in PbB	Data from NHANES III. Models included: age, sex, ethnicity, and poverty-income ratio. Models also considered head of household education, exposure to cigarette smoke, nutrient intake, iron status, anemia, history of anemia, previous testing for high PbB, and previous treatment for lead poisoning.	Ballew et al. 1999
1,706 girls, 8–16 years old	General population	1–22 µg/dL (PbB range)	Delayed sexual maturation	Data from NHANES III. Covariates: race/ ethnicity, age, family size, residence in metropolitan area, poverty-income ratio, and body mass index.	Wu et al. 2003b
2,741 girls, 8–18 years old	General population	3 µg/dL (geometric mean PbB)	Delayed sexual maturation	Data from NHANES III. Covariates: age, height, body mass index, history of tobacco smoking or anemia, dietary intake of iron, vitamin C, calcium, and family income.	Selevan et al. 2003

[a]See also Table 3-2.
[b]See also Table 3-3.

ALAD = δ-aminolevulinic acid dehydratase; BP = blood pressure; BUN = blood urea nitrogen; EKG = electrocardiogram; EP = erythrocyte protoporphyrin; GFR glomerular filtration rate; HDL = high density lipoprotein; Ig = immunoglobin; NHANES III = Third National Health and Nutrition Examination; NM = not measured; SES = socioeconomic status; TSH = thyroid stimulating hormone

hypertension and nephritis; and "ill-defined" causes. Three additional studies provided suggestive evidence of increased mortality due to cerebrovascular disease in lead workers (Fanning 1988; Malcolm and Barnett 1982; Michaels et al. 1991). Malcolm and Barnett (1982) studied causes of death between 1921 and 1976 among lead acid battery plant workers and found a significant increase in deaths due to cerebrovascular disease among workers 65–69 years of age. In addition, a marginally significant increase in the incidence of deaths due to nephritis and nephrosis was observed in the lead workers during 1935–1958, but not at later periods, compared to workers with no lead exposure. Fanning (1988) compared the causes of death among 867 workers exposed to lead from 1926 to 1985 with 1,206 workers having low or no lead exposure and found a significant increase in deaths due to cerebrovascular disease among workers who died between 1946 and 1965 as compared to controls. No other cause produced an excess of deaths in lead workers. Environmental lead levels and biological monitoring for body lead burdens were not available for the entire period. The author suggested that the increased risk of death due to cerebrovascular disease was not present from 1965 to 1985 because of stricter occupational standards resulting in lower levels of exposure. Michaels et al. (1991) followed a cohort of 1,261 white male newspaper printers (typesetters) from January 1961 through December 1984. These workers had little or no occupational exposure to any other potentially toxic agents. It was assumed that lead exposure ceased in 1976 when the transition to computerized typesetting occurred. SMRs were calculated for 92 cause-of-death categories using the mortality rates of New York City as the comparison population. The authors found that there were no significantly elevated nonmalignant or malignant causes of death in this cohort. In fact, the SMRs were generally less than unity, indicating that there were fewer deaths than expected, which the authors attributed to the "healthy worker effect." However, the SMR for cerebrovascular disease was significantly elevated in those members of the cohort employed for >30 years. Since there was no excess of arteriosclerotic heart disease, it appeared that lead exposure selectively increased cerebrovascular disease.

Few studies of the general population have been conducted. McDonald and Potter (1996) studied the possible effects of lead exposure on mortality in a series of 454 children who were hospitalized for lead poisoning at Boston’s Children Hospital between 1923 and 1966 and who were traced through 1991. Of the 454 patients eligible for the study, 88% had a history of paint pica or known lead exposure; 90% had radiologic evidence of skeletal changes consistent with lead poisoning; and 97% had characteristic gastrointestinal, hematologic, and/or neurologic symptoms. The average PbB level in 23 children tested was 113 μg/dL; PbB tests were performed routinely at the hospital only after 1963. A total of 86 deaths were observed, 17 of these cases were attributed to lead poisoning. Although the distribution of causes of mortality generally agreed with expectations, there was a statistically significant excess of death from

cardiovascular disease (observed/expected [O/E], 2.1; 95% confidence interval [CI], 1.3–3.2). Three of four deaths from cerebrovascular accidents occurred in females, and 9 of 12 deaths from arteriosclerotic heart disease occurred in males. Two men died from pancreatic cancer (O/E, 10.2; 95% CI, 1.1–36.2) and two from non-Hodgkin's lymphoma (O/E, 13.0; 95% CI, 1.5–46.9).

Lustberg and Silbergeld (2002) used data from the Second National Health and Nutrition Examination Survey (NHANES II) to examine the association of lead exposure and mortality in the United States. A total of 4,292 blood lead measurements were available from participants aged 30–74 years who were followed up through December 31, 1992. After adjusting for potential confounders, individuals with PbB between 20 and 29 μg/dL had 46% increased all-cause mortality, 39% increased circulatory mortality, and 68% increased cancer mortality compared with those with PbB <10 μg/dL. The results also showed that nonwhite subjects had significantly increased mortality at lower PbB than did white subjects, and that smoking was associated with higher cancer mortality in those with PbB of 20–29 μg/dL compared with those with PbB <20 μg/dL. Recently, Schober et al. (2006) used data from NHANES III (1988–1994) to determine relative risk of mortality from all causes, cancer, and cardiovascular disease in 9,757 participants who were ≥40 years of age. After adjusting for covariates, relative to PbBs <5 μg/dL, the relative risks of mortality from all causes for those with PbB 5–9 and ≥10 μg/dL were 1.24 (95% CI, 1.05–1.48) and 1.59 (95% CI, 1.28–1.98), respectively. Similar observations were reported for deaths due to cardiovascular disease and cancer, and tests for trend were statistically significant ($p<0.01$) for both causes of death. Of interest also is a study that describes trends in lead poisoning-related deaths in the United States between 1979 and 1998 (Kaufmann et al. 2003). Reviews of death certificates revealed that approximately 200 lead poisoning-related deaths occurred from 1979 to 1998. The majority were among males (74%), African Americans (67%), adults of age ≥45 years (76%), people living in the South region of the United States (70%), and residents in cities with populations <100,000 habitants (73%). Lead poisoning was the underlying cause of death in 47% of the deaths. The authors also found that alcohol (moonshine ingestion) was a significant contributing cause for 28% of adults.

In summary, the information available suggests a potential association between lead exposure and cerebrovascular disease. There is no information from studies in animals that would support or refute the existence of a possible association between lead exposure and mortality due to cerebrovascular disease.

3.2.2 Systemic Effects

Respiratory Effects. Very limited information was located regarding respiratory effects in humans associated with lead exposure. A study of 62 male lead workers in Turkey reported significant alterations in tests of pulmonary function among the workers compared to control subjects (Bagci et al. 2004). The cohort consisted of 22 battery workers, 40 exhaust workers, and 24 hospital workers with current PbB of 37, 27, and 15 μg/dL, respectively. Workers and controls were matched for age, height, weight, and smoking habit. No association was found between PbB and duration of employment. No information was provided regarding exposure levels, medical histories of the workers or potential exposure to other chemicals. No relevant information was located from studies in animals.

Cardiovascular Effects. Although lead has been shown to produce various cardiovascular effects in animals (Vaziri and Sica 2004), end points of greatest concern for humans at low exposures and low PbBs are elevations in systemic blood pressure and decrements in glomerular filtration rate. These effects may be mechanistically related and, furthermore, can be confounders and covariables in epidemiological studies. Decrements in glomerular filtration rate may contribute to elevations in blood pressure, and elevated blood pressure may predispose people to glomerular disease. Effects of lead on glomerular filtration are discussed in Section 3.2.2, Renal Effects. Other cardiovascular changes have been noted in association with increasing lead body burdens and/or lead exposures in humans that include changes in cardiac conduction and rhythm (Böckelmann et al. 2002; Cheng et al. 1998; Kirkby and Gyntelberg 1985; Kosmider and Petelenz 1962), which may be secondary to lead-induced impairment of peripheral nerve conduction (see Section 3.2.4, Neurological Effects).

Effects on Blood Pressure. Numerous epidemiological studies have examined associations between lead exposure (as indicated by PbB or bone lead concentration) and blood pressure. Meta-analyses of the epidemiological findings have found a persistent trend in the data that supports a relatively weak, but significant association. Quantitatively, this association amounts to an increase in systolic blood pressure of approximately 1 mmHg with each doubling of PbB (Nawrot et al. 2002; Schwartz 1995; Staessen et al. 1994). The results of more recent epidemiology studies indicate that the lead contribution to elevated blood pressure is more pronounced in middle age than at younger ages. Numerous covariables and confounders affect studies of associations between PbB and blood pressure, including age, body mass, race, smoking, alcohol consumption, ongoing or family history of cardiovascular/renal disease, and various dietary factors (e.g., dietary calcium). Including confounders in a regression model will attenuate the apparent association between lead exposure and the measured health outcome (e.g., Moller and

Kristensen 1992). For example, adjusting for alcohol consumption will decrease the apparent association between blood lead concentration and blood pressure, if alcohol consumption contributes to lead intake and, thereby, blood lead concentration (Bost et al. 1999; Hense et al. 1993; Hertz-Picciotto and Croft 1993; Wolf et al. 1995). Conversely, failure to account for important effect modifiers (e.g., inherited disease) will result in overestimation of the apparent strength of the association. Varying approaches and breadth of inclusion of these may account for the disparity of results that have been reported. Measurement error may also be an important factor. Blood pressure estimates based on multiple measurements or, preferably, 24-hour ambulatory measurements, are more reproducible than single measurements (Staessen et al. 2000). Few studies have employed such techniques and, when used, have not found significant associations between PbB and blood pressure (Staessen et al. 1996b).

An additional limitation of blood lead studies, in general, is that PbB may not provide the ideal biomarker for long-term exposure to target tissues that contribute a hypertensive effect of lead. Bone lead, a metric of cumulative or long-term exposure to lead, appears to be a better predictor of lead-induced elevations in blood pressure than PbB (Cheng et al. 2001; Gerr et al. 2002; Hu et al. 1996a; Korrick et al. 1999; Rothenberg et al. 2002a). In a recent prospective analysis of the Normative Aging Study, higher patellar lead levels, but not PbB, were associated with higher systolic blood pressure and abnormalities in electrocardiographic conduction (Cheng et al. 1998, 2001).

Epidemiology studies, alone, cannot prove cause and effect relationships between lead exposure and blood pressure or cardiovascular disease. However, studies conducted in animal models support the plausibility of blood pressure effects of lead in humans. These studies have shown that long-term lead exposure can elevate blood pressure in nutritionally replete rats (Carmignani et al. 1988; Iannaccone et al. 1981; Khalil-Manesh et al. 1993; Victery et al. 1982a, 1982b), and have identified potential mechanisms for the effect (Carmignani et al. 2000; Ding et al. 1998; Gonick et al. 1997; Purdy et al. 1997; Vaziri and Ding 2001; Vaziri et al. 1999a, 1999b, 2001).

Meta-analyses. A recent meta-analysis of 31 studies published between 1980 and 2001, which included a total of 58,518 subjects (Nawrot et al. 2002), estimated the increase in systolic pressure per doubling of PbB to be 1 mmHg (95% CI, 0.5–1.5) and the increase in diastolic pressure to be 0.6 mmHg (95% CI, 0.4–0.8) (Table 3-2; Figures 3-1 and 3-2). This outcome is similar to two other meta-analyses. A meta-analysis reported by Staessen et al. (1994) included 23 studies (published between 1984 and 1993; 33,141 subjects) and found a 1 mmHg (95% CI, 0.4–1.6) increase in systolic blood pressure and 0.6 mmHg (95% CI, 0.2–1.0) in diastolic pressure per doubling of PbB. Schwartz (1995) conducted a

Table 3-2. Characteristics of the Study Population in Meta-Analyses of Effects of Lead on Blood Pressure

	Reference	No.[a]	Pop.[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
1[h]	Pocock et al. 1984; Shaper et al. 1981	7,379	GP	100	Y	49 (40–59)	145	82	15.13 (2.07–66.3)[Ae]
2	Kromhout 1988; Kromhout et al. 1985	152	GP	100	Y	67 (57–76)	154	92	18.23 (10.77–27.97)[Ac]
3	Moreau et al. 1982, 1988; Orssaud et al. 1985	431	WC	100	Y	41 (24–55)	131	75	18.23 (8.91–49.94)[Ae]
4	Weiss et al. 1986, 1988	89	WC	100	Y	47 (30–64)	122	83	24.45 (18.65–29.01)[Mx]
5	de Kort and Zwennis 1988; de Kort et al. 1987	105	BC	100	N	40 (25–80)	136	83	29.22 (4.35–83.29)[Ae]
6	Lockett and Arbuckle 1987	116	BC	100	Y	32 (?–?)	119	80	37.5 (14.92–95.52)[Ae]
7	Parkinson et al. 1987	428	BC	100	Y	36 (18–60)	127	80	27.97 (6.01–49.52)[Ac]
8	Rabinowitz et al. 1987	3,851	GP	0	Y	28 (18–38)	121	76	7.04 (3.73–10.15)[Ac]
9	Elwood et al. 1988a, 1988b[i]	1,136	GP	100	Y	56 (49–65)	146	87	12.64 (6.01–26.11)[Gc]
10	Elwood et al. 1988a, 1988b[j]	1,721	GP	50	Y	41 (18–64)	127	78	10.15 (4.56–23.21)[Gc]
11	Gartside 1988; Harlan 1988; Harlan et al. 1985; Pirkle et al. 1985; Ravnskov 1992[k]	6,289	GP	53	Y	30 (10–74)	127	80	13.47 (2.07–95.93)[Ge]
12	Neri et al. 1988[l]	288	BC	100	?	? (?–?)	?	?	45.17 (6.01–65.06)[Ae]
13	Neri et al. 1988[m]	2,193	GP	?	Y	45 (25–65)	?	?	23.41 (0–47.03)[Me]
14	Grandjean et al. 1989, 1991[n]	1,050	GP	48	Y	40 (40–40)	?	?	11.6 (3.94–60.09)[Ae]
15	Reimer and Tittelbach 1989	58	BC	100	?	32 (?–?)	134	81	39.99 (12.85–70.24)[Ac]
16	Apostoli et al. 1990	525	GP	48	Y	45 (21–60)	132	84	13.05 (2.07–28.18)[Ae]
17	Morris et al. 1990	251	GP	58	Y	? (23–79)	?	?	7.46 (4.97–38.95)[Ae]
18	Sharp et al. 1988, 1989, 1990	249	WC	100	N	43 (31–65)	128	83	6.63 (2.07–14.92)[Pe]
19	Staessen et al. 1984[o]	531	WC	75	Y	48 (37–58)	126	78	11.4 (4.14–35.22)[Ge]
20	Møller and Kristensen 1992[p]	439	GP	100	Y	40 (40–40)	?	?	13.68 (4.97–60.09)[Ae]

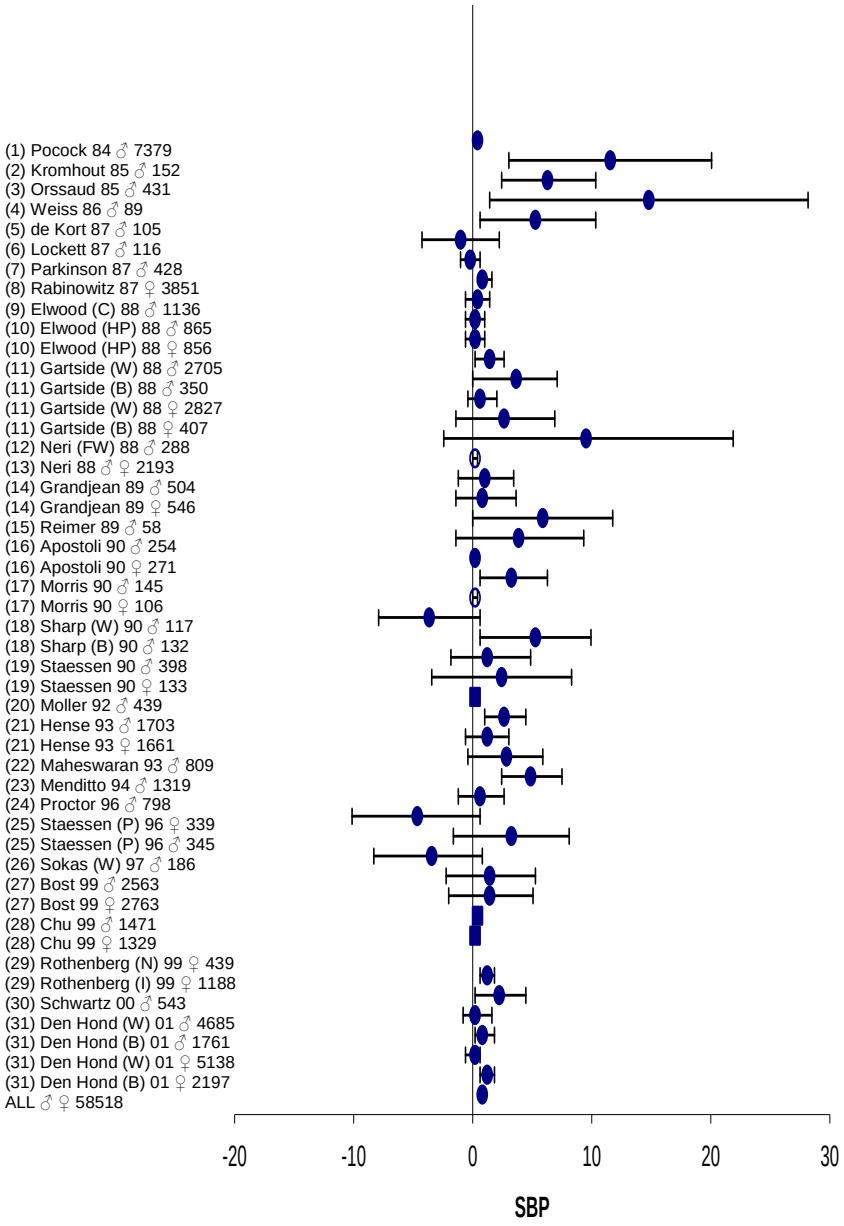
Table 3-2. Characteristics of the Study Population in Meta-Analyses of Effects of Lead on Blood Pressure

	Reference	No.[a]	Pop.[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
21	Hense et al. 1993	3,364	GP	51	Y	48 (28–67)	129	80	7.87 (1.24–37.09)[Ae]
22	Maheswaran et al. 1993	809	BC	100	Y	43 (20–65)	129	84	31.7 (0–98.01)[Ae]
23	Menditto et al. 1994	1,319	GP	100	Y	63 (55–75)	140	84	11.19 (6.22–24.66)
24	Hu et al. 1996a; Proctor et al. 1996[q]	798	GP	100	Y	66 (43–93)	134	80	5.59 (0.41–35.02)[Pe]
25	Staessen et al. 1996a, 1996b[r]	728	GP	49.3	Y	46 (20–82)	130	77	9.12 (1.66–72.52)[Ge]
26	Sokas et al. 1997[s]	186	BC	99	Y	43 (18–79)	130	85	7.46 (2.07–30.04)[Pe]
27	Bost et al. 1999	5,326	GP	48	Y	48 (16–?)	135	75	63.82 (?–?)[G]
28	Chu et al. 1999	2,800	GP	53	Y	44 (15–85)	123	78	6.42 (0.41–69)[Ae]
29	Rothenberg et al. 1999a, 1999b	1,627	GP	0	Y	27 (?–?)	110	59	2.28 (?–?)[G]
30	Schwartz and Stewart 2000	543	BC	100	Y	58 (41–73)	128	77	4.56 (1.04–20.1)[Ae]
31	Den Hond et al. 2001[t]	13,781	GP	53.2	Y	48 (20–90)	125	73	3.11 (0.62–55.94)[Ge]

[a]No.: Number of persons in whom relevant data were available.
[b]Pop.: Study population: BC = blue collar workers; GP = sample from general population; WC = white collar employees
[c]Men: Percentage of men
[d]HT: Indicates whether the sample included (Y = yes) or did not include (N = no) hypertensive patients.
[e]Age: Mean age or midpoint of age span (range or approximate range given between parentheses).
[f]SBP, DBP: Mean systolic and diastolic blood pressures
[g]Lead: Measure of central tendency: A = arithmetic mean; G = geometric mean; M = midpoint of range; P = P_{50} (median). The spread of blood lead is given between parentheses: c = P_5–P_{05} interval; P_{10}–P_{90} interval, or interval equal to 4 times the standard deviation; e = extremes; x = approximate limits of distribution.
[h]Number refers to reference in Figures 3-1 and 3-2.
[i]Caerphilly Study
[j]Welsh Heart Program
[k]NHANES (National Health and Nutrition Examination Survey)
[l]foundry workers
[m]Canadian Health Survey
[n]Glostrup Population Study, cross-sectional analysis (1976)
[o]London Civil Servants
[p]Glostrup Population Study, longitudinal analysis (1976–1987)
[q]Normative aging study
[r]PheeCad (Public Health and Environmental Exposure to Cadmium) Study
[s]Because of missing information, only the effect in whites is included.
[t]NHANES III Survey

Source: Nawrot et al. 2002

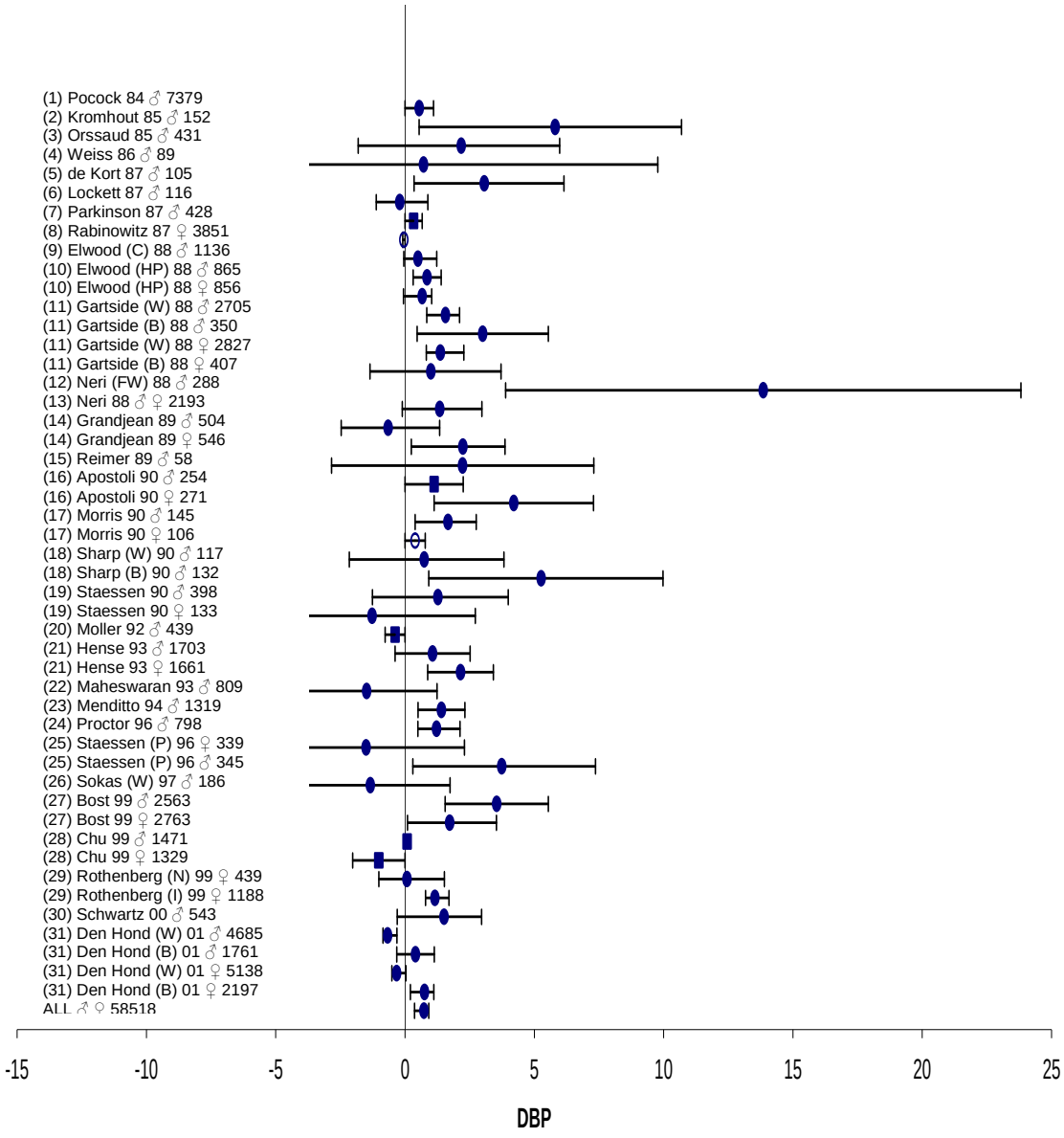
Figure 3-1. Change in the Systolic Pressure Associated with a Doubling of the Blood Lead Concentration*



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 3-2 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; NI = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

Figure 3-2. Change in the Diastolic Pressure Associated with a Doubling of the Blood Lead Concentration*



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 3-2 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; NI = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

meta-analysis that encompassed a similar time frame (15 studies published between 1985 and 1993) and found a 1.25 mmHg (95% CI, 0.87–1.63) increase in systolic blood pressure per doubling of PbB (diastolic not reported). The latter analysis included only those studies that reported a standard error on effect measurement (e.g., increase in blood pressure per doubling of PbB). Of the 15 studies included in the Schwartz (1995) analysis, 8 were also included in the Staessen et al. (1994) analysis.

Longitudinal Studies—General Populations—Adults. The Normative Aging Study is a longitudinal study of health outcomes in males, initially enrolled in the Boston area of the United States between 1963 and 1968. At enrollment, subjects ranged in age from 21 to 80 years (mean, 67 years) and had no history of heart disease, hypertension, cancer, peptic ulcer, gout, bronchitis, or sinusitus. Physical examinations, including seated blood pressure and medical history follow-ups, have been conducted at approximately 3–5-year intervals. Beginning in 1991, PbB and bone x-ray fluorescence (XRF) measurements (mid-tibia and patella) were included in the examinations. Data collected for a subset of the study population (840 subjects) observed between 1991 and 1997 were analyzed for associations between blood pressure and blood or bone lead concentrations (Cheng et al. 2001). Mean baseline PbB was 6.1 μg/dL (standard deviation [SD], 4.0) for the entire study group and 5.87 μg/dL (SD, 4.01) in the normotensive group (n=323). Mean bone lead concentrations in the normotensive subjects (n=337) were: tibia, 20.27 μg/g (SD, 11.55); patella, 28.95 (SD, 18.01). Based on a cross-sectional linear multivariate regression analysis of 519 subjects who had no hypertension at the time of first bone and blood lead measurement, covariate-adjusted systolic blood pressure was not significantly associated with PbB or patella lead concentration; however, increasing tibia lead concentration was associated with increasing systolic blood pressure. Follow-up examinations were completed on 474 subjects, allowing a longitudinal analysis of hypertension risk. Covariate-adjusted risk (risk ratio, RR; proportional hazards model) of hypertension (systolic >160 mm Hg or diastolic >95 mm Hg) was significantly associated with patella bone lead concentrations (RR, 1.29; 95% CI, 1.04–1.61), but not with PbB (RR, 1.00; 95% CI, 0.76–1.33) or tibia bone lead concentration (RR, 1.22; 95% CI, 0.95–1.57). Increases in patella lead concentration from 12.0 μg/g (mid-point of lowest quintile) to 53.0 μg/g (mid-point of highest quintile) were associated with a rate ratio of 1.71 (95% CI, 1.08–2.70). Covariates considered in the analyses included age and body mass index; race; family history of hypertension; education; tobacco smoking and alcohol consumption; and dietary intakes of sodium and calcium. A cross-sectional case-control analysis of the Normative Aging Study also found significant associations between bone lead concentration and risk of hypertension (see discussion of Hu et al. 1996a). The observation that risk of hypertension in middle-aged males increased in association with increasing patella bone lead concentration, but not tibia bone lead or PbB, is consistent with a similar finding in middle-aged females, derived from the Nurses Health

Study (Korrick et al. 1999). Associations between PbB and hypertension risk in middle-aged women have been found in larger cross-sectional studies (Nash et al. 2003). These observations suggest that, in some populations, blood pressure increases may be more strongly associated with cumulative lead exposure (reflected in bone lead levels) than more contemporaneous exposures (reflected in blood lead concentrations).

A random sample from the general population of Belgium (728 subjects, 49% male, age 20–82 years old) was studied during the period 1985 through 1989 (baseline; from Cadmibel study, Dolenc et al. 1993) and reexamined from 1991 through 1995 (follow-up) (Staessen et al. 1996b). Multiple seated blood pressure measurements were taken during the baseline and follow-up periods; multiple ambulatory measurements were taken during the follow-up period. The baseline PbB for the study group was 8.7 μg/dL (range, 1.7–72.5). Based on a linear multivariate regression analysis (with log-transformed blood lead concentrations), covariate-adjusted time-integrated systolic or diastolic blood pressure, or changes in systolic or diastolic blood pressure (follow-up compared to baseline) were not significantly associated with PbB or zinc photoporphyrin (ZPP) concentrations. The covariate adjusted risk for hypertension of doubling of the baseline PbB was not significantly >1. Covariates considered in the above analyses included gender, age, and body mass index; menopausal status; smoking and alcohol consumption; physical activity; occupational exposure to heavy metals; use of antihypertensive drugs, oral contraceptives, and hormonal replacement therapy; hematocrit or blood hemoglobin concentration; and urinary sodium, potassium, and γ-glutamyltransferase activity.

A random sample of the general population of Denmark (451 males, 410 females, age 40 years) was studied in 1976 (baseline) and reexamined in 1981 (Grandjean et al. 1989). Baseline and follow-up observations included sitting blood pressure measurements, physical examination and health histories, and PbB measurements. The median baseline PbB was 13 μg/dL (90^{th} percentile, 20) and 9 μg/dL (90^{th} percentile, 13) in males and females, respectively. Covariate adjusted linear regression coefficients for relating systolic or diastolic blood pressure with PbB (log-transformed) were not statistically significant in males or females. Covariates considered in the analysis included height-adjusted weight index, exercise, smoking, alcohol intake, occupation, blood hemoglobin, serum cholesterol, and serum triglycerides. Similar conclusions were reported from a prospective study of this same population; adjustment for cardiovascular risk factors (i.e., body mass index, tobacco smoking, alcohol consumption, physical fitness) attenuated an apparent association between PbB and systolic and diastolic blood pressure (Moller and Kirstensen 1992).

Longitudinal Studies—General Population—Pregnancy. A longitudinal study examined associations between blood pressure and lead exposure during pregnancy and postpartum (Rothenberg et al. 2002b). The study included 667 subjects (age 15–44 years) registered at prenatal care clinics in Los Angeles during the period 1995–2001, and who had no history of renal or cardiovascular disease, postnatal obesity (body mass index >40), or use of stimulant drugs (e.g., cocaine, amphetamines). Measurements of sitting blood pressure and PbB were made during the third trimester and at 10 weeks postnatal. Tibia and calcaneus bone lead concentrations (XRF) were measured at the postnatal visit. Mean (geometric) PbBs were 1.9 μg/dL (+3.6/-1.0, geometric standard deviation [GSD]) during the third trimester and 2.3 μg/dL (+4.3/-1.2, GSD) postnatal. Mean (arithmetic) bone lead concentrations were 8.0 μg/g (11.4, SD) in tibia and 10.7 μg/g (11.9, SD) in calcaneus. Covariate-adjusted risk (odds ratio, OR) of hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) in the third trimester was significantly associated with increasing calcaneous bone lead concentration (OR, 1.86; 95% CI, 1.04–3.32). A 10 μg/g increase in calcaneous bone lead concentration was associated with a 0.77 mmHg (95% CI, 0.04–1.36) increase systolic blood pressure in the third trimester and a 0.54 mmHg (95% CI, 0.01–1.08) increase in diastolic blood pressure. Covariates included in the final model were age and body mass index, parity, postpartum hypertension, tobacco smoking, and education.

Longitudinal Studies—General Population—Children. Possible associations between blood pressure and lead exposure in young children were studied as part of a prospective study of pregnancy outcomes (Factor-Litvak et al. 1996). The study group consisted of 281 children, age 5.5 years, from the Kosovo, Yugoslavia prospective study (see Section 3.2.4 for more details on this cohort). Approximately half of the children (n=137) lived in a town with heavy lead contamination (exposed group) and the other half (n=144) were from a relatively uncontaminated town (reference group). Mean PbBs were 37.3 μg/dL in the exposed group and 8.7 μg/dL in the reference group. Covariate-adjusted linear regression coefficients relating blood pressure and PbB at 5.5 years of age were not significantly >0: systolic, 0.054 (95% CI, -0.024–0.13); diastolic, -0.042 (95% CI, -0.01–0.090). Regression coefficients for the integrated average PbB (assessed every 6 months from birth) were similar in magnitude: systolic, 0.047 (95% CI, -0.037–0.13), diastolic, 0.041 (95% CI, -0.016–0.098). Covariates included in the analysis were gender, height and body mass index, birth order, and ethnicity.

A prospective study designed to assess various environmental factors on development examined possible associations between PbB and blood pressure in a group of 122 children (66 females) at 9 years of age (Gump et al. 2005). The mean PbB at the time of evaluation was 4.62 μg/dL (SD±2.51). Outcomes measured included heart rate, diastolic and systolic blood pressure, stroke volume, cardiac output, and

total peripheral resistance; these were assessed at rest and following an acute pressor stress (arm immersion in ice water). General linear models were used to explore associations between PbB and outcomes. Increasing cord PbB was significantly associated with increasing covariate-adjusted resting systolic blood pressure (β, 12.16; Standard error [SE], 4.96; p= 0.016). Increasing childhood PbB was significantly associated with an increased total peripheral vascular resistance in response to the acute pressor stress (β, 0.88 dyn-s/cm^5 per µg/dL; 95% CI, 0.024–0.152; p=0.007). Covariates considered in the models included: maternal age, education, IQ, socioeconomic status (SES), HOME score, health, nutrition; substance use during pregnancy; infant birth characteristics (e.g., gestational age, birth weight, head circumference, Ballard score); and childhood characteristics (e.g., body mass index, SES).

Longitudinal Studies—Occupational. A population of 496 current and former employees of an organic lead manufacturing facility (mean age, 55.8 years) located in the eastern United States, was studied during the period 1994–1996 with follow-up examinations at approximately 4–14-month intervals through 1998 (Glenn et al. 2003). Multiple seated blood pressure measurements were taken at each examination. PbB was measured at the initial examination (baseline) and tibia bone XRF measurements were taken in 1997. The mean PbB was 4.6 µg/dL and the mean tibia bone lead concentration was 14.7 µg/g. Based on a generalized estimating equation model, covariate-adjusted systolic blood pressure was significantly associated with baseline PbB or tibia bone lead concentration. A one standard deviation increase in PbB was associated with a 0.64 mmHg (95% CI, 0.14–1.14) increase in systolic blood pressure and a 0.009 (95% CI, -0.24–0.43) increase in diastolic blood pressure. A one standard deviation increase in tibia bone lead concentration was associated with a 0.73 mmHg (95% CI, 0.23–1.23) increase in systolic blood pressure and a 0.07 mmHg (95% CI, -0.29–0.42) increase in diastolic blood pressure. Covariates considered in the analyses included race; age and body mass index; diagnosis of diabetes, arthritis, or thyroid disease; education; and blood pressure measurement interval.

A population of 288 foundry workers was studied during the period 1979–1985, during which multiple blood pressure and PbB measurements were taken (Neri et al. 1988). Linear regression coefficients were estimated for the relationship between PbB and systolic or diastolic blood pressure, for each of 288 subjects. The average covariate (age and body weight) adjusted regression coefficient (mmHg per µg/dL blood lead) was 0.210 (SE, 0.139, p=0.064) for systolic pressure and 0.298 (SE, 0.111, p<0.05) for diastolic pressure.

A population of 70 Boston policemen was studied during the period 1969–1975, during which multiple seated blood pressure measurements were taken (years 2–5) and PbB measurements were taken in

year 2 (Weiss et al. 1986, 1988). Covariate adjusted linear regression coefficients (mmHg per μg/dL) were determined, with exposure represented as low (20–29 μg/dL) or high (≥30 μg/dL). After adjusting for covariates, high PbB was a significant predictor of subsequent elevation in systolic blood pressure of 1.5–11 mmHg in the working policemen with normal blood pressure. Low PbB (20–29 μg/dL) was not a predictor of subsequent systolic blood pressure elevations. Diastolic pressure was unrelated to PbB. Covariates retained in the model were previous systolic blood pressure, body mass index, age, and cigarette smoking.

Case-control Studies—General Population. A case-control study examined potential associations between blood pressure and blood and bone lead concentrations in a population of middle-aged women (mean age, 61 years; Korrick et al. 1999). Cases (n=89) and age-matched controls (n=195) were a subset of women who resided in the Boston area of the United States (recruited during the period 1993–1995) who were enrolled in the National Nurses Health Study (NHS). Cases were selected based on self-reported physician diagnosis of hypertension as part of the NHS. Potential controls were excluded from consideration if they had a history of hypertension or other cardiovascular disease, renal disease, diabetes, malignancies, obesity, or use of antihypertensive or hypoglycemic medication. Controls were stratified based on measured blood pressure: low normal (<115 mm Hg systolic and <75 mmHg diastolic), or high normal (>134 and <140 mmHg systolic or >85 and <90 mmHg diastolic). Multiple sitting blood pressure measurements, PbB, and tibia and patella bone lead concentration measurements were taken at the beginning of the study. Self-reported information on medical history was provided as part of the NHS every 2 years. The mean PbB (cases and controls combined) was 3 μg/dL (range, <1–14 μg/dL). Mean bone lead concentrations were: tibia, 13.3 μg/g and patella, 17.3 μg/g. Risk of hypertension was assessed using a logistic regression model. Covariate-adjusted risk of hypertension (defined as systolic pressure ≥140 mm Hg or diastolic ≥90 mm Hg) was significantly associated with increasing patella lead concentration, but not with tibia bone concentration or PbB. An increase from the 10^{th} to the 90^{th} percentile of patella bone lead concentration (from 6 to 31 μg/g) was associated with an increase in the odds of hypertension of 1.86 (95% CI, 1.09–3.19). Covariates considered in the regression models included: age and body mass index; dietary calcium and sodium intakes; alcohol consumption and tobacco smoking, and family history of hypertension. Of these, age and body mass index, dietary sodium intake, and family history of hypertension were included in the final model. The OR (odds of being a case/odds of being in control group) of hypertension with increasing patella lead concentration was 1.03 (95% CI, 1.00–1.05). When stratified by age, the ORs were 1.04 (95% CI, 1.01–1.07) in the >55 years of age groups and 1.01 (95% CI, 0.97–1.04) in the age group ≤55 years. Stratification by menopausal status resulted in ORs of 1.04 (95% CI, 1.01–1.06) for the postmenopausal group and

0.98 (95% CI, 0.91–1.04) for the premenopausal group (78 of 89 of the cases, 93%, were postmenopausal). The observation that risk of hypertension in women increased in association with increasing patella bone lead concentration, but not tibia bone lead or PbB, is consistent with a similar finding in men, derived from the longitudinal Normative Aging Study (Cheng et al. 2001). Associations between PbB and hypertension risk in postmenopausal women also have been found in larger cross-sectional studies (Nash et al. 2003; see below).

As part of the Normative Aging Study, a case-control study examined potential associations between blood pressure and blood and bone lead concentrations in a population of middle-aged males (mean age, 66 years; Hu et al. 1996a). The Normative Aging Study is a longitudinal study of health outcomes in males, initially enrolled in the Boston area of the United States between 1963 and 1968. At enrollment, subjects ranged in age from 21 to 80 years (mean, 67 years) and had no history of heart disease, hypertension, cancer, peptic ulcer, gout, bronchitis, or sinusitus. Physical examinations, including seated blood pressure and medical history follow-ups, have been conducted at approximately 3–5-year intervals. Beginning in 1991, PbB and bone x-ray fluorescence (XRF) measurements (mid-tibia and patella) were included in the examinations. Cases (n=146) and age-matched controls (n=444) were a subset of the study group who resided in the Boston area of the United States (recruited during the period 1993–1995) who were observed between 1991 and 1994. Hypertension cases were taking daily medication for the management of hypertension and/or had a systolic blood pressure >160 mmHg or diastolic pressure ≥96 mmHg. The mean PbBs in cases and controls were 6.9 μg/dL (4.3, SD) and 6.1 μg/dL (4.0, SD), respectively. Mean bone lead concentrations in cases and controls were: tibia, 23.7 μg/g (14.0, SD) and 20.9 μg/g (11.4, SD), respectively; and patella, 35.1 μg/g (19.5, SD) and 31.1 μg/g (18.3, SD), respectively. Risk of hypertension (OR) was assessed using a logistic regression model. Covariate-adjusted risk of hypertension was significantly associated with increasing tibia lead concentration, but not with patella bone concentration or PbB. An increase in tibia bone lead concentration from the mid-point of the lowest quintile (8 μg/g) to the mid-point of the highest quintile (37 μg/g) was associated with an OR of 1.5 (95% CI, 1.1–1.8). Covariates in the final regression model included body mass index and family history of hypertension. A longitudinal analysis of the Normative Aging Study also found significant associations between bone lead concentration and risk of hypertension (see discussion of Cheng et al. 2001).

A case-control study examined the association between PbB and hypertension risk in middle-aged and menopausal women (Al-Saleh et al. 2005). Hypertension cases (n=100; age, 47–92 years) and controls (n=85; age, 45–82 years) were selected from the King Faisal Hospital Hypertension Clinic (Saudi Arabia)

during the period 2001–2002. Hypertension case inclusion criteria were: taking medication, or >160 mm Hg systolic pressure, or >95 mm Hg diastolic pressure. Control inclusion criteria were: average systolic/diastolic pressure <120/80 mm Hg, and no record of >130/85 mm Hg). Mean PbB of the case group was 4.8 μg/dL (range, 1.4–28) and of the control group was 4.6 μg/dL (range, 1.2–18). Covariate adjusted ORs in association with a median PbB ≥3.86 μg/dL was 5.27 (95% CI, 0.93–30; p=0.06).

Cross-sectional Studies—General Population. Several analyses of possible associations between blood pressure and PbB have been conducted with data collected in the NHANES (II and III). The NHANES III collected data on blood pressure and PbB on approximately 20,000 U.S. residents during the period 1988–1994. The results of two analyses of the NHANES III data on adult subjects provides evidence for an association between increasing PbB and increasing blood pressure that is more pronounced in blacks than whites (Den Hond et al. 2002; Vupputuri et al. 2003). Den Hond et al. (2002) analyzed data collected on 13,781 subjects of age 20 years or older who were white (4,685 males; 5,138 females) or black (1,761 males; 2,197 females). Median PbBs (μg/dL, inter-quartile range) were: white males, 3.6 (2.3–5.3); white females, 2.1 (1.3–3.4); black males, 4.2 (2.7–6.5); and black females, 2.3 (1.4–3.9). Based on multivariate linear regression (with log-transformed blood lead concentration), the predicted covariate-adjusted increments in systolic blood pressure per doubling of PbB (95% CI) were: white males, 0.3 (95% CI, -0.2–0.7, p=0.29); white females, 0.1 (95% CI, -0.4–0.5, p=0.80); black males, 0.9 (95% CI, 0.04–1.8, p=0.04); and black females, 1.2 (95% CI, 0.4–2.0, p=0.004). The predicted covariate-adjusted increments in diastolic blood pressure per doubling of PbB (95% CI) were: white males, -0.6 (95% CI, -0.9– -0.3, p=0.0003); white females, -0.2 (95% CI, -0.5– -0.1, p=0.13); black males, 0.3 (95% CI, -0.3–1.0, p=0.28); and black females, 0.5 (95% CI, 0.01–1.1, p=0.047). Covariates included in the regression models were: age and body mass index; hematocrit, total serum calcium, and protein concentrations; tobacco smoking; alcohol and coffee consumption; dietary calcium, potassium, and sodium intakes; diabetes; and use of antihypertensive drugs. Poverty index was not included as a covariate in the above predictions because its independent effect was not significant; however, when included in the regression model for black males, the effect size was not significant.

Vupputuri et al. (2003) analyzed the NHANES III subset of 14,952 subjects of age 18 years or older who were white (5,360 males; 5,188 females) or black (2,104 males; 2,197 females). Mean PbBs (μg/dL, ±SE) were: white males, 4.4±0.1; white females, 3.0±0.1; black males, 5.4±0.2; and black females, 3.4±0.1. Based on multivariate linear regression, the predicted covariate-adjusted increments in systolic blood pressure per one standard deviation increase of PbB (95% CI) were: white males, 0.29 (95% CI, -0.24–0.83, p≥0.05); white females, 0.34 (95% CI, -0.49–1.17, p≥0.05); black males, 0.83 (95% CI, 0.19–

1.44, $p<0.05$); and black females, 1.55 (95% CI, 0.47–2.64, $p<0.010$). The predicted covariate-adjusted increments in diastolic blood pressure per one standard deviation increase in PbB (95% CI) were: white males, 0.01 (95% CI, -0.38–0.40, $p\geq0.05$); white females, -0.04 (95% CI, -0.56–0.47, $p\geq0.05$); black males, 0.64 (95% CI, -0.08–1.20, $p<0.05$); and black females, 1.07 (95% CI, 0.37–1.77, $p<0.01$). Covariates included in the regression models were: age and body mass index; alcohol consumption; dietary calorie, potassium, and sodium intakes; and physical activity. The analyses of Den Hond et al. (2002) and Vupputuri et al. (2003) suggest an association between blood pressure and PbB in blacks but not in whites; among blacks, the association was significant for women and or borderline significance for men.

A more recent analysis of the NHANES III data focused on females between the ages of 40 and 59 years (Nash et al. 2003). The study group (n=2,165) had a mean age of 48.2 years and mean PbB of 2.9 μg/dL (range, 0.50–31.1). Based on multivariate linear regression, covariate-adjusted systolic and diastolic blood pressure was significantly associated with increasing PbB. Increasing PbB from the lowest (0.5–1.6 μg/dL) to highest (4.0–31.1 μg/dL) quartile was associated with a 1.7 mmHg increase in systolic pressure and a 1.4 mmHg increase in diastolic pressure. The study group was stratified by blood lead concentration (quartile), and into pre- and postmenopausal categories. Increased risk of diastolic (but not systolic) hypertension (systolic ≥140 mmHg diastolic ≥90 mmHg) was significantly associated with increased blood lead concentration. When stratified by menopausal status, the effect was more pronounced in the postmenopausal group. Covariates included in the models were race, age, and body mass index; tobacco smoking, and alcohol consumption. The Nursing Health Study (Korrick et al. 1999) found significant associations between hypertension risk and patella lead concentration in postmenopausal women, but not with PbB. However, the Nash et al. (2003) study included 850 postmenopausal subjects, compared to 78 in the Korrick et al. (1999) case-control study.

The NHANES II collected data on PbB and blood pressure during the period 1976–1980. In general, PbBs were higher in the NHANES II sample than in NHANES III sample (Pirkle et al. 1998), providing a means to explore possible associations between blood pressure and higher PbB than is possible with the NHANES III data. While various analyses have yielded somewhat conflicting results (Gartside 1988; Harlan 1988; Harlan et al. 1985; Landis and Flegal 1988; Pirkle et al. 1985; Schwartz 1988), they support the general findings of the more recent longitudinal and case-control studies (including those of the NHANES III) that increasing PbB is associated with increasing blood pressure in middle-aged adults.

An analysis of the NHANES II data on white males (40–59 years of age, n=564) found a significant association between increasing systolic or diastolic blood pressure and increasing PbB, after accounting for significant covariates (Pirkle et al. 1985). Covariates considered in the analysis included 87 nutritional and diet variables, cigarette smoking, alcohol consumption, socioeconomic status, and family history of hypertension. Those included in the final linear regression model for diastolic blood pressure were age and body mass index; blood hemoglobin concentration and serum albumin concentration; and dietary potassium and vitamin C intakes. Additional covariates included in the systolic blood pressure model were dietary riboflavin, oleic acid, and vitamin C. Blood lead statistics for the study group were not reported; however, the association appeared to have been evaluated over a range of 7–38 μg/dL. Lead was also a significant predictor of diastolic hypertension (≥90 mm Hg). Gartside (1988) stratified the NHANES II data into age and race categories and also found significant associations between systolic (but not diastolic) blood pressure and PbB in white males in age categories between 36 and 55 years. In these age categories, doubling PbB was associated with an increase in systolic blood pressure of approximately 4 mmHg. The statistical model used was a forward linear regression; however, the covariates retained in the final models were not reported. Other analyses of the NHANES II data for men have addressed the issue of possible time-trend effects confounded by variations in sampling sites (Landis and Flegal 1988; Schwartz 1988). These analyses confirm that correlations between systolic or diastolic blood pressure and PbB in middle-aged white males remain significant when sampling site is included as a variable in multiple regression analyses. Accuracy of blood pressure data in the NHANES II has been challenged (e.g., digit preference by people recording the measurements, differing variability among survey sites). When these sources of variability are accounted for, the magnitude of the covariate-adjusted PbB—blood pressure relationship decreases; however, it remains significant, and strongest, for white males in the 49–50-year-old group (Coate and Fowles 1989).

Relationships between PbB and hypertension were evaluated in a survey of 7,731 males, aged 40–59 years, from 24 British towns in the British Regional Heart Study (BHRS) (Pocock et al. 1984, 1988). The PbB distributions in the study group were approximately: <12.4 μg/dL, 27%; 12.4–16.6 μg/dL, 45%; 18.6–22.8 μg/dL, 19%; and >24.9 μg/dL, 8%. The most recent, multivariate analysis of the data from this survey (Pocock et al. 1988), found that covariate-adjusted systolic blood pressure increased by 1.45 mmHg and diastolic blood pressure increased by 1.25 mmHg for every doubling in PbB. Covariates included in the regression model included age, body mass index, alcohol consumption, cigarette smoking, and socioeconomic factors. Covariate-adjusted risk of ischemic heart disease (OR) was not significantly associated with PbB. PbBs in cases (n=316) of ischemic heart disease were not statistically different,

when compared to those of the rest of the study group, after adjustment was made for age, number of years smoking cigarettes, and town of residence.

A more recent survey conducted in Great Britain (Health Survey for England, HSE) collected data annually on blood pressure and PbB. An analysis of the HSE data collected in 1995 included 2,563 males (mean age, 47.5 years) and 2,394 females (mean age, 47.7) (Bost et al. 1999). Multiple seated blood pressure measurements were taken. Mean (geometric) PbBs were 3.7 μg/dL in males and 2.6 μg/dL in females. Based on multivariate linear regression (with log-transformed PbB), increasing covariate-adjusted diastolic blood pressure was significantly associated with increasing PbB in males, but not in females. Covariates included in the above model were: age and body mass index, alcohol consumption and tobacco smoking, socioeconomic status, and region of residence; subjects who were on antihypertensive agents were excluded.

A cross-sectional study of potential associations between blood and bone lead, and blood pressure in older adults was conducted as part of the longitudinal Baltimore Memory Study (Martin et al. 2006). The study group consisted of 964 adults (age, 50–70 years, 65% female) who were evaluated for blood pressure and PbB during the period 2001–2002, and tibia lead during the period 2002–2004. Mean PbB concentration in the study group was 3.5 μg/dL (SD±2.3) and tibia lead was 18.8 μg/g (SD±12.4). Increasing PbB (but not tibia lead) was significantly associated (linear regression model) with increasing covariate-adjusted systolic (β, 0.99 mm Hg per μg/dL; 95% CI, 0.47–1.51; $p<0.01$) and diastolic blood pressure (β, 0.51; 95% CI, 0.24–0.79; $p<0.01$). Covariates included in the model included age, gender, body mass index, sodium and potassium intakes, SES, and race/ethnicity). Covariate-adjusted ORs for hypertension (>140 mm Hg systolic pressure or >90 mmHg diastolic pressure) were significantly associated with tibia lead (but not PbB) only when the multivariate logistic model excluded SES (OR, 1.21; 95% CI, 1.02–1.43; $p=0.03$) or SES and race/ethnicity (OR, 1.24; 95% CI, 1.05–1.47; $p=0.01$) from the model. When SES and race/ethnicity were included in the model, the odds ratios were not significant for tibia lead (OR, 1.16; 95% CI, 0.98–1.77; $p=0.09$) or PbB (OR, 1.01; 95% CI, 0.86–1.19).

The potential effects of childhood exposure to lead on bone lead—blood pressure relationships in adulthood have been examined in a cohort study (Gerr et al. 2002). The exposed cohort consisted of 251 people (ages 19–24 years in 1994), who resided in any of five towns near the former Bunker Hill smelter in Silver Valley, Idaho and were between the ages of 9 months and 9 years during the period 1974–1975, when uncontrolled emissions from the smelter resulted in contamination of the region and elevated PbB in local children. The reference cohort consisted of 257 Spokane, Washington residents in

the same age range as the exposed cohort. Individuals were excluded from participating in the study if they were black, pregnant, had a history of hypertension or chronic renal failure, or had a PbB exceeding 15 μg/dL at the initial examination. Subjects were given a physical examination, which included medical history, multiple measurements of sitting blood pressure, PbB measurement, and XRF measurement of tibia bone lead concentration. Relationships between blood pressure and bone lead were assessed using the general linear model, in which bone lead was expressed categorically (μg/g): <1, 1–5, >5–10, and >10. Covariate-adjusted systolic and diastolic blood pressures were significantly higher in the highest bone lead category compared to the lowest category; the differences being 4.26 mmHg (p=0.014) systolic pressure and 2.80 mmHg (p=0.03) diastolic pressure. Covariates retained in the final models included gender, age and body mass index; blood hemoglobin and serum albumin concentrations; education; tobacco smoking and alcohol consumption; current use of birth control pills; income; and current PbB. While residence (exposed vs. reference) was not a significant variable in predicting blood pressure, 82% of subjects in the highest bone lead group were members of the exposed group (i.e., residents of the contaminated towns in 1974–1975). Mean PbB during the exposure period, 1974–1975, was also higher in the high bone lead group (65 μg/dL) compared to the lower bone lead groups (2–2.4 μg/dL). Similar findings were reported by Hu et al. (1991a) in a pilot study of subjects with well-documented lead poisoning in 1930–1942 in a Boston area. Exposed subjects (mean current age, 55 years; mean current PbB, 6 μg/dL) and controls were matched for age, race, and neighborhood. Comparison of 21 matched pairs showed that the risk of hypertension was significantly higher in subjects who had experienced plumbism (RR, 7.0; 95% CI, 1.2–42.3). Kidney function, evaluated by measurements of creatinine clearance rate was significantly higher in subjects with plumbism than in controls, but serum creatinine was not significantly different than in controls subjects. The results from these two studies (Gerr et al. 2002; Hu 1991a) suggest the possibility that high childhood exposures to lead may contribute to higher blood pressure in adulthood. However, epidemiological studies of children have not found significant associations between increasing PbB and blood pressure (Factor-Litvak et al. 1996; Friedlander 1981; Rogan et al. 1978; Selbst et al. 1993).

Studies in Animal Models. Early studies in experimental animals suggested that long-term lead exposure could elevate blood pressure in nutritionally replete rats (Carmignani et al. 1988; Iannaccone et al. 1981; Khalil-Manesh et al. 1993; Victery et al. 1982a, 1982b). These observations have been corroborated with more recent studies, as well as studies that have identified numerous potential mechanisms for the effect that are relevant to humans (Carmignani et al. 2000; Ding et al. 1998; Gonick et al. 1997; Purdy et al. 1997; Vaziri and Ding 2001; Vaziri et al. 1999a, 1999b, 2001).

Other Cardiovascular Effects. Several studies have explored possible associations between lead exposure and cardiovascular disease mortality and morbidity. In a multivariate analysis of the data from the British Regional Heart Study (7,731 males, age 40–59 years; 8% of cohort had PbB >24.9 μg/dL), covariate-adjusted risk of ischemic heart disease (OR) was not significantly associated with PbB (Pocock et al. 1988). Cooper (1988) reported significantly elevated SMRs for "other hypertensive disease" (i.e., malignant hypertension, or essential benign hypertension, or hypertensive renal disease) among male battery plant workers (n= 4,519; mean PbB, 63 μg/dL) and lead production workers (n=2,300; mean PbB, 80 μg/dL). The study did not explore associations between SMRs and biomarkers of lead exposure (e.g., PbB). SMRs for cardiovascular disease were not elevated among 1,987 male lead smelter workers who worked at the Bunker Hill smelter facility in northern Idaho (i.e., who were hired between 1950 and 1965 and who worked at least 1 year) (Selevan et al. 1985, 1988). The study did not explore associations between SMRs and biomarkers of lead exposure (e.g., PbB). SMRs for ischemic heart disease were significantly elevated (SMR, 1.72; 95% CI, 1.16–1.79) among male smelter workers (n=644) who worked for at least 3 months during the period 1942–1987; however, the SMRs were across time-integrated PbB quartiles (Gerhardsson et al. 1995a).

Data from a subset of the Normative Aging Study were analyzed to assess possible associations between electrocardiographic abnormalities and body lead burdens (Cheng et al. 1998). The Normative Aging Study is a longitudinal study of health outcomes in males, initially enrolled in the Boston area of the United States. Subjects enrolled in the study, between 1963 and 1968, ranged in age from 21 to 80 years (mean, 67; SD, 7), and had no history of heart disease or hypertension. Physical examinations, including electrocardiograms and medical history follow-ups, have been conducted at approximately 3–5-year intervals. Beginning in 1991, PbB and bone XRF measurements (midtibia and patella) were included in the examinations. Data collected for a subset of the study population (775 subjects) observed between 1991 and 1995 and for whom complete data were acquired, were analyzed for associations between blood and bone lead concentrations and electrocardiographic abnormalities (e.g., heart rate, conduction defects, arrhythmia). The mean age of the subjects at the time of evaluation was 68 years (range, 48–93). Lead levels were: blood, 5.79 μg/dL (SD, 3.44); tibia bone, 22.19 μg/g (SD, 13.36); and patella bone, 30.82 μg/g (SD, 19.19). The study group was stratified by age (<65 or ≥65 years) for multivariate regression (linear and logistic) analyses. Covariate-adjusted QT and QRS intervals were significantly associated with tibia bone lead in subjects <65 years of age. A 10 μg/g increase in tibia lead concentration was associated with a 5.01 millisecond increase in the QT interval and 4.83 millisecond increase in QRS interval. Covariates included in the analyses were age, body mass index, diastolic blood pressure, fasting blood glucose level, and alcohol consumption. Covariate-adjusted OR for

intraventricular conduction defect was significantly associated with increasing tibia bone lead in the <65 year-age group; ORs were not significant for the older age group. In the age group ≥65 years, the OR for atrioventricular conduction defect with increasing tibia bone lead concentration was 1.22 (95% CI, 1.02–1.47; p=0.03), and for patella bone lead concentration, 1.16 (95% CI, 1.00–1.29; p<0.01); ORs were not significant for the younger age group. Covariates included in the models were age and serum HDL concentration. Risk of arrhythmia was not significantly associated with blood or bone lead concentrations.

A study of 95 lead smelter workers and matched (age, occupational status, duration of employment) unexposed reference group found a significantly higher incidence of ischemic ECG changes (20%) in the lead workers than in the reference group (6%) (Kirkby and Gyntelberg 1985). Mean PbB was 53 μg/dL in the exposed group and 11 μg/dL in the reference group.

A cross-sectional analysis of the NHANES (for the period 1999–2000) data found a significant association between PbB and risk of peripheral artery disease (Navas-Acien et al. 2004). The analysis included 2,125 subjects (1,055 females, 1,070 males) whose ages were ≥40 years. Geometric mean PbB was 2.1 μg/dL (25^{th}–75^{th} percentile range, 1.5–2.9). The increasing PbB was significantly associated with increasing covariate-adjusted OR for peripheral artery disease (ankle brachial index <0.9 in one or both legs). For the upper quartile PbB (>2.9 μg/dL), the ORs were 4.07 (95% CI, 1.21–13.73), without adjustment for smoking status and 2.52 (95% CI, 0.75–8.51) with adjustment for smoking. Other covariates included in the analysis were age, gender, race, education, body mass index, alcohol consumption, hypertension, diabetes, hypercholesterolemia, glomerular filtration, and C-reactive protein.

As part of the Baltimore-Washington Infant Study, a case-control study examined possible associations between lead exposure and risk of total anomalous pulmonary venous return (TAPVR), a rare congenital malformation in which pulmonary veins deliver oxygenated blood to the right atria rather than the left atria (Jackson et al. 2004). Cases (n=54) were recruited during the period 1981–1989. Controls (n=522) consisted of a stratified random sample of live-born infants without birth defects (excluding twins, low birth weight infants, and infants whose race was other than black or white). Subjects were classified as having been exposed to lead (or not) during critical maternal (i.e., from 3 months prior to conception through third trimester) or paternal (i.e., within 6 months prior to conception) periods based on self-reporting of occupational or environmental exposures, reported in an administered questionnaire. Prevalence of maternal lead exposure was 17% among cases and 11% among controls; prevalence of paternal lead exposure was 61% among cases and 46% among controls. The OR for TAPVR in

association with any maternal lead exposure during the critical maternal period was 1.57 (95% CI, 0.64–3.47; p=0.27); the OR for any paternal lead exposure was 1.83 (95% CI, 1.00–3.42, p=0.045).

Several small-scale studies have reported changes in peripheral hemodynamics in association with occupational exposures to lead. Effects observed in these studies may represent effects of lead on either the cardiovascular and/or autonomic nervous systems. A study conducted in Japan compared the results of finger plethysmographic assessments in 48 male workers in a lead refinery and 43 male controls who had no occupational lead exposure (Aiba et al. 1999). Ages of the exposed and reference groups were similar (mean±SD; 46±15 and 49±11 years, respectively). Mean PbB in the exposed group was 43.2 μg/dL (25.2, SD), PbBs for the control group were not measured. Covariate-adjusted acceleration plethysmography parameters were significantly different in the exposure group compared to the reference group and were significantly associated with PbB. The prevalence of abnormal parameter values (<25th percentile value) was significantly higher in the exposure group and prevalence increased with increasing duration of employment or increasing PbB. A study of ceramic painters in Japan evaluated postural changes in finger blood flow in relation to PbB (Ishida et al. 1996). Subjects of the study were 50 males (age, 55±12 years) and 78 females (age, 52±8 years) who were not currently receiving pharmacological treatment. Finger blood flow parameters evaluated were the percent change in finger blood flow in response to standing from a supine position, and the rate of decrease in blood flow in response to standing. The mean (geometric) PbB was 16.5 μg/dL (2.1, SD; range, 3.5–69.5 μg/dL) in males and 11.1 μg/dL (1.7, SD; range, 2.1–31.5 μg/dL) in females. Both percent change in blood flow and rate of decrease in blood flow significantly decreased with increasing PbB in both males and females. Covariate-adjusted postural change in finger blood flow was significantly associated with PbB. Covariates included in the regression model were age, body mass index total blood cholesterol concentration, skin temperature, alcohol consumption and tobacco smoking.

Gastrointestinal Effects. Colic is a consistent early symptom of lead poisoning in occupationally exposed cases or in individuals acutely exposed to high levels of lead, such as occurs during the removal of lead-based paint. Colic is characterized by a combination of the following symptoms: abdominal pain, constipation, cramps, nausea, vomiting, anorexia, and weight loss. Although gastrointestinal symptoms typically occur at PbBs of 100–200 μg/dL, they have sometimes been noted in workers whose PbBs were between 40 and 60 μg/dL (Awad El Karim et al. 1986; Baker et al. 1979; Haenninen et al. 1979; Holness and Nethercott 1988; Kumar et al. 1987; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Pollock and Ibels 1986; Rosenman et al. 2003; Schneitzer et al. 1990).

Colic is also a symptom of lead poisoning in children. EPA (1986a) has identified a LOAEL of approximately 60–100 μg/dL for children. This value apparently is based on a National Academy of Sciences (NAS 1972) compilation of unpublished data from the patient groups originally discussed in Chisolm (1962, 1965) and Chisolm and Harrison (1956) in which other signs of acute lead poisoning, such as severe constipation, anorexia, and intermittent vomiting, occurred at ≥60 μg/dL.

Hematological Effects. Lead has long been known to alter the hematological system. The anemia induced by lead is microcytic and hypochromic and results primarily from both inhibition of heme synthesis and shortening of the erythrocyte lifespan. Lead interferes with heme synthesis by altering the activities of δ-aminolevulinic acid dehydratase (ALAD) and ferrochelatase. As a consequence of these changes, heme biosynthesis is decreased and the activity of the rate-limiting enzyme of the pathway, δ-aminolevulinic synthetase (ALAS), which is feedback inhibited by heme, is subsequently increased. The end results of these changes in enzyme activities are increased urinary porphyrins, coproporphyrin, and δ-aminolevulinic acid (ALA); increased blood and plasma ALA; and increased erythrocyte protoporphyrin (EP).

Studies of lead workers have shown that ALAD activity correlated inversely with PbB (Alessio et al. 1976; Gurer-Orhan et al. 2004; Hernberg et al. 1970; Meredith et al. 1978; Schuhmacher et al. 1997; Tola et al. 1973; Wada et al. 1973), as has been seen in subjects with no occupational exposure (Secchi et al. 1974). Erythrocyte ALAD and hepatic ALAD activities were correlated directly with each other and correlated inversely with PbBs in the range of 12–56 μg/dL (Secchi et al. 1974).

General population studies indicate that the activity of ALAD is inhibited at very low PbB, with no threshold yet apparent. ALAD activity was inversely correlated with PbB over the entire range of 3–34 μg/dL in urban subjects never exposed occupationally (Hernberg and Nikkanen 1970). Other reports have confirmed the correlation and apparent lack of threshold in different age groups and exposure categories (children—Chisolm et al. 1985; Roels and Lauwerys 1987; adults—Roels et al. 1976). Studies of children in India and China also have reported significant decreases in ALAD activity associated with PbB ≥10 μg/dL (Ahamed et al. 2005; Jin et al. 2006). Inverse correlations between PbB and ALAD activity were found in mothers (at delivery) and their newborns (cord blood). PbB ranged from approximately 3 to 30 μg/dL (Lauwerys et al. 1978). In a study in male volunteers exposed to particulate lead in air at 0.003 or 0.01 mg lead/m^3 for 23 hours/day for 3–4 months mean PbB increased from 20 μg/dL (pre-exposure) to 27 μg/dL at the 0.003 mg/m^3 exposure level and from 20 μg/dL (pre-exposure) to 37 μg/dL at the 0.01 mg/m^3 exposure level. ALAD decreased to approximately 80% of

preexposure values in the 0.003 mg/m^3 group after 5 weeks of exposure and to approximately 53% of preexposure values in the 0.01 mg/m^3 group after 4 weeks of exposure (Griffin et al. 1975). Similar observations were made in a study of volunteers who ingested lead acetate at 0.02 mg lead/kg/day every day for 21 days (Stuik 1974). The decrease in erythrocyte ALAD could be noticed by day 3 of lead ingestion and reached a maximum by day 14. Mean PbB was approximately 15 μg/dL before exposure and increased to approximately 40 μg/dL during exposure. Cools et al. (1976) reported similar results in a study of 11 volunteers who ingested lead acetate that resulted in a mean PbB of 40 μg/dL; the mean pre-exposure PbB was 17.2 μg/dL.

Inhibition of ALAD and stimulation of ALAS result in increased levels of ALA in blood or plasma and in urine. For example, in a case report of a 53-year-old man with an 11-year exposure to lead from removing old lead-based paint from a bridge, a PbB of 55 μg/dL was associated with elevated urinary ALA (Pollock and Ibels 1986). The results of the Meredith et al. (1978) study on lead workers and controls indicated an exponential relationship between PbB and blood ALA. Numerous studies reported direct correlations between PbB and log urinary ALA in workers. Some of these studies indicated that correlations can be seen at PbB of <40 μg/dL (Lauwerys et al. 1974; Selander and Cramer 1970; Solliway et al. 1996), although the slope may be different (less steep) than at PbBs >40 μg/dL. In a study of 98 occupationally exposed subjects (mean PbB, 51 μg/dL) and 85 matched referents (mean PbB, 20.9 μg/dL), it was found that log ZPP and log ALA in urine correlated well with PbB (Gennart et al. 1992a). In the exposed group, the mean ZPP was 4 times higher than in the comparison group, whereas urinary ALA was increased 2-fold.

Correlations between PbBs and urinary ALA similar to those observed in occupationally exposed adults have also been reported in nonoccupationally exposed adults (Roels and Lauwerys 1987) and children (unpublished data of J.J. Chisolm, Jr., reported by NAS 1972). Linear regression analyses conducted on data obtained from 39 men and 36 women revealed that increases in urinary ALA may occur at PbB >35 μg/dL in women and >45 μg/dL in men (Roels and Lauwerys 1987). A significant linear correlation between PbB and log ALA was obtained for data in children 1–5 years old with PbBs 25–75 μg/dL. The correlation was seen primarily at PbBs >40 μg/dL, but some correlation may persist at <40 μg/dL (NAS 1972).

A dose-related elevation of EP or ZPP in lead workers has been documented extensively (Herber 1980; Matte et al. 1989). Correlations between PbB and log EP or ZPP indicate an apparent threshold for EP elevation in male workers at 25–35 μg/dL (Grandjean and Lintrup 1978; Roels et al. 1975) for FEP and a

threshold of 30–40 μg/dL for EP (Roels and Lauwerys 1987; Roels et al. 1979). The threshold for EP elevation appears to be somewhat lower (20–30 μg/dL) in women than in men (Roels and Lauwerys 1987; Roels et al. 1975, 1976, 1979; Stuik 1974), regardless of whether exposure is primarily by inhalation (occupational) or oral (nonoccupational). These studies were controlled for possible confounding factors such as iron deficiency or age, both of which increase erythrocyte ZPP.

Many studies have reported the elevation of EP or ZPP as being exponentially correlated with PbBs in children. However, peak ZPP levels lag behind peak levels of PbB. The threshold for this effect in children is approximately 15 μg/dL (Hammond et al. 1985; Piomelli et al. 1982; Rabinowitz et al. 1986; Roels and Lauwerys 1987; Roels et al. 1976), and may be lower in the presence of iron deficiency (Mahaffey and Annest 1986; Marcus and Schwartz 1987). A study of 95 mother-infant pairs from Toronto showed a significant inverse correlation between maternal and umbilical cord lead levels and FEP (Koren et al. 1990). Most (99%) infants had cord PbBs below 7 μg/dL; in 11 cases, the levels were below the detection limit. The cord blood FEP levels were higher than the maternal levels. This may reflect immature heme synthesis and increased erythrocyte volume rather than lead poisoning, or perhaps an early effect of lead poisoning.

The threshold PbB for a decrease in hemoglobin in occupationally exposed adults is estimated by EPA (1986a) to be 50 μg/dL, based on evaluations of the data of Baker et al. (1979), Grandjean (1979), Lilis et al. (1978), Tola et al. (1973), and Wada et al. (1973). For example, 5% of smelter workers with PbBs of 40–59 μg/dL, 14% with levels of 60–79 μg/dL, and 36% with levels of >80 μg/dL had anemia. In a study of 98 workers from a lead acid battery factory with a mean PbB of 51 μg/dL, the mean hemoglobin concentration was not significantly different than in an unexposed group of 85 subjects (mean PbB, 21 μg/dL). However, four exposed workers, but no controls, had hemoglobin levels below the level considered as the limit value for defining anemia (13 μg/dL) (Gennart et al. 1992a). Similar lack of correlation between PbB and hemoglobin was reported in a study of 94 Israeli lead workers with a mean PbB of 38.1 μg/dL (range, 6–113 μg/dL) (Froom et al. 1999). Solliway et al. (1996) also reported no significant differences in hemoglobin concentration between a group of 34 workers from a battery factory (mean PbB 40.7 μg/dL, range 23–66 μg/dL) and a group of 56 nonexposed persons (mean PbB 6.7 μg/dL, range 1–13 μg/dL). However, red blood cell count was significantly lower in exposed workers than in the controls. Lead-induced anemia is often accompanied by basophilic stippling of erythrocytes (Awad El Karim et al. 1986; Pagliuca et al. 1990). In a study of workers with a relatively low mean PbB of 8.3 μg/dL (range, 2–25 μg/dL), it was found that PbB did not correlate with either hemoglobin or hematocrit; however, patellar lead significantly correlated with a decrease in hemoglobin and hematocrit

even after adjusting a number of confounders (Hu et al. 1994). The PbB threshold for decreased hemoglobin levels in children is judged to be approximately 40 μg/dL (EPA 1986a; WHO 1977), based on the data of Adebonojo (1974), Betts et al. (1973), Pueschel et al. (1972), and Rosen et al. (1974). In a pilot study of subjects who suffered lead poisoning in 1930–1942 in a Boston area, hemoglobin and hematocrit were significantly decreased compared to unexposed matched controls (Hu 1991a). The mean current age of the subjects was 55 years and the mean current PbB was 6 μg/dL. No difference was noticed in red blood cell size or shape between exposed and control subjects. Hu et al. (1991a) suggested that the effect observed may have represented a subclinical effect of accumulated bone lead stores on hematopoiesis.

Other studies have shown that adverse effects on hematocrit may occur at even lower PbBs in children (Schwartz et al. 1990). Anemia was defined as a hematocrit of <35% and was not observed at PbB below 20 μg/dL. Analyses revealed that there is a strong negative nonlinear dose-response relationship between PbBs and hematocrit. Between 20 and 100 μg/dL, the decrease in hematocrit was greater than proportional to the increase in PbB. The effect was strongest in the youngest children. The analysis also revealed that at PbBs of 25 μg/dL, there is a dose-related depression of hematocrit in young children. Similar results also have been reported by others (Kutbi et al. 1989).

Lead also inhibits the enzyme pyrimidine-5’-nucleotidase within the erythrocyte, which results in an accumulation of pyrimidine nucleotides (cytidine and uridine phosphates) in the erythrocyte or reticulocyte and subsequent destruction of these cells. This has been reported in lead workers, with the greatest inhibition and marked accumulations of pyrimidine nucleotides apparent in workers with overt intoxication, including anemia (Paglia et al. 1975, 1977). PbBs in these workers ranged between 45 and 110 μg/dL, and 7 of 9 were anemic. Pyrimidine-5'-nucleotidase activity was correlated inversely with PbB when corrected for an enhanced population of young cells due to hemolytic anemia in some of the workers (Buc and Kaplan 1978). Erythrocyte pyrimidine-5'-nucleotidase is inhibited in children at very low PbBs. A significant negative linear correlation between pyrimidine-5'-nucleotidase and PbB level was seen in 21 children with PbBs ranging from 7 to 80 μg/dL (Angle and McIntire 1978). Similar results were seen in another study with 42 children whose PbB ranged from <10 to 72 μg/dL (Angle et al. 1982). Additional findings included a direct correlation between cytidine phosphate levels and PbBs (log-log). There was no indication of a threshold for these effects of lead in these two studies.

In summary, of all the parameters examined, ALAD activity appears to be the most sensitive indicator of lead exposure. In studies of the general population, ALAD activity was inversely correlated with PbBs

over the entire range of 3–34 μg/dL. In contrast, the threshold PbB for increase in urinary ALA in adults is approximately 40 μg/dL; for increases in blood EP or ZPP, the threshold in adults is around 30 μg/dL, and the threshold for increased ZPP in children is about 15 μg/dL in children. Threshold PbBs for decreased hemoglobin levels in adults and children have been estimated at 50 and 40 μg/dL, respectively. Although the measurement of ALAD activity seems to be a very sensitive hematological marker of lead exposure, the inhibition of the enzyme is so extensive at PbBs ≥30 μg/dL that the assay cannot distinguish between moderate and severe exposure.

Studies in animals, in general, support the findings in humans and indicate that the effects depend on the chemical form of lead, duration of exposure, and animal species. Of particular interest are the results of a study in a cohort of 52 monkeys administered lead acetate orally for up to 14 years (Rice 1996b). PbB was dose-related and ranged between 10 and 90 μg/dL. Decreased hematocrit and hemoglobin was observed in monkeys at 7 (PbB 25 μg/dL) and 11 years (PbB 90 μg/dL) of age; hemoglobin also was decreased at 6 years of age when PbB was 23 μg/dL. All changes that occurred were within normal ranges, which led Rice (1996b) to conclude that under the conditions of the study, there were no lead-related hematological effects.

Musculoskeletal Effects. Several case reports of individuals who experienced high exposures to lead either occupationally or through the consumption of illicit lead contaminated whiskey described the occurrence of a bluish-tinged line in the gums (Eskew et al. 1961; Pagliuca et al. 1990). The etiology of this "lead line" has not been elucidated. This effect has also been observed in workers exposed to high lead levels who had exposures via dust or fume. Individuals having high exposures to lead have also been reported to complain of muscle weakness, cramps, and joint pain (Holness and Nethercott 1988; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990). Rosenman et al. (2003) described musculoskeletal effects (frequent pain/soreness and/or muscle weakness) in lead workers with PbB ≥40 μg/dL.

A study of the association between lead exposure and bone density in children was recently published (Campbell et al. 2004). The cohort consisted of 35 African American children 8–10 years of age from Monroe County, New York State. The cohort was divided into two groups, one (n=16) with mean cumulative PbB of 6.5 μg/dL (low-exposure group) and the other (n=19) with mean cumulative PbB of 23.6 μg/dL (high-exposure group). The groups were similar by sex, age, body mass index, socio-economic status, physical activity, or calcium intake. Contrary to what was expected, subjects with high cumulative exposure had a higher bone mineral density than subjects with low-lead cumulative exposure. Among 17 bony sites examined, four were significantly different ($p<0.05$). Campbell et al. (2004)

speculated that lead accelerates skeletal maturation by inhibiting proteins that decrease the rate of maturation of chondrocytes in endochondral bone formation. A lower peak bone mineral density achieved in young adulthood might predispose to osteoporosis in later life.

A limited number of studies have explored the effects of oral lead exposure on bone growth and metabolism in animals (Escribano et al. 1997; Gonzalez-Riola et al. 1997; Gruber et al. 1997; Hamilton and O'Flaherty 1994, 1995; Ronis et al. 2001). These data, all from intermediate-duration studies in rats, indicate that oral lead exposure may impair normal bone growth and remodeling as indicated by decreased bone density and bone calcium content, decreased trabecular bone volume, increased bone resorption activity, and altered growth plate morphology. In general, rats appear to be less sensitive than humans to lead effects in bone. A recent study in mice reported that lead delays fracture healing at environmentally relevant doses and induces fibrous nonunions at higher doses by the progression of endochondral ossification (Carmouche et al. 2005). In studies in cultured osteoblast-like cells, lead disrupted the modulation of intracellular calcium by 1,25-dihydroxyvitamin D in a biphasic manner (Long and Rosen 1994). Another effect seen in this culture system was the inhibition by lead of 1,25-dihydroxyvitamin D3-stimulated synthesis of osteocalcin, a protein constituent of bone that may play a major role in normal mineralization of bone. Reduced plasma levels of osteocalcin have been reported in "moderately lead-poisoned" children (Pounds et al. 1991). Lead also inhibited secretion of osteonectin/SPARC, a component of bone matrix, and decreased the levels of osteonectin/SPARC mRNA from osteoblast-like cells in culture (Sauk et al. 1992). Lead inclusion bodies are commonly found in the cytoplasm and nuclei of osteoclasts, but not other bone cells, following *in vivo* lead exposure (Pounds et al. 1991).

The studies that have examined relationships between lead exposure, as reflected by PbB, and the occurrence of dental caries in children have, for the most part, found a positive association (Campbell et al. 2000a; Gemmel et al. 2002; Moss et al. 1999). Moss et al. (1999) conducted a cross-sectional analysis of measurements of PbB and dental caries in 24,901 people, including 6,541 children 2–11 years of age, recorded in the NHANES III (1988–1994). Mean (geometric) PbBs were 2.9 μg/dL in children 2–5 years of age and 2.1 μg/dL in children 6–11 years of age. Increasing PbB was significantly associated with increased number of dental caries in both age groups, after adjustment for covariates. An increase in PbB of 5 μg/dL was associated with an adjusted OR of 1.8 (95% CI, 1.3–2.5) for the age group 5–17 years. Covariates included in the models were age, gender, race/ethnicity, poverty income ratio, exposure to cigarette smoke, geographic region, educational level of head of household, carbohydrate and calcium intakes, and dental visits. A retrospective cohort study conducted in Rochester, New York compared the

risk of dental caries among 154 children 7–12 years of age associated with PbB less than or exceeding 10 μg/dL, measured at ages 18 and 37 months of age (Campbell et al. 2000a). The OR (adjusted for age at examination, grade in school, and number of dental surfaces at risk) for caries on permanent teeth associated with a PbB exceeding 10 μg/dL was 0.95 (95% CI, 0.43–2.09; p=0.89) and for deciduous teeth, 1.77 (95% CI, 0.97–3.24; p=0.07). Other covariates examined in the models, all of which had no significant effect on the outcome, were gender, race/ethnicity, SES, parental education and residence in community supplied with fluoridated drinking water, and various dental hygiene variables. Gemmel et al. (2002) conducted a cross-sectional study of associations between PbB and dental caries in 543 children, 6–10 years of age, who resided either in an urban (n=290) or rural (n=253) setting. Increasing PbB was significantly associated with the number of caries in the urban cohort, but not in the rural cohort. The mean PbBs were 2.9 μg/dL (SD, 2.0) in the urban group and 1.7 μg/dL (SD, 1.0) in the rural group. Covariates examined in the models were gender, race/ethnicity, SES, maternal smoking, parental education, and various dental hygiene variables.

Dye et al. (2002) conducted a cross-sectional analysis of measurements of blood lead concentration and indices of periodontal bone loss in 10,033 people, 20–69 years of age, recorded in the NHANES III (1988–1994). Mean (geometric) PbB was 2.5 μg/dL (SE, 0.08). Increasing blood lead concentration was significantly associated with periodontal bone loss, after adjustment for covariates. Covariates examined in the analysis included age, gender, race/ethnicity, education, SES, age of home, smoking, and dental furcation (an indicator of severe periodontal disease) as well as an interaction term for smoking and dental furcation.

Studies in animals also have examined the effect of lead exposure on teeth. For example, young rats whose mothers were exposed to lead since young adults, during pregnancy, and lactation had a significantly higher mean caries score than a control group (Watson et al. 1997). The mean PbB achieved in the dams was 48 μg/dL and in the breast milk 500 μg/dL; PbB in the offspring was not determined. Lead also has been reported to delay mineralization in teeth, resulting in less hard enamel (Gerlach et al. 2002) and eruption rate in hypofunctional teeth (Gerlach et al. 2000).

Hepatic Effects. In children, exposure to lead has been shown to inhibit formation of the heme-containing protein cytochrome P-450, as reflected in decreased activity of hepatic mixed-function oxygenases. Two children with clinical manifestations of acute lead poisoning did not metabolize the test drug antipyrine as rapidly as did controls (Alvares et al. 1975). Another study found a significant reduction in 6β-hydroxylation of cortisol in children who had positive urinary excretion of lead

(≥500 µg/24 hours) upon ethylenediamine tetraacetic acid (EDTA) provocative tests compared with an age-matched control group (Saenger et al. 1984). These biochemical transformations are mediated by hepatic mixed-function oxygenases.

The association between lead exposure and serum lipid profile was examined in a study of Israeli workers (Kristal-Boneh et al. 1999). The mean PbB of the 87 workers was 42.3 µg/dL and that of 56 control subjects was 2.7 µg/dL. After adjusting for confounders including nutritional variables, the authors found statistically higher values for total cholesterol (212 vs. 200 mg/dL) and HDL cholesterol (47 vs. 42 mg/dL) in the workers compared to controls; no significant differences were seen for LDL cholesterol and triglycerides. These findings are of dubious biological significance, particularly since the HDL/total cholesterol ratio was the same in the two groups. A study in rats administered lead acetate for 7 weeks that resulted in PbBs of 17 and 32 µg/dL reported a dose-related increase in triglycerides and decrease in HDL cholesterol (Skoczynska et al. 1993). The authors speculated that the increase in serum triglycerides could have been caused by lead-induced inhibition of lipoprotein lipase activity or decreased activity of hepatic lipase; no possible explanation was offered for the decrease in HDL cholesterol.

A study of workers in the United Arab Emirates reported that a group of 100 workers with a mean PbB of 78 µg/dL had significantly higher concentrations of amino acids in serum than 100 controls whose mean PbB was 20 µg/dL (Al-Neamy et al. 2001). Tests for liver function that included serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities found small (≤10%) but statistically significant increases in alkaline phosphatase and lactate dehydrogenase activities in the serum of the workers. A study in rats treated with lead acetate for 4 months found decreased AST and ALT activities in hepatic homogenates, but activities in serum were not monitored (Singh et al. 1994).

Collectively, the information regarding effects of lead on the liver in humans and animals is scarce and does not allow for generalizations.

Renal Effects. Lead nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis and interstitial fibrosis (Diamond 2005; Goyer 1989; Loghman-Adham 1997). Functional deficits in humans that have been associated with excessive lead exposure include enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate. A few studies have revealed histopathological features of renal injury in humans, including intranuclear inclusion bodies and cellular necrosis in the proximal tubule and interstitial fibrosis (Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979).

A large number of studies of lead nephropathy in humans have been published (Table 3-3). Most of these studies are of adults whose exposures were of occupational origin; however, a few environmental and/or mixed exposures are represented and a few studies of children are also included (Bernard et al. 1995; Fels et al. 1998; Verberk et al. 1996). In most of these studies, PbB was the biomarker for exposure, although more recent epidemiological studies have explored associations between toxicity and bone lead concentrations. These studies provide a basis for establishing blood lead, and in some cases, bone lead concentration ranges associated with specific nephrotoxicity outcome. The studies are sorted in Figure 3-3 by the central tendency blood lead concentration reported in each study; details about the subjects and exposures are provided in Table 3-3. End points of kidney status captured in this data set include various measures of glomerular and tubular dysfunction. Data on changes in glomerular filtration rate represent measurements of either creatinine clearance or serum creatinine concentration. Measurements of enzymuria represent, mainly, urinary N-acetyl-D-glucosaminidase (NAG), are also represented. Increased excretion of NAG has been found in lead-exposed workers in the absence of increased excretion of other proximal tubule enzymes (e.g., alanine aminopeptidase, alkaline phosphatase, glutamyltransferase) (Pergande et al. 1994). Data points indicating proteinuria refer to total urinary protein, urinary albumin, or urinary LMW protein (e.g., 2μG or RBP). Indices of impaired transport include clearance or transport maxima for organic anions (e.g., p-aminohippurate, urate) or glucose (Biagini et al. 1977; Hong et al. 1980; Wedeen et al. 1975). A few studies have provided histo-pathological confirmation of proximal tubular injury (Biagini et al. 1977; Wedeen et al. 1975, 1979).

Figure 3-3 illustrates a few general trends regarding the relationship between PbB and qualitative aspects of the kidney response. A cluster of observations of decrements in glomerular filtration rate appear at the low end of the PbB range (<20 μg/dL); the significance of these studies is discussed in greater detail below. Outcomes for the various renal toxicity end points are mixed over the PbB range 20–50 μg/dL. Enzymuria or proteinuria were detected in most studies in which these end points were evaluated, whereas indications of depressed glomerular filtration rate were, with only one exception, not observed over this PbB range. At PbBs >50 μg/dL, functional deficits, including enzymuria, proteinuria, impaired transport, and depressed glomerular filtration rate, dominate the observations. The overall dose-effect pattern suggests an increasing severity of nephrotoxicity associated with increasing PbB, with effects on glomerular filtration evident at PbBs below 20 μg/dL, enzymuria and proteinuria becoming evident above 30 μg/dL, and severe deficits in function and pathological changes occurring in association with PbBs exceeding 50 μg/dL.

Table 3-3. Selected Studies of Lead-Induced Nephrotoxicity in Humans[a]

No.	Reference	Exposure type	Number of subjects	Age (year)	Exposure duration (year)	Blood lead concentration (µg/dL)[b]	Biomarker evaluated[c]
1	Muntner at al. 2003	Unknown	4,831	>20	NA	5 (<1–56)	SCr*
2	Hu 1991b	Environmental	22	55	NA	6 (2–11)	CCr*[d]
3	Lin et al. 2001	Unknown	55	57	NA	7 (1–16)	CCr*
4	Staessen et al. 1992	Environmental	1,981	48	NA	8 (~2–70)	CCr*, SCr*
5	Payton et al. 1994	Environmental	744	64	NA	8 (4–26)	CCr*
6	Kim et al. 1996a	Unknown	459	57	NA	10 (<1–54)	SCr*
7	Staessen et al. 1990	Environmental	531	48	NA	10 (<4–35)	SCr*
8	Bernard et al. 1995	Environmental	154	13	NA	12 (3–35)	UNAG*, URBP*
9	Fels et al. 1998	Environmental	62	10	NA	13 (SD=6)	SCr, UE, UP, ULMWP
10	Sonmez et al. 2002	Occupational	13	32	0.14	25 (SD=10)	SCr, UNAG*
11	Chia et al. 1994	Occupational	128	28	3	30 (4–66)	UNAG*
12	Chia et al. 1995a, 1995b	Occupational	137	28	>0.5	30 (4–66)	SCr, $S\beta_2\mu G$*, UAlb, $U\beta_2\mu G$, URBP
13	Weaver et al. 2003a, 2005	Occupational	803	40	1–36	32 (4–86)	BUN*[e], SCr*[e], CCr, UNAG*[e], URBP
14	Mortada et al. 2001	Occupational	43	33	10	32 (SD=17)	SCr, UNAG*, UAlb*
15	Gerhardsson et al. 1992	Occupational	100	37–68	14–32	32 (5–47)	CCr, SCr, $U\beta_2\mu G$*, UNAG*
16	Verberk et al. 1996	Environmental	151	4.6	NA	34 (<5–~110)	UNAG*
17	Factor-Litvak et al. 1999	Environmental	394	6	6	35 (20–40)	UP*
18	Omae et al. 1990	Occupational	165	18–57	0.1–26	37 (9–60)	CCr, CUA, $U\beta_2\mu G$, $C\beta_2\mu G$

Table 3-3. Selected Studies of Lead-Induced Nephrotoxicity in Humans[a]

No.	Reference	Exposure type	Number of subjects	Age (year)	Exposure duration (year)	Blood lead concentration (µg/dL)[b]	Biomarker evaluated[c]
19	Cardozo dos Santos et al. 1994	Occupational	166	33	4.5	37 (16–88)[f]	SCr, UNAG*, UAlb, UP
20	Wedeen et al. 1975	Occupational	4	36	5–8	40 (29–52)	GFR, RPF, TMPAH, HP
21	Hsiao et al. 2001	Occupational	30	38	13	40 (<10–98)	SCr[g]
22	Huang et al. 2002	Occupational	40	30	5	42 (24–63)	$U\beta_2\mu G$, UP
23	Fels et al. 1994	Occupational	81	30	7	42 (21–73)	UP*
24	Pergande et al. 1994	Occupational	82	30	7	42 (21–73)	SCr, UP*, UE*
25	Roels et al. 1994	Occupational	76	44	6–36	43 (26–68)	CCr*[d], UNAG*
26	Kumar and Krishnaswamy 1995	Occupational	22	32.5	NA	43 (30–69)	CCr, $U\beta_2\mu G$*, UNAG*
27	Buchet et al. 1980	Occupational	25	45	13	44 (34–61)	CCr, SCr, $U\beta_2\mu G$, UP
28	de Kort et al. 1987	Occupational	53	42	12	47 (44–51)	SCr, BUN
29	Verschoor et al. 1987	Occupational	155	30–51	<2–>10	47 (34–66)	UNAG*, URPB*
30	Cardenas et al. 1993	Occupational	41	39	14	48 (36–65)	SCr, UP, $U\beta_2\mu G$, UNAG*, UTBX*, UPG*
31	Wedeen et al. 1975	Occupational	1	40	5	48	GFR*, TMPAH*, HP*
32	Gennart et al. 1992	Ocupational	98	38	8	51 (45–70)	SCr, UNAG, $U\beta_2\mu G$, URBP
33	Wedeen et al. 1979	Occupational	15	41	14	52 (20–98)	GFR*, HP*
34	Ehrlich et al. 1998	Occupational	382	41	12	54 (23–110)	SCr,* SUA*
35	Pinto de Almeida et al. 1987	Occupational	52	38	NA	64 (SD=16)	SCr*
36	Hong et al. 1980	Occupational	6	35	7	68 (34–110)	GFR*, TMG*
37	Wedeen et al. 1975	Occupational	3	28	3–5	72 (51–98)	GFR*, RPF*, TMPAH*, HP*

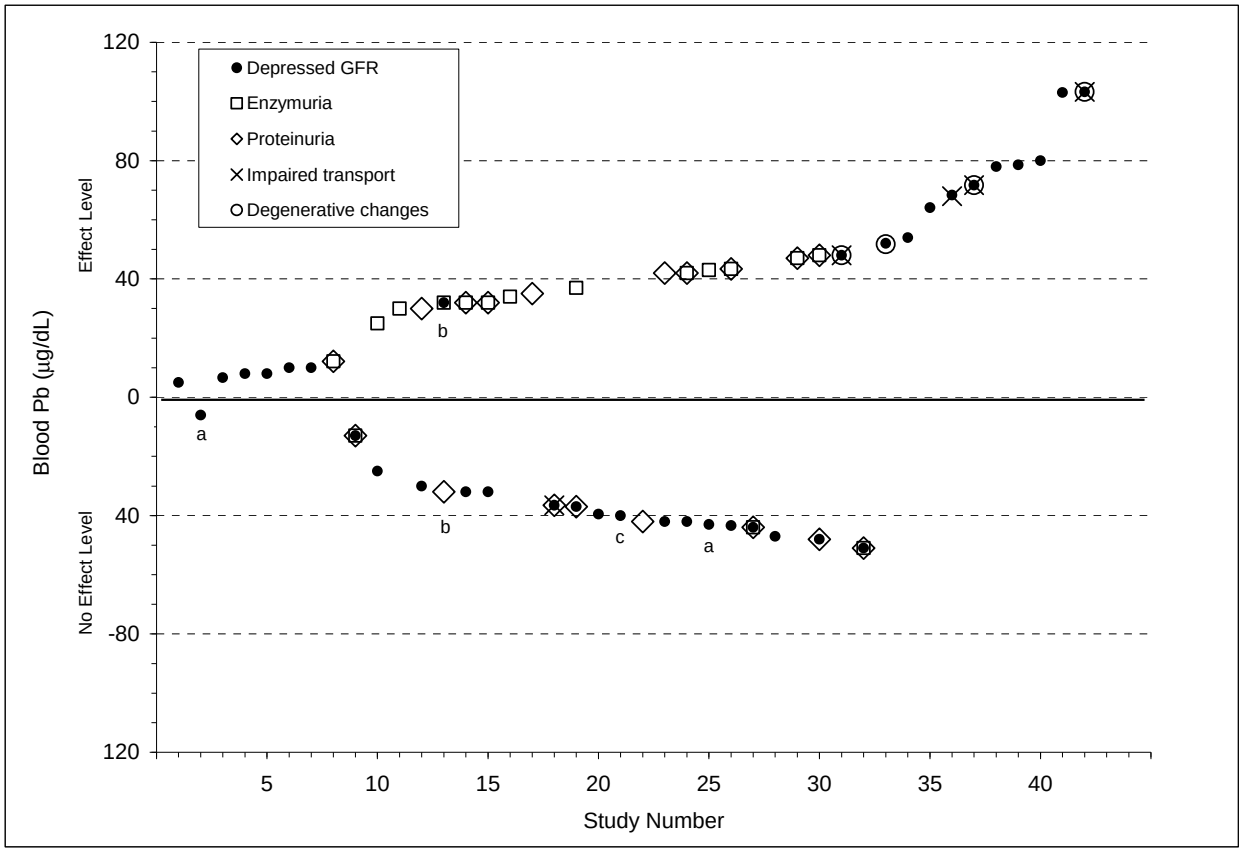
Table 3-3. Selected Studies of Lead-Induced Nephrotoxicity in Humans[a]

No.	Reference	Exposure type	Number of subjects	Age (year)	Exposure duration (year)	Blood lead concentration (µg/dL)[b]	Biomarker evaluated[c]
38	Baker et al. 1979	Occupational	160	29–62	4–31	77 (16–280)	GFR*, BUN*
39	Lilis et al. 1968	Occupational	102	32–61	>10	79 (42–149)	GFR*, SCr*
40	Lilis et al. 1980	Occupational	449	NA	12	80 (<40>80)	SCr*, BUN*
41	Cramer et al. 1974	Occupational	7	45	9	103 (71–109)	GFR*, HP*
42	Biagini et al. 1977	Occupational	11	44	12	103 (60–200)	GFR*, CPAH*, HP*

[a]See Figure 3-3 for graphical representation of lead-induced renal effects.
[b]Blood lead concentrations are reported central tendencies with range or SD in parentheses.
[c]Asterisk indicates association with lead exposure.
[d]Significant increase in creatinine clearance.
[e]Significant in upper age tertile (>46 years).
[f]3rd and 97th percentile.
[g]Significant decrease in serum creatinine concentration.

BUN = blood urea nitrogen, CCr = creatinine clearance; Cβ_2µG = β_2µG clearance, CPAH=p-aminohippurate (PAH) clearance; CUA = uric acid clearance; GFR = glomerular filtration rate; HP = histopathology; Sβ_2µG = serum β_2µG; SCr = serum creatinine; SD = standard deviation; SUA = serum uric acid; RPF= renal plasma flow; TMG = transport maximum for glucose; TMPAH = transport maximum for PAH; UAlb = urine albumin; Uβ_2µG = urine β_2µG; UE = urine enzymes; ULMWP = urine low molecular weight proteins; UNAG = urine N-acetyl-β-D-glucosaminidase; UP = urine protein; UPG = urine prostaglandins; URBP = urine retinol binding protein; UTBX = urine thromboxane

Figure 3-3. Indicators of Renal Functional Impairment Observed at Various Blood Lead Concentrations in Humans*



*Refer to Table 3-3 for study details (indexed by study number)

a = Increase in creatinine clearance; b = >46 years of age; c = Decrease in serum creatinine; GFR = glomerular filtration rate

Source: Diamond 2005

Inconsistencies in the reported outcomes across studies may derive from several causes. Varying uncertainty also exists, across studies, in exposure history of subjects and in the biomarkers assessed. In addition, occupational studies are subject to a healthy worker bias (i.e., tendency for workers who experience adverse effects to remove themselves, or be removed, from exposure).

Observations made in animal models provide evidence for the plausibility of effects of lead on renal glomerular and tubular function in humans. In rats, proximal tubular injury involves the convoluted and straight portions of the tubule (Aviv et al. 1980; Dieter et al. 1993; Khalil-Manesh et al. 1992a, 1992b; Vyskocil et al. 1989), with greater severity, at least initially, in the straight (S3) segment (Fowler et al. 1980; Murakami et al. 1983). Typical histological features include, in the acute phase, the formation of intranuclear inclusion bodies in proximal tubule cells (see below for further discussion); abnormal morphology (e.g., swelling and budding) of proximal tubular mitochondria (Fowler et al. 1980; Goyer and Krall 1969); karyomegaly and cytomegaly; and cellular necrosis, at sufficiently high dosage. These changes appear to progress, in the chronic phase of toxicity and with sufficient dosage, to tubular atrophy and interstitial fibrosis (Goyer 1971; Khalil-Manesh et al. 1992a, 1992b). Glomerular sclerosis has also been reported (Khalil-Manesh et al. 1992a). Adenocarcinomas of the kidney have been observed in long-term studies in rodents in which animals also developed proximal tubular nephropathy (Azar et al. 1973; Goyer 1993; Koller et al. 1985; Moore and Meredith 1979; Van Esch and Kroes 1969).

Effects on Glomerular Filtration Rate. In humans, reduced glomerular filtration rate (i.e., indicated by decreases in creatinine clearance or increases in serum creatinine concentration) has been observed in association with exposures resulting in average PbBs <20 μg/dL (Figure 3-3, Table 3-3).

The results of epidemiological studies of general populations have shown a significant effect of age on the relationship between glomerular filtration rate (assessed from creatinine clearance of serum creatinine concentration) and PbB (Kim et al. 1996a; Muntner et al. 2003; Payton et al. 1994; Staessen et al. 1990, 1992; Weaver et al. 2003a, 2005b). Furthermore, hypertension can be both a confounder in studies of associations between lead exposure and creatinine clearance (Perneger et al. 1993) and a covariable with lead exposure (Harlan et al. 1985; Muntner et al. 2003; Payton et al. 1994; Pirkle et al. 1985; Pocock et al. 1984, 1988; Tsaih et al. 2004; Weiss et al. 1986). These factors may explain some of the variable outcomes of smaller studies in which the age and hypertension effects were not fully taken into account. When age and other covariables that might contribute to glomerular disease are factored into the dose-response analysis, decreased glomerular filtration rate has been consistently observed in populations that have average PbB <20 μg/dL (Table 3-4). In the Kim et al. (1996a) and Muntner et al. (2003) studies, a

Table 3-4. Summary of Dose-Response Relationships for Effects of Lead Exposure on Biomarkers of Glomerular Filtration Rate

Reference	Exposure	Number of Subjects	Mean PbB (range) (µg/dL)	End point	Change in end point (per 10-fold increase in blood lead)
Payton et al. 1994	Mixed[a]	744 M	8.1 (4–26)	CCr (mL/minute)	-10[b]
Staessen et al. 1992	Environmental	1,016 F 965 M	7.5 (1.7–65)	CCr (mL/minute)	-10 F[c] -13 M
Kim et al. 1996a	Mixed[a]	459 M	9.9 (0.2–54)	SCr (mg/dL)	0.08[d] 0.14[e]
Staessen et al. 1990	Environmental	133 F 398 M	12 (6–35)	SCr (mg/dL)	0.07 M[f]

[a]U.S. Veterans Administration Normative Aging Study
[b]Partial regression coefficient, -0.040 ln mL/minute creatinine clearance per ln µmol/L blood lead concentration.
[c]Partial regression coefficient, -9.51 mL/minute creatinine clearance per log µmol/L blood lead concentration.
[d]Partial regression coefficient, 2.89 µmol/L serum creatinine per ln µmol/L blood lead concentration.
[e]In subjects with blood lead concentrations less than 10 µg/dL, the partial regression coefficient was 5.29 µmol/L serum creatinine per ln µmol/L blood lead concentration.
[f]Reported 0.6 increase in serum creatinine (µmol/L) per 25% increase in blood lead concentration (µmol/L, log-transformed) in males (two subjects with serum creatinine concentrations exceeding 180 µmol/L excluded; regression coefficient not reported for females).

CCr = creatinine clearance; F = females; ln = natural logarithm; M = males; PbB = blood lead concentration; SCr = serum creatinine concentration

significant relationship between serum creatinine and PbB was evident in subjects who had PbB below 10 μg/dL (serum creatinine increased 0.14 mg/dL per 10-fold increase in PbB). Assuming a glomerular filtration rate of approximately 90–100 mL/minute in the studies reported in Table 3-4, a change in creatinine clearance of 10–14 mL/minute would represent a 9–16% change in glomerular filtration rate per 10-fold increase in PbB. Estimating the change in glomerular filtration rate from the incremental changes in serum creatinine concentration reported in Table 3-4 is far less certain because decrements in glomerular filtration do not necessarily give rise to proportional increases in serum creatinine concentrations. A 50% decrement in glomerular filtration rate can occur without a measurable change in serum creatinine excretion (Brady et al. 2000). Nevertheless, the changes reported in Table 3-4 (0.07–0.14 mg/dL) would represent a 6–16% increase, assuming a mean serum creatinine concentration of 0.9–1.2 mg/dL. This suggests at least a similar, and possibly a substantially larger, decrement in glomerular filtration rate. The confounding and covariable effects of hypertension are also relevant to the interpretation of the regression coefficients reported in these studies. Given the evidence for an association between lead exposure and hypertension, and that decrements in glomerular filtration rate can be a contributor to hypertension, it is possible that the reported hypertension-adjusted regression coefficients may underestimate the actual slope of the blood lead concentration relationship with serum creatinine concentration or creatinine clearance.

Another important complication in the assessment of associations between lead exposure and adverse effects on glomerular filtration is the potential confounding effect of decrements in glomerular filtration rate and increased lead body burden. Lead exposure has also been associated with increases in glomerular filtration rate (Hsiao et al. 2001; Hu 1991b; Roels et al. 1994). This may represent a benign outcome or a potentially adverse hyperfiltration, which may contribute to subsequent adverse renal effects. Increases in glomerular filtration rate have been observed in the early phases of development of chronic renal injury in rats (Khalil-Manesh et al. 1992a).

The observations suggestive of a relationship between PbB and decrements in glomerular filtration rate derived from the studies presented in Table 3-3 are consistent with those of a smaller prospective clinical study in which progression of renal insufficiency was related to higher lead body burden among patients whose PbB was <15 μg/dL (Lin et al. 2001; Yu et al. 2004). Mean PbB in a high lead body burden group (EDTA provocation test yielded >600 μg excreted/72 hours) were 6.6 μg/dL (range, 1.0–15 μg/dL) compared to 3.9 μg/dL (1–7.9 μg/dL) in a low body burden group.

The above observations suggest that significant decrements in glomerular filtration rate may occur in association with PbB below 20 μg/dL and, possibly, below 10 μg/dL (Kim et al. 1996a; Muntner et al. 2003). This range is used as the basis for estimates of lead intakes that would place individuals at risk for renal functional deficits.

Longitudinal Studies—General Population. Three studies of glomerular function and lead exposure were conducted as part of the Normative Aging Study, a longitudinal study of health outcomes in 2,280 males, initially enrolled in the Boston area of the United States between 1963 and 1968. At enrollment, subjects ranged in age from 21 to 80 years (mean, 67), and had no history of heart disease, hypertension, cancer, peptic ulcer, gout, bronchitis, or sinusitus. Physical examinations, including seated blood pressure and medical history follow-ups, were conducted at approximately 3–5-year intervals. Beginning in 1987, participants were requested to provide 24-hour urine samples for analysis, including urine creatinine; and beginning in 1991, blood and bone concentrations were included in the examinations. Data collected from a subset of the study population (744 subjects, observed between 1988 and 1991) were analyzed for associations between serum creatinine, renal creatinine clearance, and blood lead concentrations (Payton et al. 1994). Mean age of the study group was 64.0 years (range, 43–90). Mean baseline PbB was 8.1 μg/dL (range, <4–26 μg/dL). Based on multi-variate linear regression (with log-transformed PbB), covariate-adjusted creatinine clearance was significantly associated with blood lead concentration (regression coefficient, -0.0403; SE, 0.0198; p=0.04). A 10-fold increase in PbB was associated with a decrease in creatinine clearance of 10.4 mL/minute. This would represent a decrease in creatinine clearance of approximately 11% from the group mean of 88 mL/minute. Co-variates included in the regression model were age and body mass index; systolic and diastolic blood pressure; alcohol consumption and tobacco smoking; and analgesic or diuretic medications.

In a subsequent longitudinal study, data collected from a random subset of the Normative Aging Study population (459 subjects, observed between 1991 and 1994) were analyzed for associations between serum creatinine and PbB (Kim et al. 1996a). Mean age of the study group was 56.9 years (range, 37.7–87.5). Mean PbB was 9.9 μg/dL (range, 0.2–54.1 μg/dL). Based on multivariate linear regression (with log-transformed PbB), covariate-adjusted serum creatinine concentration (mg/dL) was significantly associated with PbB. A 10-fold increase in PbB was associated with an increase of 0.08 mg/dL in co-variate-adjusted serum creatinine (95% CI, 0.02–0.13). This would represent an increase of approximately 7% from the group mean of 1.2 mg/dL. When subjects were stratified by PbB, the association was significant for three blood lead categories: ≤40, ≤25, and ≤10 μg/dL. In subjects who had PbB ≤10 μg/dL, serum creatinine was predicted to increase 0.14 mg/dL per 10-fold increase in PbB

(approximately 11% increase from the unstratified group mean). Covariates included in the models were age and body mass index; hypertension; alcohol consumption and tobacco smoking; and education.

A prospective study included 707 subjects from the Normative Aging Study who had serum creatinine, blood lead and bone lead measurements taken during the period 1991–1995 (baseline), and a subset of the latter group (n=448) for which follow-up serum creatinine measurements made 4–8 years later (Tsaih et al. 2004). Mean age of the study group was 66 years at the time of baseline evaluation and 72 years at follow-up. Mean PbB was 6.5 μg/dL at baseline and 4.5 at follow-up. Baseline bone lead concentrations were: tibia, 21.5 μg/g and patella, 32.4 μg/g and were essentially the same at follow-up. Associations between covariate-adjusted serum creatinine concentrations and lead measures were significant ($p<0.05$) in the study group only for blood lead and follow-up serum creatinine. Covariates included in the models were age and body mass index; diabetes and hypertension; alcohol consumption and tobacco smoking; and education. When stratified by diabetes and hypertension status, significant associations between serum creatinine concentration and lead measures (blood or bone lead) were found in the diabetic (n=26) and hypertensive groups (n=115), suggesting the possibility of interactions between lead exposure, glomerular function, diabetes, or hypertension. An increase in tibia bone lead concentration from the mid-point of the lowest to the highest quintile (9–34 μg/g) was associated with a significantly greater increment in serum creatinine concentration among diabetics (1.08 mg/dL per 10 years) compared to non-diabetics (0.062 mg/dL per 10 years).

Cross-sectional Studies—General Population. The NHANES III collected data on serum creatinine concentrations and PbB on approximately 20,000 U.S. residents during the period 1988–1994. Muntner et al. (2003) analyzed data collected on 15,211 subjects of age 20 years or older. Subjects were stratified into normotensive (n=10,398) or hypertensive categories (n=4,813; ≥140 mmHg systolic pressure or ≥90 mmHg diastolic pressure). Mean PbB was 3.30 μg/dL in the normotensive group and 4.21 μg/dL in the hypertensive group. Associations between PbB and risk of elevated serum creatinine concentrations or chronic renal disease (i.e., depressed glomerular filtration rate) were explored using multivariate regression. Elevated serum creatinine concentration was defined as ≥1.5 or ≥1.3 mg/dL in non-Hispanic Caucasian males and females, respectively; ≥1.6 mg/dL (males) or 1.4 mg/dL (females) for non-Hispanic African Americans; or ≥1.4 mg/dL (males) or ≥1.2 mg/dL (females) for Mexican Americans. Glomerular filtration rate was estimated from serum creatinine concentration using a predictive algorithm (Levey et al. 1999). Chronic renal disease was defined as glomerular filtration rate <60 mL/minute per 1.73 m^2 of body surface area. Covariate-adjusted ORs were estimated for PbB quartiles 2 (2.5–3.8 μg/dL), 3 (3.9–5.9 μg/dL), and 4 (6.0–56.0 μg/dL), relative to the 1st quartile (0.7–2.4 μg/dL). The ORs for elevated

serum creatinine concentration and chronic renal disease, but not in the normotensive group, exceeded unity in all quartiles of PbB and showed a significant upward trend with PbB. Covariate-adjusted ORs for chronic renal disease were: 2nd quartile, 1.44 (95% CI, 1.00–2.09); 3rd quartile, 1.85 (95% CI, 1.32–2.59); and 4th quartile, 2.60 (95% CI, 1.52–4.45). A 2-fold increase in PbB was associated with an OR of 1.43 (95% CI, 1.20–1.72) for elevated serum creatinine concentration or 1.38 (95% CI, 1.15–1.66) of chronic renal disease. Covariates included in the models were age, gender and body mass index; systolic blood pressure; cardiovascular disease and diabetes mellitus; alcohol consumption and cigarette smoking; and household income, marital status, and health insurance. A stronger association between PbB and depressed glomerular filtration rate (i.e., creatinine clearance) also was found in people who have hypertension, compared to normotensive people, in the smaller prospective study (Tsaih et al. 2004).

An analysis of relationships between PbB and renal creatinine clearance was conducted as part of the Belgian Cadmibel Study (Staessen et al. 1992). The Cadmibel Study was a cross-sectional study, originally intended to assess health outcomes from cadmium exposure. Subjects recruited during the period 1985–1989 resided for at least 8 years in one of four areas (two urban, two rural) in Belgium. One of the urban and rural areas had been impacted by emissions from heavy metal smelting and processing. PbB and creatinine clearance measurements were obtained for 965 males (mean age, 48 years) and 1,016 females (mean age, 48 years). Mean PbB was 11.4 μg/dL (range, 2.3–72.5) in males and 7.4 μg/dL (range, 1.7–6.0) in females. Based on multivariate linear regression (with log-transformed PbB), co-variate-adjusted creatinine clearance was significantly associated with PbB in males. A 10-fold increase in PbB was associated with a decrease in creatinine clearance of 13 mL/minute in males and 30 mL/minute in females. This would represent a decrease in creatinine clearance of approximately 13% from the group mean of 99 mL/minute in males, or 38% from the group mean of 80 mL/minute in females. Covariates included in the regression model were age and body mass index; urinary γ-glutamyl-transferase activity; and diuretic therapy. A logistic regression model was applied to the data to examine the relationship between risk of impaired renal function, defined as less than the 5th percentile value for creatinine clearance in subjects who were not taking analgesics or diuretics (<52 mL/minute in males or 48 mL/minute in females). A 10-fold increase in PbB was associated with a covariate-adjusted risk for impaired renal function of 3.76 (95% CI, 1.37–10.4; p=0.01). Covariates included in the logistic model were age and body mass index; urinary γ-glutamyltransferase activity; diabetes mellitus; and analgesic or diuretic therapy.

A cross-sectional study of civil servants in London examined relationships between PbB and serum creatinine concentration (Staessen et al. 1990). Participants included 398 males (mean age, 47.8 years)

and 133 females (mean age, 47.5 years). Mean PbB was 12.4 μg/dL in males and 10.2 μg/dL in females. Serum creatinine concentration was significantly (p=0.04, linear regression with log-transformed PbB) associated with PbB in males, but not in females. The association was no longer significant after excluding two subjects from the analysis who had serum creatinine concentrations exceeding 180 μmol/L (2 mg/dL). The predicted increase in serum creatinine concentration per 25% increase in PbB was 0.6 μmol/L (95% CI, -0.2–1.36). Although several covariates were considered in the analysis of the blood lead concentration data, covariates included in the regression model for serum creatinine concentration were not reported.

The Agency for Toxic Substances and Disease Registry (1995) conducted a cross-sectional analysis of possible associations between lead exposure and serum creatinine concentration or BUN among residents of four NPL sites (Granite City, Illinois; Galena, Kansas; Joplin, Mississippi; Palmerton, Pennsylvania). The study consisted of a target group of NPL site residents (n=1,645) and a comparison group (n=493) that had similar distributions of gender, age, SES, education, and housing age. Geometric mean blood lead concentrations were 4.26 μg/dL (SD±0.71) in the target group and 3.45 μg/dL (SD±0.74) in the comparison group. Multivariate regression analyses (linear and logistic) of subsets of the study group (e.g., age strata) did not reveal significant associations between PbB and either serum creatinine concentration or BUN.

Cross-sectional Studies—Occupational Exposures. As part of a longitudinal study of health outcomes among Korean lead workers, cross-sectional studies of potential associations between biomarkers of lead exposure (PbB, tibia lead, DMSA evoked urinary lead) have been conducted (Weaver et al. 2003a, 2003b, 2005a, 2005b). The cross-sectional study of the first of three longitudinal evaluations included 803 current and former lead workers (age range, 18–65 years; 639 males) and 135 controls (age range, 22–60 years; 124 males), enrolled in the study during the period 1997–1999 (Weaver et al. 2003a, 2005a). Mean PbB of the lead workers was 32 μg/dL (range, 4–86 μg/dL); mean tibia lead was 37 μg/g (range, -7–338 μg/dL). Significant associations were evident in the upper age tertile (>46 years), but not at younger ages, between increasing covariate-adjusted tibia lead and increasing serum creatinine (β, 0.0008 mg/dL per μg/dL; p<0.01) and increasing serum uric acid concentration (β, 0.0036 mg/dL per μg/dL; p=0.04); and between increasing PbB and increasing BUN (β, 0.0615 mg/dL per μg/dL; p<0.01). Covariates included age, gender, body mass index, current/former exposure status, and hypertension. In a subsequent cross-sectional study of the third evaluation of this same study group (n=652), performed during the period 1999–2001, similar age-dependent outcomes were observed (Weaver et al. 2005b). Significant associations between increasing serum creatinine and increasing tibia lead (β, 0.000451;

p=0.04), patella lead (β, 0.000147; p=0.04), or PbB (β, 0.001266; p=0.02) were evident in the upper age tertile (46 years).

Experimental studies in laboratory animals have shown that exposures to lead that result in blood lead concentrations exceeding 50 μg/dL can depress glomerular filtration rate and renal blood flow and produce glomerular sclerosis (Aviv et al. 1980; Khalil-Manesh et al. 1992a, 1992b).

Endocrine Effects. Occupational studies provide evidence for an association between high exposures to lead and changes in thyroid, pituitary, and testicular hormones. There are a number of inconsistencies in the available findings that are related in part to small sample sizes, possible confounding effects by age, tobacco use, and other factors, responses that remained within reference limits, and differences in laboratory methods of hormonal evaluation. Changes in circulating levels of thyroid hormones, particularly serum thyroxine (T_4) and thyroid stimulating hormone (TSH), generally occurred in workers having mean PbB ≥40–60 μg/dL. Altered serum levels of reproductive hormones, particularly follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone, have been observed at PbB ≥30–40 μg/dL. Some data, mainly results of tests of hormonal stimulation tests, suggest that the changes in thyroid and testicular hormones are secondary to effects of lead on pituitary function.

Decreases in serum T_4 were found in studies of workers with very high PbB (Cullen et al. 1984; Robins et al. 1983). Serum T_4 and estimated free thyroxine (EFT_4) were reduced in three of seven men who had symptomatic occupational lead poisoning and a mean PbB of 87.4 μg/dL (range, 66–139 μg/dL) (Cullen et al. 1984). There were no effects on thyroid binding globulin (TBG), total triiodothyronine (T_3), TSH, or TSH response to thyrotrophin releasing hormone (TRH) stimulation. A clinical study similarly found subnormal (low to borderline) serum T_4 and EFT_4 values in 7 of 12 (58%) foundry workers with a mean PbB of 65.8 μg/dL (Robins et al. 1983). However, in a cross-sectional study of 47 men from the same foundry with PbB <50 μg/dL and a mean employment duration of 5.8 years, only 12 (26%) had evidence of reduced T_4 and EFT_4 (Robins et al. 1983). Serum T_3 and TSH levels (only measured in the clinical study) and thyroid binding capacity (TBC, only measured in the cross-sectional study) were normal, and regression analyses showed no clear correlation between T_4 or EFT_4 and PbB. The thyroid effects in these studies (i.e., reduced T_4 with inappropriately low TSH or poor TRH response) are consistent with a primary pituitary or hypothalamic insufficiency. Evaluation of 176 Kenyan male car battery factory and secondary lead smelter workers (mean PbB, 56 μg/dL; mean lead exposure duration 7.6±5.1 years) showed that serum T_4, FT_4, T_3, and TSH levels were similar in subgroups of 93 workers with PbB ≤56 μg/dL and 83 workers with PbB ≥56 μg/dL (Tuppurainen et al. 1988). Regression analysis found no

significant correlations between PbB and any of the thyroid measures. However, there were weak but statistically significant negative correlations between duration of exposure and levels of T_4 and FT_4, and these associations were stronger in the ≥56 μg/dL subgroup.

Several studies found alterations in serum thyroid hormone and TSH in the PbB range of 40–60 μg/dL (Gustafson et al. 1989; López et al. 2000; Singh et al. 2000a). Mean serum levels of T_4 and FT_4 were significantly higher in 75 male lead-battery factory workers with a mean PbB of 50.9 μg/dL (mean work duration 6.1 years) than in 62 unexposed referents (no workplace lead exposure) with a mean PbB of 19.1 μg/dL (López et al. 2000). There were no group differences in serum T_3 and TSH. Regression analyses showed significant positive correlations for serum T_4, FT_4, T_3, and TSH vs. PbB in the range 8–50 μg/dL, and significant negative correlations for T_4 and T_3 vs. PbB in the range 50–98 μg/dL, indicating a drop in circulating hormones at PbBs around 50 μg/dL that is consistent with the results of the Cullen et al. (1984) and Robins et al. (1983) studies cited above. There were no significant associations between PbB or hormone levels vs. time in workplace or age, and all hormone values were within normal reference ranges. Gustafson et al. (1989) measured serum levels of T_3, T_4, and TSH in 25 male lead smelter workers (mean PbB, 39 μg/dL) and 25 matched controls without occupational lead exposure (mean PbB, 4 μg/dL). There were no overall group differences in the three thyroid measures, although serum TSH was significantly increased in the most heavily exposed individuals (mean PbB, >41 μg/dL). Analysis of a subgroup that reported no intake of selenium pills showed that serum T_4 was significantly higher in the exposed workers. Additionally, serum T_4 was significantly increased in a subgroup of 14 workers under the age of 40 (mean PbB, 39 μg/dL). Serum T_4, T_3, and TSH were assessed in 58 male petrol pump workers or automobile mechanics who had a mean PbB of 51.9 μg/dL and mean lead exposure duration of 13 years (Singh et al. 2000a). Comparison with an unexposed control group of 35 men (mean PbB, 9.5 μg/dL) showed no significant differences in T_4 and T_3 levels, although T_3 was significantly lower in a subgroup of 17 workers with a longer mean exposure time (17.5 years) than in 41 workers with shorter exposure (2.4 years). Serum TSH was significantly higher in the exposed workers compared to controls, as well as in a subgroup of 50 workers with higher mean PbB (55.4 μg/dL) than in 8 workers with a lower mean PbB (31.5 μg/dL), although all TSH values remained within the normal laboratory range.

Workers with PbBs of approximately 20–30 μg/dL showed no clear indications of thyroid dysfunction (Dursun and Tutus 1999; Erfurth et al. 2001; Refowitz 1984; Schumacher et al. 1998). Serum T_4, EFT_4, and TSH were assessed in a cross-sectional study of 151 male lead smelter workers that examined dose-response relationships across specifically defined levels of lead exposure (Schumacher et al. 1998). The

mean duration of employment in lead-exposed areas was 4.3 years, the mean current PbB was 24 μg/dL (15% exceeded 40 μg/dL), and the mean PbB for the preceding 10 years was 31 μg/dL (26% exceeded 40 μg/dL). The thyroid hormones were evaluated in relation to four levels of current and 10-year cumulative lead exposure (<15, 14–24, 25–39, and ≥40 μg/dL). Mean levels of T_4, EFT_4, and TSH were similar in all exposure categories and within laboratory normal limits for both current and cumulative exposure. There was no evidence of an exposure response with increasing lead burden, and controlling for age and alcohol consumption did not significantly alter the findings. Erfurth et al. (2001) found that serum concentrations of FT_4, FT_3, and TSH were similar in groups of 62 secondary lead smelter workers (median PbB, 33.2 μg/dL, median exposure time, 8 years) and 26 matched referents with no known occupational exposure to lead (median PbB, 4.1 μg/dL). There were no significant associations between these hormones and PbB, plasma lead, and bone lead levels after adjustment for age. Additionally, there was no difference in TSH response to TRH stimulation in subgroups of 9 exposed workers (median PbB, 35.2 μg/dL) and 11 referents (median PbB, 4.1 μg/dL). There were no adverse changes in thyroid hormones in workers with a mean PbB of 17.1 μg/dL who were exposed to lead for an average of 16.70 years (range, 1–22 years) in a Turkish metal powder-producing factory (Dursun and Tutus 1999). Comparison with 30 subjects from the general population (mean PbB, 2.37 μg/dL) showed that serum levels of T_4, FT_4, and FT_3, but not T_3 or TSH, were statistically significantly increased in the workers. However, all five thyroid measures were within normal reference limits. Refowitz (1984) found no correlation between levels of T_4 or EFT_4 and PbB in 58 secondary copper smelter workers in which the preponderance of PbBs were below 40 μg/dL.

No significant effects of lead on thyroid function have been found in children, but the number and/or quality of the available studies do not allow drawing firm conclusions. Thirty-six male and 32 female children ranging in age from 11 months to 7 years (median age of 25 months) took part in a study of the effects of lead exposure on thyroid function in inner city children (Siegel et al. 1989). PbB, T_4, and T_4 uptake were determined, and sex, race, socioeconomic status, and hemoglobin were also assessed for each child. The PbBs ranged from 2.0 to 77 μg/dL, with a mean of 25 μg/dL. Forty-four percent of the children had moderately elevated lead levels (>24 μg/dL). Linear regression analysis revealed that there was no association between PbB and either T_4 or FT_4. The results of this study are consistent with the findings of a small study of 12 children (2–5 years old) from the Omaha Lead and Poison Prevention Program with PbBs in the range of 41–72 μg/dL (Huseman et al. 1992). The authors found that basal TSH, T_4, T_3, and prolactin were within normal ranges. Also, TSH and prolactin responses to TRH, and cortisol responses to insulin were not altered by lead. However, Huseman et al. (1992) did find that the peak human growth hormone (HGH) response to an L-dopa and insulin test, although within normal

limits, was significantly lower in children with toxic levels of lead compared with the peak response in children with lower PbB (<30 μg/dL). Furthermore, the mean 24-hour HGH in children with high PbB was not only significantly lower than those of normal children, but was comparable with that of children with HGH neurosecretory dysfunction. High PbB was also associated with a lower mean insulin-like growth factor I. A study of male adolescents in Turkey reported that 42 subjects who worked at auto repair workshops and had a mean PbB of 7.3 μg/dL (SD±2.92 μg/dL) had a significantly lower ($p<0.05$) serum level of FT4 (1.12 ng/mL) compared to 55 control subjects (1.02 ng/mL) with a mean PbB of 2.1 μg/dL (SD±1.24 μg/dL) (Dundar et al. 2006). There were no significant effects on serum FT3 or TSH levels or in thyroid volume. Based on the small difference in FT4 values between exposed and unexposed subjects, the lack of increase in TSH, and the fact that many other chemicals normally present at auto repair workshops could have influenced the results, the significance of these findings is unknown.

Effects of occupational exposure to lead on pituitary gonadotrophins and testicular hormones were investigated in male workers (see also Section 3.2.5, Reproductive Effects). Changes in serum FSH, LH, and testosterone were found in several studies of highly exposed workers, but there are no clear patterns of response. The preponderance of evidence is consistent with an indirect effect(s) of lead on the hypothalamic-pituitary axis (i.e., a disruption of gonadotrophin secretions), although direct effects on testicular hormonal production are possible. Plasma concentrations of FSH, LH, testosterone, and prolactin were measured in a study of 122 male lead battery factory workers with a mean current PbB of 35.2 μg/dL and mean exposure duration of 6 years (Ng et al. 1991). Levels of FSH and LH were significantly increased compared to a control group of 49 nonexposed workers (8.3 μg/dL), and concentrations of these hormones increased with increasing PbB in the range of 10–40 μg/dL. Age was not a confounding factor, although duration of exposure affected the results. Workers exposed for <10 years had significantly increased LH and FSH and normal testosterone and prolactin levels, whereas those exposed for ≥10 years had increased testosterone and normal LH, FSH, and prolactin. Rodamilans et al. (1988) assessed serum levels of LH, FSH, testosterone, and steroid binding globulin (SBG) in 23 male lead smelter workers with PbB in the range of 60–80 μg/dL. Comparison with an unexposed group of 20 men (PbB 17 μg/dL) showed that serum LH was significantly increased in the workers and that the magnitude of the effect did not increase with duration of exposure. A significantly lower free testosterone index (testosterone/SBG ratio) in the workers exposed for 1–5 years and significant changes in serum testosterone (lower), SGB (higher), and free testosterone index (lower) in the workers exposed for >5 years indicated an exposure duration-related effect on serum testosterone.

Other studies of male workers have found different results. Erfurth et al. (2001) found no significant differences in basal serum levels of FSH, LH, prolactin, testosterone, sex hormone binding globulin, and cortisol in groups of 11 lead male workers (median PbB, 35.2 μg/dL) and 9 matched referents (median PbB, 4.1 μg/dL), although there was a tendency toward lower serum FSH concentrations in the exposed group. Additionally, measurements of serum FSH, LH, and prolactin after administration of gonadotrophin-releasing hormone (GRH) showed that the level of stimulated FSH was significantly lower in the workers. None of the basal or stimulated hormone levels correlated with lead exposure indices (blood lead, plasma lead, or bone lead) or age. Gustafson et al. (1989) found that plasma FSH, plasma LH, and serum cortisol levels were lower in male workers (mean PbB, 39 μg/dL) than in unexposed controls (mean PbB, 4 μg/dL); however, all hormone values were within normal reference limits. Serum FSH and LH values were similar in 98 male lead acid battery workers with a mean PbB of 51 of μg/dL and a group of 85 nonoccupationally exposed subjects (mean PbB, 20.9 μg/dL) (Gennart et al. 1992a), although the high PbB in the comparison group might have obscured detection of an effect. Cullen et al. (1984) found increased serum FSH and LH and borderline low serum testosterone levels in one of seven men with symptomatic occupational lead poisoning and a mean PbB of 87.4 μg/dL. Although serum testosterone concentration was normal in most of these patients, five had defects in spermatogenesis and six had subnormal glucocorticoid production. Serum testosterone levels were significantly lower in groups of male workers with lead poisoning (n=6, mean PbB, 38.7 μg/dL) and lead exposure (n=4, mean PbB, 29.0 μg/dL) than in an unexposed control group (n=9, mean PbB 16.1 μg/dL), but testosterone-estradiol-binding globulin capacity and serum levels of estradiol, LH, FSH, and prolactin were normal (Braunstein et al. 1978). Both lead groups had appropriate responses for serum testosterone and FSH to stimulation by human chorionic gonadotrophin (HCG) and clomiphene, and serum FSH to stimulation by gonadotrophin releasing hormone (GRH) and clomiphene citrate. The lead exposed group also had a normal LH response to challenge by GRH and clomiphene citrate, although the LH response was suppressed in the lead poisoned group. Both lead groups had reduced estradiol response to stimulation by clomiphene citrate, although there was no effect following stimulation by HCG. Testicular biopsies performed on the two most heavily exposed men showed oligospermia and testicular lesions. Further information regarding effects of lead on sex hormone levels in humans and animals can be found in Section 3.2.5.

Information is also available on the effects of lead exposure on serum erythropoietin (EPO) concentration. EPO is a glycoprotein hormone that regulates both steady-state and accelerated erythrocyte production. More than 90% of EPO is produced in the proximal renal tubules. Serum EPO was evaluated in a group of women from the Yugoslavia Prospective Study (see Section 3.2.4 for a detailed description of the Yugoslavia Prospective Study) in mid-pregnancy (n=5) and at time of delivery (n=48) (Graziano et al.

1991). Analysis of the variance showed that women with higher PbB had inappropriately low levels of EPO both at mid-pregnancy and at delivery. Graziano et al. (1991) speculated that lead may interfere with the mechanism of EPO biosynthesis, which appears to begin with increased calcium entry into the renal cells. In a study of lead workers, serum EPO levels from two groups of 28 exposed workers were significantly lower than in 113 control subjects (Romeo et al. 1996). Mean PbBs in the two exposed groups and in the controls were 38.3, 65.1, and 10.4 μg/dL, respectively. However, there was no correlation between PbB and EPO in any group. Hemoglobin levels were not affected by lead and were comparable among the three groups. In an additional study of male lead workers (n=20) with and without anemia, those with PbBs ≥60 μg/dL showed a significant reduction in erythroid progenitor cells and in granulocyte/macrophage progenitor cells (Osterode et al. 1999). However, EPO was in the normal range and did not increase in the presence of lead-induced anemia. Osterode et al. (1999) suggested that lead-induced kidney toxicity might be the reason why EPO was not adequately generated at higher PbB.

Ocular Effects. Lead is known to affect visual evoked potentials in adults and children (see Section 3.2.4 and review by Otto and Fox [1993]), but less is known regarding effects of lead on other eye structures. Recently, Schaumberg et al. (2004) examined the relationship of cumulative lead exposure with the development of cataracts in a group of 642 participants in the Normative Aging Study. Lead exposure was assessed by measuring PbB (mean, 5 μg/dL; range, 0–35 μg/dL) and lead in the tibia (mean, 20 ppm; range, 0–126 ppm) and patella (mean, 29 ppm; range, 0–165 ppm). The mean age of the subjects was 69 years (range, 60–93 years). A total of 122 cases of cataract were found. After controlling for age, tibia lead, but not patella lead, was a significant predictor of cataract. Also, PbB was not associated with increased risk of developing cataracts. Schaumberg et al. (2004) suggested that lead might be disrupting the lens redox status by inducing oxidative damage to lens epithelial cells. Changes consistent with lens opacity also were observed in Fisher 344 rats exposed to 2,000 ppm lead in the drinking water for 5 weeks, which produced a mean PbB of approximately 30 μg/dL (Neal et al. 2005). Examination of two-dimensional protein spot patterns of the rats' lenses showed significant alterations in the protein expression profile of both αA- and βA4-crystallins, alterations of which may decrease lens clarity through increased light scattering. The mechanism for this effect has not been elucidated.

In their review on lead effects on visual function, Otto and Fox (1993) mention that earlier studies reported alterations of the electroretinogram (ERG) in lead workers. Rothenberg et al. (2002a) reported alterations in scotopic (rod-mediated) retinal function in a group of 45 children (7–10 years old) participants in the Mexico City Lead Study (Rothenberg et al. 2002a). These alterations, consisting of increased a- and b-waves, appeared to be a new form of rod dysfunction and were associated with

maternal blood lead levels measured during the first trimester of pregnancy; the threshold for the effect was 10.5 μg/dL. Alterations in rod function, evidenced by the appearance of central scotoma, also had been reported earlier in lead workers with moderate PbB (mean, 47 μg/dL) (Cavalleri et al. 1982). Changes in ERG components also have been reported in rats (Fox and Chu 1988; Fox and Farber 1988; Fox and Katz 1992; Fox and Rubinstein 1989) and monkeys exposed during development (Bushnell et al. 1977; Kohler et al. 1997; Lilienthal et al. 1988, 1994). Tests conducted in monkeys >2 years after cessation of life exposure to lead revealed alterations in the ERG under scotopic conditions similar to those recorded during lead exposure, and at a time when PbB was below 10 μg/dL (Lilienthal et al. 1994). Since the alteration could be reproduced by treatment with dopamine antagonists, Lilienthal et al. (1994) suggested that the observed effects may be mediated by a permanent change of dopamine function. The series of studies from Fox and coworkers in the rat showed that low-level lead exposure during postnatal development has a detrimental effect on the rods of the retina, but not on cones. They also showed that developing and adult retinas exhibited qualitatively similar structural and functional alterations, but developing retinas were much more sensitive, and in both cases, alterations in retinal cGMP metabolism was the underlying mechanism leading to lead-induced ERG deficits and rod and bipolar cell death (Fox et al. 1997). Using a preparation of rat retina *in vitro*, Fox and coworkers demonstrated that rod mitochondria are the target site for calcium and lead and that these ions bind to the internal metal binding site of the mitochondrial permeability transition pore, which initiates a cascade of apoptosis in rods (He et al. 2000).

Other Systemic Effects. Lead interferes with the conversion of vitamin D to its hormonal form, 1,25-dihydroxyvitamin D. This conversion takes place via hydroxylation to 25-hydroxyvitamin D in the liver followed by 1-hydroxylation in the mitochondria of the renal tubule by a complex cytochrome P-450 system (Mahaffey et al. 1982; Rosen and Chesney 1983). Evidence for this effect comes primarily from studies of children with high lead exposure.

Lead-exposed children with PbBs of 33–120 μg/dL had marked reductions in serum levels of 1,25-dihydroxyvitamin D (Rosen et al. 1980). Even in the range of 33–55 μg/dL, highly significant depressions in circulating 1,25-dihydroxyvitamin D were found, but the most striking decreases occurred in children whose PbB was >62 μg/dL. In addition, children with PbB >62 μg/dL also had significant decreases in serum total calcium and ionized calcium and significant increases in serum parathyroid hormone. These conditions would tend to enhance production of 1,25-dihydroxyvitamin D; thus, the inhibition caused by lead may have been greater than was indicated by 1,25-dihydroxyvitamin D levels. Serum levels of 1,25-dihydroxyvitamin D returned to normal within 2 days after chelation therapy. These results are

consistent with an effect of lead on renal biosynthesis of 1,25-dihydroxyvitamin D. A strong inverse correlation between 1,25-dihydroxyvitamin D levels and PbB was also found among children with PbB ranging from 12 to 120 μg/dL, with no change in the slope of the line at levels <30 μg/dL (Mahaffey et al. 1982).

Results obtained by Koo et al. (1991) indicate that low to moderate lead exposure (average lifetime PbB between 4.9 and 23.6 μg/dL, geometric mean, 9.8 μg/dL) of young children (n=105) with adequate nutritional status, particularly with respect to calcium, phosphorus, and vitamin D, had no effect on vitamin D metabolism, calcium and phosphorus homeostasis, or bone mineral content. The authors attributed the difference in results from those other studies to the fact that the children in their study had lower PbB (only 5 children had PbB >60 μg/dL and all 105 children had average lifetime PbB <45 μg/dL at the time of assessment) and had adequate dietary intakes of calcium, phosphorus, and vitamin D. They concluded that the effects of lead on vitamin D metabolism observed in previous studies may only be apparent in children with chronic nutritional deficiency and chronically elevated PbB. Similar conclusions were reached by IPCS (1995) after review of the epidemiological data.

In general, data in animals support the findings in humans. For example, depression of plasma levels of 1,25-dihydroxyvitamin D was observed in rats fed 0.82% lead in the diet as lead acetate for 7–14 days (Smith et al. 1981). High calcium diets protected against this effect. An additional finding was that lead blocked the intestinal calcium transport response to exogenous 1,25-dihydroxyvitamin D, but had no effect on bone response to the vitamin D hormone. Although the lead exposure and resulting PbB (≥174 μg/dL) were high in this study, the results provide support for the disturbances in vitamin D metabolism observed in children exposed to high levels of lead.

3.2.3 Immunological and Lymphoreticular Effects

Numerous studies have examined the effects of lead exposure on immunological parameters in lead workers and a smaller number of studies provide information on effects in members of the general population, including children. The results although mixed, give some indication that lead may have an effect on the cellular component of the immune system, while the humoral component is relatively unaffected. However, it should be noted that the clinical significance of these relationships is as yet unknown.

Workers exposed occupationally for 4–30 years, and whose PbB at the time of testing ranged from 25 to 53 μg/dL (mean, 38.4 μg/dL), had serum concentrations of IgG, IgA, and IgM not significantly different from unexposed controls whose PbB at the time of testing ranged from 8 to 17 μg/dL (mean, 11.8 μg/dL) (Kimber et al. 1986). Alomran and Shleamoon (1988) also reported nonsignificant alterations in serum IgG and IgA levels in 39 workers exposed to lead oxides with a mean PbB of 64 μg/dL compared to 19 unexposed subjects (PbB not provided). Another study found no alterations in serum IgA and IgM levels among 25 workers with a mean PbB of 74.8 μg/dL (range, 38–100 μg/dL) compared to 16.7 μg/dL (range, 11–30 μg/dL) among 25 controls; however, IgG was significantly reduced among the workers (Basaran and Ündeger 2000; Ündeger et al. 1996). A study of 145 lead-exposed male workers from a large secondary lead smelter in the United States with a median PbB of 39 μg/dL (range, 25–55 μg/dL) also found no significant differences in serum immunoglobulin levels between the workers and a group of 84 unexposed workers with a mean PbB of <2 μg/dL (range, 2–12 μg/dL) (Pinkerton et al. 1998). Ewers et al. (1982) reported that lead workers with PbB of 21–90 μg/dL (median, 59 μg/dL) had more colds and influenza infections per year and had a significant suppression of serum IgM levels relative to a comparison group (median PbB, 11.7 μg/dL); neither serum IgA or IgG levels in workers were significantly different than in the comparison group. However, salivary IgA levels were significantly lower in the workers than in the control group. Secretory IgA is a major factor in the defense against respiratory and gastrointestinal infections (Koller 1985). A study of 606 Korean workers found that mean serum IgE levels were positively related to PbB in the range of <10–≥30 μg/dL (Heo et al. 2004).

Alterations in response to T-cell mitogens also have been reported in lead workers. Mishra et al. (2003) studied three groups of workers (n=84) who had mean PbBs of 6.5, 17.8, and 128 μg/dL and found that lymphocyte proliferation to phytohemagglutinin (PHA) was inhibited relative to a control group; natural killer (NK) cell activity was unaffected. The lymphocytes from the workers studied by Alomran and Shleamoon (1988) (mean PbB, 64 μg/dL) also were significantly less responsive to stimulation by PHA and concanavalin A (con A) than those from the controls (PbB not provided), and the severity of the depression was related to the duration of exposure. Impaired response to T-cell mitogens was also reported among a group of 51 firearm instructors (Fischbein et al. 1993). Fifteen of the 51 firearm instructors had PbBs ≥25 μg/dL (mean 31.4 μg/dL), whereas the rest had a mean PbB of 14.6 μg/dL. In contrast, Kimber et al. (1986) reported that responses to PHA and NK cell activity were not altered in their study of workers whose mean PbB was 34.8 μg/dL, compared with an unexposed group with a mean PbB of 11.8 μg/dL. Pinkerton et al. (1998) found no alterations in lymphoproliferative responses to tetanus toxoid or in NK cell activity in workers with a median PbB of 39 μg/dL. It should be noted,

however, that firearm instructors are likely to be exposed to a number of metal haptens, such as nickel and antimony.

Changes in T-cell subpopulations also have been reported. Ündeger et al. (1996) and Basaran and Ündeger (2000) described a significant decrease in the number of $CD4^+$ cells and C3 and C4 complement levels in workers with a mean PbB of 74.8 μg/dL. A significant decrease in percentage and number of $CD3^+$ and $CD4^+$ cells also was observed in the study of firearm instructors, but other cell types including $CD8^+$, B-lymphocytes, or NK cells were not significantly altered relative to controls (Fischbein et al. 1993). Pinkerton et al. (1998) found no significant differences in the percentages of $CD3^+$ cells, $CD4^+$ T cells, $CD8^+$ T cells, B cells, or NK cells between exposed and unexposed workers, but reported that the percentage and number of $CD4^+/CD45RA^+$ cells was positively associated with cumulative lead exposure. A study of 71 male workers engaged in the manufacturing of lead stearate who had a mean PbB of 19 μg/dL (range, 7–50 μg/dL) did not find significant differences in the number or percentages of $CD4^+$ or $CD3^+$ cells between the lead-exposed workers and a control group (PbB not measured) of 28 workers with no known occupational exposure to lead (Sata et al. 1998). However, the exposed workers had a significant reduction in the number of $CD3^+CD45RO^+$ (memory T) cells and a significant increase in the percentage of $CD8^+$ cells compared to controls. Also, there was a significant correlation between the percentage of $CD3^+CD45RA^+$ cells and PbBs in the exposed workers. At the time of the study, no subject had any signs or symptoms indicative of infection.

A small study of 10 occupationally-exposed workers whose mean PbB was 33 μg/dL reported that chemotaxis of polymorphonuclear leukocytes (PMN), stimulated through a specific membrane receptor, was impaired, compared to a group of 10 unexposed subjects with a mean PbB of 12.6 μg/dL (Valentino et al. 1991). The investigators suggested that the reduction of chemotaxis might be partially due to a lead-related modification of plasma membrane lipids, because PMN locomotion is influenced by fatty acids.

The data available on the immunologic effects of lead exposure on children are sparse. In a comparison of 12 preschool children having a mean PbB of 45.3 μg/dL (range, 41–51 μg/dL) and elevated FEP with 7 preschool children with a mean PbB of 22.6 μg/dL (range, 14–30 μg/dL), it was found that there were no differences between groups with respect to complement levels, immunoglobulin levels (IgM, IgG, IgA), or antitoxoid titers following booster immunization with tetanus toxoid (Reigart and Graher 1976). The small number of children and the relatively high PbB of the control group, as judged by current views, limit the conclusions that can be drawn from this report. Lutz et al. (1999) conducted a survey of the immune system's function in a cohort of 279 children aged 9 months to 6 years, with PbB ranging

from 1 to 45 μg/dL. Exposure was due primarily to lead-based paint. Of the comprehensive number of parameters of cellular and humoral immunity evaluated, only the serum IgE levels showed a statistically significant relationship with PbB, as PbB increased so did IgE levels. Variables controlled for in this study included age, race, gender, nutrition, and socioeconomic level. The assessment of IgE levels in this and other studies is important because IgE is the primary mediator for type-I hypersensitivity and is involved in various allergic diseases such as asthma. Some investigators have suggested that lead may be a risk factor for childhood asthma (Dietert et al. 2002), although recently, Joseph et al. (2005) conducted a study of 4,634 children screened for lead from 1995 to 1998 and found that PbB was less a predictor of asthma than was race and did not affect the relationship of race to prevalent or incident asthma. IgE levels were not monitored in the study.

A study of Chinese children (3–6 years old) also examined the association between PbB and serum IgG, IgM, and IgE levels (Sun et al. 2003). The cohort consisted of 38 children with PbB ≥10 μg/dL (high-lead group) and 35 children with PbB <10 μg/dL (controls). No significant association between immunoglobulins and PbB was found for the entire group (n=73). However, when the cohort was divided by sex, IgG and IgM were significantly lower and IgE was significantly higher in high-dose females (n=16) than in control females (n=17); no such relationship was seen among males. A study of 374 French mother-infant pairs reported a significant correlation ($p<0.001$) between infant hair level and cord blood IgE levels (Annesi-Maesano et al. 2003). In this cohort, mean PbB was relatively high, 96 μg/dL (SD, 58 μg/dL) in the mothers and 67 μg/dL (SD, 48 μg/dL) in cord blood. No significant association was found between placental lead level or cord PbB and IgE levels. Further suggestive evidence for an association between IgE and lead burden is provided by a study of 331 German children (7–8 years of age) with a geometric mean PbB of 2.7 μg/dL, which found a significant association ($p<0.05$) between PbB and increased serum IgE levels (Karmaus et al. 2005). Analysis of stratified data showed that the highest IgE levels were observed in the children with PbB in the range between 2.8–3.4 and >3.4 μg/dL. No significant associations were seen between PbB and serum levels of IgA, IgG, or IgM (Karmaus et al. 2005).

A small study of 70 Chinese children (3–6 years old) reported that 35 of them with a mean PbB of 14.1 μg/dL (SD, 4.0 μg/dL) had a significantly lower ($p<0.01$) serum levels of CD4+ cells than 35 children with a mean PbB of 6.4 μg/dL (SD, 1.3 μg/dL) (Li et al. 2005). There were no significant differences between the two groups regarding B, CD3+, CD8+, or NK cells. Sarasua et al. (2000) conducted a much bigger study of 2,041 children and adults who lived in areas with elevated soil levels of cadmium and lead (n=1,561) or in comparison communities (n=480) in the United States. Mean blood

lead levels were 7 μg/dL for participants aged 6–35 months; 6 μg/dL for participants aged 36–71 months; 4 μg/dL for participants aged 6–15 years, and 4.3 μg/dL for participants aged 16–75 years. Parameters monitored included IgA, IgG, and IgM, and peripheral blood lymphocyte phenotypes (T cells B cells, NK cells, and CD4/CD8 subsets). The results of the multivariate analyses showed no significant differences in any of the immune marker distributions attributed to lead for subjects over 3 years of age. However, in children under 3 years, there were small but significant associations between increased PbB, particularly in those over 15 μg/dL, and increases in IgA, IgG, IgM, and circulating B-lymphocytes.

Many studies have been published on the effects of lead on immune parameters in animals. Developing organisms appear to be more sensitive than adult animals and a number of studies have been designed to determine critical windows of vulnerability during development, including fetal development. Studies conducted in the late 1970s showed that prenatal and postnatal exposure of rats to lead leading to a PbB of approximately 29 μg/dL induced several alterations in the offspring tested at 35–45 days of age, including depression of antibody responses to sheep red blood cells, decreased serum IgG (but not IgA or IgM) levels, decreased lymphocyte responsiveness to mitogen stimulation, impaired DTH, and decreased thymus weights as compared with controls (Faith et al. 1979; Luster et al. 1978). In a later study, exposure of mice to lead through gestation and lactation resulted in reduced humoral immunity in the pups tested at 8 weeks of age (Talcott and Koller 1983). The DTH response was reduced but the difference with controls was not statistically significant. Blood lead levels were not available in this study. Miller et al. (1998) compared responses of the immune system between fetal and adult exposures. Exposure of pregnant rats to lead acetate in the drinking water during breeding and pregnancy resulted in PbBs of up to 112.0 μg/dL during pregnancy and lactation. Immune function was assessed in the offspring at 13 weeks of age and in the dams at 7–8 weeks postpartum. At these times, PbB was approximately 12 μg/dL in the dams and 0.68–2.63 μg/dL in offspring. Results from a comprehensive battery of tests showed no significant effects in lead-exposed dams. However, alterations were observed in the offspring and included decreased DTH response, altered cytokine production, and elevated serum IgE. Also, total leukocyte counts were significantly decreased, but analyses of subpopulation distribution revealed no significant treatment-related effects. These findings indicate that exposure *in utero* may result in alterations in immune parameters that persist beyond the exposure period when PbB had returned to the normal range. Similar results were reported in a study in mice in which immunotoxic changes were found at PbB <20 μg/dL (Snyder et al. 2000). Altered DTH responses were seen in adult mice at PbBs of 87 μg/dL but not 49 μg/dL (McCabe et al. 1999) providing further evidence of increased sensitivity in developing animals compared to adults. More recent studies by Dietert and coworkers have shown that gestational exposure to lead resulting in PbB of approximately 38 μg/dL has a greater immunotoxic effect

in female offspring than in male offspring (Bunn et al. 2001a) and that the embryo is more sensitive if exposure occurs late in gestation (gestation day [Gd] 15–21) than earlier during gestation (Gd 3–9) (Bunn et al. 2001b).

While many responses of the immune system observed in humans can be reproduced in experimental animals, recent observations from studies of perinatal exposure of animals suggest that caution should be exercised when extrapolating from animals to humans, since the immune functions depend on animal species, gender, and specially, developmental stage.

3.2.4 Neurological Effects

Neurological Effects in Adults. The most severe neurological effect of lead in adults is lead encephalopathy, which is a general term to describe various diseases that affect brain function. Early symptoms that may develop within weeks of initial exposure include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. The condition may then worsen, sometimes abruptly, to delirium, convulsions, paralysis, coma, and death (Kumar et al. 1987). Histopathological findings in fatal cases of lead encephalopathy in adults are similar to those in children.

Severe lead encephalopathy is generally not observed in adults except at extremely high PbBs (e.g., 460 μg/dL [Kehoe 1961]). Other data (Smith et al. 1938) suggest that acute lead poisoning, including severe gastrointestinal symptoms and/or signs of encephalopathy, can occur in some adults at PbBs that range from approximately 50 to >300 μg/dL, but the data are somewhat ambiguous.

Neurobehavioral Effects in Adults. Occupational exposure to lead has often been associated with signs of neurotoxicity. The literature contains numerous case reports and small cohort studies that describe a higher incidence of these symptoms, including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, and paresthesia at PbBs that range from approximately 40 to 120 μg/dL following acute-, intermediate-, and chronic-duration occupational exposure (Awad El Karim et al. 1986; Baker et al. 1979, 1983; Campara et al. 1984; Haenninen et al. 1979; Holness and Nethercott 1988; Lucchini et al. 2000; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Pasternak et al. 1989; Pollock and Ibels 1986; Rosenman et al. 2003; Schneitzer et al. 1990; Zimmerman-Tanselia et al. 1983).

In addition to the findings mentioned above, numerous studies have reported neuropsychological effects in lead workers. PbB in these studies ranged between 40 and 80 μg/dL. For instance, Parkinson et al. (1986) reported that lead workers exhibited greater levels of conflict in interpersonal relationships compared with unexposed workers. In another study, lead workers (45–60 μg/dL) performed much worse than workers with lower PbB on neurobehavioral tests, with general performance on cognitive and visual-motor coordination tasks and verbal reasoning ability most markedly impaired (Campara et al. 1984). Disturbances in oculomotor function (saccadic eye movements) in lead workers with mean PbB of 57–61 μg/dL were reported in a study by Baloh et al. (1979) and a follow-up by Spivey et al. (1980), and in a study by Glickman et al. (1984). Deficits in hand-eye coordination and reaction time were reported in 190 lead-exposed workers (mean PbB, 60.5 μg/dL) (NIOSH 1974). Most of the workers had been exposed between 5 and 20 years. A similar study, however, reported no differences in arousal, reaction time, or grip strength between a reference group (mean PbB, 28 μg/dL) and workers who had been exposed to lead for 12±9.5 years (mean PbB, 61 μg/dL) (Milburn et al. 1976); however, the relatively high mean PbB in the referents may have obscured the results. Disturbances in reaction time, visual motor performance, hand dexterity, IQ test and cognitive performance, nervousness, mood, or coping ability were observed in lead workers with PbBs of 50–80 μg/dL (Arnvig et al. 1980; Haenninen et al. 1978; Hogstedt et al. 1983; Mantere et al. 1982; Valciukas et al. 1978). Baker et al. (1983) reported impaired verbal concept formation, memory, and visual/motor performance among workers with PbB >40 μg/dL. Similar findings were reported in a cohort of 43 Venezuelan workers from a lead smelter who had a mean-employment duration of 4 years and a mean PbB of 42 μg/dL (Maizlish et al. 1995). The authors observed a significant association between altered mood states and current, peak, and time-weighted average (TWA) blood lead levels. Other parameters such as memory, perceptual speed, reaction time, and manual dexterity tended to be poorer with increasing exposure, but the magnitude of the effect was small.

A study of 91 workers divided into three groups based on PbBs (<20, 21–40, and 41–80 μg/dL) noted that workers with high PbB concentrations showed evidence of impairment on tests of serial reaction time and category search, with only weak impairment on tasks measuring syntactic reasoning and delayed verbal free recall (Stollery et al. 1989, 1991). In general, the magnitude of the impairment correlated with PbB. The impairment of serial reaction time was the best predictor of PbB. The main deficit was a slowing of sensory motor reaction time, which was seen most clearly when the cognitive demands of the task were low. The response tended to be restricted to workers in the high PbB level group. A subsequent study of 70 workers showed that lead impaired both the speed of making simple movements, as well as decisions, and suggested that decision slowing is due to central rather than peripheral factors (Stollery 1996). A

study of 427 Canadian lead workers whose mean current PbB was 27.5 μg/dL, and mean duration of employment was 17.7 years examined the correlation between short- and long-term measures of exposure to lead and performance on neuropsychological tests (Lindgren et al. 1996). Tasks that tested primarily visuomotor skills were significantly associated with a cumulative dose-estimate. Lindgren et al. (1996) indicated that the lack of an association between current blood lead or a TWA and neuropsychological performance was not necessarily inconsistent with other studies that found such an association since in their study the current mean PbBs were lower than in other studies. Current PbB as well as a TWA may have lacked the sensitivity to detect the decrement in performance.

Ehle and McKee (1990) reviewed the methodology and conclusions of 14 published reports to determine if any consensus regarding neurobehavioral effects of low-level lead exposure in adults could be reached. A PbB of 60 μg/dL was set as the upper limit of exposure. The investigators concluded that "the methodologies in the studies reviewed were so varied and the cultures in which the studies were conducted so diverse that it is impossible to generalize across findings." However, Ehle and McKee (1990) found some evidence that increased irritability and fatigue may lead to interpersonal problems. They also found suggestive evidence for subtle changes in the ability to process information quickly and for impaired ability to input and integrate novel information and to store this information in short-term memory. Balbus-Kornfeld et al. (1995) reviewed 21 studies for evidence that cumulative exposure to lead is associated with decreased performance in neurobehavioral tests in adults. Only three studies used a measure of cumulative exposure and two others used duration of exposure as a surrogate for cumulative exposure. The conclusion of the analysis was that "the current (at the time of the Balbus-Kornfeld study) scientific literature provides inadequate evidence to conclude whether or not cumulative exposure to or absorption of lead adversely affects performance in neurobehavioral tests in adults."

More recent studies of lead workers have reported significant associations between longitudinal decrements in cognitive function and past high PbB (Bleecker et al. 2005; Chen et al. 2005; Hänninen et al. 1998; Lindgren et al. 2003) and past high tibial lead (Schwartz et al. 2000b; Stewart et al. 1999). In the Lindgren et al. (2003) study, results of five neuropsychological measures showed that verbal memory was significantly better in a group with past high exposure followed by lower exposure than in a group with continuous high exposure, suggesting that reversibility of function may occur when PbB is maintained below 40 μg/dL. A small study of 27 Chinese lead workers also reported improvement in neurobehavioral performance over a period of 4 years during which the mean PbB was reduced from 26 to 8 μg/dL (Chuang et al. 2005). From a battery of 10 neurobehavioral tests, finger tapping, pattern comparison reaction time, and memory (visual patterns) significantly improved during the study period.

Past high tibia lead (mean peak was 24 ppm), as a measure of cumulative lead dose, also was found significantly related to smaller total brain volume, frontal and total gray matter volume, and parietal white matter volume in 532 former organolead workers (Stewart et al. 2006). Of nine smaller regions of interest, higher tibia lead was associated with reduced volume of the cingulated gyrus and insula. Changes in brain morphology were assessed by brain MRI. Potential confounders assessed were age, systolic and diastolic blood pressure, smoking history, ApoE genotype, education, alcohol consumption, depression status, and race. Previous studies of this cohort had found tibia lead associated with a decline in cognitive function (Schwartz et al. 2000b; Stewart et al. 1999).

Lucchini et al. (2000) reported that in a group of 66 workers with a mean current PbB of 27 μg/dL (range, 6–61 μg/dL) and exposure of 11 years, current, but not cumulative, exposure was associated with impaired visual contrast sensitivity; results from neurobehavioral tests were unaffected. Barth et al. (2002) also found in a group of 47 workers a significant correlation between current exposure (mean PbB, 31 μg/dL, range, 11–62 μg/dL) and cognitive deficits, particularly visuo-spatial abilities and executive functions related to the prefrontal cortex; however, no correlation was found between cumulative exposure measures and cognitive parameters. Recently, Schwartz et al. (2005) reported on a longitudinal study of the effects of lead on neurobehavioral test scores using both PbB and tibia lead as measures of dose. The cohort comprised 576 former and current lead workers who were evaluated from 1997 to 2001. At baseline (Schwartz et al. 2001), mean PbB was 32 μg/dL (SD±15 μg/dL) and mean tibia lead was 37 ppm (SD±40 ppm). In the recent publication, the investigators developed regression models that separated recent from cumulative dose, acute from chronic effects, and cross-sectional from longitudinal relations. The results showed consistent associations of both PbB and tibia lead with current neurobehavioral test scores and also with declines in test scores over time; the associations with PbB were stronger than those with tibia lead. The stronger associations were mainly in executive abilities, manual dexterity, and peripheral vibration threshold; the magnitude across an interquartile range of exposure was equivalent to 1–5 years of aging. Schwartz et al. (2005) pointed out that: “the significant measurement error, especially for tibia lead and change measures, and the relatively short follow-up interval, could obscure the relations between lead dose and changes in test scores” and that this knowledge must be factored into their inferences about the likely health effects.

Meyer-Baron and Seeber (2000) did a meta-analysis to determine the size of performance effects caused by exposure to inorganic lead that translated into PbBs <70 μg/dL. A total of 22 studies that met some minimum requirements were considered, and of these, 12 studies provided data to analyze the results of 13 tests. The mean PbB in the lead workers ranged from 31 to 52 μg/dL and those of the controls ranged

from 6 to 20 μg/dL. Statistically significant effects were observed for the Block Design, Logical Memory, and Santa Ana (dominant hand) tests. The first two tests indicate impairments of central information processing, particularly for the functions visuo-spatial organization and short-term verbal memory; Santa Ana tests manual dexterity. Meyer-Baron and Seeber (2000) stated that the extent of decreased performance was comparable to changes of performance that can be expected during aging of up to 20 years. Goodman et al. (2002) conducted a meta-analysis of 22 studies that met inclusion criteria. The PbB among the study subjects ranged from 24 to 63 μg/dL for exposed and from 0 to 28 μg/dL for unexposed workers. Only 2 tests (Digit Symbol and D2) out of 22 neurobehavioral tests analyzed showed a significant effect between exposed and unexposed workers. Digit Symbol evaluated motor persistence, sustained attention, response-speed, and visuo-motor coordination, whereas D2 requires visual selectivity at a fast speed on a repetitive motor response task. The tests that were found altered in the Meyer-Baron and Seeber (2000) study were not significantly affected in the analysis of Goodman et al. (2002). The latter investigators concluded that the available data are inconclusive and unable to provide adequate information on the neurobehavioral effects of moderate PbB.

In summary, in studies where adults were exposed occupationally to lead, a number of neurobehavioral parameters were reportedly affected. Although as Goodman et al. (2002) pointed out, the lack of true measures of pre-morbid state, observer bias, and publication bias affect the overall assessment, the preponderance of the evidence indicates that lead is associated with neurobehavioral impairment in adult workers at PbBs below 70 μg/dL.

Krieg et al. (2005) used data from the NHANES III to assess the relationship between PbB in adults and performance on the three computerized neurobehavioral tests included in the survey: simple reaction time, symbol-digit substitution, and serial-digit learning. The age of the participants ranged from 20 to 59 years old and a total of 4,937 completed all three tests. The study also evaluated 26 previously published cross-sectional occupational studies conducted in various countries that used the same neurobehavioral tests included in the survey. Potential confounders evaluated in the analysis included sex, age, education, family income, race/ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase. In the NHANES III, the PbB of those taking the neurobehavioral tests ranged from 0.7 to 42 μg/dL and the geometric and arithmetic means were 2.5 and 3.3 μg/dL, respectively. The results showed no statistically significant relationships between PbB and neurobehavioral test performance after adjustment for confounders. In the occupational studies, the mean PbB in the controls was 11.4 μg/dL (range, 3.7–20.4 μg/dL), whereas the mean in the exposed groups was 41.1 μg/dL (range, 24.0–72 μg/dL). The groups exposed to lead in the occupational studies consistently

performed worse than control groups on the simple reaction time and digit-symbol substitution tests. Some possible explanations for the lack of association between PbB and neurobehavioral scores in the survey mentioned by Krieg et al. (2005) include lack of toxicity of lead in adults at the levels investigated, a sample size or study design that did not allow enough precision to detect a relationship, or neurobehavioral tests that are not sensitive to the toxicity of lead at the levels investigated.

The effects of lead exposure on neurobehavioral parameters in nonoccupational cohorts of older persons also have been evaluated. Muldoon et al. (1996) conducted a wide range of cognitive tests designed to assess memory, language, visuo-spatial ability, and general intellectual status, as well as sensorimotor function in a group of 530 female participants in the Study of Osteoporotic Fractures. The cohort consisted of 325 rural dwellers and 205 urban dwellers with geometric mean PbB of 4.5 μg/dL and 5.4 μg/dL, respectively; the overall range was 1–21 μg/dL. The corresponding mean ages were 71.1 and 69.4 years. For the group, the scores on the various tests were average, consistent with normal values reported for older women. PbB showed a significant inverse association with performance only among the rural dwellers. After adjusting for age, education, and tobacco and alcohol consumption, women with PbB ≥8 μg/dL performed significantly worse in tests of psychomotor speed, manual dexterity, sustained attention, and mental flexibility than women with PbB ≤3 μg/dL. Similar results were found for reaction time tests after further adjusting for history of diabetes and/or arthritis. A similar study was conducted in a cohort of 141 men participants in the Normative Aging Study (Payton et al. 1998). In this study, in addition to PbBs, lead in bone (tibia and patella) was also measured. The mean PbB among the participants was 5.5 μg/dL (range not provided), and the mean age was 66.8 years. Tibial and patellar bone lead showed a stronger correlation with each other than either of them with blood lead. After adjusting for age and education, the results showed that men with higher PbB recalled and defined fewer words, identified fewer line-drawn objects, and required more time to attain the same level of accuracy on a perceptual comparison test as men with the lowest level of PbB. In addition, men with higher blood and tibial lead copied spatial figures less accurately, and men with higher tibial lead had slower response for pattern memory. The results showed that PbB was the strongest predictor of performance on most tests. Also of interest was the finding that lead in the tibia, which changes at a slower rate, showed more significant relationships with cognitive test scores than patellar bone lead, which changes more rapidly.

A more recent study of 526 participants of the Normative Aging Study with a mean age of 67.1 years and mean PbB of 6.3 μg/dL reported that patellar lead was significantly associated with psychiatric symptoms such as anxiety, depression, and phobic anxiety (Rhodes et al. 2003). In an additional study of Normative Aging Study participants (mean PbB, 4.5 μg/dL; mean patella Pb, 29.5 ppm), it was found that both bone

and blood lead were associated with poor test performance (Weisskopf et al. 2004; Wright et al. 2003c). According to the investigators, these findings are consistent with the theory that bone lead chronically remobilizes into blood, thus accelerating cognitive decline. In yet an additional study, Shih et al. (2006) reported that in a group of 985 of sociodemographically diverse urban-dwelling adults in the United States (mean age, 59.4 years) higher tibia lead levels were consistently associated with worse performance in tests of cognitive function after adjusting for confounders; no such association was found with PbB. Mean tibia lead was 18.7 ppm (SD±11.2 ppm) and mean PbB was 3.5 μg/dL (SD±2.2 μg/dL). An increase in one interquantil range of tibia lead was equivalent to 2.2–6.1 more years of age across the tests conducted, the average tibia lead effects was 36% of the age effect. Shih et al. (2006) suggested that, in the population studied, a proportion of what was termed normal age-related decrements in cognitive function may be attributable to neurotoxicants such as lead.

Peripheral Physiological Effects in Adults. There are numerous studies available on peripheral nerve function that measured the conduction velocity of electrically stimulated nerves in the arm or leg of lead workers. Representative studies are summarized below. A prospective occupational study found decreased nerve conduction velocities (NCVs) in the median (motor and sensory) and ulnar (motor and sensory) nerves of newly employed high-exposure workers after 1 year of exposure and in the motor nerve conduction velocity of the median nerve of this group after 2 or 4 years of exposure (Seppalainen et al. 1983); PbBs ranged from 30 to 48 μg/dL. Although the severity of the effects on NCV appeared to lessen with continued exposure, several of the high-exposure workers in this study quit 1 or 2 years after starting. Thus, the apparent improvement in NCVs may have been due to a healthy worker effect. A similar healthy worker effect may have accounted for the negative results of Spivey et al. (1980) who tested ulnar (motor and slow fiber) and peroneal (motor) nerves in 55 workers exposed for 1 year or more and whose PbBs ranged from 60 to 80 μg/dL. The studies differed in design; one prospectively obtained exposure history, while the other did it retrospectively. The end points that were measured also differed; Spivey et al. (1980) did not test the median nerve, which was the most sensitive end point in the study by Seppalainen et al. (1983). Ishida et al. (1996) found no significant association between PbBs of 2.1–69.5 μg/dL and median nerve conduction velocity among a group of 58 male and 70 female ceramic painters.

In cross-sectional occupational studies, significant decreases in NCVs were observed in fibular (motor) and sural (sensory) nerves as a function of PbB with duration of exposure showing no effect (Rosen and Chesney 1983). In another study, decreases in NCVs of ulnar (sensory, distal) and median (motor) nerves were seen primarily at PbBs >70 μg/dL (Triebig et al. 1984). Duration of exposure and number of lead-

exposed workers in these two studies were 0.5–28 years and 15 workers (Rosen and Chesney 1983), and 1–28 years and 133 workers (Triebig et al. 1984). Results of an earlier study by Araki et al. (1980) suggest that the decrease in NCV is probably due to lead since median (motor) NCVs in workers with a mean PbB of 48.3 μg/dL were improved significantly when PbB was lowered through $CaNa_2EDTA$ chelation therapy. A study by Muijser et al. (1987) presented evidence of improvement of motor NCV after cessation of exposure. After a 5-month exposure, the PbB was 82.5 μg/dL and decreased to 29 μg/dL 15 months after the termination of exposure, at which time, NCVs were not different from a control group.

The results of these studies indicate that NCV effects occur in adults at PbBs <70 μg/dL, and possibly as low as 30 μg/dL. Ehle (1986), in reviewing many of the studies of NCV effects, concluded that a mild slowing of certain motor and sensory NCVs may occur at PbBs <60 μg/dL, but that the majority of studies did not find correlations between PbB and NCV below 70 μg/dL and that slowing of NCV is neither a clinical nor a subclinical manifestation of lead neuropathy in humans. Other reviewers have pointed out that decreases in NCV are slight in peripheral neuropathies (such as that induced by lead) that involve axonal degeneration (Le Quesne 1987), and that although changes in conduction velocity usually indicate neurotoxicity, considerable nerve damage can occur without an effect on conduction velocity (Anderson 1987). EPA (1986a) noted that although many of the observed changes in NCV may fall within the range of normal variation, the effects represent departures from normal neurological functioning. NCV effects are seen consistently across studies and although the effects may not be clinically significant for an individual, they are significant when viewed on a population basis. This is further supported by the meta-analysis of 32 studies of effects of lead exposure on NCV (Davis and Svendsgaard 1990).

More recent studies also have produced mixed results. Chia et al. (1996a) measured NCV in a group of 72 male workers from a lead battery-manufacturing factory and 82 unexposed referents. Measurements of NCV in the median and ulnar nerves, as well as of PbB were performed every 6 months over a 3-year period. The geometric mean PbB for the exposed workers at the beginning of the study was 36.9 μg/dL compared to 10.5 μg/dL for the referents. Baseline measurements revealed significant slower NCV in workers, mostly in the median nerve. Serial measurements in the exposed workers over the 3-year period showed a peak in PbB in the third test which was followed by a decrease in median sensory conduction velocity and ulnar sensory nerve conduction velocity in the fourth test. Evaluation at the end of the study of 28 workers who completed the 3-year period showed significant associations between PbB and five out

of the eight parameters measured. The same was observed when only workers with PbB ≥40 μg/dL were included in the analysis, but no significant association was found among workers with PbB <40 μg/dL.

Yeh et al. (1995) evaluated nerve conduction velocity and electromyographic (EMG) activity in a group of 31 workers from a battery recycling factory and 31 sex- and age-matched controls. The mean duration of exposure to lead was 30.4 months and the mean PbB was 63 μg/dL (range, 17–186 μg/dL); PbB was not measured in the control group. Eighty percent of the workers (n=25) had extensor weakness of the distal upper limbs and six of these workers had weakness in dorsiflexion of the foot; data for the control group were not provided. These 25 workers were classified as the lead neuropathy subgroup and the remaining 6 as the lead exposure subgroup. Studies of motor nerve conduction experiments showed a significantly increased distal latency in the median nerve from exposed workers relative to controls, but no such effect was seen in the ulnar, peroneal, and tibial nerves. Studies of sensory nerve conduction did not reveal any significant differences between exposed and control workers. Ninety-four percent of the exposed workers had abnormal EMG, but no mention was made regarding the control group. After controlling for age and sex, the authors found a significant positive association between an index of cumulative exposure to lead (ICL) and the distal motor latencies of tibial nerves and significant negative association between ICL and the NCVs of sural nerves. No correlation was found between current PbB or duration of exposure and neurophysiological data. Taken together, the data available suggest that in lead workers slowing of NCV starts at a mean PbB of 30–40 μg/dL.

Other Physiological Effects in Adults. Studies also have shown that exposure to lead affects postural balance. For example, Chia et al. (1996b) evaluated the possible association between postural sway parameters and current PbB, cumulative PbB at different years of exposure, and an index of total cumulative exposure to lead in a group of 60 workers; 60 unexposed subjects served as a control group. The current mean PbB was 36 μg/dL (range, 6.4–64.5 μg/dL) among the workers and 6.3 μg/dL (range, 3.1–10.9 μg/dL) among the referents. Exposed and referents differed significantly in postural sway parameters when the tests were conducted with the eyes closed, but not with the eyes open. Although the postural sway parameters were not significantly correlated with current PbB or with total cumulative lead exposure, a significant correlation existed with exposure during the 2 years prior to testing. The authors speculated that the lack of correlation between postural sway and cumulative lead exposure could be due to underestimation of cumulative exposure and/or to the effects of lead being reversible. A similar study of 49 male lead workers employed at a chemical factory producing lead stearate found that an increase in postural sway with the eyes open in the anterior-posterior direction observed in exposed workers was related to current PbB (mean, 18 μg/dL) (Yokoyama et al. 1997). Also, an increase in sway with the eyes

closed in the right-left direction was significantly related to the mean PbB in the past. According to Yokoyama et al. (1997), the change in the vestibulo-cerebellum seemed to reflect current lead absorption, whereas the change in the anterior cerebellar lobe reflected past lead absorption. Changes in postural balance observed in a group of 29 female lead workers with a mean PbB of 55.7 μg/dL in a more recent study from the same group of investigators led them to suggest that lead affects the anterior cerebellar lobe, and the vestibulo-cerebellar and spinocerebellar afferent systems (Yokoyama et al. 2002). Other studies also have reported decreased postural stability in lead workers (Dick et al. 1999; Iwata et al. 2005; Ratzon et al. 2000), but whether the alterations are associated with current measures of exposure or measures of cumulative exposure remains to be elucidated.

The effect of lead exposure on somatosensory evoked potentials has been evaluated in numerous studies of lead workers. Comprehensive reviews on this topic are available (Araki et al. 2000; Otto and Fox 1993). For example, delayed latencies of visual evoked potentials have been reported in several studies of lead workers with PbB of approximately 40 μg/dL (Abbate et al. 1995; Araki et al. 1987; Hirata and Kosaka 1993). In contrast, no significant association was found between exposure to lead and the latencies of visual and brainstem auditory evoked potentials in a group of 36 female glass workers with a mean PbB of 56 μg/dL and mean exposure duration of 7.8 years (Murata et al. 1995). Also, in a similar study of 29 female lead workers with a mean PbB of 55.7 μg/dL (range, 26–79 μg/dL) and a mean employment duration of 7.9 years in a glass factory, Yokoyama et al. (2002) reported no significant differences in the latencies of brain auditory evoked potentials (BAEP) between the workers and 14 control workers (mean PbB, 6.1 μg/dL). Counter and Buchanan (2002) reported delayed wave latencies consistent with sensory-neural hearing impairment in adults with chronic exposure to lead through ceramic-glazing work and with mean PbB of 47 μg/dL, and suggested that this finding may be attributable to occupational noise exposure in combination with lead intoxication. Bleecker et al. (2003) found dose-dependent alterations in BAEP among lead workers with a mean PbB of 28 μg/dL and a mean-employment duration of 17 years. Analysis of the results led them to suggest that current lead exposure preferentially affected conduction in the distal auditory nerve while chronic lead exposure appeared to impair conduction in the auditory nerve and the auditory pathways in the lower brainstem.

An additional parameter that has been studied in lead-exposed workers is the electrocardiographic R-R interval variability, a measure of peripheral autonomic function. R-R interval variability was significantly depressed in a group of 36 female glass workers compared to a group of 17 referents with no known occupational exposure to lead (Murata et al. 1995). The mean PbB was 55.6 μg/dL and the mean exposure duration was 7.8 years. However, Gennart et al. (1992a) found no association between exposure

and R-R interval variations in the electrocardiogram. The study group consisted of 98 workers from a lead acid battery factory (exposure group) and 85 people who had no occupation exposure to lead (reference group). The mean duration of occupational exposure was 10.6 years. Mean PbB at the time of the examination was 51 μg/dL (range, 40–75 mg/dL) in the exposure group, and 20.9 μg/dL (range, 4.4–39 mg/dL) in the reference group. More studies are needed to establish whether this parameter is truly affected by lead exposure, and if so, to evaluate the shape of the dose-response relationship.

Neurological Effects in Children. High-level exposure to lead produces encephalopathy in children. The most extensive compilation of dose-response information on a pediatric population is the summarization by the National Academy of Sciences (1972) of unpublished data from the patient populations reported in Chisolm (1962, 1965) and Chisolm and Harrison (1956). This compilation relates the occurrence of acute encephalopathy and death in children in Baltimore, Maryland, associated with PbBs determined by the Baltimore City Health Department between 1930 and 1970. Other signs of acute lead poisoning and blood lead levels formerly regarded as asymptomatic were also summarized. An absence of signs or symptoms was observed in some children at PbB of 60–300 μg/dL (mean, 105 μg/dL). Acute lead poisoning symptoms other than signs of encephalopathy were observed at PbB of approximately 60–450 μg/dL (mean, 178 μg/dL). Signs of encephalopathy such as hyperirritability, ataxia, convulsions, stupor, and coma were associated with PbB of approximately 90–800 μg/dL (mean, 330 μg/dL). The distribution of PbBs associated with death (mean, 327 μg/dL) was virtually the same as for levels associated with encephalopathy.

Additional evidence from medical reports (Bradley and Baumgartner 1958; Bradley et al. 1956; Gant 1938; Rummo et al. 1979; Smith et al. 1983) suggests that acute encephalopathy in the most susceptible children may be associated with PbBs in the range of 80–100 μg/dL. However, a study reported 19 cases of acute encephalopathy in infants of mean age 3.8 months and with mean PbB of 74.5 μg/dL (range, 49.7–331 μg/dL) following use of traditional medicines containing lead (surma, Bint al Thahab) (Al Khayat et al. 1997a). Seven cases had PbB ≤70 μg/dL. In this report, lead level at 2 months postchelation was a significant predictor of abnormal results in the Denver Developmental Screening Test carried out for a mean period of 20 months.

Histopathological findings in fatal cases of lead encephalopathy in children include cerebral edema, altered capillaries, and perivascular glial proliferation. Neuronal damage is variable and may be caused by anoxia (EPA 1986a).

Numerous studies clearly show that childhood lead poisoning with encephalopathy results in a greatly increased incidence of permanent neurological and cognitive impairments. Additional studies indicate that children with symptomatic lead poisoning without encephalopathy (PbB, >80–100 μg/dL) also have an increased incidence of lasting neurological and behavioral damage.

Neurobehavioral Effects in Children. The literature on the neurobehavioral effects of lead in children is extensive. With the improvement in analytical methods to detect lead in the various biological media in recent years and in study design, the concentrations of lead, particularly in blood, associated with alterations in neurobehavioral outcomes keep decreasing. In fact, the results of some recent studies suggest that there may be no threshold for the effects of lead on intellectual function. Due to the enormous size of the database on neurobehavioral effects of lead in children, below are summaries of representative and/or major studies published on specific areas. For further information, the reader is referred to recent reviews on this topic (Bellinger 2004; Koller et al. 2004; Lidsky and Schneider 2003; Needleman 2004).

Many studies conducted decades ago reported negative associations between intellectual function, usually measured as IQ on various intelligence scales, and increased PbB, although other exposure indices were sometimes used. For example, de la Burde and Choate (1972) reported a mean Stanford-Binet IQ decrement of 5 points, fine motor dysfunction, and altered behavioral profiles in 70 preschool children exhibiting pica for paint and plaster and elevated PbBs (mean, 58 μg/dL), when compared with results for matched control subjects not engaged in pica for paint and plaster. A follow-up study on these children (ages 1–3 years) at 7–8 years of age reported a mean Wechsler Intelligence Scale for Children (WISC) full-scale IQ decrement of 3 points and impairment in learning and behavior, despite decreases in PbB since the original study (de la Burde and Choate 1975). Rummo et al. (1979) observed hyperactivity and a decrement of approximately 16 IQ points on the McCarthy General Cognitive Index (GCI) among children who had previously had encephalopathy and whose average maximum PbB at the time of encephalopathy were 88 μg/dL (average PbB, 59–64 μg/dL). Asymptomatic children with long-term lead exposures and average maximum PbB of 68 μg/dL (average PbB level, 51–56 μg/dL versus 21 μg/dL in a control group) had an average decrement of 5 IQ points on the McCarthy GCI. Their scores on several McCarthy Subscales were generally lower than those for controls, but the difference was not statistically significant. Children with short-term exposure and average maximum PbB of 61 μg/dL (average PbB, 46–50 μg/dL) did not differ from controls. PbB in the referent group averaged 21 μg/dL, which is high for so-called “controls.” Fulton et al. (1987) provided evidence of changes in intellectual function at lower PbB in a study of 501 children, 6–9 years old from Edinburgh, Scotland, exposed to lead primarily

via drinking water. The geometric mean PbB of the study population was 11.5 μg/dL, with a range of 3.3–34 μg/dL and ten children had PbB >25 μg/dL. Multiple regression analyses revealed a significant relation between tests of cognitive ability and educational attainment (British Ability Scales [BAS]) and PbB after adjustment for confounding variables. The strongest relation was with the reading score. Stratification of the children into 10 groups of approximately 50 each based on PbB and plotting the group mean lead values against the group mean difference from the school mean score revealed a dose-effect relationship extending from the mean PbB of the highest lead groups (22.1 μg/dL) down through the mean PbB of the lowest-lead group (5.6 μg/dL), without an obvious threshold. It should be mentioned, however, that the size of the effect on the score was small compared with the effect of other factors. For the combined BAS score, only 0.9% of a total 45.5% variance explained by the covariates in the optimal regression model could be attributed to the effect of lead.

Needleman et al. (1979) examined the relationship between intellectual function and lead in dentin in a group of 158 first- and second-grade children. In comparison with children having dentin lead levels <10 ppm, children having dentin lead levels >20 ppm had significantly lower full-scale WISC-Revised scores; IQ deficits of approximately 4 points; and significantly poorer scores on tests of auditory and verbal processing, on a test of attention performance, and on a teachers' behavioral rating. A concentration of lead in dentin of 20 ppm corresponds to a PbB of approximately 30 μg/dL (EPA 1986a). Further analysis of Needleman's data showed that for children with elevated lead levels, the observed IQ was an average 3.94 points below the expected based on their mother's IQ scores, whereas for children with low lead levels, it was 1.97 points greater than the expected IQ (Bellinger and Needleman 1983). This meant that the children in the elevated lead group had a lower mean IQ than those in the low lead group when maternal IQ was partialled out. When 132 children from the initial study were reexamined 11 years later, impairment of neurobehavioral function was still related to the lead content of teeth shed at the ages of 6 and 7 years (Needleman et al. 1990). Higher lead levels in childhood were significantly associated with lower class standing in high school, increased absenteeism, lower grammatical-reasoning scores, lower vocabulary, poorer hand-eye coordination, longer reaction times, and slower finger tapping. However, no significant associations were found with the results of 10 other tests of neurobehavioral functioning. These later effects could stem from a poor academic start as opposed to effects of lead exposure; however, it could also be that the early lead exposure resulted in long-term consequences. Other studies of lead dentin and intellectual functions support Needleman's findings in that deficits have not been found below lead dentin concentrations of approximately 10 ppm (Damm et al. 1993; Hansen et al. 1989; Pocock et al. 1987). The association between bone lead and intellectual function also has been studied. A study of 156 male adolescents, 11–14 years of age, in the Pittsburgh school system reported

that increasing bone lead levels (10–53 ppm) was significantly associated with poorer performance on complex language processing tasks (e.g., 4-syllable Nonword Repetition Task, subset 8 of Revised Token Task, responding to spoken commands) (Campbell et al. 2000b). Covariates considered in the analysis included child age, race, SES, and maternal IQ.

Low Lead Level and Intellectual Function. Several studies have been published in recent years that support the view that there is no apparent threshold in the relationship between PbB and neurobehavioral functions. Most of these studies have been cross-sectional studies with the inherent limitation that such type of study of school-age children might reflect latent damage done by a higher PbB at an earlier age, which could only be reliably detected at school age. However, recent data from Chen et al. (2005) showed that the effect of concurrent PbB on IQ may be greater than currently believed. These investigators analyzed data from a clinical trial of 780 children who were treated for elevated PbB (20–44 μg/dL) at approximately 2 years of age and followed until 7 years of age with serial IQ tests and measurements of PbB. Mean PbB at 5 and 7 years of age was 12 and 8 μg/dL, respectively. The results showed that concurrent PbB always had the strongest association with IQ and, as the children aged, the relationship grew stronger. The peak PbB from baseline (approximately 2 years old) to 7 years of age was not associated with IQ at 7 years of age. Futhermore, in the model including both prior and concurrent PbB, concurrent PbB was always more predictive of later IQ scores. The results were interpreted as support for the idea that lead exposure continues to be toxic to children as they reach school age, and that not all of the damage is done by the time the child is 2 or 3 years old.

Lanphear et al. (2000a) analyzed data on blood lead concentrations and various assessments of cognitive abilities conducted on 4,853 U.S. children, ages 6–16 years, as part of the NHANES III, 1988–1994. Four cognitive measures were tested: arithmetic skills, reading skills, nonverbal reasoning (block design), and short-term memory (digit span). Potential confounders that were assessed included gender, racial/ethnic background, child's serum ferritin levels, serum cotinine level, region of the country, marital status and education level of primary caregiver, and poverty index ratio. Although no data were available on important potential confounding factors such as maternal IQ or direct observations of caretaking quality in the home, control for the poverty index ratio and education of the primary caregiver may have served as surrogate. The geometric mean PbB of the sample was 1.9 μg/dL and 2.1% exceeded 10 μg/dL. After adjustment for potential covariables, an inverse association between PbB and cognitive scores was evident, which was significant for all end points when PbBs of only <10 μg/dL were included in the analysis. When the PbB range was restricted to <7.5 μg/dL, the inverse relationship was significant for

arithmetic skills, reading skills, and nonverbal reasoning; when restricted to <5.0 μg/dL, the inverse relationship was significant for arithmetic skills and reading skills.

Canfield et al. (2003) reported the results of evaluations of 172 children from the Rochester Longitudinal Study. Fifty-eight percent of the children had PbBs below 10 μg/dL. PbB was measured at ages 6, 12, 24, 36, 48, and 60 months. IQ of children was assessed with the Stanford-Binet Intelligence Scale at the age of 3 and 5 years. The highest mean PbB was observed at age 2 years (9.7 μg/dL) and the lowest at the age of 6 months (3.4 μg/dL). The mean PbB at 5 years of age was 6.0 μg/dL. After adjustment for covariables, an increase in lifetime average PbB of 1 μg/dL was associated with a decrease in IQ of 0.46 IQ points (95% CI=-0.76–0.15). Similar findings were obtained when the children were tested at 3 and 5 years of age. When the analysis was limited to children whose highest observed PbB were <10 μg/dL, an increase in the lifetime average PbB of 1 μg/dL was associated with a decrease in IQ of 1.37 IQ points (95% CI=-2.56–0.17). The results also showed a nonlinear relationship between IQ and PbB (i.e., an increase from 1 to 10 μg/dL was associated with a decline of 8.0 points in IQ, whereas, an increase from 10 to 30 μg/dL was associated with a decline of approximately 2.5 points). At the age of 5.5 years, the children were given the Working Memory and Planning Battery of the Cambridge Neuropsychological Test Automated Battery to evaluate specific cognitive functions (Canfield et al. 2004). The results showed that children with the greatest exposure performed more poorly on tests of spatial working memory, spatial memory span, intradimensional and extradimensional shifts, and an analog of the Tower of London task.

Evidence for absence of a lower-bound threshold for postnatal lead exposure also was provided in a study of 237 African-American, inner-city children 7.5 years of age with a current mean PbB of 5.4 μg/dL (Chiodo et al. 2004). The children were assessed in areas of intelligence, reaction time, visual-motor integration, fine motor skills, attention (including executive function), off-task behaviors, and teacher-reported withdrawn behaviors. A total of 21 variables were considered as potential confounders. Multiple regression analysis showed negative association with lead exposure in the areas of overall IQ, performance IQ, reaction time, visual-motor integration, fine motor skills, and attention including executive function, off-task behaviors, and teacher-reported withdrawn behavior. Regression analyses in which lead exposure was dichotomized at 10 μg/dL were no more likely to be significant than analyses dichotomizing exposure at 5 μg/dL. Chiodo et al. (2004) indicated that data on maternal and child nutritional status, including iron deficiency, were not available so that their possible influence on the association between lead neurobehavioral outcomes could not be controlled.

Kordas et al. (2006) studied the association between lead and cognitive function in 594 first-grade children exposed to lead from a metal foundry in Torreón, Mexico. Their ages ranged from 6.2 to 8.5 years and their mean PbB was 11.4 μg/dL (SD±6.1 μg/dL). Fifty-one percent of the children had PbBs ≥10 μg/dL. Children were assessed on performance on 14 tests of global or specific cognitive function. Examiners were experienced testing children and were unaware the children's PbB. The nature of the lead-cognition relation was described using both linear and spline (segmented) regression methods. Covariates included in the analyses were age, gender, SES, maternal formal education, parental involvement in schooling family structure, birth order, arsenic exposure, and hemoglobin concentration. Also, all models were adjusted for the tester administering cognitive tasks and the school each child attended. After adjusting for covariates, PbB was significantly associated ($p<0.05$) with poorer scores measuring math abilities, vocabulary, and visual short-term memory. Using segmented regressions, the investigators observed that the slope describing the associations of PbB with the math and vocabulary test scores below a cutoff of 12 and 10 μg/dL, respectively, were steeper than slopes above those cutoff points. Examination of segmented lead coefficients using a stratified analysis at various levels of covariates showed that the pattern of steeper estimates at low PbBs vs. higher PbBs was generally conserved. Furthermore, the data showed that the nonlinear relationship was most pronounced for children who already tended to be at risk for poorer performance (fewer family resources, lower maternal education, and lower parental involvement in school work). Although some important covariates such as HOME inventory and maternal IQ were not controlled for in the study, control for other family background characteristics may have served as surrogates.

Using data from a prospective study conducted in Mexico City, Mexico, Téllez-Rojo et al. (2006) evaluated the relationship between PbB and neurodevelopment in 294 children at 12 and 24 months of age. Two cohorts comprised the sample: one recruited at the time of delivery and another recruited prenatally. To be included in the study, children needed to have a PbB <10 μg/dL at both 12 and 24 months of age, a gestation age of 37 weeks or longer, and a birth weight >2,000 g. MDI and PDI scores of a Spanish version of the Bayley Scales of Infant Development II (BSID II) were the primary dependent variables. Non-lead variables that were related to BDID II scores at $p<0.1$ in bivariate analysis were included in multivariate models. Also included in the multivariate models were maternal age and IQ and children's gender and birth weight. Adjusting for covariates, children's PbBs at 24 months were significantly inversely associated ($p<0.01$) with both MDI and PDI scores at 24 months. PbB at 12 months of age was not associated with concurrent MDI or PDI, or with MDI scores at 24 months of age, but was significantly associated ($p<0.01$) with PDI scores at 24 months. An increase of 1 logarithmic unit in 24-month PbB was associated with a reduction of 4.7 points in MDI score at

24 months. For both the MDI and PDI scores at 24 months of age, the coefficients that were associated with PbB were significantly larger ($p \leq 0.01$) among children with PbBs <10 μg/dL than in children with PbBs >10 μg/dL. Moreover, for MDI scores, the slope of the association was steeper over the range up to 5 μg/dL than between 5 and 10 μg/dL.

Perhaps the strongest evidence for an association between low PbB and intellectual impairment in children as well as for a nonlinear dose-response is provided by a pooled analysis of 1,333 children who participated in seven international prospective cohort studies and were followed from birth or infancy until 5–10 years of age (Lanphear et al. 2005). The participant sites included Boston, Massachusetts; Cincinnati, Ohio; Cleveland, Ohio; Rochester, New York; Mexico City; Port Pirie, Australia; and Kosovo, Yugoslavia. The full-scale IQ score was the primary outcome measured. The median lifetime PbB was 12.4 μg/dL (5^{th}–95^{th} percentiles, 4.1–34.8 μg/dL), while the concurrent mean PbB was 9.7 μg/dL (5^{th}–95^{th} percentiles, 2.5–33.2 μg/dL); 244 children (18%) had PbBs that never exceeded 10 μg/dL. Four measures of blood lead were examined: concurrent PbB (PbB closest to the IQ test), maximum PbB (peak PbB measured at any time before IQ test), average lifetime PbB (mean PbB from 6 months to concurrent PbB tests), and early childhood PbB (mean PbB from 6 to 24 months). In the subsequent analyses, concurrent PbB and average lifetime PbB were generally stronger predictors of lead-associated intellectual deficits than the other two indices. Potential confounding effects of other factors associated with IQ scores were examined by multiple regression analysis and included HOME inventory, child's sex, birth weight, birth order, maternal education, maternal IQ, maternal age, marital status, prenatal smoking status, and prenatal alcohol use. Using various models, including the linear model, cubic spline function, the log-linear model, and the piece-wise model, Lanphear et al. (2005) determined that the nonlinear model was a better fit for the data. Using a log-linear model, the investigators found a 6.9 IQ point decrement (95% CI, 4.2–9.4) for an increase in concurrent PbB from 2.4 to 30 μg/dL. However, the decrease in IQ points was greatest in the lowest ranges of PbB. The estimated IQ decrements associated with increases in PbB of 2.4–10, 10–20, and 20–30 μg/dL were 3.9 (95% CI, 2.4–5.3), 1.9 (95% CI, 1.2–2.6), and 1.1 (95% CI, 0.7–1.5), respectively. To further investigate whether the lead-associated decrement was greater at lower PbBs, the investigators divided the data at two cut-off points *a priori*, a maximal PbB of 7.5 and 10 μg/dL. They then fit separate linear models to the data in each of those ranges and compared the PbB coefficients for the concurrent PbB index. The coefficient for the 103 children with maximal PbB <7.5 μg/dL was significantly greater than the coefficient for the 1,230 children with maximal PbB ≥7.5 μg/dL (linear β=-2.94 [CI 95%, -5.16–-0.71]) vs. -0.16 (95% CI, -2.4–-0.08). The coefficient for the 244 children who had maximal PbB<10 μg/dL was not significantly greater than that for 1,089 children who had maximal PbB ≥10 μg/dL. Potential limitations

acknowledged by the authors included the fact that the HOME inventory and IQ tests had not been validated in all cultural or ethnic communities, lack of examination of other predictors of neurodevelopmental outcomes such as maternal depression, and the unique limitations of each individual study.

A nonlinear relationship between first trimester of pregnancy blood lead and the MDI at 24 months was recently reported by Hu et al. (2006). In the study, the investigators measured lead in maternal plasma and whole blood lead during each trimester in 146 pregnant women in Mexico City. Measurements were also conducted in cord blood at delivery and when the infants were 12 and 24 months old. The primary outcome was the MDI scores at 24 months of age. The criteria for inclusion in the study were: child born with at least 37 weeks of gestational age; at least one valid measurement of plasma lead during any of the three visits made during pregnancy; complete information on maternal age and IQ; and child's PbB at 24 months, sex, weight, and height. Potential confounders included in the analyses were child's sex, PbB at 24 months of age, height for age and weight, and maternal age and IQ. Mean maternal PbB during the first, second, third trimester, and delivery ranged from 6.1 μg/dL (SD±3.2 μg/dL) to 7.3 μg/dL (SD±4.3 μg/dL); plasma lead during pregnancy ranged between 0.014 and 0.016 μg/dL. Mean PbB in the cord, at 12 months, and 24 months were 6.2 μg/dL (SD±3.9 μg/dL), 5.2 μg/dL (SD±3.4 μg/dL), and 4.8 μg/dL (SD±3.8 μg/dL), respectively. The results of the analyses showed that both maternal plasma and whole blood lead during the first trimester (but not in the second or third trimester) were significant predictors ($p<0.05$) of poorer MDI scores. Also, in models combining all three trimester measures and using standardized coefficients, the effect of first-trimester maternal plasma was substantially greater than the effects of second- and third-trimester plasma lead. A one standard deviation change in first-trimester plasma lead was associated with a reduction in MDI scores of 3.5 points ($p=0.03$). Inspection of the relationship between first-trimester plasma lead and MDI at 24 months showed that the slope was steeper at plasma lead levels corresponding to whole blood lead levels <10 μg/dL than at higher plasma lead concentrations, as observed also in the studies summarized above. As a possible explanation, Hu et al. (2006) speculated that lead might be affecting the process of neuronal differentiation, which is primarily a first-trimester event. Limitations of the study acknowledged by the investigators include the relatively small sample size, the lack of control for a measure of home conditions, and the fact that infant PbB at 24 months did not significantly predict lower MDI score (as observed, for example, in Téllez-Rojo et al. [2006]). Another recent study that reported an association between prenatal lead exposure and intellectual function is that of Schnaas et al. (2006) who reported that IQ of 6–10-year-old children decreased significantly ($p<0.0029$; 95% CI, -6.45–-1.36) only with increasing natural-log third trimester PbB, but not with PbB at other times during pregnancy or postnatal PbB measurements. However,

because their observations began after the 12th week of pregnancy, the effects of the first trimester PbB could not be examined. As with other studies, the dose-response PbB-IQ function was log-linear, with a steeper slope at PbB <10 μg/dL.

Other studies that have reported cognitive impairments associated with low lead exposure include Al-Saleh et al. (2001), Bellinger and Needleman (2003), Carta et al. (2003), Emory et al. (2003), Gomaa et al. (2002), and Shen et al. (1998). Although individually all of these studies have limitations, collectively, they support the association between low blood lead and intellectual impairment in children.

Major Prospective Studies. The Port Pirie, Australia, prospective study examined cohorts of infants born to mothers living in the vicinity of a large lead smelting operation in Port Pirie and infants from outside the Port Pirie area. The study population consisted initially of 723 singleton infants. The children were followed from birth to age 11–13 years old; at this later age, 375 children remained in the cohort. Maternal blood and cord lead levels were slightly, but significantly, higher in the Port Pirie cohort than in the cohort from outside Port Pirie (e.g., mean cord blood lead was 10 vs. 6 μg/dL). The main outcome measures were the Bayley Mental Developmental Index (MDI) at age 2 years, the McCarthy GCI at age 4 years, and IQ from the Wechsler Intelligence Scale at ages 7 and 11–13 years (Baghurst et al. 1987, 1992, 1995; McMichael et al. 1988, 1994; Tong et al. 1996). Covariates in the models included: child gender, birth weight, siblings, infant feeding style and duration of breast feeding; maternal IQ, age at child's birth and marital status; parental tobacco use; SES, and HOME score. Analysis of the associations between blood lead concentrations (tertiles) in children of ages 2 or 11–13 years, and developmental status showed that the covariate-adjusted differences in development scores between the top and bottom tertiles were 4 points on the MDI at age 2; 4.8 points on the McCarthy GCI at age 4; and 4.9 and 4.5 IQ points at age 7 and 11–13 years, respectively. At age 7 years, both prenatal and postnatal PbB were inversely associated with visual motor performance (Baghurst et al. 1995). Analysis of the relationship between individual changes in PbB and individual changes in measures of cognitive development during the life of the cohort found that the mean PbB in the children decreased from 21.2 μg/dL at age 2 years to 7.9 μg/dL at age 11–13 years; however, cognitive scores in children whose blood lead concentration declined the most were generally not improved relative to the scores of children whose PbB declined least (Tong et al. 1998). Changes in IQ and declines in PbB that occurred between the ages of 7 and 11–13 years suggested better cognition among children whose PbB declined most. The overall conclusion was that the cognitive deficits associated with exposure to lead in early childhood appeared to be only partially reversed by a subsequent decline in PbB. Throughout the various assessments, it was noted that children from disadvantaged backgrounds were more sensitive to the effects of lead than those of a higher

socioeconomic status, and that girls were more sensitive to the effects of lead than boys (Tong et al. 2000).

The Mexico City, Mexico, Prospective Study evaluated children born to mothers residing in Mexico City (Rothenberg et al. 1989, 1994a; Schnaas et al. 2000). The study recruited 502 pregnant women; 436 ultimately were included in the study. An analysis of a subset of 112 children for whom complete data were available for evaluation of GCI (McCarthy scales) at 6-month intervals between ages 36 and 60 months revealed significant associations between PbB and GCI, after adjusting for covariates. Mean PbBs were 10.1 μg/dL at 6–18 months, 9.7 μg/dL at 24–36 months, and 8.4 μg/dL at 42–54 months of age. Increasing PbBs at 24–36 months, but not 6–18 months or prenatal, were associated with significant declines in GCI at 48 months; increasing PbBs at 42–54 months were associated with decreased GCI at 54 months. Covariates included in the models were child gender, 5-minute Apgar score, birth weight, and birth order; maternal education and IQ; and family SES. HOME scores were not included and were assumed to have been accounted for by maternal IQ because of the strong correlation between the latter and HOME score. The main finding of this series of studies was that postnatal, but not prenatal, PbBs were associated with intellectual function and that the strength of the association between mean PbB and GCI increases with age up to 4 years, after which, it becomes less strong and continues to decrease.

The Yugoslavia Prospective Study evaluated children born to women from two towns in Kosovo, Yugoslavia; Kosovska Mitrovica (K. Mitrovica), the site of a lead smelter, refinery, and battery plant; and Pristina, a town 25 miles to the south of K. Mitrovica, which was considered not to have been impacted by industrial lead emissions (Factor-Litvak et al. 1991, 1999; Wasserman et al. 1992). A total of 1,502 women were recruited at mid-pregnancy: 900 women from Pristina and 602 from K. Mitrovica. A sample of 392 infants was selected for follow-up based on umbilical cord lead, town of residence, and parental education. The infants from K. Mitrovica were assigned to one of three groups based on cord PbB: low (<15 μg/dL), middle (15–20 μg/dL), and high (>20 μg/dL). Outcomes examined in the follow-up included measures of intelligence at ages 2 (MDI of the Bayley Scales), 4 (McCarthy Scales of Children's Abilities), and 7 years (Wechsler Intelligence Scale for Children-III), and behavior problems at age 3 (Child Behavior Checklist) and 12 years (Wechsler Intelligence Scale for Children-III). Covariates included in the models were child gender, birth weight, iron status (blood hemoglobin), siblings and ethnicity (language spoken in home); maternal age, education and Raven's test score; and HOME score. The geometric mean PbB in children in K. Mitrovica increased from 22.4 μg/dL, at birth, to 39.9 μg/dL, at age 4; in children from Pristina, it increased from 5.4 to 9.6 μg/dL over this same age range (Wasserman et al. 1994). PbB was significantly associated with poorer intellectual function at ages

2 years (Wasserman et al. 1992), 4 years (Wasserman et al. 1994), and 7 years (Wasserman et al. 1997). An increase in PbB from 10 to 30 μg/dL was predicted to be associated with loss in intellectual function of 2.5 points at age 2 years, 4.5 points at age 4 years, and 4.3 points at age 7 years. In both towns combined, PbB measured concurrently with the Child Behavior Checklist was associated with small increases in behavioral problems, which the authors considered small compared with the effects of social factors (Wasserman et al. 1998). In a subsequent publication, Wasserman et al. (2000a) observed that while postnatal elevations that occurred before the age of 2 years and continued afterwards were associated with the largest decrements in IQ (50% increase in postnatal lead associated with 2.71 point IQ loss), elevations in PbB that occurred only after the age of 2 years were also associated with decrements. Thus, prenatal and postnatal exposures that occurred at any time during the first 7 years were independently associated with small decrements in later IQ scores (Wasserman et al. 2000a); identification of a particularly critical period of vulnerability during brain growth and maturation within this age range was not evident from this analysis.

In addition, evaluation of 283 children at the age of 54 months showed that PbB was significantly associated with poorer fine motor and visual motor function, but was unrelated to gross motor coordination. An estimated 2.6 and 5.8% of the variance in fine motor composite and visual motor integration was due to PbB, respectively. At age 12, the assessment of the children included measurements of tibial bone in addition to current PbB (Wasserman et al. 2003). At this age, mean PbB in the exposed children was approximately 31 μg/dL and mean tibial bone lead was 39 ppm, both measures significantly higher than those of a comparison group. Both bone lead and PbB were associated with intelligence decrements, but the bone lead-IQ associations were stronger than those for PbB. For each doubling of tibial bone, Full Scale, Performance, and Verbal IQ decreased by an estimated 5.5, 6.2, and 4.1 points, respectively. Analyses conducted in a subsample stratified by quartiles showed that the greatest decrements in intelligence appeared to occur at relatively low lead exposure, from quartile 1 to quartile 2. These transitions corresponded to tibial lead up to 1.85 ppm, mean serial PbB up to 7 μg/dL, and current PbB up to 5.6 μg/dL.

The Boston, Massachusetts, study examined the association between lead exposure and neurobehavioral parameters in 249 middle-class and upper-middle class Boston children (Bellinger et al. 1984, 1985a, 1985b, 1986a, 1986b, 1987a, 1987b, 1989a, 1989b, 1991, 1992). Cord PbBs were determined at delivery and MDI and PDI scores were measured every 6 months thereafter. Infants born at <34 weeks of gestation were excluded from the study. Cord PbBs were <16 μg/dL for 90% of the subjects, with the highest value being 25 μg/dL. On the basis of cord PbBs, the children were divided into low-dose

(<3 μg/dL; mean, 1.8 μg/dL), medium-dose (6–7 μg/dL; mean, 6.5 μg/dL), and high-dose (≥10 μg/dL; mean, 14.6 μg/dL) exposure groups. Multivariate regression analysis revealed an inverse correlation between cord PbB and MDI scores at 6, 12, 18, and 24 months of age (Bellinger et al. 1985a, 1985b, 1986a, 1986b, 1987a). The high-lead group had an average deficit of 4.8 points on the covariate-adjusted MDI score as compared with the low-lead group. MDI did not correlate with postnatal PbB lead levels. No correlations between PDI and cord or postnatal blood lead levels were seen. Subsequent studies of this cohort showed that the younger the infants, the more vulnerable they are to lead-induced developmental toxicity (Bellinger et al. 1989a, 1989b). Infants in lower socioeconomic groups showed deficits at lower levels of prenatal exposure (mean PbB, 6–7 μg/dL) than children in higher socioeconomic groups. The early postnatal PbBs (range, 10–25 μg/dL) were also associated with lower MDI scores, but only among children in lower socioeconomic groups. Evaluation of the children at approximately 5 years of age showed that deficits in GCI scores correlated significantly with PbB at 24 months of age (mean 7 μg/dL), but not with prenatal PbB (Bellinger et al. 1991). These results suggest that prenatal PbB is a better predictor of cognitive development in infants than in 4–5-year-old children and that early developmental deficits associated with elevated PbB may not persist to 4–5 years of age, especially in socioeconomically advantaged families. Evaluation of 148 of the Boston cohort children at age 10 years showed that all postnatal blood lead levels were inversely associated with Full Scale IQ measured at age 10; however, only the associations involving PbB at ages 10 years, 57 months, and 24 months were statistically significant (Bellinger et al. 1992). This was also seen for both Verbal and Performance IQ scores. After adjusting for confounding, only the coefficient associated with 24-month blood lead level remained significant. It was also shown that the association between 24-month PbB and Full Scale IQ at age 10 years was not due simply to the high correlation between GCI scores at age 5 years and IQ. The decline in Full Scale IQ corresponded to 5.8 points per 10 μg/dL of increase in 24-month PbB. PbB at 24 months was also significantly associated with Verbal IQ and five WISC-R subtest scores. Only PbBs at 24 months were significantly associated with adjusted K-TEA scores. For each 10 μg/dL of increase in 24-month PbB, the battery composite score declined 8.9 points. The results suggested that timing of exposure may be more important than magnitude alone and supported the hypothesis of an age-specific vulnerability. Reanalyses of data, from 48 children whose PbB never exceeded 10 μg/dL at birth or at any of the evaluations throughout the study, showed that an inverse association between IQ and PbB persisted at PbBs below 5 μg/dL and that the inverse slope was greater at lower PbBs than at higher PbBs (Bellinger and Needleman 2003).

The Cincinnati, Ohio, study sample consisted of 305 mothers residing in predesignated lead-hazardous areas of the city (>80% black) (Dietrich et al. 1986, 1987a, 1987b). Maternal PbBs were measured at the

first prenatal visit; cord PbB was measured at delivery; infant PbB was measured at 10 days and at 3 months of age; and neurobehavioral tests were performed at 3 and 6 months of age. Mean PbBs were as follows: prenatal (maternal), 8.0 μg/dL (range, 1–27 μg/dL); umbilical cord, 6.3 μg/dL (range, 1–28 μg/dL); 10-day-old and 3-month-old infants, 4.6 and 5.9 μg/dL (range, 1–22 μg/dL for each). Multiple regression analyses, with perinatal health factors such as birth weight and gestational age treated as confounders, showed inverse correlations between prenatal or cord PbB and performance on the MDI at 3 months, and between prenatal or 10-day neonatal PbB and performance on the MDI at 6 months. No significant correlation of PbB with PDI was seen. Male infants and low socioeconomic status infants appeared to be more sensitive to the effect on the MDI. Multiple regression analyses for male or low socioeconomic status infants showed covariate-adjusted decrements of 0.84 or 0.73 MDI points per μg/dL of prenatal or 10-day neonatal PbB, respectively (i.e., an approximate 8-point deficit for a 10-μg/dL increase in PbB) (Dietrich et al. 1987a). Cognitive development of 258 children was assessed by the Kaufman Assessment Battery for Children (K-ABC) when the children were 4 years old (Dietrich et al. 1991). Higher neonatal PbBs were associated with poorer performance in all K-ABC subscales; however, there was a significant interaction between neonatal PbB and socioeconomic status, which suggested that children from less advantaged environments express cognitive deficits at lower PbBs than do children from families of relatively higher socioeconomic status. Prenatal (maternal) PbBs were not related to 4-year cognitive status. No statistically significant effects of postnatal PbB on any of the K-ABC subscales was found after covariate adjustment. Evaluation of 253 children at 6.5 years of age showed that when PbB regression coefficients were adjusted for HOME score, maternal IQ, birth weight, birth length, child sex, and cigarette consumption during pregnancy, postnatal PbB continued to be associated with lower Performance IQ (Dietrich et al. 1993a). Also, examination of the PbB concentration for the group from 3 to 60 months of age showed that PbB peaked at approximately 2 years of age and declined thereafter. It was also found that, of the various cofactors, maternal IQ was usually the strongest predictor of a child's Full Scale IQ. Further analysis of the results suggested that average lifetime PbB concentrations in excess of 20 μg/dL were associated with deficits in Performance IQ on the order of about 7 points when compared with children with mean PbB concentrations ≤10 μg/dL. At 72 months of age, 245 children were evaluated for motor development status (Dietrich et al. 1993b). The authors hypothesized that measures of motor development may be less confounded with socio-hereditary cofactors in lower socioeconomic status populations than cognitive or other language-based indices. After adjusting for HOME scores, maternal IQ, social class, and child sex and race, both neonatal and postnatal PbB were associated with poorer performance on a measure of upper-limb speed and dexterity and a composite index of fine motor coordination. Prenatal (maternal) PbB was not related to motor proficiency. Further analysis of the results revealed that children having a mean lifetime PbB of ≥9 μg/dL

appeared to experience a deficit on both the Bilateral Coordination subtests and Fine Motor Composite relative to children in the lowest PbB quartile. Information collected at approximately 6.5, 11, and 15 years of age showed that children with the highest PbB at age 15 years (mean, 2.8 μg/dL; range, 1–11.3 μg/dL) had lower verbal comprehension scores over time and greater decline in their rate of vocabulary development at age 15 than children with lower PbB (Coscia et al. 2003). The study also showed that socioeconomic status and maternal intelligence were statistically significantly associated with growth patterns in both tests scores, independent of the effects of lead. The most recent publication in this series provides the results of a neuropsychological evaluation of 195 adolescents age 15–17 years old from this cohort (Ris et al. 2004). The neuropsychological tests yielded five factors labeled Memory, Learning/IQ, Attention, Visual Construction, and Fine-Motor. The results showed a significant effect of PbB at 78 months on the Fine-Motor factor. The results also showed a stronger association between lead exposure and Attention and Visuoconstruction in males than in females. The study also confirmed that adolescents from disadvantaged homes had increased vulnerability toward the effects of lead.

The Cleveland, Ohio, study evaluated neurodevelopmental effects in a sample of urban, disadvantaged, mother-infant pairs (33% black) (Ernhart et al. 1985, 1986, 1987). The mean PbBs at the time of delivery were 6.5 μg/dL (range, 2.7–11.8 μg/dL) for 185 maternal samples and 5.8 μg/dL (range, 2.6–14.7 μg/dL) for 162 cord samples. There were 132 mother-infant pairs with complete data. The infants were evaluated for anomalies using a systematic, detailed protocol and for neurobehavioral effects using the NBAS and part of the Graham-Rosenblith Behavioral Examination for Newborns (G-R), including a Neurological Soft Signs scale. Hierarchical regression analysis was performed. No evidence of an association between PbB and morphological anomalies was found. Using the complete set of data, abnormal reflexes and neurological soft signs scales were significantly related to cord PbB and the muscle tonicity scale was significantly related to maternal PbB. Using data from the mother-infant pairs, the only significant association that was found was between the Neurological Soft Signs score and cord PbB, which averaged 5.8 μg/dL and ranged up to only 14.7 μg/dL; no association with maternal PbBs was seen (Ernhart et al. 1985, 1986). A later analysis related PbBs obtained at delivery (maternal and cord blood) and at 6 months, 2 years, and 3 years of age to developmental tests (MDI, PDI, Kent Infant Development Scale [KID], and Stanford-Binet IQ) administered at 6 months, 1 year, 2 years, and 3 years of age, as appropriate (Ernhart et al. 1987). After controlling for covariates and confounding risk factors, the only significant associations of PbB with concurrent or later development were an inverse association between maternal (but not cord) PbB and MDI, PDI, and KID at 6 months, and a positive association between 6-month PbB and 6-month KID. The investigators concluded that, taken as a whole, the results of the

21 analyses of correlation between PbB and developmental test scores were "reasonably consistent with what might be expected on the basis of sampling variability," that any association of PbB with measures of development was likely to be due to the dependence of both PbB and development on the caretaking environment, and that if low-level lead exposure has an effect on development, the effect is quite small. Ernhart et al. (1987) also analyzed for reverse causality (i.e., whether developmental deficit or psychomotor superiority in infants at 6 months of age contributes to increases in subsequent blood lead levels). No significant correlations were observed when covariates were controlled. Greene and Ernhart (1991) conducted further analyses of the 132 mother-infant pairs in the Cleveland Prospective Study searching for a potential relationship between prenatal lead exposure and neonatal size measures (weight, height, and head circumference) and gestational age. No such relationship was observed.

Table 3-5 presents a summary of the major prospective studies.

While the majority of the available studies of neurobehavioral effects of lead in children have observed associations between increasing lead burden and measures of cognitive development, a smaller number of studies failed to detect such effects. Harvey et al. (1988) found no significant correlation between PbB (mean 13 μg/dL) and measures of IQ in a study of 201 children 5.5 years of age in England. Similar results were reported by McBride et al. (1982), Smith et al. (1983), Lansdown et al. (1986), Ernhart and Greene (1990), Wolf et al. (1994), Minder et al. (1998), and Prpić-Majić et al. (2000). In the former five studies, the mean PbB was between 10 and 16 μg/dL, whereas in the Minder et al. (1998) and Prpić-Majić et al. (2000) studies, the mean PbBs were 4.4 μg/dL (range, 0.8–16 μg/dL) and 7.1μg/dL (range, 2.4–14.2 μg/dL), respectively. Finding diverging results in the assessment of such complex parameters is not totally unexpected given the differences in methodology and the statistical issues involved (see Chapter 2 for further discussion).

Meta-analyses. Needleman and Gatsonis (1990) did a meta-analysis of 12 studies, 7 of which used blood lead as a measure of exposure and 5 used tooth lead. Covariates examined by the studies were SES; parental factors (i.e., parent health score); parent IQ; parental rearing measures; perinatal factors (i.e., birth weight, length of hospital stay after birth); physical factors (i.e., age, weight, medical history), and gender. The t-value of the regression coefficient for lead was negative in all but one study, and ranged from -0.36 to 0.48 in the PbB group and from -3 to -0.03 in the tooth lead group. Their analysis also showed that no single study appeared to be responsible for the significance of the final finding. Somewhat unusual in this analysis is the fact that the evaluation is based on accumulated p values rather than accumulated effect sizes. Pocock et al. (1994) analyzed 5 prospective studies, 14 cross-sectional

Table 3-5. Major Prospective Studies of Intellectual Development in Children

Study cohort	Lead biomarker	Outcome measured	Results and main conclusions	Reference
592 Infants born to women living near a smelter in Port Pirie, Australia, followed from birth to age 11–13.	Mean cord PbB was 10 µg/dL; 21.2 µg/dL at age 2; 7.9 µg/dL at age 11–13	MDI, GCI, IQ	Four point difference in MDI score between top and bottom PbB tertiles at age 2; 4.8 point difference in GCI score at age 4; 4.5 IQ points difference at age 11–13. Deficits associated with lead were only partially reversed by decline in blood lead past infancy.	Baghurst et al. 1987, 1992, 1995; McMichael et al. 1988, 1994; Tong et al. 1996, 1998
112 Infants born to women in Mexico City, Mexico, followed at 6 months intervals between ages 6 and 60 months.	Mean PbB at 6–18 months was 10.1 µg/dL; 9.7 µg/dL at 24–63 months; 8.4 µg/dL at 42–54 months	GCI	Increasing PbB at 24–36 months associated with lowed GCI at 48 months; increasing PbB at 42–54 months associated with lower GCI at 54 months. Postnatal, but not prenatal PbB associated with intellectual function.	Rothenberg et al. 1989, 1994a; Schnaas et al. 2000
577 Infants born to women living near a lead smelter, refinery, and battery plant in K. Mitrovica, Yugoslavia, followed from birth to age 12.	Mean PbB at birth was 22.4 µg/dL; 39.9 µg/dL at age 4; 31 µg/dL at age 12; mean tibia lead was 39 ppm at age 12	MDI, GCI, WISC, IQ	PbB was associated with poorer MDI at age 2, GCI at age 4, WISC at age 7. Tibia lead showed stronger association with IQ decrements than PbB at age 12. Both prenatal and postnatal PbB independently associated with small decrements in IQ.	Factor-Litvak et al. 1991, 1999; Wasserman et al. 1992, 1994, 1998, 2000a, 2003
216 Middle- and upper-class Boston, Massachusetts, children followed from birth to age 10.	90% of cord PbB was <16 µg/dL; mean PbB of 7 µg/dL at 24 months	MDI, PDI, GCI, WISC, IQ	Inverse correlation between cord PbB and MDI scores at 6, 12, 18, and 24 months. No correlation between PDI scores and PbB. Lower GCI at age 5 correlated with PbB at age 2, but not prenatal PbB. Full scale IQ at age 10 associated with PbB at 24 months. Timing of exposure more important than magnitude alone.	Bellinger et al. 1984, 1985a, 1986b, 1987a, 1987b, 19889a, 1989b, 1991, 1992

Table 3-5. Major Prospective Studies of Intellectual Development in Children

Study cohort	Lead biomarker	Outcome measured	Results and main conclusions	Reference
305 Children born to women living in pre-designated lead-hazardous areas of Cincinnati, Ohio, followed to age 15–17.	Mean prenatal PbB was 8 µg/dL; cord PbB was 6.3 µg/dL; 5.9 µg/dL at 3 months; 2.8 µg/dL at age 15 years	K-ABC, MDI, PDI	Prenatal PbB inversely correlated with MDI at 3 and 6 months. Lower KABC scores at 4 years associated with higher neonatal PbB. Postnatal PbB associated with lower performance IQ at 6.5 years. Neonatal and postnatal PbB associated with altered motor development at age 6.	Coscia et al. 2003; Dietrich et al. 1986, 1987a, 1987b, 1991, 1993a, 1993b; Ris et al. 2004
389 Children born to urban disadvantaged women in Cleveland, Ohio followed from birth to 7 years old.	Mean PbB in cord was 5.8 µg/dL; mean prenatal PbB was 6.5 µg/dL	MDI, PDI, KID, NBAS, IQ	Neurological soft signs associated with cord PbB. Only maternal PbB at delivery (6.5 µg/dL) associated with MDI, PDI, and KID scores at 6 months. Dentine lead at 5 years associated with decreased verbal and full scale IQ.	Ernhart et al. 1985, 1986, 1987, 1988; Greene and Ernhart 1991

GCI = McCarthy General Cognitive Index; KABC = Kaufman Assessment Battery for Children; KID = Kent Infant Development Scale; MDI = Mental Developmental Index; NBAS = Brazelton Neonatal Behavioral Assessment Scale; PDI = Psychomotor Developmental Index; WISC = Weschler Intelligence Scale for Children

studies of blood lead, and 7 cross-sectional studies of tooth lead separately and together. Only studies published since 1979 were included in the analysis. Analyses of the prospective studies showed no association of cord blood lead or antenatal maternal blood lead with subsequent IQ. PbB at around age 2 had a small and significant inverse association with IQ, which was greater than that for mean PbB over the preschool years; the estimated mean change was -1.85 IQ points for a change in PbB from 10 to 20 μg/dL. For the cross-sectional studies of PbB, the combined estimate for mean change in IQ for a change in PbB from 10 to 20 μg/dL was -2.53 IQ points. For the cross-sectional studies of tooth lead, the mean change in IQ for a change in tooth lead from 5 to 10 μg/g was -1.03 IQ points. Comparison of the association with and without adjustment for covariates showed that, with few exceptions, adjusting reduced the association by <1.5 points. Analysis of the 26 studies simultaneously indicated that a doubling of PbB from 10 to 20 μg/dL or of tooth lead from 5 to 10 μg/g is associated with a mean deficit in Full Scale IQ of around 1–2 IQ points. A threshold below which there is negligible influence of lead could not be determined.

An analysis carried out by Schwartz (1994) included a total of eight studies, three longitudinal and five cross-sectional, relating blood lead to Full Scale IQ in school age children. To evaluate potential confounding, the baseline meta-analysis was followed by sensitivity analyses in order to contrast results across studies that differ on key factors that are potential confounders. The analyses showed an estimated decrease of 2.57 IQ points for an increase in PbB from 10 to 20 μg/dL. Analyses that excluded individual studies showed that no single study appeared to dominate the results. For longitudinal studies, the loss was 2.96 IQ points and for cross-sectional studies, the loss was 2.69 IQ points. For studies in disadvantaged populations, the estimated IQ loss was 1.85 IQ points versus 2.89 IQ points in nondisadvantaged populations. Also of interest in Schwartz's analysis was the fact that a trend towards a higher slope at lower blood lead levels was seen. Direct analysis of the Boston prospective study (Bellinger et al. 1992), which had the lowest mean PbB concentration (6.5 μg/dL) showed no evidence of a threshold for the effects of lead on IQ.

The European Multicenter Study (Winneke et al. 1990) combined eight individual cross-sectional studies from eight European countries that shared a common protocol with inherent quality assurance elements. A total of 1,879 children, age 6–11 years, were studied. PbB concentration was used as a measure of exposure, and the range was 5–60 μg/dL. The overall statistical analysis was done using a uniform predetermined regression model with age, gender, occupational status of the father, and maternal education as confounders or covariates. The results of the analyses showed an inverse association between PbB and IQ of only borderline significance ($p<0.1$), and a decrease of 3 IQ points was estimated

for a PbB increase from 5 to 20 μg/dL. Much higher and significant associations were found for tests of visual-motor integration and in serial choice reaction performance. Yet, the outcome variance explained by lead never exceeded 0.8% of the total variance. No obvious threshold could be located on the dose-effect curves.

A Task Group on Environmental Health Criteria for Inorganic Lead conducted separate meta-analyses on four prospective studies and four cross-sectional studies (IPCS 1995). The European Multicenter Study was one of the cross-sectional studies included in the analyses. The outcome measured was Full Scale IQ at age 6–10 years old, and the measure of exposure was PbB. In the analyses of prospective studies, when cumulative exposure rather than lead at a specific time was used as measure of exposure, the association between changes in PbB and changes in IQ did not reach statistical significance ($p>0.05$). However, weighing studies according to the inverse of their variance produced a weighed mean decrease in Full Scale IQ of 2 points for a 10 μg/dL increase in PbB. When PbB at specific times were considered, the inverse association varied from significant and very strong to less strong and of borderline significance, depending on the specific time chosen. Analyses of cross-sectional studies showed a significant inverse association between increase in PbB and decrease in IQ in only 2 out 10 studies; however, there was no evidence of statistical heterogeneity. The meta-analysis estimated that Full Scale IQ was reduced by 2.15 IQ points for an increase on PbB from 10 to 20 μg/dL. IPCS (1995) also confirmed the positive association between lead measures and indicators of social disadvantage. When social and other confounding factors are controlled, the effect in most cases was to reduce the strength of the association between lead measures and IQ without, however, changing the direction. IPCS (1995) concluded that their analysis revealed a consistency between studies which pointed towards a “collectively significant” inverse association between PbB and full-scale IQ. IPCS (1995) also noted that below the 10–20 μg/dL PbB range, “uncertainties increased, concerning firstly the existence of an association and secondly estimates of the magnitude of any putative association.”

Thacker et al. (1992) reviewed 35 reports from five prospective studies that examined the relationship between PbB and mental development in children. However, efforts to pool the data with meta-analytic techniques were unsuccessful because the methods used in the studies to analyze and report data were inconsistent. Specific issues mentioned by Thacker et al. (1992) included (a) IQ and PbB were not always measured at comparable times in different studies, (b) there were differences among studies in independent variable, data transformations, and statistical parameters reported, (c) results conflicted when measurement intervals were comparable, (d) patterns of regression and correlation coefficients were inconsistent, and (e) data were insufficient to interconvert the parameters reported.

Lead and Delinquent Behavior. The possible association between lead and antisocial behavior has been examined in several studies. In 1996, Needleman and coworkers published the results of a study of 301 young males in the Pittsburgh School System. After adjustment for covariates, the investigators found that bone lead levels at 12 years of age were significantly related to parents and teacher's Child Behavior Checklist ratings of aggression, attention, and delinquency. A later study from the same group of investigators reported the results of a case-control study of 194 youths aged 12–18, arrested and adjudicated as delinquent by the Juvenile Court of Allegheny County, Pennsylvania, and 146 non-delinquent controls from high schools in the city of Pittsburgh (Needleman et al. 2002). The association between delinquent status and bone lead concentrations was modeled using logistic regression. Also, separate regression analyses were conducted after stratification by race. Care was taken to insure that unidentified delinquents did not populate the control group. Bone lead was significantly higher in cases than in controls (11.0 vs. 1.5 ppm) and this also applied to both racial categories, white and African American. After adjusting for covariates and interactions, and removal of noninfluential covariates, adjudicated delinquents were 4 times more likely to have bone lead concentrations higher than 25 ppm than controls. Covariates included in the models were child race; parental education and occupation; absence of two parental figures in the home; number of children in the home; and neighborhood crime rate. Limitations of the study include the lack of blood lead data and definition of dose-effect relationships. Also, explicit information on SES factors was not provided and there were large differences in social confounders between cases and controls.

Dietrich et al. (2001) examined the relationships between prenatal and postnatal exposure to lead and antisocial and delinquent behaviors in a cohort study of 195 urban, inner city adolescents recruited from the Cincinnati Prospective Lead Study between 1979 and 1985. At the time of the study, the subjects were between approximately 15 and 17 years of age; 92% were African-American and 53% were male. The mean prenatal (maternal) PbB concentration was 8.9 μg/dL. Blood was sampled shortly after birth and on a quarterly basis thereafter, until the children were 5 years old. From birth to 5 years of age, 35% of the cohort had PbBs in excess of 25 μg/dL, 79% >15 μg/dL, and 99% >10 μg/dL. As adolescents, the mean PbB was 2.8 μg/dL. After adjustment for covariables that were independently associated with delinquent behavior, prenatal blood lead concentration was significantly associated with an increase in the frequency of parent-reported delinquent and antisocial behaviors, while prenatal and postnatal blood lead concentrations (i.e., at 78 months or childhood average) were significantly associated with an increase in the frequency of self-reported delinquent and antisocial behaviors, including marijuana use. Limitations of the study are the inclusion of only four variables in the covariate analysis despite the fact that nine

were selected, only total scores were reported omitting the results for all delinquency variables, and maternal levels but not cord levels were used in the analysis.

Two ecological investigations correlated leaded gasoline sales or ambient lead levels with crime rates. Stretesky and Lynch (2001) examined the relationship between air lead concentrations and the incidence of homicides across 3,111 counties in the Unites States. The estimated air lead concentrations across all counties ranged from 0 to 0.17 μg/m^3. After adjusting for sociologic confounding and nine measures of air pollution, they reported a 4-fold increase in homicide rate in those counties with the highest air lead levels compared to controls. Nevin (2000) found a statistical association between sales of leaded gasoline and violent crime rates in the United States after adjusting for unemployment and percent of population in the high-crime age group. As with most ecological investigations, the results are difficult to interpret because there are no measurements of individual exposure levels or controls of confounders.

Many of the behavioral deficits observed in children exposed to lead have been reproduced in studies in animals, particularly monkeys, and at similar blood lead levels. Such studies have suggested that the impaired performance on a variety of tasks is the result, at least in part, of a combination of distractibility, inability to inhibit inappropriate responding, and perseveration in behavior that are no longer appropriate. Behavioral tests that have been proven useful in this area of research include discrimination reversal, spatial delayed alternation, delayed matching to sample, and intermittent schedules of reinforcement. Representative studies are summarized below. Additional information can be found in reviews about this topic and references therein (Cory-Slechta 1995, 1997, 2003; Rice 1993, 1996a).

Rhesus monkeys treated orally from birth with doses of lead that produced PbBs ≥32 μg/dL for 5 months to 1 year showed impairment in a series of discrimination reversal tasks early in life and when they were tested at 33 months of age and at 49–55 months of age (Bushnell and Bowman 1979a, 1979b). The monkeys tested at 49–55 months of age had mean PbBs of 4, 5, and 6 μg/dL, for controls, low-dose, and high-dose monkeys, respectively. The corresponding mean PbBs during the year of treatment were 4, 32, and 65 μg/dL. Additional experiments were conducted in monkeys exposed to lower levels of lead that peaked at approximately 15 or 25 μg/dL, and then decreased to steady state PbBs of about 11 and 13 μg/dL, respectively (Rice 1985). At 3 years of age, the monkeys were tested on a series of nonspatial discrimination reversal problems with irrelevant form cues, which provided the opportunity to study distractibility. The results showed that the treated monkeys attended to irrelevant cues in a systematic way. This suggested that the treated monkeys were being distracted by the irrelevant cues to a greater degree than the controls. Similar conclusions were reached when these same monkeys were tested again

at 9–10 years of age on a series of spatial discrimination reversal tasks without irrelevant cues. Studies in which the dosing periods varied in order to evaluate possible sensitive periods of exposure showed that spatial and nonspatial tasks were affected differentially depending on the developmental period of lead exposure (Rice 1990; Rice and Gilbert 1990a). These studies also suggested that while exposure beginning after infancy produces impairment, continuous exposure during and after infancy magnifies the effects.

Spatial delayed alternation testing has provided evidence of perseverative behavior and inability to inhibit inappropriate responding. For example, Levin and Bowman (1986) dosed monkeys from birth to 1 year of age, a regimen that produced PbBs of approximately 80 μg/dL during most of the treatment period, although peak PbB reached near 300 μg/dL during the initial phase of treatment. Tests conducted when the monkeys were 5–6 years of age, when mean PbB was about 5μg/dL, indicated that the treated monkeys perseverated on an alternation strategy even when it was not rewarded. Inappropriate responding also was observed in monkeys that had much lower (11–13 μg/dL) steady state PbBs and were tested at 7–8 years of age (Rice and Karpinski 1988). Further studies to determine possible sensitive periods of exposure showed no significant difference in the degree of impairment on a spatial delayed alternation task among three groups of monkeys exposed at different times during development (Rice and Gilbert 1990b). One group of monkeys was dosed with lead from birth onward; another group was dosed from birth to 400 days of age, and a third group began to receive lead at 300 days of age; testing was conducted at that 6–7 years of age. Perseverative behavior has also been put in evidence in studies in monkeys using the delayed matching to sample paradigm (Rice 1984).

Further evidence that lead induces behavior that can be characterized as failure to inhibit inappropriate responding has been obtained using intermittent schedules of reinforcement, particularly, the fixed interval (FI) schedule of reinforcement. For instance, monkeys with a steady-state PbB of approximately 30 μg/dL tended to respond excessively or inappropriately (e.g., with more responses than controls during time-outs) when responses were not rewarded (Rice and Willes 1979). In addition, lead-treated monkeys with a steady-state PbB of 11 or 13 μg/dL were also slower to learn reinforcement schedule, which required a low rate of responding (Rice and Gilbert 1985). Similar observations were made in adult monkeys dosed with lead from birth, having a peak PbB of 115 μg/dL by 100 days of age and a steady state PbB of 33 μg/dL at 270 days of age (Rice 1992). Increases in response rate on FI performance have been seen in rats at comparable PbB to those in monkeys. For example, Cory-Slechta et al. (1985) reported that postweaning exposure of rats having PbBs of 15–20 μg/dL had a significantly higher rate of response and significantly shorter interval bar-press responses on a FI operant schedule of food

reinforcement than control rats. Similar results were obtained at higher exposure levels in a series of earlier studies (Cory-Slechta and Thompson 1979; Cory-Slechta et al. 1981, 1983). The same group of investigators also showed that rats exposed to lead after weaning and having a PbB of approximately 11 μg/dL showed inappropriate responding in a Fixed-Ratio (FR) waiting-for-reward paradigm (Brockel and Cory-Slechta 1998). Treated rats increased the response rates and decreased the mean longest waiting time than control rats.

Peripheral Neurological Effects in Children. Effects of lead on peripheral nerve function have been documented in children. Frank peripheral neuropathy has been observed in children at PbBs of 60–136 μg/dL (Erenberg et al. 1974). Of a total of 14 cases of childhood lead neuropathy reviewed by Erenberg et al. (1974), 5 also had sickle cell disease (4 were black), a finding that the authors suggested might indicate an increased susceptibility to lead neuropathy among children with sickle cell disease. Seto and Freeman (1964) reported signs of peripheral neuropathy in a child with a PbB of 30 μg/dL, but lead lines in the long bones suggested past exposures leading to peak PbB of ≥40–60 μg/dL and probably in excess of 60 μg/dL (EPA 1986a). NCV studies have indicated an inverse correlation between peroneal NCV and PbB over a PbB range of 13–97 μg/dL in children living near a smelter in Kellogg, Idaho (Landrigan et al. 1976). These data were reanalyzed to determine whether a threshold exists for this effect. Three different methods of analysis revealed evidence of a threshold for NCV at PbBs of 20–30 μg/dL (Schwartz et al. 1988). NCV in the sural and peroneal nerves from young adults exposed to lead during childhood (20 years prior to testing) while living near a lead smelter in the Silver Valley, Idaho, were not significantly different than in a control group. Current PbBs in the exposed and control groups were 2.9 and 1.6 μg/dL, respectively. Data from past blood lead surveillance indicated a mean childhood PbB of approximately 45 μg/dL.

Other Neurological Effects in Children. Several studies of associations between lead exposure and hearing thresholds in children have been reported, with mixed results. A study of 49 children aged 6–12 years revealed an increase in latencies of waves III and V of the BAEP associated with PbB measured 5 years prior to the tests (mean, 28 μg/dL) (Otto et al. 1985). The current mean PbB was 14 μg/dL (range, 6–59 μg/dL). Assessment of a group of children from the Mexico City prospective study revealed significant associations between maternal PbB at 20 weeks of pregnancy (geometric mean, 7.7 μg/dL; range, 1–31 μg/dL) and brainstem auditory evoked responses in 9–39-day-old infants, 3-month-old infants, and children at 67 months of age (Rothenberg et al. 1994b, 2000). In the most recent assessment, I–V and III–V interpeak intervals decreased as PbB increased from 1 to 8 μg/dL and then increased as PbB rose from 8 to 31 μg/dL. Rothenberg et al. (2000) hypothesized that the negative linear term was

related to lead effect on brainstem auditory pathway length, and that the positive term was related to neurotoxic lead effect on synaptic transmission or conduction velocity.

Robinson et al. (1985) and Schwartz and Otto (1987, 1991) provided suggestive evidence of a lead-related decrease in hearing acuity in 75 asymptomatic black children, 3–7 years old, with a mean PbB of 26.7 μg/dL (range, 6–59 μg/dL). Hearing thresholds at 2,000 Hertz increased linearly with maximum blood lead levels, indicating that lead adversely affects auditory function. These results were confirmed in an examination of a group of 3,545 subjects aged 6–19 years who participated in the Hispanic Health and Nutrition Survey (Schwartz and Otto 1991). An increase in PbB from 6 to 18 μg/dL was associated with a 2-dB loss in hearing at all frequencies, and an additional 15% of the children had hearing thresholds that were below the standard at 2,000 Hz.

Osman et al. (1999) found a significant association between blood lead concentration (2–39 μg/dL) and hearing thresholds in a group of 155 children ages 4–14 years, after adjustment for covariates. The association remained significant when the analysis was confined to 107 children who had blood lead concentrations below 10 μg/dL. Osman et al. (1999) also reported increased latency of wave I of the BAEP in children with PbB above 10 μg/dL compared to children with PbB below 4.6 μg/dL. Covariates included in the regression models were child gender age, Apgar score, absence of ear and nasopharynx pathologies; history of ear diseases, frequent colds, mumps, gentamycin use, or exposure to environmental noise; and maternal smoking during pregnancy. Increased BAEP interpeak latencies was also described in a study of Chinese children with a mean PbB of 8.8 μg/dL (range, 3.2–38 μg/dL) after controlling for age and gender as confounding factors (Zou et al. 2003).

In contrast with results of the studies mentioned above, Counter et al. (1997a) found no difference in hearing threshold between groups of children who had relatively low or higher exposures to lead (mainly from local ceramics glazing and automobile battery disposal). PbBs were 6 μg/dL (range, 4–12 μg/dL, n=14) and 53 μg/dL (10–110 μg/dL, n=62), respectively. In a separate study of the same cohort, Counter et al. (1997b) found normal wave latencies and neural transmission times, and no correlation between PbB and interpeak latencies in children with a median PbB of 40 μg/dL (range, 6.2–128.2 μg/dL). Furthermore, audiological tests showed normal cochlear function and no statistical relation between auditory thresholds and PbB concentration. Subsequent studies of these children showed no evidence that PbB affected the cochlea (Buchanan et al. 1999) or BAEP interpeak conduction (Counter 2002). It is worth noting that Counter and coworkers studied children in small villages in the Andes mountains who may not be very representative of the general population.

Studies in animals also have provided mixed results regarding exposure to lead and auditory function. Some monkeys dosed with lead from birth through 13 years of age had elevated thresholds for pure tones, particularly at higher frequencies (Rice 1997). These monkeys had a PbB of approximately 30 μg/dL until 10–11 years old and 50–70 μg/dL when they were tested at 13 years of age. Studies by Lasky et al. (1995) and Lilienthal and Winneke et al. (1996) in monkeys chronically exposed to lead and with moderate PbBs suggested that lead might be altering cochlear function. However, a more recent study by Lasky and coworkers showed that continuous exposure of monkeys beginning shortly after birth until 1–2 years old, resulting in PbB 35–40 μg/dL, had no significant effect on middle ear function, cochlear function, or auditory evoked potentials assessed at least 1 year after exposure to lead (Lasky et al. 2001c).

A study of 384 6-year-old German children with a geometric mean PbB concentration of 4.3 μg/dL (range, 1.4–17.4 μg/dL) from three environmentally contaminated areas in East and West Germany found significant lead-related deficits for two out of three visual evoked potentials (VEP) interpeak latencies after adjusting for confounding effects (Altmann et al. 1998). No association was found between PbB concentrations and VEP amplitudes. These results confirmed previous findings from the same group of investigators (Winneke et al. 1994). Altmann et al. (1998) also measured visual contrast sensitivity and found no significant association between this parameter and lead. Alterations in scotopic (rod-mediated) retinal function were reported in a group of 45 children (7–10 years old) participants in the Mexico City Lead Study (Rothenberg et al. 2002a). The association was significant only with lead measures during the first trimester of pregnancy and not with other periods during pregnancy or throughout postnatal development. The threshold for the effect was 10.5 μg/dL. Results from studies in animals are in general agreement with the findings in humans. For example, studies in rats exposed to lead via the mother's milk, which produced PbBs of approximately 19 μg/dL in the pups, reported reductions in retinal sensitivity attributed to selective alterations of the rods (Fox et al. 1991, 1997). Impairment of scotopic visual function was reported in monkeys treated with lead during the first year of life to produce mean PbBs of 55 or 85 μg/dL and tested 18 months later when PbBs had returned near controls levels (14 μg/dL) (Bushnell et al. 1977). Lilienthal et al. (1988) reported alterations in visual evoked potentials and in the ERG in monkeys exposed to lead during gestation and then for life, and tested at approximately 7 years old; at this time, the PbBs in the two treated groups were approximately 40 and 60 μg/dL. Alterations of the ERG under scotopic conditions were still present when the monkeys were tested again more than 2 years after termination of exposure (Lilienthal et al. 1994). Rice (1998) reported that life-time exposure of monkeys to lead producing steady-state PbBs between 25 and 35 μg/dL altered temporal

visual function, in six out of nine animals; however, there was no evidence of impairment of spatial visual function.

Bhattacharya et al. (1993) examined the effect of lead exposure on postural balance in 109 children from the Cincinnati Lead Program Project. The mean age of the children was 5.8 years and the geometric mean PbB for the first 5 years of life was 11.9 μg/dL (range, 5.1–28.2 μg/dL). Balance was assessed in a system that provided a quantitative description of postural sway by measuring the movement pattern of the body's center of gravity during testing. Sway area was significantly correlated with PbB in tests performed with the eyes closed, but not in a test performed with the eyes open. This led the authors to suggest that lead-induced sway impairment might be related to modifications of the functions of vestibular and proprioception systems, on which close-eye tests rely more. Sway length was significantly correlated with blood lead under all test conditions.

3.2.5 Reproductive Effects

A number of studies have examined the potential association between lead exposure and reproductive parameters in humans. The available evidence suggest that occupational and environmental exposure resulting in moderately high PbBs might result in abortion and pre-term delivery in women, and in alterations in sperm and decreased fertility in men.

Effects in Females. Female workers at a lead smelter in Sweden had an increased frequency of spontaneous miscarriage when employed during pregnancy (294 pregnancies, 13.9% ended in spontaneous abortion) or when employed at the smelter prior to pregnancy and still living within 10 km of the smelter (176 pregnancies, 17% ended in spontaneous abortion) (Nordstrom et al. 1979). The abortion rates in these two groups of pregnant women were significantly higher than in women who were pregnant before they became employed at the smelter and in women who became pregnant after employment but lived >10 km from the smelter. Although no environmental or biological monitoring for lead was available, women who worked in more highly contaminated areas of the smelter were more likely to have aborted than were other women. A nested control-case study of a cohort of 668 pregnant women in Mexico City showed that the risk of spontaneous abortion (defined as loss of pregnancy by gestation week 20) increased with increasing PbB (Borja-Aburto et al. 1999). Notably, there was a 1.13-fold increase in the risk of spontaneous abortion per μg/dL increase in PbB. Mean PbBs in cases and controls were 12.0 and 10.1 μg/dL, respectively.

Negative associations also have been reported. For instance, no association was found between PbBs and spontaneous abortions in a cohort of women living in Port Pirie, a lead smelter community in South Australia and the surrounding rural area and neighboring towns (Baghurst et al. 1987). Mean, midpregnancy PbBs in women living in Port Pirie or outside of the town were 10.6 μg/dL (n=531) and 7.6 μg/dL (n=171), respectively (Baghurst et al. 1987; McMichael et al. 1986). While no association was found between PbB and spontaneous abortions, 22 of 23 miscarriages and 10 of 11 stillbirths occurred among the Port Pirie residents, with only 1 miscarriage and 1 stillbirth occurring among residents outside Port Pirie. Maternal PbB was lower in the cases of stillbirth than in the cases of live birth, but fetal and placental levels in this and another study (Wibberley et al. 1977) were higher than in cases of normal birth. Davis and Svendsgaard (1987) suggested that these findings may be due to a transfer of lead from mother to fetus, which is toxic to the fetus. Alexander and Delves (1981) showed a reduction in maternal PbB during the progression of pregnancy and concluded that the reduction could not be explained by dilution of PbB in an increasing plasma volume. The authors suggested that lead was being transferred to placental or fetal tissues or eliminated from maternal blood via other pathways. The rates of spontaneous abortions were also compared in a prospective study of females living close to a lead smelter (midpregnancy mean PbB, 15.9 μg/dL; n=304) and females living 25 miles away (midpregnancy mean PbB, 5.2 μg/dL; n=335) (Murphy et al. 1990). Women were recruited at midpregnancy and their past reproductive history (first pregnancy; spontaneous abortion/fetal loss prior to 7th month; stillbirth/fetal loss from 7th month) was examined. The results indicated no difference between the two groups. The spontaneous abortion rates in women living close to the smelter or 25 miles away were 16.4 and 14.0%, respectively, but the differences were not statistically significant.

In the study of Australian women mentioned above, the rate of preterm delivery (delivery before the 37th week) was significantly higher in women living in the smelter town (566 pregnancies, 5.3% preterm deliveries; mean PbB, 11.2 μg/dL at the time of delivery) than in women not living in the town (174 pregnancies, 2.9% preterm deliveries; mean PbB, 7.5 μg/dL at the time of delivery) (McMichael et al. 1986). Similarly, Torres-Sánchez et al. (1999) observed that preterm births were almost 3 times more frequent in women with umbilical PbB ≥5.1 μg/dL than in women with PbB <5.1 μg/dL. In a study of 121 women biologically monitored for exposure to lead at the Finnish Institute of Occupational Health from 1973 to 1983, there was no evidence of alterations in the time-to-pregnancy (TTP) or decreased fecundability (Sallmen et al. 1995). Women were categorized as having very low exposure (PbB, <10 μg/dL), low exposure (PbB, between 10 and 19 μg/dL), or moderate-to-high exposure (PbB, ≥20 μg/dL).

Stillbirths have been reported in rats exposed to doses of lead that resulted in PbBs much higher than those reported in the studies in women mentioned above. Treatment of Sprague-Dawley rats with lead in the drinking water on gestation days 5–21 resulted in 19% incidence of stillbirth compared to 2% observed in a control group (Ronis et al. 1996). PbBs in the dams and offspring in this experiment were >200 μg/dL. In subsequent studies using a similar experimental protocol, the same group of investigators reported that treatment of rats with lead in the drinking water on gestation days 5–21 resulted in 28% incidence of stillbirth (Ronis et al. 1998b). The mean PbB level in the pups at birth in this exposure group was 197 μg/dL. In studies with female monkeys, exposure to lead in the drinking water for 75 months resulted in reduced circulating concentration of progesterone, suggesting impaired luteal function; however, treatment with lead did not prevent ovulation; the PbB was approximately 70 μg/dL (Franks et al. 1989). The monkeys also exhibited longer and more variable menstrual cycles and shorter menstrual flow. Female Cynomolgus treated daily for up to 10 years with gelatin capsules containing lead acetate had significantly suppressed circulating levels of LH, FSH, and estradiol although progesterone concentrations were not significantly affected (Foster 1992). PbB in these monkeys was approximately 35 μg/dL. Also, a study in rats showed that exposure to lead can enhance some parameters of estrogen stimulation, inhibit other estrogenic responses, and some responses remain unaltered (Tchernitchin et al. 2003). In that study, female rats were administered lead acetate every 3 days from age 7 days and until they were 19 days old; the PbB in these rats was approximately 47 μg/dL. Lead enhanced the estrogen-induced eosinophilia and reduced the estrogen-induced edema deep in the endometrial stroma of treated rats. In addition, lead altered the proportion of eosinophils in the different histological layers in the uterus. A recent study with human granulosa cell *in vitro* showed that incubation with lead reduced aromatase activity as well as P-450 aromatase and estrogen receptor β protein levels (Taupeau et al. 2003). P-450 aromatase converts C19 androgens to C18 estrogenic steroids and is essential for follicular maturation, oogenesis, ovulation, and normal luteal functions in females. Moreover, mice that lack the ability to synthesize endogenous estrogen suffer folliculogenic disruption and fail to ovulate and are thus infertile. Mice that lack the estrogen receptor β also have a poor reproductive capacity attributed to folliculogenesis blockade (Taupeau et al. 2003).

Effects in Males. A study of 2,111 Finnish workers occupationally exposed to inorganic lead showed a significant reduction in fertility relative to 681 unexposed men (Sállmen et al. 2000a). The risk ratio (RR) for infertility in exposed men appeared to increase with increasing PbB; thus, the RRs for the PbB categories 10–20, 21–30, 31–40, 41–50, and ≥51 μg/dL were 1.27, 1.35, 1.37, 1.50, and 1.90, respectively; however, there was no evidence of decreased fertility in couples who had achieved at least one pregnancy. Based on the latter finding, the authors suggested that lead exposure was not associated

with a delay in pregnancy. A significant reduction in fertility was observed in a group of 74 exposed workers (mean exposure period, 10.7 years; mean PbB, 46.3 μg/dL) relative to a control group of 138 men (mean PbB, 10.4 μg/dL) (Gennart et al. 1992b). Duration of exposure was associated with decreased fertility. A study of 4,256 male workers with PbB >40 μg/dL (sampled before 1986) or ≥25 μg/dL (sampled from 1981–1992) showed a reduction in the number of births relative to a control group of 5,148 subjects (Lin et al. 1996). Workers with the highest cumulative exposure to lead had the most marked reduction in fertility. A study of 163 Taiwanese male lead battery workers showed decreased fertility in men with PbB in the range of 30–39 and ≥40 μg/dL, but there was no significant reduction in fertility in men with PbB of ≤29 μg/dL (Shiau et al. 2004). There was no effect on fertility among men (n=229) employed in a French battery factory (Coste et al. 1991) or among Danish men (n=1,349) exposed to lead (mean PbB of a subset of 400 workers, 39.2 μg/dL) during the manufacture of batteries (Bonde and Kolstad 1997). There was weak evidence of increased time-to-pregnancy (TTP) in the wives of 251 occupationally-exposed men in Finland with PbB ranging from 10 to 40 μg/dL or higher (Sállmen et al. 2000b). The study included only couples who had at least one pregnancy and the association was limited to men whose wives were <30 years old. A study with similar exposure levels in 251 Italian men did not find an association between lead exposure in men and delayed TTP in their wives (Apostoli et al. 2000). There was no association between occupational exposure to lead and low fertility in a multi-country (Belgium, Finland, Italy, and England) study of 638 men exposed occupationally to lead (Joffe et al. 2003). Mean PbB in exposed men ranged from 29.3 to 37.5 μg/dL, but most were below 50 μg/dL. Although the evidence for reduced fertility is not conclusive, it appears that a threshold for fertility effects in men could be in the PbB range of 30–40 μg/dL.

Studies have shown that sperm quality is affected by occupational exposure to lead. Although there is some variation in the results, most of the available studies suggest that reductions in sperm concentration, indications of adverse effects on sperm chromatin, and evidence of sperm abnormalities may occur in men with mean PbB > 40 μg/dL but not in men with lower PbBs. A study of 81 lead smelter workers showed an association between PbB and sperm concentration (Alexander et al. 1998a). In addition, although PbB concentrations were not related to serum testosterone, a reduction in serum testosterone with increasing semen lead concentration was observed. In a study of 150 male workers with long-term lead exposure, men with a mean PbB of 52.8 μg/dL showed asthenospermia, hypospermia, and teratospermia (Lancranjan et al. 1975). These effects were not evident in two groups of men with mean PbBs of 41 or 23 μg/dL. The effect of lead was thought to be directly on the testes because tests for changes in gonadotropin secretion were negative. Secretion of androgens by the testes was not affected. A cross-sectional study of 149 industrial workers in Zagreb, Croatia, found that 98 men who had

moderate occupational exposure to lead (mean PbB, 36.7 μg/dL) had significantly lower sperm density, and lower counts of total motile and viable sperm; lower percentage and count of progressively motile sperm; higher prevalence of morphologically abnormal sperm head; and lower level of indicators of prostate secretory function compared with 51 referents (mean PbB, 10.3 μg/dL) (Telisman et al. 2000). No significant differences were found for semen volume or percentages of motile, viable, and pathologic sperm. Workers also had significantly higher serum estradiol than the refernce group, but there were differences in serum FSH, LH, prolactin, and testosterone levels (Telisman et al. 2000). A study of workers in a Swedish battery factory showed decreased seminal plasma constituents, low semen volumes, and reduced functional maturity of sperm in men with mean PbB of approximately 45 μg/dL during the study period (Wildt et al. 1983). The unexposed (control) group of men had a mean PbB of about 21 μg/dL. A study of men employed in a lead smelter showed that workers with current PbB of ≥40 μg/dL had an increased risk of below normal sperm and total sperm count relative to those with PbBs <15 μg/dL (Alexander et al. 1996). A cross-sectional survey of 503 European workers showed a 49% reduction in the median sperm concentration in men with PbB ≥50 μg/dL, whereas there was no significant difference in sperm concentration between the reference group of men (mean PbB, ≤10 μg/dL) and men with mean PbB of 10–50 μg/dL (Bonde et al. 2002). Although there was no association between PbBs and abnormal sperm chromatin, there were indications of deterioration of the sperm chromatin in men with the highest lead concentrations in spermatozoa (Bonde et al. 2002). Changes in sperm chromatin also have been reported in monkeys exposed to lead for life and with a mean PbB of 56 μg/dL (Foster et al. 1996). In mammalian spermatozoa, DNA is tightly packaged with protamines in the nucleus. Since lead binds tightly to free thiols, it might compete or replace the zinc atoms that are normally bound with nuclear protamines. These changes could affect normal disulfide bond formation, alter DNA-protamine binding, or impair chromatin decondensation during fertilization (Quintanilla-Vega et al. 2000; Silbergeld et al. 2003). Sperm protamine plays an important role in the condensation-decondensation events that are critical to fertilization, and cases of male infertility have been associated with deficiencies in human protamine (Quintanilla-Vega et al. 2000). A recent study from the latter group supported their earlier hypothesis that lead affects sperm chromatin condensation (Hernández-Ochoa et al. 2005). In a group of 68 urban men with a geometric mean PbB of 9.3 μg/dL (range, 1.9–24.4 μg/dL) 54% of semen samples showed values for sperm chromatin condensation outside the normal range. In addition, evaluation of semen quality parameters and sperm chromatin showed that sperm concentration, motility, morphology, and viability were negatively associated with lead in spermatozoa, whereas semen volume was negatively associated with lead seminal fluid. PbB did not associate with either semen quality parameters or nuclear chromatin decondensation, and PbB did not correlate with lead levels in any semen compartment (Hernández-Ochoa et al. 2005). Smaller studies (<40 men/study) of men exposed to

lead have also shown detrimental changes in sperm quality (Assennato et al. 1987; Chowdhury et al. 1986; Lerda 1992).

Direct toxic effects of lead on the testicle might mediate the adverse reproductive effects of lead in occupationally exposed men. A study of 122 workers (mean PbB, 35.1 μg/dL; mean exposure duration, 6 years) employed in three lead battery factories in Singapore showed higher serum LH and FSH concentrations in the exposed workers than in 49 unexposed individuals (mean PbB, 8.3 μg/dL) (Ng et al. 1991). However, there was no difference in testosterone levels between these two groups. Raised LH and FSH levels are an indication of Leydig and Sertoli cell failure (Ng et al. 1991). These results are in general agreement with those of earlier studies of lead workers with high PbBs (≥66 μg/dL). These findings indicate that lead can act directly on the testes to cause depression of sperm count and peritubular testicular fibrosis, reduced testosterone synthesis, and disruption of regulation of LH (Braunstein et al. 1978; Cullen et al. 1984; Rodamilans et al. 1988).

The question of whether lead poisoning as a child can have adverse reproductive effects later in life was examined in a group of 35 survivors of childhood plumbism who had been admitted to the Boston Children's Hospital for treatment from 1930 to 1944 (Hu 1991b). Plumbism was diagnosed in children who showed repeated ingestion of lead-containing material or x-ray or clinical evidence of lead poisoning. Although the rates of spontaneous abortions or stillbirths in this group of survivors appeared to be higher than in unexposed matched subjects, the differences were not statistically significant (RR, 1.60; 95% CI, 0.6–4.0).

Sperm parameters also have been examined in animals exposed to lead. Evaluation of 15–20-year-old Cynomolgus monkeys administered lead acetate for their lifetime and having a mean PbB of 56 μg/dL showed no significant alterations in parameters of semen quality such as sperm count, viability, motility, and morphology, or in circulating levels of testosterone (Foster et al. 1996). Adverse sperm effects have been observed in rats, but at relatively high PbBs (Barratt et al. 1989; Hsu et al. 1998a, 1998b). A significant reduction in the number of spermatozoa within the epididymis was observed in mice administered lead acetate in drinking water for 6 weeks, but PbBs were not provided (Wadi and Ahmad 1999). In male rats exposed maternally to lead during gestation and lactation and administered lead for an additional 9 months after weaning, there were no significant effects on sperm count or sperm morphology (Fowler et al. 1980). The PbB in these animals ranged from 4.5 to 67 μg/dL.

Numerous studies in animals have reported testicular effects following exposure to lead. For example, Foster et al. (1998) evaluated changes in testis ultrastructure, semen characteristics, and hormone levels in monkeys exposed to lead from postnatal day 300 to 10 years of age (postinfancy), from postnatal day 0 to 400 (infancy), or for their lifetime. PbBs in lifetime and postinfancy exposed monkeys were approximately 35 μg/dL compared to <1.0 μg/dL in controls and infancy exposed animals. Electron microscopic analysis revealed disruption of the general architecture of the seminiferous epithelium that involved Sertoli cells, basal lamina, and spermatids in the groups exposed for lifetime and during infancy, with equal severity. No such alterations were seen controls or in the postinfancy exposure group. The results showed that lead exposure in monkeys during infancy can induce testicular alterations that persist in later life when blood lead concentrations had decreased considerably. Circulating concentrations of FSH, LH, and testosterone were not altered by treatment with lead, and semen characteristics were not affected by treatment with lead. Other effects reported in recent studies in rats following oral dosing with lead include disorganization and disruption of spermatogenesis and reduction in the activities of the enzymes alkaline phosphatase and Na^+-K^+-ATPase (Batra et al. 2001), and an increase in the percentage of seminiferous tubules showing apoptotic germ cells (Adhikari et al. 2001). No PbBs were reported in these two studies. Also, male rats administered lead acetate in water for 1 week (PbB, 12–28 μg/dL) showed a dose-related increase in gonadotropin-releasing hormone (GnRH) mRNA (Sokol et al. 2002). However, lead did not have an effect on the serum concentrations of hypothalamic gonadotropin-releasing hormone (GnRH) or LH, suggesting a compensatory mechanism in the hypothalamic-pituitary axis. In the only study of exposure by the inhalation route, CD-1 male mice exposed to 0.01 M lead acetate intermittently for 4 weeks showed a time-related increase in the fraction of damaged mitochondria in Sertoli cells, which according to the investigators could lead to a transformation process that may interfere with spermatogenesis (Bizarro et al. 2003).

3.2.6 Developmental Effects

This section summarizes studies of the effects of lead exposure on end points other than neurological in developing organisms exposed during the period from conception to maturity. Neurodevelopmental effects are summarized in Section 3.2.4.

No reports were found indicating low levels of lead as a cause of major congenital anomalies. However, in a study of 5,183 consecutive deliveries of at least 20 weeks of gestation, cord blood lead was associated with the incidence of minor anomalies (hemangiomas and lymphangiomas, hydrocele, skin anomalies, undescended testicles), but not with multiple or major malformations (Needleman et al. 1984). In

addition, no particular type of malformation was associated with lead. According to the investigators, the results suggested that lead may interact with other teratogenic risk factors to enhance the probability of abnormal outcome.

Anthropometric Indices. Since the report by Nye (1929) of runting in overtly lead-poisoned children, a number of epidemiological studies have reported an association between PbB and anthropometric dimensions. For example, a study of 1-month-old Mexican infants found that infant PbB (measured at birth in umbilical cord and at 1 month of age) was inversely associated with weight gain, with an estimated decline of 15.1 grams per μg/dL of blood lead (Sanín et al. 2001). The mean infant (at 1 month) and maternal PbBs (1 month postpartum) were 5.6 and 9.7 μg/dL, respectively; mean umbilical cord lead was 6.8 μg/dL. They also found that children who were exclusively breastfed had significantly higher weight gains, but this gain decreased significantly with increasing levels of maternal patella lead. An additional study from the same groups of investigators reported that birth length of newborns decreased as maternal patella lead increased, and also that patella lead was significantly related to the risk of a low head circumference score (Hernandez-Avila et al. 2002). In the Mexico City Prospective Study, an increase in PbB at 12 months of age from 6 to 12.5 μg/dL was associated with a decrease in head circumference of 0.34 cm (Rothenberg et al. 1999c). Also, a study by Stanek et al. (1998) reported that in children aged 18–36 months, with a mean PbB of 6.4 μg/dL, PbB was inversely related with head circumference.

In the Cincinnati Prospective Study, higher prenatal PbB was associated with reduced birth weight and reduced gestational age (Dietrich et al. 1987a). Analyses of the data indicated that for each natural log unit increase in PbB, the decrease in birth weight averaged 114 g, but ranged from 58 to 601 g depending on the age of the mother (Bornschein et al. 1989). The investigators reported that the threshold for this effect could be approximately 12–13 μg/dL PbB. In addition, a decrease in birth length of 2.5 cm per natural log unit of maternal PbB was seen, but only in white infants. In a later report, the prenatal PbB (mean, 8.2 μg/dL; range, 1–27 μg/dL) was related to lower birth weight (Dietrich et al. 1989). PbBs ≥10 μg/dL also were significantly associated ($p<0.05$) with a decrease in total days of gestation and an increase risk of preterm and small-for-gestational-age birth in a sample of 262 mother-infant pairs from the general population in California (Jelliffe-Pawlowski et al. 2006). Lower mean birth weight and In a study of 705 women from Camden, New Jersey, with PbBs throughout pregnancy below 1.5 μg/dL, PbB showed no significant association with low birth weight, preterm delivery, Apgar scores, or small-for-gestational age (Sowers et al. 2002a). In contrast, in a study of 148 Russian mothers and 114 Norwegian mothers with maternal and cord PbBs as low as 1.2 μg/dL, PbBs had a negative impact on birth weight

and child's body mass index (BMI, weight in kg divided by the square of the height in meters) with or without adjusting for gestational age (Odland et al. 1999). In a study of 89 mother-infant pairs from Spain, higher placental lead levels were unrelated to smaller birth weight, head and abdominal circumference, or shorter length at birth (Falcón et al. 2003).

Analyses of data for 2,695 children ≤7 years old from the NHANES II study indicated that PbB (range, 4–35 μg/dL) was a statistically significant predictor of children's height, weight, and chest circumference, after controlling for age, race, sex, and nutritional covariates (Schwartz et al. 1986). The mean PbB of the children at the average age of 59 months appeared to be associated with a reduction of approximately 1.5% in the height that would be expected if the PbB had been zero. An analysis of data on PbB for 4,391 U.S. children, ages 1–7 years, recorded in the NHANES III (1988–1994) showed that increasing PbB (1–72 μg/dL) was significantly associated with decreasing body stature (length or height) and head circumference, after adjusting for covariates (Ballew et al. 1999). An increase in PbB of 10 μg/dL was associated with a 1.57 cm decrease in stature and a 0.52 cm decrease in head circumference. A study of 1,454 Mexican-American children aged 5–12 who were participants in the Hispanic Health and Nutrition Examination Survey (HHANES) conducted in 1982–1984 found that PbBs in the range of 2.8–40 μg/dL were related with decreased stature (Frisancho and Ryan 1991). The mean PbB in males and females was 10.6 and 9.3 μg/dL, respectively. Eighty-two percent of the variance in height in males was accounted by hematocrit and PbB; in females, the same 82% was accounted by age, poverty index, and PbB. After adjusting for these covariates, children whose PbB was above the median for their age and sex (9–10 μg/dL range) were 1.2 cm shorter than children with PbBs below the median. Angle and Kuntzelman (1989) also reported reduced rates of height and weight from birth to 36 months in children with PbB of ≥30 μg/dL.

Evaluation of 260 infants from the Cincinnati Prospective Study revealed that postnatal growth rate (stature) from 3 to 15 months of age was inversely correlated with increases in PbB during the same period, but this effect was significant only for infants whose mothers had prenatal PbB >7.7 μg/dL (Shukla et al. 1989). Reevaluation of 235 infants during the second and third years of life revealed that mean PbB during the second and third years was negatively associated ($p=0.002$) with attained height at 33 months of age (Shukla et al. 1991). However, this association was observed only among children who had mean PbBs greater than the cohort median (10.8 μg/dL) during the 3–15-month interval. It also appeared that the effect of lead exposure (both prenatal and during the 3–15-month interval) was transient as long as subsequent exposure was not excessive.

An absence of significant associations between lead exposure and anthropomorphic measures has also been reported. Evaluation of 359 mother-infant pairs from the Cleveland Prospective Study found no statistically significant effect of PbBs on growth from birth through age 4 years 10 months after controlling for a variety of possible confounding factors (Greene and Ernhart 1991). Also, a study of 104 children who suffered lead poisoning (PbB up to 470 μg/dL) between the ages of 16 and 55 months and underwent chelation therapy showed normal height when they were evaluated at 8 and 18 years of age (Sachs and Moel 1989). At age 18, all patients had PbBs <27 μg/dL. A study by Kim et al. (1995) found that bone lead was not associated with physical growth in a cohort of children followed longitudinally for 13 years. The children were first assessed in 1975–1978 and then in 1989–1990. However, the study found that dentin lead was positively associated with BMI as of 1975–1978 and increased BMI between 1975–1978 and 1989–1990. Confounders controlled for included age, sex, baseline body size, and mother's socioeconomic status. According to the investigators, the results suggested that chronic lead exposure during childhood may result in obesity that persists into adulthood.

As previously mentioned under *Musculoskeletal Effects*, studies in animals, mostly rats, indicate that oral lead exposure may impair normal bone growth and remodeling as indicated by decreased bone density and bone calcium content, decreased trabecular bone volume, increased bone resorption activity, and altered growth plate morphology (Escribano et al. 1997; Gonzalez-Riola et al. 1997; Gruber et al. 1997; Hamilton and O'Flaherty 1994, 1995; Ronis et al. 2001). Ronis et al. (2001) showed that in rats, exposure to lead reduced somatic longitudinal bone growth and bone strength during the pubertal period. These effects could not be reversed by a growth hormone axis stimulator or by sex appropriate hormone, suggesting that the lead effects are not secondary to growth hormone axis disruption. It should be mentioned that the blood lead levels achieved in the pups were in the range of 67–192 μg/dL.

Sexual Maturation. Two studies provide information on the effect of lead exposure on sexual maturation in girls. Selevan et al. (2003) performed an analysis of data on blood lead concentrations and various indices of sexual maturation in a group of 2,741 U.S. female children and adolescents, ages 8–18 years, recorded in the NHANES III (1988–1994). Increasing PbB was significantly associated with decreasing stature (height) and delayed sexual development (lower Tanner stage, a numerical categorization of female sexual maturity based on breast and pubic hair development), after adjusting for covariates. The geometric mean PbB among the three major race/ethnicity categories recorded in the NHANES III was 1.4 μg/dL (95% CI, 1.2–1.5) in non-Hispanic whites, 2.1 μg/dL (95% CI, 1.9–2.3) in African Americans, and 1.7 μg/dL (95% CI, 1.6–1.9) in Mexican Americans. ORs for differences in breast and pubic hair development, and age at menarche were significant in comparisons made at PbBs of 1 and 3 μg/dL in the

African American group. Delays in sexual development, estimated for Tanner stages 2–5, ranged from 4 to 6 months. ORs were significant for breast and pubic hair development, but not for age at menarche in the Mexican American group. Covariates included in the models were age, height, body mass index; history of tobacco smoking or anemia; dietary intakes of iron, vitamin C and calcium; and family income. Selevan et al. (2003) acknowledged that other factors associated with body lead burden and pubertal development that they did not assess may be responsible for the observed associations. In addition, they noted that reporting of past events, such as age at menarche and dietary history, could have been subject to errors in recall. Finally, potential confounders that were measured at the time of the study may have differed during periods critical for pubertal development or other unmeasured confounders may have affected the results.

An additional study of the same cohort also found a significant and negative association between PbB and delayed sexual maturation (Wu et al. 2003a). The study included 1,706 girls 8–16 years old with PbB ranging from 0.7 to 21.7 μg/dL. PbBs were categorized in three levels: 0.7–2, 2.1–4.9, and 5.0–21.7 μg/dL. Covariates included in the models were race/ethnicity, age, family size, residence in a metropolitan area, poverty income ratio, and body mass index. Girls who had not reached menarche or stage 2 pubic hair had higher PbBs than did girls who had. Among girls in the three levels of PbB mentioned above, the unweighted percentages of 10-year-old girls who had attained Tanner stage 2 pubic hair were 60, 51, and 44%, respectively, and for 12-year-old girls who reported reaching menarche, the values were 68, 44, and 39%, respectively. These negative relationships remained significant in logistic regression even after adjustment for the covariates mentioned above. Interestingly, no significant association was found between PbB and breast development, in contrast to the findings of Selevan et al. (2003) who used the same database. Wu et al. (2003b) concluded that although they found a significant negative association between low PbB and some markers of sexual maturation, judicious interpretation of the results is needed given the cross-sectional study sample and limited attention to other nutritional or genetic factors that may impact the findings.

Some studies have reported delays in sexual maturation in animals exposed to lead, although associated with PbBs much higher than those measured in girls in the Selevan et al. (2003) and Wu et al. (2003b) studies. For example, Grant et al. (1980) reported delayed vaginal opening in female rats exposed *in utero* and via lactation and then directly. PbBs in these female offspring ranged between 20 and 40 μg/dL. Exposure of male and female Sprague-Dawley rats prepubertally (age 24–74 days) to lead acetate in the drinking water resulted in significant reduction in testis weight and in the weight of secondary sex organs in males and in delayed vaginal opening and disruption of estrus cycle in females

(Ronis et al. 1996). However, these effects were not observed in rats exposed postpubertally (day 60–74 in males, 60–85 in females). Mean PbBs in rats exposed prepubertally and postpubertally were 57 and 31 μg/dL, respectively. In the same study, an additional group of rats was exposed during gestation and continuing through lactation and postpubertally. In this group, the effects were much more severe than in the rats exposed only pre- or postpubertally, and were consistent with the much higher PbB achieved in the offspring, approximately 316 μg/dL. In follow-up studies, it was found that prenatal lead exposure that continued until adulthood (85 days old) delayed sexual maturation in male and female pups in a dose-related manner (Ronis et al. 1998a, 1998b, 1998c). PbBs in the pups between the ages of 21 and 85 days were >100 μg/dL and reached up to 388 μg/dL. Effects at much lower PbBs were reported by Dearth et al. (2002), who treated Fisher 344 rats with lead by gavage from 30 days before mating until weaning the pups at 21 days of age. A cross-fostering design allowed the female pups to be exposed during gestation and lactation or during only one of those periods. PbB in the dams was about 38 μg/dL at breeding, peaked at about 46 μg/dL on lactation day 1, and decreased thereafter. Pups exposed during gestation and lactation had the highest PbB of 38.5 μg/dL on day 10; at this time, the PbBs in pups exposed during gestation only and lactation only were 13.7 and 27.6 μg/dL, respectively. By day 30, all three groups had PbBs ≤3 μg/dL. Vaginal opening as well as first diestrus was significantly delayed to similar extents in all treated groups. This delay was associated with decreased serum levels of insulin-like growth factor-1 (IGF-1), LH, and estradiol. Since liver IGF-1 mRNA was not affected, it appeared that lead altered translation and/or secretion of IGF-1, which in turn decreased LH-releasing hormone at the hypothalamic level. A subsequent study in both Sprague-Dawley and Fisher 344 rats (Dearth et al. 2004) showed that the latter strain is more sensitive to maternal lead exposure than Sprague-Dawley rats regarding puberty-related effects, which could, in part, explain the discrepancy with the effect levels reported by Ronis and coworkers. Results similar to those of Dearth et al. (2002) were reported in Swiss mice by Iavicoli et al. (2004). Female offspring of mice treated with various levels of lead in the diet during pregnancy, lactation, and then directly showed dose-related delay in sexual maturation. Blood lead levels of the dams were not determined; blood lead levels of the female offspring determined once at estrus (day 24–44) ranged from 0.7 to 13.2 μg/dL. Removing lead from the control diet (0.2 ppm Pb) reduced PbB in the offspring from 2–3 to 0.7 μg/dL and accelerated puberty from age 33–37 days to age 21 days.

Hematological Effects. The hypothesis that PbB might be associated with depressed erythropoietin (EPO) in children was examined in subjects from the Yugoslavia Prospective Study (Factor-Litvak et al. 1998; Graziano et al. 2004) (see Section 3.2.4 for a detailed description of the Yugoslavia Prospective Study). EPO is a glycoprotein hormone that regulates both steady-state and accelerated erythrocyte

production. Nearly all of the EPO is produced in the proximal tubule of the kidney. PbB, EPO, and hemoglobin were measured at ages 4.5, 6.5, 9.5, and 12. In addition, tibial lead concentration was measured at age 12. Mean PbBs in the exposed children at the age of 4.5 and 9 years were 39 and 28 μg/dL, respectively, and mean hemoglobin concentration throughout the study period was within normal limits. The results of the analyses, after adjusting for hemoglobin, showed that serum EPO was positively associated with PbB at ages 4.5 and 6.5 years, but the magnitude of the association gradually declined from 4.5 to 12 years. This suggested that in children with moderate PbB, hyperproduction of EPO is necessary to maintain normal hemoglobin concentrations. The decline in slope with age suggested that the compensatory mechanism gradually begins to fail due to lead-induced loss of renal endocrine function. No association was found between tibia lead and EPO. Different results were reported by Liebelt et al. (1999) in a pilot study of 86 children between 1 and 6 years of age with a median PbB of 18 μg/dL (range, 2–84 μg/dL) recruited from a university-based lead clinic and primary care clinic. The investigators in that study found an inverse relationship between PbB and serum EPO concentration. Confounding by age in the Liebelt et al. (1999) study may have contributed to the discrepancy in results. A study of 88 children (2–15 years old) living in a highly lead-contaminated area in the Equatorian Andes reported a significant inverse correlation between PbB and hemoglobin concentration (Counter et al. 2000). The mean PbB was 43.2 μg/dL and the range was 6.2–128.2 μg/dL.

3.2.7 Genotoxic Effects

The potential genotoxic effects of lead have been studied in lead workers and members of the general population, as well as in *in vitro* cultures of mammalian cells and microorganisms. Although not always consistent, the results suggest that lead is a clastogenic agent, as judged by the induction of chromosomal aberrations, micronuclei, and sister chromatid exchanges (SCE) in peripheral blood cells (Table 3-6).

Nordenson et al. (1978) reported a significant increase in chromosomal aberrations in peripheral lymphocytes from a group of 26 lead workers with a mean PbB of approximately 65 μg/dL, and so did Schwanitz et al. (1970), Forni et al. (1976), Al-Hakkak et al. (1986), and Huang et al. (1988b) in workers with mean PbBs of 60–80 μg/dL (n=8), 40–50 μg/dL (n=11), 64 μg/dL (n=19), and 50 μg/dL (n=21), respectively. Schwanitz et al. (1975) reported a small, but not statistically significant increase in chromosomal aberrations in lead workers with a mean PbB of 38 μg/dL. Negative results were reported by Mäki-Paakkanen et al. (1981) among a group of 13 workers with a mean PbB of 49 μg/dL, by Bulsma and De France (1976) in 11 volunteers who ingested lead acetate for 49 days and had a PbB of 40 μg/dL, and by O'Riordan and Evans (1974) in 70 workers with PbBs ranging from <40 μg/dL to 120 μg/dL. A

Table 3-6. Genotoxicity of Lead *In Vivo*

Species (test system)	End point	Results	Reference
Drosophila melanogaster	Chromosome loss or nondisjunction	–	Ramel and Magnusson 1979
Mouse bone marrow, rat bone marrow, mouse leukocyte, monkey lymphocyte, rabbit	Structural chromosomal aberrations or gaps, micronucleus formation; unscheduled DNA synthesis, sister chromatid exchange	±	Bruce and Heddle 1979; Deknudt and Gerber 1979
		+	Deknudt et al. 1977
		+	Jacquet and Tachon 1981
		–	Jacquet et al. 1977
		–	Muro and Goyer 1969
		+	Tachi et al. 1985
		–	Willems et al. 1982
		+	Jagetia and Aruna 1998
Lead workers, peripheral lymphocytes	Micronuclei	+	Vaglenov et al. 2001
		+	Vaglenov et al. 1998
Lead workers, peripheral lymphocytes	DNA damage	+	Danadevi et al. 2003
		+	Fracasso et al. 2002
Lead workers, peripheral lymphocytes	Chromosomal aberration	+	Al-Hakkak et al. 1986
		+	Forni et al. 1976
		–	Mäki-Paakkanen et al. 1981
		+	Nordenson et al. 1978
		_	O'Riordan and Evans 1974
		+	Schwanitz et al. 1975
		+	Huang et al. 1988b
Children, general population	Chromosomal aberration	_	Bauchinger et al. 1977
Adults, general population	Chromosomal aberration	_	Bulsma and De France 1976
Lead workers, peripheral lymphocytes	Sister chromatid exchange	±	Grandjean et al. 1983
		–	Mäki-Paakkanen et al. 1981
		+	Huang et al. 1988b
		+	Duydu et al. 2001
		+	Wu et al. 2002
Children, general population	Sister chromatid exchange	–	Dalpra et al. 1983
Adults, general population	Altered cell division	+	Bulsma and De France 1976
Lead workers, peripheral lymphocytes	Altered cell division	+	Sarto et al. 1978
		+	Schwanitz et al. 1970

– = negative result; + = positive result; ± = inconclusive result; DNA = deoxyribonucleic acid

study of 30 children living in a town with a lead plant also found no evidence for lead-induced chromosomal aberrations; PbBs among the children ranged from 12 to 33 μg/dL (Bauchinger et al. 1977). Exposure concentrations were not reported in any of the studies mentioned above.

A significant increase in sister chromatid exchanges was reported in 23 lead workers whose mean PbB was approximately 32 μg/dL (Wu et al. 2002). In this study, the TWA exposure concentration, measured for 11 lead workers, ranged from 0.19 to 10.32 mg/m^3. Similar results were obtained in a study of 31 workers with a mean PbB of 36 μg/dL (Duydu et al. 2001). In the latter study, the urinary concentration of ALA exhibited a stronger correlation with SCE frequencies than PbB, which led the authors to suggest a possible ALA-mediated mechanism in the genotoxic effects of lead. An increase in SCE frequencies also was reported in workers with a PbB ≥80 μg/dL, but not less (Huang et al. 1988b). In contrast, in a group of 18 workers with a mean PbB of 49 μg/dL, there was no detectable increase in SCE frequency relative to controls (PbB <10μg/dL)(Mäki-Paakkanen et al. 1981); the concentration of lead in air ranged from 0.05 to 0.5 mg/m^3. Grandjean et al. (1983) observed that PbB and SCE rates decreased in lead workers after summer vacation. They also noticed that newly employed workers failed to show any increase in SCE rates during the first 4 months of employment despite increases in both ZPP and PbB, suggesting that genotoxic effects may occur after long exposure to lead. This could also suggest that current PbB is not a good biomarker of genotoxic effects. A study of 19 children living in a widely contaminated area reported no significant differences in SCE rates between the exposed children (PbB, 30–60 μg/dL) and 12 controls (PbB, 10–21 μg/dL) (Dalpra et al. 1983).

An increased incidence of micronuclei in peripheral lymphocytes was observed in a group of 22 lead workers whose mean PbB was 61 μg/dL relative to control groups with mean PbBs of 18 or 28 μg/dL (Vaglenov et al. 1998). The concentration of lead in the air ranged from 0.13 to 0.71 mg/m^3 (mean, 0.45 mg/m^3). After the workers consumed a polyvitamin-rich diet for 4 months, the micronuclei frequency showed a significant reduction, which led the authors to suggest that oxidative damage might be involved in the genotoxicity of lead. However, since concurrent controls were not administered vitamins, and the exposed workers were not divided into vitamin-treated and untreated groups, the possibility that the reduction in micronuclei was unrelated to the treatment with vitamins could not be ruled out. In a subsequent study from the same investigators in which lead workers were stratified into four exposure levels, PbBs >25 μg/dL were associated with significant increases in micronuclei frequency (Vaglenov et al. 2001).

Lead exposure also has been shown to be associated with DNA damage. For example, battery plant workers (n=37) had significantly elevated levels of DNA breaks in lymphocytes compared to unexposed subjects (n=29) (Fracasso et al. 2002). Moreover, the authors found significant correlations between DNA breaks and increased production of reactive oxygen species (ROS) and decreased glutathione levels in the lymphocytes, pointing to oxidative stress as a possible cause for the specific responses. Similar results were reported in a study in which workers were exposed to an air lead concentration of 0.004 mg/m^3 and had a mean PbB of 25 µg/dL (Danadevi et al. 2003). DNA damage also was observed in a mice model of lead inhalation (Valverde et al. 2002). A single 60-minute exposure to 6.8 µg/m^3 lead acetate induced DNA damage in the liver and lung, but subsequent inhalation induced DNA damage also in the nasal epithelium, whole blood, kidney, bone marrow, and brain; no DNA damage was seen in the testicles. In general, DNA damage in the lung, liver, and kidney was correlated with length of exposure and lead concentration in the tissue.

For the most part, mutagenicity tests in microorganisms have yielded negative results (Table 3-7).

3.2.8 Cancer

Almost all of the information regarding lead exposure and cancer in humans is derived from studies of lead workers and involves exposure to inorganic lead. Several reviews on this topic have been published recently (Landrigan et al. 2000; Silbergeld 2003; Silbergeld et al. 2000; Steenland and Boffetta 2000).

Malcolm and Barnett (1982) studied the causes of death of 754 subjects from a cohort of 1,898 retired lead acid battery workers during the period 1925–1976 in the United Kingdom. The only significant finding regarding cancer was a small but significant excess of malignant neoplasms of the digestive tract (observed/expected, 21/12.6) among men dying in service and who were classified as having the highest lead exposure; the excess was confined to the period 1963–1966, when lead levels were presumably higher than in later years. A subsequent study of workers from the same manufacturing facilities found no association between lead exposure and deaths from malignant neoplasms, either in general or for specific sites (Fanning 1988). Cooper et al. (1985) followed mortality rates among cohorts of 4,519 battery-plant workers and 2,300 lead production workers during 34 years. An increased SMR was found for total malignancies in both groups of workers (statistically significant only in the battery workers) attributed to digestive and respiratory cancers. These small excesses of cancer deaths could not be correlated with onset or duration of exposure. In addition, no adjustments could be made for other concomitant industrial exposures or for smoking. Smoking could easily explain the small increase in

Table 3-7. Genotoxicity of Lead *In Vitro*

End point	Species (test system)	Results[a] With activation	Results[a] Without activation	Reference
Salmonella typhimurium (reverse mutation); *Escherichia coli* (forward mutation, DNA modification); *Saccharomyces cerevisia* (reverse mutation); *Bacillus subtilis* (rec assay)	Gene mutation or DNA modification	–	–	Bruce and Heddle 1979; Dunkel et al. 1984; Fukunaga et al. 1982; Kharab and Singh 1985; Nestmann et al. 1979; Nishioka 1975; Rosenkranz and Poirier 1979; Simmon 1979b
S. cerevisiae	Gene conversion or mitotic recombination	–	–	Fukunaga et al. 1982; Kharab and Singh 1985; Nestmann et al. 1979; Simmon 1979a
E. coli RNA polymerase or Avian myetoblastosis DNA polymerase	RNA or DNA synthesis	NA	+	Hoffman and Niyogi 1977; Sirover and Loeb 1976
Chinese hamster ovary cells; Syrian hamster embryo cells	Chromosomal aberration, DNA repair, mitotic disturbance	NA	+	Ariza et al. 1998; Bauchinger and Schmid 1972; Costa et al. 1982; Robison et al. 1984; Zelikoff et al. 1988
Chinese hamster fibroblasts	Micronuclei	NA	+	Thier et al. 2003
Human melanoma cells	Micronuclei	NA	+	Poma et al. 2003
Human lymphocytes	Structural chromosomal aberration	NA	+ – – –	Beek and Obe 1974 Deknudt and Deminatti 1978 Gasiorek and Bauchinger 1981 Schmid et al. 1972
Human lymphocytes	DNA double-strand breaks, DNA-protein cross-links	NA	+	Woźniak and Blasiak 2003
Human lymphocytes	Sister chromatid exchange	NA	– +	Beek and Obe 1975 Niebuhr and Wulf 1984
Human melanoma cells	Sister chromatid exchange	NA	+	Poma et al. 2003

C = negative result; + = positive result; DNA = deoxyribonucleic acid; NA = not applicable; RNA = ribonucleic acid

respiratory cancer in an industrial cohort that contained an excess of heavy smokers. Cocco et al. (1998b) found a 60% increased risk of cancer of the gastric cardia for subjects with high-level exposure to lead. However, cross-tabulation of gastric cardiac cancer risk by probability and levels of exposure to lead did not show consistent trends. No association was found between lead exposure and stomach cancer in a nested case-control study at a battery plant that had 30 stomach cancer deaths (Wong and Harris 2000); the 30 cases represented half of 60 stomach cancers in the total cohort of about 6,800 workers. No dose-response was found using a variety of exposure indices.

A study of 437 Swedish smelter workers with verified high lead exposure for at least 3 years from 1950 to 1974 reported an increased SMR only for lung cancer, which did not achieve statistical significance when compared with national and county mortality rates specified for cause, sex, and calendar periods (Gerhardsson et al. 1986b). Environmental lead levels and PbBs were available for all workers since 1950. Mean PbB for the workers was 58 μg/dL in 1950 and 34 μg/dL in 1974. A follow-up study of 1,992 workers at this smelter found an increased SMR (1.5, 95% CI, 0.8–2.4) for all malignancies among a group with the highest exposure, and a considerably higher SMR (4.1, 95% CI, 1.5–9.0) for lung cancer (Lundstrom et al. 1997). However, since the workers may have been exposed to other carcinogens, including arsenic, the specific role of lead cannot be ascertained. A third study of 664 Swedish workers found an increase in deaths due to malignant neoplasms, but no dose-response pattern could be discerned, and the risk estimates did not increase when a latency period of 15 years was applied (Gerhardsson et al. 1995a). The study also found an increased incidence of gastrointestinal malignancies among the workers exposed to lead, a tendency that was related to employment before 1970 and not to lead dose or to latency time. Data regarding dietary and smoking habits were not available.

A study of 20,700 Finnish workers exposed to lead during 1973–1983 found a 1.4-fold increase in the overall cancer incidence and a 1.8-fold increase in the incidence of lung cancer among workers who had ever had a PbB ≥21 μg/dL (Anttila et al. 1995). The overall mortality for the whole cohort, however, was less than expected, and there was no clear excess mortality for specific causes of death. In a subsequent study of this same cohort, an excess risk of nervous system cancer, specifically gliomas, was found in workers with a PbB ≥29 μg/dL compared with those whose PbB had not exceeded 14.4 μg/dL (Anttila et al. 1996). However, the authors stated that no firm conclusions could be drawn because of the small number of cases, the rather short follow-up time, and the low response rate. Data from Cocco et al. (1998a) also suggested that exposure to lead may be associated with an increase in brain cancer risk. The authors analyzed 27,060 cases of brain cancer and 108,240 controls that died of nonmalignant diseases in

24 U.S. states in 1984–1992. The risk was observed mainly among men likely to have been heavily exposed to lead, which comprised 0.3–1.9% of the study population.

Cocco et al. (1997) evaluated cause-specific mortality among workers of a lead-smelting plant in Italy. The cohort consisted of 1,388 men whose vital status was followed from January 1950, or 12 months after the date of hiring, whichever was later, through December 1992. Compared with the national mortality rates, stomach cancer and lung cancer were significantly decreased, while deaths from cancer of the liver and biliary tract, bladder cancer, and kidney cancer were increased nonsignificantly above expectation. Compared to regional mortality rates, bladder cancer, kidney cancer, and brain cancer were increased. Cocco et al. (1997) noted that as kidney cancer accounts for about 0.4% of the total deaths both at the national and regional level, the small size of the cohort may not have allowed detection of small increases over the very low background rate. Selevan et al. (1985) and a follow-up by Steenland et al. (1992) also reported an excess in kidney cancer among workers employed at a lead smelter in Kellogg, Idaho.

Finally, in a study of cancer incidence in workers exposed to tetraethyl lead, a statistically significant association was found between exposure to this compound and rectal cancer (OR, 3.7; 90% CI, 1.3–10.2) (Fayerweather et al. 1997). The OR increased 4 times at the high-to-very high cumulative exposure level, demonstrating a dose-response relationship. When a latency period of 10 years was assumed, the association became even more pronounced. No increases in the incidence of cancer at other sites (i.e., brain, kidney, lung, spleen, and bone) were observed in the exposed workers.

Fu and Boffetta (1995) conducted a meta-analysis of lead-worker studies focusing on overall cancer, stomach cancer, lung cancer, kidney cancer, and bladder cancer. They found a significant excess risk of overall cancer, stomach cancer, lung cancer, and bladder cancer. More recently, Steenland and Boffetta (2000) did a meta-analysis of eight major occupational studies on cancer mortality or incidence in workers with high lead exposure. The results provided some limited evidence of increased risk of lung cancer and stomach cancer, although there might have been confounding with arsenic exposure in the study with highest relative risk of lung cancer. The results also showed a weak evidence for an association with kidney cancer and gliomas.

In the only available study of the general population, Jemal et al. (2002) examined the relationship of PbB and all cancer mortality using data from the NHANES II Mortality Study. The study consisted of 203 deaths (117 men, 86 women) among 3,992 whites (1,702 men, 1,890 women) with an average of 13.3 years of follow-up. Log-transformed PbB was either categorized into quartiles or treated as a

continuous variable in a cubic regression spline. After adjusting for confounding covariates, the analyses of the association of quartiles of PbB with all cancer mortality revealed that the risk of cancer mortality was not significantly associated with PbB among men and women combined and among separate analyses of men and women. In addition, none of the site-specific cancer relative risks were significant. Spline analyses found no dose-response for men and women combined or for men alone. However, for women, there appeared to be a threshold at about the 94^{th} percentile of lead, corresponding to a PbB of 24 μg/dL. The authors noted that the results of the spline analysis in women need to be replicated before they can be considered believable and concluded that individuals with PbB in the range of the NHANES II (weighted median, 13 μg/dL) do not appear to have increased risk of cancer mortality.

The available data on the carcinogenicity of lead following ingestion by laboratory animals indicate that lead is carcinogenic, and that the most common tumors that develop are renal tumors (Azar et al. 1973; Koller et al. 1985; Van Esch and Kroes 1969). Administration of lead compounds by the parenteral route produced similar results. Subcutaneous administration of lead phosphate to rats was associated with high incidence of renal tumors (Balo et al. 1965; Zollinger 1953). A study in mice provided suggestive evidence of carcinogenicity of lead following perinatal exposure (Waalkes et al. 1995). In that study, mice were exposed to one of three doses of lead acetate in the drinking water from gestation day 12 until 4 weeks postpartum, such that offspring were exposed *in utero* and via lactation. Offspring were not exposed directly and were sacrificed at 112 weeks postpartum. Renal tubular cell adenomas occurred in high-dose male offspring at a rate of 20% (5/25), whereas renal tubular cell carcinomas occurred in low-dose males (1/25) and in mid-dose males (1/25); no carcinomas were seen in low- or mid-dose males. In exposed male offspring, the incidence of renal tubular cell atypical hyperplasia was increased in a dose-related manner. In female offspring, lesions occurred at a lower rate.

The mechanism of lead-induced carcinogenicity in animals is not known, but some nongenotoxic mechanisms that have been proposed include inhibition of DNA synthesis and repair, alterations in cell-to-cell communication, and oxidative damage (Silbergeld et al. 2000). Based on inadequate evidence in humans and sufficient evidence in animals, EPA has classified inorganic lead in Group B2, probable human carcinogen (IRIS 2005). The Department of Health and Human Services has determined that lead and lead compounds are reasonably anticipated to be human carcinogens (NTP 2005). The International Agency for Research on Cancer has determined that inorganic lead is probably carcinogenic to humans and that organic lead compounds are not classifiable as to their carcinogenicity to humans (IARC 2004).

3.3 TOXICOKINETICS

Overview. Inorganic lead can be absorbed following inhalation, oral, and dermal exposure, but the latter route is much less efficient than the former two. Studies in animals have shown that organic lead is well absorbed through the skin. Inorganic lead in submicron size particles can be almost completely absorbed through the respiratory tract, whereas larger particles may be swallowed. The extent and rate of absorption of lead through the gastrointestinal tract depend on characteristics of the individual and on physicochemical characteristics of the medium ingested. Children can absorb 40–50% of an oral dose of water-soluble lead compared to 3–10% for adults. Gastrointestinal absorption of inorganic lead occurs primarily in the duodenum by saturable mechanisms. The distribution of lead in the body is route-independent and, in adults, approximately 94% of the total body burden of lead is in the bones compared to approximately 73% in children. Lead in blood is primarily in red blood cells. Conditions such as pregnancy, lactation, menopause, and osteoporosis increase bone resorption and consequently also increase lead in blood. Lead can be transferred from the mother to the fetus and also from the mother to infants via maternal milk. Metabolism of inorganic lead consists of formation of complexes with a variety of protein and nonprotein ligands. Organic lead compounds are actively metabolized in the liver by oxidative dealkylation by P-450 enzymes. Lead is excreted primarily in urine and feces regardless of the route of exposure. Minor routes of excretion include sweat, saliva, hair, nails, and breast milk. The elimination half-lives for inorganic lead in blood and bone are approximately 30 days and 27 years, respectively. Several models of lead pharmacokinetics have been proposed to characterize such parameters as intercompartmental lead exchange rates, retention of lead in various tissues, and relative rates of distribution among the tissue groups. Some models are currently being used or are being considered for broad application in lead risk assessment.

3.3.1 Absorption

3.3.1.1 Inhalation Exposure

Inorganic Lead. Inorganic lead in ambient air consists of aerosols of particulates that can be deposited in the respiratory tract when the aerosols are inhaled. Amounts and patterns of deposition of particulate aerosols in the respiratory tract are affected by the size of the inhaled particles, age-related factors that determine breathing patterns (e.g., nose breathing vs. mouth breathing), airway geometry, and air-stream velocity within the respiratory tract (James et al. 1994). Absorption of deposited lead is influenced by particle size and solubility as well as the pattern of regional deposition within the respiratory tract. Larger particles (>2.5 μm) that are deposited in the ciliated airways (nasopharyngeal and tracheobronchial

regions) can be transferred by mucociliary transport into the esophagus and swallowed. Smaller particles (<1 μm), which can be deposited in the alveolar region, can be absorbed after extracellular dissolution or ingestion by phagocytic cells (see Section 3.4.1 for further discussion).

The respiratory tract deposition and clearance from the respiratory tract have been measured in adult humans (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). In these studies, exposures were to lead-bearing particles having mass median aerodynamic diameters (MMAD) below 1 μm and, therefore, deposition of the inhaled lead particles can be assumed to have been primarily in the bronchiolar and alveolar regions of the respiratory tract (James et al. 1994) where transport of deposited lead to the gastrointestinal tract is likely to have been only a minor component of particle clearance (Hursh et al. 1969). Approximately 25% of inhaled lead chloride or lead hydroxide (MMAD 0.26 and 0.24 μm, respectively) was deposited in the respiratory tract in adult subjects who inhaled an inorganic lead aerosol through a standard respiratory mouthpiece for 5 minutes (Morrow et al. 1980). Approximately 95% of deposited inorganic lead that is inhaled as submicron particles is absorbed (Hursh et al. 1969; Wells et al. 1975). Rates of clearance from the respiratory tract of inorganic lead inhaled as submicron particles of lead oxide, or lead nitrate, were described with half-times of 0.8 hours (22%), 2.5 hours (34%), 9 hours (33%), and 44 hours (12%) (Chamberlain et al. 1978). These rates are thought to represent, primarily, absorption from the bronchiolar and alveolar regions of the respiratory tract.

Rates and amounts of absorption of inhaled lead particles >2.5 μm will be determined, primarily, by rates of transport to and absorption from the gastrointestinal tract. Absorption of lead from the gastrointestinal tract varies with the chemical form ingested, age, meal status (e.g., fed vs. fasted), and a variety of nutritional factors (see Section 3.3.1.2 for further discussion).

Organic Lead. Following a single exposure to vapors of radioactive (^{203}Pb) tetraethyl lead (approximately 1 mg/m^3 breathed through a mouthpiece for 1–2 minutes) in four male subjects, 37% of inhaled ^{203}Pb was initially deposited in the respiratory tract, of which approximately 20% was exhaled in the subsequent 48 hours (Heard et al. 1979). One hour after the exposure, approximately 50% of the ^{203}Pb burden was associated with liver, 5% with kidney, and the remaining burden widely distributed throughout the body (determined by external gamma counting), suggesting near complete absorption of the lead that was not exhaled. In a similar experiment conducted with (^{203}Pb) tetramethyl lead, 51% of the inhaled ^{203}Pb dose was initially deposited in the respiratory tract, of which approximately 40% was

exhaled in 48 hours. The distribution of ^{203}Pb 1 hour after the exposure was similar to that observed following exposure to tetraethyl lead.

The relatively rapid and near complete absorption of tetraalkyl lead that is inhaled and deposited in the respiratory tract is also supported by studies conducted in animal models (Boudene et al. 1977; Morgan and Holmes 1978).

3.3.1.2 Oral Exposure

Inorganic Lead. The extent and rate of gastrointestinal absorption of ingested inorganic lead are influenced by physiological states of the exposed individual (e.g., age, fasting, nutritional calcium and iron status, pregnancy) and physicochemical characteristics of the medium ingested (e.g., particle size, mineralogy, solubility, and lead species). Lead absorption may also vary with the amount of lead ingested.

Effect of Age. Gastrointestinal absorption of water-soluble lead appears to be higher in children than in adults. Estimates derived from dietary balance studies conducted in infants and children (ages 2 weeks to 8 years) indicate that approximately 40–50% of ingested lead is absorbed (Alexander et al. 1974; Ziegler et al. 1978). In adults, estimates of absorption of ingested water-soluble lead compounds (e.g., lead chloride, lead nitrate, lead acetate) ranged from 3 to 10% in fed subjects (Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1980; Watson et al. 1986). Data available on lead absorption between childhood and adulthood ages are very limited. While no absorption studies have been conducted on subjects in this age group, the kinetics of the change in stable isotope signatures of blood lead in mothers and their children as both come into equilibrium with a novel environmental lead isotope profile, suggest that children ages 6–11 years and their mothers may absorb a similar percentage of ingested lead (Gulson et al. 1997b).

Studies in experimental animals provide additional evidence for an age-dependency of gastrointestinal absorption of lead. Absorption of lead, administered as lead acetate (6.37 mg lead /kg, oral gavage), was higher in juvenile Rhesus monkeys (38% of dose) compared to adult female monkeys (26% of the dose) (Pounds et al. 1978). Rat pups absorb approximately 40–50 times more lead via the diet than do adult rats (Aungst et al. 1981; Forbes and Reina 1972; Kostial et al. 1978). This age difference in absorption may be due, in part, to the shift from the neonatal to adult diet, and to postnatal physiological development of intestine (Weis and LaVelle 1991).

Effect of Fasting. The presence of food in the gastrointestinal tract decreases absorption of water-soluble lead (Blake and Mann 1983; Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Maddaloni et al. 1998; Rabinowitz et al. 1980). In adults, absorption of a tracer dose of lead acetate in water was approximately 63% when ingested by fasted subjects and 3% when ingested with a meal (James et al. 1985). Heard and Chamberlain (1982) reported nearly identical results. The arithmetic mean of reported estimates of absorption in fasted adults was 57% (calculated by ATSDR based on Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1980). Reported fed/fasted ratios for absorption in adults range from 0.04 to 0.2 (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980). Mineral content is one contributing factor to the lower absorption of lead when lead is ingested with a meal; in particular, the presence of calcium and phosphate in a meal will depress the absorption of ingested lead (Blake and Mann 1983; Blake et al. 1983; Heard and Chamberlain 1982).

Effect of Nutrition. Lead absorption in children is affected by nutritional iron status. Children who are iron deficient have higher blood lead concentrations than similarly exposed children who are iron replete, which would suggest that iron deficiency may result in higher absorption of lead or, possibly, other changes in lead biokinetics that would contribute to lower PbB (Mahaffey and Annest 1986; Marcus and Schwartz 1987). Evidence for the effect for iron deficiency on lead absorption has been provided from animal studies. In rats, iron deficiency increases the gastrointestinal absorption of lead, possibly by enhancing binding of lead to iron binding proteins in the intestine (Bannon et al. 2003; Barton et al. 1978b; Morrison and Quaterman 1987) (see Section 3.4.1 for further discussion).

Dietary calcium intake appears to affect lead absorption. An inverse relationship has been observed between dietary calcium intake and blood lead concentration in children, suggesting that children who are calcium-deficient may absorb more lead than calcium-replete children (Mahaffey et al. 1986; Ziegler et al. 1978). An effect of calcium on lead absorption is also evident in adults. In experimental studies of adults, absorption of a single dose of lead (100–300 μg lead chloride) was lower when the lead was ingested together with calcium carbonate (0.2–1 g calcium carbonate) than when the lead was ingested without additional calcium (Blake and Mann 1983; Heard and Chamberlain 1982). A similar effect of calcium occurs in rats (Barton et al. 1978a). In other experimental animal models, absorption of lead from the gastrointestinal tract has been shown to be enhanced by dietary calcium depletion or administration of vitamin D (Mykkänen and Wasserman 1981, 1982) (see Section 3.4.1 for further discussion).

Effect of Pregnancy. Absorption of lead may increase during pregnancy. Although there is no direct evidence for this in humans, an increase in lead absorption may contribute, along with other mechanisms (e.g., increased mobilization of bone lead), to the increase in PbB that has been observed during the later half of pregnancy (Gulson et al. 1997b, 1998b, 2004; Lagerkvist et al. 1996; Rothenberg et al. 1994b; Schuhmacher et al. 1996).

Effect of Dose. Lead absorption in humans may be a capacity limited process, in which case, the percentage of ingested lead that is absorbed may decrease with increasing rate of lead intake. Studies, to date, do not provide a firm basis for discerning if the gastrointestinal absorption of lead is limited by dose. Numerous observations of nonlinear relationships between blood lead concentration and lead intake in humans provide support for the existence of a saturable absorption mechanism or some other capacity limited process in the distribution of lead in humans (Pocock et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1984) (see Section 3.4.1 for discussion of saturable uptake of lead in red blood cells). However, in immature swine that received oral doses of lead in soil, lead dose-blood lead relationships were curvilinear, whereas dose-tissue lead relationships for bone, kidney, and liver were linear. The same pattern (nonlinearity for blood lead concentration and linearity for tissues) was observed in swine administered lead acetate intravenously (Casteel et al. 1997). These results suggest that the nonlinearity in the lead dose-blood lead concentration relationship may derive from an effect of lead dose on some aspect of the biokinetics of lead other than absorption. In fasted rats, absorption was estimated at 42 and 2% following single oral administration of 1 and 100 mg lead/kg, respectively, as lead acetate, suggesting a limitation on absorption imposed by dose (Aungst et al. 1981). Evidence for capacity-limited processes at the level of the intestinal epithelium is compelling, which would suggest that the intake-uptake relationship for lead is likely to be nonlinear (see Section 3.4.1 for further discussion); however, the dose at which absorption becomes appreciably limited in humans is not known.

Effect of Particle Size. Particle size influences the degree of gastrointestinal absorption (Ruby et al. 1999). In rats, an inverse relationship was found between absorption and particle size of lead in diets containing metallic lead particles that were ≤250 μm in diameter (Barltrop and Meek 1979). Tissue lead concentration was a 2.3-fold higher when rats ingested an acute dose (37.5 mg Pb/kg) of lead particles that were <38 μm in diameter, than when rats ingested particles having diameters in the range of 150–250 μm (Barltrop and Meek 1979). Dissolution kinetics experiments with lead-bearing mine waste soil suggest that surface area effects control dissolution rates for particles sizes of <90 μm diameter; however, dissolution of 90–250 μm particle size fractions appeared to be controlled more by surface morphology

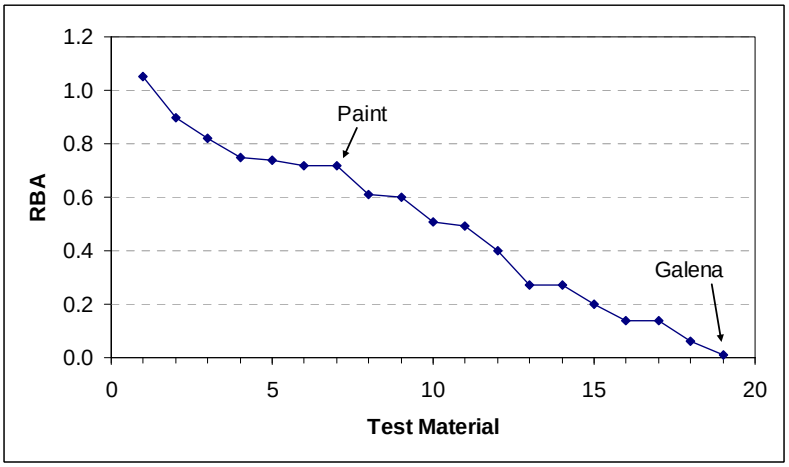
(Davis et al. 1994). Similarly, Healy et al. (1982) found that the solubility of lead sulfide in gastric acid *in vitro* was much greater for particles that were 30 μm in diameter than for particles that were 100 μm in diameter.

Absorption from Soil. Absorption of lead in soil is less than that of dissolved lead, but is similarly depressed by meals. Adult subjects who ingested soil (particle size <250 μm) collected from the Bunker Hill NPL site absorbed 26% of the resulting 250 μg/70 kg body weight lead dose when the soil was ingested in the fasted state, and 2.5% when the same soil lead dose was ingested with a meal (Maddaloni et al. 1998). The value reported for fasted subjects (26%) was approximately half that reported for soluble lead ingested by fasting adults, approximately 60% (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980). Measurements of the absorption of soil lead in infants or children have not been reported.

Additional evidence for a lower absorption of soil lead compared to dissolved lead is provided from studies in laboratory animal models. In immature swine that received oral doses of soil-like materials from various mine waste sites (75 or 225 μg Pb/kg body weight), relative bioavailability of soil-borne lead ranged from 6 to 100%, compared to that of a similar dose of highly water-soluble lead acetate (Casteel et al. 1997; EPA 2004b; Figure 3-4). Electron microprobe analyses of lead-bearing grains in the various test materials revealed that the grains ranged from as small as 1–2 μm up to a maximum of 250 μm (the sieve size used in preparation of the samples), and that the lead was present in a wide range of different mineral associations (phases), including various oxides, sulfides, sulfates, and phosphates (Table 3-8). These variations in size and mineral content of the lead-bearing grains are the suspected cause of variations in the rate and extent of gastrointestinal absorption of lead from different samples of soil. Based on these very limited data, the relative bioavailability of lead mineral phases were rank-ordered (Table 3-9).

Studies conducted in rats provide additional evidence for a lower absorption of soil-borne lead compared to water-soluble lead. Fed rats were administered lead in soil from mine waste over a 30-day period, and relative bioavailability compared to that of lead acetate was estimated from measurements of PbB (Freeman et al. 1992). For one test soil, relative bioavailability estimates for samples having lead concentrations of 1.62 and 4.05 ppm were 18.1 and 12.1% in males and 25.7 and 13.8% in females for average lead dosages of 1.13 and 3.23 mg Pb/kg/day in males, and 1.82 and 4.28 mg Pb/kg/day in females (1.62 and 4.05 ppm Pb), respectively. For a second test soil, relative bioavailability estimates for samples having lead concentrations of 78.2 and 19.5 ppm were 19.6 and 21.5% in males and 26.8 and 22.1% in

Figure 3-4. Relative Bioavailability (RBA) of Ingested Lead from Soil and Soil-like Test Materials as Assessed in an Immature Swine Model*



Test Material
1 California Gulch Fe/Mn PbO
2 Jasper Co Low Lead Yard
3 Jasper Co High Lead Mill
4 Aspen Residential
5 Aspen Berm
6 California Gulch Phase 1 Residential Soil
7 NIST Paint
8 Jasper Co High Lead Smelter
9 Palmerton Location 2
10 Murray Smelter Soil
11 Palmerton Location 4
12 Murray Smelter Slag
13 Bingham Creek Residential
14 Bingham Creek Channel
15 Califonria Gulch AV Slag
16 Midvale Slag
17 Butte Soil
18 California Gulch Oregon Gulch Tailings
19 Galena-enriched Soil

*RBA is the bioavailability (BA) of the lead in the test material compared to that of lead acetate relative to lead acetate ($BA_{test}/BA_{acetate}$). See Table 3-8 for mineral composition of test materials.

Source: EPA 2004c

Table 3-8. Percent Relative Lead Mass of Mineral Phases Observed in Test Materials Assessed for Relative Bioavailability in Immature Swine[a]

Test material	1 Cal. Gulch Fe/Mn PbO	2 Jasper County low lead yard	3 Jasper County high lead mill	4 Aspen residential	5 Aspen Berm	6 Cal. Gulch Phase I residential soil	7 NIST paint	8 Jasper County high lead smelter	9 Palmerton location 2	10 Murray smelter soil	11 Palmerton location 4	12 Murray smelter slag	13 Bingham Creek residential	14 Bingham Creek channel soil	15 Cal. Gulch AV slag	16 Midvale slag	17 Butte soil	18 Cal. Gulch Oregon Gulch tailings	19 Galena-enriched soil
Mineral phase																			
Anglesite		0.5	2	1	7	10	1	1	6		4	1.0		28	2		36		
As(M)O										0.003									
Calcite			0.1					0.2											
Cerussite		81	57	64	62	20	55	32		14		1.1	2	0.3	1	4	0.3		
Clay	0.01	0.003	0.017		0.1			0.018	0.03		0.13						0.1		
Fe-Pb oxide	8	2	10	7	9	6		14	2	0.13	2	2	6	3	51	0.3	7		
Fe-Pb sulfate	3	1	1	5	5	6		3	1	0.6		0.3	22	30	0.3	0.1	20		
Galena		8	3	17	12	2				20		9		9	3	6	12	100	100
Lead barite	0.14		0.01		0.06	0.15			1		0.1			0.04			0.007		
Lead organic	0.11			0.03	0.03	0.11								0.3	1				
Lead oxide			7				44	0.09		27		69							
Lead phos-phate	15	6	7	1	1	30		21	24		1		50	26			3.6		
Lead silicate	0.8	0.04	0.5			1.9					1.4								
Lead vanidate	0.4					0.1					18								
Mn-Pb oxide	72	2	9	5	4	22		2	66		66	0.8	18	2			20.2		
Native lead			2					22				0.7				15			
Pb(M)O										3	7	4				26			
Pb-As oxide		0.15				0.1				29		6	2	1	31	33			

Table 3-8. Percent Relative Lead Mass of Mineral Phases Observed in Test Materials Assessed for Relative Bioavailability in Immature Swine[a]

Test material	1 Cal. Gulch Fe/Mn PbO	2 Jasper County low lead yard	3 Jasper County high lead mill	4 Aspen residential	5 Aspen Berm	6 Cal. Gulch Phase I residential soil	7 NIST paint	8 Jasper County high lead smelter	9 Palmerton location 2	10 Murray smelter soil	11 Palmerton location 4	12 Murray smelter slag	13 Bingham Creek residential	14 Bingham Creek channel soil	15 Cal. Gulch AV slag	16 Midvale slag	17 Butte soil	18 Cal. Gulch Oregon Gulch tailings	19 Galena-enriched soil
PbO-cerussite						1													
Slag			1			1		4		6		7			10	16			
Sulfosalts																0.4			
Zn-Pb silicate											2	0.03							

[a]Test material numbers refer to Figure 3-4.

Source: EPA 2004c

Table 3-9. Ranking of Relative Bioavailability of Lead Mineral Phases in Soil[a]

Low bioavailability (RBA<0.25)	Medium bioavailability (RBA=0.25–0.75)	High bioavailability (RBA>0.75)
Angelsite	Lead oxide	Cerussite
Fe(M) oxide	Lead phosphate	Mn(M) oxide
Fe(m) sulfate		
Galena		
Pb(m) oxide		

[a]Estimates are based on studies of immature swine (see Figure 3-4, Table 3-8).

M = metal; RBA = relative bioavailability (compared to lead acetate)

Source: EPA 2004c

females for average lead dosages of 5.13 and 12.1 mg Pb/kg/day in males and 7.39 and 23.2 mg Pb/kg/day in females, respectively. In a subsequent follow-up study, absolute bioavailability of ingested lead acetate in rats was estimated to be 15% based on measurements of blood lead concentrations after oral or intravenous administration of lead acetate (Freeman et al. 1994). Based on this estimate, the absolute bioavailability of lead in the soils from the Freeman et al. (1992) study was estimated to be 2.7% (Freeman et al. 1994). In rats that received diets containing 17–127 mg lead/kg for 44 days in the form of lead acetate, lead sulfide, or lead-contaminated soil, bone and tissue lead levels increased in a dose-dependent manner (Freeman et al. 1996). Estimated bioavailability of lead sulfide was approximately 10% that of lead acetate. Bioavailability of lead in soil from the California Gulch NPL site (Freeman et al. 1996), a former mining site, decreased with increasing soil lead concentration in the diet and ranged from 7 to 28% of that of lead acetate. The predominant forms of lead in the NPL site soil were identified as: iron-lead oxide (40%), manganese-lead oxide (16%), lead phosphate (13%), "slag" (12%), and iron-lead sulfate (10%). The addition of "uncontaminated soil" (having a lead concentration of 54±3 mg lead/kg soil) to diets containing lead acetate decreased the bioavailability of lead acetate by approximately 76%.

3.3.1.3 Dermal Exposure

Inorganic Lead. Dermal absorption of inorganic lead compounds is generally considered to be much less than absorption by inhalation or oral routes of exposure; however, few studies have provided quantitative estimates of dermal absorption of inorganic lead in humans, and the quantitative significance of the dermal absorption pathway as a contributor to lead body burden in humans remains an uncertainty. Lead was detected in the upper layers of the stratum corneum of lead-battery workers, prior to their shifts and after cleaning of the skin surface (Sun et al. 2002), suggesting adherence and/or possible dermal penetration of lead. Following skin application of ^{203}Pb-labeled lead acetate in cosmetic preparations (0.12 mg Pb in 0.1 mL or 0.18 mg Pb in 0.1 g of a cream) to eight male volunteers for 12 hours, absorption was ≤0.3%, based on whole-body, urine and blood ^{203}Pb measurements, and was predicted to be 0.06% during normal use of such preparations (Moore et al. 1980). Most of the absorption took place within 12 hours of exposure. Lead also appears to be absorbed across human skin when applied to the skin as lead nitrate; however, quantitative estimates of absorption have not been reported. Lead (4.4 mg, as lead nitrate) was applied (vehicle or solvent not reported) to an occluded filter placed on the forearm of an adult subject for 24 hours, after which, the patch was removed, the site cover and the forearm were rinsed with water, and total lead was quantified in the cover material and rinse (Stauber et al. 1994). The amount of lead recovered from the cover material and rinse was 3.1 mg (70% of the applied dose). Based

on this recovery measurement, 1.3 mg (30%) of the applied dose remained either in the skin or had been absorbed in 24 hours; the amount that remained in or on the skin and the fate of this lead (e.g., exfoliation) was not determined. Exfoliation has been implicated as an important pathway of elimination of other metals from skin (e.g., inorganic mercury; Hursh et al. 1989). Lead concentrations in sweat collected from the right arm increased 4-fold following the application of lead to the left arm, indicating that some lead had been absorbed (amounts of sweat collected or total lead recovered in sweat were not reported). In similar experiments with three subjects, measurements of ^{203}Pb in blood, sweat and urine, made over a 24-hour period following dermal exposures to 5 mg Pb as ^{203}Pb nitrate or acetate, accounted for <1% of the applied (or adsorbed) dose. This study also reported that absorption of lead could not be detected from measurements of lead in sweat following dermal exposure to lead as lead carbonate.

Information on relative dermal permeability of inorganic and organic lead salts of lead comes from studies of *in vitro* preparations of excised skin; the rank ordering of penetration rates through excised human skin were: lead nuolate (lead linoleic and oleic acid complex) > lead naphthanate > lead acetate > lead oxide (nondetectable) (Bress and Bidanset 1991).

Studies conducted in animals provide additional evidence that dermal absorption of inorganic lead is substantially lower than absorption from the inhalation or oral route. In a comparative study of dermal absorption of inorganic and organic salts of lead conducted in rats, approximately 100 mg of lead was applied in an occluded patch to the shaved backs of rats. Based on urinary lead measurements made prior to and for 12 days following exposure, lead compounds could be ranked according to the relative amounts absorbed (i.e., percent of dose recovered in urine; calculated by ATSDR): lead naphthalene (0.17%), lead nitrate (0.03%), lead stearate (0.006%), lead sulfate (0.006%), lead oxide (0.005%), and metal lead powder (0.002%). This rank order (i.e., lead naphthalene>lead oxide) is consistent with a rank ordering of penetration rates of inorganic and organic lead salts through excised skin from humans and guinea pigs: lead nuolate (lead linoleic and oleic acid complex) > lead naphthanate > lead acetate > lead oxide (nondetectable) (Bress and Bidanset 1991).

Following application of lead acetate to the shaved clipped skin of rats, the concentration of lead in the kidneys was found to be higher relative to controls, suggesting that absorption of lead had occurred (Laug and Kunze 1948). This study also observed that dermal absorption of lead from lead arsenate was significantly less than from lead acetate, and that mechanical injury to the skin significantly increased the dermal penetration of lead.

Organic Lead. Relative to inorganic lead and organic lead salts, tetraalkyl lead compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931; Laug and Kunze 1948). A 0.75-mL amount of tetraethyl lead, which was allowed to spread uniformly over an area of 25 cm^2 on the abdominal skin of rabbits, resulted in 10.6 mg of lead in the carcass at 0.5 hours and 4.41 mg at 6 hours (Kehoe and Thamann 1931). Tetraethyl lead was reported to be absorbed by the skin of rats to a much greater extent than lead acetate, lead oleate, and lead arsenate (Laug and Kunze 1948). Evidence for higher dermal permeability of organic lead compounds compared to inorganic organic salts of lead also comes from *in vitro* studies conduced with excised skin. The rank order of absorption rates through excised skin from humans and guinea pigs was as follows: tetrabutyl lead > lead nuolate (lead linoleic and oleic acid complex) > lead naphthanate > lead acetate > lead oxide (nondetectable) (Bress and Bidanset 1991).

3.3.2 Distribution

Inorganic Lead. Absorbed inorganic lead appears to be distributed in essentially the same manner regardless of the route of absorption (Chamberlain et al. 1978; Kehoe 1987); therefore, the distribution of absorbed lead (i.e., by any route) is discussed in this section, rather than in separate sections devoted to specific routes of exposure. The expression, body burden is used here to refer to the total amount of lead in the body. Most of the available information about the distribution of lead to major organ systems (e.g., bone, soft tissues) derives from autopsy studies conducted in the 1960s and 1970s and reflect body burdens accrued during periods when ambient and occupational exposure levels were much higher than current levels (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). In general, these studies indicate that the distribution of lead appears to be similar in children and adults, although a larger fraction of the lead body burden of adults resides in bone (see Section 3.3.3 for further discussion). Several models of lead pharmacokinetics have been proposed to characterize such parameters as intercompartmental lead exchange rates, retention of lead in various tissues, and relative rates of distribution among the tissue groups (see Section 3.3.5 for further discussion of the classical compartmental models and physiologically based pharmacokinetic (PBPK) models developed for lead risk assessments).

Lead in Blood. Concentrations of lead in blood vary considerably with age, physiological state (e.g., pregnancy, lactation, menopause) and numerous factors that affect exposure to lead. The NHANES provide estimates for average blood lead concentrations in various demographic strata of the U.S. population. Samples for the most recent NHANES III were collected during the period 1999–2002. Geometric mean PbB of U.S. adults, ages 20–59 years, estimated from the NHANES III 1999–2002, were

1.5 μg/dL (95% CI, 1.5–1.6) (CDC 2005a). Among adults, blood lead concentrations were highest in the strata that included ages 60 years and older (2.2 μg/dL; 95% CI, 2.1–2.3). Geometric mean PbB of children, ages 1-5 years, was 1.9 (95% CI, 1.8–2.1) for the 1999–2002 survey period; however, the geometric mean PbB for non-Hispanic black children is higher than that for Mexican-American and non-Hispanic white children, showing that differences in risk for exposure still exist (CDC 2005a). Central estimates from NHANES 1999–2002 when compared to those from NHANES III Phase 2 (1991–1994), and from Phase 1 of the NHANES III (1988–1991) and NHANES II (1976–1980), indicate a downward temporal trend in blood lead concentrations in the United States, over this period.

The excretory half-life of lead in blood, in adult humans, is approximately 30 days (Chamberlain et al. 1978; Griffin et al. 1975; Rabinowitz et al. 1976). Lead in blood is primarily in the red blood cells (99%) (Bergdahl et al. 1997a, 1998, 1999; Hernandez-Avila et al. 1998; Manton et al. 2001; Schutz et al. 1996; Smith et al. 2002). Most of the lead found in red blood cells is bound to proteins within the cell rather than the erythrocyte membrane. Approximately 40–75% of lead in the plasma is bound to plasma proteins, of which albumin appears to be the dominant ligand (Al-Modhefer et al. 1991; Ong and Lee 1980a). Lead may also bind to γ-globulins (Ong and Lee 1980a). Lead in serum that is not bound to protein exists largely as complexes with low molecular weight sulfhydryl compounds (e.g., cysteine, homocysteine) and other ligands (Al-Modhefer et al. 1991).

Lead in Bone. In human adults, approximately 94% of the total body burden of lead is found in the bones. In contrast, bone lead accounts for 73% of the body burden in children (Barry 1975). Lead concentrations in bone increase with age throughout the lifetime, indicative of a relatively slow turnover of lead in adult bone (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). This large pool of lead in adult bone can serve to maintain blood lead levels long after exposure has ended (Fleming et al. 1997; Inskip et al. 1996; Kehoe 1987; O'Flaherty et al. 1982; Smith et al. 1996). It can also serve as a source of lead transfer to the fetus when maternal bone is resorbed for the production of the fetal skeleton (Franklin et al. 1997; Gulson et al. 1997b, 1999b, 2003).

Lead is not distributed uniformly in bone. Lead will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in cortical and trabecular bone. This suggests that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Two physiological compartments appear to exist for lead in cortical and trabecular bone, to

varying degrees. In one compartment, bone lead is essentially inert, having a half-life of several decades. A labile compartment exists as well that allows for maintenance of an equilibrium of lead between bone and soft tissue or blood (Rabinowitz et al. 1976). Although a high bone formation rate in early childhood results in the rapid uptake of circulating lead into mineralizing bone, bone lead is also recycled to other tissue compartments or excreted in accordance with a high bone resorption rate (O'Flaherty 1995a). Thus, most of the lead acquired early in life is not permanently fixed in the bone (O'Flaherty 1995a). In general, bone turnover rates decrease as a function of age, resulting in slowly increasing bone lead levels among adults (Barry 1975; Gross et al. 1975; Schroeder and Tipton 1968). An x-ray fluorescence study of tibial lead concentrations in individuals older than 10 years showed a gradual increase in bone lead after age 20 (Kosnett et al. 1994). In 60–70-year-old men, the total bone lead burden may be ≥200 mg, while children <16 years old have been shown to have a total bone lead burden of 8 mg (Barry 1975). However, in some bones (i.e., mid femur and pelvic bone), the increase in lead content plateaus at middle age and then decreases at higher ages (Drasch et al. 1987). This decrease is most pronounced in females and may be due to osteoporosis and release of lead from resorbed bone to blood (Gulson et al. 2002). Bone lead burdens in adults are slowly lost by diffusion (heteroionic exchange) as well as by resorption (O'Flaherty 1995a, 1995b).

Evidence for the exchange of bone lead and soft tissue lead stores comes from analyses of stable lead isotope signatures of lead in bone and blood. A comparison of blood and bone lead stable isotope signatures in five adults indicated that bone lead stores contributed to approximately 40–70% of the lead in blood (Smith et al. 1996). During pregnancy, the mobilization of bone lead increases, apparently as the bone is catabolized to produce the fetal skeleton. Analysis for kinetics of changes in the stable isotope signatures of blood lead in pregnant women as they came into equilibrium with a novel environmental lead isotope signature indicated that 10–88% of the lead in blood may derive from the mobilization of bone lead stores and approximately 80% of cord blood may be contributed from maternal bone lead (Gulson 2000; Gulson et al. 1997b, 1999c, 2003). The mobilization of bone lead during pregnancy may contribute, along with other mechanisms (e.g., increased absorption), to the increase in lead concentration that has been observed during the later stages of pregnancy (Gulson et al. 1997b; Lagerkvist et al. 1996; Schuhmacher et al. 1996). Bone resorption during pregnancy can be reduced by ingestion of calcium supplements (Janakiraman et al. 2003). Additional evidence for increased mobilization of bone lead into blood during pregnancy is provided from studies in nonhuman primates and rats (Franklin et al. 1997; Maldonado-Vega et al. 1996). Direct evidence for transfer of maternal bone lead to the fetus has been provided from stable lead isotope studies in Cynomolgus monkeys (*Macaca fascicularis*) that were dosed with lead having a different stable isotope ratio than the lead to which the monkeys were exposed at an

earlier age; approximately 7–39% of the maternal lead burden that was transferred to the fetus appeared to have been derived from the maternal skeleton (Franklin et al. 1997).

In addition to pregnancy, other states of increased bone resorption appear to result in release of bone lead to blood; these include lactation and osteoporosis. Analysis for kinetics of changes in the stable isotope signatures of blood lead in postpartum women as they came into equilibrium with a novel environmental lead isotope signature indicated that the release of maternal bone lead to blood appears to accelerate during lactation (Gulson et al. 2003, 2004). Similar approaches have detected increased release of bone lead to blood in women, in association with menopause (Gulson et al. 2002). These observations are consistent with epidemiological studies that have shown increases in PbB after menopause and in association with decreasing bone density in postmenopausal women (Berkowitz et al. 2004; Hernandez-Avila et al. 2000; Nash et al. 2004; Symanski and Hertz-Picciotto 1995).

Lead in Soft Tissues. Several studies have compared soft tissue concentrations of lead in autopsy samples of soft tissues (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). These studies were conducted in the 1960s and 1970s and, therefore, reflect burdens accrued during periods when ambient and occupational exposure levels were much higher than current levels. Average PbBs reported in the adult subjects were approximately 20 μg/dL in the Barry (1975) and Gross et al. (1975) studies, whereas more current estimates of the average for adults in the United States are below 5 μg/dL (Pirkle et al. 1998). Levels in other soft tissues also appear to have decreased substantially since these studies were reported. For example, average lead concentrations in kidney cortex of male adults were 0.78 μg/g wet tissue and 0.79 μg/g, as reported by Barry (1975) and Gross et al. (1975), respectively (samples in the Barry study were from subjects who had no known occupational exposures). In a more recent analysis of kidney biopsy samples collected in Sweden, the mean level of lead in kidney cortex among subjects not occupationally exposed to lead was 0.18 μg/g (maximum, 0.56μg/g) (Barregård et al. 1999). In spite of the downward trends in soft tissue lead levels, the autopsy studies provide a basis for describing the relative soft tissue distribution of lead in adults and children. Most of the lead in soft tissue is in liver. Relative amounts of lead in soft tissues as reported by Schroeder and Tipton (1968), expressed as percent of total soft tissue lead, were: liver, 33%; skeletal muscle, 18%; skin, 16%; dense connective tissue, 11%; fat, 6.4%; kidney, 4%; lung, 4%; aorta, 2%; and brain, 2% (other tissues were <1%). The highest soft tissue concentrations in adults also occur in liver and kidney cortex (Barry 1975; Gerhardsson et al. 1986a, 1995b; Gross et al. 1975; Oldereid et al. 1993). The relative distribution of lead in soft tissues, in males and females, expressed in terms of tissue:liver concentration ratios, were: liver, 1.0 (approximately 1 μg/g wet weight); kidney cortex, 0.8; kidney medulla, 0.5; pancreas, 0.4; ovary, 0.4; spleen, 0.3;

prostate, 0.2; adrenal gland, 0.2; brain, 0.1; fat, 0.1; testis, 0.08; heart, 0.07; and skeletal muscle, 0.05 (Barry 1975; Gross et al. 1975). In contrast to lead in bone, which accumulates lead with continued exposure in adulthood, concentrations in soft tissues (e.g., liver and kidney) are relatively constant in adults (Barry 1975; Treble and Thompson 1997), reflecting a faster turnover of lead in soft tissue, relative to bone.

Maternal-Fetal-Infant Transfer. The maternal/fetal blood lead concentration ratio, indicated from cord blood lead measurements, is approximately 0.9 (Carbone et al. 1998; Goyer 1990; Graziano et al. 1990). In one of the larger studies of fetal blood lead concentration, maternal and cord blood lead concentration were measured at delivery in 888 mother-infant pairs; the cord/maternal ratio was relatively constant, 0.93, over a PbB range of approximately 3–40 μg/dL (Graziano et al. 1990). A study of 159 mother-infant pairs also found a relatively constant cord/maternal ratio (0.84) over a maternal blood lead range of approximately 1–12 μg/dL (Carbone et al. 1998). As noted in the discussion of the distribution of lead in bone, measurements of stable lead isotope ratios in pregnant women and cord blood, as they came into equilibrium with a novel environmental lead isotope signature, indicated that approximately 80% of lead in fetal cord blood appears to derive from maternal bone stores (Gulson et al. 2003). A recent study looked at factors that might influence the amount of lead that infants receive (Harville et al. 2005). The analysis, conducted on 159 mother-infant pairs, revealed that higher blood pressure and alcohol consumption late in pregnancy were associated with more lead in cord blood relative to maternal PbB. In addition, higher hemoglobin and sickle cell trait were associated with reduced cord blood lead relative to maternal PbB. No associations were found for calcium intake, physical activity, or smoking.

Maternal lead can also be transferred to infants during breastfeeding. Numerous studies have reported lead concentrations in maternal blood and breast milk. In general, these studies indicate that breast milk/maternal blood concentration ratios are <0.1, although values of 0.9 have been reported (Ettinger et al. 2006; Gulson et al. 1998a). Ettinger et al. (2006) assessed factors influencing breast milk lead concentration in a group of 367 women and found that PbB (mean, 8–9 μg/dL; range, 2–30) was a stronger predictor of breast milk lead (mean, 0.9–1.4 μg/L; range, 0.2–8 μg/dL) than bone lead, and that tibia lead (mean, 9.5 μg/g; range, <1–76.5 μg/dL) was a stronger predictor of breast milk lead than patella bone lead (mean, 14.6 μg/dL; range, <1–67.2 μg/dL). Stable lead isotope dilution measurements in infant-mother pairs, measured as they came into equilibrium with a novel environmental lead isotope signature, suggested that lead in breast milk can contribute substantially to isotope profile of infant blood (approximately 40–80%; Gulson et al. 1998b).

Organic Lead. Information on the distribution of lead in humans following exposures to organic lead is extremely limited. One hour following 1–2-minute inhalation exposures to ^{203}Pb tetraethyl or tetramethyl lead (1 mg/m^3), approximately 50% of the ^{203}Pb body burden was associated with liver and 5% with kidney; the remaining ^{203}Pb was widely distributed throughout the body (Heard et al. 1979). The kinetics of ^{203}Pb in blood of these subjects showed an initial declining phase during the first 4 hours (tetramethyl lead) or 10 hours (tetraethyl lead) after the exposure, followed by a phase of gradual increase in PbB that lasted for up to 500 hours after the exposure. Radioactive lead in blood was highly volatile immediately after the exposure and transitioned to a nonvolatile state thereafter. These observations may reflect an early distribution of organic lead from the respiratory tract, followed by a redistribution of de-alkylated lead compounds (see Section 3.3.3 for further discussion of alkyl lead metabolism).

In a man and woman who accidentally inhaled a solvent containing 31% tetraethyl lead (17.6% lead by weight), lead concentrations in the tissues, from highest to lowest, were liver, kidney, brain, pancreas, muscle, and heart (Bolanowska et al. 1967). In another incident, a man ingested a chemical containing 59% tetraethyl lead (38% lead w/w); lead concentration was highest in the liver followed by kidney, pancreas, brain, and heart (Bolanowska et al. 1967).

3.3.3 Metabolism

Inorganic Lead. Metabolism of inorganic lead consists of formation of complexes with a variety of protein and nonprotein ligands. Major extracellular ligands include albumen and nonprotein sulfhydryls (see Section 3.3.2 for further discussion). The major intracellular ligand in red blood cells is ALAD (see Section 3.3.2 for further discussion). Lead also forms complexes with proteins in the cell nucleus and cytosol (see Section 3.4.2 for further discussion).

Organic Lead. Alkyl lead compounds are actively metabolized in the liver by oxidative dealkylation catalyzed by cytochrome P-450. Relatively few studies that address the metabolism of alkyl lead compounds in humans have been reported. Occupational monitoring studies of workers who were exposed to tetraethyl lead have shown that tetraethyl lead is excreted in the urine as diethyl lead, ethyl lead, and inorganic lead (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994). Trialkyl lead metabolites were found in the liver, kidney, and brain following exposure to the tetraalkyl compounds in workers; these metabolites have also been detected in brain tissue of nonoccupational subjects (Bolanowska et al. 1967; Nielsen et al. 1978). In volunteers exposed by inhalation to 0.64 and 0.78 mg lead/m^3 of ^{203}Pb-labeled tetraethyl and tetramethyl lead, respectively, lead was cleared from the

blood within 10 hours, followed by a re-appearance of radioactivity back into the blood after approximately 20 hours (Heard et al. 1979). The high level of radioactivity initially in the plasma indicates the presence of tetraalkyl/trialkyl lead. The subsequent rise in blood radioactivity, however, probably represents water-soluble inorganic lead and trialkyl and dialkyl lead compounds that were formed from the metabolic conversion of the volatile parent compounds (Heard et al. 1979).

3.3.4 Excretion

Independent of the route of exposure, absorbed lead is excreted primarily in urine and feces; sweat, saliva, hair and nails, and breast milk are minor routes of excretion (Chamberlain et al. 1978; Griffin et al. 1975; Hursh and Suomela 1968; Hursh et al. 1969; Kehoe 1987; Rabinowitz et al. 1976; Stauber et al. 1994). Fecal excretion accounts for approximately one-third of total excretion of absorbed lead (fecal/urinary excretion ratio of approximately 0.5), based on intravenous injection studies conducted in humans (Chamberlain et al. 1978). A similar value for fecal/urinary excretion ratio, approximately 0.5, has been observed following inhalation of submicron lead particles (Chamberlain et al. 1978; Hursh et al. 1969).

3.3.4.1 Inhalation Exposure

Inorganic Lead. Inorganic lead inhaled as submicron particles is deposited primarily in the bronchiolar and alveolar regions of the respiratory tract, from where it is absorbed and excreted primarily in urine and feces (Chamberlain et al. 1978; Hursh et al. 1969; Kehoe 1987). Fecal/urinary excretion ratios were approximately 0.5 following inhalation of submicron lead-bearing particles (Chamberlain et al. 1978; Hursh et al. 1969). Higher fecal-urinary ratios would be expected following inhalation of larger particle sizes (e.g., >1 μm) as these particles would be cleared to the gastrointestinal tract from where a smaller percentage would be absorbed (Kehoe 1987; see Section 3.3.1.2).

Organic Lead. Lead derived from inhaled tetraethyl and tetramethyl lead is excreted in exhaled air, urine, and feces (Heard et al. 1979). Following 1–2-minute inhalation exposures to ^{203}Pb tetraethyl (1 mg/m^3), in four male subjects, 37% of inhaled ^{203}Pb was initially deposited in the respiratory tract, of which approximately 20% was exhaled in the subsequent 48 hours (Heard et al. 1979). In a similar experiment conducted with (^{203}Pb) tetramethyl lead, 51% of the inhaled ^{203}Pb dose was initially deposited in the respiratory tract, of which approximately 40% was exhaled in 48 hours. Lead that was not exhaled was excreted in urine and feces. Fecal/urinary excretion ratios were 1.8 following exposure to tetraethyl lead and 1.0 following exposure to tetramethyl lead (Heard et al. 1979). Occupational monitoring studies of workers who were exposed to tetraethyl lead have shown that tetraethyl lead is excreted in the urine as

diethyl lead, ethyl lead, and inorganic lead (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

3.3.4.2 Oral Exposure

Inorganic Lead. Much of the available information on the excretion of ingested lead in adults derives from studies conducted on five male adults who received daily doses of ^{207}Pb nitrate for periods up to 210 days (Rabinowitz et al. 1976). The dietary intakes of the subjects were reduced to accommodate the tracer doses of ^{207}Pb without increasing daily intake, thus preserving a steady state with respect to total lead intake and excretion. Total lead intakes (diet plus tracer) ranged from approximately 210 to 360 μg/day. Urinary excretion accounted for approximately 12% of the daily intake (range for five subjects: 7–17%) and fecal excretion, approximately 90% of the daily intake (range, 87–94%). Based on measurements of tracer and total lead in saliva, gastric secretions, bile, and pancreatic secretions (samples collected from three subjects by intubation), gastrointestinal secretion of lead was estimated to be approximately 2.4% of intake (range, 1.9–3.3%). In studies conducted at higher ingestion intakes, 1–3 mg/day for up to 208 weeks, urinary lead excretion accounted for approximately 5% of the ingested dose (Kehoe 1987).

3.3.4.3 Dermal Exposure

Inorganic lead is excreted in sweat and urine following dermal exposure to lead nitrate or lead acetate (Moore et al. 1980; Stauber et al. 1994).

3.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

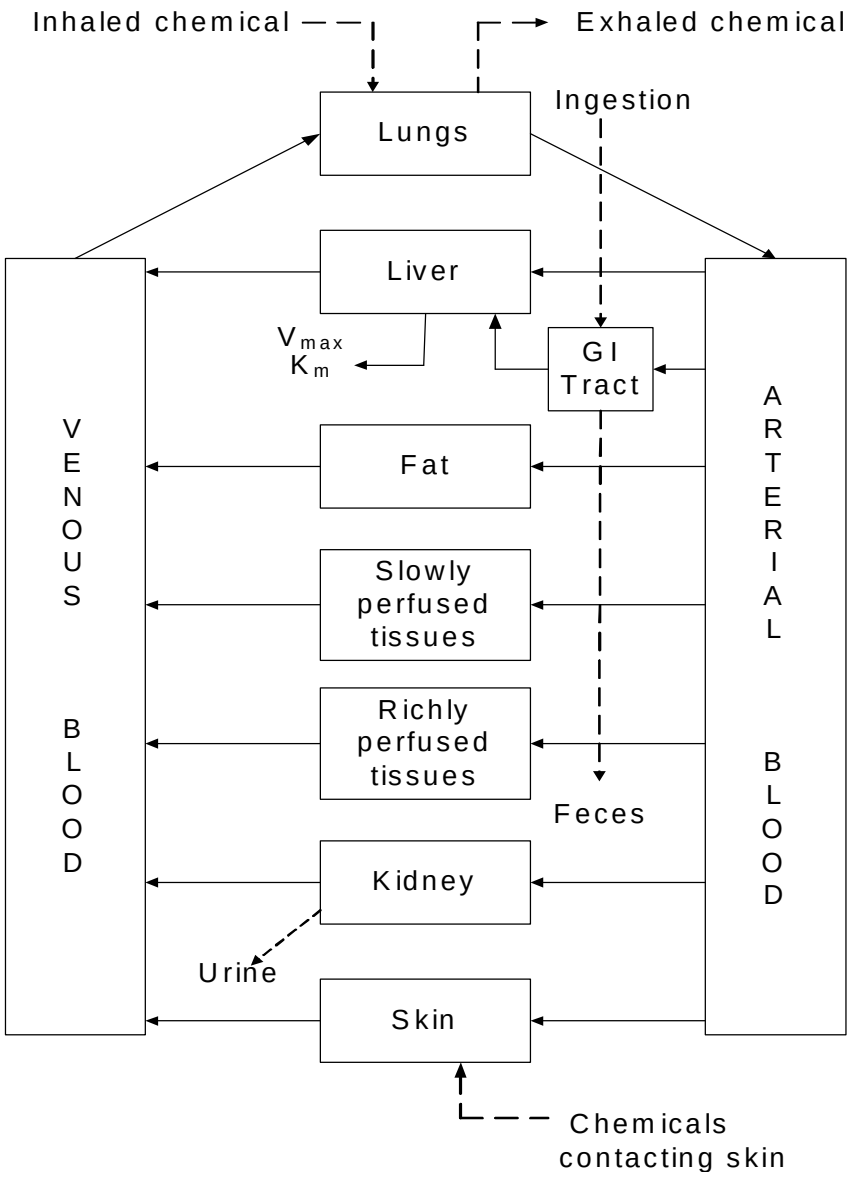
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

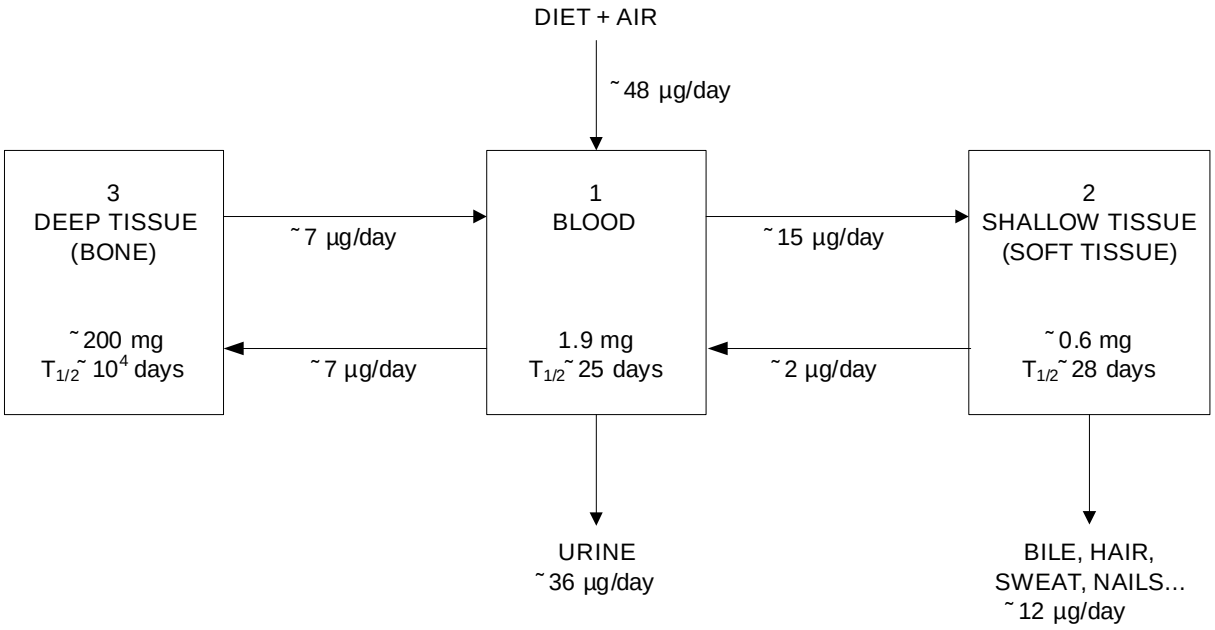
Source: adapted from Krishnan et al. 1994

If PBPK models for lead exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Early lead modeling applications relied on classical pharmacokinetics. Compartments representing individual organs or groups of organs that share a common characteristic were defined as volumes, or pools, that are kinetically homogeneous. For example, the body could be represented by a central compartment (e.g., blood plasma), and one or two peripheral compartments, which might be "shallow" or "deep" (i.e., they may exchange relatively rapidly or relatively slowly with blood plasma) (O'Flaherty 1987). One of the first of such models was proposed by Rabinowitz et al. (1976) based on a study of the kinetics of ingested stable lead isotope tracers and lead balance data in five healthy adult males. The Rabinowitz model includes three compartments: a central compartment representing blood and other tissues and spaces in rapid equilibrium with blood (e.g., interstitial fluid); a shallow tissue compartment, representing soft tissues and rapidly exchanging pools within the skeleton; and a deep tissue compartment, representing, primarily, slowly exchanging pools of lead within bone. Excretion pathways represented in the model included urinary, from the central compartment, and bile, sweat, hair, and nails, from the shallow tissue compartment. A diagram of the model is shown in Figure 3-6, along with the lead content and reported mean residence times and the rates of lead movement between compartments (residence times are the reciprocal of the sum of the individual elimination rate constants). The model predicts pseudo-first order half-times for lead of approximately 25, 28, and 10^4 days in the central, shallow tissue, and deep compartments, respectively. The slow kinetics of the deep tissue compartment leads to the prediction that it would contain most of the lead burden after lengthy exposures (e.g., years), consistent with lead measurements made in human autopsy samples (see Section 3.3.2 Distribution). Note that this model did not simulate the distribution of lead within blood (e.g., erythrocytes and plasma), nor did it simulate subcompartments within bone or physiological processes of bone turnover that might affect kinetics of the deep tissue compartment.

Marcus (1985b) reanalyzed the data from stable isotope tracer studies of Rabinowitz et al. (1976) and derived an expanded multicompartment kinetic model for lead (Figure 3-7). The model included separate compartments for cortical (slow, $t_{1/2}$ $1.2x10^4$–$3.5x10^4$ days) and trabecular (fast, $t_{1/2}$ 100–700 days), an approach subsequently adopted in several models (Bert et al. 1989; EPA 1994a, 1994b; Leggett 1993; O'Flaherty 1993, 1995a). A more complex representation of the lead disposition in bone included explicit simulation of diffusion of lead within the bone volume of the osteon and exchange with blood at the canaliculus (Marcus 1985a; Figure 3-8). The bone diffusion model was based on lead kinetics data from studies conducted in dogs. Marcus (1985c) also introduced nonlinear kinetics of exchange of lead

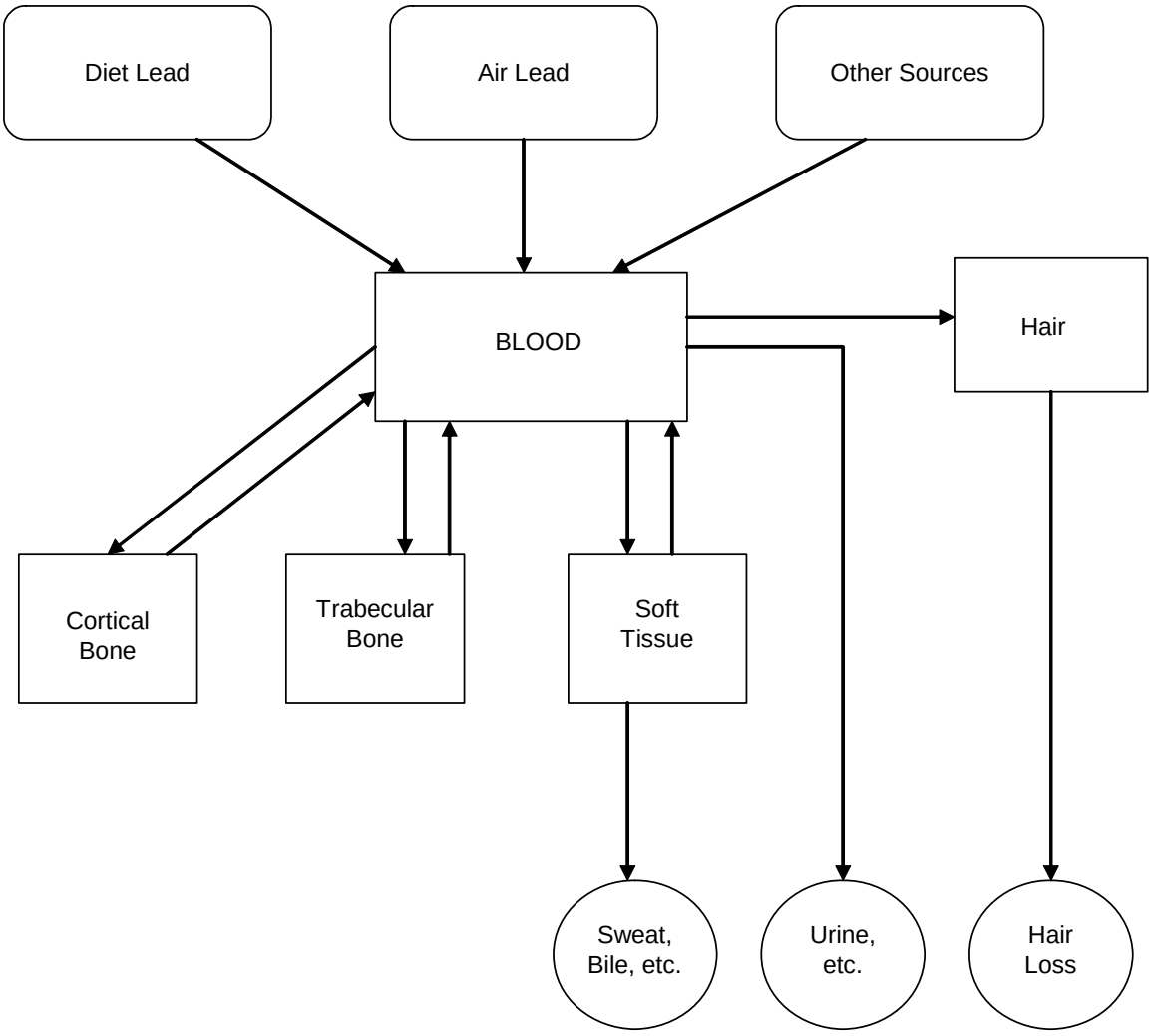
Figure 3-6. Lead Metabolism Model*



*Schematic model for lead kinetics, in which distribution is represented as a central (blood) compartment and peripheral soft-tissue (fast = $t_{1/2}$ 28 days) and deep tissue (slow = $t_{1/2}$ 10,000 days) compartments.

Source: Rabinowitz et al. 1976

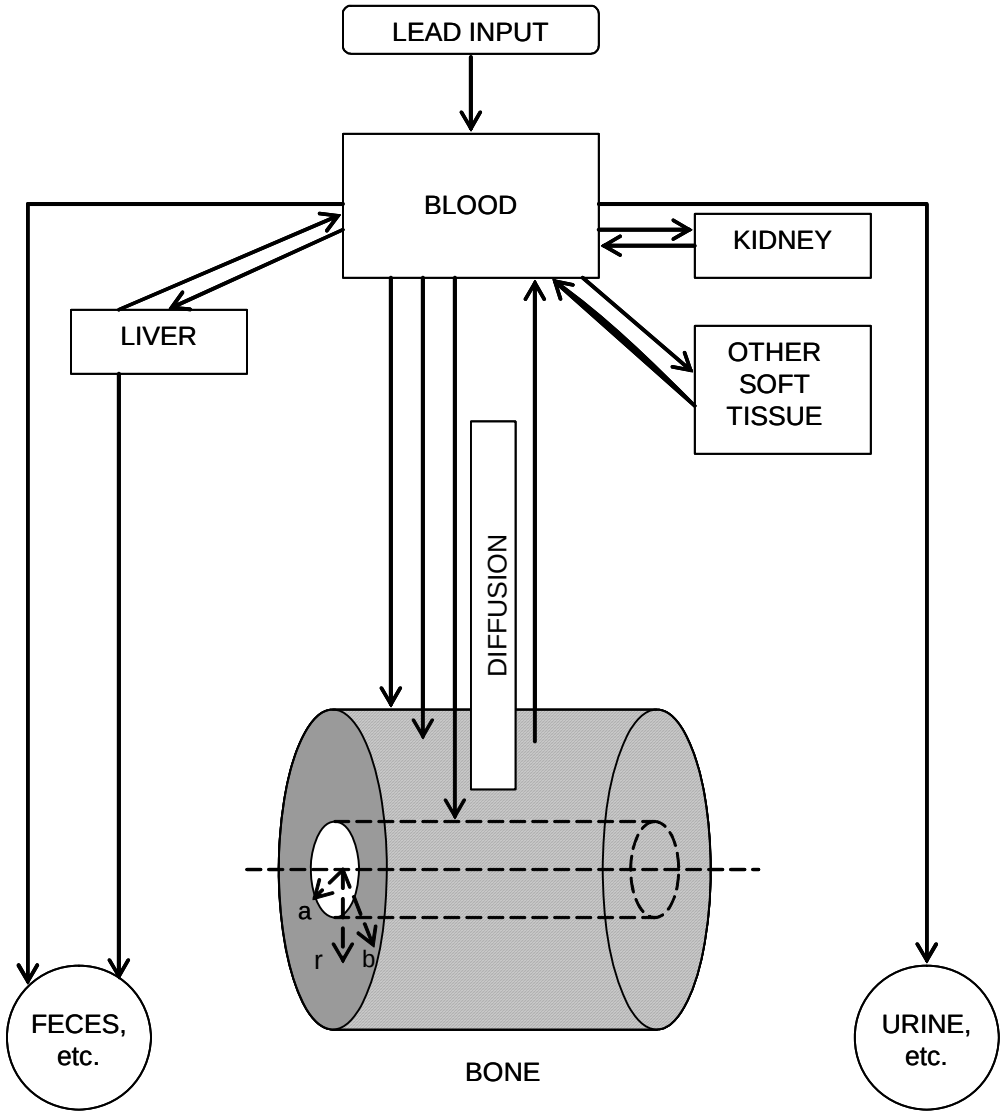
Figure 3-7. Compartments and Pathways of Lead Exchange in the Marcus (1985b) Model*



*Schematic model for lead kinetics, in which bone is represented as a cortical (slow=$t_{1/2}$ $1.2x10^4$–$3.5x10^4$ days) and trabecular (fast=$t_{1/2}$ 100–700 days) compartments.

Source: Marcus 1985b

Figure 3-8. Schematic Model for Lead Kinetics in Marcus (1985a) Bone Model*



*Schematic model for lead kinetics, in which bone is represented as an extended cylindrical *canalicular territory*. The canalicular territory has a radius b, and surrounds the canaliculus of radius a. Lead diffuses across radius r, between the fluid in the canaliculus (which is in communication with blood in the Haversian canal, not shown) and the bone volume of the canalicular territory.

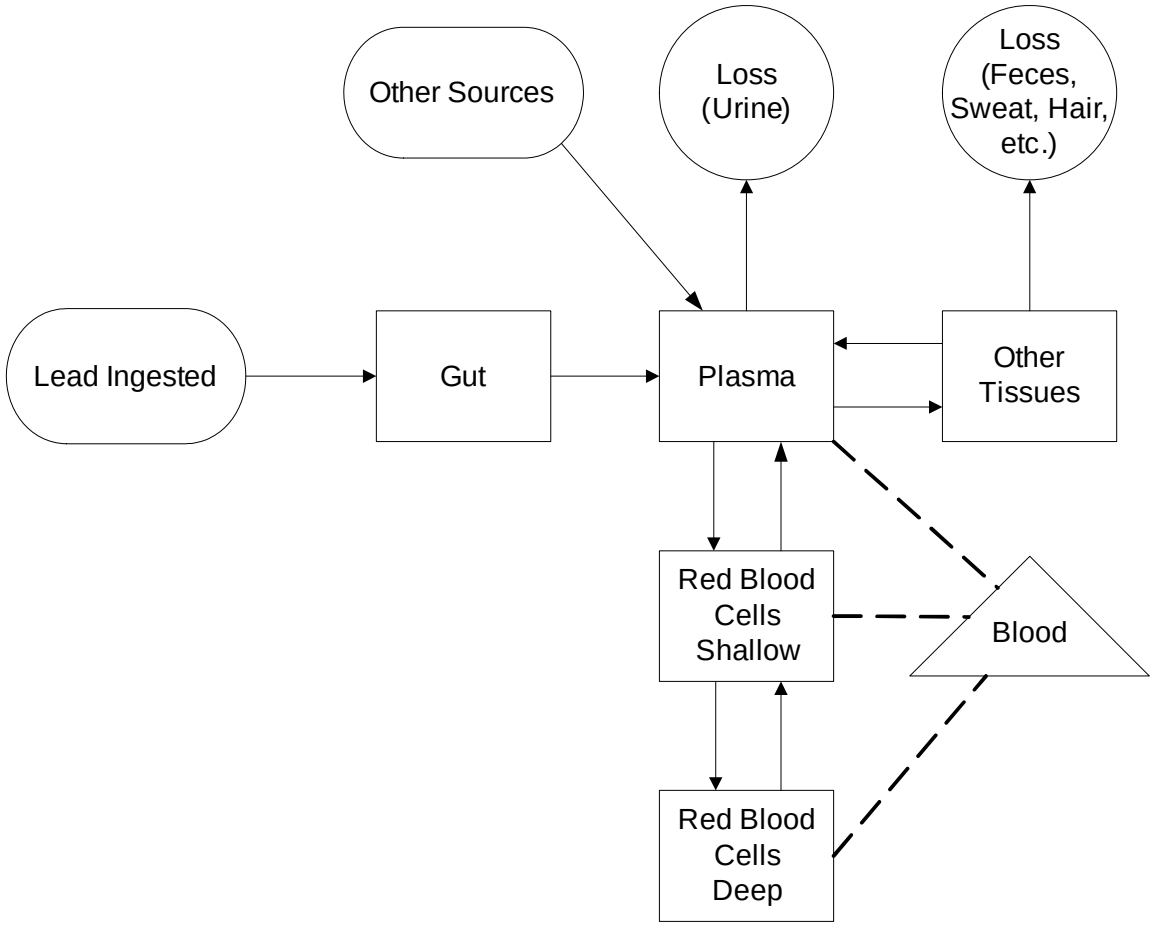
Source: Marcus 1985a

between plasma and erythrocytes. The blood model included four blood subcompartments: diffusible lead in plasma, protein-bound lead in plasma, a "shallow" erythrocyte pool, and a "deep" erythrocyte pool (see Figure 3-9). This model predicted the curvilinear relationship between plasma and blood lead concentrations observed in humans (see Section 3.3.2 Distribution for further discussion of plasma-erythrocyte lead concentrations).

Additional information on lead biokinetics, bone mineral metabolism, and lead exposures has led to further refinements and expansions of these earlier modeling efforts. Three pharmacokinetic models, in particular, are currently being used or are being considered for broad application in lead risk assessment: (1) the O'Flaherty Model, which simulates lead kinetics from birth through adulthood (O'Flaherty 1993, 1995a); (2) the Integrated Exposure Uptake BioKinetic (IEUBK) Model for Lead in Children developed by EPA (1994a, 1994b); and (3) the Leggett Model, which simulates lead kinetics from birth through adulthood (Leggett 1993). Of the three approaches, the O'Flaherty Model has the fewest lead-specific parameters and relies more extensively on physiologically based parameters to describe volumes, flows, composition, and metabolic activity of blood and bone that determine the disposition of lead in the human body. Both the IEUBK Model and the Leggett Model are classic multicompartmental models; the values of the age-specific transfer rate constants for lead are based on kinetics data obtained from studies conducted in animals and humans, and may not have precise physiological correlates. Thus, the structure and parameterization of the O'Flaherty Model is distinct from both the IEUBK Model and Leggett Model. All three models represent the rate of uptake of lead (i.e., amount of lead absorbed per unit of time) as relatively simple functions (f) of lead intake (e.g., uptake=intake x A, or uptake=intake x f[intake]). The values assigned to A or other variables in f(intake) are, in general, age-specific and, in some models, environmental medium-specific. However, the models do not modify the representation of uptake as functions of the many other physiologic variables that may affect lead absorption (e.g., nutritional status). While one can view this approach as a limitation of the models, it also represents a limitation of the data available to support more complex representations of lead absorption.

The IEUBK Model simulates multimedia exposures, uptake, and kinetics of lead in children ages 0–7 years; the model is not intended for use in predicting lead pharmacokinetics in adults. The O'Flaherty and Leggett models are lifetime models, and include parameters that simulate uptake and kinetics of lead during infancy, childhood, adolescence, and adulthood. Lead exposure (e.g., residence-specific environmental lead concentrations, childhood activity patterns) is not readily described by current versions of these models. By contrast, the IEUBK Model includes parameters for simulating exposures and uptake to estimate average daily uptake of lead (μg/day) among populations of children potentially

Figure 3-9. Compartmental Model for Lead in Plasma and Red Blood Cells in the Marcus (1985c) Model*



*Schematic model for lead kinetics in which blood is represented as plasma (central exchange compartment) and red blood cells, the latter having shallow and deep pools.

Source: Marcus 1985c

exposed via soil and dust ingestion, air inhalation, lead-based paint chip ingestion, tap water ingestion, and diet.

All three models have been calibrated, to varying degrees, against empirical physiological data on animals and humans, and data on blood lead concentrations in individuals and/or populations (EPA 1994a, 1994c; Leggett 1993; O'Flaherty 1993). However, applications in risk assessment require that the models accurately predict blood lead distributions in real populations, in particular the "upper tails" (e.g., 95^{th} percentile), when input to the models consists of data that describe site-specific exposure conditions (e.g., environmental lead concentrations, physicochemical properties of soil and dust) (Beck et al. 2001; Griffin et al. 1999). In evaluating models for use in risk assessment, exposure data collected at hazardous waste sites have been used to drive model simulations (Bowers and Mattuck 2001; Hogan et al. 1998). The exposure module in the IEUBK Model makes this type of evaluation feasible.

The focus on relying on blood lead concentrations for model evaluation and calibration derives from several concerns. The empirical basis for a relationship between low levels of lead exposure and behavioral dysfunction largely consists of prospective epidemiological studies relating various indices of dysfunction with blood lead concentration (see Section 3.2.2). In this context, blood lead concentration has been related to health effects of lead, and this is the main reason that the focus of interest in the models has been on estimating blood lead concentrations. Also, the most available data with which to calibrate and validate the models has been data relating exposure and/or lead intake to blood concentration. Thus, there is greater confidence in the validity of the models for estimating blood concentrations, rather than lead levels in other physiologic compartments. Although the principal adverse health effects of lead have been related to concentrations of lead in blood, other biomarkers of lead exposure, such as bone lead concentrations, are also of value in assessing associations between lead exposure and health; hence, there is a need for models that predict concentrations of lead in tissues other than blood (see Section 3.2.2).

The following three pharmacokinetic models are discussed in great detail below: (1) the O'Flaherty Model (O'Flaherty 1993, 1995a); (2) the IEUBK Model for Lead in Children (EPA 1994a, 1994b); and (3) the Leggett Model (Leggett 1993).

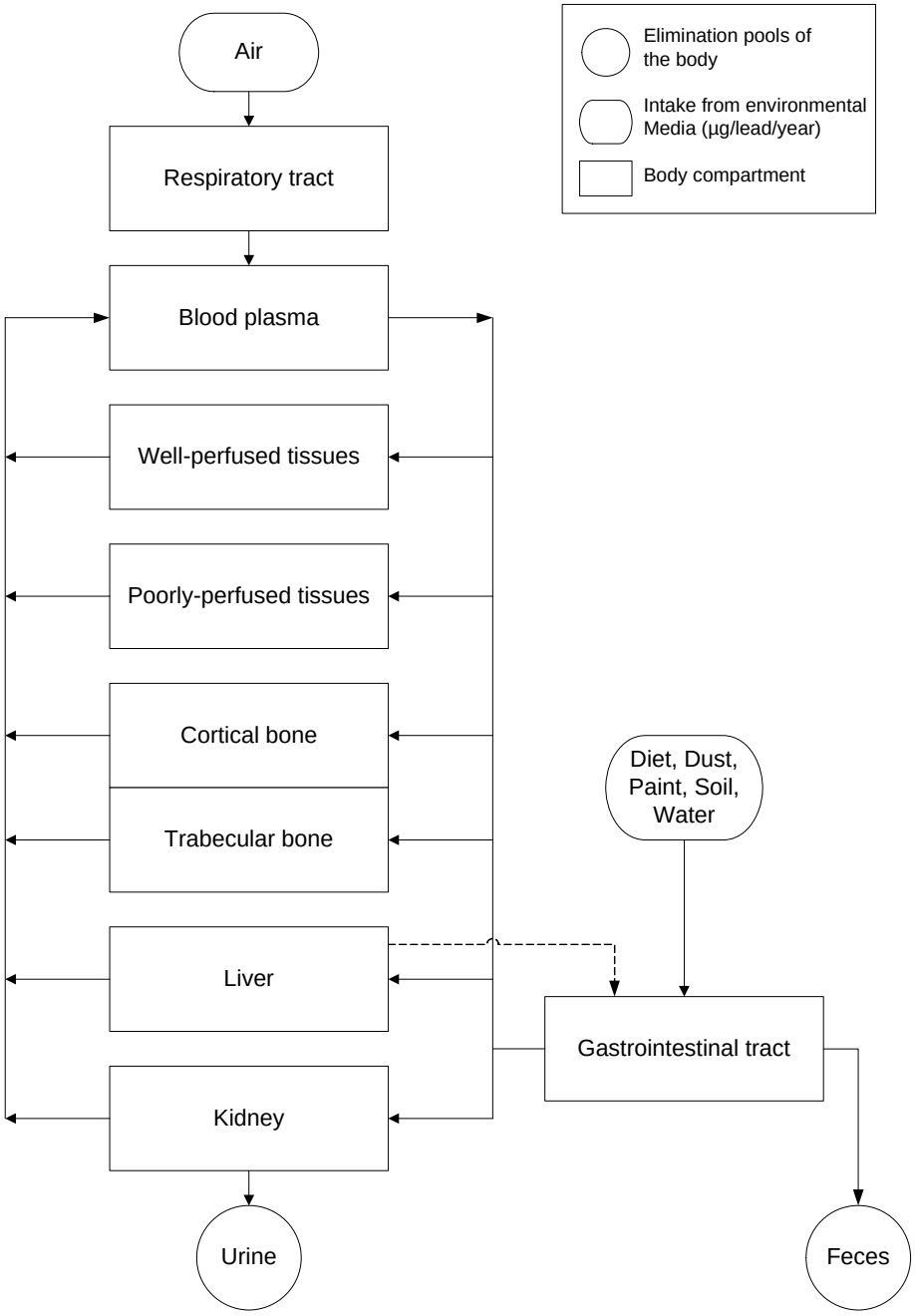
3.3.5.1 O'Flaherty Model

The O'Flaherty Model simulates lead exposure, uptake, and disposition in humans, from birth through adulthood (O'Flaherty 1993, 1995a). Figure 3-10 shows a conceptualized representation of the O'Flaherty Model, including the movement of lead from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between blood plasma, liver, kidney, richly-perfused tissues, poorly-perfused tissues, bone compartments, and excretion from liver and/or kidney. The model simulates both age- and media-specific absorption. Because many of the pharmacokinetic functions are based on body weight and age, the model can be used to estimate blood lead concentrations across a broad age range, including infants, children, adolescents, and adults. The model uses physiologically based parameters to describe the volume, composition, and metabolic activity of blood, soft tissues, and bone that determine the disposition of lead in the human body.

Description of the model. The O'Flaherty Model simulates lead absorption and disposition from birth through adulthood. A central feature of the model is the growth curve, a logistic expression relating body weight to age. The full expression relating weight to age has five parameters (constants), so that it can readily be adapted to fit a range of standardized growth curves for men and women. Tissue growth and volumes are linked to body weight; this provides explicit modeling of concentrations of lead in tissues. Other physiologic functions (e.g., bone formation) are linked to body weight, to age, or to both.

Lead exchange between blood plasma and bone is simulated as parallel processes occurring in cortical (80% of bone volume) and trabecular bone (20% of bone volume). Uptake and release of lead from trabecular bone and metabolically active cortical bone are functions of bone formation and resorption rates, respectively. Rates of bone formation and resorption are simulated as age-dependent functions, which gives rise to an age-dependence of lead kinetics in bone. The model simulates an age-related transition from immature bone, in which bone turn-over (formation and resorption) rates are relatively high, to mature bone, in which turn-over is relatively slow. Changes in bone mineral turnover associated with senescence (e.g., postmenopausal osteoporosis) are not represented in the model. In addition to metabolically active regions of bone, in which lead uptake and loss is dominated by bone formation and loss, a region of slow kinetics in mature cortical bone is also simulated, in which lead uptake and release to blood occur by heteroionic exchange with other minerals (e.g., calcium). Heteroionic exchange is simulated as a radial diffusion in bone volume of the osteon. All three processes are linked to body weight, or the rate of change of weight with age. This approach allows for explicit simulation of the effects of bone formation (e.g., growth) and loss, changes in bone volume, and bone maturation on lead

Figure 3-10. Compartments and Pathways of Lead Exchange in the O'Flaherty Model*



*Schematic model for lead kinetics in which lead distribution is represented by flows from blood plasma to liver, kidney, richly-perfused tissues, poorly-perfused tissues, and cortical and trabecular bone. The model simulates tissue growth with age, including growth and resorption of bone mineral.

Sources: O'Flaherty 1991b, 1993, 1995a

uptake and release from bone. Exchanges of lead between blood plasma and soft tissues (e.g., kidney and liver) are represented as flow-limited processes. The model simulates saturable binding of lead in erythrocytes; this replicates the curvilinear relationship between plasma and erythrocyte lead concentrations observed in humans (see Sections 3.3.2 and 3.4.1). Excretory routes include kidney to urine and liver to bile. Total excretion (clearance from plasma attributable to bile and urine) is simulated as a function of glomerular filtration rate. Biliary and urinary excretory rates are proportioned as 70 and 30% of the total plasma clearance, respectively.

The O'Flaherty Model simulates lead intake from inhalation and ingestion. Inhalation rates are age-dependent. Absorption of inhaled lead is simulated as a fraction (0.5) of the amount inhaled, and is independent of age. The model simulates ingestion exposures from infant formula, soil and dust ingestion, and drinking water ingestion. Rates of soil and dust ingestion are age-dependent, increasing to approximately 130 mg/day at age 2 years, and declining to <1 mg/day after age 10 years. Gastrointestinal absorption of lead in diet and drinking water is simulated as an age-dependent fraction, declining from 0.58 of the ingestion rate at birth to 0.08 after age 8 years. These values can be factored to account for relative bioavailability when applied to absorption of lead ingested in dust or soil.

Risk assessment. The O'Flaherty Model has several potential applications to risk assessments at hazardous waste sites. The model can be used to predict the blood lead concentrations in a broad age range, including infants, children, and adults. The model may be modified to simulate the pharmacokinetics of lead in potential sensitive subpopulations, including pregnant women and fetuses, as well as older adults. The model does not contain a detailed exposure module; however, model simulations have been run holding physiological variables fixed and allowing soil and dust lead concentrations to vary in order to estimate the range of environmental lead concentrations that would be expected to yield close correspondence between predicted and observed blood lead concentrations (O'Flaherty 1993, 1995a).

The O'Flaherty Model, as described in O'Flaherty (1993, 1995a), utilizes point estimates for parameter values and yields point estimates as output; however, a subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability in exposure, absorption, and erythrocyte lead binding capacity (Beck et al. 2001). This extension of the model can be used to predict the probability that children exposed to lead in environmental media will have blood lead concentrations exceeding a health-based level of concern (e.g., 10 μg/dL).

The model was designed to operate with an exposure time step on 1 year (the smallest time interval for a single exposure event). However, the implementation code allows constructions of simulations with an exposure time step as small as 1 day, which would allow simulation of rapidly changing intermittent exposures (e.g., an acute exposure event).

Validation of the model. The O'Flaherty Model was initially calibrated to predict blood, bone, and tissue lead concentrations in rats (O'Flaherty 1991a), and subsequently modified to reflect anatomical and physiological characteristics in children (O'Flaherty 1995a), adults (O'Flaherty 1993), and Cynomolgus monkeys (*M. fasicularis*) (O'Flaherty et al. 1998). Model parameters were modified to correspond with available information on species- and age-specific anatomy and physiological processes described above. In general, the model has been shown to reproduce blood lead observations in children and adults well, except in instances where lead is ingested at very high concentrations (O'Flaherty 1993, 1995a).

Target tissues. Output from the O'Flaherty Model is an estimate of age-specific blood lead concentrations. The O'Flaherty Model has also been used to predict lead concentrations in bone and other tissue compartments (O'Flaherty 1995a), in order to evaluate correspondence between predicted tissue concentrations and observed concentrations in different populations of children and adults.

Species extrapolation. The mathematical structure of the O'Flaherty Model for humans is designed to accept parameter values that reflect the physiology and metabolism of different species (O'Flaherty 1993). Although the model has been calibrated to predict compartmental lead masses for human children and adults; the model for humans was derived from a model for rats (O'Flaherty 1991a), and has been successfully extrapolated, with modification, to nonhuman primates (O'Flaherty et al. 1998). Crucial to the extrapolation of the model across species are the parameters describing bone formation, resorptions, and volume. Certain parameter values describing bone physiology and metabolism are likely to be relatively independent of species; for example, volume fractions of cortical bone and trabecular bone appear to be similar across species (i.e., 80% cortical, 20% trabecular) (Gong et al. 1964). However, while the potential for bone resorption and accretion of new bone is present in all species, the magnitude and age dependence of these processes are variable with species (O'Flaherty 1995a). These factors would have to be evaluated in extrapolating the model to other species.

Interroute extrapolation. The O'Flaherty Model simulates intakes and uptake of ingested and inhaled lead and includes media-specific estimates of absorption from the gastrointestinal tract.

3.3.5.2 IEUBK Model

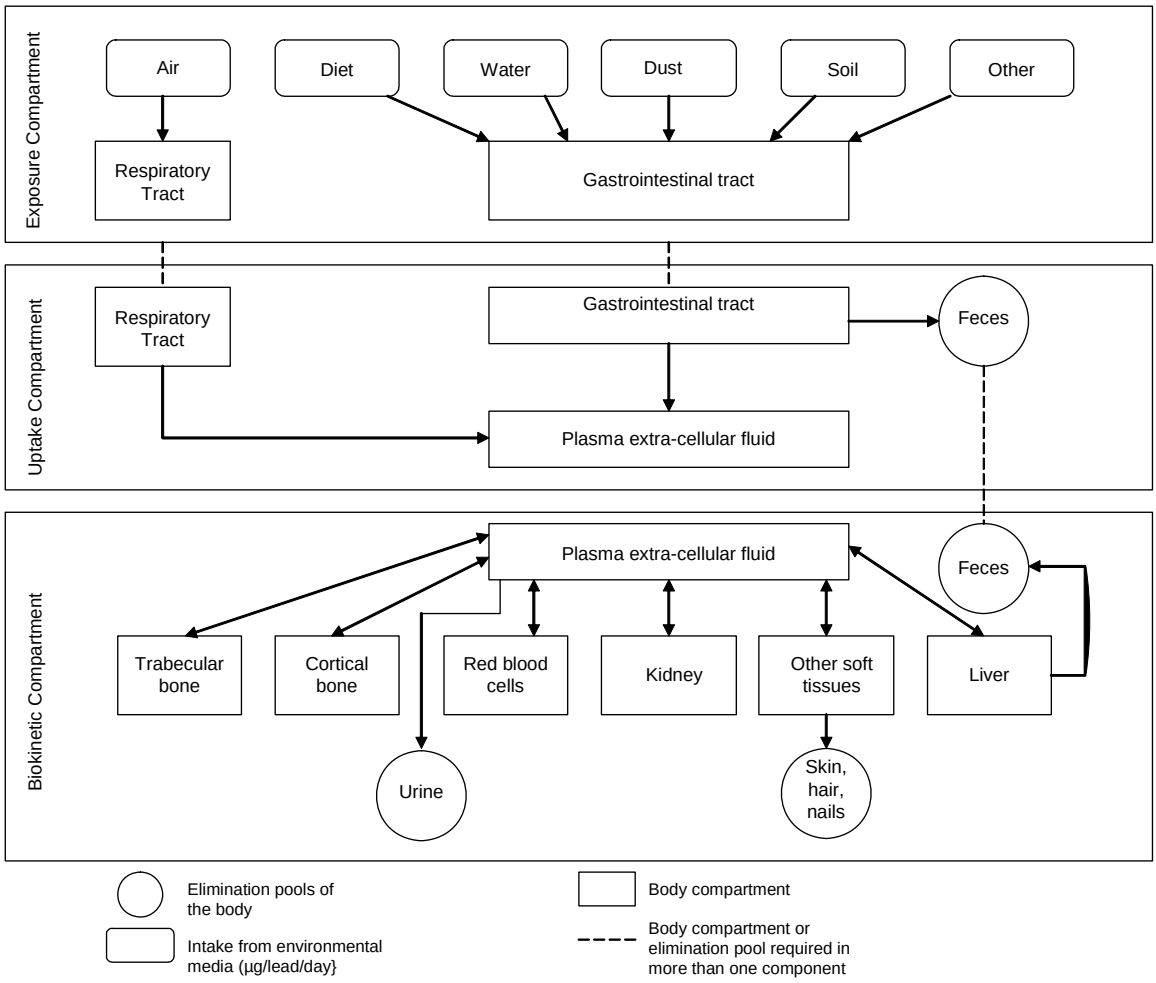
The IEUBK Model for Lead in Children is a classical multicompartmental pharmacokinetics model linked to an exposure and probabilistic model of blood lead concentration distributions in populations of children ages 0–7 years (EPA 1994a, 1994b; White et al. 1998). Figure 3-11 shows a conceptualized representation of the IEUBK Model. The model has four major submodels: (1) exposure model, in which average daily intakes of lead (μg/day) are calculated for each inputted exposure concentration (or rates) of lead in air, diet, dust, soil, and water; (2) uptake model, which converts environmental media-specific lead intake rates calculated from the exposure model into a media-specific time-averaged uptake rate (μg/day) of lead to the central compartment (blood plasma); (3) biokinetic model, which simulates the transfer of absorbed lead between blood and other body tissues, elimination of lead from the body (via urine, feces, skin, hair, and nails), and predicts an average blood lead concentration for the exposure time period of interest; and (4) blood lead probability model, which applies a log-normal distribution (with parameters geometric mean and geometric standard deviation) to predict probabilities for the occurrence of a specified given blood lead concentration in a population of similarly exposed children.

Description of the Model

Exposure Model. The exposure model simulates intake of lead (μg/day) for inputted exposures to lead in air (μg/m^3), drinking water (μg/L), soil-derived dust (μg/g), or diet (μg/day). The exposure model operates on a 1-year time step, the smallest time interval for a single exposure event. The model accepts inputs for media intake rates (e.g., air volumes breathing rates, drinking water consumption rate, soil and dust ingestion rate). The air exposure pathway is partitioned in exposures to outdoor air and indoor air; with age-dependent values for time spent outdoors and indoors (hours/day). Exposure to lead to soil-derived dust is also partitioned into outdoor and indoor contributions. The intakes from all ingested exposure media (diet, drinking water, soil-derived dust) are summed to calculate a total intake to the gastrointestinal tract, for estimating capacity-limited absorption (see description of the uptake model).

Uptake Model. The uptake model simulates lead absorption for the gastrointestinal tract as the sum of a capacity-limited (represented by a Michaelis-Menten type relationship) and unlimited processes (represented by a first-order, linear, relationship). These two terms are intended to represent two different mechanisms of lead absorption, an approach that is in accord with limited available data in humans and animals that suggest a capacity limitation to lead absorption (see Sections 3.3.2 and 3.4.1). One of the parameters for the capacity-limited absorption process (that represents that maximum rate of absorption)

Figure 3-11. Structure of the IEUBK Model for Lead in Children*



*Schematic for integrated lead exposure-kinetics model in which simulated multi-media exposures are linked to simulations of lead uptake (i.e., absorption into the plasma-ECF) tissue distribution, and excretion.

Sources: EPA 1994a, 1994b

is age-dependent. The above representation gives rise to a decrease in the fractional absorption of ingested lead as a function of total lead intake as well as an age-dependence of fractional lead absorption. Absorption fractions are also medium-specific. At 30 months of age, at low intakes (<200 μg/day), below the rates at which capacity-limitation has a significant impact on absorption, the fraction of ingested lead in food or drinking water that is absorbed is 0.5 and decreases to approximately 0.11 (intake, >5,000 μg/day). For lead ingested in soil or dust, fractional absorption is 0.35 at low intakes (<200 μg/day) and decreases to 0.09 (intake, >5,000 μg/day).

The uptake model assumes that 32% of inhaled lead is absorbed. This value was originally assigned based on a scenario of exposure to active smelter emissions, which assumed the particle size distribution in the vicinity of an active lead smelter (<1 μm, 12.5%; 1–2.5 μm, 12.5%; 2–15 μm, 20%; 15–30 μm, 40%; >30 μm, 15%); size-specific deposition fractions for the nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract; and region-specific absorption fractions. Lead deposited in the alveolar region is assumed to be completely absorbed from the respiratory tract, whereas lead deposited in the nasopharyngeal and tracheobronchial regions (30–80% of the lead particles in the size range 1–15 μm) is assumed to be transported to the gastrointestinal tract.

Biokinetics Model. The biokinetics model includes a central compartment, six peripheral body compartments, and three elimination pools. The body compartments include plasma and extra cellular fluid (central compartment), kidney, liver, trabecular bone, cortical bone, and other soft tissue (EPA 1994a). The model simulates growth of the body and tissues, compartment volumes, and lead masses and concentrations in each compartment. Blood lead concentration at birth (neonatal) is assumed to be 0.85 of the maternal blood lead. Neonatal lead masses and concentrations are assigned to other compartments based on a weighted distribution of the neonatal blood lead concentration. Exchanges between the central compartment and tissue compartments are simulated as first-order processes, which are parameterized with unidirectional, first-order rate constants. Bone is simulated as two compartments: a relatively fast trabecular bone compartment (representing 20% of bone volume) and a relatively slow cortical bone compartment (representing 80% of the bone volume). Saturable uptake of lead into erythrocytes is simulated, with a maximum erythrocyte lead concentration of 120 μg/L. Excretory routes simulated include urine, from the central compartment; bile-feces, from the liver; and a lumped excretory pathway represented losses from skin, hair and nail, from the other soft tissue compartment.

Blood Lead Probability Model. Inputs to the IEUBK Model are exposure point estimates that are intended to represent time-averaged central tendency exposures. The output of the model is a central

tendency estimate of blood lead concentration for children who might experience the inputted exposures. However, within a group of similarly exposed children, blood lead concentrations would be expected to vary among children as a result of inter-individual variability in media intakes, absorption, and biokinetics. The model simulates the combined impact of these sources of variability as a lognormal distribution of blood lead concentration for which the geometric mean (GM) is given by the central tendency blood lead concentration outputted from the biokinetics model and the GSD is an input parameter. The resulting lognormal distribution also provides the basis for predicting the probability of occurrence of given blood lead concentration within a population of similarly exposed children. The model can be iterated for varying exposure concentrations (e.g., a series of increasing soil lead concentration) to predict the media concentration that would be associated with a probability of 0.05 for the occurrence of a blood lead concentration exceeding 10 μg/dL. A subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability and uncertainty in exposure and absorption (Goodrum et al. 1996; Griffin et al. 1999). This extension of the model provides an alterative to the blood lead probability model for incorporating, explicitly, estimates of variability (and uncertainty in variability) in exposure and absorption into predictions of an expected probability distribution of blood lead concentrations.

Risk assessment. The IEUBK Model was developed to predict the probability of elevated blood lead concentrations in children. The model addresses three components of human health risk assessment: (1) the multimedia nature of exposures to lead; (2) lead pharmacokinetics; and (3) significant variability in exposure and risk. Thus, the IEUBK Model can be used to predict the probability that children of ages up to 7 years who are exposed to lead in multiple environmental media would have blood lead concentrations exceeding a given health-based level of concern (e.g., 10 μg/dL). These risk estimates can be useful in assessing the possible consequences of alternative lead exposure scenarios following intervention, abatement, or other remedial actions. The IEUBK Model was not developed to assess lead risks for age groups older than 7 years. The model operates with an exposure time step on 1 year (the smallest time interval for a single exposure event) and, therefore, is more suited to applications in which long-term (i.e., >1 year) average exposures and blood lead concentrations are to be simulated (Lorenzana et al. 2005).

Validation of the model. An evaluation of the IEUBK Model has been conducted in which model predictions of blood lead concentrations in children were compared to observations from epidemiologic studies of hazardous waste sites (Hogan et al. 1998). Data characterizing residential lead exposures and blood lead concentrations in children living at four Superfund NPL sites were collected in a study

designed by ATSDR and EPA. The residential exposure data were used as inputs to the IEUBK Model and the resulting predicted blood lead concentration distributions were compared to the observed distributions in children living at the same residences. The IEUBK Model predictions agreed reasonably well with observations for children whose exposures were predominantly from their residence (e.g., who spent no more than 10 hours/week away from home). The predicted geometric mean blood lead concentrations were within 0.7 μg/dL of the observed geometric means at each site. The prediction of the percentage of children expected to have blood lead concentrations exceeding 10 μg/dL were within 4% of the observed percentage at each site. This evaluation provides support for the validity of the IEUBK Model for estimating blood lead concentrations in children at sites where their residential exposures can be adequately characterized. Similar empirical comparisons of the IEUBK Model have shown that agreement between model predictions and observed blood lead concentrations at specific locations is influenced by numerous factors, including the extent to which the exposure and blood lead measurements are adequately matched, and site-specific factors (e.g., soil characteristics, behavior patterns, bioavailability) that may affect lead intake or uptake in children (Bowers and Mattuck 2001; EPA 2001c). In addition to the above empirical comparisons, the computer code used to implement the IEUBK Model (IEUBK version 0.99d) has undergone an independent validation and verification and has been shown to accurately implement the conceptual IEUBK Model (Zaragoza and Hogan 1998).

Target tissues. The output from the IEUBK Model is an estimate of age-specific blood lead concentrations. The current version of the IEUBK Model does not save as output the interim parameter values determined for lead in other tissues or tissue compartments.

Species extrapolation. Data in both animals and humans (children and adults) describing the absorption, distribution, metabolism, and excretion of lead provide the biological basis of the biokinetic model and parameter values used in the IEUBK Model. The model is calibrated to predict compartmental lead masses for human children ages 6 months to 7 years, and is not intended to be applied to other species or age groups.

Interroute extrapolation. The IEUBK Model includes an exposure module that simulates age-specific lead exposures via inhalation and ingestion of lead in diet, dust, lead-based paint, soil, and water. The total exposure from each route is defined as the total lead uptake (μg/day) over a 1-month period. Other routes of exposure may be simulated by the IEUBK Model pending available information from which to characterize both the exposure and media-specific absorption variables. Values for variables in the biokinetic component of the IEUBK Model are independent of the route of exposure.

3.3.5.3 Leggett Model

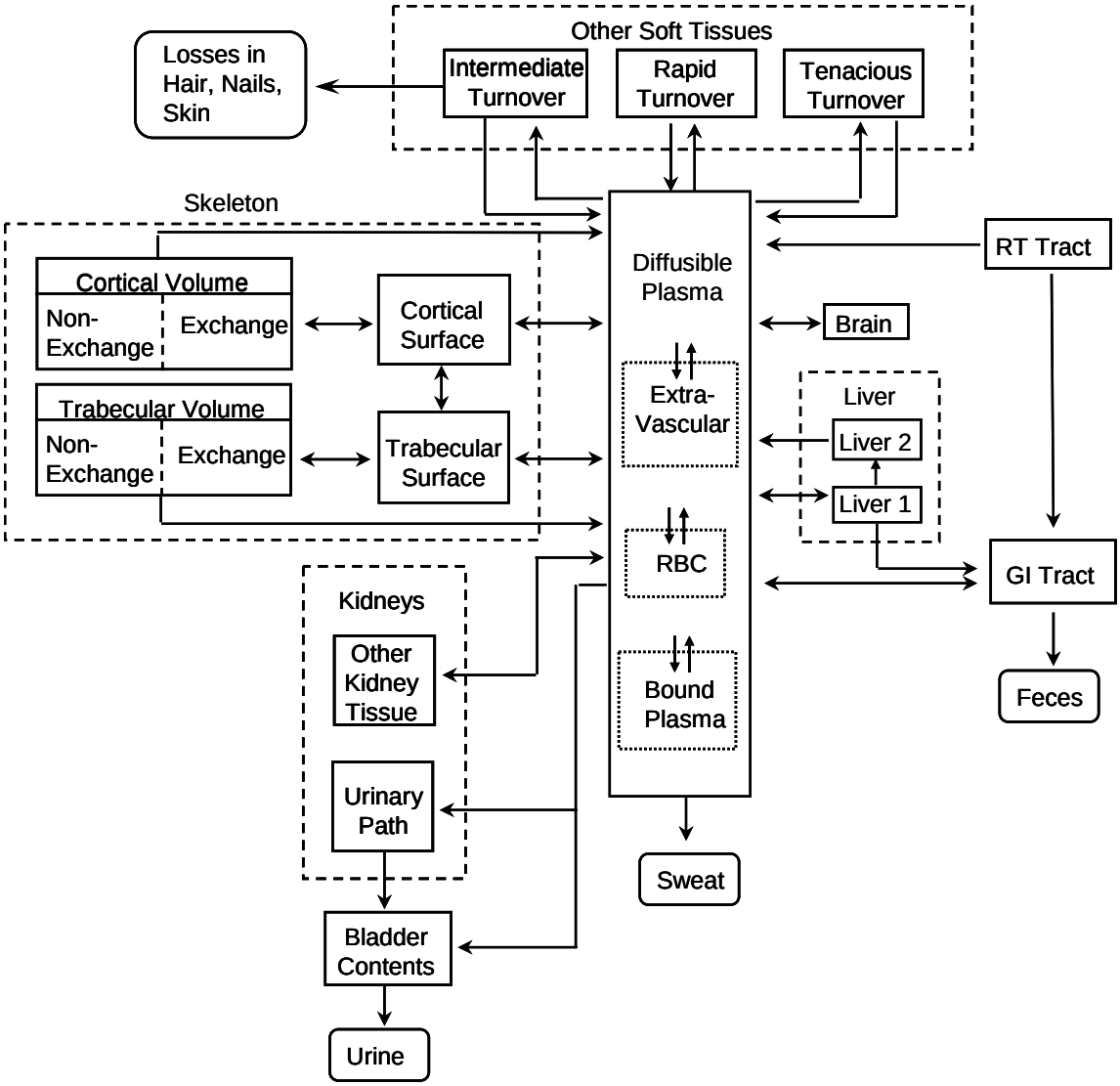
The Leggett Model is a classical multicompartmental pharmacokinetic model of lead uptake and disposition in children and adults (Leggett 1993). Figure 3-12 shows a conceptualized representation of the model, including the movement of lead from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between diffusible blood plasma, soft tissues, bone compartments, and excretion from liver, kidneys, and sweat. A detailed exposure module is not linked to the Leggett Model; rather, lead exposure estimates are incorporated into the model as age-specific point estimates of average daily intake (μg/day) from inhalation and ingestion. A detailed description of the model and its potential application to risk assessment are provided below.

Description of the model. The Leggett Model includes a central compartment, 15 peripheral body compartments, and 3 elimination pools, as illustrated in Figure 3-12. Transport of lead from blood plasma to tissues is assumed to follow first-order kinetics. Transfer rate constants vary with age and blood lead concentration. Above a nonlinear threshold concentration in red blood cells (assumed to be 60 μg/dL), the rate constant for transfer to red blood cells declines and constants to all other tissues increase proportionally (Leggett 1993). This replicates the nonlinear relationship between plasma and red blood observed in humans (see Section 3.4.1). The model simulates blood volume as an age-dependent function, which allows simulation of plasma and blood lead concentrations. Lead masses are simulated in all other tissues (tissue volumes are not simulated).

Unidirectional, first-order transfer rates (day^{-1}) between compartments were developed for six age groups, and intermediate age-specific values are obtained by linear interpolation. The total transfer rate from diffusible plasma to all destinations combined is assumed to be 2,000 day^{-1}, based on isotope tracer studies in humans receiving lead via injection or inhalation. Values for transfer rates in various tissues and tissue compartments are based on measured deposition fractions or instantaneous fractional outflows of lead between tissue compartments (Leggett 1993).

The Leggett Model was developed from a biokinetic model originally developed for the International Commission on Radiological Protection (ICRP) for calculating radiation doses from environmentally important radionuclides, including radioisotopes of lead (Leggett 1993). The Leggett Model simulates age-dependent bone physiology using a model structure developed for application to the alkaline earth elements, but parameterized using data specific to lead where possible. The model simulates both rapid

Figure 3-12. Compartments and Pathways of Lead Exchange in the Leggett Model*



*Schematic model for lead kinetics in which lead distribution is represented by exchanges between the central plasma-ECF and tissue compartments. Bone is represented as having surface (which rapidly exchanges with plasma-ECF), and volume compartments; the latter simulates slow exchange with the surface and slow return of lead to the plasma-ECF from bone resorption.

Source: Leggett 1993

exchange of lead with plasma via bone surface and slow loss by bone resorption. Cortical bone volume (80% of bone volume) and trabecular bone volume (20% of bone volume) are simulated as bone surface compartments, which rapidly exchange with lead the blood plasma, and bone volume, within which are *exchangeable* and *nonexchangeable* pools. Lead enters the exchangeable pool of bone volume via the bone surface and can return to the bone surface, or move to the nonexchangeable pool, from where it can return to the blood only when bone is resorbed. Rate constants for transfer of lead from the nonexchangeable pools and blood plasma vary with age to reflect the age-dependence of bone turnover.

The liver is simulated as two compartments; one compartment has a relatively rapid uptake of lead from plasma and a relatively short removal half-life (days) for transfers to plasma and to the small intestine by biliary secretion; a second compartment simulates a more gradual transfer to plasma of approximately 10% of lead uptake in liver. The kidney is simulated as two compartments, one that exchanges slowly with blood plasma and accounts for lead accumulation kidney tissue and a second compartment that receives lead from blood plasma and rapidly transfers lead to urine, with essentially no accumulation (urinary pathway). Other soft tissues are simulated as three compartments representing rapid, intermediate, and slow turnover rates (without specific physiologic correlates). Other excretory pathways (hair nails and skin) are represented as a lumped pathway from the intermediate turnover rate soft tissue compartment.

The Leggett Model simulates lead intakes from inhalation, ingestion, or intravenous injection. The latter was included to accommodate model evaluations based on intravenous injection studies in humans and animal models. The respiratory tract is simulated as four compartments into which inhaled lead is deposited and absorbed with half-times of 1, 3, 10, and 48 hours. Four percent of the inhaled lead is assumed to be transferred to the gastrointestinal tract. These parameter values reflect the data on which the model was based, which were derived from studies in which human subjects inhaled submicron lead-bearing particles (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). These assumptions would not necessarily apply to exposures to large airborne particles (see Section 3.3.1.1). Absorption of ingested lead simulated as an age-dependent fraction of the ingestion rate, declining from 0.45 at birth to 0.3 at age 1 year (to age 15 years), and to 0.15 after age 25 years.

Risk assessment. The Leggett Model has several potential applications to risk assessment at hazardous waste sites. The model can be used to predict blood lead concentrations in both children and adults. The model allows the simulation of lifetime exposures, including assumptions of blood lead

concentrations at birth (from which levels in other tissue in the first time step after birth are calculated). Thus, exposures and absorption of lead prior to any given period of time during the lifetime can be simulated with the Leggett Model. The model operates with an exposure time step on 1 day (the smallest time interval for a single exposure event), which allows simulation of rapidly changing intermittent exposures (Khoury and Diamond 2003; Lorenzana et al. 2005). The model does not contain a detailed exposure module and, therefore, requires assumptions regarding total lead intake from multiple exposure media. In addition, the model utilizes point estimates for intakes and yields point estimates as output (e.g., blood lead concentration) and predicted blood lead distributions in exposed populations.

Validation of the model. Output from the Leggett Model has been compared with data in children and adult subjects exposed to lead in order to calibrate model parameters. The model appears to predict blood lead concentrations in adults exposed to relatively low levels of lead; however, no information could be found describing efforts to compare predicted blood lead concentrations with observations in children.

Target tissues. The output from the Leggett Model is an estimate of age-specific PbB concentrations. The current version of the Leggett Model does not save as output the interim parameter values determined for lead in other tissues or tissue compartments.

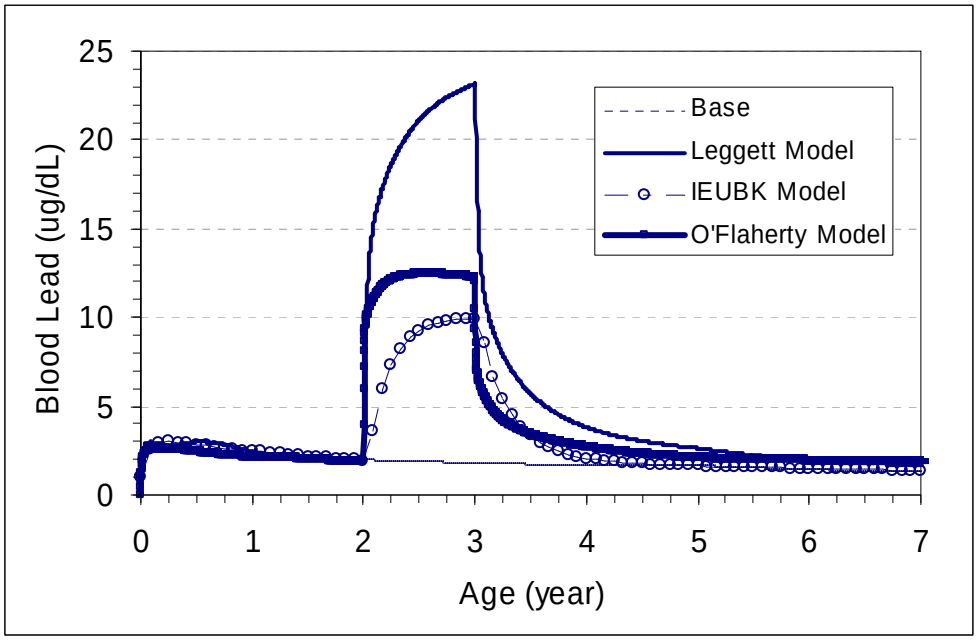
Species extrapolation. Data on both animals and humans (children and adults) describing the absorption, distribution, metabolism, and excretion of lead provide the biological basis of the biokinetic model and parameter values used in the Leggett Model. The model is calibrated to predict compartmental lead masses only for humans, both children and adults.

Interroute extrapolation. The values for pharmacokinetic variables in the Leggett Model are independent of the route of exposure. Based on the description of the inputs to the model provided by Leggett (1993), lead intake from different exposure routes is defined as a total lead intake from all routes of exposure.

3.3.5.4 Model Comparisons

The O'Flaherty, IEUBK, and Leggett Models differ considerably in the way each represents tissues, exchanges of lead between tissues, and lead exposure. Figure 3-13 compares the PbBs predicted by each model for a hypothetical child who ingests 100 μg lead/day in soil for a period of 1 year beginning at the

Figure 3-13. Blood Lead Concentrations in Children Predicted by the O'Flaherty, IEUBK, and Leggett Models*



*The simulations are of a hypothetical child who has a PbB of 2 ⏭g/dL at age 2 years, and then experiences a 1-year exposure to 100 ⏭g Pb/day. The 100 ⏭g/day exposure was simulated as an exposure to lead in soil in the IEUBK Model. Default bioavailability assumptions were applied in all three models.

age of 2 years (e.g., equivalent to ingestion of 100 μg soil/day at a soil lead concentration of 1,000 mg lead/g soil). The 100-μg/day exposure is superimposed on a baseline exposure that yields a PbB of approximately 2 μg/dL at 2 years of age. All three models predict an increase in PbB towards a quasi-steady state during the exposure period, followed by a decline towards the pre-exposure baseline PbB with a half-time of approximately 1 month. Predicted PbBs at the end of the 12-month soil exposure period were 6, 10, and 23 μg/dL for the IEUBK, O'Flaherty, and Leggett Models, respectively. Differences in the magnitude of the predicted impact of the soil exposure on PbB reflect differences in assumptions about lead biokinetics and cannot be attributed solely to different assumptions about lead bioavailability. Bioavailability assumptions in the three models for the age range 2–3 years are: O'Flaherty Model, 45% (50% at age 2 years, decreasing to 40% at age 3 years); IEUBK Model, 30% (soil lead at low intakes); and Leggett Model, 30%. A comparison of model predictions for a similar exposure during adulthood (100 μg Pb/day for 1 year, beginning at age 25) is shown in Figure 3-14. Predicted PbBs at the end of the12-month soil exposure period were: 3 and 8 μg/dL for the O'Flaherty and Leggett Models, respectively. Both the O'Flaherty and Leggett Models predict a smaller change in PbB in adults, compared to children, for a similar increment in exposure. This is attributed, in part, to assumptions of lower lead bioavailability in adults (i.e., O'Flaherty, 8%; Leggett, 15%).

3.3.5.5 Slope Factor Models

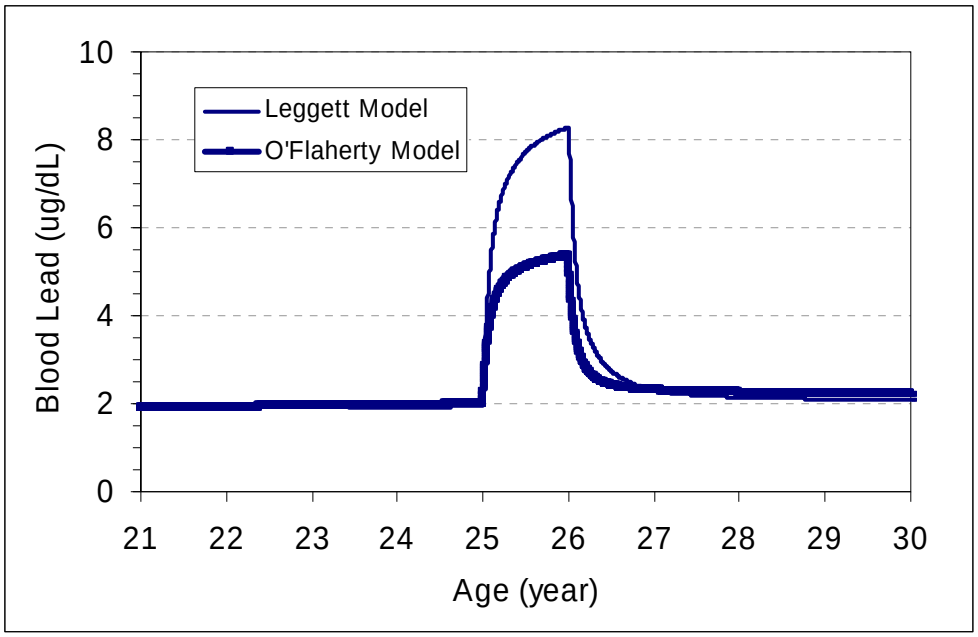
Slope factor models have been used as simpler alternatives to compartmental models for predicting PbBs, or the change in PbB, associated with a given exposure (Abadin et al. 1997a; Bowers et al. 1994; Carlisle and Wade 1992; EPA 2003b, Stern 1994, 1996). In slope factor models, lead biokinetics is represented with a simple linear relationship between the PbB and either lead uptake (biokinetic slope factor, BSF) or lead intake (intake slope factor, ISF). The models take the general mathematical forms:

$$PbB = E \cdot ISF$$

$$PbB = E \cdot AF \cdot BSF$$

where E is a expression for exposure (e.g., soil intake x soil lead concentration) and AF is the absorption fraction for lead in the specific exposure medium of interest. Intake slope factors are based on ingested rather than absorbed lead and, therefore, integrate both absorption and biokinetics into a single slope factor, whereas models that utilize a biokinetic slope factor to account for absorption in the relationship include an absorption parameter. Slope factors used in various models are presented in Table 3-10. Of

Figure 3-14. Blood Lead Concentrations in Adults Predicted by the O'Flaherty and Leggett Models*



*The simulations are of a hypothetical adult who has a PbB of 2 ⏭g/dL at age 25 years, and then experiences a 1-year exposure to 100 ⏭g Pb/day. Default bioavailability assumptions were applied in all three models.

Table 3-10. Comparison of Slope Factors in Selected Slope Factor Models

Model	Receptor	Slope factor		Absorption fraction
		Intake	Biokinetics	
Bowers et al. 1994	Adult	ND	0.375	0.08
Carisle and Wade 1992	Child	Soil/dust: 0.07 Water: 0.04	ND	ND
Carisle and Wade 1992	Adult	Soil/dust: 0.018 Water: 0.04	ND	ND
EPA 1996	Adult	ND	0.4	0.12
Stern 1994	Child	Residential: T (0.056, 0.16, 0.18)	ND	ND
Stern 1996	Adult	Non-residential: U (0.014, 0.034)	ND	ND

ND = No data; T = triangular probability distribution function (PDF); U = uniform PDF

the various models presented in Table 3-9, two Bowers et al. (1994) and EPA (2003b) models implement BSFs. The slope factors used in both models (approximately 0.4 μg/dL per μg Pb/day) are similar to biokinetic slope factors predicted from the O'Flaherty Model (0.65 μg/dL per μg Pb uptake/day) and Legget Model (0.43 μg/dL per μg Pb uptake/day) for simulations of adult exposures (Maddaloni et al. 2005). In general, intake slope factors are derived from epidemiologic observations. A review of slope factors relating medium-specific exposures and blood lead concentrations derived from epidemiologic studies is provided in Appendix D (Abadin et al. 1997a).

3.4 MECHANISMS OF ACTION

3.4.1 Pharmacokinetic Mechanisms

Absorption

Gastrointestinal Absorption of Inorganic Lead. Gastrointestinal absorption of inorganic lead occurs primarily in the duodenum (Mushak 1991). The exact mechanisms of absorption are unknown and may involve active transport and/or diffusion through intestinal epithelial cells (transcellular) or between cells (paracellular), and may involve ionized lead (Pb^{+2}) and/or inorganic or organic complexes of lead. *In vitro* studies of lead speciation in simulated human intestinal chyme indicate that the concentration of ionized lead is negligible at lead concentrations below 10^{-3} M (207 mg/L) and that lead phosphate and bile acid complexes are the dominant forms when inorganic lead salts (e.g., lead nitrate) are added to chyme (Oomen et al. 2003a). However, these complexes may be sufficiently labile to provide ionized lead for transport across cell membranes (Oomen et al. 2003b). Saturable mechanisms of absorption have been inferred from measurements of net flux kinetics of lead in the *in situ* perfused mouse intestine, the *in situ* ligated chicken intestine, and in *in vitro* isolated segments of rat intestine (Aungst and Fung 1981; Barton 1984; Flanagan et al. 1979; Mykkänen and Wasserman 1981). By analogy to other divalent cations, saturable transport mechanisms for Pb^{+2} may exist within the mucosal and serosal membranes and within the intestinal epithelial cell. For calcium and iron, these are thought to represent membrane carriers (e.g., Ca^{2+}-Mg^{2+}-ATPase, Ca^{2+}/Na^{+} exchange, DMT1) or facilitated diffusion pathways (e.g., Ca^{2+} channel) and intracellular binding proteins for Ca^{2+} (Bronner et al. 1986; Fleming et al. 1998b; Gross and Kumar 1990; Teichmann and Stremmel 1990). Numerous observations of nonlinear relationships between blood lead concentration and lead intake in humans suggest the existence of a saturable absorption mechanism or some other capacity-limited process in the distribution of lead in humans (Pocock et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1984). In immature swine that received oral doses of lead in soil, lead dose-blood lead relationships were nonlinear; however, dose-tissue lead

relationships for bone, kidney, and liver were linear. The same pattern (nonlinearity for blood lead and linearity for tissues) was observed in swine administered lead acetate intravenously (Casteel et al. 1997). These results raise the question of whether there is an effect of dose on absorption or on some other aspect of the biokinetics of lead.

Gastrointestinal absorption of lead is influenced by dietary and nutritional calcium and iron status. An inverse relationship has been observed between dietary calcium intake and blood lead concentration (Mahaffey et al. 1986; Ziegler et al. 1978). Complexation with calcium (and phosphate) in the gastrointestinal tract and competition for a common transport protein have been proposed as possible mechanisms for this interaction (Barton et al. 1978a; Heard and Chamberlain 1982). Absorption of lead from the gastrointestinal tract is enhanced by dietary calcium depletion or administration of cholecalciferol. This "cholecalciferol-dependent" component of lead absorption appears to involve a stimulation of the serosal transfer of lead from the epithelium, not stimulation of mucosal uptake of lead (Mykkänen and Wasserman 1981, 1982). This is similar to the effects of cholecalciferol on calcium absorption (Bronner et al. 1986; Fullmer and Rosen 1990).

Iron deficiency is also associated with increased blood lead concentration in children (Mahaffey and Annest 1986; Marcus and Schwartz 1987). In rats, iron deficiency increases the gastrointestinal absorption of lead, possibly by enhancing binding of lead to iron binding proteins in the intestine (Morrison and Quaterman 1987). Iron ($FeCl_2$) added to the mucosal fluid of the everted rat duodenal sac decreases serosal transfer, but not mucosal uptake of lead (Barton 1984).

Thus, interactions between iron and lead also appear to involve either intracellular transfer or basolateral transfer mechanisms. When mRNA for DMT1, a mucosal membrane carrier for iron, was suppressed in Caco 2 cells (a human gastrointestinal cell line) the rate of iron and cadmium uptake decreased by 50% compared to cells in which DMT1 mRNA was not suppressed; however, DMT1 mRNA suppression did not alter the rate of lead uptake by Caco 2 cells, indicating that lead may enter Caco 2 cells through a mechanism that is independent of DMT1 (Bannon et al. 2003). The above observations suggest that rate-limiting saturable mechanisms for lead absorption are associated with transfer of lead from cell to blood rather than with mucosal transfer. Similar mechanisms may contribute to lead-iron and lead-calcium absorption interactions in humans, and, possibly interactions between lead and other divalent cations such as cadmium, copper, magnesium and zinc.

Distribution

Red Blood Cells. Lead in blood is rapidly taken by red blood cells, where it binds to several intracellular proteins. Although the mechanisms by which lead crosses cell membranes have not been fully elucidated, results of studies in intact red blood cells and red blood cell ghosts indicate that there are two, and possibly three, pathways for facilitated transfer of lead across the red cell membrane. The major proposed pathway is an anion exchanger that is dependent upon HCO_3^- and is blocked by anion exchange inhibitors (Bannon et al. 2000, Simons 1985, 1986a, 1986b, 1993). A second minor pathway, which does not exhibit HCO_3^- dependence and is not sensitive to anion exchange inhibitors, may also exist (Simons 1986b). Lead and calcium may also share a permeability pathway, which may be a Ca^{2+}-channel (Calderon-Salinas et al. 1999). Lead is extruded from the erythrocyte by an active transport pathway, most likely a (Ca^{2+}, Mg^{2+})-ATPase (Simons 1988).

ALAD is the primary binding ligand for lead in erythrocytes (Bergdahl et al. 1997a, 1998; Sakai et al. 1982; Xie et al. 1998). Lead binding to ALAD is saturable; the binding capacity has been estimated to be approximately 850 µg/dL red blood cells (or approximately 40 µg/dL whole blood) and the apparent dissociation constant has been estimated to be approximately 1.5 µg/L (Bergdahl et al. 1998). Two other lead-binding proteins have been identified in the red cell, a 45 kDa protein (Kd 5.5 µg/L) and a smaller protein(s) having a molecular weight <10 kDa (Bergdahl et al. 1996, 1997a, 1998). Of the three principal lead-binding proteins identified in red blood cells, ALAD has the strongest affinity for lead (Bergdahl et al. 1998) and appears to dominate the ligand distribution of lead (35–84% of total erythrocyte lead) at blood lead levels below 40 µg/dL (Bergdahl et al. 1996, 1998; Sakai et al. 1982).

Lead binds to and inhibits the activity of ALAD (Gercken and Barnes 1991; Gibbs et al. 1985; Sakai et al. 1982, 1983). Synthesis of ALAD appears to be induced in response to inhibition of ALAD and, therefore, in response to lead exposure and binding of lead to ALAD (Boudene et al. 1984; Fujita et al. 1982). Several mechanisms may participate in the induction of ALAD, including (1) inhibition of ALAD directly by lead; (2) inhibition by protoporphyrin, secondary to accumulation of protoporphyrin as a result of lead inhibition of ferrochelatase; and (3) accumulation of ALA, secondary to inhibition of ALAD, which may stimulate ALAD synthesis in bone marrow cells (Boudene et al. 1984; Fujita et al. 1982).

ALAD is a polymorphic enzyme with two alleles (ALAD 1 and ALAD 2) and three genotypes: ALAD 1,1, ALAD 1,2, and ALAD 2,2 (Battistuzzi et al. 1981). Higher PbBs were observed in individuals with the ALAD 1,2 and ALAD 2,2 genotypes compared to similarly exposed individuals with

the ALAD 1,1 genotype (Astrin et al. 1987; Hsieh et al. 2000, Schwartz et al. 2000b; Wetmur et al. 1991). This observation has prompted the suggestion that the ALAD-2 allele may have a higher binding affinity for lead than the ALAD 1 allele (Bergdahl et al. 1997b), a difference that could alter lead-mediated outcomes. Several studies have been conducted to specifically evaluate whether ALAD genotypes are associated with differences in partitioning of lead between red blood cells and plasma, differences in distribution of lead to other tissue compartments, and altered susceptibility to lead toxicity. Further details on ALAD and other polymorphisms involved in lead toxicity are presented in Section 3.8, Populations that are Unusually Susceptible.

Lead in Blood Plasma. Lead binds to several constituents in plasma and it has been proposed that lead in plasma exists in four states: loosely bound to serum albumin or other proteins with relatively low affinity for lead, complexed to low molecular weight ligands such as amino acids and carboxylic acids, tightly bound to a circulating metalloprotein, and as free Pb^{2+} (Al-Modhefer et al. 1991). Free ionized lead (i.e., Pb^{2+}) in plasma represents an extremely small percentage of total plasma lead. The concentration of Pb^{2+} in fresh serum, as measured by an ion-selective lead electrode, was reported to be 1/5,000 of the total serum lead (Al-Modhefer et al. 1991). Approximately 40–75% of lead in the plasma is bound to plasma proteins, of which albumin appears to be the dominant ligand (Al-Modhefer et al. 1991; Ong and Lee 1980a). Lead may also bind to γ-globulins (Ong and Lee 1980a). Lead in serum that is not bound to protein exists largely as complexes with low molecular weight sulfhydryl compounds (e.g., cysteine, homocysteine). Other potential low molecular weight lead-binding ligands in serum may include citrate, cysteamine, ergothioneine, glutathione, histidine, and oxylate (Al-Modhefer et al. 1991).

Lead in Bone. Approximately 95% of lead in adult tissues, and approximately 70% in children, resides in mineralized tissues such as bone and teeth (Barry 1975, 1981). A portion of lead in bone readily exchanges with the plasma lead pool and, as a result, bone lead is a reservoir for replenishment of lead eliminated from blood by excretion (Alessio 1988; Chettle et al. 1991; Hryhirczuk et al. 1985; Nilsson et al. 1991; Rabinowitz et al. 1976). Lead forms highly stable complexes with phosphate and can replace calcium in the calcium-phosphate salt, hydroxyapatite, which comprises the primary crystalline matrix of bone (Lloyd et al. 1975). As a result, lead deposits in bone during the normal mineralization process that occurs during bone growth and remodeling and is released to the blood during the process of bone resorption (O'Flaherty 1991b, 1993). The distribution of lead in bone reflects these mechanisms; lead tends to be more highly concentrated at bone surfaces where growth and remodeling are most active (Aufderheide and Wittmers 1992). This also gives rise to an age-dependence in bone lead distribution. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood,

calcification occurs at sites of remodeling in cortical and trabecular bone. This suggests that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Bone lead burdens in adults are slowly lost by diffusion (heteroionic exchange) as well as by resorption (O'Flaherty 1995a, 1995b). The association of lead uptake and release from bone with the normal physiological processes of bone formation and resorption renders lead biokinetics sensitive to these processes. Physiological states (e.g., pregnancy, menopause, advanced age) or disease states (e.g., osteoporosis, prolonged immobilization) that are associated with increased bone resorption will tend to promote the release of lead from bone, which, in turn, may contribute to an increase in the concentration of lead in blood (Berkowtiz et al. 2004; Bonithon-Kopp et al. 1986c; Hernandez-Avila et al. 2000; Markowitz and Weinberger 1990; Nash et al. 2004; Silbergeld et al. 1988; Symanski and Hertz-Picciotto 1995; Thompson et al. 1985).

Soft Tissues. Mechanisms by which lead enters soft tissues have not been fully characterized (Bressler et al. 2005). Studies conducted in preparations of mammalian small intestine support the existence of saturable and nonsaturable pathways of lead transfer and suggest that lead can interact with transport mechanisms for calcium and iron (see Section 3.4.2, Absorption). Lead can enter cells through voltage-gated L-type Ca^{2+} channels in bovine adrenal medullary cells (Legare et al. 1998; Simons and Pocock 1987; Tomsig and Suszkiw 1991) and through store-operated Ca^{2+} channels in pituitary GH3, glial C3, human embyronic kidney, and bovine brain capillary endothelial cells (Kerper and Hinkle 1997a, 1997b). Anion exchangers may also participate in lead transport in astrocytes (Bressler et al. 2005). In addition to the small intestine, DMT1 is expressed in the kidney (Canonne-Hergaux et al. 1999); however, little information is available regarding the transport of lead across the renal tubular epithelium. In Madin-Darby canine kidney cells (MDCK), lead has been shown to undergo transepithelial transport by a mechanism distinct from the anion exchanger that has been identified in red blood cells (Bannon et al. 2000). The uptake of lead into MDCK cells was both time and temperature dependent. Overexpression of DMT1 in the human embryonic kidney fibroblast cells (HEK293) resulted in increased lead uptake compared to HEK293 cells in which DMT1 was not overexpressed (Bannon et al. 2002). Based on this limited information, it appears that DMT1 may play a role in the renal transport of lead.

Lead in other soft tissues such as kidney, liver, and brain exists predominantly bound to protein. High affinity cytosolic lead binding proteins (PbBPs) have been identified in rat kidney and brain (DuVal and Fowler 1989; Fowler 1989). The PbBPs of rat are cleavage products of α2μ globulin, a member of the protein superfamily known as retinol-binding proteins (Fowler and DuVal 1991). α2μ-Globulin is synthesized in the liver under androgen control and has been implicated in the mechanism of male rat

hyaline droplet nephropathy produced by certain hydrocarbons (EPA 1991c; Swenberg et al. 1989); however, there is no evidence that lead induces male-specific nephropathy or hyaline droplet nephropathy. The precise role for PbBP in the toxicokinetics and toxicity of lead has not been firmly established; however, it has been proposed that PbBP may serve as a cytosolic lead "receptor" that, when transported into the nucleus, binds to chromatin and modulates gene expression (Fowler and DuVal 1991; Mistry et al. 1985, 1986). Other high-affinity lead binding proteins (Kd approximately 14 nM) have been isolated in human kidney, two of which have been identified as a 5 kD peptide, thymosin 4 and a 9 kD peptide, acyl-CoA binding protein (Smith et al. 1998b). Lead also binds to metallothionein, but does not appear to be a significant inducer of the protein in comparison with the inducers of cadmium and zinc (Eaton et al. 1980; Waalkes and Klaassen 1985). *In vivo*, only a small fraction of the lead in the kidney is bound to metallothionein, and appears to have a binding affinity that is less than Cd^{2+}, but higher than Zn^{2+} (Ulmer and Vallee 1969); thus, lead will more readily displace zinc from metallothionein than cadmium (Goering and Fowler 1987; Nielson et al. 1985; Waalkes et al. 1984).

Metabolism. Metabolism of inorganic lead consists primarily of reversible ligand reactions, including the formation of complexes with amino acids and nonprotein thiols, and binding to various proteins (DeSilva 1981; Everson and Patterson 1980; Goering and Fowler 1987; Goering et al. 1986; Ong and Lee 1980a, 1980b, 1980c; Raghavan and Gonick 1977).

Tetraethyl and tetramethyl lead undego oxidative dealkylation to the highly neurotoxic metabolites, triethyl and trimethyl lead, respectively (Bolanowska 1968; Kehoe and Thamann 1931). In the liver, the reaction is catalyzed by a cytochrome P-450 dependent monoxygenase system (Kimmel et al. 1977). Complete oxidation of alkyl lead to inorganic lead also occurs (Bolanowska 1968).

Excretion

Urinary Excretion. Mechanisms by which inorganic lead is excreted in urine have not been fully characterized. Such studies have been hampered by the difficulties associated with measuring ultrafilterable lead in plasma and thereby in measuring the rate of glomerular filtration of lead. Renal plasma clearance was approximately 20–30 mL/minute in a subject who received a single intravenous injection of a ^{203}Pb chloride tracer (Chamberlain et al. 1978). Measurement of the renal clearance of ultrafilterable lead in plasma indicates that, in dogs and humans, lead undergoes glomerular filtration and net tubular reabsorption (Araki et al. 1986, 1990; Victery et al. 1979). Net tubular secretion of lead has been demonstrated in dogs made alkalotic by infusions of bicarbonate (Victery et al. 1979). Renal

clearance of blood lead increases with increasing blood lead concentrations above 25 µg/dL (Chamberlain 1983). The mechanism for this has not been elucidated and could involve a shift in the distribution of lead in blood towards a fraction having a higher glomerular filtration rate (e.g., lower molecular weight complex), a capacity-limited mechanism in the tubular reabsorption of lead, or the effects of lead-induced nephrotoxicity on lead reabsorption.

Mechanisms of secretory and absorptive transfer of lead in the kidney have not been characterized. Studies conducted in preparations of mammalian small intestine support the existence of saturable and nonsaturable pathways of lead transfer and suggest that lead can interact with transport mechanisms for calcium and iron. Although these observations may be applicable to the kidney, empirical evidence for specific transport mechanisms in the renal tubule are lacking (Diamond 2005).

Fecal Excretion. In humans, absorbed inorganic lead is excreted in feces (Chamberlain et al. 1978; Rabinowitz et al. 1976). The mechanisms for fecal excretion of absorbed lead have not been elucidated; however, pathways of excretion may include secretion into the bile, gastric fluid and saliva (Rabinowitz et al. 1976). Biliary excretion of lead has also been observed in the dog, rat, and rabbit (Klaassen and Shoeman 1974; O'Flaherty 1993).

3.4.2 Mechanisms of Toxicity

Target Organ Toxicity. This section focuses on mechanisms for sensitive health effects of major concern for lead—cardiovascular/renal effects, hematological effects, and neurological effects, particularly in children.

Cardiovascular Effects. A variety of diverse mechanisms may contribute to the increased blood pressure that is observed with chronic exposure to lead. Lead affects important hormonal and neural systems that contribute to the regulation of peripheral vascular resistance, heart rate and cardiac output (Carmignani et al. 2000; Khalil-Manesh et al. 1993; Ni et al. 2004; Vaziri and Sica 2004). Lead-induced hypertension in rats is accompanied by depletion of nitric oxide (NO), which plays an important role in regulating blood pressure, through peripheral (i.e., vasodilation, naturesis) and central (anti-sympathetic) mechanisms (Gonick et al. 1997; Vaziri et al. 1997). NO depletion induced by lead is thought to derive, at least in part, from oxidative stress and associated increased activity of reactive oxygen species (ROS) and reactivity with NO (Ding et al. 2001; Vaziri et al. 1999a, 199b). Lead may also disrupt the vasodilatory actions of NO by altering cell-signaling mechanisms in endothelial cells. Lead exposure in rats is

associated with a down regulation of the expression of soluble guanylate cyclase, the enzyme that produces cyclic GMP, which mediates NO-induced vasodilation (Marques et al. 2001). Lead-induced hypertension is also associated with abnormalities in the adrenergic system, including increased central sympathetic nervous system activity, elevated plasma norepinephrine, and decreased vascular β-adrenergic receptor density (Carmignani et al. 2000; Chang et al. 1996; Tsao et al. 2000). Chronic lead exposure also activates the renin-angiotensin-aldosterone system, either directly or indirectly, through stimulation of the sympathetic nervous system. Chronic exposure to lead elevates plasma renin activity, plasma angiotensin-converting-enzyme (ACE), and plasma aldosterone concentrations (Boscolo and Carmignani 1988; Carmignani et al. 1988). Lead-induced hypertension is also associated with alterations in the regulation of kallikrein-kinin system and the production of associated vasodilatory hormones (Carmignani et al. 1999) and alterations in production of renal prostaglandins (Gonick et al. 1998; Hotter et al. 1995). Lead exerts direct constrictive effects on vascular smooth muscle, which are thought to be mediated by inhibition or Na-K-ATPase activity and associated elevation of intracellular Ca^{2+} levels, and possibly through activation of protein kinase C (Hwang et al. 2001; Kramer et al. 1986; Piccinini et al. 1977; Watts et al. 1995).

Renal Effects. Lead in cells binds to a variety of proteins, some of which have been implicated in lead toxicity (see Section 3.4.1 for further discussion). A characteristic histologic feature of lead nephrotoxicity is the formation of intranuclear inclusion bodies in the renal proximal tubule (Choie and Richter 1972; Goyer et al. 1970a, 1970b). Inclusion bodies contain lead complexed with protein (Moore et al. 1973). Appearance of nuclear inclusion bodies is associated with a shift in compartmentalization of lead from the cytosol to the nuclear fraction (Oskarsson and Fowler 1985). Sequestration of lead in nuclear inclusion bodies can achieve a lead concentration that is 100 times higher (μg Pb/mg protein) than that in kidney cytosol (Goyer et al. 1970a, 1970b; Horn 1970); thus, the bodies can have a profound effect on the intracellular disposition of lead in the kidney.

The sequestration of lead in intranuclear inclusion bodies may limit or prevent toxic interactions with other molecular targets of lead. In rats exposed to nephrotoxic doses of lead acetate, few intranuclear inclusion bodies occurred in the S3 segment of the proximal tubule, where acute injury was most severe, whereas, intranuclear inclusion bodies were more numerous in the S2 segment, where the injury was less severe (Murakami et al. 1983).

The exact identity of the lead-protein complex in inclusion bodies remains unknown, as is the mechanism of formation of the inclusion body itself. Although proteins that appear to be unique to lead-induced

inclusion bodies have been isolated, their role in the lead sequestration has not been elucidated (Shelton and Egle 1982). Cytosolic proteins may serve as carriers of lead or intermediary ligands for uptake of lead into the nucleus. Two cytosolic proteins, which appear to be cleavage products of 2-microglobulin (Fowler and DuVal 1991), have been isolated from rat kidney cytosol that have high affinity binding sites for lead (Kd=13 and 40 nM, respectively) and can mediate uptake of lead into isolated nuclei (Mistry et al. 1985, 1986). These proteins can also participate in ligand exchange reactions with other cytosolic binding sites, including δ-aminolevulinic dehydratase, which binds and is inhibited by lead (Goering and Fowler 1984, 1985). Other high-affinity lead binding proteins (Kd approximately 14 nM) have been isolated in human kidney, two of which have been identified as a 5 kD peptide, thymosin 4 and a 9 kD peptide, acyl-CoA binding protein (Smith et al. 1998b). Lead also binds to metallothionein, but does not appear to be a significant inducer of the protein in comparison with the inducers of cadmium and zinc (Eaton et al. 1980; Waalkes and Klaassen 1985). *In vivo*, only a small fraction of the lead in the kidney is bound to metallothionein, and appears to have a binding affinity that is less than Cd^{2+}, but higher than Zn^{2+} (Ulmer and Vallee 1969); thus, lead will more readily displace zinc from metallothionein than cadmium (Goering and Fowler 1987; Nielson et al. 1985; Waalkes et al. 1984). The precise role of cytosolic lead binding proteins in inclusion body formation has not been determined, although it has been hypothesized that aggregations of 2-microglobulin may contribute to the lead-protein complex observed in nuclear inclusion bodies (Fowler and DuVal 1991).

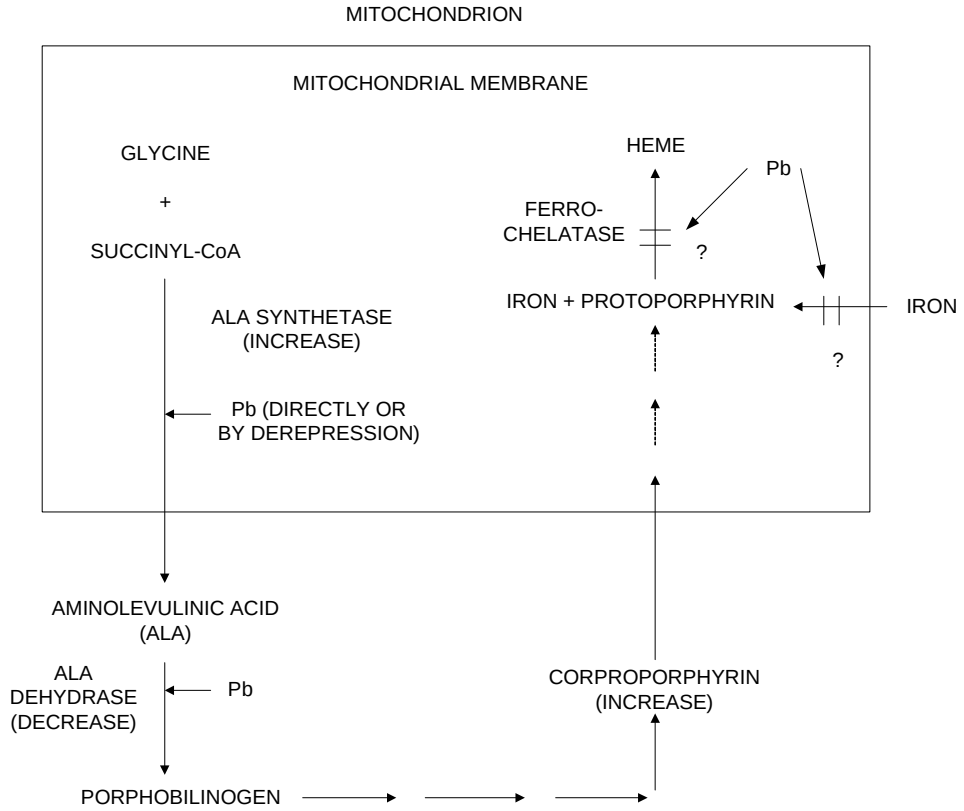
A consistent feature of lead-induced nephropathy is the finding of structural abnormalities of mitochondria of renal proximal tubule cells (Fowler et al. 1980; Goyer 1968; Goyer and Krall 1969). Mitochondria isolated from intoxicated rats contain lead, principally associated with the intramembrane space or bound to the inner and outer membranes, and show abnormal respiratory function, including decreased respiratory control ratio during pyruvate/malate- or succinate-mediated respiration (Fowler et al. 1980; Oskarsson and Fowler 1985). Lead inhibits uptake of calcium into isolated renal mitochondria and may enter mitochondria as a substrate for a calcium transporter (Kapoor et al. 1985). This would be consistent with evidence that lead can interact with calcium binding proteins and thereby affect calcium-mediated or regulated events in a variety of tissues (Fullmer et al. 1985; Goldstein 1993; Goldstein and Ar 1983; Habermann et al. 1983; Platt and Busselberg 1994; Pounds 1984; Richardt et al. 1986; Rosen and Pounds 1989; Simons and Pocock 1987; Sun and Suszkiw 1995; Tomsig and Suszkiw 1995; Watts et al. 1995). Impairments of oxidative metabolism could conceivably contribute to transport deficits and cellular degeneration; however, the exact role this plays in lead-induced nephrotoxicity has not been elucidated.

Lead exposure also appears to produce an oxidative stress of unknown, and possibly multi-pathway, origin (Daggett et al. 1998; Ding et al. 2001; Hermes-Lima et al. 1991; Lawton and Donaldson 1991; Monteiro et al. 1991; Nakagawa 1991; Sandhir et al. 1994; Sugawara et al. 1991). Secondary responses to lead-induced oxidative stress include induction of nitric oxide synthase, glutathione S-transferase and transketolase in the kidney (Daggett et al. 1998; Moser et al. 1995; Vaziri et al. 2001; Witzmann et al. 1999; Wright et al. 1998). Depletion of nitric oxide has been implicated as a contributor to lead-induced hypertension in the rat (Carmignani et al. 2000; Gonick et al. 1997; Vaziri et al. 1997, 1999a, 1999b) and thereby may contribute to impairments in glomerular filtration and possibly in the production of glomerular lesions; however, a direct role of this mechanism in lead-induced proximal tubular injury has not be elucidated. Both lead and L-N-(G)-nitro arginine methyl ester (L-NAME), an inhibitor of nitric oxide synthetase, increased the release of N-acetyl-D-glucosaminidase (NAG) from isolated rat kidneys perfused with an albumin-free perfusate (Dehpour et al. 1999). The addition of L-arginine decreased the effect of lead on NAG release. This observation is consistent with an oxidative stress mechanism possibly contributing to lead-induced enzymuria and increased urinary excretion of NAG (see Section 3.2.2, Renal Effects).

Experimental studies in laboratory animals have shown that lead can depress glomerular filtration rate and renal blood flow (Aviv et al. 1980; Khalil-Manesh et al. 1992a, 1992b). In rats, depressed glomerular filtration rate appears to be proceeded with a period of increased filtration (Khalil-Manesh et al. 1992a; O'Flaherty et al. 1986). The mechanism by which lead alters glomerular filtration rate is unknown and, its mechanistic connection to lead-induced hypertension has not been fully elucidated. Glomerular sclerosis or proximal tubule injury and impairment could directly affect renin release (Boscolo and Carmignani 1988) and/or renal insufficiency could secondarily contribute to hypertension.

Hematological Effects. The effects of lead on the hematopoietic system have been well documented. These effects, which are seen in both humans and animals, include increased urinary porphyrins, coproporphyrins, ALA, EP, FEP, ZPP, and anemia. The process of heme biosynthesis is outlined in Figure 3-15. Lead interferes with heme biosynthesis by altering the activity of three enzymes: ALAS, ALAD, and ferrochelatase. Lead indirectly stimulates the mitochondrial enzyme ALAS, which catalyzes the condensation of glycine and succinyl-coenzyme A to form ALA. The activity of ALAS is the rate-limiting step in heme biosynthesis; increase of ALAS activity occurs through feedback derepression. Lead inhibits the zinc-containing cytosolic enzyme ALAD, which catalyzes the condensation of two units of ALA to form porphobilinogen. This inhibition is noncompetitive, and occurs through the binding of lead to vicinal sulfhydryls at the active site of ALAD. Lead bridges the vicinal sulfhydryls, whereas Zn,

Figure 3-15. Effects of Lead on Heme Biosynthesis



Source: EPA 1986a

which is normally found at the active site, binds to only one of these sulfhydryls. Inhibition of ALAD and feedback derepression of ALAS results in accumulation of ALA. Lead decreases, in a noncompetitive fashion, the activity of the zinc-containing mitochondrial enzyme ferrochelatase, which catalyzes the insertion of iron (II) into the protoporphyrin ring to form heme. Inhibition of ferrochelatase (a mitochondrial enzyme) may occur through binding of lead to the vicinal sulfhydryl groups of the active site. Another possible mechanism is indirect, through impaired transport of iron in the mitochondrion, due to disruption of mitochondrial structure. Some other enzymes of the heme synthesis pathway contain single sulfhydryl groups at their active sites and are not as sensitive to inhibition by lead as are ALAD and ferrochelatase (EPA 1986a; Goering 1993).

Lead inhibition of ferrochelatase results in an accumulation of protoporphyrin IX, which is present in the circulating erythrocytes as ZPP, because of the placement of zinc, rather than iron, in the porphyrin moiety. ZPP is bound in the heme pockets of hemoglobin and remains there throughout the life of the erythrocyte. In the past, assays used in studies of protoporphyrin accumulation measured ZPP or FEP, because ZPP is converted to FEP during extraction and older technology could not differentiate FEP from ZPP. However, contemporary technology permits the direct quantification of ZPP, a far more clinically useful parameter. Because accumulation of ZPP occurs only in erythrocytes formed during the presence of lead in erythropoietic tissue, this effect is detectable in circulating erythrocytes only after a lag time reflecting maturation of erythrocytes and does not reach steady state until the entire population of erythrocytes has turned over, in approximately 120 days (EPA 1986a).

A marked interference with heme synthesis results in a reduction of the hemoglobin concentration in blood. Decreased hemoglobin production, coupled with an increase in erythrocyte destruction, results in a hypochromic, normocytic anemia with associated reticulocytosis. Decreased hemoglobin and anemia have been observed in lead workers and in children with prolonged exposure at higher PbBs than those noted as threshold levels for inhibition or stimulation of enzyme activities involved in heme synthesis (EPA 1986a). Inappropriate renal production of erythropoietin due to renal damage, leading to inadequate maturation of erythoid progenitor cells, also has been suggested as a contributing mechanism for lead-induced anemia (Osterode et al. 1999).

The increase in erythrocyte destruction may be due in part to inhibition by lead of pyrimidine-5'-nucleotidase, which results in an accumulation of pyrimidine nucleotides (cytidine and uridine phosphates) in the erythrocyte or reticulocyte. This enzyme inhibition and nucleotide accumulation affect erythrocyte membrane stability and survival by alteration of cellular energetics (Angle et al. 1982; EPA

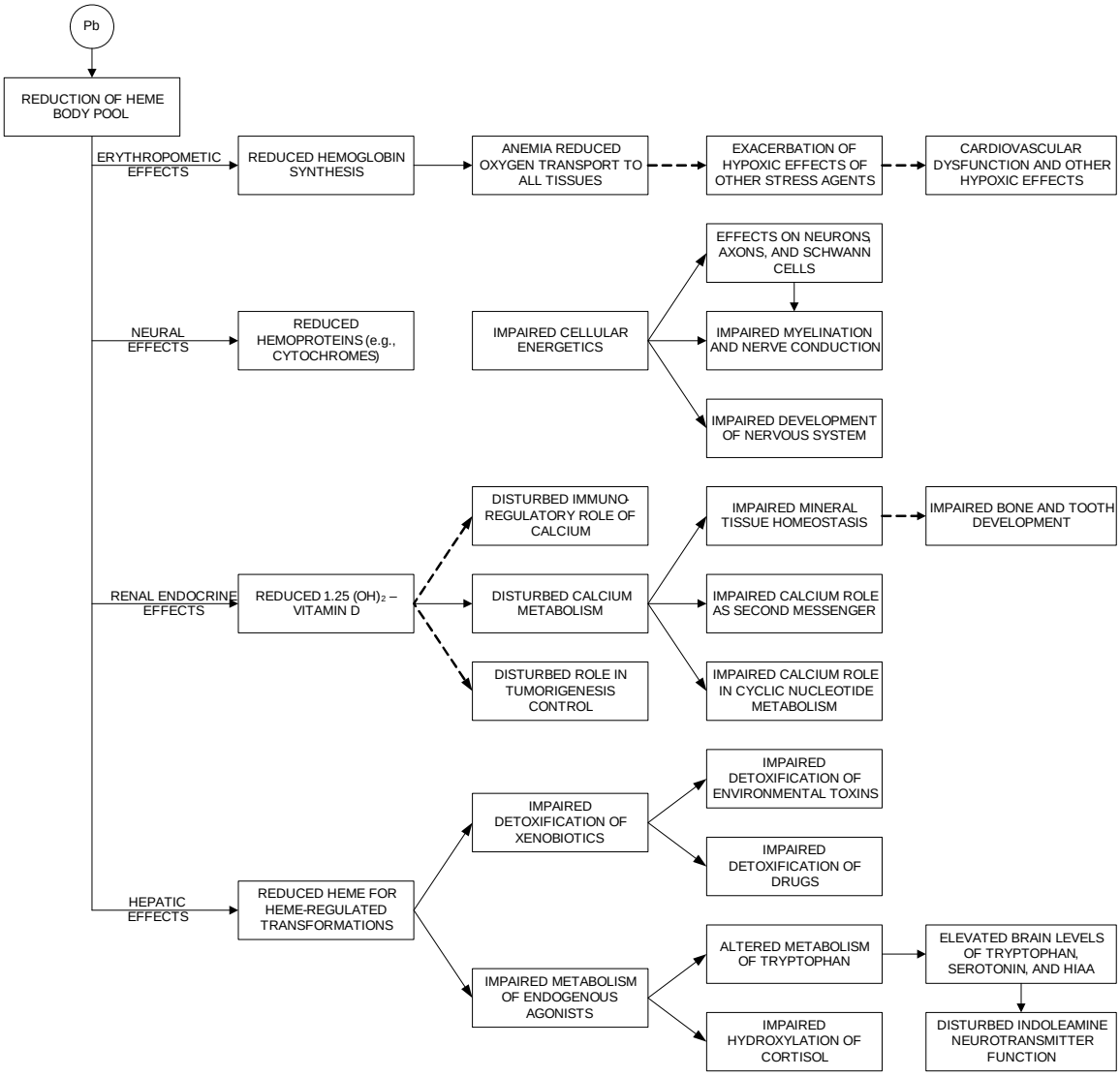
1986a). Formation of the heme-containing cytochromes is inhibited in animals treated intraperitoneally or orally with lead compounds. An inverse dose-effect relationship between lead exposure and P-450 content of hepatic microsomes and also activity of microsomal mixed-function oxygenases has been observed (Goldberg et al. 1978). Increasing duration of exposure to lead was associated with decreasing microsomal P-450 content and decreasing microsomal heme content (Meredith and Moore 1979). In addition, delays in the synthesis of the respiratory chain hemoprotein cytochrome C have been noted during administration of lead to neonatal rats (Bull et al. 1979).

The impairment of heme synthesis by lead may have a far-ranging impact not limited to the hematopoietic system. EPA (1986a) provided an overview of the known and potential consequences of the reduction of heme synthesis as shown in Figure 3-16. Solid arrows indicate well-documented effects, whereas dashed arrows indicate effects considered to be plausible further consequences of the impairment of heme synthesis. More detailed information on the exposure levels or blood lead levels at which these impacts may be experienced was provided in Section 3.2.

Neurotoxicity. The literature on mechanisms of neurotoxicity of lead is enormous. Most studies conducted in recent years have focused on trying to determine the biochemical or molecular basis of the intellectual deficits observed in exposed children using animal models. Trying to cite all of the studies that have contributed to our current knowledge is an almost impossible task. Therefore, the major topics summarized below have been extracted from experts' reviews and the reader is referred to references cited therein for more detailed information (Bouton and Pevsner 2000; Bressler et al. 1999; Cory-Slechta 1995, 2003; Gilbert and Lasley 2002; Lasley and Gilbert 2000; Nihei and Guilarte 2002; Suszkiw 2004; Toscano and Guilarte 2005; Zawia et al. 2000).

Lead can affect the nervous system by multiple mechanisms, one of the most important of which is by mimicking calcium action and/or disruption of calcium homeostasis. Because calcium is involved as a cofactor in many cellular processes, it is not surprising that many cell-signaling pathways are affected by lead. One pathway that has been studied with more detail is the activation of protein kinase C (PKC). PKC is a serine/threonine protein kinase involved in many processes important for synaptic transmission such as the synthesis of neurotransmitters, ligand-receptor interactions, conductance of ionic channels, and dendritic branching. The PKC family is made up of 12 isozymes, each with different enzymatic cofactor requirements, tissue expression, and cellular distributions. The γ-isoform is one of several calcium-dependent forms of PKC and is a likely target for lead neurotoxicity; it is neuron-specific and is

Figure 3-16. Multiorgan Impact of Reduction of Heme Body Pool by Lead



Source: EPA 1986a

involved in long-term potentiation (see below), spatial learning, and memory processes. PKC has the capacity to both activate and inhibit PKCs. Studies have shown that micromolar concentrations of lead can activate PKC-dependent phosphorylation in cultured brain microvessels, whereas picomolar concentrations of lead activate preparations of PKC *in vitro*. Interestingly, studies in rats exposed to low lead levels have shown few significant changes in PKC activity or expression, suggesting that the whole animal may be able to compensate for lead PKC-mediated effects compared to a system *in vitro*. PKC induces the formation of the AP-1 transcriptional regulatory complex, which regulates the expression of a large number of target genes via AP-1 promoter elements. A gene regulated by lead via AP-1 promoters is the glial fibrillary acidic protein (GFAP), an astrocytic intermediate filament protein that is induced during periods of reactive astrocytic gliosis. Astrocytes along with endothelial cells make up the blood brain barrier (BBB). Studies in rats exposed chronically to low lead levels have reported alterations in the normal pattern of GFAP gene expression in the brain, and the most marked long-lasting effects occurred when the rats were exposed during the developmental period. In immature brain microvessels, most of the protein kinase C is in the cytosol, whereas in mature brain microvessels, this enzyme is membrane-bound. Activation of protein kinase C in other systems is known to result in a change in distribution from cytosol to membrane, and has been observed with exposure of immature brain microvessels to lead. An inhibition of microvascular formation has been observed with lead concentrations that are effective in activating PKC. Thus, it appears that premature activation of PKC by lead may impair brain microvascular formation and function, and at high levels of lead exposure, may account for gross defects in the blood-brain barrier that contribute to acute lead encephalopathy. The blood-brain barrier normally excludes plasma proteins and many organic molecules, and limits the passage of ions. With disruption of this barrier, molecules such as albumin freely enter the brain and ions and water follow. Because the brain lacks a well-developed lymphatic system, clearance of plasma constituents is slow, edema occurs, and intracranial pressure rises. The particular vulnerability of the fetus and infant to the neurotoxicity of lead may be due in part to immaturity of the blood-brain barrier and to the lack of the high-affinity lead-binding protein in astroglia, which sequester lead.

Another enzyme altered by lead is calmodulin, a major intracellular receptor for calcium in eukaryotes. Normally, calcium induces a conformational change in calmodulin that converts the protein to an active form; lead improperly activates the enzyme. Some studies suggest that activation of calmodulin by lead results in protein phosphorylation in the rat brain and brain membrane preparations and can alter proper functioning of cAMP messenger pathways. It has been shown that calmodulin can mediate gene expression via calmodulin-dependent kinases. The effects of lead on gene expression via activation of

calmodulin are not as marked as those via PKC because activation of calmodulin requires 100-fold more lead than activation of PKC.

Lead also can substitute for zinc in some enzymes and in zinc-finger proteins, which coordinate one or more zinc cations as cofactors. The substitution of lead for zinc in zinc-finger proteins can have significant effects on *de novo* expression of the bound proteins and in any genes transcriptionally-regulated by a particular protein. Lead has been found to alter the binding of zinc-finger transcriptional regulator Sp1 to its specific DNA sequences. This is accompanied by aberrant expression of Sp1 target genes such as myelin basic protein and proteolipid protein. Another gene regulated by Sp1 is the β-amyloid precursor protein (APP) gene. Recently, it was shown that lead exposure in neonatal rats transiently induces APP mRNA, which is overexpressed with a delay of 20 months after exposure to lead ceased. In contrast, APP expression, Sp1 activity, as well as APP ans β-amyloid protein levels, were unresponsive to lead during old age, suggesting that exposures occurring during brain development may predetermine the expression and regulation of APP later in life. It has been suggested that the multiple responses to lead exposure are due to lead specifically targeting zinc-finger proteins found in enzymes, channels, and receptors.

Lead affects virtually every neurotransmitter system in the brain, but most information on changes is available on the glutamatergic, dopaminergic, and cholinergic systems. Of these, special attention has been paid to the glutamatergic system and its role in hippocampal long-term potentiation (LTP). Hippocampal LTP is a cellular model of learning and memory characterized by a persistent increase in synaptic efficacy following delivery of brief tetanic stimulation (high-frequency stimulation). LTP provides a neurophysiological substrate for learning and storing information and is thought to utilize the same synaptic mechanisms as the learning process. LTP is established only with complex patterns of stimulation but not with single pulse stimulation. While it has been studied primarily in the hippocampal subregions CA1 and dentate gyrus, it can also be evoked in cortical areas. Exposure of intact animals or tissue slices to lead diminishes LTP by a combination of three actions: increasing the threshold for induction, reducing the magnitude of potentiation, and shortening its duration by accelerating its rate of decay. This effect on LTP involves actions of lead on glutamate release (presynaptic effects) and on the N-methyl-D-aspartate (NMDA) receptor function. Studies have shown that the effects of lead vary as a function of the developmental exposure period and that lead exposure early in life is critical for production of impaired LTP in adult animals. LTP is more readily affected by lead during early development, but exposure initiated after weaning also affects synaptic plasticity. Studies also have shown that both LTP magnitude and threshold exhibit a U-shape type response with increasing lead

doses. While LTP is primarily a glutamatergic phenomenon, it can be modulated through input from extrahippocampal sources including noradrenergic, dopaminergic, and cholinergic sources.

Studies in animals treated with lead (PbB 30–40 μg/dL) have shown that induction of pair-pulse facilitation in dentate gyrus is impaired. Since the phenomenon is mediated primarily by increased glutamate release, the reasonable assumption is that lead reduces glutamate release. Support for this assumption is also derived from studies in which depolarization-induced hippocampal glutamate release was reduced in awake animals with similar PbBs. This inhibition of glutamate release was shown to be due to lead-related decrements in a calcium-dependent component. The exact mechanism for the inhibition of glutamate release by lead is not known, but is consistent with lead at nanomolar concentrations preventing maximal activation of PKC, rather than lead blocking calcium influx into the presynaptic terminal through voltage-gated calcium channels. Reduced glutamate release can be observed in rats exposed from conception through weaning and tested as adults, when lead was no longer present, suggesting that a direct action of lead is not necessary and that other mechanisms, such as reductions in synaptogenesis, also may be involved. As with LTP, depolarization-evoked hippocampal glutamate release in rats treated chronically with several dose levels of lead exhibited a U-shaped response. That is, glutamate release was inhibited in rats treated with the lower lead doses, but not in those exposed to the higher concentrations of lead. Although speculative, this was interpreted as lead at the higher doses mimicking calcium in promoting transmitter release and overriding the inhibitory effects of lead that occur at lower lead levels.

The findings regarding the effects of lead on postsynaptic glutamatergic function have been inconsistent across laboratories, but a direct inhibitory action of lead on the NMDA receptor is unlikely at environmentally relevant exposure levels. Some studies have shown that continuous exposure of rats from gestation to adulthood results in a significant increase in NMDA receptor numbers in cortical areas, hippocampus, and forebrain. This was observed in the forebrain at PbB of 14 μg/dL. Other studies, however, have reported changes in the opposite direction and the reason for the discrepancy in results may be due to the different exposure protocols used. From a functional point of view, it seems plausible that a lead-induced reduction in presynaptic transmitter release be compensated by a postsynaptic increase in number or density of receptors in order to maintain a viable function.

The dopaminergic system also has a role in aspects of cognitive function since lesions of dopaminergic neurons impair behavior in various types of learning and cognitive tasks. Also, individuals who suffer from Parkinson’s disease, a disease associated with dopamine depletion in the striatum, sometimes show

difficulties in cognitive functions. Most of the evidence available suggests that lead may impair regulation of dopamine synthesis and release, indicating a presynaptic site of action. Studies in animals often report opposing effects of lead on nigrostriatal and mesolimbic dopamine systems regarding receptor binding, dopamine synthesis, turnover, and uptake. Postweaning exposure of rats to lead resulted in supersensitivity of D1 and D2 dopamine receptors, which can be interpreted as a compensatory response to decreased synthesis and/or release of dopamine. Lesions to the nucleus acumbens (a terminal dopamine projection area) and the frontal cortex result in perseverative deficits, suggesting that the mesolimbic system is preferentially involved in the effects of lead. Results of studies using dopaminergic compounds seem to indicate that changes in dopamine systems do not play a role in the effects of lead on learning. Instead, it has been suggested that changes in dopaminergic systems may play a role in the altered response rates on Fixed-Interval (FI) schedules of reinforcement that have been observed in animals exposed to lead. This type of changes has been thought to represent a failure to inhibit inappropriate responding.

It is widely accepted that the cholinergic system plays a role in learning and memory processes. Some cognitive deficits observed in patients with Alzheimer's disease have been attributed to impaired cholinergic function in the cortex and hippocampus. Exposure to lead induces numerous changes in cholinergic system function, but the results, in general, have been inconsistently detected, or are of opposite direction in different studies, which may be attributed to the different exposure protocols used in the different studies. However, it is clear that lead blocks evoked release of acetylcholine and diminishes cholinergic function. This has been demonstrated in central and peripheral synapses. Studies with the neuromuscular junction showed that lead reduces acetylcholine release by blocking calcium entry into the terminal. At the same time, lead prevents sequestration of intracellular calcium by organelles, which results in increased spontaneous release of the neurotransmitter. Studies *in vitro* show that lead can block nicotinic cholinergic receptors, but it is unclear whether such effects occur *in vivo* or whether lead alters the expression of nicotinic cholinergic receptors in developing brain. Evidence for an involvement in lead-induced behavioral deficits has been presented based on the observation that intrahippocampal transplants of cholinergic-rich septal and nucleus basalis tissue improve the deficits and that treatment with nicotinic agonists can improve learning and memory impairments following perinatal lead treatment of rats. Chronic exposure of rats to lead has resulted in decreased muscarinic-receptor expression in the hippocampus. Whether or not lead exposure during development alters muscarinic receptor sensitivity is unclear as there are reports with opposite results. The preponderance of the binding data suggests that lead does not directly affect muscarinic receptors with the exception of visual cortex, where lead may have a direct inhibitory effect on muscarinic receptors from rods and bipolar of the retina.

3.4.3 Animal-to-Human Extrapolations

Studies in rodents, dogs, and nonhuman primates have demonstrated all of the major types of health effects of lead that have been observed in humans, including cardiovascular, hematological, neuro-developmental, and renal effects (EPA 1986a). These studies also provide support for the concept of blood lead concentration as a metric of internal dose for use in dose-response assessments in humans.

The effects of low-level lead exposure on cognitive development and function in humans are difficult to discern against the background of genetic, environmental, and socioeconomic factors that would be expected to affect these end points in children. Experimental studies in animals have been helpful for establishing the plausibility of the hypothesis that low-level exposures to lead can affect cognitive function in mammals and for providing insights into possible mechanisms for these effects. Studies in rats and nonhuman primates have demonstrated deficits in learning associated with blood lead concentrations between 10 and 15 μg/dL, a range that is comparable to those reported in epidemiological studies, which found learning deficits in children (Cory-Slechta 2003; Rice 1996b).

The lead-induced nephropathy observed in humans and rodents shows a comparable early pathology (Goyer 1993). However, in rodents, proximal tubular cell injury induced by lead can progress to adenocarcinomas of the kidney (see Section 3.2.2). The observation of lead-induced kidney tumors in rats may not be relevant to humans. Conclusive evidence for lead-induced renal cancers (or any other type of cancer) in humans is lacking, even in populations in which chronic lead nephropathy is evident.

3.5 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Health effects that have been associated with lead exposures during infancy or childhood include anemia (Schwartz et al. 1990) (and related disorders of heme synthesis), neurological impairment (e.g., encephalopathy), renal alterations, colic (Chisolm 1962, 1965; Chisolm and Harrison 1956), and impaired metabolism of vitamin D (Mahaffey et al. 1982; Rosen and Chesney 1983). Death from encephalopathy may occur with PbBs ≥125 μg/dL. In addition to the above effects, the following health effects have been associated with lead exposures either *in utero*, during infancy, or during childhood: delays or impairment of neurological development, neurobehavioral deficits including IQ deficits, low birth weight, and low gestational age, growth retardation, and delayed sexual maturation in girls (Bellinger et al. 1992; Canfield et al. 2004; Coscia et al. 2003; Lanphear et al. 2000a; Ris et al. 2004; Schnaas et al. 2000; Selevan et al. 2003; Tong et al. 1998; Wu et al. 2003a). These effects, which are discussed in Section 3.2, are consistent with findings in animals exposed to lead. Effects of lead observed at relatively high exposures such as anemia, colic, and encephalopathy, also occur in adults. There is no evidence that exposure to lead causes structural birth defects in humans or in animals, although Needleman et al. (1984) reported an association between cord blood lead and the incidence of minor anomalies (hemangiomas and lymphangiomas, hydrocele, skin anomalies, undescended testicles) in a study of 5,183 women who delivered neonates of at least 20 weeks of gestational age. Exposure to lead during childhood may result in neurobehavioral effects that persist into adulthood (e.g., Byers and Lord 1943; Stokes et al. 1998; White et al. 1993).

Children and developing organisms in general, are more susceptible to lead toxicity than adults. This higher susceptibility derives from numerous factors. Children exhibit more severe toxicity at lower exposures than adults, as indicated by lower PbB concentrations and time-integrated PbB concentrations that are associated with toxicity in children (see Section 3.2 for more detailed discussion). This suggests that children are more vulnerable to absorbed lead than adults. The mechanism for this increased vulnerability is not completely understood. Lead affects processes such as cell migration and synaptogenesis, as well as pruning of unnecessary connections between neurons, all key processes during brain development. Lead also affects glial cells and the blood brain barrier. Alterations in any of these parameters can produce permanent improper connections that will lead to altered specific brain functions. Children also absorb a larger fraction of ingested lead than do adults; thus, children will experience a higher internal lead dose per unit of body mass than adults at similar exposure concentrations (Alexander et al. 1974; Blake et al. 1983; James et al. 1985; Rabinowitz et al. 1980; Ziegler et al. 1978). Absorption of lead appears to be higher in children who have low dietary iron or calcium intakes; thus, dietary insufficiencies, which are not uncommon in lower socioeconomic children, may contribute to their lead absorption (Mahaffey and Annest 1986; Mahaffey et al. 1986; Marcus and Schwartz 1987; Ziegler et al.

1978) (see Section 3.3.1.2 for more detailed discussion of lead absorption in children). Insufficient dietary zinc, also not uncommon in children, may contribute to their increased susceptibility to lead, since lead impairs the activity of zinc-requiring enzymes in the heme biosynthesis pathway (see Section 3.4.2). Infants are born with a lead body burden that reflects the burden of the mother (Goyer 1990; Graziano et al. 1990; Schuhmacher et al. 1996). During gestation, lead from the maternal skeleton is transferred across the placenta to the fetus (Gulson 2000; Gulson et al. 1997b, 1999b, 2003). Additional lead exposure may occur during breast feeding (Gulson et al. 1998b) (see Section 3.3.2 for more detailed discussion). This means that lead stored in the mother's body from exposure prior to conception can result in exposure to the fetus or nursing neonate. Behavioral patterns of children can result in higher rates of ingestion of soil and dust, both of which are often important environmental depots for lead (Barnes 1990; Binder et al. 1986; Calabrese et al. 1989, 1997a; Clausing et al. 1987). Examples of activities that tend to promote soil and dust ingestion preferentially in children include playing and crawling on the ground and floor, hand-to-mouth activity, mouthing of objects, and indiscriminate eating of food items dropped or found on the ground or floor (see Section 6.6 for more detailed discussion). Some children engage in pica, or the ingestion of nonfood items (e.g., soil). This behavior can lead to excess exposure if a child consumes soil contaminated with lead.

The toxicokinetics of lead in children appears to be similar to that in adults, with the exception of the higher absorption of ingested lead in children. Most of the lead body burden in both children and adults is in bone; a slightly large fraction of the body burden in adults resides in bone (Barry 1975). The difference may reflect the larger amount of trabecular bone and bone turnover during growth; trabecular bone has a shorter retention halftime for lead than does cortical bone (see Section 3.3.2 for details). Limited information suggests that organic lead compounds undergo enzymatic (cytochrome P-450) biotransformation and that inorganic lead is complexed (nonenzymatically) with proteins and nonprotein ligands. However, the information available is insufficient to determine whether the metabolism of lead in children is similar to adults. Several models of lead pharmacokinetics in children have been developed (EPA 1994a, 1994b; Leggett 1993; O'Flaherty 1993, 1995a); these are described in Section 3.3.5.

The important biomarkers of exposure that have been explored in children include PbB concentration (CDC 1991), bone lead levels (as measured from noninvasive XRF measurements of phalanx, patella, tibia, or ulna), and lead levels in deciduous teeth (Hu et al. 1998). Lead in blood has a much shorter retention half-time than lead in bone (days compared to years); therefore, PbB concentration provides a marker for more recent exposure, while lead in bone appears to reflect longer-term cumulative exposures (Borjesson et al. 1997; Nilsson et al. 1991; Schutz et al. 1987). Lead in tooth enamel is thought to reflect

exposures *in utero* and during early infancy, during which development of tooth enamel and coronal dentine is completed. Lead appears to accumulate in dentin after formation of the dentin is complete; therefore, lead in dentin is thought to reflect exposures that occur up to the time the tooth is shed (Gulson 1996; Gulson and Wilson 1994; Rabinowitz 1995; Rabinowitz et al. 1993). A more detailed discussion of the above biomarkers of exposure, as well as other less important biomarkers, is presented in Section 3.6.1. The most sensitive biomarkers of effects of lead in children relate to the effects of lead on heme metabolism, they include ALAD activity, EP, FEP, and ZPP; however, these are not specific for lead (Bernard and Becker 1988; CDC 1991; Hernberg et al. 1970). EP has been used as a screening test. However, it is not sensitive below a PbB of about 25 µg/dL. These and other biomarkers of effects of lead are discussed in Section 3.6.2.

Methods for preventing or decreasing the absorption of lead following acute exposures to potentially toxic levels of lead include removal of the child from the exposure source, removal of lead-containing dirt and dust from the skin, and, if the lead has been ingested, standard treatments to induce vomiting. Ensuring a diet that is nutritionally adequate in calcium and iron may decrease the absorbed dose of lead associated with a given exposure level, because lead absorption appears to be higher in children who have low levels of iron or calcium in their diets (Mahaffey and Annest 1986; Mahaffey et al. 1986; Marcus and Schwartz 1987; Ziegler et al. 1978). Diets that are nutritionally adequate in zinc also may be helpful for reducing the risks of lead toxicity because zinc may protect against lead-induced inhibition of zinc-dependent enzymes, such as ALAD (Chisolm 1981; Johnson and Tenuta 1979; Markowitz and Rosen 1981). Methods for reducing the toxicity of absorbed lead include the injection or oral administration of chelating or complexing agents (e.g., EDTA, penicillamine, dimercaptosuccinic acid [DMSA]) (CDC 1991). These agents form complexes with lead that are more rapidly excreted and thereby decrease the body burden of lead. These methods for reducing the toxic effects of lead are described in greater detail in Section 3.9. Several studies (described in Section 3.9) have examined whether lead-lowering interventions, such as with chelators, are paralleled by improvement in health outcomes reportedly altered by lead (Dietrich et al. 2004; Liu et al. 2002; Rogan et al. 2001; Ruff et al. 1993). The conclusion of these studies was that chelation therapy is not indicated in children with moderate PbB (≤40 µg/dL).

3.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to lead are discussed in Section 3.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by lead are discussed in Section 3.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.8, Populations That Are Unusually Susceptible.

3.6.1 Biomarkers Used to Identify or Quantify Exposure to Lead

The ideal biomarker of lead exposure would be a measurement of total lead body burden. Biomarkers of exposure in practical use today are measurements of total lead levels in tissues or body fluids, such as blood, bone, urine, or hair; or measurement of certain biological responses to lead (e.g., zinc protoporphyrin). Tetraalkyl lead compounds may also be measured in the breath. Of these, blood lead concentration (PbB) is the most widely used and considered to be the most reliable biomarker for general clinical use and public health surveillance. Currently, blood lead measurement is the screening test of choice to identify children with elevated PbBs (CDC 1991). Venous sampling of blood is preferable to finger prick sampling, which has a considerable risk of surface lead contamination from the finger if proper finger cleaning is not carried out. In children, PbBs between 10 and 14 μg/dL should trigger community-wide childhood lead poisoning prevention activities (CDC 1991). Since the elimination half-time of lead in blood is approximately 30 days, PbBs generally reflect relatively recent exposure and cannot be used to distinguish between low-level intermediate or chronic exposure and high-level acute exposure. In 1997, the CDC issued new guidance on screening children for lead poisoning that recommends a systematic approach to the development of appropriate lead screening in states and communities (CDC 1997c). The objective of the new guidelines is maximum screening of high-risk children and reduced screening of low-risk children, as contrasted with previous guidelines (CDC 1991), which recommended universal screening.

Blood Lead Concentration. Measurement of PbB is the most widely used biomarker of lead exposure. Elevated blood lead concentration (e.g., >10 μg/dL) is an indication of excessive exposure in infants and children (CDC 1991) and is considered to be excessive for women of child-bearing age (ACGIH 1998). The biological exposure index (BEI) for lead in blood of exposed workers is 30 μg/dL (ACGIH 2004). The NIOSH recommended exposure limit (REL) for workers (50 $\mu g/m^3$ air, 8-hour TWA) is established to ensure that the blood lead concentration does not exceed 60 μg/dL (NIOSH 2005).

The extensive use of blood lead as a dose metric reflects mainly the greater feasibility of incorporating blood lead measurements into clinical or epidemiological studies, compared to other potential dose indicators, such as lead in kidney, plasma, urine, or bone (Skerfving 1988). PbB measurements have several limitations as measures of lead body burden. Blood comprises <2% of the total lead burden; most of the lead burden resides in bone (Barry 1975). The elimination half-time of lead in blood is approximately 30 days (Chamberlain et al. 1978; Griffin et al. 1975; Rabinowitz et al. 1976); therefore, the lead concentration in blood relatively reflects, mainly, the exposure history of the previous few

months and does not necessarily reflect the larger burden and much slower elimination kinetics of lead in bone (Graziano 1994; Lyngbye et al. 1990b). The relationship between lead intake and PbB is curvilinear; the increment in PbB per unit of intake decreases with increasing PbB (Ryu et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1982, 1984). Lead intake-blood lead relationships also vary with age as a result of age-dependency of gastrointestinal absorption of lead, and vary with diet and nutritional status (Mushak 1991). A practical outcome of the above characteristics of PbB is that PbB can change relatively rapidly (e.g., weeks) in response to changes in exposure; thus, PbB can be influenced by short-term variability in exposure that may have only minor effects on lead body burden. A single blood lead determination cannot distinguish between lower-level intermediate or chronic exposure and higher-level acute exposure. Similarly, a single measurement may fail to detect a higher exposure that occurred (or ended) several months earlier. Time-integrated measurements of PbB may provide a means for accounting for some of these factors and thereby provide a better measure of long-term exposure (Roels et al. 1995).

Bone and Tooth Lead Measurements. The development of noninvasive XRF techniques for measuring lead concentrations in bone has enabled the exploration of bone lead as a biomarker of lead exposure in children and in adults (Batuman et al. 1989; Hu 1991b; Hu et al. 1989, 1990, 1995; Rosen et al. 1993; Wedeen 1988, 1990, 1992). Lead in bone is considered a biomarker of cumulative exposure to lead because lead accumulates in bone over the lifetime and most of the lead body burden resides in bone. Lead is not distributed uniformly in bone. Lead will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in cortical and trabecular bone. This suggests that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Patella, calcaneus, and sternum XRF measurements primarily reflect lead in trabecular bone, whereas XRF measurements of midtibia, phalanx, or ulna reflect primarily lead in cortical bone. Lead levels in cortical bone may be a better indicator of long-term cumulative exposure than lead in trabecular bone, possibly because lead in trabecular bone may exchange more actively with lead in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of lead in cortical bone, compared to trabecular bone (Borjesson et al. 1997; Brito et al. 2005; Nilsson et al. 1991; Schutz et al. 1987). Longitudinal measures of bone lead over a 3-year period showed no significant decline in cortical bone lead, whereas trabecular bone lead declined by approximately 15% (Kim et al. 1997). Estimates of cortical bone lead elimination half-times (5–50 years) show a dependence on lead burden, with longer half-times in people who have higher bone lead burdens (Brito et al. 2005). Further evidence that cortical

bone lead measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone lead measurements have been compared to PbB. Lead levels in trabecular bone (in adults) correlate more highly with contemporary PbB than do levels of lead in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical bone lead measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary blood lead measurements (Borjesson et al. 1997; Roels et al. 1994). Bone lead levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone lead may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

Relationships between bone lead levels and health outcomes have been studied in several epidemiology studies, but not as extensively as have other biomarkers of exposure such as PbB. These studies suggest that bone lead levels may be predictors of certain health outcomes, including neurodevelopmental and behavioral outcomes in children and adolescents (Campbell et al. 2000a; Needleman et al. 1996, 2002; Payton et al. 1998); and hypertension and declines in renal function in adults (Cheng et al. 2001; Gerr et al. 2002; Hu et al. 1996a, 1998; Korrick et al. 1999; Rothenberg et al. 2002a; Tsaih et al. 2004).

Tooth lead has been considered a potential biomarker for measuring long-term exposure to lead (e.g., years) because lead that accumulates in tooth dentin and enamel appears to be retained until the tooth is shed or extracted (Ericson 2001; Gomes et al. 2004; Omar et al. 2001; Rabinowitz et al. 1989; Steenhout and Pourtois 1987). Formation of enamel and coronal dentin of deciduous teeth is complete prior to the time children begin to crawl; however, lead in shed deciduous teeth is not uniformly distributed. Differences in lead levels and stable isotope signatures of the enamel and dentin suggest that lead uptake occurs differentially in enamel and dentin after eruption of the tooth (Gulson 1996; Gulson and Wilson 1994). Lead in enamel is thought to reflect primarily lead exposure that occurs *in utero* and early infancy, prior to tooth eruption. Dentin appears to continue to accumulate lead after eruption of the tooth, therefore, dentin lead is thought to reflect exposure that occurs up to the time the teeth are shed or extracted (Gulson 1996; Gulson and Wilson 1994; Rabinowitz 1995; Rabinowitz et al. 1993). Accumulation of lead in dentin of permanent teeth may continue for the life of the tooth (Steenhout 1982; Steenhout and Pourtois 1981). Because it is in direct contact with the external environment, enamel lead levels may be more influenced than dentin lead by external lead levels and tooth wear (Purchase and Fergusson 1986).

An analysis of eight cross-sectional and/or prospective studies that reported tooth lead and PbBs of the same children found considerable consistency among the studies (Rabinowitz 1995). The mean tooth lead levels ranged from <3 to >12 μg/g. In a study of 63 subjects, dentin lead was found to be predictive of concentrations of lead in the tibia, patella, and mean bone lead 13 years after tooth lead assessment in half of them (Kim et al. 1996b). The authors estimated that a 10 μg/g increase in dentin lead levels in childhood was predictive of a 1 μg/g increase in tibia lead levels, a 5 μg/g in patella lead levels, and a 3 μg/g increase in mean bone lead among the young adults.

Plasma Lead Concentration. The concentration of lead in plasma is extremely difficult to measure accurately because levels in plasma are near the quantitation limits of most analytical techniques (e.g., approximately 0.4 μg/L at blood lead concentration of 100 μg/L (Bergdahl and Skerfving 1997; Bergdahl et al. 1997a) and because hemolysis that occurs with typical analytical practices can contribute substantial measurement error (Bergdahl et al. 1998, 2006; Cavalleri et al. 1978; Smith et al. 1998a). Recent advances in inductively-coupled plasma mass spectrometry (ICP-MS) offer sensitivity sufficient for measurements of lead in plasma (Schütz et al. 1996). The technique has been applied to assessing lead exposures in adults (Cake et al. 1996; Hernandez-Avila et al. 1998; Manton et al. 2001; Smith et al. 2002; Tellez-Rojo et al. 2004). A direct comparison of lead concentrations in plasma and serum yielded similar results (Bergdahl et al. 2006); however, the interchangeability of plasma and serum lead measurements for biomonitoring of lead exposure or body burden had not been thoroughly evaluated in large numbers of subjects (Bergdahl et al. 2006; Manton et al. 2001; Smith et al. 2002).

Urinary Lead. Measurements of urinary lead levels have been used to assess lead exposure (e.g., Fels et al. 1998; Gerhardsson et al. 1992; Lilis et al. 1968; Lin et al. 2001; Mortada et al. 2001; Roels et al. 1994). However, like PbB, urinary lead excretion reflects, mainly, recent exposure and, thus, shares many of the same limitations for assessing lead body burden or long-term exposure (Sakai 2000; Skerfving 1988). The measurement is further complicated by variability in urine volume, which can affect concentrations independent of excretion rate (Diamond 1988) and the potential effects of decrements in kidney function on excretion, in association with high, nephrotoxic lead exposures or kidney disease (Lilis et al. 1968; Wedeen et al. 1975). Urinary lead concentration increases exponentially with PbB and can exhibit relatively high intra-individual variability, even at similar PbBs (Gulson et al. 1998a; Skerfving et al. 1985). Urinary diethyl lead has been proposed as a qualitative marker of exposure to tetraethyl lead (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

The measurement of lead excreted in urine following an injection (intravenous or intramuscular) of the chelating agent, calcium disodium EDTA (*EDTA provocation*) has been used to detect elevated body burden of lead in adults (Biagini et al. 1977; Lilis et al. 1968; Wedeen 1992; Wedeen et al. 1975) and children (Chisolm et al. 1976; Markowitz and Rosen 1981), and is considered to be a reliable measure of the potentially toxic fraction of the lead body burden (WHO 1995). The assay is not a substitute for blood lead measurements in the clinical setting. Children whose PbBs are ≥45 μg/dL should not receive a provocative chelation test; they should be immediately referred for appropriate chelation therapy (CDC 1991). Further limitations for routine use of the test are that EDTA must be given parenterally and requires timed urine collections. A study conducted in rats found that intraperitoneal administration of a single dose of EDTA following 3–4-month exposures to lead in drinking water increased levels of lead in the liver and brain (Cory-Slechta et al. 1987) raising concern for similar effects in humans who undergo the EDTA provocation test. The use of EDTA to assess bone stores of lead (Wedeen 1992) are largely being supplanted by more direct, noninvasive procedures for measuring lead in bone.

Lead in Saliva and Sweat. Lead is excreted in human saliva and sweat (Lilley et al. 1988; Rabinowitz et al. 1976; Stauber and Florence 1988; Stauber et al. 1994). However, sweat has not been widely adopted for monitoring lead exposures. Lilley et al. (1988) found that lead concentrations in sweat were elevated in lead workers; however, sweat and blood lead concentrations were poorly correlated. This may reflect excretion of lead in or on the skin that had not been absorbed into blood. Studies conducted in rats have found relatively strong correlations between lead concentrations in plasma and saliva (e.g., $r^2>0.9$), compared to blood lead and saliva; therefore, saliva may serve as a better predictor of plasma lead than blood lead concentration (Timchalk et al. 2006).

Hair and Nail Lead. Lead is incorporated into human hair and hair roots (Bos et al. 1985; Rabinowitz et al. 1976) and has been explored as a possibly noninvasive approach for estimating lead body burden (Gerhardsson et al. 1995b; Wilhelm et al. 1989). The method is subject to error from contamination of the surface with environmental lead and contaminants in artificial hair treatments (i.e., dyeing, bleaching, permanents) and is a relatively poor predictor of PbB, particularly at low concentrations (<12 μg/dL) (Campbell and Toribara 2001; Drasch et al. 1997; Esteban et al. 1999). Nevertheless, levels of lead in hair were positively correlated with children's classroom attention deficit behavior in a study (Tuthill 1996). Lead in hair was correlated with liver and kidney lead in a study of deceased smelter workers (Gerhardsson et al. 1995b). Nail lead has also been utilized as a marker (Gerhardsson et al. 1995b).

Semen Lead. Correlations between concentrations of lead in semen and blood have been reported and vary in strength across studies (Alexander et al. 1998a, 1998b; Farias et al. 2005; Telisman et al. 2000). This variation may relate, in part, to analytical challenges in the measurement of the relatively low concentrations of lead in semen. Using ICP-MS and rigorous collection methods to avoid contamination, Farias et al. (2005) reported a detection limit of 0.2 μg/L semen. Mean semen lead concentration in a group of 160 adults (age range: 19–48 years) who were not exposed to lead occupationally was 2.66 μg/L (range: 0.08–19.42) and significantly correlated with blood lead concentration (mean: 10.8 μg/dL, range: 4.5–40.2) and tibia bone lead (mean: 14.51 μg/g, range: non-detect–44.71 μg/g).

Stable Lead Isotopes. Analysis of the relative abundance of stable isotopes of lead in blood and other accessible body fluids (e.g., breast milk, urine) has been used to differentiate exposures from multiple sources (Flegal and Smith 1995). Relative abundances of stable isotopes of lead (^{204}Pb, ^{206}Pb, ^{207}Pb, and ^{208}Pb) in lead ores vary with the age of the ore (which determines the extent to which the parent isotopes have undergone radioactive decay to stable lead). Humans have lead isotope abundance profiles that reflect the profiles of lead deposits to which they have been exposed. Conversely, if exposure is to lead from a predominant deposit, that source can be identified by the relative abundance profile in blood (or other biological sample). Similarly, if exposure abruptly changes to a lead source having a different isotope abundance profile, the kinetics of the change in profile in the person can be measured, reflecting the kinetics of uptake and distribution of lead from the new source (Gulson et al. 2003; Maddaloni et al. 1998; Manton et al. 2003). Numerous examples of the application of stable isotope abundance measurements for studying sources of lead exposures have been reported (Angle et al. 1995; Graziano et al. 1996; Gulson and Wilson 1994; Gulson et al. 1996; Manton 1977, 1998).

Effect Biomarkers Used to Assess Exposure to Lead. Certain physiological changes that are associated with lead exposure have been used as biomarkers of exposure (see Section 3.6.2). These include measurement of biomarkers of impaired heme biosynthesis (blood zinc protoporphyrin, urinary coproporphyrin, erythrocyte ALAD activity). These types of measurements have largely been supplanted with measurement of blood lead concentration for the purpose of assessing lead exposure.

3.6.2 Biomarkers Used to Characterize Effects Caused by Lead

One of the most sensitive effects of lead exposure is the inhibition of the heme biosynthesis pathway, which is necessary for the production of red blood cells. Hematologic tests such as hemoglobin concentration may suggest toxicity, but this is not specific for lead (Bernard and Becker 1988). However,

inhibition of ferrochelatase in the heme pathway causes accumulation of protoporphyrin in erythrocytes (CDC 1985). Most protoporphyrin in erythrocytes (about 90%) exists as ZPP. This fraction is preferentially measured by hematofluorometers. Extraction methods measure all of the protoporphyrin present, but strip the zinc from the ZPP during the extraction process. For this reason, extraction results are sometimes referred to as (zinc) FEP. Although the chemical forms measured by the two methods differ slightly, on a weight basis they are roughly equivalent; thus, results reported as EP, ZPP, or FEP all reflect essentially the same analyte. An elevated EP level is one of the earliest and most reliable indicators of impairment of heme biosynthesis and reflects average lead levels at the site of erythropoiesis over the previous 4 months (Janin et al. 1985). The concentration of EP rises above background at PbBs of 25–30 μg/dL, above which, there is a positive correlation between PbB and EP (CDC 1985; Gennart et al. 1992a; Roels and Lauwerys 1987; Soldin et al. 2003; Wildt et al. 1987). Lead toxicity is generally considered to be present when a PbB ≥10 μg/dL is associated with an EP level of ≥35 μg/dL (CDC 1991; Somashekaraiah et al. 1990). This effect is detectable in circulating erythrocytes only after a lag time reflecting maturation in which the entire population of red blood cells has turned over (i.e., 120 days) (EPA 1986a; Moore and Goldberg 1985). Similarly, elevated erythrocyte protoporphyrin can reflect iron deficiency, sickle cell anemia, and hyperbilirubinemia (jaundice). Therefore, reliance on EP levels alone for initial screening could result in an appreciable number of false positive cases (CDC 1985; Mahaffey and Annest 1986; Marcus and Schwartz 1987). Conversely, since EP does not go up until the PbB exceeds 25 μg/dL, and the level of concern is 10 μg/dL, relying on EP measures would result in many false negative cases. Some have estimated that relying only on ZPP screening to predict future lead toxicity would miss approximately 3 cases with toxic blood lead concentrations in every 200 workers at risk (Froom et al. 1998). A limitation of measuring porphyrin accumulation is that porphyrin is labile because of photochemical decomposition; thus, assay samples must be protected from light. However, other diseases or conditions such as porphyria, liver cirrhosis, iron deficiency, age, and alcoholism may also produce similar effects on heme synthesis (Somashekaraiah et al. 1990).

ALAD, an enzyme occurring early in the heme pathway, is also considered a sensitive indicator of lead effect (Graziano 1994; Hernberg et al. 1970; Morris et al. 1988; Somashekaraiah et al. 1990; Tola et al. 1973). ALAD activity is negatively correlated with PbBs of 5–95 μg/dL, with >50% inhibition occurring at PbBs >20 μg/dL (Hernberg et al. 1970; Morita et al. 1997; Roels and Lauwerys 1987). However, ALAD activity may also be decreased with other diseases or conditions such as porphyria, liver cirrhosis, and alcoholism (Somashekaraiah et al. 1990). ALAD was found to be a more sensitive biomarker than urinary ALA and ZPP at PbBs between 21 and 30 μg/dL (Schuhmacher et al. 1997). A marked increase in urinary excretion of ALA, the intermediate that accumulates from decreased ALAD, can be detected

when PbB exceeds 35 μg/dL in adults and 25–75 μg/dL in children (NAS 1972; Roels and Lauwerys 1987; Sakai and Morita 1996; Schuhmacher et al. 1997).

Another potential biomarker for hematologic effects of lead is the observation of basophilic stippling and premature erythrocyte hemolysis (Paglia et al. 1975, 1977). Lead can impair the activity of pyrimidine 5'-nucleotidase, resulting in a corresponding increase in pyrimidine nucleotides in red blood cells, which leads to a deficiency in maturing erythroid elements and thus, decreased red blood cells. However, this effect is nonspecific; it is encountered with benzene and arsenic poisoning (Smith et al. 1938) and in a genetically-induced enzyme-deficiency syndrome (Paglia et al. 1975, 1977). Furthermore, since basophilic stippling is not universally found in chronic lead poisoning, it is relatively insensitive to lesser degrees of lead toxicity (CDC 1985). The activity of adenine dinucleotide synthetase (NADS) in erythrocytes has also been explored as a biomarker for predicting PbBs >40 μg/dL; NADS activity is negatively correlated with PbB over the range 5–80 μg/dL (Morita et al. 1997).

A multisite study of populations living near four NPL sites was conducted to assess the relationship between exposure (PbB and area of residence) and biomarkers of four organ systems: immune function disorders, kidney dysfunction, liver dysfunction, and hematopoietic dysfunction (Agency for Toxic Substances and Disease Registry 1995). The geometric mean PbB in those living in the target areas was 4.26 μg/dL (n=1,645) compared with 3.45 μg/dL for a group living in comparison areas (n=493). In children <6 years old, the corresponding means were 5.37 versus 3.96 μg/dL. In subjects ≥15 years old, the target and comparison values were 3.06 and 3.63 μg/dL, respectively. Ninety percent of target and 93% of comparison area participants had PbBs <10 μg/dL. Lead in soil and in water was found to be higher in comparison areas than in the target areas, but lead in house dust and in interior paint was higher in the target areas. PbB correlated with lead in soil and dust, but not with lead in paint and water. Multivariate regression analyses showed that of all the biomarkers analyzed, PbB was significantly associated with and predictive of hematocrit in adults 15 years of age or older and with increased mean serum IgA in children 6–71 months of age. The biological significance of these associations is unclear since both hematocrit and IgA levels were well within normal ranges and were hardly different than levels in subjects from the comparison areas.

Reduction in the serum 1,25-dihydroxyvitamin D concentration has been reported as an indicator of increased lead absorption or lead concentrations in the blood (Rosen et al. 1980). Lead inhibits the formation of this active metabolite of vitamin D, which occurs in bone mineral metabolism (EPA 1986a; Landrigan 1989). Children with PbBs of 12–120 μg/dL showed decreased serum 1,25-dihydroxyvita-

min D concentrations comparable to those found in patients with hypoparathyroidism, uremia, and metabolic bone disease (Mahaffey et al. 1982; Rosen et al. 1980). This biomarker is clearly not specific for lead exposure and several diseases can influence this measurement.

One of the most sensitive systems affected by lead exposure is the nervous system. Encephalopathy is characterized by symptoms such as coma, seizures, ataxia, apathy, bizarre behavior, and incoordination (CDC 1985). Children are more sensitive to neurological changes. In children, encephalopathy has been associated with PbBs as low as 70 μg/dL (CDC 1985). An early sign of peripheral manifestations of neurotoxicity is gastrointestinal colic, which can occur with PbBs above 50 μg/dL. The most sensitive peripheral index of neurotoxicity of lead is reported to be slowed conduction velocity in small motor fibers of the ulnar nerve in workers with PbBs of 30–40 μg/dL (Landrigan 1989). Other potential biomarkers of lead suggested for neurotoxicity in workers are neurological and behavioral tests, as well as cognitive and visual sensory function tests (Williamson and Teo 1986). However, these tests are not specific to elevated lead exposure.

Functional deficits associated with lead-induced nephrotoxicity increase in severity with increasing PbB. Effects on glomerular filtration evident at PbBs below 20 μg/dL, enzymuria and proteinuria occurs above 30 μg/dL, and severe deficits in function and pathological changes occur in association with PbBs exceeding 50 μg/dL (see Table 3-3 and Figure 3-3). Biomarkers for these changes include elevation of serum creatinine, urinary enzymes (e.g., NAG), or protein (albumin, β2μ-globulin, α1μ-globulin, retinol binding protein). However, none of these markers are specific for lead-induced nephrotoxicity. A characteristic histologic feature of lead nephrotoxicity is the formation of intranuclear inclusion bodies in the renal proximal tubule (Choie and Richter 1972; Goyer et al. 1970a, 1970b).

3.7 INTERACTIONS WITH OTHER CHEMICALS

The toxicokinetics and toxicological behavior of lead can be affected by interactions with essential elements and nutrients (for a review, see Mushak and Crocetti 1996). In humans, the interactive behavior of lead and various nutritional factors is particularly significant for children, since this age group is not only sensitive to the effects of lead, but also experiences the greatest changes in relative nutrient status. Nutritional deficiencies are especially pronounced in children of lower socioeconomic status; however, children of all socioeconomic strata can be affected.

Available data from a number of reports document the association of lead absorption with suboptimal nutritional status. In infants and children 1–6 years of age, lead retention (as measured by PbB content) was inversely correlated with calcium intake, expressed either as a percentage of total or on a weight basis (Johnson and Tenuta 1979; Mahaffey et al. 1986; Sorrell et al. 1977; Ziegler et al. 1978). Dietary intakes of calcium and vitamin D were significantly ($p<0.001$) lower in children with PbBs >60 μg/dL (Johnson and Tenuta 1979). The gastrointestinal uptake of ^{203}Pb was monitored in eight adult subjects as a function of dietary calcium and phosphorus intakes (Heard and Chamberlain 1982). The label absorption rate was 63% without supplementation of these minerals in fasting subjects, compared with 10% in subjects supplemented with 200 mg calcium plus 140 mg phosphorus, the amounts present in an average meal. Calcium and phosphorus alone reduced lead uptake by a factor of 1.3 and 1.2, respectively; both together yielded a reduction factor of 6. Copper, iron, and zinc have also been postulated to affect lead absorption (Klauder and Petering 1975).

Children with elevated PbB (12–120 μg/dL) were found to have significantly lower serum concentrations of the vitamin D metabolite 1,25-dihydroxyvitamin D compared with age-matched controls ($p<0.001$), and showed a negative correlation of serum 1,25-dihydroxyvitamin D with lead over the range of blood lead levels measured (Mahaffey et al. 1982; Rosen et al. 1980).

Zinc is in the active site of ALAD and can play a protective role in lead intoxication by reversing the enzyme-inhibiting effects of lead. Children with high PbBs (50–67 μg/dL) were reported to consume less zinc than children with lower PbB (12–29 μg/dL) (Johnson and Tenuta 1979). In a group of 13 children, Markowitz and Rosen (1981) reported that the mean serum zinc levels in children with plumbism were significantly below the values seen in normal children; chelation therapy reduced the mean level even further. An inverse relationship between ALA in urine and the amount of chelatable or systemically active zinc was reported in 66 children challenged with EDTA and having PbBs ranging from 45 to 60 μg/dL (Chisolm 1981). Zinc sulfate administration to a lead-intoxicated man following calcium disodium EDTA therapy restored the erythrocyte ALAD activity that was inhibited by lead (Thomasino et al. 1977).

Forty-three children with elevated PbB (>30 μg/dL) and EP (>35 μg/dL) had an increased prevalence of iron deficiency (Yip et al. 1981). An inverse relationship between chelatable iron and chelatable body lead levels as indexed by urinary ALA levels was observed in 66 children with elevated PbB (Chisolm 1981). Another study reported that the lead absorption rate was 2–3 times greater in iron-deficient adults compared to subjects who were iron-replete (Watson et al. 1980). Daily nutritional intake of dietary fiber,

iron, and thiamine were negatively correlated with PbB in male workers occupationally exposed to lead in a steel factory (Ito et al. 1987). Results from the NHANES II national survey showed that in children low iron status increases the lead hematotoxic dose response curves (Marcus and Schwartz 1987) and that iron deficiency plus elevated PbB produce a greater degree of hematotoxicity compared with either factor alone (Mahaffey and Annest 1986). A study of 299 children from 9 months to 5 years old from an urban area found a significant negative association between PbB and dietary iron intake (Hammad et al. 1996). Graziano et al. (1990) studied a population of pregnant women in Kosovo, Yugoslavia. They found that serum ferritin concentrations were associated with lower PbBs, suggesting that dietary iron may inhibit lead absorption. A study of 319 children ages 1–5 from Sacramento, California found that iron-deficient children had an unadjusted geometric mean PbB 1 μg/dL higher than iron-replete children (Bradman et al. 2001). The difference persisted after adjusting for potential confounders by multivariate regression; the largest difference in PbB was approximately 3μg/dL and was present among those living in the most contaminated areas. While the studies mentioned above point to a link between iron deficiency and lead poisoning, it is unclear whether there is a causal link or whether iron deficiency is just a marker of high environmental lead. Also considered should be the possibility that children who do not get adequate nutrition (including iron) may be more prone to ingestion of paint chips and this may confound the type of study that attempts to associate iron deficiency with lead poisoning. A longitudinal analysis of 1,275 children whose blood was screened for lead and complete blood count on two consecutive visits to a clinic suggested that the risk of subsequent lead poisoning associated with iron deficiency is 4–5 times greater than the baseline risk of lead poisoning (Wright et al. 2003c). The subject of lead/iron interactions was recently reviewed by Kwong et al. (2004).

The relationship between nutritional factors, other than those mentioned above, and PbB of preschool children was examined by Lucas et al. (1996). The objective of the study was to determine whether total caloric intake, dietary fat, dietary protein, and carbohydrates are associated with PbB while simultaneously controlling for other nutrient and environmental exposures. The cohort comprised 296 children aged 9–72 months, predominantly black (82%), from an urban area. The mean PbB was 11.4 μg/dL (range, 1–55 μg/dL). After adjusting for confounders, the study found significant positive associations for total caloric intake and dietary fat with PbB. Lucas et al. (1996) speculated that bile secreted into the gastrointestinal to aid in the digestion and absorption of fat may increase lead absorption, as shown in rats (Cikrt and Tichy 1975). The influence of total caloric intake may just reflect increased intake of lead through contaminated food.

Reports of lead-nutrient interactions in experimental animals have generally described such relationships in terms of a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the data are concerned with the impact of dietary levels of calcium, iron, phosphorus, and vitamin D. These interaction studies are summarized in Table 3-11.

People who live near waste sites may be simultaneously exposed to more than one chemical, and there is concern that chemicals in a mixture may interact with each other in such a manner that the toxicity of chemical A may be increased in the presence of chemical B. Studies have shown that both the toxicity and toxicokinetics of lead can be influenced by the presence of other chemicals that are commonly found together with lead at hazardous waste sites, particularly other metals. The studies available indicate that the outcome of the interaction of lead with other metals depends on many factors such as exposure levels, timing of exposure, and end point examined, to name a few. As a result, global statements cannot be made. However, it appears that, in general, zinc and copper are protective of the effects of lead. For details on the interactive effects of lead with other metals, the reader is referred to the *Interaction Profile for Arsenic, Cadmium, Chromium, and Lead* (Agency for Toxic Substances and Disease Registry 2004a), *Interaction Profile for Lead, Manganese, Zinc, and Copper* (Agency for Toxic Substances and Disease Registry 2004b), and *Interaction Profile for Chlorpyrifos, Lead, Mercury, and Methylmercury* (Agency for Toxic Substances and Disease Registry 2006).

3.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to lead than will most persons exposed to the same level of lead in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of lead, or compromised function of organs affected by lead. Populations who are at greater risk due to their unusually high exposure to lead are discussed in Section 6.7, Populations with Potentially High Exposures.

Certain subgroups of the population may be more susceptible to the toxic effects of lead exposure. These include crawling and house-bound children (<6 years old), pregnant women (and the fetus), the elderly, smokers, alcoholics, and people with genetic diseases affecting heme synthesis, nutritional deficiencies, and neurological or kidney dysfunction. This is not an exhaustive list and reflects only current data available; further research may identify additional susceptible subgroups.

Table 3-11. Effects of Nutritional Factors on Lead Uptake in Animals

Factor	Species	Index of effect	Interactive effect	References
Calcium	Rat	Lead in tissues and severity of effect at low levels of dietary calcium	Low dietary calcium (0.1%) increase lead absorption and severity of effects	Mahaffey et al. 1973; Six and Goyer 1970
Calcium	Rat	Lead retention	Retention increased in calcium deficiency	Barton et al. 1978a
Calcium	Rat	Lead in tissues at high levels of dietary calcium during pregnancy	Reduced release of lead from bone	Bogden et al. 1995
Calcium	Pig	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Hsu et al. 1975
Calcium	Horse	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Willoughby et al. 1972
Calcium	Lamb	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Morrison et al. 1977
Iron	Rat	Tissue levels and relative toxicity of lead	Iron deficiency increases lead absorption and toxicity	Six and Goyer 1972
Iron	Rat	Lead absorption in everted duodenal sac preparation	Reduction in intubated iron increases lead absorption; increased levels decrease lead uptake	Barton et al. 1978b
Iron	Rat	*In utero* or milk transfer of lead in pregnant or lactating rats	Iron deficiency increases both *in utero* and milk transfer of lead to sucklings	Cerklewski 1980
Iron	Mouse	Lead retention	Iron deficiency has no effect on lead retention	Hamilton 1978
Protein	Rat	Body lead retention	Low dietary protein either reduces or does not affect retention in various tissues	Quarterman et al. 1978
Protein	Rat	Tissue levels of lead	Casein diet increases lead uptake compared to soybean meal	Anders et al. 1982
Protein	Rat	Lead uptake by tissues	Both low and high protein in diet increases lead absorption	Barltrop and Khoo 1975
Milk components	Rat	Lead absorption	Lactose-hydrolyzed milk does not increase lead absorption, but ordinary milk does	Bell and Spickett 1981
Milk components	Rat	Lead absorption	Lactose in diet enhances lead absorption compared to glucose	Bushnell and DeLuca 1981
Zinc	Rat	Lead absorption	Low zinc in diets increases lead absorption	Cerklewski and Forbes 1976

Table 3-11. Effects of Nutritional Factors on Lead Uptake in Animals

Factor	Species	Index of effect	Interactive effect	References
Zinc	Rat	Lead transfer *in utero* and in milk during lactation	Low-zinc diet of mother increases lead transfer *in utero* and in maternal milk	Cerklewski 1979
Zinc	Rat	Tissue retention	Low zinc diet enhances brain lead levels	Bushnell and Levin 1983
Copper	Rat	Lead absorption	Low copper in diet increases lead absorption	Klauder and Petering 1975
Phosphorus	Rat	Lead uptake in tissues	Reduced phosphorus increases ^{203}Pb uptake 2.7-fold	Barltrop and Khoo 1975
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances lead retention; no effect on lead resorption in bone	Quarterman and Morrison 1975
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances both lead retention and lead deposition in bone	Barton and Conrad 1981
Vitamin D	Rat	Lead absorption using everted sac techniques	Increasing vitamin D increases intubated lead absorption	Smith et al. 1978
Vitamin D	Rat	Lead absorption using everted sac techniques	Both low and excess levels of vitamin D increase lead uptake by affecting motility	Barton et al. 1980
Thiamin	Mouse	Whole-body lead retention	Increased retention with increased thiamin concentration	Kim et al. 1992
Lipid	Rat	Lead absorption	Increases in lipid (corn oil) content up to 40% enhance lead absorption	Barltrop and Khoo 1975

^{203}Pb = Lead 203

Children. Children are at the greatest risk for experiencing lead-induced health effects, particularly in the urbanized, low-income segments of this pediatric population. Young children (<5 years old) have been documented to absorb lead via the gastrointestinal tract more efficiently (50% relative absorption) than adults (15% relative absorption) (Chamberlain et al. 1978). The use of leaded seams in cans used for canned food is not nearly as prevalent as it once was, so this is no longer as important a source of dietary exposure to lead. Behavior such as thumb sucking and pica result in an elevated transfer of lead-contaminated dust and dirt to the gastrointestinal tract (Schroeder and Hawk 1987). Also, children frequently have a greater prevalence of nutrient deficiency (Yip et al. 1981; Ziegler et al. 1978). For example, the diets of young children are commonly deficient in zinc, a condition that exacerbates some of the toxic effects of lead. Children have also been documented to have lower blood thresholds for the hematological and neurological effects induced by lead exposure. In addition, the resultant encephalopathy, central nervous system deficits, and neurologic sequelae tend to be much more severe in children than adults (Bellinger et al. 1989a; Bradley et al. 1956; Wang et al. 1989). Breast-fed infants of lead-exposed mothers are also a susceptible group since lead is also secreted in the breast milk (Dabeka et al. 1988; Ettinger et al. 2006; Gulson et al. 1998a). Calcium supplementation during lactation has been shown to decrease both maternal PbB and lead concentration in breast milk (Ettinger et al. 2006; Hernandez-Avila et al. 2003).

Susceptibility to lead toxicity is influenced by dietary levels of calcium, iron, phosphorus, vitamins A and D, dietary protein, and alcohol (Calabrese 1978). Low dietary ingestion of calcium or iron increased the predisposition to lead toxicity in animals (Barton et al. 1978a; Carpenter 1982; Hashmi et al. 1989; Six and Goyer 1972; Waxman and Rabinowitz 1966). Iron deficiency combined with lead exposure acts synergistically to impair heme synthesis and cell metabolism (Waxman and Rabinowitz 1966). Nutritional surveys indicate that children of low-income groups consume less than recommended dietary allowances of calcium and iron. Dietary deficiencies of these two minerals have been shown to increase the risk of lead poisoning (Bradman et al. 2001; Johnson and Tenuta 1979; Wright et al. 2003c; Yip et al. 1981; Ziegler et al. 1978). Thus, nutrient deficiencies in conjunction with a developmental predisposition to absorb lead makes this subset of children at a substantially elevated risk. More information on children's susceptibility to lead is presented in Section 3.5.

Embryo/Fetus. The embryo/fetus are at increased risk because of transplacental transfer of maternal lead (Bellinger et al. 1987a; Moore et al. 1982). Thompson et al. (1985) reported the case of a woman whose PbB increased to 74 μg/dL over the course of pregnancy resulting in the baby's PbB level of 55 μg/dL and showing clinical signs of intoxication. No evidence of increased exposure to external lead source

during this period was apparent, but it was found that the mother had excessive exposure to lead 30 years prior to the pregnancy. Bone resorption during pregnancy can be reduced by ingestion of calcium supplements (Janakiraman et al. 2003). Lead has been demonstrated in animal studies to increase the incidence of fetal resorptions (McClain and Becker 1972) and to induce adverse neurobehavioral effects in offspring exposed *in utero* (Section 3.2.4).

Women. Studies of women suggest that conditions of pregnancy, lactation, and osteoporosis may intensify bone demineralization, thus mobilizing bone lead into the blood resulting in increased body burdens of lead (Silbergeld et al. 1988). For example, women show an increased rate of bone lead loss with age relative to men (Drasch et al. 1987). Women with postmenopausal osteoporosis may be at an increased risk since lead inhibits activation of vitamin D, uptake of calcium, and several aspects of bone cell function to aggravate the course of osteoporosis. An increased release of bone lead to blood occurs in women, in association with menopause (Gulson et al. 2002). These observations are consistent with epidemiological studies that have shown increases in PbB after menopause and in association with decreasing bone density in postmenopausal women (Berkowtiz et al. 2004; Bonithon-Kopp et al. 1986c; Ewers et al. 1990; Hernandez-Avila et al. 2000; Korrick et al. 2002; Markowitz and Weinberger 1990; Nash et al. 2004; Silbergeld et al. 1988; Symanski and Hertz-Picciotto 1995). Long-term effects of lead exposure were also reported by Hu (1991b) who found that pregnant women who had experienced childhood plumbism had a higher rate of spontaneous abortion or stillbirth than matched controls, and their offspring were more likely to experience learning disabilities.

Elders. The aged population may be at an increased risk for toxic effects of lead as suggested by two studies that found an association between decreased neurobehavioral performance and PbB in aging subjects with PbB around 5 μg/dL (Muldoon et al. 1996; Payton et al. 1998). A more recent study of 526 participants of the Normative Aging Study with a mean age of 67.1 years and mean PbB of 6.3 μg/dL reported that patellar lead was significantly associated with psychiatric symptoms such as anxiety, depression, and phobic anxiety (Rhodes et al. 2003). In yet an additional study of Normative Aging Study participants (mean PbB, 4.5 μg/dL), it was found that both bone and blood lead were associated with poor test performance (Wright et al. 2003c). According to the investigators, these findings are consistent with the theory that bone lead chronically remobilizes into blood, thus accelerating cognitive decline.

People with Genetic Diseases and Gene Polymorphisms. The toxic effects of lead exposure become exacerbated in individuals with inherited genetic diseases, such as thalassemia, which is characterized by

an abnormality in the rate of hemoglobin synthesis (Calabrese 1978). Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are also unusually susceptible and may exhibit hemolytic anemia following lead exposure (Calabrese 1978). In a study of 148 subjects, Cocco et al. (1991) found that chronic lead poisoning tended to decrease total cholesterol and LDL in both G6PD-deficient and G6PD-nondeficient populations, but positive slopes were seen for cholesterol esters in G6PD deficient subjects and for HDL in G6DP normal subjects. Another study from the same group found that mortality from all causes and cancer mortality were lower among lead smelter workers with the G6PD-deficient phenotype compared to coworkers with the wild phenotype; the study comprised 867 workers with the wild phenotype and 213 with the deficient phenotype (Cocco et al. 1996). Because of the relatively small number of subjects with the deficient phenotype, the study may have lacked statistical power to examine deaths among this group. It has also been postulated that children with sickle cell disease have an increased risk of developing neuropathy with exposure to lead (Erenberg et al. 1974). People with metabolic disorders associated with the synthesis of porphyrins (important intermediates in the synthesis of hemoglobin, cytochromes, and vitamin B12), collectively known as porphyrias, are especially susceptible to lead exposure since lead inhibits two critical enzymes, ALAD and ferrochelatase, concerned with heme synthesis in erythrocytes (Hubermont et al. 1976; Silbergeld et al. 1982). The presence of genetic disorders that induce excessive ALA synthetase activity in addition to lead exposure produce higher than normal levels of ALA, resulting in excessive ALA excretion, accumulation, and lack of negative feedback on the ALA synthetase activity from heme (Calabrese 1978).

ALAD is a polymorphic enzyme with two alleles (ALAD-1 and ALAD-2) and three genotypes: ALAD 1,1;, ALAD 1,2; and ALAD 2,2 (Battistuzzi et al. 1981). Various single nucleotide polymorphisms of the ALAD gene have been reported (Chia et al. 2005). Approximately 80% of Caucasians have the ALAD 1,1 genotype, 19% have the ALAD 1,2 genotype, and only 1% have the ALAD 2,2 genotype (Astrin et al. 1987; Battistuzzi et al. 1981). Studies of the relationship between ALAD genotype and blood lead levels have yielded conflicting results. Higher blood lead levels were observed in individuals with the ALAD 1,2 and ALAD 2,2 genotypes compared to similarly exposed individuals with the ALAD 1,1 genotype (Astrin et al. 1987; Hsieh et al. 2000; Schwartz et al. 2000b; Wetmur et al. 1991). There are also reports of children with the ALAD 2,2 having higher PbB than noncarriers (Pérez-Bravo et al. 2004; Shen et al. 2001). However, results of several other studies have found no association between blood lead levels and ALAD genotype in lead-exposed workers (Alexander et al. 1998b; Bergdahl et al. 1997b; Schwartz 1995; Schwartz et al. 1997a, 1997b; Smith et al. 1995; Süzen et al. 2003), although ALAD-2 carriers were 2.3 times more likely to have blood levels ≥40 μg/dL (Schwartz et al. 1997a). The observations of higher blood level levels in ALAD 2 carriers has prompted

the suggestion that the ALAD-2 allele may have a higher binding affinity for lead than the ALAD-1 allele (Bergdahl et al. 1997b), a difference that could alter lead-mediated outcomes. Several studies have been conducted to specifically evaluate whether ALAD genotypes are associated with differences in partitioning of lead between red blood cells and plasma, differences in distribution of lead to other tissue compartments, and altered susceptibility to lead toxicity.

Studies investigating the effects of ALAD polymorphism on the distribution of lead in the blood have also yielded conflicting results. In lead-exposed workers, a higher percentage of erythrocyte lead was bound to ALAD in carriers of the ALAD-2 allele (84%) compared to carriers of the ALAD-1 allele (81%) (Bergdahl et al. 1997b). Although this difference is small, it did reach statistical significance ($p<0.03$), supporting the hypothesis that the ALAD-2 allele has a higher binding affinity for lead than the ALAD-1 allele. However, higher whole blood levels were not observed for ALAD-2 carriers compared to ALAD-1 homozygotes. Furthermore, no ALAD allele-specific differences were detected for the ratio of blood lead to plasma lead. Results of studies by Fleming et al. (1998a) substantiate earlier reports of higher blood lead levels for carriers of the ALAD-2 allele and indicate that ALAD polymorphism has an effect on the distribution of lead in the blood and, ultimately, to other tissue compartments. Serum lead levels for carriers of the ALAD-2 allele were higher than for ALAD-1 homozygotes (ALAD-2 carriers = 0.335±0.025 μg/dL; ALAD-1 homozygotes = 0.285±0.009 μg/dL), an 18% difference that approached statistical significance ($p<0.06$) (Fleming et al. 1998a).

Based on the higher plasma lead levels observed for ALAD-2 carriers, it is reasonable to project that distribution of lead to other tissue compartments could be higher for ALAD-2 carriers, in which case, the ALAD genotype could exert effects on the dose-response relationship for lead. In lead-exposed workers, urinary excretion of lead following oral administration of DMSA was less in ALAD-2 carriers than in ALAD-1 homozygotes ($p=0.07$), suggesting that carriers of the ALAD-2 allele may have lower levels of lead, or, at least, lower amounts of lead accessible to complexation with DMSA (Schwartz et al. 1997b). Studies investigating the effects of ALAD polymorphism on the distribution of lead to bone have also yielded conflicting results. No ALAD allele-specific differences were observed for the net accumulation of lead in bone (Bergdahl et al. 1997b, Fleming et al. 1998a; Lee et al. 2001) or for patellar bone (Lee et al. 2001; Theppeang et al. 2004). However, ALAD-2 carriers accumulated slightly more lead in bone than ALAD-1 homozygotes ($p=0.06$) (Fleming et al. 1998a). Higher bone lead levels were reported in lead-exposed workers carrying the ALAD-2 gene compared to ALAD-1 homozygotes (Smith et al. 1995). The cortical-trabecular bone lead differential (patellar minus tibial lead concentration) in ALAD-1 homozygotes was lower than in ALAD-2 carriers ($p=0.06$). In these same workers, blood urea

nitrogen (BUN) and uric acid (UA) were elevated in ALAD-2 carriers (BUN, p=0.03; UA, p=0.07), indicating that ALAD-2 carriers could be more susceptible to the renal toxicity of lead. However, in a multivariate logistic regression model that included PbB and ALAD genotype (along with age and alcohol consumption), increases in BUN and serum uric acid concentration were significantly associated with increases in PbB (regression coefficient, 0.13 mg/dL per μg Pb/dL; p=0.005), but not ALAD genotype (p=0.06). Wu et al. (2003a) also found apparent effects of ALAD genotype on the relationship between bone lead levels and serum uric acid levels in a study conducted as part of the Normative Aging Study. Increasing patella bone lead levels above a threshold of 15 μg/g was positively associated with serum uric acid levels among ALAD 1-1/2-2 heterozygotes; however, among ALAD 1-1 homozygotes, the threshold for the association was 101 μg/g. In contrast, young adults with ALAD 1-2 genotype did better on cognitive tests given the same amount of lead exposure (Bellinger et al. 1994), suggesting possible age-specific interactions. Chia et al. (2005) examined interactions between PbB and the presence of various single nucleotide polymorphisms (SNP) in the ALAD gene on various kidney outcomes among a group of lead workers in Vietnam (n=323). This study found significant interactions between increasing PbB and the HpyCH4 SNP on increasing urinary retinal binding protein, α1μ-globulin, β2μ-globulin, and albumin. Lee et al. (2001) examined the possible influence of ALAD genotype on systolic and diastolic blood pressure in a cohort of Korean lead workers (789 workers, 135 controls). Lead body burden measures (i.e., PbB, tibia blood lead, DMSA-chelatable lead) and blood pressures were not significantly different between ALAD 1-1 and ALAD 1-2 genotypes.

The finding of associations between ALAD-2 and bone lead concentrations and ALAD-2 and markers of renal toxicity suggest that differential binding of lead to ALAD-2 may influence both the toxicokinetics and certain aspects of the toxicodynamics of lead. No information is available on the distribution of lead to other tissue compartments relative to ALAD genotype. Thus, based on the limited data available, it appears that ALAD polymorphism may be a genetic factor in the kinetic behavior of lead in the body. However, the exact nature and significance of ALAD polymorphism remains to be elucidated. A recent meta-analysis of 24 studies that included lead workers, the general population, and children found a statistically significant association beween ALAD-2 carriers and higher PbB in lead-exposed workers (Scinicariello et al. 2007). However, the ALAD-2 genotype did not appear to be a significant determinant of PbB among adults with PbBs <10 μg/dL. The study also found that ALAD-2 carriers appeared to be protected against adverse hematopoietic effects of lead as measured by hemoglobin levels, possibly because of decreased lead bioavailability to enzymes of the heme pathway.

The role of the vitamin D receptor (VDR) polymorphism in lead intoxication also has been studied. The VDR gene regulates the production of calcium-binding proteins and is reported to account for up to 75% of the total genetic effect on bone density (Onalaja and Claudio 2000). The VDR exists in several polymorphic forms in humans (Morrison et al. 1992). Restriction enzyme digestion of the VDR results in three genotypes commonly termed bb, when the restriction site is present, BB when the site is absent, and Bb when the two alleles are present. Schwartz et al. (2000a) studied the association of tibial lead and VDR genotype in 504 former organolead manufacturing workers in the United States. Tibial and blood lead concentrations were relatively low, with means of 14.4 ppm, and 4.6 μg/dL, respectively. Analyses of unadjusted data showed that there were only small differences in tibial lead concentrations by VDR genotype. However, in a multiple linear regression model of tibial lead concentrations, subjects with the B allele had larger increases in tibial lead concentrations with increasing age. In addition, whereas in subjects with the bb genotype, tibial lead declined since their last exposure to lead, subjects with Bb and BB showed increases in tibial lead. A study of 798 Korean lead workers whose mean tibial lead concentration and mean PbB were 37.2 ppm and 32 μg/dL, respectively, reported that lead workers with the VDR B allele had significantly higher PbB, chelatable lead level, and tibial lead than did workers with the VDR bb genotype (Schwartz et al. 2000b). A more recent study of this cohort reported that workers with the VDR B allele had significantly higher patellar lead than lead workers with the VDR bb genotype (Theppeang et al. 2004).

Two other genetic polymorphisms have been studied in the context of potential influence on lead associations with blood pressure. The endothelial nitric oxide synthase (eNOS) converts L-arginine into nitric oxide in the endothelium, resulting in the relaxation of vascular smooth muscle and contributes to the regulation of peripheral vascular resistance and blood pressure. Theppeang et al. (2004) reported that, in a cohort of Korean lead workers, there was no association of the endothelial nitric oxide synthase (eNOS) gene with patella lead. Polymorphisms in the α2 subunit of Na+-K+ ATPase (ATP1A2) have also been shown to influence associations between lead exposure and blood pressure (Glenn et al. 2001).

Another genetic susceptibility that has been studied in relation to lead toxicity is that of the hemochromatosis gene. Results published so far provided seemingly conflicting results. Hemochromatosis is a disease in which the absorption of iron is increased, resulting in excess iron depositing in many internal organs, particularly the liver, and leading to progressive damage (Onalaja and Claudio 2000). The gene codes for a protein designated HFE and has two variants: C282Y and H63D. Wright et al. (2004) studied 730 men from the Normative Aging Study and found that the presence of a hemochromatosis variant, either C282Y or H63D, predicted lower bone and blood lead concentration. Based on the fact that iron

status is inversely related to lead absorption, Wright et al. (2004) hypothesized that the results may be secondary to increased iron stores among HFE variant carriers leading to decreased lead absorption in the gastrointestinal tract. Previously, Barton et al. (1994) found that homozygous individuals who suffered from hemochromatosis had higher PbB than individuals who did not have the gene. An additional study found no difference in PbB between subjects with hemochromatosis and controls (Åkesson et al. 2000). Wright et al. (2004) speculated that the different results could be due to the different characteristics of the participants studied in terms of age, health status, and sex.

Finally, the possible association between Apolipoprotein E (APOE) genotype and susceptibility to lead toxicity also has been studied. APOE is an intracellular transporter of cholesterol and fatty acids that is synthesized by astrocytes in the brain and that plays a key role in the structure of cell membranes and myelin. There are three alleles of the APOE gene: E2, E3, and E4. Wright et al. (2003b) evaluated the relationship between the APOE gene and infant neurodevelopment in a sample of 311 mother-infant pairs living in and around Mexico City. The primary outcome assessed in the study was the 24-month MDI of the Bayley Scale. The authors also evaluated the modifying effect of APOE genotype on the association between PbB in umbilical cord and MDI score. After adjustment for potential confounders, infants carrying at least one copy of the APOE4 allele scored 4.4 points higher in the MDI than E3/E2 carriers. Furthermore, APOE genotype modified the dose–response relationship between umbilical PbB and MDI score in a manner that suggested that those with APOE4 were more protected against lead exposure than E3/E2 carriers. The APOE genotype also was reported to influence the relation between tibia lead and neurobehavioral test scores in a group of 529 former organolead workers (Stewart et al. 2002). The authors used linear regression to model the relations between each of 20 neurobehavioral test scores and tibia lead, a binary variable for APOE genotype. In 19 of the 20 regression models, the coefficients for the APOE and tibia lead interaction were negative. This meant that the slope for the relation between tibia lead and each neurobehavioral test was more negative for individuals with at least one APOE4 allele than for those who did not have an APOE4 allele. Stewart et al. (2002) concluded that some persistent effects of lead may be more toxic in individuals who have at least one APOE4 allele. The apparent contrast between the results of Stewart et al. (2002) and Wright et al. (2003b) may reflect age-specific gene-lead interactions.

Alcoholics and Smokers. Alcoholics, and people who consume excess amounts of alcohol, may be at increased risk of hematological, neurological, and hepatotoxic effects. In animal studies, lead and alcohol synergistically inhibited blood ALAD activity and hepatic glutamic oxaloacetic transaminase (GOT, AST) and glutamic pyruvic transaminase (GPT, ALT) activity, depressed dopamine and 5-hydroxy-

tryptamine levels in rat brain, increased lead burdens in tissue organs, and elevated blood ZPP (Dhawan et al. 1989; Flora and Tandon 1987). Smokers are also at elevated risks of lead intoxication since cigarette smoke contains lead and other heavy metals such as cadmium and mercury (Calabrese 1978), which have been shown to be synergistic in experimental animals (Congiu et al. 1979; Exon et al. 1979; Fahim and Khare 1980).

People with Neurologic Dysfunction or Kidney Disease. This population is unusually susceptible to lead exposure. The neurologic and renal systems are the primary target organs of lead intoxication, which may become overburdened at much lower threshold concentrations to elicit manifestations of lead intoxication (Benetou-Marantidou et al. 1988; Chisolm 1962, 1968; Lilis et al. 1968; Pollock and Ibels 1986).

3.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to lead. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to lead. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to lead:

Ellenhorn MJ. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. Metals and related compounds. 2nd ed. Baltimore, MD: Williams and Wilkins, 1563-1579.

Homan CS, Brogan GX, Orava RS. 1998. Emergency toxicology: Lead toxicity. Philadelphia, PA: Lippincott-Raven, 363-378.

Leikin JB, Paloucek FP. 2002. Poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 725-731.

3.9.1 Reducing Peak Absorption Following Exposure

Individuals potentially exposed to lead can prevent inhalation exposure to particles by wearing the appropriate respirator. The mechanism and rate of lead absorption from the gastrointestinal tract is not completely understood, but it is believed that absorption occurs in the small intestine by both active and passive transport following solubilization of lead salts by gastric acid (see Section 3.3, Toxicokinetics). Lead is poorly absorbed from the gastrointestinal tract; however, toxic effects can result from the relatively small amount of lead that is absorbed. It has been estimated that adults absorb approximately

10% of an administered dose, whereas children absorb 4–50% of ingested lead (see Section 3.3, Toxicokinetics). Lead absorption from the gut appears to be blocked by calcium, iron, and zinc. Although no treatment modalities to reduce lead absorption have yet been developed that make use of these observations, it is recommended that a child's diet contain ample amounts of iron and calcium to reduce the likelihood of increased absorption of lead and that children eat regular meals since more lead is absorbed on an empty stomach (CDC 1991). Good sources of iron include liver, fortified cereal, cooked legumes, and spinach, whereas milk, yogurt, cheese, and cooked greens are good sources of calcium (CDC 1991).

General recommendations to reduce absorption of lead following acute exposure include removing the individual from the source of exposure and decontaminating exposed areas of the body. Contaminated skin is washed with soap and water, and eyes exposed to lead are thoroughly flushed with water or saline (Stutz and Janusz 1988). Once lead is ingested, it is suggested that syrup of ipecac be administered to induce emesis. Administration of activated charcoal following emesis has not been proven to reduce absorption of any lead remaining in the gastrointestinal system, but is frequently recommended (Kosnett 2004; Stutz and Janusz 1988). Gastric lavage has been used to remove ingested lead compounds. Whole gut lavage with an osmotically neutral polyethylene glycol electrolyte solution (GO-Lytely®, Co-lyte®) has successfully removed ingested lead-containing pottery glazes according to anecdotal case reports. However, this procedure is not universally accepted. Patients who ingest lead foreign objects should be observed for the possible, although rare, development of signs or symptoms of lead poisoning until the ingested object has been proven to have passed through the gut. Surgical excision has been recommended when lead bullets or shrapnel are lodged near joint capsules (reaction with synovial fluid leads to systemic uptake of lead in some cases) (Kosnett 2004). The blood lead level can be monitored and used as an indication for surgical removal of the projectile.

3.9.2 Reducing Body Burden

Lead is initially distributed throughout the body and then redistributed to soft tissues and bone. In human adults and children, approximately 94 and 73% of the total body burden of lead is found in bones, respectively. Lead may be stored in bone for long periods of time, but may be mobilized, thus achieving a steady state of intercompartmental distribution (see Section 3.3.2).

All of the currently available methods to obviate the toxic effects of lead are based on their ability to reduce the body burden of lead by chelation. All of the chelating agents bind inorganic lead, enhance its

excretion, and facilitate the transfer of lead from soft tissues to the circulation where it can be excreted. Since the success of chelation therapy depends on excretion of chelated lead via the kidney, caution should be used when treating a patient with renal failure. The standard chelating agents currently in use are dimercaprol (British Anti-Lewisite, or BAL), $CaNa_2$-EDTA (or EDTA), penicillamine, and 2,3-dimercaptosuccinic acid (DMSA; Succimer®). Most of the information below regarding chelators has been extracted from Homan et al. (1998).

Dimercaprol (BAL) is the chelator of choice in the presence of renal compromise. Sulfhydryl ligands in BAL form stable chelate-metal compounds intra- and extracellularly. The onset of action for BAL is 30 minutes. BAL increases fecal excretion of lead as chelated lead is excreted predominantly in bile within 4–6 hours; BAL also increases urinary excretion of chelated lead. The use of BAL is indicated in cases of high lead levels without symptoms, in acute encephalopathy, and in symptomatic plumbism characterized by abdominal pain, anemia, headache, peripheral neuropathy, ataxia, memory loss, lethargy, anorexia, dysarthria, and encephalopathy. BAL is administered intramuscularly as a 10% solution in oil and the recommended dosage is 50–75 mg/m^2 every 4 hours. The full course is 3–5 days. Contra-indications for the use of BAL include liver failure, since BAL chelates are excreted primarily in bile. Also, patients with glucose-6-phosphate dehydrogenase deficiency develop hemolysis if BAL is administered. Concurrent administration of iron is contraindicated due to the high toxicity of the BAL-iron chelate. BAL also is contraindicated in subjects with a history of peanut oil allergy and in pregnancy. A number of adverse reactions have been described in BAL user including nausea, vomiting, hypertension, tachycardia, headache, increased secretions, anxiety, abdominal pain, and fever. Premedication with diphenylhydramine may mitigate these effects. Elevated liver function tests and sterile abscesses may also occur.

$CaNa_2$-EDTA (or EDTA) works by forming a stable metal-chelate complex that is excreted by the kidney. It increases renal excretion of lead 20–50 times. Numerous adverse effects have been described due to treatment with EDTA including rash, fever, fatigue, thirst, myalgias, chills, and cardiac dysrhythmias. EDTA should be used together with BAL (4 hours after the first dose of BAL) because acute lead encephalopathy may progress if EDTA given alone secondary to lead from soft tissue lead mobilization resulting in increased PbB. Since EDTA chelates zinc, patients with low zinc stores may be adversely affected by EDTA. Since EDTA also chelates other metals, administration of EDTA (or BAL) to persons occupationally exposed to cadmium may result in increased renal excretion of cadmium and renal damage. The dosage recommended for children is 1,000–1,500 mg/m^2/24 hours in 0.5% procaine i.m. to avoid fluid overload, although the preferred route of administration of EDTA is intravenously. This dose

may be given in up to six divided daily doses. For adults, the recommended dose is 1.5 g/24 hours in two divided doses. The full course for EDTA therapy is 5 days, but the course may be repeated if the patient is still symptomatic or when PbB is >50μg/dL.

D-Penicillamine is an orally-administered lead chelator whose mechanism of action is unknown, and that increased urinary excretion of lead. The FDA has not approved the use of d-penicillamine during pregnancy. Administration of d-penicillamine is contraindicated in subjects allergic to penicillin because of cross-reactivity with the latter. Among the adverse effects are rash, fever, anorexia, nausea, vomiting, leucopenia, thrombocytopenis, eosinophilia, hemolytic anemia, Stevens-Johnson syndrome (severe erythema multiforme), nephrotoxicity, and proteinuria. Furthermore, continued exposure to lead will result in continued absorption of lead at a higher rate. The recommended dose is 10 mg/kg/24 hours for 7 days, but may be increased to 10–15 mg/kg every 12 hours over 2–4 weeks. One way to minimize toxicity is to start medication at ¼ the dosage and gradually increase it to full dosage over 3–4 weeks. The CDC recommends giving children an entire dose on an empty stomach 2 hours before breakfast and to give adults an entire dose in two or three divided doses on an empty stomach 2 hours before meals.

2,3-Dimercaptosuccinic acid (DMSA; Succimer®) has a mechanism of action similar to BAL, but is far less toxic than BAL. DMSA is currently approved for asymptomatic children with PbB <45 μg/dL and an experimental protocol is available for mild encephalopathy and use in the adult. DMSA can be used with concurrent administration of iron. DMSA has been shown to be as effective as EDTA in increasing the urinary excretion of lead. Minimal adverse effects that have been reported include anorexia, nausea, vomiting, and rashes. DMSA increases the excretion of zinc, but to a much lesser extent than other chelators, and has minimal effects on Ca, Fe, Mg, and Cu. The recommended dosage is 10 mg/kg 3 times/day for 5 days, then 10 mg/kg 3 times/day for 14 days.

The following are treatment guidelines for lead exposure in children developed by the American Academy of Pediatrics (Berlin et al. 1995).

1. *Chelation treatment is not indicated in patients with blood lead levels of less than 25 μg/dL, although environmental intervention should occur.*

2. *Patients with blood levels of 25 to 45 μg/dL need aggressive environmental intervention but should not routinely receive chelation therapy, because no evidence exists that chelation avoids or reverses neurotoxicity. If blood lead levels persist in this range despite repeated environmental study and abatement, some patients may benefit from (oral) chelation therapy by enhanced lead excretion.*

3. *Chelation therapy is indicated in patients with blood lead levels between 45 and 70 μg/dL. In the absence of clinical symptoms suggesting encephalopathy (e.g., obtundation, headache, and persisting vomiting), patients may be treated with succimer at 30 mg/kg per day for 5 days, followed by 20 mg/day for 14 days. Children may need to be hospitalized for the initiation of therapy to monitor for adverse effects and institute environmental abatement. Discharge should be considered only if the safety of the environment after hospitalization can be guaranteed. An alternate regimen would be to use $CaNa_2EDTA$ as inpatient therapy at 25 mg/kg for 5 days. Before chelation with either agent is begun, if an abdominal radiograph shows that enteral lead is present, bowel decontamination may be considered as an adjunct to treatment.*

4. *Patients with blood lead levels of greater than 70 μg/dL or with clinical symptoms suggesting encephalopathy require inpatient chelation therapy using the most efficacious parenteral agents available. Lead encephalopathy is a life-threatening emergency that should be treated using contemporary standards or intensive care treatment of increased intracranial pressure, including appropriate pressure monitoring, osmotic therapy, and drug therapy in addition to chelation therapy. Therapy is initiated with intramuscular dimercaprol (BAL) at 25 mg/kg per day divided into six doses. The second dose of BAL is given 4 hours later, followed immediately by intravenous $CaNa_2EDTA$ at 50 mg/day as a single dose infused during several hours or as a continuous infusion. Current labeling of $CaNa_2EDTA$ does not support the intravenous route of administration, but clinical experience suggests that it is safe and more appropriate in the pediatric population. The hemodynamic stability of these patients, as well as changes in neurologic status that may herald encephalopathy, needs to be closely monitored.*

5. *Therapy needs to be continued for a minimum of 72 hours. After this initial treatment, two alternatives are possible: (1) the parenteral therapy with two drugs ($CaNa_2EDTA$ and BAL) may be continued for a total of 5 days; or (2) therapy with $CaNa_2EDTA$ alone may be continued for a total of 5 days. If BAL and $CaNa_2EDTA$ are used for the full 5 days, a minimum of 2 days with no treatment should elapse before considering another 5-day course of treatment. In patients with lead encephalopathy, parenteral chelation should be continued with both drugs until they are clinically stable before therapy is changed.*

6. *After chelation therapy, a period of reequilibration of 10 to 14 days should be allowed, and another blood lead concentration should be obtained. Subsequent treatment should be based on this determination, following the categories presented above.*

3.9.3 Interfering with the Mechanism of Action for Toxic Effects

Lead has multiple mechanisms of action at many different levels that affect many enzyme systems and cellular processes throughout the body. Thus, while it seems plausible that specific effects could be prevented or at least minimized, it is unlikely that one could prevent all of the physiological alterations that have been attributed to exposure to lead. However, several studies have examined whether lead-lowering interventions, such as with chelators, are paralleled by improvement in health outcomes

reportedly altered by lead. For example, Ruff et al. (1993) studied a group of 154 children with PbB between 25 and 55 μg/dL who were treated with $CaNa_2EDTA$ if eligible and/or with orally administered iron supplement if iron deficient. The outcome measured was a global index of cognitive functioning. It was found that within a period of 6 months, improvement in performance was significantly related to decreases in PbB, but there was no effect of chelation treatment. Ruff et al. (1993) speculated that a reduction or elimination of exposure may have led to decreases in PbB, and this may have occurred for chelated and nonchelated children.

Rogan et al. (2001) studied a group of 780 children enrolled in a randomized, placebo-controlled, double-blind trial of up to three 26-day courses of treatment with succimer. The PbB for the group ranged from 20 to 44 μg/dL. Although treatment with succimer lowered PbB by a mean of 4.5 μg/dL during the 6 months after initiation of treatment, it did not improve scores on tests of cognition, behavior, or neuropsychological function in children with PbB below 45 μg/dL. Rogan et al. (2001) noted that the failure to demonstrate a significant difference in test scores could have been due to the small difference in PbB between the two groups. Re-analysis of these data using change in PbB as the independent variable showed that improvement in test scores was associated with greater falls in PbB only in the placebo group and suggested that factors other than declining PbB were responsible for cognitive improvement (Liu et al. 2002). A further evaluation of this cohort at the age of 7 years showed that chelation therapy with succimer, although lowering mean PbB for approximately 6 months, produced no benefit in cognitive, behavioral, and neuromotor end points (Dietrich et al. 2004). Also in this cohort, treatment with succimer did not have a beneficial effect on blood pressure (Chen et al. 2006) or growth during or after treatment (Peterson et al. 2004). In fact, from baseline to 9 months, children receiving succimer were on the average 0.27 cm shorter than children receiving placebo, and 0.43 cm shorter during 34 months of follow-up. The conclusion of this series of studies reached by the investigators was that chelation therapy is not indicated in children with moderate PbB (≤40 μg/dL). Additional information regarding the safety and efficacy of succimer in children can be found in O'Connor and Rich (1999) and Chisolm (2000).

In a study similar to those described above, Kordas et al. (2005) tested the hypothesis that iron and zinc supplementation could improve behavior ratings in a population of first-grade children who attended a school near a metal foundry in Torreón, Mexico. The mean PbB for the whole sample was 11.5 μg/dL (SD, ±6.1 μg/dL). The overall prevalency of iron and zinc deficiency was 21.7 and 28.9%, respectively. During the trial, which lasted 6 months, parents and teachers provided ratings of child behavior using the Conners Rating Scales. Neither iron nor zinc (combined or separately) induced a marked reduction in PbB. Although all parent ratings and some teacher ratings improved with time, the change was unrelated

to treatment and the clinical significance was unclear. The only beneficial change was that children receiving any zinc had a higher likelihood of no longer receiving clinically-significant teacher ratings of oppositional behaviors.

A series of studies in monkeys provide relevant information regarding lead exposure and succimer. In adult Rhesus monkeys treated chronically with lead to maintain a target PbB of 35–40 μg/dL, treatment with succimer was ineffective in reducing brain lead levels (Cremin et al. 1999). However, cessation of exposure reduced brain lead levels by 34% both in succimer- and placebo-treated monkeys. In addition, the concentration of lead in the prefrontal cortex prior to treatment with succimer was significantly correlated with the integrated PbB (AUC) over the period of exposure to lead, but not with the single pretreatment PbB sample collected concurrently with the brain biopsy. These results indicated that succimer treatment did not reduce brain lead levels beyond the cessation of lead exposure alone. A subsequent study in this series showed that treatment with succimer did not reduce skeletal levels of lead and that the efficacy of succimer in reducing PbB did not persist beyond the completion of treatment due to posttreatment rebounds in PbB from endogenous sources (Smith et al. 2000).

3.10 ADEQUACY OF THE DATABASE

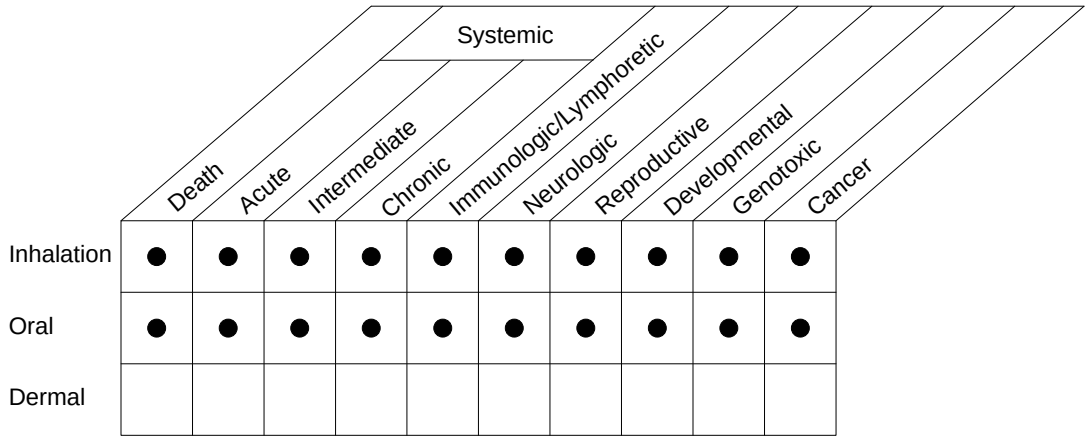
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of lead is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of lead.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

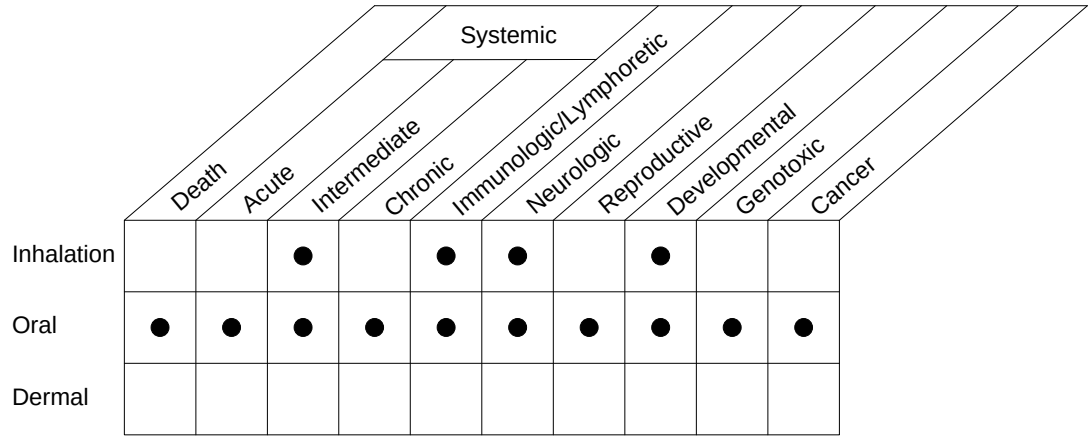
3.10.1 Existing Information on Health Effects of Lead

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to lead are summarized in Figure 3-17. The purpose of this figure is to illustrate the existing information

Figure 3-17. Existing Information on Health Effects of Lead



Human



Animal

● Existing Studies

concerning the health effects of lead. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

There is a wealth of information regarding the health effects of lead in humans and in animals. In fact, lead may be a chemical for which there is as much information in humans as there is in animals. Human data consist of studies of children and adults, occupational exposures, and exposures of the general population. A number of studies of children are studies of cohorts that have been followed for years, and these have provided the most valuable information. Children and developing organisms, in general, are more vulnerable to the toxic effects of lead than adults, and therefore, much of the lead research in the past decades has focused on these populations. The most sensitive end points for lead toxicity are the developing nervous system, and the cardiovascular, renal, and hematological systems, but lead can affect any system or organ in the body. The most significant routes of exposure to lead for humans are the inhalation and oral routes; the latter is the main route of exposure for young children mainly due to their hand-to-mouth activities. The toxicity of lead is not route-specific. Studies in animals support the findings in humans and have been of great utility in elucidating the underlying mechanisms of lead toxicity.

3.10.2 Identification of Data Needs

Acute-Duration Exposure. There are relatively few data available for acute exposures in humans and most are derived from cases of accidental or intentional ingestion of lead-containing dirt or lead-based paint in adults and children. Exposure to high amounts of lead can induce encephalopathy, a general term that describes various diseases that affect brain function. Symptoms develop following prolonged exposure and include dullness, irritability, poor attention span, epigastric pain, constipation, vomiting, convulsions, coma, and death (Chisolm 1962, 1965; Chisolm and Harrison 1956; Kehoe 1961; Kumar et al. 1987). The utility of further acute-duration exposure studies in animals for the sole purpose of obtaining dose-response relationships is questionable. However, further short-term studies or studies

in vitro designed to elucidate mechanisms of action for the various toxicities discussed below might be useful.

Intermediate-Duration Exposure. Intermediate and chronic exposures in humans should be considered together because the duration of exposure is not usually known. Specific studies that have evaluated a variety of end points are presented below under *Chronic-Duration Exposure and Cancer.* As with acute-duration exposure, additional standard 90-day toxicity studies in animals are unlikely to produce new key information about the toxicity of lead, but studies could be designed to elucidate mechanisms of action involved in the specific toxicities described below. For example, exposures during different developmental periods can help identify critical periods of vulnerability for immunocompetence, development of sex organs, or neurobehavioral parameters.

Chronic-Duration Exposure and Cancer. The effects of chronic-duration exposure to lead in humans and in animals have been relatively well-studied. In humans, exposure to lead has been associated with (only representative citations are included) cardiovascular effects (Nawrot et al. 2002; Schwartz 1995; Staessen et al. 1994), hematological effects (Chisolm et al. 1985; Hernberg and Nikkanen 1970; Roels and Lauwerys 1987; Roels et al. 1976), musculoskeletal effects (Holness and Nethercott 1988; Marino et al. 1989; Pagliuca et al. 1990), effects on teeth in children (Gemmel et al. 2002; Moss et al. 1999), renal effects (Kim et al. 1996a; Muntner et al. 2003), alterations in serum hormone levels (Gustafson et al. 1989; López et al. 2000; Singh et al. 2000a), cataracts (Schaumberg et al. 2004), alterations in electroretinograms (Cavalleri et al. 1982; Otto and Fox 1993; Rothenberg et al. 2002a), altered vitamin D metabolism (Rosen et al. 1980), alterations in immunological parameters (Fischbein et al. 1993; Karmaus et al. 2005; Lutz et al. 1999; Pinkerton et al. 1998; Sata et al. 1998; Sun et al. 2003; Ündeger et al. 1996), neurobehavioral effects in adults (Awad El Karim et al. 1986; Baker et al. 1979, 1983; Haenninen et al. 1979; Holness and Nethercott 1988; Lucchini et al. 2000; Matte et al. 1989; Pagliuca et al. 1990; Pollock and Ibels 1986; Schwartz et al. 2005; Stollery 1996; Stollery et al. 1991) and children (Bellinger et al. 1992; Canfield et al. 2003; Chiodo et al. 2004; Kordas et al. 2006; Lanphear et al. 2000a; Ris et al. 2004; Schnaas et al. 2000; Téllez-Rojo et al. 2006; Tong et al. 1998; Wasserman et al. 2003), reproductive effects in females (Borja-Aburto et al. 1999; Nordstrom et al. 1979; Torres-Sánchez et al. 1999) and males (Gennart et al. 1992b; Hernández-Ochoa et al. 2005; Lancranjan et al. 1975; Sállmen et al. 2000a), altered children's growth (Dietrich et al. 1987a; Hernández-Avila et al. 2002; Schwartz et al. 1986), delayed sexual maturation in girls (Selevan et al. 2003; Wu et al. 2003a), decreased erythropoietin in children (Graziano et al. 2004), genotoxic effects in workers (Forni et al. 1976; Fracasso et al. 2002; Nordenson et al. 1978; Vaglenov et al. 2001; Wu et al. 2002), and possibly increased risk of

lung cancer and stomach cancer in lead workers (Steenland and Boffetta 2000). It is unlikely that additional standard chronic-duration exposure studies in animals would provide new key information on the toxicity of lead, but special studies that examine biochemical and morphological effects of lead may provide new information on mechanisms of action of lead, particularly for the effects of greatest concern such as neurobehavioral alterations in children. However, as indicated below under *Epidemiological Studies*, the children and adolescents from the prospective studies should continue to undergo periodic comprehensive evaluations.

There are several studies of cancer on lead-exposed workers (Anttila et al. 1995; Cocco et al. 1997, 1998a, 1998b; Cooper et al. 1985; Fanning 1988; Gerhardsson et al. 1986b; Lundstrom et al. 1997; Malcolm and Barnett 1982; Wong and Harris 2000), which provided inconclusive evidence of carcinogenicity. A meta-analysis of eight major occupational studies on cancer mortality or incidence in workers with high lead exposure concluded that there is some limited evidence of increased risk of lung cancer and stomach cancer, although there might have been confounding with arsenic exposure in the study with highest relative risk of lung cancer (Steenland and Boffetta 2000). The results also showed weak evidence for an association with kidney cancer and gliomas. Follow-up of the cohorts from the prospective lead studies may provide information on possible shifts in age-related cancer incidence and on associations between perinatal exposure to lead and increased cancer risk.

Exposure of rodents to lead has produced mainly renal tumors (Azar et al. 1973; Koller et al. 1985; Van Esch and Kroes 1969). In a study in mice exposed to lead during pregnancy, the offspring developed renal proliferative lesions and renal tumors; no renal tumors occurred in controls (Waalkes et al. 1995). Replication of these findings would be useful. In addition, studies could be conducted in which animals are exposed at different times during pregnancy to determine the existence of potential windows of vulnerability. Silbergeld et al. (2000) suggest that the hypothesis that lead-induced cancer is secondary to cytotoxicity and target organ damage needs further testing. Silbergeld et al. (2000) also identified the need for studies examining the potential role of lead-zinc interactions in transcription regulation and DNA protection using reporter gene systems and combined exposures to lead and other mutagens. Other types of studies suggested include evaluation of the effects of lead on the expression of specific genes, such as oncogenes and suppressor genes, and evaluation of the potential role of lead-induced inhibition of DNA repair on systems where the fidelity of DNA replication can be directly studied.

Genotoxicity. Lead is a clastogenic agent, as shown by the induction of chromosomal aberrations, micronuclei, and sister chromatid exchanges in peripheral blood cells from lead workers (i.e., Duydu et al.

2001; Forni et al. 1976; Nordenson et al. 1978; Vaglenov et al. 1998, 2001). *In vitro* mutagenicity studies in microorganisms have yielded mostly negative results for lead, and additional studies of this type are unlikely to provide new key information. The lines of research suggested previously with regard to cancer also apply for genotoxicity. In addition, studies of chromosomal changes in germ cells involved in gametogenesis would provide valuable information on potential transgenerational effects of lead.

Reproductive Toxicity. Some studies of humans occupationally or environmentally exposed to lead have reported associations between PbB and abortion and pre-term delivery in women (Borja-Aburto et al. 1999; Nordstrom et al. 1979) and alterations in sperm and decreased fertility in men (Gennart et al. 1992b; Sállmen et al. 2000a; Shiau et al. 2004). For the effects in males, the threshold PbB appears to be in the range of 30–40 μg/dL. Additional research might be warranted to study the effects of lead on the gonado-hypothalamic-pituitary axis. An earlier study by Cullen et al. (1984) found increased serum FSH and LH and borderline low serum testosterone levels in one of seven men with symptomatic occupational lead poisoning and a mean PbB of 87.4 μg/dL. Although serum testosterone concentration was normal in most of these patients, five had defects in spermatogenesis. Studies in monkeys using protocols designed to evaluate age of exposure on lead-induced effects have reported structural alterations in the testis at PbBs relevant to the human population (Foster et al. 1996, 1998). Studies in rats exposed to lead concentrations that produced relatively high PbB have suggested that continuous lead exposure delays sexual maturation by suppressing normal sex steroid surges at birth and during puberty (Ronis et al. 1998b, 1998c). Replication of these studies in primates would be useful. Also, further research on the interaction of lead and protamines could provide valuable information on lead-induced effects in sperm. Protamines specifically are bound to sperm DNA and their interaction with lead has been suggested to possibly decrease the protection of DNA to mutagens (Quintanilla-Vega et al. 2000).

Developmental Toxicity. In addition to inducing neurobehavioral alterations in developing organisms (see below under Neurotoxicity), exposure to lead has been associated in some studies with reduced birth weight and gestational age (Dietrich et al. 1987a; Jelliffe-Pawlowski et al. 2006), reduced stature in children (Hernández-Avila et al. 2002; Sanín et al. 2001; Schwartz et al. 1986), and delayed sexual maturation in girls (Selevan et al. 2003; Wu et al. 2003a). These findings are supported by results from studies in animals (Dearth et al. 2002; Grant et al. 1980; Ronis et al. 1996, 1998a, 1998b, 1998c, 2001). It would be useful to collect data on growth of children from the ongoing lead prospective studies, although some information is available from the Cincinnati Prospective Study (Shukla et al. 1989, 1991), the Cleveland Prospective Study (Greene and Ernhart 1991), and a study of children from Boston (Kim et al. 1995). Because of the enormous influence of nutrition on growth and on lead toxicity, it would be

advantageous to conduct studies of populations of children as homogeneous as possible with respect to nutrition, even if the cohort size is less than optimal. A study in rats reported that lead reduced somatic longitudinal bone growth and bone strength during the pubertal period by a mechanism that appeared not to involve disruption of the growth hormone axis (Ronis et al. 2001). Further studies in animals as well as in bone cells *in vitro* should help elucidate the mechanism(s) of lead on growth.

Studies have shown that exposure of rats and mice to lead during various developmental periods alters sexual maturation of both male and female animals (Dearth et al. 2002; Iavicoli et al. 2004; Ronis et al. 1996, 1998a, 1998b, 1998c). Therefore, it would be desirable to evaluate adolescents of both sexes who are participating in the ongoing prospective lead studies to determine possible delays in sexual maturation, and if found, determine which lead biomarker best predicts the outcome. Follow-up of the children studied by Selevan et al. (2003) and Wu et al. (2003a) or the cohorts studied longitudinally could provide information on whether lead exposure during infancy has long-term effects on parameters such as fertility in males and females or on female's ability to maintain pregnancy. Dearth et al. (2004) recently reported that Fisher 344 rats are more sensitive than Sprague-Dawley rats regarding puberty-related effects. Researchers should be aware of this strain difference when comparing results between these two strains of rats. As with other lead-induced toxicities, the role of some polymorphisms (i.e., ALAD genotype) on growth and sexual maturation could be evaluated.

Immunotoxicity. Altered immune parameters have been described in lead workers. Reported effects have included changes in some T-cell subpopulations (Fischbein et al. 1993; Pinkerton et al. 1998; Sata et al. 1998; Ündeger et al. 1996), altered response to T-cell mitogens (Mishra et al. 2003), and reduced chemotaxis of polymorphonuclear leukocytes (Valentino et al. 1991). Three studies of children reported significant associations between PbB and increases in serum IgE levels (Karmaus et al. 2005; Lutz et al. 1999; Sun et al. 2003). IgE is the primary mediator for type-I hypersensitivity and is involved in various allergic diseases such as asthma; therefore, the suggestion has been raised that *in utero* exposure to lead may be a risk factor for childhood asthma (Dietert et al. 2002). Perinatal exposure of rodents to lead also has induced increased IgE levels in the offspring (Miller et al. 1998; Snyder et al. 2000). Additional studies in which animals are exposed at different developmental periods are necessary to identify vulnerable periods during development and to determine potential long-term consequences of exposures during discrete periods of development (Dietert et al. 2002, 2004). Also, studies that compare the effects of lead on immunological end points in different species, different strains, and animals of both sexes would provide valuable information, as there is some evidence that the immune response may depend on the species, strain, and/or gender (Bunn et al. 2001a, 2001b, 2001c). In addition, further information on

how lead-induced changes in immune balance (Heo et al. 1998; McCabe et al. 1999) affect the immune response profile and the host's defense capabilities would be valuable. This is important because there is evidence that suggests that lead or other chemicals during development may cause inappropriate Th1 development and a potentially serious imbalance toward Th2-associated capacity resulting in elevated IgE production and increased risk for atopy and asthma (Peden 2000).

Neurotoxicity. The nervous system is a sensitive target for lead toxicity in humans (for representative references, see Chronic-Duration Exposure and Cancer, above) and in animals. Of special concern are the results of recent studies that have reported neurobehavioral deficits in children associated with PbBs <10 μg/dL and an apparent lack of threshold down to even the lowest PbBs recorded in these studies (Bellinger and Needleman 2003; Canfield et al. 2003; Chiodo et al. 2004; Kordas et al. 2006; Lanphear et al. 2000a, 2005; Téllez-Rojo et al. 2006). Some of these studies found that the slope of the dose-response is steeper at lower PbBs than at higher PbBs; that is, the effects of lead on cognitive function is greater in children with lower PbB than in children with higher PbB. However, a mechanism that could produce this result has not yet been identified, and this represents a data need. The neurotoxicity of lead is the result of multiple modes of action and research needs can be identified at almost any level of action, from studies of basic biochemical and physiological mechanisms (i.e., transport of lead across biological barriers in general and nerve membranes in particular) to studies of populations. There are several ongoing prospective studies of lead in children (i.e., Bellinger et al. 1992; Ris et al. 2004; Schnaas et al. 2000; Tong et al. 1998; Wasserman et al. 2003) and it is assumed that follow-up of some of these cohorts will continue. With regard to these and other studies in humans, researchers have identified some specific needs. For example, there is a need to develop new and more sensitive tests of specific neuropsychological functions (Bellinger 1995). Also, not enough research has been conducted in adults using measures of cumulative exposure to lead. Another area where additional research would be valuable is to determine the extent to which lead contributes as a risk factor to disease and dysfunction. There is a limited number of studies that have linked lead to amyotrophic lateral sclerosis (Kamel et al. 2002), essential tremor (Louis et al. 2003), schizophrenia (Opler et al. 2004), and Parkinson's disease (Gorell et al. 1997, 1999). Also, the possibility that lead contributes to attention deficit disorder has never been adequately addressed, despite the increased levels of diagnosis of this disorder in children over the past 20 years. Studies in animal models of these diseases can provide valuable information to answer such questions. With regard to the interpretation of studies with seemingly differing results, it would be important to identify the basis of individual differences in sensitivity to neurotoxicants (Bellinger 2000). In addition, epidemiological studies should be designed in a manner that permits more rigorous assessments of effect modification. In order to minimize confounding and effect modification,

researchers should make greater use of more focused sampling frames that ensure adequate representation of specific subgroups of interest (Bellinger 2000). Additional information is needed to characterize the nature of the relationships between lead and nutritional factors, as well as determining what dietary modifications might be particularly beneficial in alleviating lead uptake and or effects. Banks et al. (1997) suggest that further studies using electrophysiological methods in infancy and early childhood can add to knowledge about the effects of lead on specific sensory systems such as vision and audition, as well as on higher, more cortically-controlled cognitive processes.

With regard to studies in animals, further studies of the specific behavioral nature of lead-induced learning impairments and of the behavioral mechanisms contributing to such effects would be valuable (Cory-Slechta 1995). Such studies in conjunction with microdialysis and microinjection techniques could provide critical information related to the roles of various neurotransmitter systems and different brain regions in behavioral manifestations (Cory-Slechta 1995). Such research may also shed light on possible interactions between neurotransmitter systems that might contribute to lead effects and allow researchers to examine the efficacy of potential behavioral or chemical therapeutic approaches for reversing behavioral impairments (Cory-Slechta 2003). Additional studies of the roles of developmental periods of lead exposure and the levels of lead exposure should be conducted to resolve the possibility of differential mechanisms at different stages of the life cycle (Cory-Slechta 1997). Further development of molecular techniques to study the action of lead on the function of specific components of proteins associated with synaptic transmission also would be helpful (Atchison 2004; Suszkiw 2004). Additional research on lead-gene interactions is critical to further the understanding of these issues.

Epidemiological and Human Dosimetry Studies. There are dozens of epidemiological studies that investigated the health effects of lead in both adults and children. The studies listed above under *Chronic-Duration Exposure and Cancer* and others cited throughout Section 3.2, *Discussion of Health Effects*, provide information on lead-induced effects on multiple systems and organs, but the most sensitive targets for lead toxicity are the nervous system, heme synthesis, and kidney function. Children are more sensitive than adults to lead toxicity and a great number of studies conducted in the last decades have focused on the evaluation of neurobehavioral effects of lead in children that have been associated with relative low blood lead levels (i.e., <10 μg/dL) (Bellinger and Needleman 2003; Canfield et al. 2003; Chiodo et al. 2004; Kordas et al. 2006; Lanphear et al. 2000a, 2005; Téllez-Rojo et al. 2006). Although the preponderance of the evidence suggests that lead exposure in children is associated with small decrements in intelligence, there are studies that have not found such an association. In this regard, a major information need regarding epidemiological studies of lead is identifying the basis of individual

differences in sensitivity to lead toxicity. Another important issue that future studies need to consider is the presence of modifying factors. Bellinger (2000) states that effect modification is a property of a true association and should be distinguished from confounding. Effect modification can explain inconsistencies in findings, and if it exists, failure to address it will lead to an error in inference. Maternal stress and environmental enrichment have recently been identified as modifying factors of lead-induced behavioral effects in studies in animals (Cory-Slechta 2006; Cory-Slechta et al. 2004; Guilarte et al. 2003; Schneider et al. 2001) and continued research in these areas may provide valuable information for understanding effects in humans. Effects of lead through alterations in corticoids may have enormous implications since changes in the hypothalamic-pituitary-adrenal axis could be a mechanism for multiple effects of lead, including those on the immune system as well as on the brain.

Most of the research gaps identified in the preceding sections could also be listed in this section. For example, it is expected that children from some of the prospective studies of lead will continue to be evaluated periodically with appropriate neurobehavioral tests. As children in these cohorts (or in newly identified cohorts) go through adolescence and eventually into adulthood, it would be desirable also to evaluate other end points for potential late-appearing effects. Such evaluations may include, but not be limited to, immunocompetence, sexual development, fertility, kidney and cardiovascular functions, or cancer incidence. The usefulness of studies involving adult populations exposed to lead as adults (i.e., lead workers) in understanding neurotoxicity of lead in children is questionable. This is because the impact of a brain lesion experienced as an adult can be dramatically different than that of a lesion incurred during periods in which the brain is still undergoing substantial changes (Bellinger 2004). However, studies regarding other end points of interest would be useful. For example, associations between lead exposure and decreases in glomerular filtration rate have been observed, but not fully characterized (Kim et al. 1996a; Muntner et al. 2003; Payton et al. 1994; Staessen et al. 1990, 1992; Weaver et al. 2003a). Major uncertainties in the dose-response relationship include: (1) the appropriate exposure biomarker (i.e., PbB or bone lead concentration); and (2) the strength of the interactions between glomerular filtration rate, blood pressure, and certain diseases such as diabetes. Regarding cardiovascular effects, meta-analyses of the association between blood pressure and PbB have found an average effect size of approximately 1 mmHg increase in blood pressure per doubling of PbB (Nawrot et al. 2002; Schwartz 1995; Staessen et al. 1994); however, more recent studies have observed a larger effect in older populations and associations between blood pressure and bone lead concentrations that is stronger than the association with PbB (Cheng et al. 2001; Korrick et al. 1999; Nash et al. 2003). Major uncertainties in the dose-response relationship for blood pressure effects include: (1) the appropriate exposure

biomarker (i.e., PbB or bone lead concentration); and (2) the strength of the association in older males and post-menopausal women.

Biomarkers of Exposure and Effect.

Exposure. Inorganic lead can be measured in blood, serum, urine, sweat, cerebrospinal fluid, tissues, bone, teeth, and hair and nails (see Section 3.6.1). While measurements of lead in any of the above tissues can be useful as an indicator of excessive exposure to lead, quantitative associations with exposure levels and health effects have been most rigorously explored for blood lead concentration (PbB). Currently, PbB is the most widely used biomarker of lead exposure in humans. However, because of the relatively rapid elimination of lead from blood (elimination half-time <30 days), PbB reflects exposures that occurred within a few months previous to the measurement. The need exists for the development of a biomarker that would accurately reflect the total body burden from both acute and chronic durations at both low- and high-level exposures. Bone lead concentration may serve as a more reliable biomarker of long-term exposure because lead is eliminated slowly from bone (elimination half-time of decades). It may also provide a better reflection of long-term time-integrated plasma lead concentration (Cake et al. 1996; Chuang et al. 2001; Tellez-Rojo et al. 2004). This may explain why bone lead concentration has been observed to be a better predictor of cardiovascular/renal effects in older populations than is PbB (Cheng et al. 1998, 2001; Korrick et al. 1999; Tsaih et al. 2004). Further characterization of bone lead concentration as a biomarker of exposure for various effect end points in adults may improve lead dose-response assessment and characterization of health risks from exposure to lead in humans.

The development of inductively-coupled plasma mass spectrometry (ICP-MS) (see Chapter 7) has provided adequate analytical sensitivity to measure plasma lead concentrations with greater confidence than in the past (Schutz et al. 1996). Recent studies using this technique have shown that plasma lead concentrations in adults correlate more strongly with bone lead levels than do PbB (Cake et al. 1996; Chuang et al. 2001; Hernandez-Avila et al. 1998; Tellez-Rojo et al. 2004). Since most of the body lead burden resides in bone, measurements of plasma lead concentration may turn out to be a better predictor of lead body burden than measurements of PbB. This observation has not been explored in children, and few studies have attempted to explore relationships between plasma lead concentration and health outcomes in children.

Effect. No clinical disease state is pathognomonic for lead exposure. The neurotoxic and hematopoietic effects of lead are well recognized. The primary biomarkers of effect for lead are EP, ALAD, basophilic

stippling and premature erythrocyte hemolysis, and presence of intranuclear lead inclusion bodies in the kidneys. Of these, activity of ALAD is a sensitive indicator of lead exposure (see Section 3.6.1). Biomarkers for the nephrotoxic effects of lead in humans include elevation of serum creatinine, urinary enzymes (e.g., NAG), or protein (albumin, β2μ-globulin, α1μ-globulin, retinol binding protein; see Table 3-3 and Figure 3-3). However, none of these markers are specific for lead-induced nephrotoxicity. More specific biomarkers of effects for lead may improve the assessment of health risks derived from exposure to lead.

Absorption, Distribution, Metabolism, and Excretion. Inhalation of airborne lead-bearing surface dusts can be an important exposure pathway for human. However, available studies of the deposition and absorption of inhaled lead in humans are of exposures of adults to submicron lead-bearing particles (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). No studies are available on deposition and absorption of larger particles that might be encountered from inhalation of airborne surface dusts. No data are available on the deposition and absorption of inhaled lead in children. However, models of age-related changes in airway geometry and physiology predict that particle deposition in the various regions of the respiratory tract in children may be higher or lower than in adults depending on particle size; for submicron particles, fractional deposition in 2-year-old children has been estimated to be 1.5 times greater than in adults (Xu and Yu 1986).

Ingestion of lead can occur as a result of consuming lead-containing food, drinking water, and beverages, from ingesting lead-containing dusts, and from swallowing lead deposited in the upper respiratory tract after inhalation exposure. Children can ingest lead-containing dusts, lead-based paint, and other nonfood materials through their normal mouthing activity and pica (abnormal ingestion of nonfood items). Fractional absorption of ingested lead appears to vary in magnitude with age, being as much as 5–10 times greater in infants and young children than in adults (Alexander et al. 1974; Chamberlain et al. 1978; James et al. 1985; Ziegler et al. 1978). However, there are no data on the absorption of lead in older children and adolescents; thus, it is uncertain whether lead absorption in this population is more similar to that of adults or to that of infants and young children. While no absorption studies have been conducted on subjects in this age group, the kinetics of the change in stable isotope signatures of blood lead in mothers and their children, as both come into equilibrium with a novel environmental lead isotope profile, suggest that children ages 6–11 years and their mothers may absorb a similar percentage of ingested lead (Gulson et al. 1997b).

Ingested soil lead is less readily absorbed than ingested water-soluble lead acetate (Casteel et al. 1997; EPA 2004b; Freeman et al. 1996). This difference may reflect a lower solubility of soil lead because of its chemical or physical form; for example, there is an inverse relationship between lead particle size and gastrointestinal absorption (Barltrop and Meek 1979). There is one published study that assessed the bioavailability of lead in adults who ingested hazardous waste site soil (Maddaloni et al. 1998). Additional studies of this type would provide an improved basis for estimating lead uptake in people who are exposed to lead in soil and soil-derived dusts. A variety of other factors are known to influence the absorption of ingested lead, including the chemical form of the ingested lead, the presence of food in the gastrointestinal tract, diet, and nutritional status with respect to calcium, vitamin D, and iron (Mushak 1991); however, for the most part, the mechanisms by which these interactions occur are not fully understood. This reflects, in part, a lack of understanding of the mechanisms by which lead is absorbed in the gastrointestinal tract and studies aimed at elucidating such mechanisms are needed. A better understanding of absorption mechanisms is critical to developing physiologically based models that accurately simulate relationships between lead exposure and lead in blood and other target and biomarker tissues.

Few studies are available on the absorption after dermal exposure of inorganic lead compounds in humans. In contrast, alkyl lead compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931; Laug and Kunze 1948). Recent studies provide evidence for rapid dermal absorption of inorganic lead in adults; however, these studies have not quantified the fraction of applied dose that was absorbed (Stauber et al. 1994; Sun et al. 2002). The quantitative significance of the dermal absorption pathway as a contributor to lead body burden remains an uncertainty. In children who may experience extensive dermal contact with lead in soil, sand, or surface water and suspended sediment (e.g., beach or shoreline exposure scenario), even a low percent absorption across the skin may represent a significant internal dose. Therefore, additional studies designed to quantify dermal absorption of inorganic lead compounds from both aqueous media and from soil, in particular, studies that enable measurements to be extrapolated to children, are important for estimating internal doses that children might receive in relatively common exposure scenarios.

Several models of the toxicokinetics of lead in humans have been developed (Bert et al. 1989; EPA 1994a, 1994c; Leggett 1993; Marcus 1986a, 1986b, 1986c; O'Flaherty 1993; Rabinowitz et al. 1976). Major uncertainties in these models include: (1) absence of calibration data for the kinetics of lead in blood and bone in children in association with exposures that have been quantified with high certainty; (2) absence of calibration data on bone lead concentrations in adolescents and adults in association with

exposures that have been quantified with high certainty; (3) absence of data on the absolute bioavailability of ingested lead in older children and adolescents; (4) incomplete understanding of lead kinetics during periods of changing bone metabolism, including adolescence, pregnancy, and menopause; and (5) incomplete understanding of inter- and intra-individual variability in model parameters values in humans. In addition, there is a need for models that predict concentrations of lead in tissues other than blood.

Comparative Toxicokinetics. The immature swine has been used extensively as a model for assessing relative bioavailability of lead in ingested soil in humans (Casteel et al. 1997; EPA 2004c) and for evaluating *in vitro* approaches to assessing bioaccessibility of lead (EPA 2004c; Ruby et al. 1999). However, no studies are available in which the absolute or relative bioavailability of ingested lead has been quantitatively compared in swine and humans. Such studies would be useful for validating both the *in vivo* swine model and the *in vitro* bioaccessibility model.

Methods for Reducing Toxic Effects. The extent of lead absorption in the gastrointestinal tract depends on numerous factors including nutritional factors and the presence or absence of other metals that interact with lead (Kwong et al. 2004; Mahaffey and Annest 1986; Mahaffey et al. 1986; Ziegler et al. 1978). Thus, further studies that could identify additional factors that affect lead absorption would be valuable. These factors may be nutritional factors or specific pathologic conditions. Chelators have been used in the management of lead poisoning, particularly in children (Berlin et al. 1995; Homan et al. 1998). However, further research should address questions such as what blood lead levels warrant chelation therapy and whether chelation therapy may redistribute lead from bone to other tissues. Moreover, the effectiveness of chelation therapy in reducing neuropsychologic impairment in children with clinically inapparent lead poisoning is questionable, as shown in a series of recent studies (Dietrich et al. 2004; Liu et al. 2002; Rogan et al. 2001). Clinical studies of oral chelation should monitor not only PbB, but also the possibility of ongoing lead exposure, the child's age, sources of lead exposure, length of exposure, and general health status. Also, the potential benefits of chelation in reducing chronic impairments in adults are completely unknown. Lead inhibits heme synthesis by inhibiting the enzyme ALAD, and this results in a diffuse effect that involves many systems and organs. Even if ALAD inhibition could be prevented, because of the ability of lead to inhibit and/or substitute for calcium in many cellular processes (such as neurotransmitter exocytosis), it is unlikely that one could prevent all of the physiological alterations that have been attributed to exposure to lead.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Many of the known health effects that have been associated with low-level lead exposure have been detected in children who experienced lead exposures both *in utero* and postnatally. Considerable uncertainty remains about the relative contribution of *in utero* and postnatal exposures to the development of health outcomes that are expressed later in childhood. This information is important for distinguishing those health outcomes that might be mitigated during the postnatal period from those that must be mitigated by limiting *in utero* exposure. Considerable uncertainty also remains about the long-term consequences of the lead-related neurobehavioral deficits detected in infants and children with respect to manifestation of chronic neurobehavioral problems in adolescence and adulthood. An additional important issue that needs to be studied is the potential prevalence of elevated bone lead stores in women of reproductive age and the associated risk that this poses to fetal development by mobilization of maternal bone stores during pregnancy.

The interaction between exposure intensity and duration of exposure in the development of neuro-behavioral deficits is not understood, in part because of a lack of biomarkers of long-term lead exposure. The strongest evidence for health effects of low-level lead exposures on neurodevelopmental deficits is based on relationships between measured health outcomes and PbB. Although these studies suggest that a significant amount of the variability in the health outcomes (e.g., neurobehavioral deficits) can be attributed to variability in PbB, a substantial amount of variability in the outcomes usually cannot be assigned to PbB, even after many known potential confounders have been considered (i.e., Needleman and Gatsonis 1990; Pocock et al. 1994; Schwartz 1994; Winneke et al. 1996).

Efforts to explore alternative biomarkers of exposure that provide a better reflection of long-term cumulative exposure may be of value for exploring the above issues. Two potential biomarkers of long-term exposure are bone lead measurements and plasma lead measurements (Cake et al. 1996; Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Recent advances in XRF techniques have made it possible to estimate lead levels in bone. Such measurements hold promise as biomarkers of long-term cumulative exposure during childhood. However, standard techniques for measuring bone lead have not yet been developed. Moreover, there continues to be uncertainty about how to interpret bone lead measurements in terms of lead exposure, their relationship to PbB concentrations, and their relationships to the various health effects that have been associated with lead

exposure in children. Thus, while dose-response relationships based on PbB are becoming understood, much less is known about bone lead-response relationships. This information is important for gaining a better understanding of the relationship between cumulative exposures and toxicity. The development of ICP-MS (see Chapter 7) has provided adequate analytical sensitivity to measure plasma lead concentrations with greater confidence than in the past. Studies using this technique have shown that plasma lead concentrations in adults correlate more strongly with bone lead levels than does PbB (Cake et al. 1996; Hernandez-Avila et al. 1998). Since most of the body lead burden resides in bone, measurements of plasma lead concentration may turn out to be a better predictor of lead body burden than are measurements of PbB. This observation has not been explored in children, and few studies have attempted to explore relationships between plasma lead concentration and health outcomes in children.

Studies in animals have provided abundant support for the plausibility of the neurodevelopmental effects of lead that have been associated with lead exposure in children, and researchers have begun to identify potential mechanisms (i.e., Cory-Slechta 1995, 2003; Rice 1993, 1996a). However, mechanistic connections between behavioral deficits, or changes observed in animals, and those that have been associated with lead exposure in children have not been completely elucidated. Understanding of such connections would be valuable for developing better and more relevant animal models of lead toxicity.

Studies of the effects of lead on bone metabolism indicate that, in addition to being a reservoir for the lead body burden, bone may also be a toxicological target (Hamilton and O'Flaherty 1994, 1995). Studies in rats have shown effects of lead on bone mineralization and bone growth. The effects observed in rats may be relevant to our understanding of the mechanisms for the growth deficits that have been associated with low-level *in utero* and childhood lead exposures (Ballew et al. 1999; Frisancho and Ryan 1991; Shukla et al. 1989, 1991). Additional studies of the effects of lead on bone metabolism in humans and in animal models would improve our understanding of the toxicological significance of lead in bone.

Further research on the relationship between paternal lead exposure and fetal/infant development should be conducted. Additional information on relationships between nutritional deficits and vulnerability of the fetus and child to lead would be valuable.

Absorption of ingested lead is higher in infants and young children than in adults; however, available data on lead absorption during the ages between childhood and adulthood are very limited (Alexander et al. 1974; Ziegler et al. 1978). The higher absorption of lead in childhood contributes to the greater susceptibility of children to lead; therefore, it is important to know at what age the higher absorption

status of the child changes to the lower absorption status observed in adults. Limited data suggest that this conversion may occur early in adolescence. This information is particularly important for accurately simulating biokinetics of lead in older children and adolescents. Additional information on interactions between nutritional deficiencies and lead absorption and other aspects of lead biokinetics would be valuable.

Dermal absorption of inorganic lead compounds occurs, but the quantitative significance of the dermal absorption pathway as a contributor to lead body burden remains an uncertainty, although it is generally considered to be much lower than absorption by the inhalation or oral routes of exposure. In children who experience extensive dermal contact with lead in soil, sand, or surface water and suspended sediment (e.g., beach or shoreline exposure scenario), even a low percent absorption across the skin may represent a significant internal dose. Therefore, additional studies designed to quantify dermal absorption of inorganic lead compounds from both aqueous media and soil, in particular, studies that enable measurements to be extrapolated to children, are important for estimating internal doses that children might receive in relatively common exposure scenarios.

The kinetics of bone formation and remodeling are important factors in the overall biokinetics of lead. Most of the body burden of lead resides in bone; a portion of the maternal bone lead stores is transferred to the fetus during gestation and incorporated into fetal bone during the development of the fetal skeleton (Franklin et al. 1997; Gulson et al. 1997b, 1999b, 2003). Thus, changes in maternal bone metabolism (e.g., formation and remodeling) are likely to have a significant impact on *in utero* exposure of the fetus. Approximately 80% of lead in cord blood appears to derive from maternal bone stores (Gulson et al. 2003). Further information about the kinetics of the mobilization of maternal bone lead, or its incorporation into the fetal skeleton is critical for developing models that accurately simulate *in utero* exposures and maternal lead biokinetics during pregnancy and for understanding how changes in maternal bone metabolism might affect the susceptibility of the fetus to lead toxicity. Bone formation undergoes rapid changes during infancy, childhood, and adolescence. These changes may give rise to periods of greater or lower susceptibility to environmental lead; however, little is known about the potential consequences of these changes on the biokinetics of lead in children.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.10.3 Ongoing Studies

Ongoing studies pertaining to lead have been identified and are shown in Table 3-12.

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Audesirk GJ	University of Colorado at Denver/Health Science Center, Denver, Colorado	Differential lead toxicity in neurons and astrocytes	National Institute of Environmental Health Sciences
Benoff SH	Jewish Research Institute, Manhasset, New York	Developing an understanding of toxic metal action in the human testis	National Institute of Environmental Health Sciences
Berkowitz GS	Mount Sinai School of Medicine, New York, New York	Lead mobilization during pregnancy and lactation in urban women	National Center for Research Resources
Blum CB	Columbia University Health Sciences, New York, New York	Bioavailability of soil lead and arsenic in humans	National Institute of Environmental Health Sciences
Bornschein RL	University of Cincinnati, Cincinnati, Ohio	Treatment of lead exposed children follow up	National Institutes of Health
Brain JD	Harvard School of Public Health, Boston, Massachusetts	Transport of lead, manganese, iron, and cadmium from the environment to critical organs	National Institutes of Health
Burchiel SW	University of New Mexico School of Medicine, Albuquerque, New Mexico	Effects of immunotoxic xenobiotics on human peripheral blood	National Center for Research Resources
Burt BA	University of Michigan Dental School, Ann Arbor, Michigan	Lead exposure/dietary factors in children's oral health	National Institute of Dental and Craniofacial Research
Cecil KM	Children's Hospital Medical Center, Cincinnati, Ohio	MR assessment of brain function altered by lead exposure	National Institute of Environmental Health Sciences
Cohen MD	New York University School of Medicine, Tuxedo, New York	Investigation of how properties of metals may govern toxicities in the lungs	National Institute of General Medical Sciences
Cory-Slechta DA	University of Rochester, Rochester, New York	Behavioral toxicity of lead--a pharmacological analysis	National Institute of Environmental Health Sciences
Ehrich M, Meldrum JB, Parran D, Magnin-Bissel G, and Inzana KD	Virginia Polytechnic Institute, College of Veterinary Medicine, Blacksburg, Virginia	Insecticide exposure and the permeability of the blood-brain barrier to lead	Department of Agriculture
Ercal N	University of Missouri, Rolla, Missouri	Role of selenocystine in lead toxicity	National Institute of Environmental Health Sciences

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Evanylo GK, Daniels WL, and Zelazny LW	Virginia Polytechnic Institute, Crop and Soil Environmental Sciences, Blacksburg, Virginia	Chemistry and bioavailability of waste constituents in soils	Department of Agriculture
Fox DA	University of Houston, Houston, Texas	Low-level prenatal lead exposure and retinal toxicity	National Institute of Environmental Health Sciences
Gao F-B	J David Gladstone Institutes, San Francisco, California	Genetic analysis of heavy metals neurotoxicity	National Institute of Neurological Disorders and Stroke
Garshick E	Department of Veterans Affairs, Medical Center, Brockton, Massachusetts	Lead intoxication-prevalence and its relation to anemia in India	Department of Veterans Affairs
Gonick H	Department of Veterans Affairs, Medical Center, West Los Angeles, California	Influence of lead on blood vessel contraction	Department of Veterans Affairs
Godwin HA	Northwestern University, Evanston, Illinois	Mechanisms of lead toxicity	National Institute of General Medical Sciences
Gray LC	University of Texas, Health Science Center, Houston, Texas	Effects of lead on deficits in hearing rapid changes in sound	National Institute on Deafness and Other Communication Disorders
Graziano JH	Columbia University Health Sciences, New York, New York	Health effects and geochemistry of arsenic and lead	National Institute of Environmental Health Sciences
Guilarte TR	Johns Hopkins University, Baltimore, Maryland	NMDA receptor function in lead neurotoxicity	National Institute of Environmental Health Sciences
Harry GJ	Not specified	Environmental effects and development of neuron and glia	National Institute of Environmental Health Sciences
Hassett JJ	University of Illinois, Natural Resources and Environmental Sciences, Urbana, Illinois	Continued studies on bioavailability of lead in soil	Department of Agriculture
Henkens RW	Alderon Biosciences, Inc., Durham, North Carolina	One-step rapid screening for childhood lead poisoning	National Institute of Environmental Health Sciences
Hu H	Harvard University School of Public Health, Boston, Massachusetts	Dietary supplements and suppression of bone resorption and lead mobilization	National Institute of Environmental Health Sciences

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Hu H	Brigham and Women's Hospital, Boston, Massachusetts	Lead, blood pressure, neurologic and renal function in two study populations	National Center for Research Resources
Hu H	Brigham and Women's Hospital, Boston, Massachusetts	Lead-gene interactions and cognition	National Institute of Environmental Health Sciences
Hu H	Brigham and Women's Hospital, Boston, Massachusetts	Development of Parkinson's disease and the exposure to lead	National Institute of Environmental Health Sciences
Ike JO	Fisk University, Nashville, Tennessee	Lead toxicity and serotonergic system in developing rat brain	National Institute of General Medical Sciences
Kamel F	Not specified	Lead and other neurotoxins as risk factors for amyotrophic lateral sclerosis	National Institute of Environmental Health Sciences
Knight JQ	Safer Pest Control Project, Chicago, Illinois	Asthma and lead prevention in Chicago public housing	National Institute of Environmental Health Sciences
Korrick SA	Harvard University School of Public Health, Boston, Massachusetts	*In utero* PCB, pesticide and metal exposure and childhood cognition	National Institute of Environmental Health Sciences
Korrick SA	Brigham and Women's Hospital, Boston, Massachusetts	Lead exposure, genetics and osteoporosis epidemiology	National Center for Research Resources
Lanphear BP	Children's Hospital Medical Center, Cincinnati, Ohio	Neurobehavioral effects of prevalent toxicants in children	National Institute of Environmental Health Sciences
Lawrence DA	Wadsworth Center, Rensselaer, New York	Immunotoxic effects of lead on cytokine expression	National Institute of Environmental Health Sciences
Lubin BH	University of California San Francisco, California	Erythrocyte isozyme biomarkers of low lead overburden	National Center for Research Resources
Lurie D	University of Montana, Center of Environmental Health Sciences, Missoula, Montana	Lead on development of auditory temporal process	National Center for Research Resources
Lutz PM	University of Missouri Rolla, Rolla, Michigan	Immunity in children with exposure to environmental lead	National Institute of Environmental Health Sciences
Mori S	Johns Hopkins University, Baltimore, Maryland	MR-based study of hypomyelination by lead poisoning	National Institute of Environmental Health Sciences

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Neary JT	Department of Veterans Affairs, Medical Center, Miami, Florida	Molecular mechanisms of lead neurotoxicity	Department of Veterans Affairs
Oteiza P	University of California, Davis, California	Exposure during gestation and infancy and its impact on neurobehavioral and learning capacities	Not specified
Pettit DL	Albert Einstein College of Medicine, Yeshiva University, New York, New York	Micromapping of lead induced changes to NMDA receptors	National Institute of Environmental Health Sciences
Pevsner JA	Kennedy Krieger Research Institute, Inc., Baltimore, Maryland	Effects of lead on calcium-binding proteins in rats	National Institute of Environmental Health Sciences
Pitts DK	Wayne State University, College of Pharmacy and AHP, Wayne State University, Detroit, Michigan	Lead toxicity—midbrain dopaminergic system	National Institute of Environmental Health Sciences
Pollitt E	University of California, Independent, Davis, California	The relationship between lead and iron and behavioral development in infants and young children	Department of Agriculture
Poretz RD	Rutgers University, Biochemistry and Microbiology, New Brunswick, New Jersey	A mechanism for lead-induced neurotoxicity	Department of Agriculture
Puzas JE	University of Rochester, Rochester, New York	Lead toxicity in the skeleton and its role in osteoporosis	National Institute of Environmental Health Sciences
Rajanna B	Alcorn State University, Lorman, Mississippi	Mechanism of lead neurotoxicity	National Institute of General Medical Sciences
Ris MD	Children's Hospital Medical Center, Cincinnati, Ohio	Early exposure to lead and adult antisocial outcome	National Institute of Environmental Health Sciences
Rogan W	Not specified	Toxicity of lead in children—clinical trial	National Institute of Environmental Health Sciences
Rosen HN	Beth Israel Deaconess Medical Center, Boston, Massachusetts	Lead and skeletal health in Boston area women	National Center for Research Resources
Ruden DM	University of Alabama at Birmingham, Birmingham, Alabama	QTL and microarray mapping lead sensitivity genes	National Institute of Environmental Health Sciences

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Schwab AP and Joern BC	Purdue University, Agronomy, West Lafayette, Indiana	Bioavailability and chemical lability of lead in agricultural soils amended with metal-containing biosolids	Department of Agriculture
Schwartz BS	Johns Hopkins University, Baltimore, Maryland	Role of lead in the decline in cognitive function in older adults	National Institute of Aging
Schwarz D	Children's Hospital of Philadelphia, Philadelphia, Pennsylvania	Treatment of lead in children	National Center for Research Resources
Shine JP	Harvard University, School of public Health, Boston, Massachusetts	Transport and fate of metals from mine wastes	National Institute of Environmental Health Sciences
Soliman KFA	Florida Agricultural and Mechanical University, Tallahassee, Florida	Neonatal lead exposure effects on the adrenal cortex function	National Institute of General Medical Sciences
Sparrow D	Department of Veterans Affairs, Medical Center, Boston, Massachusetts	Neurochemical and genetic markers of lead toxicity	Department of Veterans Affairs
Sparrow D	Department of Veterans Affairs, Medical Center, Boston, Massachusetts	Lead biomarkers, aging, and chronic disease	Department of Veterans Affairs
Timchalk C	Battelle Memorial Institute, Pacific Northwest Laboratories, Richland, Washington	Innovative biomonitoring for lead in saliva	National Institute of Environmental Health Sciences
Todd AC	Mount Sinai, School of Medicine, New York, New York	African-Americans, hypertension and lead exposure	National Institute of Diabetes and Digestive and Kidney Diseases
Watson GE, II	Department of Dentistry, University of Rochester, Rochester, New York	A longitudinal study of lead exposure and dental caries	National Institute of Dental and Craniofacial Research
Weisskopf MG	Harvard University, School of Public Health, Boston, Massachusetts	New biomarkers of neurotoxicity	National Institute of Environmental Health Sciences
White RF	Department of Veterans Affairs, Medical Center, Boston, Massachusetts	Functional neuroimaging in lead exposed adults	Department of Veterans Affairs, Research And Development

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Worobey J	Rutgers University, Nutritional Sciences, New Brunswick, New Jersey	Behavioral outcomes in children screened for lead burden and nutritional risk	Department of Agriculture
Wright RO	Harvard School of Public Health, Boston, Massachusetts	Metals, nutrition, and stress in child development	National Institute of Environmental Health Sciences
Wright RO	Brigham And Women's Hospital, Boston, Massachusetts	Neurochemical and genetic markers of lead toxicity	National Institute of Environmental Health Sciences

MR = magnetic resonance; NMDA = N-methyl-D-aspartate; PCBs = polychlorinated biphenyls; QTL = quantitative trait loci

Source: FEDRIP 2005

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Lead is a naturally occurring element and is a member of Group 14 (IVA) of the periodic table. Natural lead is a mixture of four stable isotopes, ^{208}Pb (51–53%), ^{206}Pb (23.5– -27%), ^{207}Pb (20.5–23%), and ^{204}Pb (1.35–1.5%). Lead isotopes are the stable decay product of three naturally radioactive elements: ^{206}Pb from uranium, ^{207}Pb from actinium, and ^{208}Pb from thorium.

Lead is not a particularly abundant element, but its ore deposits are readily accessible and widely distributed throughout the world. Its properties, such as corrosion resistance, density, and low melting point, make it a familiar metal in pipes, solder, weights, and storage batteries. The chemical identities of lead and several of its compounds are given in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Lead exists in three oxidation states: Pb(0), the metal; Pb(II); and Pb(IV). In the environment, lead primarily exists as Pb(II). Pb(IV) is only formed under extremely oxidizing conditions and inorganic Pb(IV) compounds are not found under ordinary environmental conditions. While organolead(II) compounds are known, organolead chemistry is dominated by the tetravalent (+4) oxidation state. Metallic lead, Pb(0) exists in nature, but its occurrence is rare.

Lead's extensive use is largely due to its low melting point and excellent corrosion resistance in the environment. When exposed to air and water, films of lead sulfate, lead oxides, and lead carbonates are formed; these films act as a protective barrier that slows or halts corrosion of the underlying metal. Lead is amphoteric, forming plumbous and plumbic salts in acid and plumbites and plumbates in alkali. Lead is positioned slightly above hydrogen in the electromotive series and therefore should theoretically replace hydrogen in acids. However, the potential difference is small and the high hydrogen overvoltage prevents replacement (King and Ramachandran 1995; Sutherland and Milner 1990).

Data on the physical and chemical properties of lead and several of its compounds are given in Table 4-2.

Table 4-1. Chemical Identity of Lead and Compounds

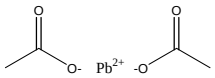
Characteristic	Lead[a]	Lead acetate[a]	Lead azide[b]	Lead bromide[c]
Synonyms	Lead metal; plumbum; pigment metal	Lead(2+) acetic acid; plumbous acetate	Lead (2+) azide; Lead diazinde	Lead (II) bromide[d]
Trade name	CI77575	Salt of Saturn; sugar of lead; Unichem PBA	RD 1333	No data
Chemical formula	Pb	$C_4H_6O_4Pb$	N_6Pb	Br_2Pb
Chemical structure[e]	Pb		$Pb(N_3)_2$	$PbBr_2$
Identification numbers:				
CAS registry	7439-92-1	301-04-2	13424-46-9	10031-22-8
NIOSH RTECS	OF7525000[b]	AI5250000[b]	OF8650000	No data
EPA hazardous waste	D008	U144, D008	No data	No data
OHM/TADS	7216776	7217255	No data	No data
DOT/UN/NA/IMCO shipping	NA	UN 1616, IMO 6.1	UN 0129	No data
HSDB	231	1404	No data	No data
NCI	No data	No data	No data	No data

Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead chloride[a]	Lead chromate[a]	Lead fluoroborate[a]	Lead iodide[a]
Synonyms	Lead(2+) chloride; lead (II) chloride; plumbous chloride	Chromic acid (H_2CrO_4) lead(2+) salt; lead chromate (VI); Yellow 34	Borate(1-), tetrafluoro, lead(2+); lead borofluoride; lead boron fluoride; lead tetrafluoroborate	Lead diiodide; lead(II) iodide; plumbous iodide
Trade name	No data	Canary Chrome Yellow 40-2250; Cologne Yellow; King's Yellow	No data	No data
Chemical formula	Cl_2Pb	CrO_4Pb	$B_{24}F_8Pb$	I_2Pb
Chemical structure[e]	$PbCl_2$	$PbCrO_4$	$Pb(BF_4)_2$	PbI_2
Identification numbers:				
CAS registry	7758-95-4	7758-97-6	13814-96-5	10101-63-0
NIOSH RTECS	OF9450000[b]	GB2975000[b]	ED2700000[b]	OG1515000[b]
EPA hazardous waste	No data	D007, D008	D008	D008
OHM/TADS	7217256	No data	7217378	No data
DOT/UN/NA/IMCO shipping	NA 2291	No data	NA 2291; 1MO 6.1	NA 2811
HSDB	6309	1650	1991	636
NCI	No data	No data	No data	No data

Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead molybdenum chromate[b]	Lead nitrate[a]	Lead oxide[a]
Synonyms	Chromic acid, lead and molybdenum salt; molybdenum-lead chromate; molybdenum orange; Scarlet chrome; Red 104	Lead dinitrate; nitric acid lead(2+) salt; lead (II) nitrate; plumbous nitrate	Lead(2+) oxide; lead oxide, yellow lead monoxide; litharge; massicot
Trade name	C.I. Pigment Red 104	No data	CI 77577; CI Pigment Yellow 46
Chemical formula	CRMoOPb	N_2O_6Pb	OPb
Chemical structure[e]	No data	$Pb(NO_3)_2$	PbO
Identification numbers:			
CAS registry	12709-98-7	10099-74-8	1317-36-8
NIOSH RTECS	OG1625000	OG2100000[b]	OG1750000[b]
EPA hazardous waste	No data	D008	D008
OHM/TADS	No data	7217257	No data
DOT/UN/NA/IMCO shipping	No data	UN 1469, IMO 5.1	No data
HSDB	No data	637	638
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Lead and Compounds

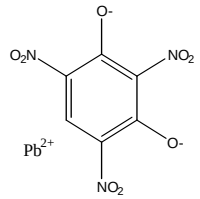
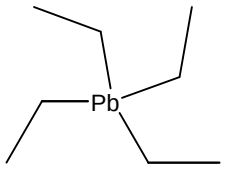
Characteristic	Lead phosphate[a]	Lead styphnate[f]	Lead sulfate[a]
Synonyms	Lead(2+) phosphate; phosphoric acid lead(2+) salt	1,3-benzenediol, 2,4,6-trinitro, lead (2+) salt (1:1); resorcinol, 2,4,6-trinitro; lead (2+) salt (1:1); lead (II) styphnate	Sulfuric acid lead(2+) salt; lead (II) sulfate
Trade name	Perlex Paste 500; Perlex Paste 600A; CI 77622	No data	CI 77630; Fast White; Lead Bottoms; Mulhouse White
Chemical formula	$O_8P_2Pb_3$	$C_6H_3N_3O_8 \cdot Pb$	O_4PbS
Chemical structure[e]	$Pb_3(PO_4)_2$		$PbSO_4$
Identification numbers:			
CAS registry	7446-27-7	15245-44-0	7446-14-2
NIOSH RTECS	OG3675000[b]	No data	OG4375000[b]
EPA hazardous waste	D008, U145	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	UN 1794; NA 1794; IMO 8.0
HSDB	2637	No data	6308
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead sulfide[a]	Tetraethyl lead[a]	Lead carbonate[a]
Synonyms	Lead monosulfide; lead(2+) sulfide; Lead (II) sulfide; plumbous sulfide; natural galena	Lead, tetraethyl; TEL; tetraethyllead; tetraethyl-plumbane	Carbonic acid lead salt; cerussite
Trade name	No data	No data	No data
Chemical formula	PbS	$C_8H_{20}Pb$	$PbCO_3$
Chemical structure[e]	PbS		$PbCO_3$
Identification numbers:			
CAS registry	1314-87-0	78-00-2	598-63-0
NIOSH RTECS	OG4550000	TP4550000	OF9275000
EPA hazardous waste	D008	P110; D008	D008
OHM/TADS	7800071	7216922	No data
DOT/UN/NA/IMCO shipping	NA 2291; IMO 6.1	NA 1649; IMO 6.1	No data
HSDB	639	841	1649
NCI	No data	C54988	No data

[a]HSDB 2007
[b]RTECS 2007
[c]Lewis 1993
[d]Lenga 1988
[e]ChemIDplus 2005
[f]EPA 2006

CAS = Chemical Abstracts Services; DOT/UN/NA/IMO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead[a]	Lead acetate[a]	Lead azide[b]	Lead bromide[b]
Molecular weight	207.20	325.28	291.25	367.04
Color	Bluish-gray	White	White	White
Physical state	Solid	Solid	Needles or powder	Crystalline powder
Melting point	327.4 °C	280 °C	No data	373 °C
Boiling point	1,740 °C	Decomposes above 200 °C	Explodes at 350 °C	916 °C
Density at 20 °C	11.34 g/cm^3	3.25 g/cm^3	No data	6.66 g/cm^3 [d]
Odor	None	Slightly acetic	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 25 °C	Insoluble	443,000 mg/L at 520 °C	230 mg/L at 18 °C	8,441 mg/L at 20 °C
Nitric acid	Soluble	No data	No data	No data
Hot conc. sulfuric acid	Soluble	No data	No data	No data
Organic solvents	Insoluble	Soluble in glycerol, very slight in alcohol	Acetic acid[c]	Insoluble in alcohol
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1.77 mmHg at 1,000 °C	No data	No data	1 mm Hg at 513 °C
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	Not flammable	No data
Conversion factors[j]	Not relevant[e]	Not relevant[e]	Not relevant[e]	Not relevant[e]
Explosive limits	No data	Lead acetate-lead bromate double salt is explosive	No data	No data
Valence state	0[f]	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead chloride[a]	Lead chromate[a]	Lead fluoroborate[b]	Lead iodide[a]
Molecular weight	278.11	323.19	380.81	461.01
Color	White	(Orange-)yellow	Colorless	Bright or golden yellow
Physical state	Solid	Solid	Crystalline powder	Hexagonal crystals; powder
Melting point	501 °C	844 °C	No data	402 °C
Boiling point	950 °C	Decomposes[c]	No data	Decomposes at 872 °C
Density at 20 °C	5.85 g/cm^3	6.12 g/cm^3 at 15 °C	1.75 g/cm^3	6.16 g/cm^3
Odor	No data	Faint odor (solution)	Odorless	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water at 25 °C	9,900 mg/L at 20 °C	0.2 mg/L	No data	630 mg/L at 20 °C
Nitric acid	No data	Soluble in dilute acid	No data	No data
Hot conc. sulfuric acid	No data	No data	No data	No data
Organic solvents	Insoluble in alcohol[c]	Insoluble in acetic acid	Decomposes in alcohol[c]	Insoluble in alcohol[b]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1 mm Hg at 547 °C	No data	No data	1 mm Hg at 479 °C
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	Flammable with combustible organic or other oxidizable materials	Not ignited readily	Not flammable
Conversion factors	Not relevant[e]	Not relevant[e]	Not relevant[e]	Not relevant[e]
Explosive limits	No data	No data	No data	No data
Valence state	+2	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead molybdenum chromate[a]	Lead nitrate[a]	Lead oxide[a]
Molecular weight	886.26[g]	331.21	223.20
Color	No data	Colorless or white	Reddish-yellow; yellow (above 489 °C)
Physical state	No data	Solid	Solid
Melting point	No data	Decomposes at 470 °C	888 °C
Boiling point	No data	No data	Decomposes at 1,472 °C
Density at 20 °C	No data	4.53 g/cm^3	9.3 g/cm^3 (Litharge); 8.0 g/cm^3 (Massicot)[d]
Odor	No data	Odorless	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water at 25 °C	No data	376,500 mg/L at 0 °C 565,000 mg/L at 20 °C	17 mg/L at 20 °C
Nitric acid	No data	Insoluble	Soluble (Litharge)
Hot conc. sulfuric acid	No data	No data	No data
Organic solvents	No data	1 g in 2,500 mL absolute alcohol; 1 g in 75 mL absolute alcohol	Soluble in alkali chlorides; soluble in alkali (Massicot); insoluble in alcohol
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	Fire risk with organics	Not readily ignited
Conversion factors	Not relevant[e]	Not relevant[e]	Not relevant[e]
Explosive limits	No data	Explosive with easily oxidizable substances, and lead nitrate-lead hypophosphite double salt	2B3 drops 90% peroxyformic acid causes violent explosion
Valence state	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead phosphate[a]	Lead styphnate[h]	Lead sulfate[a]
Molecular weight	811.54	450.29[g]	303.26
Color	White	Orange-yellow (monohydrate)	White
Physical state	Solid	Monoclinic crystals	Solid
Melting point	1,014 °C	No data	1,170 °C
Boiling point	No data	No data	No data
Density at 20 °C	6.9B7.3 g/cm^3 [d]	No data	6.2 g/cm^3[c]
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water at 25 °C	0.14 mg/L at 20 °C	Insoluble	42.5 mg/L
Nitric acid	Soluble	No data	More than in water
Hot conc. sulfuric acid	No data	No data	Slightly soluble
Organic solvents	Soluble in fixed alkali hydroxides; insoluble in alcohol	No data	Insoluble in alcohol
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	Detonates at 260 °C	Not flammable
Conversion factors	Not relevant[e]	Not relevant[e]	Not relevant
Explosive limits	No data	No data	No data
Valence state	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead sulfide[a]	Tetraethyl lead[a]	Lead carbonate[a]
Molecular weight	239.27	323.45	267.2
Color	Black, blue, or silvery	Colorless	Colorless rhombic crystals
Physical state	Cubic or metallic crystals; powder	Oily liquid	Solid
Melting point	1,114 °C	No data	315 °C (decomposes)
Boiling point	Sublimes at 1,281 °C	200 °C; 227.7 °C (with decomposition)	No data
Density at 20 °C	7.57–-7.59 g/cm^3	1.653 g/cm^3	6.6 g/cm
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water at 25 °C	0.86 mg/L at 13 °C	0.29 mg/L	1.1 mg/L
Nitric acid	Soluble	No data	Soluble
Hot conc. sulfuric acid	Soluble (in acid)	No data	Soluble
Organic solvents	Nitric acid, hot diluted hydrochloric acid[b]; insoluble in alcohol	Benzene, ethanol, diethyl ether, gasoline petroleum ether	Insoluble in ammonia and alcohol
Partition coefficients:			
Log K_{ow}	No data	4.15	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	10 mmHg at 975 °C	0.26 mm Hg at 25 °C	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	93 °C (closed cup); 85 °C (open cup)	No data
Flammability limits	Noncombustible	1.8%	Not flammable
Conversion factors	Not relevant	Not relevant	Not relevant
Explosive limits	No data	Potentially, above 80 °C	No data
Valence state	+2	+4	+2

[a]HSDB 2007
[b]Budavari et al. 1989
[c]Lide 1996
[d]Temperature not specified.
[e]Since these compounds exist in the atmosphere in the particulate state, their concentrations are expressed as µg/m^3 only.
[f]Howe 1981
[g]Molecular weight calculated from atomic weights.
[h]Lewis 1993

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

The most important lead ore is galena (PbS) followed by anglesite ($PbSO_4$) and cerussite ($PbCO_3$). The latter two minerals are formed from the weathering of galena. Five lead mines in Missouri plus lead-producing mines in Alaska, Idaho, Montana, and Washington produce most of the primary lead. In 2003, Alaska and Missouri ("lead-belt" in southeastern part of the state) accounted for 96% of domestic mine production. Lead can be recovered from ore deposits of lead, zinc, lead-zinc, and silver. Lead ore is mined underground except when it is mined with copper ores, which are typically open pit mines. The United States is third in world lead production after Australia and China. Together with Peru, Canada, and Mexico, these six countries account for 82% of the world's mine production.

Primary lead is obtained from mined ore. The crude ore is first beneficiated, which involves processes such as crushing, dense-medium separation, grinding, and froth floatation to obtain concentrates with higher lead concentrations. Primary metal is generally produced from the sulfide concentrate by a two-step process involving (1) an oxidative roast to remove sulfur with the formation of PbO and (2) blast furnace reduction of the PbO. Lead concentrates produced from ore were processed into primary metal at two smelter refineries operated by a company in Missouri.

Secondary lead is obtained from scrap lead. Ninety-nine percent of secondary production of lead was produced at 23 plants in the United States, 15 of which had annual capacities of 15,000 tons or more. In 2003, secondary lead accounted for 82% of refined lead production. Secondary lead is obtained primarily from recycled lead-acid batteries. Almost all of the lead recycled in 2003 was produced by 7 companies operating 15 plants in Alabama, California, Florida, Indiana, Louisiana, Minnesota, Missouri, New York, Tennessee, and Texas (USGS 2003).

Tables 5-1 and 5-2 list facilities in each state that respectively manufacture, process, or use lead and lead compounds, the intended use, and the range of maximum amounts of these substances that are stored on site. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI04 2006). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list. In comparing Toxics Release Inventory (TRI) data with that of previous years, it is important to note that starting in 2001 the threshold for reporting lead was reduced to 100 pounds. Previously, reporting was only required of facilities that manufactured or processed 25,000 pounds or more annually or that used 10,000 pounds or more annually. Additionally, in 1998, additional industries were required to report,

Table 5-1. Facilities that Produce, Process, or Use Lead

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	10	100	99,999	1, 5, 7, 9, 12, 13, 14
AL	126	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	74	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	76	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	281	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	56	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CT	104	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DC	4	100	99,999	1, 8, 11, 12, 13
DE	15	100	9,999,999	2, 3, 7, 8, 9, 11, 12, 13, 14
FL	119	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	117	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GU	3	0	999	1, 5, 12
HI	15	0	999,999	1, 7, 8, 11, 12, 13, 14
IA	91	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	37	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
IL	217	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	174	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	61	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
KY	107	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	77	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	103	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MD	51	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
ME	39	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
MI	176	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	84	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	112	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	74	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	19	0	99,999	1, 2, 5, 6, 7, 8, 9, 12, 13, 14
NC	138	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	17	0	99,999	1, 2, 3, 5, 7, 8, 9, 10, 12, 13, 14
NE	58	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NH	44	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
NJ	161	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	28	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 14
NV	55	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
NY	178	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	268	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	93	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	75	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-1. Facilities that Produce, Process, or Use Lead

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PA	238	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	31	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12
RI	50	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SC	113	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	21	0	499,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TN	156	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	223	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	63	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	109	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VI	3	100	99,999	1, 5, 12, 14
VT	17	0	9,999,999	2, 6, 7, 8, 9, 10, 11, 12, 13, 14
WA	90	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	129	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	64	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
WY	15	0	999,999	1, 4, 7, 8, 9, 12, 13, 14

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI04 2006 (Data are from 2004)

Table 5-2. Facilities that Produce, Process, or Use Lead Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	30	0	999,999,999	1, 2, 4, 5, 7, 9, 10, 12, 13, 14
AL	159	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	111	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
AZ	129	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	324	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	87	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
CT	111	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DE	38	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
FL	136	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	187	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GU	5	0	9,999	1, 2, 3, 4, 5, 7, 9, 12, 13, 14
HI	11	0	99,999	1, 2, 5, 7, 9, 12, 13, 14
IA	107	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	41	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
IL	287	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	259	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	104	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	148	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	116	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	148	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MD	80	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ME	33	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
MI	209	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	103	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	161	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MP	4	0	9,999	1, 2, 3, 4, 5, 7, 9, 12, 13, 14
MS	93	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	43	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 14
NC	156	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	17	0	999,999	1, 2, 5, 7, 9, 10, 12, 13, 14
NE	65	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NH	51	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NJ	182	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	55	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
NV	74	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	197	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	330	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	96	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Lead Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
OR	92	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PA	331	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	38	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
RI	59	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SC	123	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	24	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TN	166	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	288	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	88	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	120	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VI	7	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12
VT	18	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 11, 12, 13, 14
WA	113	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	136	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	70	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
WY	36	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI04 2006 (Data are from 2004)

including metal mining, coal mining, electrical utilities, and Resource Conservation and Recovery Act (RCRA)/Solvent Recovery. Table 5-3 lists the producers of primary lead metal and selected lead compounds. Companies listed are those producing lead compounds in commercial quantities, exceeding 5,000 pounds or $10,000 in value annually. Table 5-4 shows the U.S. production volumes for lead for 1999 through 2003. During this time, the primary lead production declined while secondary lead production was fairly constant.

5.2 IMPORT/EXPORT

No lead in ore and concentrates and base bullion were imported into the United States in 2003, while 175,000 metric tons were imported in pigs, bars, and reclaimed scrap. Imports were down from 1999 when 12,300 metric tons, 90 metric tons, and 311,000 metric tons were imported in ore and concentrates; base bullion; and pigs bars and reclaimed scrap, respectively. In 2003, 36,000 metric tons, lead content of lead pigments and compounds were imported in the United States (USGS 2003).

Exports of lead in ore and concentrates and lead materials, excluding scrap, rose from 93,500 and 103,000 metric tons in 1999 to 253,000 and 123,000 metric tons, respectively, in 2003. In 2003, 92,800 metric tons of lead scrap were exported (USGS 2003).

5.3 USE

Lead may be used in the form of metal, either pure or alloyed with other metals, or as chemical compounds. The commercial importance of lead is based on its ease of casting, high density, low melting point, low strength, ease of fabrication, acid resistance, electrochemical reaction with sulfuric acid, and chemical stability in air, water, and soil (King and Ramachandran 1995; Shea 1996; Sutherland and Milner 1990). Lead is used in the manufacture of storage batteries; lead alloys used in bearings, brass and bronze and some solders; sheets and pipe for nuclear and x-ray shielding, cable covering, noise control materials; chemical resistant linings; ammunition; and pigments and lead compounds used in glass making, ceramic glazes, plastic stabilizers, caulk, and paints. Consumption of lead in lead-acid batteries, including SLI (Start, Light, Ignition) batteries used in cars, trucks, and other vehicles and industrial type lead acid batteries is the major use of lead today. In 2003, the U.S. consumption for lead was: 84.2%, storage batteries; 3.5%, ammunition, shot, and bullets; 2.6%, other oxides (paint, glass and ceramic products, other pigments and chemicals); 2.3%, casting metals (electrical machinery and equipment, motor vehicles and equipment, other transportation equipment, and nuclear radiation shielding); and 1.7%, sheet lead (building construction, storage tanks, process vessels, etc., and medical radiation

Table 5-3. Current U.S. Manufacturers of Lead Metal and Selected Lead Compounds[a]

Company	Location
Lead metal[b]:	
Doe Run Resources Corp.	St. Louis, Missouri
Lead chromate (Yellow 34):	
Dominion Colour Corp. (USA)	Paterson, New Jersey
Engelhard Corporation	Louisville, Kentucky
Nichem Corp.	Chicago, Illinois
Rockwood Pigments, NA, Inc.	Beltsville, Maryland
Wayne Pigment Corporation	Milwaukee, Wisconsin
Lead fluoborate:	
Atotech USA Inc	Rock Hill, South Carolina
General Chemical Corporation	Claymont, Delaware
OMG Fidelity, Inc.	Newark, New Jersey
Solvay Fluorides, LLC.	St. Louis, Missouri
Lead molybdenum chromate (Red 104):	
Englehard Corporation	Louisville, Kentucky
Wayne Pigment Corporation	Milwaukee, Wisconsin
Lead nitrate:	
GFS Chemicals, Inc.	Columbus, Ohio
Lead oxide, yellow:	
Eagle-Picher Industries, Inc	Joplin, Missouri
Hammond Group, Inc.	Hammond, Indiana, Pottstown, Pennsylvania
OMNI Oxide	Lancaster, Ohio
Lead sulfate:	
Nichem Corp.[c]	Chicago, Illinois
Hammond Group, Inc.[d]	Hammond, Indiana
Eagle-Pitcher Industries, Inc.[e]	Joplin, Missouri

[a]Derived from SRI 2004 unless otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed.
[b]USGS 2004. Primary producer
[c]Lead sulfate, Dibasic lead sulfate ($2PbO.PBSO_4$) and Tribasic lead sulfate ($3PbO.PbSO_4$)
[d]Dibasic lead sulfate ($2PbO.PBSO_4$) and tribasic lead sulfate ($3PbO.PbSO_4$)
[e]Tribasic lead sulfate ($3PbO.PbSO_4$)

Table 5-4. U.S. Lead Production 1999–2003

Production	Production volumes in metric tons				
	1999	2000	2001	2002	2003
Mined (recovered): domestic ores, recoverable lead content	503,000	449,000	454,000	440,000	449,000
Primary (refined): domestic/foreign ores and base bullion	350,000	341,000	290,000	262,000	245,000
Secondary (refined): lead content	1,110,000	1,130,000	1,100,000	1,120,000	1,150,000

Source: USGS 2003

shielding) (USGS 2003). Certain dispersive uses of lead that led to widespread exposure, such as tetraethyl lead in gasoline, water pipe, solder in food cans, lead shot and sinkers, and in house paints, have been or are being phased out due to environmental and health concerns (Larrabee 1998).

Prior to the EPA beginning to regulate the lead content in gasoline during the early 1970s, approximately 250,000 tons of organic lead (e.g., tetraethyl lead) were added to gasoline on an annual basis in the United States (Giddings 1973). These lead-based "anti-knock" additives increased the octane rating of the gasoline and as a result increased engine efficiency (Giddings 1973). In 1971, the average lead content for a gallon of gasoline purchased in the United States was 2.2 grams per gallon (Giddings 1973). After determining that lead additives would impair the performance of emission control systems installed on motor vehicles, and that lead particle emission from motor vehicles presented a significant health risk to urban populations, EPA, in 1973, initiated a phase-down program designed to minimize the amount of lead in gasoline over time. By 1988, the phase-down program had reduced the total lead usage in gasoline to <1% of the amount of lead used in the peak year of 1970 (EPA 1996a).

In 1990, a Congressional amendment to the Clean Air Act (CAA) banned the use of gasoline containing lead or lead additives as fuel in motor vehicles. On February 2, 1996, the EPA incorporated the statutory ban in a direct final rule which defined unleaded gasoline as gasoline containing trace amounts of lead up to 0.05 gram per gallon (EPA 1996a). The definition still allowed trace amounts of lead but expressly prohibited the use of any lead additive in the production of unleaded gasoline. The term "lead additive" was defined to include pure lead as well as lead compounds (EPA 1996a). Although the regulatory action of Congress banned the use of leaded gasoline as fuel in motor vehicles, it did not restrict other potential uses of gasoline containing lead or lead additives (EPA 1996a). Gasoline produced with lead additives continues to be made and marketed for use as fuels in aircraft, race cars, and non-road engines such as farm equipment engines and marine engines, to the extent allowed by law (EPA 1996a), but tetraethyl lead has not been produced in the United States since March 1991. All gasoline sold for motor vehicle use since January 1, 1996, has been unleaded (EPA 1997).

Table 5-5 lists the uses of the specific lead compounds identified in Chapter 4.

Lead arsenate, basic lead arsenate, and lead arsenite were formerly used as herbicides, insecticides, or rodenticides. Until the 1960s, they were widely used to control pests in fruit orchards, especially apple orchards (EPA 2002; PAN Pesticides Database 2004; Peryea 1998; Wisconsin Department of Health and

Table 5-5. Current and Former Uses of Selected Lead Compounds

Compound	Uses
Lead acetate	Dyeing of textiles, waterproofing, varnishes, lead driers, chrome pigments, gold cyanidation process, insecticide, anti-fouling paints, analytical reagent, hair dye
Lead azide	Primary detonating compound for high explosives
Lead bromide	Photopolymerization catalyst, inorganic filler in fire-retardant plastics, general purpose welding flux
Lead chloride	Preparation of lead salts, lead chromate pigments, analytical reagent
Lead chromate	Pigment in industrial paints, rubber, plastics, ceramic coatings; organic analysis
Lead fluoborate	Salt for electroplating lead; can be mixed with stannous fluoborate to electroplate any composition of tin and lead as an alloy
Lead iodide	Bronzing, printing, photography, cloud seeding
Lead molybdate	Analytical chemistry, pigments
Lead nitrate	Lead salts, mordant in dyeing and printing calico, matches, mordant for staining mother of pearl, oxidizer in the dye industry, sensitizer in photography, explosives, tanning, process engraving, and lithography
Lead oxide, black	Storage batteries, ceramic cements and fluxes, pottery and glazes, glass, chromium pigments, oil refining, varnishes, paints, enamels, assay of precious metal ores, manufacture of red lead, cement (with glycerol), acid-resisting compositions, match-head compositions, other lead compounds, rubber accelerator
Lead phosphate	Stabilizing agent in plastics
Lead styphnate	Primary explosive
Lead sulfate	Storage batteries, paints, ceramics, pigments, Electrical and other vinyl compounds requiring high heat stability
Lead sulfide	Ceramics, infrared radiation detector, semi-conductor, ceramic glaze, source of lead
Tetraethyl lead	Anti-knock agent in aviation gasoline

Sources: Boileau et al. 1987; Carr 1995; EPA 2001

Family Services 2002). All insecticidal use of lead arsenate was officially banned on August 1, 1988. However, all registrations for its insecticidal use had lapsed before that time.

5.4 DISPOSAL

Although certain uses of lead preclude recycling (e.g., use as a gasoline additive), lead has a higher recycling rate than any other metal (Larrabee 1998). In 2002, about 81% of refined lead production in the United States was recovered from recycled scrap. The primary source was recycled lead-acid batteries. About 6% of recycled lead was obtained from other sources, namely new scrap, obtained from primary lead production, building construction materials, cable covering, and solder. About 99% of the 1.10 million tons of lead recycled in 2002 was produced by 7 companies operating 15 secondary smelter-refineries in Alabama, California, Florida, Indiana, Louisiana, Minnesota, Missouri, New York, Pennsylvania, Tennessee, and Texas. An estimated 90–95% of the lead consumed in the United States is considered to be recyclable. In 1996, 77.1% of U.S. lead consumption was satisfied by recycled lead products (mostly lead-acid batteries). This compares to 69.5% in 1990 and 55.2% in 1980 (Larrabee 1997, 1998; USGS 2002).

Disposal of wastes containing lead or lead compounds is controlled by a number of federal regulations (see Chapter 8). Lead is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 2001e). Lead-containing waste products include storage batteries, ammunition waste, ordnance, sheet lead, solder, pipes, traps, and other metal products; solid waste and tailings from lead mining; items covered with lead-based paint; and solid wastes created by mineral ore processing, iron and steel production, copper and zinc smelting, and the production and use of various lead-containing products (EPA 1982a).

Presently, 37 states have enacted legislation to encourage recycling of lead-acid batteries. These states have adopted laws that prohibit disposal of lead-acid batteries in municipal solid waste streams and require all levels of the collection chain to accept spent lead-acid batteries. Four other states ban only the land-filling and incineration of lead-acid batteries. Battery recycling rates are determined by comparing the amount of lead recycled from batteries with the quantity available for recycling in a given year. Recycling facilities can usually provide data on the amount of lead produced from scrapped batteries; however, the amount of lead available for recycling is largely influenced by the battery's useful life span. Therefore, to determine the amount of lead available from batteries for a given year requires historical

data on battery production and average lead content, as well as import and export data on new batteries, vehicles containing batteries, scrap lead and scrapped batteries (Larrabee 1998). According to the Battery Council International, 97% of all lead-acid batteries are recycled and new batteries contain between 60 and 80% recycled lead and plastic (Battery Council International 2003).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Lead has been identified in at least 1,272 of the 1,684 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2006). However, the number of sites evaluated for lead is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 1,258 are located within the United States, 2 are located in Guam, 10 are located in the Commonwealth of Puerto Rico, and 2 are located in the Virgin Islands (not shown).

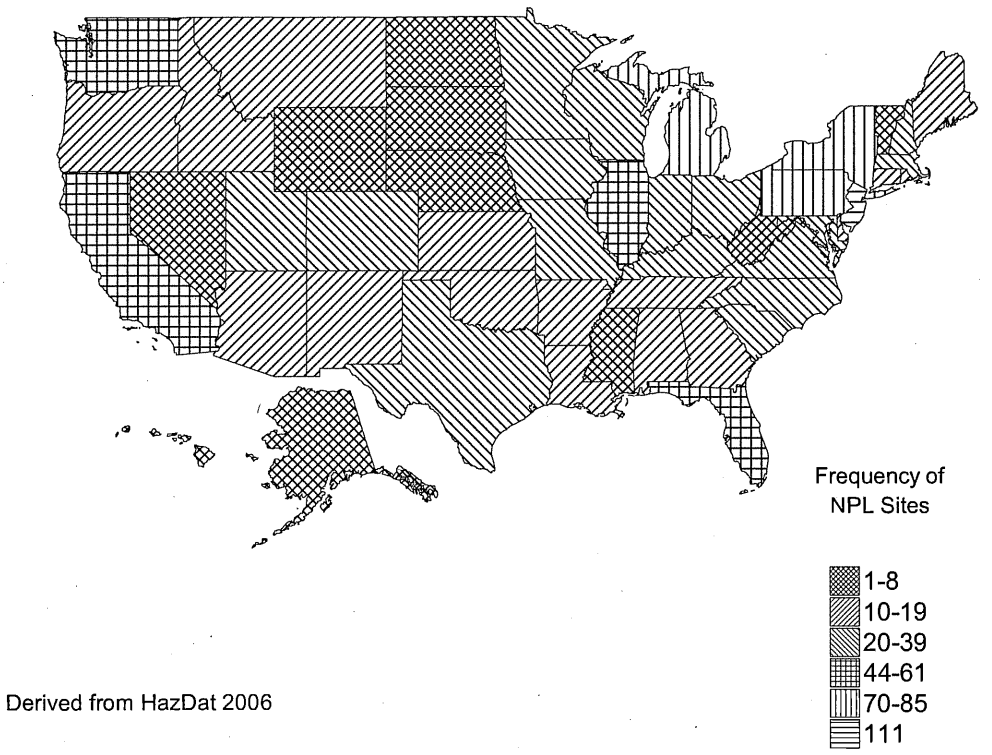
Lead is dispersed throughout the environment primarily as the result of anthropogenic activities. In the air, lead is in the form of particles and is removed by rain or gravitational settling. The solubility of lead compounds in water is a function of pH, hardness, salinity, and the presence of humic material. Solubility is highest in soft, acidic water. The sink for lead is the soil and sediment. Because it is strongly adsorbed to soil, it generally is retained in the upper layers of soil and does not leach appreciably into the subsoil and groundwater. Lead compounds may be transformed in the environment to other lead compounds; however, lead is an element and cannot be destroyed. Anthropogenic sources of lead include the mining and smelting of ore, manufacture of lead-containing products, combustion of coal and oil, and waste incineration. Many anthropogenic sources of lead, most notably leaded gasoline, lead-based paint, lead solder in food cans, lead-arsenate pesticides, and shot and sinkers, have been eliminated or strictly regulated due to lead's persistence and toxicity. Because lead does not degrade, these former uses leave their legacy as higher concentrations of lead in the environment.

Plants and animals may bioconcentrate lead, but lead is not biomagnified in the aquatic or terrestrial food chain.

The general population may be exposed to lead in ambient air, foods, drinking water, soil, and dust. Segments of the general population at highest risk of health effects from lead exposure are preschool-age children and pregnant women and their fetuses. Within these groups, relationships have been established between lead exposure and adverse health effects. Other segments of the general population at high risk include individuals living near sites where lead was produced or disposed.

Human exposure to lead above baseline levels is common. Baseline refers to the naturally-occurring level of lead in soil or dust that is not due to the influence of humans. Some of the more important lead

Figure 6-1. Frequency of NPL Sites with Lead Contamination



exposures have occurred as a result of living in urban environments, particularly in areas near stationary emission sources (e.g., smelters); consumption of produce from family gardens; renovation of homes containing lead-based paint; pica (an abnormal eating habit in children); contact with interior lead paint dust; occupational exposure; secondary occupational exposure (e.g., families of workers using lead); smoking; and wine consumption. Higher than normal exposures may also occur to residents living in close proximity to NPL sites that contain elevated levels of lead. The highest and most prolonged lead exposures are found among workers in the lead smelting, refining, and manufacturing industries.

The primary source of lead in the environment has historically been anthropogenic emissions to the atmosphere. In 1984, combustion of leaded gasoline was responsible for approximately 90% of all anthropogenic lead emissions. EPA gradually phased out the use of lead alkyls in gasoline, and by 1990, auto emissions accounted for only 33% of the annual lead emissions (EPA 1996b). Use of lead additives in motor fuels was totally banned after December 31, 1995 (EPA 1996a). The ban went into effect on February 2, 1996. Atmospheric deposition is the largest source of lead found in soils. Lead is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for lead. Lead particles are removed from the atmosphere primarily by wet and dry deposition. The average residence time in the atmosphere is 10 days. Over this time, long-distance transport, up to thousands of kilometers, may take place. Lead is extremely persistent in both water and soil. The speciation of lead in these media varies widely depending upon such factors as temperature, pH, and the presence of humic materials. Lead is largely associated with suspended solids and sediments in aquatic systems, and it occurs in relatively immobile forms in soil.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005i). This is not an exhaustive list. Manufacturers, processors, and users of lead and lead compounds are required to report information to the TRI only if they employ 10 or more full-time employees; if they operate in certain industrial sectors; and if their facility produces, imports, processes, or uses at least 100 pounds of lead, (exclusive of that contained in stainless steel, brass, or bronze alloys), or lead compounds in a calendar year. Prior to 2001, the threshold for reporting was much higher for persistent, bioaccumulative, toxic (PBT) chemicals such as lead. Facilities then had to report only when they manufactured, imported, or processed >25,000 pounds or used >10,000 pounds of lead or lead compounds in a calendar year. This higher threshold still applies to lead contained in

stainless steel, brass, or bronze alloys. The threshold for lead is determined using the weight of the metal, whereas the threshold for lead compounds is determined by the weight of the entire compound. Prior to 1998, only facilities classified within the SIC codes 20–39 (Manufacturing Industries) were required to report. After 1998, the industrial sector required to report was enlarged to include other industrial sectors, such as metal mining, coal mining, electrical utilities, and hazardous waste treatment (EPA 2001a).

While lead is a naturally-occurring chemical, it is rarely found in its elemental form. It occurs in the Earth's crust primarily as the mineral galena (PbS), and to a lesser extent as anglesite ($PbSO_4$) and cerussite ($PbCO_3$). Lead minerals are found in association with zinc, copper, and iron sulfides as well as gold, silver, bismuth, and antimony minerals. It also occurs as a trace element in coal, oil, and wood. Typical lead concentration in some ores and fuels are: copper ores, 11,000 ppm; lead and zinc ores, 24,000 ppm; gold ores, 6.60 ppm; bituminous coal, 3–111 ppm; crude oil, 0.31 ppm; No. 6 fuel oil, 1 ppm; and wood, 20 ppm (EPA 2001a).

Lead released from natural sources, such as volcanoes, windblown dust, and erosion, are minor compared with anthropogenic sources. Industrial sources of lead can result from the mining and smelting of lead ores, as well as other ores in which lead is a by-product or contaminant. In these processes, lead may be released to land, water, and air. Electrical utilities emit lead in flue gas from the burning of fuels, such as coal, in which lead is a contaminant. Because of the large quantities of fuel burned by these facilities, large amounts of lead can be released. For example, using the EPA emission factor for lignite coal, $4.2x10^{-4}$ pounds of lead/ton of coal, a boiler burning a million pounds of lignite coal will release 420 pounds of lead into the atmosphere (EPA 2001a). Many of the anthropogenic sources of lead have been eliminated or phased out because of lead's persistence, bioaccumulative nature, and toxicity. These include, most notably, lead in gasoline, lead-based paint, and lead-containing pesticides, and lead in ammunition and sinkers. Because lead does not degrade, these former uses leave their legacy as higher concentrations of lead in the environment.

According to the TRI, in 2004, a total of 12,112,037 pounds of lead were released to the environment from 4,347 reporting facilities (TRI04 2006). Another 4,767,316 pounds were transferred off-site. Table 6-1 lists amounts of lead released from these facilities grouped by state. In addition, a total of 405,285,570pounds of lead compounds were released to the environment from 4,294 reporting facilities and another 20,809,590 pounds were transferred off-site (TRI04 2006). Table 6-2 lists amounts of lead

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Lead[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	7	292	2	0	39,203	13	39,497	13	39,510
AL	115	11,377	625	39	1,857,435	904	1,800,604	69,778	1,870,382
AR	52	2,642	193	0	56,661	35,279	46,126	48,649	94,775
AZ	77	652	6,112	0	56,020	43,185	55,184	50,786	105,969
CA	290	2,208	1,669	359	35,634	47,985	31,094	56,761	87,855
CO	49	424	59	143	115,238	22,117	94,378	43,604	137,981
CT	69	286	36	0	138	11,454	311	11,603	11,914
DC	2	0	0	0	403	0	0	403	403
DE	3	3	1	0	0	0	4	0	4
FL	156	4,640	371	0	152,932	10,593	152,988	15,548	168,536
GA	123	3,786	150	0	78,219	37,659	76,673	43,140	119,813
GU	1	120	0	0	0	0	120	0	120
HI	10	784	1	1	125,691	1,681	126,477	1,682	128,159
IA	76	3,999	446	140	5,939	50,150	8,280	52,395	60,674
ID	20	580	29	0	4,397,661	831	4,398,246	855	4,399,101
IL	220	20,391	1,713	401	156,127	14,987	22,120	171,499	193,619
IN	191	6,973	1,411	176	784,642	825,635	19,525	1,599,312	1,618,837
KS	45	5,123	64	99	42,320	5,206	26,399	26,413	52,812
KY	85	13,914	377	1,250	84,887	101,249	91,819	109,859	201,678
LA	59	1,386	1,913	279	2,400	795	4,914	1,858	6,772
MA	103	722	34	0	3,200	12,226	2,188	13,994	16,182
MD	38	587	34	0	11,669	2,731	10,399	4,622	15,021
ME	18	516	159	0	1,386	15	1,363	714	2,077
MI	182	8,600	526	0	101,768	11,209	14,625	107,478	122,103
MN	97	629	519	0	3,058	800	630	4,376	5,006
MO	90	2,581	262	157	142,943	1,733	125,168	22,508	147,676
MS	57	1,986	393	27	44,196	449	43,659	3,392	47,050
MT	7	366	11	0	332,755	669	332,252	1,549	333,801
NC	141	2,197	563	0	223,107	8,242	212,004	22,104	234,108
ND	10	406	474	0	8,313	200	4,470	4,922	9,392
NE	54	6,788	70	0	5,155	5,535	7,692	9,855	17,547
NH	34	364	121	0	2,171	3,449	644	5,461	6,105
NJ	73	1,612	169	0	1,299	37,414	2,921	37,573	40,494
NM	17	90	0	0	32,544	3,413	32,634	3,413	36,047
NV	21	2,522	0	0	96,301	2,563	98,588	2,798	101,386
NY	169	4,296	7,241	1	26,877	38,864	18,677	58,602	77,279

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Lead[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
OH	311	21,200	6,974	28,852	2,396,501	831,963	2,294,828	990,663	3,285,490
OK	59	6,250	25	162	84,903	712	55,964	36,088	92,052
OR	54	389	17	0	198,334	1,019	198,327	1,432	199,759
PA	229	18,426	2,534	0	44,891	336,150	49,233	352,768	402,001
PR	22	41	0	0	0	420	41	420	461
RI	25	58	46	0	0	2,176	70	2,209	2,280
SC	78	6,116	492	19,107	34,974	18,570	11,829	67,430	79,259
SD	17	105	26	0	11,103	1	11,208	28	11,236
TN	107	8,958	832	198	24,456	33,552	15,650	52,346	67,996
TX	232	19,573	2,036	133,133	339,613	39,359	453,503	80,211	533,714
UT	37	539	74	0	154,967	26,984	145,376	37,189	182,565
VA	91	6,437	1,152	0	385,614	26,809	32,753	387,259	420,012
VI	2	114	0	0	426	23	516	47	563
VT	6	14	18	0	0	2,658	14	2,676	2,691
WA	76	861	1,545	0	864,384	12,312	855,186	23,917	879,102
WI	178	10,688	1,015	0	79,703	32,974	11,181	113,200	124,380
WV	42	1,538	46	0	50,653	6,245	46,684	11,798	58,482
WY	10	66	0	0	27,052	0	27,003	115	27,118
Total	4,337	215,216	42,581	184,525	13,725,870	2,711,160	12,112,037	4,767,316	16,879,353

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Lead Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	13	11,686	792	8,493,212	141,141,748	3	149,643,055	4,387	149,647,441
AL	108	30,437	10,300	1,001	1,709,923	786,593	1,450,722	1,087,531	2,538,253
AR	71	7,871	1,744	0	174,136	192,907	137,497	239,162	376,659
AZ	60	14,142	214	0	5,510,961	9,540	5,499,714	35,144	5,534,857
CA	276	9,530	1,462	123	4,989,235	124,884	3,760,943	1,364,291	5,125,234
CO	53	6,310	820	0	6,775,795	2,753	6,577,849	207,830	6,785,679
CT	72	1,842	50,808	0	55,894	46,837	2,552	152,828	155,380
DE	13	2,930	1,161	0	72,923	16,714	31,159	62,568	93,728
FA	110	23,635	2,624	0	505,968	21,557	444,097	109,687	553,784
FL	133	19,762	2,502	0	439,521	15,659	337,497	139,948	477,445
GU	3	4	1	0	4	0	10	0	10
HI	13	3,902	22	11	1,304	206	3,935	1,510	5,444
IA	62	19,705	1,919	3	250,083	104,373	54,916	321,167	376,084
ID	31	4,652	682	0	2,432,819	3,756	2,421,469	20,439	2,441,908
IL	223	27,715	6,780	1,139	2,252,474	166,469	1,752,530	702,047	2,454,577
IN	183	54,164	7,662	1,202	3,736,474	1,318,189	1,273,823	3,843,869	5,117,691
KS	54	11,010	309	0	104,267	83,899	100,975	98,510	199,485
KY	82	22,586	1,937	40	908,615	41,149	865,666	108,660	974,327
LA	76	16,143	26,110	0	1,104,894	3,061	948,072	202,136	1,150,209
MA	135	4,088	243	0	304,852	38,052	9,549	337,686	347,234
MD	38	4,202	1,873	9	261,495	56,339	235,657	88,260	323,918
ME	29	1,346	1,373	0	12,061	9,811	11,991	12,601	24,592
MI	136	23,248	9,161	80	711,353	94,813	296,369	542,284	838,653
MN	74	9,093	948	0	254,293	132,931	89,773	307,491	397,264
MO	111	181,782	10,114	0	28,889,783	3,098	27,669,492	1,415,285	29,084,777
MP	3	1	0	0	1	0	2	0	2
MS	59	14,205	1,624	254,800	112,794	3,928	330,719	56,634	387,352
MT	20	6,339	393	3,098	15,029,303	851	15,030,211	9,772	15,039,984
NC	154	19,778	2,287	13	452,288	365,461	422,797	417,030	839,828
ND	10	7,745	14	66	130,165	80	86,306	51,764	138,070
NE	28	4,918	135	0	52,093	32,663	52,489	37,321	89,810
NH	31	490	71	0	55,741	911	743	56,469	57,213
NJ	98	7,008	8,201	0	496,387	222,789	153,985	580,400	734,385
NM	22	1,252	881	0	596,749	17,894	583,007	33,768	616,776
NV	32	4,073	541	4	105,668,551	5,296	105,667,734	10,731	105,678,465
NY	129	16,840	9,737	0	744,058	168,013	687,725	250,922	938,648
OH	263	60,447	13,753	15,937	1,905,688	568,837	801,235	1,763,427	2,564,663
OK	47	54,622	363	401	290,227	73,571	338,813	80,372	419,184
OR	61	2,037	3,165	0	55,083	530	11,787	49,027	60,814

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Lead Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
PA	246	69,995	6,769	987	3,479,169	1,229,509	1,714,804	3,071,625	4,786,428
PR	18	2,948	18	0	394	2,936	3,028	3,268	6,296
RI	24	38	67	1	3,701	805	44	4,568	4,612
SC	84	16,757	2,239	0	354,464	28,224	255,034	146,649	401,683
SD	17	1,936	762	0	1,446,132	386	1,446,330	2,884	1,449,215
TN	108	16,735	4,380	0	8,765,194	35,448	8,635,566	186,192	8,821,758
TX	236	45,373	5,779	1,089	2,492,627	54,544	2,015,842	583,571	2,599,413
UT	36	14,630	277	0	59,676,521	298,324	59,596,136	393,616	59,989,752
VA	98	14,524	4,397	558	381,233	35,396	267,225	168,883	436,108
VI	2	389	0	0	0	0	389	0	389
VT	10	25	50	0	2,712	7,136	41	9,882	9,923
WA	87	6,775	6,896	0	2,788,908	792,545	2,759,956	835,168	3,595,124
WI	136	11,702	2,165	0	389,469	56,300	110,108	349,527	459,636
WV	59	4,743	1,970	54	810,502	9,651	597,011	229,908	826,919
WY	17	5,336	20	0	112,415	309	97,189	20,891	118,080
Total	4,294	923,449	218,510	8,773,829	408,893,442	7,285,930	405,285,570	20,809,590	426,095,160

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment0(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II0V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on0site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off0site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off0site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

compounds released from these facilities grouped by state. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Lead has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 1,272 of the 1,684 current and former NPL hazardous waste sites (HazDat 2006). Lead is the most frequently found metal at hazardous waste sites (Reed et al. 1995).

6.2.1 Air

According to the TRI, in 2004, a total of 215,216 pounds of lead were released to air from 4,337 reporting facilities (TRI04 2006). Table 6-1 lists amounts of lead released from these facilities grouped by state. In addition, a total of 923,449 pounds of lead compounds were released to air from 4,294 reporting facilities (TRI04 2006). Table 6-2 lists amounts of lead compounds released from these facilities grouped by state. Releases of lead and lead compounds to air constitute, respectively, 1.78 and 4 0.23% of all on-site releases. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Lead has been identified in air samples collected at 96 of the 1,272 NPL hazardous waste sites where it was detected in some environmental medium (HazDat 2006).

The emissions of lead and lead compounds to the atmosphere reported to TRI has declined from 2.8 million pounds in 1988 to about 1.1 million pounds in 2004 as new industries were added to TRI reporting requirements (TRI04 2006). In 2000, before the reporting thresholds were drastically reduced, air emissions were 1.5 million pounds. In the past, transportation, particularly automotive sources, were the major contributor to air emissions of lead. Today, industrial processes, especially metal processing, are the major sources of lead emissions to the atmosphere with the highest lead concentrations found around smelters and battery manufacturers (EPA 2003a). Based on emission estimates, EPA reports a 93% reduction in lead emissions to the atmosphere between 1982 and 2002 and a 5% reduction between 1993 and 2002. Air quality levels for lead, namely the maximum quarterly mean concentrations, declined 93% between 1983 and 2002 and 57% between 1993 and 2002. EPA estimated that 78% of emissions in 2001 were from industrial processes, 12% from transportation, and 10% from fuel combustion. It should be noted that aviation gasoline and racing fuels are not regulated for lead content and can use significant quantities of lead (EPA 2003a). Historical trends of lead emissions in the United States are provided in Table 6-3 (EPA 2007a).

Table 6-3. Historic Levels of Lead Emissions to the Atmosphere in the United States

Pounds of lead emitted annually								
1970	1975	1980	1985	1990	1995	2000	2005	2006
$4.4x10^8$	$3.2x10^8$	$1.5x10^8$	$4.6x10^7$	$1.0x10^7$	$8.0x10^6$	$4.0x10^6$	$6.0x10^6$	$4.0x10^6$

Source: EPA 2007a

EPA (2000) estimated lead emission between 1990 and 1993 from all sources, not just those covered by TRI, which is limited to certain industries. During this period, lead emissions were estimated to average 3,307 tons/year. The major contributors to these emissions were: metals processors (840 tons/year), chemical manufacturers (181 tons/year), other manufacturing operations (553 tons/year), waste disposal and recycling (270 tons/year), onroad (e.g., automobiles, trucks, buses, and motorcycles) mobile sources (418 tons/year), and nonroad (e.g., airplanes, boats, railway engines, lawnmowers, and off-road vehicles) mobile sources (778 tons/year).

A study that estimated the historical rate of atmospheric metal fluxes into Central Park Lake, New York City by analyzing sediment cores for levels of trace metals, indicated that lead fluxes were extremely high throughout the 20th century, reaching maximum values (>70 μg cm^{-2} year^{-1}) from the late 1930s to the early 1960. This occurred decades before the maximum emissions from the use of leaded gasoline (Chillrud et al. 1999). The trends closely resemble the history of solid waste incineration in the city. These results, and the widespread use of solid waste incineration during that time, suggest that this may have been the dominant source of lead in urban areas. The decline in the prevalence of small incinerators, increased recycling, and the decline in the use of lead in a variety of consumer and commercial products would indicate that atmospheric releases of lead from solid waste incineration is a much less important source of lead emissions today than it was in the past.

As indicated in Table 6-4, by 1988, transportation (i.e., automotive) emissions were no longer the dominant source of lead emitted to the atmosphere. When such emissions were prevalent, >90% (mass basis) of automotive lead emissions from leaded gasoline were in the form of inorganic particulate matter (e.g., lead bromochloride [PbBrCl]) and <10% (mass basis) were in the form of organolead vapors (e.g., lead alkyls). In 1984 the average lead content of gasoline was 0.44 g lead/gallon (EPA 1986a); however, as of January 1986, the allowable lead content of leaded gasoline dropped to 0.1 g lead/gallon (EPA 1985d). Between January and June of 1990, the actual average lead concentration in leaded gasoline was 0.085 g lead/gallon, indicating consumption of approximately 230,000 kg of lead for the production of 2.74 billion gallons of leaded gasoline. In the early 1980s EPA allowed up to 0.05 g of lead in a gallon of unleaded gasoline (EPA 1982b).

In 1996, estimated mobile transportation source emissions of lead into air for the 48 contiguous states decreased from an average of 1,196 tons/year derived for 1990–1993 to 546.1 tons/year in 1996 (EPA 2000, 2001b). The estimates are based on data obtained from the 1996 National Toxics Inventory. The onroad estimate of 18.9 tons/year for 1996 was a dramatic decrease from the average estimate of

Table 6-4. National Lead Emission Estimates (in 103 Metric Tons/Year), 1979–1989

Source category	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
Transportation	94.6	59.4	46.9	46.9	40.8	34.7	15.5	3.5	3.0	2.6	2.2
Fuel combustion	4.9	3.9	2.8	1.7	0.6	0.5	0.5	0.5	0.5	0.5	0.5
Industrial processes	5.2	3.6	3.0	2.7	2.4	2.3	2.3	1.9	1.9	2.0	2.3
Solid waste	4.0	3.7	3.7	3.1	2.6	2.6	2.8	2.7	2.6	2.5	2.3
Total[a]	108.7	70.6	56.4	54.4	46.4	40.1	21.1	8.6	8.0	7.6	7.2

[a]The sums of categories may not equal the total because of rounding.

Source: derived from EPA 1991e

418 tons/year given for 1990–1993 (EPA 2000, 2001b). Likewise, nonroad emissions decreased from an average of 778 tons/year in 1990–1993 to 527.2 tons/year in 1996. These decreases were the result of the complete phase-out of leaded gasoline in 1996. Projected estimates of lead emissions in 2007 for onroad and nonroad sources were 22.0 and 585.2 tons/year, respectively. The major onroad lead emissions in 1996 were generated from light-duty gasoline vehicles (13.9 tons/year) and light-duty gasoline trucks (5.0 tons/year). The major generators of lead emissions in 1996 from nonroad sources were airports (526.1 tons/year).

Emissions of lead from electric utility steam generating plants totaled 71.37 tons/year in 1994 (EPA 1998b). The emissions varied depending on the fuel used in the electric generating facility; coal (62 tons/year), oil (8.9 tons/year), and natural gas (0.47 tons/year). It is projected that total lead emissions from electric steam generating plants will increase to 93.08 tons/year in 2010. This increase will be due to increased demand for electric power and an increased use of coal and natural gas as fuel sources to generate electricity. Lead emissions for coal, oil, and natural powered electric steam utilities are projected to be 87, 5.4, and 0.68 tons/year, respectively, in 2010.

Releases from lead-based paints are frequently confined to the area in the immediate vicinity of painted surfaces, and deterioration or removal of the paint by sanding or sandblasting can result in high localized concentrations of lead dust in both indoor and outdoor air.

The largest volume of organolead vapors released to the atmosphere results from industrial processes; prior to its phaseout and ban, leaded gasoline containing tetraethyl lead as an anti-knock additive was also a major contributor. Tetraalkyl lead vapors are photoreactive, and their presence in local atmospheres is transitory. Halogenated lead compounds are formed during combustion by reaction of the tetraalkyl lead compounds with halogenated lead scavenger compounds. These halogenated lead compounds ultimately give rise to lead oxides and carbonates in the environment (EPA 1985b). Tetraalkyl lead compounds once contributed 5–10% of the total particulate lead present in the atmosphere. Organolead vapors were most likely to occur in occupational settings (e.g., gasoline transport and handling operations, gas stations, and parking garages) and high-traffic areas (Nielsen 1984).

6.2.2 Water

According to the TRI, in 2004, a total of 42,581 pounds of lead were released to water from 4,337 reporting facilities (TRI04 2006). Table 6-1 lists amounts of lead released from these facilities

grouped by state. In addition, a total of 218,510 pounds of lead compounds were released to water from, 4,294 reporting facilities (TRI04 2006). Table 6-2 lists amounts of lead compounds released from these facilities grouped by state. Releases of lead and lead compounds to water constitute, respectively, 0.35 and 0.05 % of all on-site releases. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Of the known aquatic releases of lead, the largest ones are from the steel and iron industries and lead production and processing operations (EPA 1982a). Urban runoff and atmospheric deposition are significant indirect sources of lead found in the aquatic environment. Lead reaching surface waters is sorbed to suspended solids and sediments (EPA 1982a).

Lead is released into surface water from lead shot and lead sinkers. A study of a shooting range in Southwestern Virginia found that the dissolved lead content of surface water ranged up to 473 ppb with the highest concentrations closest to the backstop (Craig et al. 1999). Upstream from the site the lead concentration was 0.5 ppb. In 1991, the U.S. Fish and Wildlife Service banned the use of lead shot when hunting waterfowl, such as geese or ducks, in order to avoid releasing lead directly to surface water.

Although aquatic releases of lead from industrial facilities are expected to be small with respect to emissions to land and air, lead may be present in significant levels in drinking water. In areas receiving acid rain (e.g., northeastern United States) the acidity of drinking water may increase; this increases the corrosivity of the water, which may, in turn, result in the leaching of lead from water systems, particularly from older systems during the first flush of water through the pipes (McDonald 1985). In addition, the grounding of household electrical systems to the plumbing can increase corrosion rates and the subsequent leaching of lead from the lead solder used for copper pipes. The age of a home or building and the type of plumbing installed will be a major factor regarding the levels of lead in drinking water (EPA 2005h). Lead-contaminated drinking water is most problematic in buildings and residences that are either very old or very new. It was not uncommon to use lead pipes for interior plumbing purposes at the start of the 20th century in the United States. Also, lead piping was often used for the service connections that join residences to public water supplies (this practice ended only recently in some localities). Plumbing installed before 1930 is most likely to contain lead pipes. In most new homes, copper pipes have replaced lead pipes and lead-free solder is used. However, lead-free means that solders and flux may not contain >0.2% lead, while pipes, pipe fittings, and well pumps may not contain >8% lead. New brass faucets and fittings can also leach lead, which is released directly into the water. Lead levels

decrease as the residence ages because as time passes, mineral deposits form a coating on the inside of the pipes, which insulates the water from the lead.

Lead has been identified in groundwater samples collected at 949 of the 1,272 NPL hazardous waste sites, and in surface water samples collected at 567 of the 1,272 NPL hazardous waste sites where it was detected in some environmental medium (HazDat 2006).

6.2.3 Soil

According to the TRI, in 2004, a total of 13,725,870 pounds of lead were released to the land, both on-site and off-site, by 4,337 reporting facilities (TRI04 2006). Table 6-1 lists amounts of lead released from these facilities grouped by state. In addition, a total of 408,893,442 pounds of lead compounds were released to land, both on-site and off-site, by 4,294 reporting facilities (TRI04 2006). Table 6-2 lists amounts of lead compounds released from these facilities grouped by state. In addition, 184,525 and 8,773,829 pounds of lead and lead compounds, respectively, were injected underground. Ninety-seven percent of lead compounds injected underground were by one facility, Kennecott Greens Creek Mining Co. in Juneau, Alaska. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

While the majority of lead releases are to land, they constitute much lower exposure risks than releases to air and water. In 1997, before new industries were added to TRI, 95% of lead and lead compound releases to land reported to TRI were from the primary metals industrial sector, primarily metal smelters. In 2004, metal mining, coal mining, electrical utilities, and Resource Conservation and Recovery Act (RCRA)/solvent recoveries (hazardous waste facilities), as well as primary metals, are the industrial sectors contributing most heavily to releases to land. Many of these facilities with large releases, such as metal mines, are located in sparsely populated areas. Hazardous waste facilities are highly regulated. Most of the lead released to land becomes tightly bound and immobile.

Lead-containing material from home and commercial use may be sent to municipal landfills. It is important to note that land is the ultimate repository for lead, and lead released to air and water ultimately is deposited in soil or sediment. For example, lead released to the air from leaded gasoline or in stack gas from smelters and power plants will settle on soil, sediment, foliage, or other surfaces. The heaviest contamination occurs near the highway, in the case of leaded gasoline, or near the facility, in the case of a power plant or smelter.

Lead has been identified in soil samples collected at 901 of the 1,272 NPL hazardous waste sites, and in sediment samples collected at 605 of the 1,272 NPL hazardous waste sites where it was detected in some environmental medium (HazDat 2006).

6.2.4 Paint

Although the sale of residential lead-based paint was banned in the United States in 1978, flaking paint, paint chips, and weathered powdered paint, which are most commonly associated with deteriorated housing stock in urban areas, remain major sources of lead exposure for young children residing in these houses, particularly for children afflicted with pica (the compulsive, habitual consumption of nonfood items) (Bornschein et al. 1986; EPA 1986a). Lead concentrations of 1–5 mg/cm^2 have been found in chips of lead-based paint (Billick and Gray 1978), suggesting that consumption of a single chip of paint would provide greater short-term exposure than any other source of lead (EPA 1986a). An estimated 40–50% of occupied housing in the United States may contain lead-based paint on exposed surfaces (Chisolm 1986).

In the late 1980s, the U.S. Department of Housing and Urban Development (HUD) conducted a national survey of lead-based paint in housing. The EPA subsequently sponsored a comprehensive technical report on the HUD-sponsored survey to provide estimates of the extent of lead-based paint in housing. In the EPA report, a home is considered to have lead-based paint if the measured lead concentration on any painted surface is ≥1.0 mg/cm^2. The EPA report estimates that 64 million (±7 million) homes, or 83% (±9%) of privately-owned housing units built before 1980, have lead-based paint somewhere in the building. Approximately 12 million (±5 million) of these homes are occupied by families with children under the age of 7 years. Approximately 49 million (±7 million) privately owned homes have lead-based paint in their interiors. By contrast, approximately 86% (±8%) of all pre-1980 public housing family units have lead-based paint somewhere in the building (EPA 1995c).

Damaged lead-based paint is associated with excessive dust lead levels. Approximately 14 million homes (19% of pre-1980 housing) have >5 square feet of damaged lead-based paint, and nearly half (47%) of those homes have excessive dust lead levels (EPA 1995c).

In the Cincinnati prospective lead study of public and private low- and moderate-income housing, the lead concentration ranges were: painted interior walls, 0.1–35 mg/cm^2; interior home surface dust, 0.04–

39 mg/m^2 and 72–16,200 µg/g; interior home dustfall, 0.0040–60 mg/m^2/30 days; exterior dust scrapings, 20–108,000 µg/g; and dust on children's hands, 1–191 µg. The lead levels in older private deteriorating or dilapidated housing were higher than the levels in newer public and rehabilitated housing (Clark et al. 1985).

Releases from lead-based paints are frequently confined to the area in the immediate vicinity of painted surfaces, and deterioration or removal of the paint can result in high localized concentrations of lead in dust in air (from sanding and sandblasting) and on exposed surfaces. A study was conducted in New Orleans where power sanding is a common practice during repainting old houses and median, 90^{th} percentile, and maximum lead concentrations in 31 study houses were 35, 126, and 257 mg/g, respectively (Mielke et al. 2001). Lead concentrations in dust and soil samples from one study of a house where the paint chips contained about 90 mg Pb/g were very high. If the house had been sanded down to bare wood, 7.4 kg of lead would have been released to the environment. Disturbance of older structures containing lead-based paints is now a significant contributor to total lead releases.

The authors of a report of findings from the Third National Health and Nutrition Examination Survey (NHANES III), conducted in 1988–1991, comment that of the multiple sources of exposure, lead-based paint is the principal high-dose source of lead. Exposure occurs not only through the direct ingestion of flaking and chalking paint, but also through the inhalation of dust and soil contaminated with paint (Brody et al. 1994). According to a study by the New York State Department of Health, renovation and remodeling activities that disturb lead-based paints in homes can produce significant amounts of lead dust, which can be inhaled or ingested (CDC 1997d).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

In the atmosphere, non-organic compounds of lead exist primarily in the particulate form. The median particle distribution for lead emissions from smelters is 1.5 µm with 86% of the particle sizes under 10 µm (Corrin and Natusch 1977). The smallest lead-containing particulate matter (<1 µm) is associated with high-temperature combustion processes. Upon release to the atmosphere, lead particles are dispersed and ultimately removed from the atmosphere by wet or dry deposition. Approximately 40–70% of the deposition of lead is by wet fallout; 20–60% of particulate lead once emitted from automobiles is deposited near the source. An important factor in determining the atmospheric transport of lead is particle size distribution. Large particles, particularly those with aerodynamic diameters of >2 µm, settle out of

the atmosphere fairly rapidly and are deposited relatively close to emission sources (e.g., 25 m from the roadway for those size particles emitted in motor vehicle exhaust in the past); smaller particles may be transported thousands of kilometers. The dry deposition velocity for lead particles with aerodynamic diameters of 0.06–2.0 μm was estimated to range between 0.2 and 0.5 cm/second in a coniferous forest in Sweden, with an overall particle-size weighted dry deposition velocity of 0.41 cm/second (Lannefors et al. 1983). However, the use of an average net deposition velocity of 0.6 cm/second and an average atmospheric residence time of 10 days has been recommended by the National Academy of Sciences (NAS 1980). The amount of lead scavenged from the atmosphere by wet deposition varies widely; wet deposition can account for 40–70% of lead deposition depending on such factors as geographic location and amount of emissions in the area (Nielsen 1984). An annual scavenging ratio (concentration in precipitation, mg/L, to concentration in air, $\mu g/m^3$) of 0.18×10^{-6} has been calculated for lead, making it the lowest value among seven trace metals studied (iron, aluminum, manganese, copper, zinc, cadmium); this indicates that lead (which initially exists as fine particles in the atmosphere) is removed from the atmosphere by wet deposition relatively inefficiently. Wet deposition is more important than dry deposition for removing lead from the atmosphere; the ratio of wet to dry deposition was calculated to be 1.63, 1.99, and 2.50 for sites in southern, central, and northern Ontario, Canada, respectively (Chan et al. 1986). While lead particles from automobile emissions are quite small (<0.1 μm in diameter), they may coagulate, resulting in larger particulates (Chamberlain et al. 1979). Lead has been found in sediment cores of lakes in Ontario and Quebec, Canada far from any point sources of lead releases, suggesting that long-range atmospheric transport was occurring (Evans and Rigler 1985). However, the results reported by Allen-Gil et al. (1997) do not support the contention of long-range transport of lead from smelters in the Arctic, based on lead concentrations in sediments obtained from Arctic lakes in the United States. In fact, data summarized by Berndtsson (1993) indicate that local sources dominate the deposition of lead; lead is primarily deposited <10 kilometers from emission sources.

The amount of soluble lead in surface waters depends upon the pH of the water and the dissolved salt content. Equilibrium calculations show that at pH >5.4, the total solubility of lead is approximately 30 μg/L in hard water and approximately 500 μg/L in soft water. Sulfate ions, if present in soft water, limit the lead concentration in solution through the formation of lead sulfate. Above pH 5.4, the lead carbonates, $PbCO_3$ and $Pb_2(OH)_2CO_3$, limit the amount of soluble lead. The carbonate concentration is in turn dependent upon the partial pressure of carbon dioxide, pH, and temperature (EPA 1986a).

A significant fraction of lead carried by river water is expected to be in an undissolved form, which can consist of colloidal particles or larger undissolved particles of lead carbonate, lead oxide, lead hydroxide,

or other lead compounds incorporated in other components of surface particulate matters from runoff. Lead may occur either as sorbed ions or surface coatings on sediment mineral particles, or it may be carried as a part of suspended living or nonliving organic matter in water. The ratio of lead in suspended solids to lead in dissolved form has been found to vary from 4:1 in rural streams to 27:1 in urban streams (NSF 1977).

The fate of lead in soil is affected by the adsorption at mineral interfaces, the precipitation of sparingly soluble solid forms of the compound, and the formation of relatively stable organic-metal complexes or chelates with soil organic matter. These processes are dependent on such factors as soil pH, soil type, particle size, organic matter content of soil, the presence of inorganic colloids and iron oxides, cation exchange capacity (CEC), and the amount of lead in soil (NSF 1977; Reddy et al. 1995). Soil samples were extracted from the Powder River Basin in Wyoming to determine the relative distribution and speciation of lead and other metals in acidic environments (Reddy et al. 1995). At near neutral pH, organic carbon-lead complexes were the predominant species in the soil water extracts. At low pH, dissolved lead in ionic form (Pb^{2+}) and ion pairs (e.g., $PbSO_4$) were the predominant species. It was concluded that the mobility of lead will increase in environments having low pH due to the enhanced solubility of lead under acidic conditions. The accumulation of lead in most soils is primarily a function of the rate of deposition from the atmosphere. Most lead is retained strongly in soil, and very little is transported through runoff to surface water or leaching to groundwater except under acidic conditions (EPA 1986a; NSF 1977). Clays, silts, iron and manganese oxides, and soil organic matter can bind metals electrostatically (cation exchange) as well as chemically (specific adsorption) (Reed et al. 1995). Lead is strongly sorbed to organic matter in soil, and although not subject to leaching, it may enter surface waters as a result of erosion of lead-containing soil particulates. Lead bromochloride, the primary form of lead emitted from motor vehicles, which once burned leaded gasoline in the presence of organohalogen scavenger compounds, are converted to the less soluble lead sulfate either by reactions in the atmosphere or by reactions at the soil surface, thus limiting it's mobility in soil. It has been determined that lead oxides, carbonates, oxycarbonates, sulfates, and oxysulfates become the most prominent constituents of aged automobile exhaust particles (i.e., those collected at locations more remote from traffic sources) (Ter Haar and Bayard 1971). Lead may also be immobilized by ion exchange with hydrous oxides or clays or by chelation with humic or fulvic acids in the soil (Olson and Skogerboe 1975). In soils with pH $\geq$5 and with at least 5% organic matter content, atmospheric lead is retained in the upper 2–5 cm of undisturbed soil. Inorganic lead may be bound into crystalline matrices of rocks and remain essentially immobile; it can also occur in water entrapped in soil macro- and micropores (Reed et al. 1995). Lead complexes and precipitates in soil. In soil with high organic matter content and a pH of 6–8, lead may form insoluble

organic lead complexes; if the soil has less organic matter at the same pH, hydrous lead oxide complexes may form or lead may precipitate out with carbonate or phosphate ions. At a pH of 4–6, the organic lead complexes become soluble and leach out or may be taken up by plants (EPA 1986a). Entrainment or suspension of soil particles in moving air is another route of lead transport (EPA 1982c). This process may be important in contributing to the atmospheric burden of lead around some lead smelting facilities and NPL sites that contain elevated levels of lead in soil.

The downward movement of elemental lead and inorganic lead compounds from soil to groundwater by leaching is very slow under most natural conditions except for highly acidic situations (NSF 1977). The conditions that induce leaching are the presence of lead in soil at concentrations that either approach or exceed the CEC of the soil, the presence of materials in soil that are capable of forming soluble chelates with lead, and a decrease in the pH of the leaching solution (e.g., acid rain) (NSF 1977). Favorable conditions for leaching may be present in some soils near lead smelting and NPL sites. Tetraalkyl lead compounds, such as tetraethyl lead, are insoluble in water and would not be expected to leach in soil. However, they can be transported through a soil column when it is present in a migrating plume of gasoline (USAF 1995). In aqueous media, tetraalkyl lead compounds are first degraded to their respective ionic trialkyl lead species and are eventually mineralized to inorganic lead (Pb^{2+}) by biological and chemical degradation processes (Ou et al. 1995).

Plants and animals may bioconcentrate lead, but biomagnification is not expected. In general, the highest lead concentrations are found in aquatic and terrestrial organisms with habitats near lead mining, smelting, and refining facilities; storage battery recycling plants; areas affected by high automobile and truck traffic; sewage sludge and spoil disposal areas; sites where dredging has occurred; areas of heavy hunting and fishing (lead from spent shot or sinkers); and in urban and industrialized areas. Lead may be present on plant surfaces as a result of atmospheric deposition; its presence in internal plant tissues indicates biological uptake from the soil and leaf surfaces. Although the bioavailability of lead in soil to plants is limited because of the strong adsorption of lead to soil organic matter, the bioavailability increases as the pH and the organic matter content of the soil are reduced. Plants grown in lead-contaminated soils were shown to accumulate low levels of lead in the edible portions of the plant from adherence of dusts and translocation into the tissues (Finster et al. 2004). Thirty-two different types of fruits or vegetables were grown in urban gardens with soils containing high lead levels (27–4,580 mg/kg). Samples were harvested and washed with either water or detergents and analyzed for lead content. Only one fruiting vegetable among 52 samples contained lead levels greater than the detection limit of 10 μg/g

in the edible portion. However, 39% of the leafy vegetables and herbs had lead levels >10 μg/g in the edible shoot portion following washing of the vegetables with detergent and water (Finster et al. 2004).

Lead may be taken up in edible plants from the soil via the root system, by direct foliar uptake and translocation within the plant, and by surface deposition of particulate matter. The amount of lead in soil that is bioavailable to a vegetable plant depends on factors such as cation exchange capacity, pH, amount of organic matter present, soil moisture content, and type of amendments added to the soil. Background agricultural soil lead concentrations for major growing areas of the United States have been determined (Holmgren et al. 1993).

The influence of various combinations of soil amendments on lead uptake by soybeans was studied for a metal-contaminated alluvial soil (Pierzynski and Schwab 1993). Addition of limestone was found to be most effective in reducing the bioavailability of metals (including lead) as indicated by the reduction in labile soil metals, increased yields, and decreased soybean tissue metal content. Uptake of metals by lettuce and radishes grown in a loam soil spiked with cadmium chloride and lead nitrate (from 100 to 1,000 mg/kg) was also studied (Nwosu et al. 1995). Results indicated that the mean uptake of lead by lettuce increased as the concentration of lead rose in the soil mixture. However, the uptake was low and this finding is inconsistent with other reports. Lead was not bioaccumulated by either plant regardless of soil lead concentrations. The response of kidney bean growth to the concentration and chemical form of lead in soils obtained near a zinc smelter in Japan has been studied (Xian 1989). It was found that the amount of lead in the total plant (approximately 35–80 μg) correlated strongly with the concentration of lead in the soil (0–240 mg/kg). The best relationship was found between the amount of metal uptake and the concentration of exchangeable and carbonate forms of lead in the soil.

Uptake of lead in animals may occur as a result of inhalation of contaminated ambient air or ingestion of contaminated plants. However, lead is not biomagnified in aquatic or terrestrial food chains. Older organisms tend to contain the greatest body burdens of lead. In aquatic organisms, lead concentrations are usually highest in benthic organisms and algae, and lowest in upper trophic level predators (e.g., carnivorous fish). Exposure of a fresh-water fish to several sublethal concentrations of lead for a period of 30 days showed significant accumulation of lead in the blood and tissues. The lead accumulation in tissues was found to increase with lead in water up to a concentration of 5 mg/L (μg/mL); at concentrations of 10 and 20 mg/L, the lead accumulation in the tissues, although indicating an increase, was not proportional to the lead concentration in water (Tulasi et al. 1992). High bioconcentration factors (BCFs) were determined in studies using oysters (6,600 for *Crassostrea virginica*), fresh-water algae (92,000 for

Senenastrum capricornutum), and rainbow trout (726 for *Salmo gairdneri*). However, most median BCF values for aquatic biota are significantly lower: 42 for fish, 536 for oysters, 500 for insects, 725 for algae, and 2,570 for mussels (Eisler 1988). Lead is toxic to all aquatic biota, and organisms higher up in the food chain may experience lead poisoning as a result of eating lead-contaminated food. Organolead compounds, such as trialkyl and tetraalkyl lead compounds, are more toxic than inorganic forms and have been shown to bioconcentrate in aquatic organisms.

Biomagnification of organolead compounds has not been found to occur. Depuration is relatively rapid, with half-life values of 30–45 hours for rainbow trout exposed to tetramethyl lead. Tetraalkyl lead compounds are more toxic than trialkyl lead compounds, and ethyl forms are more toxic than methyl forms (Eisler 1988). Isolation of a *Pseudomonas aeruginosa* strain designated CHL004, which is able to remove lead from solidified media and soil, has been reported (Vesper et al. 1996). The rate of uptake of lead nitrate by CHL004 was very rapid initially and then decreased greatly.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Information available regarding the chemistry of lead in air is limited. Before the ban on sales of leaded gasoline, lead particles were emitted to the atmosphere from automobile exhaust as lead halides (mostly PbBrCl) and as double salts with ammonium halides (e.g., $2PbBrCl \cdot NH_4Cl$, $Pb_3[PO_4]_2$, and $PbSO_4$) (Biggins and Harrison 1979; Ter Haar and Bayard 1971). After 18 hours, approximately 75% of the bromine and 30–40% of the chlorine was released, and lead carbonates, oxycarbonates and oxides were produced. These lead oxides are subject to further weathering to form additional carbonates and sulfates (Olson and Skogerboe 1975). Lead particles are emitted from mines and smelters primarily in the form of elemental lead and lead-sulfur compounds, $PbSO_4$, $PbO \cdot PbSO_4$, and PbS (Corrin and Natusch 1977; EPA 1986a; Spear et al. 1998). The lead emitted from the combustion of waste oil was found to be in the form of $PbCl_2$, PbO, and elemental lead (Pb^0) (Nerin et al. 1999). In the atmosphere, lead exists primarily in the form of $PbSO_4$ and $PbCO_3$. It is not completely clear how the chemical composition of lead changes during dispersion (EPA 1986a).

Tetraalkyl lead compounds, once added to gasoline, are no longer present in significant quantities in the air. However, their degradation products are still present. Based on the vapor pressure of tetraethyl lead (0.26 mm Hg at 25 °C) and tetramethyl lead (26.0 mm Hg at 20 °C), these two compounds exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981). When exposed to sunlight, they

decompose rapidly to trialkyl and dialkyl lead compounds, and eventually to inorganic lead oxides by a combination of direct photolysis, reaction with hydroxyl radicals, and reaction with ozone. The half-life of tetraethyl lead in reactions with hydroxyl radicals during summer is approximately 5.7 hours, based on a rate constant of $6.8x10^{-11}$ cm^3/molecule - sec (Nielsen et al. 1991). The half-life for tetramethyl lead is about 65 hours based on a rate constant of $5.9x10^{-12}$ cm^3/molecule - sec. In the winter, both compounds have half-lives of up to several days since the concentration of atmospheric hydroxyl radicals is lower than in summer months (DeJonghe and Adams 1986). Trialkyl compounds occur almost entirely in the vapor phase and have life-times in air that are 3 times longer than for the corresponding tetraalkyl compounds (Hewitt and Harrison 1986, 1987). Dialkyl compounds occur almost entirely in particulate form. Because of the relatively high water solubility of trialkyl and dialkyl lead compounds, washout in wet deposition would be the major process for removing these compounds from air. Dialkyl lead compounds would be removed from the air by dry deposition. Adsorption of tetraethyl and tetramethyl lead to atmospheric particles does not appear to be an important fate process (DeJonghe and Adams 1986; EPA 1985a). Monitoring studies in England indicate that urban air advected to rural areas may contain up to 5% of total lead as alkyl lead; this percentage may increase to 20% for maritime air, with trialkyl lead being the predominant species (Hewitt and Harrison 1987).

6.3.2.2 Water

The chemistry of lead in aqueous solution is highly complex because this element can be found in multiple forms. Lead has a tendency to form compounds of low solubility with the major anions found in natural waters. The amount of lead dissolved in surface waters is dependent on the pH and the dissolved salt content of the water. The maximum solubility of lead in hard water is about 30 μg/L at pH>5.4 and the maximum solubility of lead in soft water is approximately 500 μg/L at pH>5.4 (EPA 1977). In the environment, the divalent form (Pb^{2+}) is the stable ionic species of lead. Hydroxide, carbonate, sulfide, and, more rarely, sulfate may act as solubility controls in precipitating lead from water. At pH<5.4, the formation of lead sulfate limits the concentration of soluble lead in water, while at pH>5.4, the formation of lead carbonates limits the amount of soluble lead (EPA 1979). The relatively volatile organolead compound, tetramethyl lead, may form as a result of biological alkylation of organic and inorganic lead compounds by microorganisms in anaerobic lake sediments; however, if the water over the sediments is aerobic, volatilization of tetramethyl lead from the sediments is not considered to be important because the tetramethyl lead will be oxidized (EPA 1979).

The speciation of lead was found to differ in fresh water and seawater. In fresh water, lead may partially exist as the divalent cation (Pb^{2+}) at pHs below 7.5, but complexes with dissolved carbonate to form insoluble $PbCO_3$ under alkaline conditions (Long and Angino 1977). Even small amounts of carbonate ions formed in the dissolution of atmospheric CO_2 are sufficient to keep lead concentrations in rivers at the 500 µg/L solubility limit (EPA 1979). Lead chloride and lead carbonate are the primary complexes formed in seawater (Long and Angino 1977). The speciation of lead in water is also dependent on the presence of other ligands in water. Lead is known to form strong complexes with humic acid and other organic matter (Denaix et al. 2001; Gao et al. 1999; Guibaud et al. 2003). Lead-organic matter complexes are stable to a pH of 3 with the affinity increasing with increasing pH, but decreasing with increased water hardness (EPA 1979). In seawater, there is the presence of lead complexed to Fe-Mn oxides, which is due to the content of these oxides in seawater (Elbaz-Poulichet et al. 1984). Sorption of lead to polar particulate matter in freshwater and estuarine environments is an important process for the removal of lead from these surface waters. The adsorption of lead to organic matter, clay and mineral surfaces, and coprecipitation and/or sorption by hydrous iron and manganese oxides increases with increasing pH (EPA 1979).

In water, tetraalkyl lead compounds, such as tetraethyl lead and tetramethyl lead, are subject to photolysis and volatilization. Degradation proceeds from trialkyl species to dialkyl species, and eventually to inorganic lead oxides. Removal of tetraalkyl lead compounds from seawater occurs at rates that provide half-lives measurable in days (DeJonghe and Adams 1986). Some of the degradation products include trialkyl lead carbonates, hydroxides, and halides. These products are more persistent than the original tetraalkyl lead compounds.

6.3.2.3 Sediment and Soil

Lead in its naturally-occurring mineral forms is a very minor component of many soils in the United States. Additional sources of lead are incorporated to soils from atmospheric wet and dry deposition. Since the ban on leaded gasoline, the major source of lead emissions to the environment arise from industrial processes (EPA 1996b). Smelters in Pennsylvania, Missouri, and Nebraska are among the top 10 emitters. Lead particles emitted from mining operations and smelters are primarily in the form of lead-sulfur compounds $PbSO_4$, $PbO{\cdot}PbSO_4$, and PbS (EPA 1986a). In the atmosphere, lead most likely exists primarily as $PbSO_4$ and $PbCO_3$ and is deposited onto soil as lead sulfates and lead carbonates. Organic tetraalkyl lead compounds, once used extensively in motor fuel, are emitted from automobiles primarily in the form of lead bromochloride, which is ultimately transformed to lead sulfate. The organolead

compounds also undergo photolysis and other reactions in the atmosphere to form lead carbonates, oxycarbonates, and oxides. Once these compounds encounter components of the soil, further reactions can occur, resulting in a complex variety of lead compounds. The speciation of lead in soils is dependent upon the properties of the soil. In a calcareous soil, PbSO4 and PbCO3 were shown to account for <5% of the total lead content, whereas in road side dust, $PbSO_4$, elemental lead, Pb_3O_4, $PbO{\cdot}PbSO_4$, and $2PbCO_3{\cdot}Pb(OH)_2$ were present in significant quantities (Chaney et al. 1988). It was also reported that after adding 3,000–4,000 mg/kg of lead in the form of PbSO4, subsequent extractions revealed that the lead sulfate was rapidly transformed to other lead compounds in the soil (Chaney et al. 1988).

Nearly all forms of lead that are released to soil from anthropogenic sources, such as $PbSO_4$, $PbCO_3$, PbS, $Pb(OH)_2$, $PbCrO_4$, and PbClBr, are transformed by chemical and biotic processes to adsorbed forms in soil (Chaney et al. 1988). The transformation process involves the formation of lead complexes with binding sites on clay minerals, humic acid and other organic matter, and hydrous iron oxides (Chaney et al. 1988; Chuan et al. 1996; Sauve et al. 1997). The ability of soils to bind lead is dependent on soil pH and the cation exchange capacity of the soil components (e.g., hydrous iron oxides on clay and organic matter) (Chaney et al. 1988; EPA 1986a). Only a small fraction (0.1–1%) of lead appears to remain water-soluble in soil (Khan and Frankland 1983). The solubility of lead in soil is dependent on pH, being sparingly soluble at pH 8 and becoming more soluble as the pH approaches 5 (Chuan et al. 1996). Between pH 5 and 3.3, large increases in lead solubility in soil are observed. These changes in lead solubility appear to correlate with the pH-dependent adsorption and dissolution of Fe-Mn oxyhydroxides. In addition to pH, other factors that influence lead solubility in soil are total lead content and the concentrations of phosphate and carbonate in soils (Bradley and Cox 1988; Ge et al. 2000; Pardo et al. 1990; Sauve et al. 1997).

Since the ban on the use of leaded gasoline, atmospheric lead deposition to soil has decreased considerably. However, the deposited organolead compounds and their transformation products remain in the soil. Limited data indicate that tetraethyl and tetramethyl lead are converted into water-soluble lead compounds in soil through microbial metabolism (Ou et al. 1994). Using an Arredondo fine sand from Florida (92% sand, 7% silt, 1% clay, 11.8 g/kg organic carbon, pH 5.5), tetraethyl lead was shown to degrade sequentially to monoionic triethyl lead, diionic diethyl lead, and eventually Pb^{+2} (Ou et al. 1994). Experiments were conducted using non sterilized and autoclaved soil samples. The presence of monoionic triethyl lead and diionic diethyl lead was generally lower in the autoclaved samples, suggesting that both abiotic and biotic mechanisms are responsible for the degradation of tetraethyl lead. At the end of a 28-day incubation period, no tetraethyl lead was present in the soil; however, there were

significant quantities of monoionic triethyl lead and diionic diethyl lead, which suggest that the degradation products are more persistent than the original species. Although tetraethyl and tetramethyl lead are not expected to leach significantly through soil, their more water-soluble metabolites may be subject to leaching (EPA 1985a).

In a study of lead migration in forest soils in Vermont, Miller and Friedland (1994) used lead deposition time series and measurements of organic soil horizon lead content made in 1966, 1980, and 1990 to compute dynamic response times for lead storage in several types of soil. The authors concluded that maximum lead concentrations in organic soil occurred around 1980, with concentrations of about 85 μg/g in soils of the northern hardwood forests of the study area and about 200 μg/g in soils of the spruce-fir forests. The large surge of atmospheric lead deposited in these forests during the time when leaded gasoline was routinely used in motor vehicles is being redistributed in the soil profile rather than being retained in the organic horizon. Based on an analysis of lead transit times through mineral soil horizons, the pulse of lead may begin to be released to upland streams sometime in the middle of the next century (Miller and Friedland 1994). However, Wang et al. (1995) observed that lead migration in forest soils is slowed considerably due to a decrease in solubility when lead moves from the soil surface horizon to streams. Their results suggest that lead is effectively trapped in the subsurface soil horizons, which may greatly reduce its release to streams.

Lead content in plants is largely the result of atmospheric deposition. This is due to the strong retention of particulate matter on plant surfaces that is difficult to remove through washing (EPA 1977). Some plants are capable of taking up lead from soil through their root systems, although this uptake does not appear to be appreciable (IARC 1980; Nwosu et al. 1995). The distribution of lead in plants is mainly in the roots and much less in the stems or leaves (Deng et al. 2004; Nan and Cheng 2001). Eventually, the lead will be returned to soil when these plants decay unless they are harvested (to possibly enter the food chain) or removed (EPA 1986a).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to lead depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of lead in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on lead levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to

the amount that is bioavailable. The analytical methods available for monitoring lead in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Lead levels in the ambient air have been monitored in a number of remote, urban, and nonurban areas of the United States and other countries (EPA 1986a). Atmospheric lead concentrations vary widely, but usually decrease with vertical and horizontal distance from emission sources; they are generally 0.3–0.8 times lower indoors than outdoors, with an average ratio of 0.5. Lead levels in ambient air range from $7.6x10^{-5}$ μg/m^3 in remote areas such as Antarctica (Maenhaut et al. 1979) to >10 μg/m^3 near stationary sources such as smelters. Due to decreases in lead emissions to the atmosphere from automobiles, the level of lead in air has declined significantly over the past 3 decades. Monitoring data from a composite of 147 sampling sites throughout the United States indicated that the maximum quarterly average lead levels in urban air were 0.36 μg/m^3 during 1984 and 0.2–0.4 μg/m^3 during 1986 (EPA 1986a, 1989e). Between 1979 and 1983, lead concentrations in precipitation in Minnesota decreased from 29 to 4.3 μg/L at urban locations and from 5.7 to 1.5 μg/L at rural locations, indicating a reduction in lead emissions of >80%. This reduction resulted primarily from the decreased use of leaded gasoline and the use of more efficient emission controls on stationary lead sources (Eisenreich et al. 1986).

Since 1979, elemental concentrations of fine particles have been monitored in remote areas of the United States in networks operated for the National Park Service (NPS) and the EPA (Eldred and Cahill 1994). Lead at all sites decreased sharply through 1986, corresponding to the shift to unleaded gasoline, but has since leveled off at 1–2 ng/m^3 (0.001–0.002 μg/m^3), which is approximately 18% of the 1982 mean. The elevated lead concentrations (up to 5 ng/m^3) since 1986 at 3 of the 12 sites are thought to be associated with mining activity.

In the 1960s, the National Air Surveillance Network (NASN) was established to monitor ambient air quality levels of total particulate solids and trace metals, including lead, at sites in larger American cities. In 1981 some old sites were eliminated and new ones were added to give 139 urban sites for air monitoring purposes. In 1988, the average lead concentration for all 139 sites was 0.085 μg/m^3, well below the National Ambient Air Quality Standard of 1.5 μg/m^3, quarterly average concentration, that has been established for lead (EPA 1996b). Data from the EPA National Air Quality Monitoring Program indicated that the 2002 average air quality concentration for lead is about 94% lower than in the early 1980s, with a mean atmospheric concentration below 0.05 μg/m^3 in 2002 (EPA 2005k). In 1988, the

average concentration of 18-point-source sites was 0.4 μg/m^3, down from 2.9 μg/m^3 in 1979, and the average concentration for urban sites was 0.1 μg/m^3, down from 0.8 μg/m^3 in 1979 (EPA 1990). This decrease was undoubtedly caused by decreased use of leaded gasoline in the period leading up to its total ban after December 1995. Composite urban air concentrations of lead for 1989 and 1991 were 0.11 and 0.08 μg/m^3 (EPA 1996b). Although lead concentration in urban air continues to decline, there are indications that the rate of decline has slowed. Between 1976 and 1995, ambient concentrations of lead in the United States declined by 97%. Between 1994 and 1995, national average lead concentrations remained unchanged at 0.04 μg/m^3 even though lead emissions declined 1% (EPA 1996b).

Concentrations of lead in ambient air that result from emission, both mobile and stationary, have been estimated to average 0.0058 μg/m^3 in 1996, while the concentration of lead attributed to mobile sources alone was 0.0035 μg/m^3 (EPA 2001a).

Lead concentrations in air and dust in the indoor environment were measured in residential homes as part of the National Human Exposure Assessment Survey (NHEXAS) in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin). Mean (±1 standard deviation [SD]) and median concentrations of lead in indoor air from 213 residences were 15.2 ng/m^3 (37.6 ng/m^3) and 6.17 ng/m^3, respectively, with a maximum value of 293.5 ng/m^3 (Bonanno et al. 2001). The median lead concentration in outdoor air was 8.84 ng/m^3 (Clayton et al. 2002). Lead concentrations were higher in households where one or more residents smoked indoors (mean concentration of 21.8 ng/m^3) as compared to households with nonsmoking residents (mean concentration of 7.79 ng/m^3) (Bonanno et al. 2001). In dust collected from the living areas of 238 residences, the mean (±1 SD) and median lead concentrations were 467.4 μg/g (2,100 μg/g) and 131.6 μg/g, respectively, with a maximum value of 30,578 μg/g. Dust samples collected from window sills had mean (±1 SD) and median lead concentrations of 987 μg/g (2,723 μg/g) and 207.5 μg/g, respectively, with a maximum value of 21,120 μg/g. For both indoor air and dust measurements, higher concentrations of lead were correlated with dilapidated and suburban homes.

In another analysis of the NHEXAS EPA Region V data, Pellizzari et al. (1999) looked at potential differences in lead concentrations in indoor air and personal air exposures between minorities (e.g., Hispanics and African-Americans) and nonminorities (e.g., Caucasian). Some differences were noted in the mean (±1 SD) lead concentrations between minorities of 57 ng/m^3 (±24 ng/m^3) and nonminorities of 22 ng/m^3 (±3.4 ng/m^3) in personal air exposures, although the differences were not significant (p=0.147). Similarly, differences were noted between minorities (26±12 ng/m^3) and nonminorities (13±2.6 ng/m^3) in indoor air, although these too were not significantly different (p=0.266). When the age of the home was

considered in the analysis, it was found that lead concentrations were significantly (p=0.036) higher in homes built before 1940 than in homes built between 1960 and 1979, with mean (±1 SD) values of 46 ng/m^3 (±1.6 ng/m^3) and 13 ng/m^3 (±2.1 ng/m^3), respectively. The lead concentrations measured in indoor air in homes built before 1940 were not significantly different from mean (±1 SD) lead concentrations of 22 ng/m^3 (±5.1 ng/m^3) and 23 ng/m^3 (±5.1 ng/m^3) measured in indoor air in homes built between 1940 and 1959 and between 1980 and 1995, respectively.

6.4.2 Water

Lead has been monitored in surface water, groundwater, and drinking water throughout the United States and other countries. The concentration of lead in surface water is highly variable depending upon sources of pollution, lead content of sediments, and characteristics of the system (pH, temperature, etc.). Levels of lead in surface water and groundwater throughout the United States typically range between 5 and 30 μg/L, although levels as high as 890 μg/L have been measured (EPA 1986a). Mean levels of lead in surface water measured at 50,000 surface water stations throughout the United States are 3.9 μg/L (based on 39,490 occurrences) (Eckel and Jacob 1988). The median lead level in natural river water is 5 μg/L, with a range of 0.6–120 μg/L (Bowen 1966). Lead levels in seawater are estimated as 0.005 μg/L (EPA 1982c). Lead concentrations in surface water are higher in urban areas than in rural areas (EPA 1982c). Using the EPA Storage and Retrieval (STORET) database, from January 1, 2005 to May 16, 2005, lead had been detected in surface water in Washington, Utah at concentrations of 20.5 and 142 μg/L and surface water from Salt Lake City, Utah at 7.75 μg/L (EPA 2005j). Lead was not detected above the detection limits in 224 other surface water samples obtained from various locations in Utah and Iowa over the sampling period (EPA 2005j).

Urban storm water runoff is an important source of lead entering receiving waterways. Lead is found in building material (brick, concrete, painted and unpainted wood, roofing, and vinyl), and automotive sources (brakes, used oil), which contribute to runoff (Davis et al. 2001). The largest contributing sources were siding and roofing.

Based on a survey of 900 public water supply systems, EPA (1988b) estimated that 99% of the 219 million people in the United States using public water supplies are exposed to drinking water with levels of lead <5 μg/L and approximately 2 million people are served by drinking water with levels of lead >5 μg/L. A survey of 580 cities in 47 states indicated that the national mean concentration of lead in drinking water was 29 μg/L after a 30-second flushing period (EPA 1986a, 1989e); however, it was

estimated that in 1988 the average lead content of drinking water decreased to 17 μg/L (Cohen 1988). In 1986, the Safe Drinking Water Act Amendments banned the use of lead solder or flux containing >0.2% lead and the use of lead pipes or fittings that contained >8% lead (EPA 1986a, 1989e).

In a more recent Federal Register notice (EPA 1991d), EPA examined the occurrences of lead in source water and distributed water. By resampling at the entry point to the distribution system, few samples were found to contain lead at levels above 5 μg/L. EPA now estimates that approximately 600 groundwater systems may have water leaving the treatment plant with lead levels above 5 μg/L. Based on several data sets, it is estimated that <1% of the public water systems in the United States have water entering the distribution system with lead levels above 5 μg/L. These systems are estimated to serve <3% of the population that receives drinking water from public systems (EPA 1991d).

Lead levels ranging between 10 and 30 μg/L can be found in drinking water from households, schools, and office buildings as a result of plumbing corrosion and subsequent leaching of lead. The combination of corrosive water and lead pipes or lead-soldered joints in either the distribution system or individual houses can create localized zones of high lead concentrations that exceed 500 μg/L (EPA 1989d).

Quantitative data on the nationwide range of lead levels in drinking water drawn from the tap (which would include lead corrosion by-product) were insufficient to assign a national value at the time of the 1991 EPA publication. One set of data comprised of 782 samples taken in 58 cities in 47 states shows that the average lead level in tap water was 13 μg/L with 90% of the values below 33 μg/L (EPA 1991d). In the NHEXAS study that was conducted during 1995–1996, lead concentrations were measured in tap drinking water (flushed for 15 minutes) taken from 82 homes in Arizona (O'Rourke et al. 1999), 441–444 homes in EPA Region V (Thomas et al. 1999), and 381 homes in Maryland (Ryan et al. 2000). Median lead concentrations of 0.4, 0.37, and 0.33 μg/L were determined in the Arizona, EPA Region V, and Maryland regional studies, respectively. Mean values (±1 SD) of 0.84 μg/L (±1.8 μg/L) and 1.08 μg/L (±2.01 μg/L) were calculated for the EPA Region V and Maryland studies, respectively, and are much lower than the mean concentrations of lead in drinking water determined in previous EPA estimates.

According to EPA's National Compliance Report for calendar year 1998 (EPA 1999), the vast majority of people in the nation received water from systems that had no reported violations of the maximum contaminant level and treatment technique requirements or significant monitoring and reporting requirements. Lead and copper are regulated in a treatment technique that requires systems to take tap

water samples at sites with lead pipes or copper pipes that have lead solder and/or are served by lead service lines. The water system is required to take treatment steps if the action level (15 μg/L for lead) is exceeded in >10% of tap water samples.

A survey of 1,484 drinking water samples taken from various districts of the American Water Works Service Company showed that average lead levels in a 1-L first-draw sample for copper, galvanized, and plastic pipes were 9, 4.2, and 4.5 μg/L, respectively. These data show that even plumbing that did not use lead solder for copper pipes (e.g., plastic pipes) contained significant levels of lead, primarily from the brass faucet fixtures, which are used in almost all plumbing. The brass fixtures may account for approximately one-third of the lead in the first-draw water (Lee et al. 1989). Lead levels are also known to increase when tap water is heated in boiling kettles that contain lead in their heating elements. Lead concentrations in tap water were found to vary depending on the age of nine homes in New Jersey. In homes built in the 1980s, median lead concentrations in the first-draw sample were higher (17.9 μg/L) than in first-draw samples (1.86 μg/L) taken from homes built in the 1970s (Murphy and Hall 2000). Leaching of lead from kitchen plumbing fixtures was given as the reason for the high lead concentrations in the first-draw samples. An additional water draw (>2 L) found decreased lead concentrations in tap water for all homes. However, the median concentration of lead in samples taken from homes built in the 1980s was higher (2.45 μg/L) than in samples taken from 1970s homes (0.14 μg/L). The lead concentrations in these higher volume samples are attributed to lead leaching from solder joints in basement piping and the water meter on the public water service line that may be more prevalent in the more recently built homes.

Concentrations of lead in water at NPL sites can be at much higher levels. For example, in 1986, an NPL hazardous waste site was identified in Genesee County, Michigan, that contained a landfill and nine surface impoundments. The facility had accepted sludge and residual waste from a chemical warehouse as well as other hazardous wastes. Water samples taken from the impoundments had a maximum lead concentration of 25 mg/L (EPA 1986b).

6.4.3 Sediment and Soil

Sediments contain considerably higher levels of lead than corresponding surface waters. Concentrations of lead in river sediments have been estimated at about 23 mg/kg (EPA 1982c; Fitchko and Hutchinson 1975), and concentrations of lead in coastal sediments range from 1 to 912 mg/kg with a mean value of 87 mg/kg (EPA 1982c; Nriagu 1978). Data from the STORET (1973–1979) database of Eastern and

Midwestern river basins indicates maximum lead concentrations in river sediments of 440–1,000 mg/kg, and mean lead concentrations of 27–267 mg/kg (EPA 1982c). More current data obtained from the EPA STORET database (from January 1, 2004 to May 16, 2005), showed that lead has been detected in sediment samples from Honolulu, Hawaii (0.75–6.2 mg/kg), various locations of South Carolina (<1–21 mg/kg), Dade County, Florida (4.7–17.9 mg/kg), and various locations in Tennessee (6–50 mg/kg) (EPA 2005k). Surface sediment concentrations in Puget Sound ranged from 13 to 53 mg/kg (Bloom and Crecelius 1987). An analysis of sediments taken from 10 lakes in Pennsylvania indicated that the elevated lead values were not derived from leaching of lead from the native rocks as a result of acid deposition, but rather originated from anthropogenic lead deposition (probably from automotive emissions) on the soil surface and subsequent runoff of soil particulates into the lake (Case et al. 1989). Local sources of lead releases can also contribute significantly to lead content in sediments (Gale et al. 2004). For example, lead concentrations in sediments located near mines and or sites containing mine tailings in the old lead belt of Missouri were greatly elevated, 10,550–12,400 mg/kg sediment (dry weight) compared to unaffected sediments (72–400 mg/kg dry weight) (Gale et al. 2002).

The natural lead content of soil derived from crustal rock, mostly as galena (PbS), typically ranges from <10 to 30 μg/g soil. However, the concentration of lead in the top layers of soil varies widely due to deposition and accumulation of atmospheric particulates from anthropogenic sources. The concentration of soil lead generally decreases as distance from contaminating sources increases. The estimated lead levels in the upper layer of soil beside roadways are typically 30–2,000 μg/g higher than natural levels, although these levels drop exponentially up to 25 m from the roadway (EPA 1986a). Soil adjacent to a smelter in Missouri had lead levels in excess of 60,000 μg/g (Palmer and Kucera 1980). Soils adjacent to houses with exterior lead-based paints may have lead levels of >10,000 μg/g (EPA 1986a). As a result of lead reactions with the soil, extractable lead in surface soil samples (0–5 cm depth) from an agricultural area near a car battery manufacturing plant (taken at 0.3 km from the source) decreased from 117 μg/g to 1 μg/g within 1 year after the plant stopped operating (Schalscha et al. 1987). Soil collected by scraping the top 2.5 cm of soil surface near homes and streetside in Louisiana and Minnesota contained median lead concentrations of >840 μg/g in New Orleans and 265 μg/g in Minneapolis. In contrast, the small towns of Natchitoches, Louisiana, and Rochester, Minnesota, had soil lead concentrations of <50 and 58 μg/g, respectively. These data suggest that lead-contaminated soil is a major source of lead exposure in urban areas (Mielke 1993). As would be expected, soils in elementary school properties were also found to have the same pattern of lead levels as the soils in the surrounding residences. Lead concentrations in soils collected from inner-city schools in New Orleans were higher (median

concentration of 96.5 μg/g) than soils collected from mid-city (30.0 μg/g) and outer-city (16.4 μg/g) elementary schools (Higgs et al. 1999).

Studies conducted in Maryland and Minnesota indicate that within large, light-industrial, urban settings such as Baltimore, the highest soil lead levels generally occur near inner-city areas, especially where high traffic flows have long prevailed (Mielke et al. 1983, 1984/1985, 1989) and that the amount of lead in the soil is correlated with the size of the city (Mielke 1991). In 1981, soil lead levels in the Minneapolis/St. Paul inner-city area were 60 times higher (423 μg/g) than levels found in rural Minnesota (6.7 μg/g), with almost all the increase (95%) resulting from the combustion of leaded gasoline. A study conducted in Minneapolis, Minnesota, after the lead content of gasoline had been significantly reduced, found that median soil lead levels taken from the foundations of homes, in yards, and adjacent to the street were 700, 210, and 160 μg/g, respectively; median soil lead concentrations in comparable samples from the smaller city of Rochester, Minnesota, did not exceed 100 μg/g at any location tested (Mielke et al. 1989). The Minneapolis data suggested that average lead levels were elevated in soil samples taken from the foundations of homes, but that lead levels were low (<50 μg/g) in areas where children could be expected to play, such as parks that were located away from traffic, but were higher in play areas around private residences. Soil samples taken from around the foundations of homes with painted exteriors had the highest lead levels (mean concentrations of 522 μg/g), but levels around homes composed of brick or stucco were significantly lower (mean concentration 158 μg/g) (Schmitt et al. 1988). Severely contaminated soils (levels as high as 20,136 μg/g) were located near house foundations adjacent to private dwellings with exterior lead-based paint. Elevated soil lead concentrations were found in larger urban areas with 27, 26, 32, and 42% of the soil samples exceeding 300 μg/g lead in Duluth, inner-city North Minneapolis, inner-city St. Paul, and inner-city South Minneapolis, respectively. Only 5% of the soil samples taken from the smaller urban areas of Rochester and St. Cloud, Minnesota, had lead levels >150 μg/g. It has been suggested that the higher lead levels associated with soils taken from around painted homes in the inner city are the result of greater atmospheric lead content, resulting from the burning of leaded gasoline in cars and the washdown of building surfaces to which the small lead particles adhere by rain (Mielke et al. 1989). A state-wide Minnesota study concluded that exterior lead-based paint was the major source of contamination in severely contaminated soils located near the foundations of private residences and that aerosol lead accounted for virtually all of the contamination found in soils removed from the influence of lead-based paint. Contamination due to lead-based paint was found to be “highly concentrated over a limited area, while contamination due to aerosol lead was found to be less concentrated, but more widespread” (MPCA 1987).

Lead was analyzed in dust wipes and soil samples from 67 public housing projects containing 487 dwelling units across the United States (Succop et al. 2001). A total of 5,906 dust wipes and 1,222 soil samples were included in the data set. The median soil levels were 194 ppm near the foundation, 177 ppm near the walkways, and 145 ppm elsewhere in the yard. The maximum level, 3,900 ppm, was found in a foundation sample. Median dust lead loading from kitchens, living rooms, and two children's bedrooms were 151, 936, and 8,560 μg m^{-2} for floor window sills and window troughs, respectively. Thirteen percent of the floor samples and 30% of the window sill samples from the rooms exceeded the HUD Interim Dust Lead Standards of 431 and 2,690 μg m^{-2} for floor and window sill samples, respectively.

Blood lead levels (PbBs) in children have been shown to correlate with lead concentration in soils in urban areas. In a study of children in New Orleans, Mielke et al. (1999) found that those living in areas classified as high (median soil lead concentrations >310 μg/kg) and low (median soil lead concentrations <310 μg/kg) metal census tract regions correlated well with median PbB above and below 9 μg/dL, respectively. In an analysis of data collected in an ATSDR study of children living near four NPL sites, it was concluded that a PbB of 5.99 μg/dL could be predicted for children exposed to soil lead levels of 500 mg/kg (Lewin et al. 1999). However, there was a high degree of uncertainty and variability associated with the predicted correlation between blood and soil lead levels, suggesting the contribution of other factors to PbB, such as lead levels in household dust, interior paint, and drinking water.

In a study of associations between soil lead levels and childhood blood lead levels (PbBs) in urban New Orleans and rural Lafourche Parish in Louisiana, childhood PbBs appeared more closely associated with soil lead levels than with age of housing. In the study, over 2,600 lead-containing soil and 6,000 PbB samples were paired by their median values and pre-1940 housing percentages for 172 census tracts. Census tracts with low median lead-containing soil levels were associated with new housing, but census tracts with high median lead-containing soil levels were split evenly between old and new housing. The same pattern was also observed for childhood PbBs. High lead-containing soil levels were associated with high PbB, and low lead-containing soil levels were associated with low PbB. Risk factors for lead exposure were found to be low in Lafourche Parish, where there was no census tract in which median PbB was >9 μg/dL and no indication of a statistical association between median PbB and either median lead levels in soil or age of housing (Mielke et al. 1997a).

In the state of Maine, soil samples taken from areas where the risk of lead contamination was considered high (within 1–2 feet of a foundation of a building >30 years old) indicated that 37% of the samples had

high lead concentrations (>1,000 μg/g). In 44% of the private dwellings, high lead levels were found in the soil adjacent to the foundation; high levels were found in only 10% of the public locations (playgrounds, parks, etc.). In addition, the largest percentage (54%) of highly contaminated soil was found surrounding homes built prior to 1950; homes built after 1978 did not have any lead contamination in the soil (Krueger and Duguay 1989). Environmental health studies conducted near four NPL sites measured mean concentrations of lead in soil ranging from 317 to 529 mg/kg, and mean concentrations of lead in dust ranging from 206 to 469 mg/kg (Agency for Toxic Substances and Disease Registry 1995).

In 1972, household dust samples taken near nonferrous ore smelters in El Paso, Texas, which were known to emit 1,012 metric tons of lead/year, had lead levels of 22,191 μg/g (geometric mean) and 973 μg/g at distances from the smelter of 1.6 km and 6.4 km, respectively (Landrigan and Baker 1981).

Lead was measured in soil from a port facility where galena ore concentrate and smelter dross arriving by rail were offloaded, stored, and reloaded onto seagoing vessels from 1974 through 1985. The lead concentrations ranged from 1,900 to 183,000 mg/kg (μg/g) (Ruby et al. 1994).

In 1986, an NPL hazardous waste site that contained a landfill and nine surface impoundments was identified in Genesee County, Michigan. The facility had accepted sludge and residual waste from a chemical warehouse as well as other hazardous wastes. Lead was present in sludge samples taken from the impoundments at a maximum concentration of 11.6 mg/L, in sediment samples at a maximum concentration of 4,770 mg/kg dry weight, and in soil samples at 1,560 mg/kg (EPA 1986b).

6.4.4 Paint

Weathering of lead-based paint can contribute to the lead content of dust and soil. A 1974 study indicated that elevated PbBs in children were most likely a result of ingesting lead-contaminated soil, and that the most likely source was lead-based paint rather than lead from automotive exhaust (Ter Haar and Aronow 1974). A state-wide Minnesota study concluded that exterior lead-based paint was the major source of contamination in severely contaminated soils located near the foundations of private residences (MPCA 1987). A soil lead study in Minneapolis, Minnesota, found that soil samples taken from around the foundations of homes with painted exteriors had a mean concentration of 522 μg/g while soil samples taken from around the foundations of brick or stucco had a mean concentration of 158 μg/g (Schmitt et al. 1988). Lead-based paint, removed from surfaces by burning (gas torch or hot air gun), scraping, or

sanding have been found to result, at least temporarily, in higher levels of exposure for families residing in these homes.

6.4.5 Other Sources

Concentrations of lead (wet weight basis) in samples of 11 raw edible plants have been reported for growing areas in the United States that are uncontaminated by human activities other than normal agricultural practices (Wolnik et al. 1983a, 1983b). Results are as follows: plant (mean μg/g wet weight); lettuce (0.013); peanut (0.010); potato (0.009); soybean (0.042); sweet corn (0.0033); wheat (0.037); field corn (0.022); onion (0.005); rice (0.007); spinach (0.045); and tomato (0.002).

Lead has been detected in a variety of foods. Lead may be introduced into food through uptake from soil into plants or atmospheric deposition onto plant surfaces, during transport to market, processing, and kitchen preparation (EPA 1986a). In the FDA Total Diet Study (TDS) 1991–1996, food was purchased 4 times/year from each of four geographic regions of the United States and a market basket consisting of about 260 foods from three representative cities within the geographical region analyzed for different elements, including lead (Capar and Cunningham 2000). Lead was below the limit of quantitation in all TDS food in the following food categories: milk and cheese; eggs; meat, poultry, and fish; legumes and nuts; grain and cereal products; vegetables; mixed dishes and meals; desserts; snacks; fats and dressings; and infant and junior foods. Only five products had quantifiable concentrations of lead, namely: canned peaches (0.032 mg/kg), canned pineapple (0.013 mg/kg), canned fruit cocktail (0.031 mg/kg), sweet cucumber pickles (0.036 mg/kg), and dry table wine (0.023 mg/kg). Typical concentrations of lead in various foods are shown in Table 6-5 for the TDS 1991–1996. Results of a previous FDA TDS in which samples were collected in 27 cities between October 1980 and March 1983 are shown for comparison (Gartrell et al. 1986a).

Other factors such as absorption of lead from cooking water and cookware can influence the amount of lead in cooked vegetables. Ceramic dishes may contain lead in their glazes, and lead in glass has been shown to leach into wine. The degree to which lead is released from food once it is consumed also influences a person's uptake of lead.

A survey conducted in five Canadian cities during 1986–1988 in which food was purchased from retail stores and analyzed for lead in composite samples (n=756), determined the lead levels in 11 food categories as well as the average dietary intake of different population groups (Dabeka and McKenzie

Table 6-5. Lead Levels in Various Food Categories

	Mean concentration (µg/g)	
Food category	TDS 1980–1982a	TDS 1991–1996b
Dairy products	0.006	
Milk and cheese		<0.02–<0.05
Eggs		<0.03
Meat, fish, and poultry	0.016	nd–<0.05
Grain and cereal products	0.023	nd–<0.05
Vegetables	0.010–0.041	nd–<0.05
Legumes and nuts	0.124	nd–<0.05
Fruits	0.046–0.060	nd–0.032
Mixed dishes and meals		nd–<0.04
Desserts		nd–<0.04
Snacks		<0.05
Oils, fats, shortenings, and dressings	0.017	nd–<0.04
Sugar, adjuncts, condiments, and sweeteners	0.028	<0.03–0.036
Infant and junior foods		nd–<0.04
Beverages	0.010	nd–0.0.023

[a]Gartrell et al. 1986b
[b]Capar and Cunningham 2000

nd = not detectable (<0.008 µg/g); TDS = Total Dietary Study

1995). Results of this study are found in Table 6-6. The lead level in all of the foods ranged from <0.4 to 523.4 ng/g with a mean of 23.2 ng/g for all food categories. The highest mean Pb levels were found in canned luncheon meats (163 ng/g), canned beans (158 ng/g), canned citrus fruit (126 ng/g), and canned peaches (133 ng/g). In canned foods, mean Pb levels decreased from 73.6 ng/g in 1985 to 46 ng/g in 1988, at which time it was estimated that 97–99% of Canadian canned foods were in lead-free cans. Canning foods in lead-soldered cans may increase levels of lead 8–10-fold; however, the impact of canning appears to be decreasing as a result of a decrease in the use of lead-soldered cans. The use of three-piece lead-soldered cans ceased in 1991; however, older lead- soldered cans may still be present in some households. In 1974, for example, the lead level in evaporated milk in lead-soldered cans was 0.12 μg/g; in 1986, after these cans were phased out, the lead level in evaporated milk dropped to 0.006 μg/g (Capar and Rigsby 1989). A survey conducted in five Canadian cities during 1986–1988 in which food was purchased from retail stores and analyzed for lead in composite samples (n=756), determined the lead levels in 11 food categories as well as the average dietary intake of different population groups (Dabeka and McKenzie 1995). Results of this study are found in Table 6-6. The lead level in all of the foods ranged from <0.4 to 523.4 ng/g with a mean of 23.2 ng/g for all food categories. The highest mean Pb levels were found in canned luncheon meats (163 ng/g), canned beans (158 ng/g), canned citrus fruit (126 ng/g), and canned peaches (133 ng/g). In canned foods, mean Pb levels decreased from 73.6 ng/g in 1985 to 46 ng/g in 1988, at which time it was estimated that 97–99% of Canadian canned foods were in lead-free cans. Canning foods in lead-soldered cans may increase levels of lead 8–10-fold; however, the impact of canning appears to be decreasing as a result of a decrease in the use of lead-soldered cans. The use of three-piece lead-soldered cans ceased in 1991; however, older lead-soldered cans may still be present in some households. In 1974, for example, the lead level in evaporated milk in lead-soldered cans was 0.12 μg/g; in 1986, after these cans were phased out, the lead level in evaporated milk dropped to 0.006 μg/g (Capar and Rigsby 1989).

The U.S. Fish and Wildlife Service reported on the concentration of metals in a total of 315 composite samples of whole fish sampled from 109 stations nationwide from late 1994 to early 1995. For lead, the geometric mean, maximum, and 85th percentile concentrations (μg/g wet weight) were 0.11, 4.88, and 0.22, respectively. The mean concentration of lead was significantly lower than in the 1980–1981 survey. Lead concentrations in fish have declined steadily from 1976 to 1984, suggesting that reductions of leaded gasoline and controls on mining and industrial discharges have reduced lead in the aquatic environment (Schmitt and Brumbaugh 1990).

Table 6-6. Lead Levels in Canadian Foods 1986–1988

Food category	Number of samples	Concentration (ng/g)		
		Mean	Median	Maximum
Milk and milk products	64	7.7	3.9	44.7
Meat and poultry	89	20.2	8.2	523.2
Fish	28	19.3	13.7	72.8
Soups	20	15.5	8.7	48.7
Bakery goods and cereals	120	13.7	10.5	66.4
Vegetables	190	24.4	8.7	331.7
Fruits and fruit juices	127	44.4	15.9	372.7
Fats and oils	15	9.6	<8.8	19.7
Sugar and candies	35	18.3	10.3	111.6
Beverages	35	9.9	<3.1	88.8
Miscellaneous	33	41.7	23.4	178.9
All categories	756	23.2	9.2	523.4

Source: Dabeka and McKenzie 1995

In order to reduce lead exposure from consumption of lead-contaminated fish and shellfish, consumption advisories are issued by states recommending that individuals restrict their consumption of specific fish and shellfish species from certain waterbodies where lead concentrations in fish and shellfish tissues exceed the human health level of concern. This level of concern is set by individual state agencies and used to issue advisories recommending no consumption, or restricted consumption, of contaminated fish and shellfish from certain waterbody types (e.g., lakes and/or rivers). In 1995, the EPA Office of Water issued guidance to states on sampling and analysis procedures to use in assessing the health risks from consuming locally caught fish and shellfish. The risk assessment method proposed by EPA was specifically designed to assist states in developing fish consumption advisories for recreational and subsistence fishers (EPA 1995b). These two groups within the general population consume larger quantities of fish and shellfish than the general population and frequently fish the same waterbodies routinely. Because of this, these populations are at greater risk of exposure to lead and other chemical contaminants if the waters they fish are contaminated. In 2007, 8 advisories restricting the consumption of lead-contaminated fish and shellfish were in effect in 5 states (Hawaii, Idaho, Washington, Kansas, and Missouri) and 1 territory (American Samoa) (EPA 2007b).

Elevated levels of lead in the blood of cattle grazing near a lead smelter have been reported, although no implications regarding lead in beef were made. The mean lead levels for the herd were highest near the smelter and decreased with distance. Ingestion of soil along with the forage was thought to be a large source of additional metal (Neuman and Dollhopf 1992). Evidence has also been shown for transfer of lead to milk and edible tissue in cattle poisoned by licking the remains of storage batteries burned and left in a pasture (Oskarsson et al. 1992). Levels of lead in muscle of acutely sick cows that were slaughtered ranged from 0.23 to 0.5 mg/kg (wet weight basis). Normal lead levels in bovine meat from Swedish farms are <0.005 mg/kg. For eight cows that were less exposed, levels of lead in milk taken 2 weeks after the exposure were 0.08±0.04 mg/kg. The highest lead level found in the milk of eight cows studied for 18 weeks was 0.22 mg/kg. Lead in most milk samples decreased to values <0.03 mg/kg 6 weeks after exposure. Two affected cows delivered a calf at 35 and 38 weeks after the exposure. There was a high lead level in the blood of the cows at the time of delivery, which suggests mobilization of lead in connection with the latter stages of gestation and delivery. Lead levels in colostrum were increased as compared to mature milk samples taken 18 weeks after exposure. The concentration of lead in milk produced after delivery decreased rapidly with time and was almost down to the limit of detection in mature milk.

The FDA investigated the prevalence and concentration of lead in a variety of dietary supplements with an emphasis on botanical-based products (Dolan et al. 2003). The concentration of lead in the 95 major product components tested was <20–48,600 μg/kg and the median concentration was 403 μg/kg. Levels of lead found in 11 products would result in exposures that exceed the tolerable lead intakes for children and women of child-bearing age, particularly pregnant women, 6 and 25 μg Pb/day. Of the 136 brands of nutritional supplements containing calcium (calcium supplements, mineral-vitamin supplements, antacids, and baby formulas) purchased in California in 1996, two-thirds failed to meet the 1999 California criteria for acceptable lead levels in consumer products, >1.5 μg lead/g calcium (Scelfo and Flegal 2000). The lowest levels were found in infant formulas and antacids, which all contained either synthesized or refined calcium. Lead concentrations were undetectable (<0.02 μg/g) in all infant formulas tested. Of the natural calcium supplements, none of the dolomite brands (n=5), five of the oyster shell brands (n=26), and half of the bonemeal brands (n=9) met the 1999 California criteria, while two dolomite brands and one oyster shell brand exceeded the federal limit, 7.5 μg Pb/g calcium.

Many non-Western folk remedies used to treat diarrhea or other ailments may contain substantial amounts of lead. Examples of these include: Alarcon, Ghasard, Alkohl, Greta, Azarcon, Liga, Bali Goli, Pay-loo-ah, Coral, and Rueda. In addition, an adult case of lead poisoning was recently attributed to an Asian remedy for menstrual cramps known as Koo Sar. The pills contained lead at levels as high as 12 ppm (CDC 1998). The source of the lead was thought to be in the red dye used to color the pills. Lead was the most common heavy metal contaminant/adulterant found in samples (n=54) of Asian traditional remedies available at health food stores and Asian groceries in Florida, New York, and New Jersey (Garvey et al. 2001). Sixty percent of the remedies tested would give a daily dose of lead in excess of 300 mg when taken according to labeling instructions. Lead poisoning has been caused by ingestion of a Chinese herbal medicine to which metallic lead was added to increase its weight and sales price (Wu et al. 1996). Ayurveda is a traditional form of medicine practiced in India and other South Asian countries; the medications used often contain herbs, minerals, metals, or animal products and are made in standardized and nonstandardized formulations (CDC 2004). During 2000–2003, 12 cases of lead poisoning among adults were reported in five states due to the use of ayurveda medications obtained from ayurvedic physicians (CDC 2004).

Because lead concentrations in urban soil can be very high, a pilot study was conducted in an urban neighborhood in Chicago in order to gauge the levels of lead in an array of fruits, vegetables, and herbs (Finster et al. 2004). The soil lead concentrations where the plants were sampled varied from 27 to 4,580 ppm (median 800 ppm, geometric mean 639 ppm). Detectable lead levels in the edible fruit,

vegetables, and herbs sampled ranged from 11 to 81 ppm. Only one fruiting vegetable (cucumber 81 ppm) among the 52 sampled had detectable levels of lead in the edible portion. However, 12 of the 31 leafy vegetables and herbs sampled contained lead in the edible shoot part of the plant (range, 11–60 ppm). The lead concentrations in the four samples of root vegetables ranged from 10 to 21 ppm. No significant correlation was found between the lead concentrations in the edible portion of plant and the soil lead level.

Tamarindo jellied fruit candy from Mexico, and lozeena, a bright orange powder from Iraq used to color rice and meat, have been implicated in lead poisoning (CDC 1998). The lozeena, containing 7.8–8.9% lead, was purchased in Iraq and brought into the United States. Tamarindo candy and jam products, restricted from importation into the United States since 1993, were purchased by a woman visiting her family in Mexico. Although no product was available for testing, several commercial retail lots of tamarindo and tejocote jellied fruit candy were embargoed by the state of California in 1993 because of high lead levels. The fruit candies were packaged in stoneware or ceramic jars. The lead-based glazing applied to the jars appeared to have been the major source of the lead, although some of the fruits from plastic-lined jars also contained substantial amounts of lead.

Lead may leach from lead crystal decanters and glasses into the liquids they contain. Port wine that contained an initial concentration of 89 μg/L lead was stored for 4 months in crystal decanters containing up to 32% lead oxide. At the end of 4 months lead concentrations in the port were 5,331, 3,061, and 2,162 μg/L in decanters containing 32, 32, and 24% lead oxide, respectively. Lead was also found to elute from lead crystal wine glasses within minutes. Mean lead concentrations in wine contained in 12 glasses rose from 33 μg/L initially to 68, 81, 92, and 99 μg/L after 1, 2, 3, and 4 hours, respectively (Graziano and Blum 1991).

Lead is also present in tobacco at concentrations of approximately 2.5–12.2 μg/cigarette, of which approximately 2–6% may actually be inhaled by the smoker (WHO 1977). This lead may have been due to the use of lead arsenate pesticides or lead-containing vehicle exhaust contaminating the tobacco plants. While no recent data were found on the concentration of lead in tobacco, higher levels of lead in indoor air and PbBs are associated with households with smokers (Bonanno et al. 2001; Mannino et al. 2003).

Hair dyes and some cosmetics may contain lead compounds (Cohen and Roe 1991). Hair dyes formulated with lead acetate may have lead concentrations 3–10 times the allowable concentration in paint. Measured lead concentrations of 2,300–6,000 μg of lead/gram of product have been reported

(Mielke et al. 1997b). Lead acetate is soluble in water and easily transferred to hands and other surfaces during and following application of a hair dye product. Measurements of 150–700 μg of lead on each hand following application have been reported (Mielke et al. 1997b). In addition to transfer of lead to the hand-to-mouth pathway of the person applying the product, lead is transferred to any other surface (comb, hair dryer, outside of product container, counter top, etc.) that comes into contact with the product. It is also on the hair it is applied to and the hands applying it. Objects coming into contact with hair dyed with a lead-containing product also become contaminated. A dry hand passed through dry hair dyed with a lead-containing product in cream form has been shown to pick up about 786 μg of lead. A dry hand passed through dry hair dyed using foam or liquid lead-containing hair dye products picked up less lead: 69 μg/hand for foam products and 73 μg/hand for liquid products (Mielke et al. 1997b).

Cases of lead poisoning have been related to less common sources of exposure. Illicit "moonshine" whiskey made in stills composed of lead-soldered parts (e.g., truck radiators) may contain high levels of lead. Detectable levels of lead with a maximum concentration of 5.3 mg/L were found in 7 of 12 samples of Georgia moonshine whiskey (Gerhardt et al. 1980). Of the 115 suspected moonshine samples seized by local law enforcement between 1995 and 2001 and analyzed by the Bureau of Alcohol, Tobacco, and Firearms, 33 samples (28.7%) contained lead levels >300 μg/dL. The median and maximum levels were 44.0 and 53,200 μg/dL, respectively (Parramore et al. 2001).

Use of lead ammunition may result in exposure to lead dust generated during gun or rifle discharge at levels up to 1,000 $\mu g/m^3$ (EPA 1985c), from lead pellets ingested by or imbedded in animals that are used as food sources, and from lead pellets or fragments imbedded in humans from shooting incidents (Burger et al. 1998; Johnson and Mason 1984; Raymond et al. 2002). Exposures to airborne lead dust from firearm discharge in indoor shooting ranges has been shown to result in increases in blood lead concentration that are 1.5–2 times higher than preexposure concentrations (Greenberg and Hamilton 1999; Gulson et al. 2002). However, the use of copper-jacketed bullets, nonlead primers, and well-ventilated indoor firing ranges lessen the impact of airborne lead on blood lead levels (Gulson et al. 2002).

A lead poisoning hazard for young children exists in imported vinyl miniblinds that have had lead added to stabilize the plastic. Over time, the plastic deteriorates to produce lead dust that can be ingested when the blinds are touched by children who then put their hands in their mouths (CPSC 1996). The U.S. Consumer Product Safety Commission (CPSC) has requested that manufacturers change the manufacturing process to eliminate the lead. As a consequence, vinyl miniblinds should now be lead-

free. The CPSC recommends that consumers with young children remove old vinyl miniblinds from their homes and replace them with new miniblinds made without added lead or with alternative window coverings.

Inexpensive metallic jewelry items specifically intended for children and teenagers have been shown to contain varying levels of lead (Maas et al. 2005). A total of 311 chemical assays conducted using 285 jewelry items purchased in 20 different stores in California revealed that a considerable amount of lead was added to the items, presumably to increase their weight or to impart some type of metallic coating to the surface of the item. The mean weight percentage of lead for all 311 assays was 30.6%. Of the 311 samples tested, 169 contained at least 3% lead by weight in at least one portion of the jewelry piece and 123 of the samples were found to contain >50% lead by weight (Maas et al. 2005). In addition, 62 pieces of the purchased jewelry were tested for surface levels of lead that could potentially be transferred dermally through the routine handling of these pieces. Using standard laboratory wipes, the surface of the jewelry pieces were wiped for a total of 20 seconds and subsequently analyzed for lead content. Mean lead levels in the wipes ranged from 0.06 to 541.97 μg. The authors characterized the potential lead exposure from these dermal transfer experiments as either low exposure (<1 μg of lead transferred to the laboratory wipe), moderate exposure (1–10 μg of lead transferred to the laboratory wipe), high exposure (10–50 μg of lead transferred to the laboratory wipe), and very high exposure (>50 μg of lead transferred to the laboratory wipe). Approximately 35% of the 62 pieces tested were characterized as having low exposure, 48% were characterized as moderate exposure, 11% were characterized as high exposure, and 5% were characterized as very high exposure (Maas et al. 2005).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to lead is most likely to occur through the ingestion of contaminated food and drinking water, and by the inhalation of lead particulates in ambient air. Direct inhalation of lead accounts for only a small part of the total human exposure; however, lead that is adsorbed to soil may be inhaled as dust and reentrainment of lead-contaminated dust is common. Fruits, vegetables, and grains may contain levels of lead in excess of background levels as a result of plant uptake of lead from soils and direct deposition of lead onto plant surfaces (EPA 1986a). Between 1979 and 1989, lead-soldered food cans were virtually eliminated as a source of lead contamination of canned food. The CDC has concluded that the most common source of lead exposure for children (Section 6.6) is lead-based paint that has deteriorated into paint chips and lead dusts and that the most common sources of lead exposure for adults are occupational (CDC 1997b).

Those who use recreational shooting ranges may be exposed to lead and soluble lead compounds, such as carbonates and sulfates, in soil. Surface soil concentrations of lead at a range in Michigan were 10–100 times greater than background level of 25 mg/kg; mobilization of lead appeared to be occurring and may present a threat to groundwater and surface water (Murray et al. 1997).

Exposure may also result from engaging in hobbies that use lead. For example, molten lead can be used in casting ammunition and making fishing weights or toy soldiers; leaded solder is used in making stained glass; leaded glazes and frits are used in making pottery; artists' paints may contain lead; lead compounds are used as coloring agents in glassblowing; and lead may be present in platinum printing and screen printing materials (Grabo 1997).

In 1982–1983, the baseline value for daily intake of lead by inhalation in a nonurban environment was estimated to be 0.5 μg/day for a 2-year-old child, 1.0 μg/day for an adult working indoors, and 2.0 μg/day for adults working outdoors; these figures are based on an average atmospheric lead concentration of 0.1 $\mu g/m^3$ and an indoor/outdoor lead concentration ratio of 0.5. In an urban environment, the indoor/outdoor lead concentration ratio was assumed to be approximately 0.8, yielding an estimated lead exposure of 1.0 $\mu g/m^3$ for adults. This estimate assumed a 2-hour/day exposure to an outdoor lead concentration of 0.75 $\mu g/m^3$, a 20-hour/day exposure to an indoor lead concentration of 0.6 $\mu g/m^3$, a 2-hour/day exposure to 5 $\mu g/m^3$ in high traffic, and an average daily intake of air by an adult of 20 m^3. These estimates indicate that urban and nonurban residents inhaled approximately the same amount of lead dust (EPA 1986a). Drastic reductions in the lead content of gasoline since 1986 have resulted in a 64% decrease in lead emissions to the atmosphere (see Section 6.4.1).

Using the EPA National Air Quality Monitoring System, the average maximum 24-hour atmospheric lead concentration in the United States was 0.84 $\mu g/m^3$ in 2004 (EPA 2005k). There were two maximum 24-hour monitoring values measured in 2004 in which the 10 $\mu g/m^3$ level was exceeded (11.76 and 11.53 $\mu g/m^3$ in Muncie, Indiana). All other atmospheric lead levels measured throughout the rest of the United States were <10 $\mu g/m^3$ threshold in 2004.

Between 1979 and 1989 there was a virtual elimination of the use of lead-soldered food cans, with a concomitant drop in lead levels in food. The contribution of various food categories to the average daily intakes of lead for adults, based on an analysis of 27 market basket samples taken nationwide for a 1980–1982 Total Diet Study, are shown in Table 6-7 (Gartrell et al. 1986b). This value is only slightly higher

Table 6-7. Contribution of Various Food Categories to the Average Daily Intake (AVDI) of Lead in Adults (1980–1982)

Food category	AVDI (µg/day)
Dairy products	4.54
Meat, fish, and poultry	4.09
Grain and cereal products	9.84
Potatoes	1.39
Leafy vegetables	0.94
Leafy legumes	9.18
Root vegetables	1.39
Garden fruit	4.44
Fruits	10.00
Oils, fats, and shortenings	1.23
Sugar and adjuncts	2.34
Beverages	6.86
Total	56.50

Source: Gartrell et al. 1986b

than the estimated lead intake of 54 μg/day found in a Canadian 24-hour duplicate diet study conducted during 1981. The average lead content of the 10 food groups used in the Canadian study ranged from 0.088 μg/g for drinking water to 0.654 μg/g for cheese (Dabeka et al. 1987).

Based on data from the FDA's Total Diet Food Studies (Bolger et al. 1991; Gunderson 1988), dietary values for average daily intake of lead by different population groups from 1980 to 1990 have been estimated (Table 6-8). The estimates of lead intake presented in Table 6-8 are based on measurements of lead in foods prepared for consumption and on consumption patterns for those foods (or food groups) from dietary surveys in which survey participant data were grouped by age and sex. The Total Diet Food Studies conducted between 1982 and 1988 determined daily intakes of a variety of pesticides, industrial chemicals, and elements for eight age and sex groups. In 1984, lead residues were found in 193 of the 201 foods analyzed. A comparison of daily intakes of lead by age group (6 months, 2 years, and adult) showed that lead intakes dropped by approximately 50% for each group between 1980 and 1984 (Gunderson 1988) and continued to decrease through 1990 for all age and sex groups (Bolger et al. 1991). Data from the 1990–1991 Total Diet Survey indicate that dietary lead intake ranged from 1.8 to 4.2 μg/day for all age groups combined, primarily as a result of reduced lead solder in cans and the phase-out of leaded gasoline. Further reductions in lead exposure will be more difficult to identify and achieve (Bolger et al. 1991, 1996). The daily dietary intake of lead estimated from the 1986–1988 Canadian Survey was 24 μg/day for all ages, male and female (Dabeka and McKenzie 1995). The highest contribution among 11 food categories to Pb intake was beverages (20.9%) and bakery goods and cereals (20.6%). The FDA Total Diet Survey (TDS) 1991–1996 tested 18 market baskets consisting of about 260 foods collected from three cities (representing standard metropolitan statistical areas) within four different geographical regions (Capar and Cunningham 2000). Mean and median Pb concentrations in all foods were 0.005 and 0 mg/kg, respectively. These results are similar to those in previous TDS 1982–1988 and 1990–1991 surveys except those in canned foods. The lower Pb concentrations in canned foods for TDS 1991–1996 is attributed to the reduction and ultimate ban in 1995 on the use of lead-soldered food cans in the United States.

More recent data on lead intakes from the U.S. diet come from the results of the NHEXAS studies. Mean and median dietary intakes of lead for study participants in the EPA Region V study were calculated to be 0.25 and 0.10 μg/kg body weight/day, respectively, or 17.5 and 7.0 μg/day for a 70-kg adult, respectively (Thomas et al. 1999). These results were obtained from measurement of concentrations in water and dietary samples. The median dietary lead intake for the Region V population agrees with the 0.09–0.10 μg/kg body weight/day calculated in the FDA TDS (1986–1991) (Gunderson 1995), but is

Table 6-8. Daily Average Intake of Lead (µg Lead/Day)

Age	Sex	1980[a]	1982[a]	1984[a]	1986[a]	1988[a]	1990–1991[b]
6–11 Months	Male/female	≈34	20	16.7	10	5	1.82
2 Years	Male	≈45	25.1	23.0	12.8	5.0	1.87
	Female	No data	No data	No data	No data	No data	No data
14–16 Years	Female	No data	No data	28.7	15.2	6.1	2.63
	Male	No data	No data	40.9	21.8	8.2	3.24
25–30 Years	Female	No data	32.0	28.7	14.8	7.9	3.28
	Male	84	45.2	40.9	21.2	10.0	4.17
60–65 Years	Female	No data	No data	30.4	15.6	No data	3.05
	Male	No data	No data	37.6	19.1	No data	3.46

[a]Bolger et al. 1991
[b]Bolger et al. 1996

substantially lower than the average in the 1986–1988 Canadian study of 0.4 μg/kg body weight/day (calculated from an average intake of 24 μg/day for a 60-kg person (Dabeka and McKenzie 1995). Higher mean daily intakes of lead of 8.14 mg/day were reported from the NHEXAS Maryland study (Ryan et al. 2001). This intake was determined from the consumption levels determined in the NHEXAS Maryland study and the concentration in food from the 1997 ATSDR Toxicological Profile for Lead, 11.0 ppb. This intake would be much lower if the more recent levels of lead in food as reported in Capar and Cunningham (2000) were used. The mean and median concentrations of lead in combined solids and liquids in the EPA Region V study were 4.5 and 3.1 μg/kg, respectively. The mean (median) Pb intakes from dietary, water, and inhalation routes were 10.9 (7.3), 1.7 (0.66), and 0.333 (0.156) μg/day, respectively. While water lead contributed significantly to dietary intake, dietary intake was greater than that calculated for intake from home tap water. Mean and median flushed tap water from Region V homes contained 0.84 and 0.33 μg/L, while standing tap water contained 3.9 and 1.9 μg/L of lead, respectively.

In another approach to determining daily lead intake within subpopulations in the United States, Moschandreas et al. (2002) used the Dietary Exposure Potential Model (DEPM) and data obtained from Combined National Residue Database (CNRD) to estimate dietary lead intake based on food consumption patterns in 19 subpopulation groups. The food items used in the model are based on 11 food groups consisting of approximately 800 exposure core foods that represent 6,500 common food items. The results of their model (Table 6-9) yielded an average dietary lead intake in the U.S. population of 1.009 μg/kg body weight/day, or 70.6 μg/day for a 70-kg adult. Of the various subpopulation groups, nonnursing infants and children ages 1–6 years had much higher lead intakes/kg body weight than the general population, 3.117 and 1.952 μg/kg body weight, respectively.

The NHEXAS Arizona study evaluated exposure to lead for a study population from multiple media and pathways (O'Rourke et al. 1999). The concentrations of lead in the various media sampled are presented in Table 6-10 and the estimated total human exposure to the study population and various subpopulations is shown in Table 6-11. The daily total lead intake to the study population from all media ranged from 11 to 107 μg/day, with a mean of 36 μg/day. This compares with a range of 15–312 μg/day reported by the World Health Organization (WHO 1995).

Moonshine consumption was strongly associated with elevated PbBs (Morgan and Parramore 2001). A 2000 study found a median PbB of 11 μg/dL among 35 moonshine consumers versus 2.5 μg/dL in 68 randomly-selected nonmoonshine consumers. Gulson et al. (2001b) studied the contribution of lead

Table 6-9. Dietary Exposure Estimates of U.S. Populations to Lead Based on the Dietary Exposure Potential Model (DEPM)

Subpopulation	Lead intake (µg/kg body weight/day)
U.S. population	1.009
Age/gender	
Nonnursing infants	3.117
Children 1–6	1.952
Children 7–12	1.164
Females 13–19	0.824
Females 20+	0.920
Females 55+	0.946
Males 13–19	0.890
Males 20+	0.895
Males 55+	0.918
Ethnicity	
Hispanic	1.177
Non-Hispanic white	1.095
Non-Hispanic black	0.797
Non-Hispanic other	0.871
Geographic region[a]	
North central	0.611
Northeast	0.968
Southern	0.966
Western	1.133
Family income[b]	
Poverty 0–130%	1.094
Poverty 131%+	0.986

[a]The regional classification is as defined by the U.S. Department of Agriculture, and is based upon U.S. Census Bureau regions.
[b]Annual household income as a percentage of the Poverty Index

Source: Moschandreas et al. 2002

Table 6-10. Lead Concentrations for Various Media From the NHEXAS Arizona Study

Media	Number of samples	Percent BDL	Lead concentration—percentile			
			Units	50th	75th	90th
Air—indoors	119	100	ng/m^3	BDL	BDL	BDL
Air—outdoors	116	100	ng/m^3	BDL	BDL	BDL
Dust	135	86	µg/g	BDL	BDL	131.0
Soil	139	85	µg/g	BDL	BDL	118.1
Food	159	0.6	µg/kg	6.4	9.2	16.1
Beverage	154	29	µg/kg	1.9	4.1	7.1
Drinking water consumed	73	51	µg/L	BDL	0.4	2.0
Tap water consumed	82	1	µg/L	0.4	0.9	1.3

BDL = below detection limit

Source: O'Rourke et al. 1999

Table 6-11. Total Lead Exposure of Subject Population From the NHEXAS Arizona Study

Exposure population	Number of subjects	Lead intake (µg/day)		
		Mean	Median	Range
All subjects	176	36	31	11–107
Adult male (>18 years of age)	55	42	37	16–107
Adult female (>18 years of age)	86	35	30	11–96
Children (<18 years of age)	35	27	25	15–45
Hispanic	54	40	34	14–107
Non-Hispanic	119	34	29	11–-96

Source: O'Rourke et al. 1999

from calcium supplements to blood lead in 21 adults divided into three treatment groups over a 6-month period. One treatment group received a complex calcium supplement (carbonate/phosphate/citrate), another group received calcium carbonate, and the last, the control group, received no supplement. The isotopic composition of the supplements differed from that of the subject's blood allowing the investigators to estimate the contribution of the supplements to PbBs. While the changes from baseline to treatment in isotopic composition were significant in the treatment groups, there was no discernable increase in PbB concentration during the study. The change in isotopic contribution, however, indicates that there is a limited input of lead from the diet into the blood in adults. These results are consistent in other investigations that showed minimal gastrointestinal absorption of lead in the presence of calcium in adults.

Plastic food wrappers may be printed with pigments that contain lead chromates. Plastic wrappers used for 14 different national brands of bread collected in New Jersey contained a mean concentration of 26 mg of lead for a bag size of 2,000 cm^2. A survey of 106 homemakers who buy such breads indicated that 39% of them reused the bags and 16% of the respondents turned the bags inside out to reuse them, suggesting that the potential exists for lead leaching from the paint into the stored food (Weisel et al. 1991).

Another source of dietary lead is the use of inadequately glazed or heavily worn earthenware vessels for food storage and cooking. Due to the number of incidences of lead poisoning that have resulted from the use of earthenware vessels, the FDA has established action levels of 0.5 μg/mL lead for pitchers to 5.0 μg/mL for cups and mugs soaked for 24 hours in a 4% acetic acid solution (FDA 1992). However, inadequately glazed pottery manufactured in other countries continues to pose a significant health hazard. Likewise, homemade or craft pottery and porcelain-glazed vessels have been found to release large quantities of lead, particularly if the glaze is chipped, cracked, or improperly applied. In addition, glaze on vessels that are washed repeatedly may deteriorate, and a vessel that previously met FDA standards may become unsafe (CDC 1985; EPA 1986a).

Blood lead levels measured as a part of the NHANES revealed that between 1976 and 1991, the mean PbBs of the U.S. population aged from 1 to 74 years dropped 78%, from 12.8 to 2.8 μg/dL. The prevalence of PbBs ≥10 μg/dL also decreased sharply from 77.8 to 4.3%. The major cause of the observed decline in PbBs is most likely the removal of 99.8% of lead from gasoline and the removal of lead from soldered cans (Pirkle et al. 1994). PbBs were consistently higher for younger children than for older children, for older adults than for younger adults, for males than for females, for blacks than for

whites, and for central-city residents than for noncentral-city residents. PbBs also correlated with low income, low educational attainment, and residence in the Northeast region of the United States. Data analyses of the PbBs from NHANES surveys 1991–1994 and 1999–2002 are provided in Table 6-12 (CDC 2005a). Geometric means as well as 95% confidence intervals were calculated, and the results were organized by age, race/ethnicity, and sex. For 1999–2002, the overall prevelance of elevated PbBs (≥10 μg/dL) was 0.7%, down from 2.2% in the 1991–1994 survey. Children aged 1–5 years had the highest prevelance, 1.6%, of all age groups for levels ≥10 μg/dL in the 1999–2002 survey. This percentage is down from 4.4% in the 1991–1994 NHANES survey (CDC 2005a). Approximately 310,000 children in this age group were at risk of exposure to harmful levels of lead. The largest decline (72%) in elevated PbB in the two surveys, from 11.2 to 3.1%, was among non-Hispanic black children aged 1–5 years. In 2000, the year that had been targeted for the elimination of PbBs, >25 μg/dL in children aged 6 months–5 years, a total of 8,723 children had been identified with PbBs ≥25 μg/dL. Lead surveillance data collected by states between 1997 and 2001 also show a decline in the number of children aged 1–5 years with PbBs ≥10 μg/dL from 130,512 in 1997 to 74,887 in 2001 (Meyer et al. 2003).

The Adult Blood Lead Epidemiology and Surveillance (ABLES) program, which tracks cases of adult (aged ≥16 years) elevated PbBs from workplace exposure, reported updated results from 25 participating states for the period 1998–2001 (Roscoe et al. 2002). During that period, the prevalence of adults with PbBs ≥25 μg/dL was 13.4 per 100,000 employed adults, compared with 15.2 per 100,000 for 1994–1997. For adults with blood lead levels ≥40 μg/dL, the prevalence rate was 2.9 per 100,000 during 1998–2001, compared with 3.9 per 100,000 for 1994–1997. ABLES surveillance data from 2004 tracked the blood lead levels of females of childbearing age (16–44 years) in 37 different states (CDC 2007). The results indicated that 0.06 per 100,000 had PbBs ≥40 μg/dL, 0.7 per 100,000 had PbBs ≥25 μg/dL, 3.9 per 100,000 had PbBs ≥10 μg/dL, and 10.9 per 100,000 had PbBs ≥5 μg/dL (CDC 2007).

A 1992 survey of lead in blood of 492 Inuit adults from the Arctic region of Quebec, Canada resulted in geometric mean lead concentrations of 0.42 μmol/L, with a range of 0.04–2.28 μmol/L. Analysis of variance revealed that smoking, age, and consumption of waterfowl were associated with elevated lead levels (Dewailly et al. 2001). A Swedish study was aimed at characterizing PbBs in 176 men and 248 women, 49–92 years of age (Baecklund et al. 1999). Blood lead levels ranged from 5.6 to 150 μg Pb/L (median 27 μg Pb/L) and were higher in men than in women (median 30 versus 24 μg Pb/L). In both men and women, PbBs decreased between 50 and 70 years of age, which was thought to be a result of decreased energy intake. In women, PbBs peaked at 50–55 years of age, which is probably related to

Table 6-12. Geometric Mean Blood Lead Levels (µg/dL) and the 95th Percentile Confidence Interval, by Race/Ethnicity, Sex, and Age

Sex/age (years)	Number in sample	All racial/ethnic groups	White, non-Hispanic	Black, non-Hispanic	Mexican American
NHANES 1991–1994 geometric mean (95% confidence interval)					
			Both sexes		
≥1	13,472	2.3 (2.1–2.4)	2.2 (2.0–2.3)	2.8 (2.5–3.0)	2.4 (2.3–2.6)
1–5	2,392	2.7 (2.5–3.0)	2.3 (2.1–2.6)	4.3 (3.6–5.0)	3.1 (2.7–3.5)
6–19	2,960	1.7 (1.5–1.8)	1.5 (1.4–1.7)	2.3 (2.1–2.6)	2.0 (1.8–2.1)
20–59	5,596	2.2 (2.1–2.3)	2.1 (2.0–2.2)	2.6 (2.4–2.8)	2.5 (2.4–2.6)
≥60	2,524	3.4 (3.2–3.5)	3.3 (3.2–3.4)	4.3 (3.7–4.9)	3.1 (2.7–3.6)
			Males		
≥1	6,204	2.8 (2.6–2.9)	2.6 (2.5–2.8)	3.6 (3.3–4.0)	3.1 (2.9–3.3)
1–5	1,211	2.8 (2.5–3.1)	2.3 (2.1–2.6)	4.7 (3.9–5.5)	3.3 (2.9–3.6)
6–19	1,443	1.9 (1.7–2.1)	1.7 (1.5–1.9)	2.7 (2.4–3.1)	2.3 (2.0–2.5)
20–59	2,365	2.9 (2.7–3.1)	2.7 (2.5–3.0)	3.6 (3.2–3.9)	3.4 (3.2–3.6)
≥60	1,185	4.2 (4.0–4.4)	4.0 (3.8–4.2)	6.3 (5.4–7.1)	4.1 (3.5–4.8)
			Female		
≥1	7,268	1.9 (1.8–2.0)	1.8 (1.7–1.9)	2.2 (2.0–2.4)	1.9 (1.8–2.1)
1–5	1,181	2.7 (2.4–2.9)	2.3 (2.0–2.6)	4.0 (3.2–4.8)	2.9 (2.4–3.4)
6–19	1,517	1.5 (1.3–1.7)	1.4 (1.2–1.6)	2.0 (1.7–2.2)	1.7 (1.5–1.9)
20–59	3,231	1.7 (1.6–1.8)	1.6 (1.5–1.7)	1.9 (1.8–2.1)	1.8 (1.7–1.9)
≥60	1,339	2.9 (2.7–3.0)	2.8 (2.7–3.0)	3.3 (2.8–3.8)	2.5 (2.1–2.9)
NHANES 1999–2002 geometric mean (95% confidence interval)					
			Both sexes		
≥1	16,825	1.6 (1.5–1.6)	1.5 (1.5–1.6)	1.8 (1.7–1.9)	1.6 (1.6–1.7)
1–5	1,160	1.9 (1.8–2.1)	1.8 (1.6–2.0)	2.8 (2.5–3.1)	1.9 (1.8–2.0)
6–19	6,283	1.1 (1.1–1.2)	1.1 (1.0–1.1)	1.5 (1.4–1.6)	1.3 (1.2–1.4)
20–59	5,876	1.5 (1.5–1.6)	1.5 (1.4–1.5)	1.7 (1.6–1.8)	1.8 (1.6–1.9)
≥60	3,056	2.2 (2.1–2.3)	2.2 (2.1–2.3)	2.7 (2.5–2.8)	2.1 (1.9–2.3)
			Males		
≥1	8,202	1.9 (1.8–2.0)	1.9 (1.8–1.9)	2.1 (1.4–1.6)	2.0 (1.9–2.2)
1–5	846	1.9 (1.8–2.1)	1.8 (1.6–2.0)	2.8 (2.5–3.2)	2.0 (1.8–2.1)
6–19	3,158	1.3 (1.3–1.4)	1.2 (1.1–1.3)	1.7 (1.5–1.8)	1.5 (1.4–1.6)
20–59	2,689	2.0 (1.9–2.0)	1.9 (1.8–2.0)	2.1 (2.0–2.3)	2.3 (2.2–2.5)
≥60	1,509	2.7 (2.6–2.8)	2.6 (2.5–2.7)	3.4 (3.1–3.6)	2.6 (2.3–2.8)
			Female		
≥1	8,623	1.3 (1.3–1.3)	1.3 (1.2–1.3)	1.5 (1.4–1.6)	1.3 (1.2–1.4)
1–5	764	1.9 (1.8–2.1)	1.8 (1.5–2.1)	2.8 (2.5–3.2)	1.8 (1.7–2.0)
6–19	3,125	1.0 (0.9–1.0)	0.9 (0.8–1.0)	1.3 (1.2–1.5)	1.1 (1.0–1.2)
20–59	3,187	1.2 (1.2–1.2)	1.2 (1.1–1.2)	1.4 (1.3–1.5)	1.3 (1.2–1.4)
≥60	1,547	1.9 (1.8–2.0)	1.9 (1.8–2.0)	2.3 (2.1–2.4)	1.8 (1.6–2.0)

Source: CDC 2005a

postmenopausal bone mineralization. Increases in PbBs after age 70 was thought to be a result from higher lead exposure in the past for this group. Nash et al. (2004) reported median adjusted PbBs that were 25–30% higher than for premenopausal women (2.0 μg/dL). Users of hormone replacement therapy had significant lower median PbBs. Lead stored in the bones of women is released into the blood during post menopausal bone mineral resorption.

Mourning doves and other game birds consume lead pellets from hunting fields for grit. Recreational and subsistence hunters and their families who consume large amounts of these birds may ingest lead from this source (Burger et al. 1998).

Lead is a component of tobacco and tobacco smoke, and smokers often have higher lead blood levels than nonsmokers (Bonanno et al. 2001; Mannino et al. 2003). Using data from the NHEXAS EPA Region V study, PbB levels in smokers and nonsmokers were analyzed and a correlation between tobacco smoke and exposure levels was observed (Bonanno et al. 2001). The mean PbBs in smokers, nonsmokers exposed to environmental tobacco smoke (ETS), and nonsmokers without ETS were 2.85, 2.06, and 1.81 μg/dL, respectively (Bonanno et al. 2001).

Table 6-13 provides geometric means and selected percentiles of lead levels in the urine in segments of the U.S. population (CDC 2003, 2005b). These data will continue to be updated as new information becomes available.

Information on occupational exposure to lead is obtained primarily from the National Occupational Exposure Survey (NOES) and industry surveys of workers. While occupational exposure is widespread, environmental monitoring data on levels of exposure in many occupations are not available. OSHA has established a permissible exposure limit (PEL) for lead of 50 $\mu g/m^3$ for workplace air (OSHA 2005d; Tripathi and Llewellyn 1990). NIOSH has estimated that >1 million American workers were occupationally exposed to inorganic lead in >100 occupations (NIOSH 1978a). According to NOES, conducted by NIOSH between 1980 and 1983, an estimated 25,169 workers were exposed to tetraethyl lead (not used in gasoline since December 31, 1995); approximately 57,000 employees were exposed to various lead oxides mostly in nonferrous foundries, lead smelters, and battery plants; 3,902 workers were exposed to lead chloride; and 576,579 workers were exposed to some other form of lead in the workplace in 1980 (NIOSH 1990). Workers who operate and maintain solid waste incinerators are also exposed to air lead levels as high as 2,500 $\mu g/m^3$ (Malkin et al. 1992).

Table 6-13. Geometric Mean and Selected Percentile Urine Concentrations (µg/L) of Lead in the U.S. Population From 1999 to 2002

Group and survey years	Geometric mean	Percentile				
		50th	75th	90th	95th	Sample size
Age 6 and older						
1999–2000	0.766	0.800	1.30	2.10	2.90	2,465
2001–2002	0.677	0.600	1.20	2.00	2.60	2,690
6–11 Years						
1999–2000	1.07	1.00	1.50	2.40	3.40	340
2001–2002	0.753	0.800	1.20	2.00	2.60	368
12–19 Years						
1999–2000	0.659	0.600	1.10	1.70	2.20	719
2001–2002	0.564	0.600	0.900	1.50	1.90	762
20 Years and older						
1999–2000	0.752	0.700	1.40	2.10	2.90	1,406
2001–2002	0.688	0.700	1.20	1.90	2.80	1,560
Males						
1999–2000	0.923	0.900	1.60	2.40	3.40	1,227
2001–2002	0.808	0.700	1.30	2.40	3.20	1,335
Females						
1999–2000	0.642	0.600	1.20	1.90	2.40	1,238
2001–2002	0.573	0.500	1.00	1.50	2.20	1,335
Mexican Americans						
1999–2000	1.02	1.00	1.70	2.80	4.10	884
2001–2002	0.833	0.80	1.50	2.40	3.20	683
Non-Hispanic blacks						
1999–2000	1.11	1.10	1.90	2.90	4.20	568
2001–2002	0.940	0.900	1.50	2.60	3.70	667
Non-Hispanic whites						
1999–2000	0.695	0.700	1.30	1.90	2.60	882
2001–2002	0.610	0.600	1.00	1.80	2.40	1,132

Source: CDC 2003, 2005b

Potentially high levels of lead may occur in the following industries: lead smelting and refining industries, battery manufacturing plants, steel welding or cutting operations, construction, rubber products and plastics industries, printing industries, firing ranges, radiator repair shops and other industries requiring flame soldering of lead solder (EPA 1986a; Feldman 1978; Goldman et al. 1987; NIOSH 1978a). In these work areas, the major routes of lead exposure are inhalation and ingestion of lead-bearing dusts and fumes. In the smelting and refining of lead, mean concentrations of lead in air can reach 4,470 μg/m^3; in the manufacture of storage batteries, mean airborne concentrations of lead from 50 to 5,400 μg/m^3 have been recorded; and in the breathing zone of welders of structural steel, an average lead concentration of 1,200 μg/m^3 has been found (Fu and Boffetta 1995). Evaluations by NIOSH from 1979 to 1990 in radiator repair shops found that 68% of the workers sampled had airborne lead exposures exceeding the OSHA standard of 0.05 mg/m^3 (Tharr 1993). Also, past studies of PbBs of 56 radiator shop mechanics in the Boston area revealed that 80% had PbBs >30 μg/dL and 16 had PbBs exceeding 50 μg/dL (Tharr 1993).

Studies have been conducted to determine exposure of firearm instructors to lead at outdoor firing ranges when either nonjacketed (pure lead) or jacketed (copper-coated) bullets were used. Instructors are likely to have higher exposure than shooters because they spend more time at the range. In studies at an outdoor range in Virginia, the mean breathing zone lead level when nonjacketed bullets were fired was 67.1 μg/m^3 for one instructor and 211.1 μg/m^3 for another (Tripathi and Llewellyn 1990). When jacketed bullets were used, breathing zone levels decreased to 8.7 μg/m^3 or less. PbBs of the instructors did not exceed the OSHA return standard of 1.93 μmol/L (40 μg/dL) or removal standard of 2.4 μmol/L (50 μg/dL) in either case. When shooters fired conventional lead bullets, their mean exposures to airborne lead were 128 μg/m^3 in the personal breathing zone and 68 μg/m^3 in the general area. When totally copper-jacketed lead bullets were fired, the mean breathing zone and general area air sample concentrations were 9.53 and 5.80 μg/m^3, respectively (Tripathi and Llewellyn 1990). At an outdoor uncovered range in Los Angeles, instructors who spent an average of 15–20 hours/week behind the firing line were found to be exposed to breathing zone lead concentrations of 460 and 510 μg/m^3 measured as 3-hour, time-weighted averages. The PbB of one instructor reached 3.38 μmol/L (70 μg/dL). After reassignment to other duties, repeat testing indicated his PbB had dropped to 1.35 μmol/L (28 μg/dL) (Goldberg et al. 1991).

In 1991, NIOSH conducted a survey of the Federal Bureau of Investigations (FBI) Firearms Training Unit firing ranges and related facilities to determine occupational lead exposures among FBI and Drug Enforcement Agency (DEA) firing range personnel (NIOSH 1996). Sixty-one personal breathing-zone

and 30 area samples for airborne lead were collected. Exposures ranged up to 51.7 μg/m^3 (mean, 12.4 μg/m^3), 2.7 μg/m^3 (mean, 0.6 μg/m^3), and 4.5 μg/m^3 (mean, 0.6 μg/m^3) for range instructors, technicians, and gunsmiths, respectively. Exposure of custodians ranged from nondetectable to 220 μg/m^3 during short-term cleaning of a large indoor range. Carpet dust sampling of dormitory rooms of students who practiced at the firing ranges revealed statistically significant ($p<0.0005$) higher dust-lead concentrations when compared to nonstudent dormitories (dust-lead concentration range of 116–546 μg/g with a geometric mean of 214 μg/g in the student's rooms versus a dust-lead concentration range of 50–188 μg/g with a geometric mean of 65 μg/g for the nonstudent rooms). This suggested that the students were contaminating their living quarters with lead.

Field surveys of three radiator repair shops in the Cincinnati area revealed that local exhaust ventilation (LEV) systems are effective in controlling airborne lead levels. The highest concentration of airborne lead measured during a brief period of continuous soldering in a shop equipped with an LEV was only 7.1 μg/m^3. In a shop where no LEV was used, the 13 personal samples averaged 209 μg/m^3 with a maximum of 810 μg/m^3 measured for a 56-minute sample worn while tearing down and resoldering a single radiator (Tharr 1993).

Airborne dusts settle onto food, water, clothing, and other objects, and may subsequently be transferred to the mouth. A study suggests that lead, applied to the skin as lead acetate or lead nitrate, was rapidly absorbed through the skin and was detected in sweat, blood, and urine within 6 hours of application (Stauber et al. 1994). In this study, 4.4 mg of lead was applied to the skin under a covered wax/plastic patch on the forearms of human subjects; of the applied dose, 1.3 mg of lead was not recovered from skin washings. The amount that actually remained in (or on) the skin and the mass balance of the fate of this lead was not determined; it may have been dermally absorbed or eliminated from the skin by exfoliation of epidermal cells. Thus, while this study provides evidence for dermal absorption of lead, it did not quantify the fraction of applied dose that was absorbed. The quantitative significance of the dermal absorption pathway as a contributor to lead body burden remains uncertain.

In these occupational areas, good housekeeping and good ventilation have a significant impact on the extent of worker exposure. Workers who were (or are) involved in the production of gasoline additives, tetraethyl lead and tetramethyl lead (now banned from highway use in the United States) are exposed to both inorganic lead and alkyl lead. The major potential hazard to these workers appears to be from dermal exposure since alkyl leads may be absorbed through the skin (Bress and Bidanset 1991; EPA 1986a). Others who may be occupationally exposed to lead are artists and crafts persons who may be

exposed to lead used in paints, ceramic glazes, and lead solder for sculpture and stained glass (Fischbein et al. 1992; Hart 1987) and welders where lead concentrations in the welding fumes generated by gas metal arc welding of carbon steel ranged from 1.0 to 17.6 μg/m^3, well below the established PEL for the workplace (Larson et al. 1989). A study conducted at two lead battery factories in Taiwan revealed a high correlation between ambient air concentration of lead and PbBs in workers; improvement of hygienic practices proved to be more effective at lowering PbBs than reducing the ambient air lead concentration (Lai et al. 1997).

Lead exposure is frequently monitored by biological testing (e.g., determination of urinary lead levels, PbBs, urinary coproporphyrin levels, or δ-aminolevulinic acid [ALA] levels) rather than monitoring the workplace environment for lead concentrations (EPA 1986a; NIOSH 1978a). An employer survey of California industries that use lead indicated that 229,434 employees were potentially exposed to lead in the workplace; of these workers, 59,142 (25%) had received routine biological monitoring (i.e., determination of PbBs), and only 24,491 (10%) were in positions where environmental monitoring (workplace air lead levels) had ever been conducted. In addition, approximately 12% of the potentially exposed individuals were in the construction industry (OSHA 1993; Rudolph et al. 1990).

Workers in an electronic components plant that makes ceramic-coated capacitors and resistors using leaded glass for the ceramic coating were found to be exposed to ambient lead levels ranging from 61 to 1,700 μg/m^3, and to have PbBs ranging from 16 to 135 μg/dL. Approximately 30% of the workforce was found to be on medical leave as a result of their PbBs exceeding 40 μg/dL. An analysis of PbBs among family members of the exposed workers gave revealed levels of 10.2 μg/dL compared with 6.2 μg/dL for families of nonexposed workers, indicating possible secondary occupational exposure from workers to their families (Kaye et al. 1987).

Data from the NHANES III was used to compile statistics regarding the PbBs in U.S. workers (Yassin et al. 2004). The greatest levels tended to occur in mechanical and construction trades, while the lowest levels were observed for workers involved in professional labor categories such as managerial positions and health care professionals. Lead levels increased with age, decreased with education level, and male workers had a much higher geometric mean blood level, 3.3 μg/dL, than female workers, 1.8 μg/dL. Tables 6-14 and 6-15 summarize the results from these data for different industries and occupations. Okun et al. (2004) evaluated trends in occupational lead exposure in U.S. industries following the establishment of the general industrial lead standard in 1978 and the construction lead standard in 1993. They used data collected by OSHA under their compliance and consultation programs. On the basis of

Table 6-14. Median, Range, and Weighted Geometric Mean Blood Lead Levels in U.S. Workers, Ages 18–64 in 1988–1994

Occupation	Number of workers	µg/dL		
		Median	Range	WGM (GSD)
Vehicle mechanics	169	5.10	0.70–28.10	4.80 (3.88)
Food service workers	700	2.30	0.70–27.00	2.00 (2.69)
Management, professional, technical and sales	4,768	2.20	0.70–39.40	2.13 (4.05)
Personal service workers	1,130	2.90	0.70–25.90	2.48 (4.52)
Agricultural workers	498	3.80	0.70–23.40	2.76 (4.02)
Production workers: machine operators, material movers, etc.	1,876	3.30	0.70–52.90	2.88 (4.24)
Laborers other than construction	137	4.70	0.70–21.80	3.47 (3.36)
Transportation workers	530	3.85	0.70–22.30	3.49 (5.10)
Mechanics other than vehicles	227	4.10	0.70–16.60	3.50 (4.91)
Construction trades people	470	4.30	0.70–16.90	3.66 (4.64)
Construction workers	122	4.70	1.20–36.00	4.44 (7.84)
Health service workers	499	2.00	0.70–22.40	1.76 (2.24)
All	11,126	2.80	0.70–52.90	2.42 (6.93)

GSD = geometric standard deviation; WGM = weighted geometric mean

Source: Yassin et al. 2004

Table 6-15. Median, Range, and Weighted Geometric Mean Blood Lead Levels in U.S. Workers, Ages 18–64 by Industrial Categories[a]

Industry	Number of workers	Blood lead (µg/dL)		
		Median	Range	WGM (GSD)
Repair services (SIC 75–76)	188	4.80	0.70–28.10	4.54 (5.05)
Wholesale and retail trade (SIC 50–59)	2,229	2.50	0.70–39.40	2.25 (3.38)
Finance, insurance, and real estate (SIC 60–65, 67)	1,117	2.40	0.70–28.70	2.30 (2.74)
Agriculture (SIC 01–02, 07–08)	493	3.80	0.70–23.40	2.68 (4.09)
Transportation and utility (SIC 40–49)	764	3.10	0.70–22.30	2.58 (3.49)
Manufacturing (SIC 20–32, 34–39)	2,008	3.10	0.70–41.80	2.66 (4.51)
Metal (SIC 33)	188	3.80	0.70–52.90	3.50 (2.91)
Construction (SIC 15–17)	671	4.40	0.70–36.00	3.68 (5.66)
Mining (SIC 10, 12–14	41	3.90	1.10–12.90	4.66 (6.23)
Services (SIC 770, 72–73, 78–79, 80–84, 86–89, 91–97)	3,449	2.30	0.70–23.70	2.05 (4.39)
All	11,148	2.80	0.70–52.90	2.42 (6.93)

[a]Working population aged 18–64: U.S. Third National Health and Nutrition Examination Survey, 1988–1994

GSD = standard deviation of geometric mean, SIC = standard industrial code; WGM = weighted geometric mean

Source: Yassin et al. 2004

these data, there has been a decline in occupational lead exposures for general industry facilities since 1979. The median exposure level for these facilities declined 5–10-fold. With the exception of retail trade, these declines were for the major industry divisions and the majority of four-digit SIC codes including some high risk industries. A decline was not observed in the construction industry, but in this case, the data are only for a limited number of years.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

The American Academy of Pediatrics (AAP) (1998) has concluded that although monitoring data demonstrate a decline in the prevalence of PbBs, lead remains a common, preventable, environmental health threat. The AAP supports the CDC guidelines endorsing universal screening in certain areas and targeted screening for children at high risk (CDC 1997c). Many children continue to be at risk for ingestion of lead-based paint and of soil and dust contaminated through the deterioration of lead-based paint and the residues from combustion of leaded gasoline. A 1974 study indicated that elevated PbBs in children were most likely a result of ingesting lead-contaminated soil, and that the most likely source was lead-based paint rather than lead from automotive exhaust (Ter Haar and Aronow 1974). However, subsequent data have shown that children with the highest PbBs live in areas with high traffic flow where lead particles in the air may fall directly to the soil or adhere to the outer surfaces of building and wash to the soil with rain (Mielke et al. 1989). Studies of children in Minnesota showed that PbBs in children were correlated with soil lead levels, which were highest in inner-city areas; soil lead levels and PbBs were not correlated with the age of housing, although the presence of lead-based paint or lead abatement procedures may be of significance for individual children (Mielke et al. 1989). The CDC has concluded

that the most common source of lead exposure for children is lead-based paint that has deteriorated into paint chips and lead dusts (CDC 1997b).

The results of successive NHANES monitoring studies suggest that from 1976 to 2002, PbBs have declined, but were consistently higher for younger children than for older children (CDC 1997b, 1997d, 2003, 2005a, 2005b; Pirkle et al. 1994). In general, PbBs also correlated with low income, low educational attainment, and residence in the Northeast region of the United States. Data from Phase II of NHANES III (conducted during October 1991 to September 1994) and the most recent data (1999–2002) indicate that PbBs in the U.S. population aged ≥1 year continued to decrease and that PbBs among children aged 1–5 years were more likely to be elevated among those who were poor, non-Hispanic black, living in large metropolitan areas, or living in older housing (with potential exposure to lead from lead-based paint) (CDC 1997b, 2003. 2005a, 2005b; Pirkle et al. 1998). During 1991–1994, the overall geometric mean PbB of the population aged ≥1 year was 2.3 μg/dL. Among those aged 1–5 years, approximately 4.4% had PbBs ≥10 μg/dL, representing an estimated 930,000 children in the general population with levels high enough to be of concern (CDC 1997b). In addition, 1.3% of children aged 1–5 years had PbBs ≥15 μg/dL and 0.4% had PbBs ≥20 μg/dL. For the NHANES III Phase II data, the geometric mean PbBs were higher for children aged 1–2 years (3.1 μg/dL) than for children aged 3–5 years (2.5 μg/dL) (CDC 1997b). For the most recent 1999–2002 NHANES sample, the geometric mean PbB for children ≥1 year was 1.6 μg/dL and among those aged 1–5 years, approximately 1.6% had PbBs ≥10 μg/dL (CDC 2005a). These data have been summarized in Table 6-12.

The U.S. Navy instituted a pediatric lead surveillance program in 1995 because of public health concerns over pediatric PbBs (Bohnker et al. 2003). The database contained 38,502 samples from 1995 to 2001 with 1.6% containing levels ≥10 μg/dL. Samples were obtained at the time of the 12-month well-child visit. Results were similar to those for the NHANES survey.

Fetuses are at even greater risk. As discussed in Section 3.5, lead can readily cross the placenta; therefore, exposure of women to lead during pregnancy results in uptake by the fetus. Furthermore, since the physiological stress of pregnancy may result in mobilization of lead from maternal bone, fetal uptake of lead can occur from a mother who was exposed to lead before pregnancy, even if no lead exposure occurs during pregnancy. Prenatal exposure may be related to postnatal mental retardation, impaired postnatal neurobehavioral development, and reduced birth weight and gestational age (EPA 1986a).

Maternal PbBs during pregnancy were significantly higher for a group of 1,428 immigrant women (geometric mean, 2.3 μg/dL) than for a group of 504 non-immigrant women (geometric mean, 1.9 μg/dL) in a study conducted at a medical center in South Central Los Angeles, one of the most economically depressed regions in California. Immigrant PbBs were strongly dependent on time elapsed since immigration to the United States, with PbBs being highest in those women who had immigrated most recently. Elevated PbBs in immigrant women were also associated with pica and with low dietary calcium during pregnancy (Rothenberg et al. 1999a, 1999b).

Lead concentrations in maternal and umbilical cord blood have been reported by Greek researchers for 50 parturient women at delivery. Twenty-five of the women lived in industrial areas with high air pollution, and 25 lived in agricultural areas with low air pollution. The mean lead concentrations (expressed as mean±SD) for the women living in areas with high air pollution were 3.72±0.47 μg/dL in maternal blood and 2.0±0.34 μg/dL in umbilical cord blood (correlation coefficient, r=0.57). The mean lead concentrations for the women living in areas with low air pollution were 2.05±0.56 μg/dL in maternal blood and 1.29±0.36 μg/dL in umbilical cord blood (correlation coefficient, r=0.70). The authors concluded that the placenta demonstrates a dynamic protective function that is amplified when maternal PbBs are raised (Vasilios et al. 1997).

Concentrations of lead in umbilical cord blood of two groups of women giving birth in a Boston Hospital in 1980 and 1990 have also been reported. Mean lead concentrations of umbilical cord blood were 6.56±3.19 μg/dL for the 1980 group and 1.19±1.32 μg/dL for the 1990 group (Hu et al. 1996b).

In a study of blood samples collected from 113 mothers of 23 different nationalities and from their neonates (cord blood), mean maternal PbBs were 14.9±2.14 μg/dL (range, 6.6–27.8 μg/dL) and mean cord PbBs were 13±2.5 μg/dL (range, 6.0–30 μg/dL). Sixteen percent of mothers and nearly 10% of cord blood samples had PbBs >20 μg/dL (Al Khayat et al. 1997b).

Malcoe et al. (2002) assessed lead sources and their effect on blood lead in rural Native American and white children living in a former mining region. Blood samples, residential environmental samples (soil, dust, paint, water) and caregiver interviews (hand-mouth behaviors, socioeconomic conditions) were obtained from a representative sample of 245 children ages 1–6. There were no ethnic differences in the results. However poor children were especially vulnerable. Regression analysis showed that mean floor dust lead loading >10.1 $\mu g/ft^2$ and yard soil lead >165.3 mg/kg were independently associated with blood lead levels ≥10 μg/dL.

FDA estimated that in 1990, toddlers (2-year-olds) received 16% of their total lead exposure from food (5 μg/day), 1% from soil, 7% from water, and 75% from dust. EPA estimated that in 1990 lead intake from U.S. drinking water would be 11.9 μg/day for a 6-year-old child and 7.5 μg/day for an infant <1 year old (Cohen 1988). A study of lead in the diet of Canadian infants found an average intake by children 0–1 years of age to be 16.5 μg/day when both food and water ingestion were considered (Dabeka and McKenzie 1988).

Lead intoxication has been observed in children, but rarely in adults, in residential settings (Sedman 1989). The geometric mean blood lead level for children has dropped dramatically since the late 1970s. Results summarizing the CDC NHANES II and NHANES III, Phases I and II, study of blood lead levels for children aged 1–5 years are provided in Table 6-16 (CDC 1997b, 1997d, 2005a).

In 1982–1983, the baseline value for daily intake of lead by inhalation in a nonurban environment was estimated to be 0.5 μg/day for a 2-year-old child. The baseline value was based on an average atmospheric lead concentration of 0.1 $\mu g/m^3$ and an indoor/outdoor lead concentration ratio of 0.5. In an urban environment, the indoor/outdoor ratio was assumed to be approximately 0.8 (EPA 1986a). Drastic reductions in the lead content of gasoline since 1986 have resulted in a 64% decrease in lead emissions to the atmosphere (see Section 6.4.1).

The lead content of dusts can be a significant source of exposure, especially for young children. Baseline estimates of potential human exposure to dusts, including intake due to normal hand-to-mouth activity, are 0.2 g/day for children 1–6 years old versus 0.1 g/day for adults when both indoor and outdoor ingestion of soil including dust is considered (EPA 1989c). For children who engage in pica behavior, the ingestion rate of soil can be as high as 5 g/day. Although ingestion of lead-containing paint may lead to elevated PbBs in young children, the major source of moderately elevated PbBs (30–80 μg/dL) in inner city children is most likely to be contaminated household dust and subsequent hand contamination and repetitive mouthing (Charney et al. 1980). Weathering of lead-based paint can contribute to the lead content of dust and soil. Lead levels of indoor dust and outdoor soil were found to be strongly predictive of PbBs in over 200 urban and suburban infants followed from birth to 2 years of age; however, the PbBs were not correlated with indoor air or tap water lead levels, nor the size of nearby roadways. Indoor dust lead levels and soil lead levels in the homes of children with high PbBs (>8.8 μg/dL) were 72 μg/wipe (window sill dust) and 1,011 μg/g, respectively; children with low PbBs (<3.7 μg/dL) were exposed to 22 μg/wipe and 380 μg/g, respectively. In addition, 79% of the homes of children with high PbBs had

Table 6-16. Blood Levels of Lead in Children (1–5 Years) in 1976–2002

Children (1–5 Years)	NHANES			
	1976–1980	1988–1991	1991–1994	1999–2002
Geometric mean (µg/dL)	15.0	3.6	2.7	1.9
Blood lead ≥10 µg/dL	88.2%	8.9%	4.4%	1.6%

NHANES = National Health and Nutrition Examination Survey

Sources: CDC 1997b, 1997d, 2005a; Pirkle 1994

been renovated, while only 56% of the homes of children with low PbBs had been renovated, suggesting that renovating the interior of homes previously painted with leaded paint may increase, at least temporarily, a child's exposure to lead dust (Rabinowitz et al. 1985). Regular use of dust control methods (e.g., wet mopping of floors, damp-sponging of horizontal surfaces, high-efficiency vacuum cleaner) has been shown in some, although not all, cases to reduce indoor dust, lead dust, and blood lead levels in some, although not all, older homes containing leaded paints (Lanphear et al. 2000b; Rhoads et al. 1999). Decreases of between 17 and 43% in blood lead concentrations were observed in children where regular dust control methods had been used to reduce indoor levels of lead (Rhoads et al. 1999).

Lanphear and Roghmann (1997) and Lanphear et al. (1996a, 1996b, 1998b) studied factors affecting PbBs in urban children and found the following independent predictors of children's PbBs: dust lead loading in homes, African-American race/ethnicity, soil lead levels, ingestion of soil or dirt, lead content and condition of painted surfaces, and water lead levels (Lanphear et al. 1996a). Differences in housing conditions and exposures to lead-containing house dust appear to contribute to the racial differences in urban children's PbBs. In addition, white children were more likely to put soil in their mouths (outdoor exposure) and suck their fingers, and African-American children were more likely to put their mouths on window sills (indoor exposure) and to use a bottle. Exterior lead exposures were more significant for white children, and interior lead exposures were more significant for African-American children (Lanphear et al. 1996b). Mouthing behaviors are an important mechanism of lead exposure among urban children (Lanphear and Roghmann 1997). Community characteristics such as residence within a city, proportion of African Americans, lower housing value, housing built before 1950, higher population density, higher rates of poverty, lower percent of high school graduates, and lower rates of owner-occupied housing have been used to identify children with elevated blood levels (Lanphear et al. 1998b). An analysis of children's PbBs and multiple measures of lead concentrations in household dust, water, soil, and paint has been used to predict the effect of changing concentrations of lead in environmental media on children's PbBs. An increase in dust lead loading from background to 200 μg/ft^2 was estimated to produce an increase of 23.3% in the percentage of children estimated to have a PbB >10 μg/dL; an increase in water lead concentration from background to 15 μg/L was estimated to produce an increase of 13.7% in the percentage of children estimated to have a PbB level >10 μg/dL; and an increase in soil lead concentration from background to 400 μg/g was estimated to produce an increase of 11.6% in the percentage of children estimated to have a PbB level >10 μg/dL (Lanphear et al. 1998a).

Outdoor lead dust was found to be a more potent contaminant of children's hands than indoor dust at day care centers in New Orleans; boys, in general, had higher hand lead levels than girls. The conclusions

were based on lead analysis of hand wipe samples taken before and after children played outdoors at four different day care centers (a private inner-city site, a private outer-city site, a public inner-city site, and a public outer-city site). The private inner-city site had a severely contaminated outdoor play area with measured soil lead concentrations ranging from 287 to 1,878 mg/kg. The outdoor play area at the public inner-city site, where children exhibited the lowest hand lead measurements of any site in the study, had been completely paved over with concrete or rubberized asphalt and had well-maintained equipment (Viverette et al. 1996).

EPA conducted the Urban Soil Lead Abatement Demonstration Project (USLADP), also known as the "Three City Lead Study," in Boston, Baltimore, and Cincinnati (EPA 1996c). The purpose was to determine whether abatement of lead in soil could reduce PbBs of inner-city children. No significant evidence was found that soil abatement had any direct impact on children's PbBs in either the Baltimore or Cincinnati studies. In the Boston study, however, a mean soil lead reduction of 1,856 ppm resulted in a mean decline of 1.28 μg/dL PbB at 11 months postabatement (Weitzman et al. 1993). Phase II extended the study to 2 years and included soil abatement of the two comparison areas from Phase I (Aschengrau et al. 1994). Combined results from Phase I and II suggested a higher impact of soil remediation on PbBs (2.2–2.7 μg/dL). EPA reanalyzed the data from the USLADP in an integrated report (EPA 1996c). They concluded that when soil is a significant source of lead in the child's environment, under certain conditions, the abatement of that soil will result in a reduction in exposure and consequently, PbB level. Crump (1997) criticized the Boston data, including EPA's integrated report, for poor selection of statistical methods, failure to adequately examine confounding variables, selective interpretation of results, and lack of control group in phase II of the study. Regardless, his reevaluation of the data, based on randomization analysis, resulted in a significant, yet modest effect of soil abatement (1.37 μg/dL) consistent with the conclusions of Weitzman et al. (1993) (1.28 μg/dL). Clearly, the results of the USLADP suggest that a number of factors are important in determining the influence of soil remediation on PbBs in children. These include the site-specific exposure scenario, the magnitude of the remediation, and the magnitude of additional sources of lead exposure.

Authors of a study of PbBs in children in Toronto, Canada, before and after abatement of lead-contaminated soil and house dust found that they could neither strongly support nor refute beneficial effects of abatement. The failure to reach a definite conclusion from the results of the study, which included data from 12 cross-sectional blood-screening surveys that were conducted over an 8-year period, was due in part to a low response rate (32–75%) to questionnaires used to determine behavioral,

household, lifestyle, neighborhood, and environmental factors relating to study participants (Langlois et al. 1996).

A study by Davis et al. (1992, 1994) used electron microprobe analysis of soil and waste rock from Butte, Montana, to help explain the low PbBs observed in young children living in that mining community. They hypothesized that, if soils were ingested, the lead bioavailability would be constrained by alteration and encapsulation of the lead-bearing minerals of the Butte ore body (galena, anglesite, cerussite, and plumbojarosite), which would limit the available lead-bearing surface area. Kinetic limitations relative to the residence time of soil in the gastrointestinal tract also affect the bioavailability of lead (Ruby et al. 1992). The inherent chemical properties of soil-lead adsorption sites may reduce the bioavailability of soil-lead compared to soluble lead salts and lead compounds ingested without soil (Freeman et al. 1992). It has been shown that lead in impacted unleaded and leaded automobile exhaust particulate matter is readily leachable, but lead in paint may not be as leachable (Que Hee 1994). Thus, the differential availability may cause differential lead bioaccessibility and hence bioavailability. The extent of absorption of lead into the tissues of young Sprague-Dawley rats has been determined (Freeman et al. 1992). The animals were fed various concentrations of lead-contaminated mining waste soil mixed with a purified diet for 30 days. The overall percentage bioavailability values, based on lead acetate as the standard, were: 20% based on blood data; 9% based on bone data; and 8% based on liver data. These low bioavailabilities agree favorably with the low blood levels (average, 3.5 μg/dL) found in children in Butte, Montana (Freeman et al. 1992). EPA (1989c) uses 0.2 g/day as a typical soil ingestion rate (including both dirt and dust) for children 1–6 years of age.

Seasonal variations in PbBs in children have been observed in a number of studies. Mean PbBs in the State of New York have been shown to increase by 15–30% in the late summer as compared to mean values obtained during late winter/early spring (Haley and Talbot 2004). Blood lead measurements taken from children aged 0–6 years in Syracuse, New York over a 48-month period beginning in January 1992, showed a regular yearly periodicity in blood lead concentrations, which peaked in the late summer (Johnson and Bretsch 2002). These seasonal variations in PbBs have been attributed to ingestion of lead in soil. Indeed, the work of Johnson and Bretsch (2002), which looked at the relationship between PbBs measured in children and soil lead concentrations within small regional grids (600 m by 600 m) laid out over the City of Syracuse, New York, showed a correlation between the geometric mean PbBs and the median soil lead concentrations (r^2>0.65).

In addition to the ingestion of hand soil/dust through normal hand-to-mouth activity, some children engage in pica behavior (consumption of nonfood items), which can put them at increased risk through ingestion of large amounts of soil contaminated with lead. It has been estimated that an average child may ingest between 20 and 50 mg of soil/day and that a pica child may ingest 5,000 mg or more of soil/day (LaGoy 1987; Mielke et al. 1989). If the soil contains 100 μg/g of lead, an average child may be exposed to 5 μg of lead/day from this source alone (Mielke et al. 1989), and a pica child may be exposed to >100 times that amount. At the EPA's *Soil Screening Guidance* concentration of 400 mg Pb/kg soil, a 13-kg child who consumes 5 g of soil during a pica episode would have a dose from soil of 0.2 mg Pb/kg of body weight, which is 10 times the nonlethal toxic dose (Calabrese et al. 1997b; Stuik 1974). Yard soil containing lead concentrations >500 mg/kg has been associated with a mean PbB ≥10 μg/dL in children 6–71 months of age in a multi-site study (Agency for Toxic Substances and Disease Registry 1995).

Improper removal of lead from housing known to contain lead-based paint can significantly increase lead levels in dust, thus causing lead toxicity in children living in the home during the lead-removal process. Four such cases have been documented (Amitai et al. 1987). In January 1995, the New York State Department of Health identified 320 children in 258 households in New York State (excluding New York City) with PbBs ≥20 μg/dL that were considered to be attributable to residential renovation and remodeling (CDC 1997d).

Trace metals, including lead, have been detected in human breast milk, so breast-feeding could deliver lead to an infant. Levels of lead in human milk vary considerably depending on the mother’s exposure and occupation. For example, levels of lead in the milk of a mother who had worked in a battery factory for the first 6 months of pregnancy varied from 4 to 63 μg/L in samples taken soon after the birth of the child up to 32 weeks later. These concentrations were similar to those in control samples even though the PbB of the mother was about 3 times higher than that of the control subject. The pharmacokinetic model for lead may be complex since >90% of the lead body burden is stored in bone tissue and lead is strongly bound to hemoglobin, which may impede its partition to milk (Wolff 1983). On the other hand, an analysis of 210 human milk samples taken across Canada showed a mean lead level of 1.01 μg/L. Women who resided in homes that were >30 years old, lived in high-traffic areas for >5 years, or had drunk three or more cups of coffee in the preceding 24 hours prior to taking the milk sample, had higher lead levels. The increased lead levels resulting from coffee drinking were thought to be the result of mobilization by the coffee of the lead stored in tissues and bone (Dabeka et al. 1988). In a paper by Abadin et al. (1997b), results of several additional studies of lead in human milk are summarized and discussed from a public health perspective. Among other citations, the median lead in milk

concentrations from 41 volunteers in Sweden was 2 μg/L (Larsson et al. 1981); the mean value for urban residents of Germany in 1983 was 9.1 μg/L (Sternowsky and Wessolowski 1985); and the concentration in 3-day postpartum milk samples from 114 women in Malaysia averaged 47.8 μg/L (Ong et al. 1985).

Gulson et al. (1998a, 2001c) used measured lead isotope ratios ($^{207}Pb/^{206}Pb$ and $^{206}Pb/^{204}Pb$) in mothers' breast milk and in infants' blood to establish that, for the first 60–90 days postpartum, the contribution from breast milk to blood lead in the infants varied from 36 to 80%. Lead release during maternal bone loss and maternal diet appear to be the major sources of lead in breast milk fed infants. Other sources of lead, such as air, soil, and dust are considered to contribute minimally to lead concentrations in infant blood. Mean lead concentration (±SD) in breast milk for participants in the study was 0.73±0.70 μg/kg.

Sowers et al. (2002b) examined the relationship between lead concentrations in breast milk, maternal blood lead concentration, and maternal bone loss in 15 mothers who breast-fed compared to 30 mothers who bottle-fed commercial formula. The data showed a modest correlation ($p<0.07$) between maternal blood lead and breast milk concentrations at 1–2 months postpartum. However, a stronger correlation ($p<0.001$) was observed between the mean extent of bone loss (5.6%) and lead concentrations in breast milk in women who breast-fed between 1.5 and 6 months postpartum.

In a review of data on occupational chemicals that may contaminate breast milk (Byczkowski et al. 1994), it is stated that lead may be excreted in milk in amounts lethal to the infant and that the metal may be mobilized from bone stores to milk during the lactation period. Even when the concentration of lead in mother’s milk is low, the absorption of metals into the systemic circulation of infants is generally high when they are on a milk diet. To better understand the sensitivity of the nursing infant to chemicals, epidemiological studies, chemical monitoring, and model development and application are needed.

Lead has also been reported in home-prepared reconstituted infant formula. Two of 40 samples collected in a Boston-area study had lead concentrations >15 μg/L. In both cases, the reconstituted formula had been prepared using cold tap water run for 5–30 seconds, drawn from the plumbing of houses >20 years old. Three preparation practices for infant formula should be avoided: (1) excessive water boiling, (2) use of lead-containing vessels, and (3) morning (first-draw) water (Baum and Shannon 1997). Gulson et al. (1997a) measured lead in household water throughout the day when the plumbing system of an unoccupied test house was not flushed. Water concentration data ranged from 119 μg/L for the initial (first-draw) sample to 35–52 μg/L for hourly samples to 1.7 μg/L for a fully flushed sample. The water concentration data were used in the EPA's Integrated Exposure Uptake and Biokinetic (IEUBK) Model

for Lead in Children to predict PbBs in infants drinking water (or formula reconstituted using water) drawn from the same tap. Predicted PbBs in infants only exceeded 10 μg/L when 100% of the water consumed contained 100 μg Pb/L (Gulson et al. 1997a).

Lead-containing ceramic ware used in food preparation has also been associated with childhood lead exposure in children of Hispanic ethnicity in San Diego County, California. One study (Gersberg et al. 1997) used the IEUBK to determine that dietary lead exposure from beans prepared in Mexican ceramic bean pots may account for a major fraction of blood lead burden in children whose families use such ceramic ware.

Workers occupationally exposed to lead apparently carry lead home on clothing, bodies, or tools. PbBs of children in households of occupationally exposed workers were almost twice those of children in neighboring homes whose parents were not occupationally exposed to lead (median ranges were 10–14 and 5–8 μg/dL, respectively) (Grandjean and Bach 1986). Young children (<6 years old) of workers exposed to high levels of lead in workplace air at an electronic components plant (61–1,700 μg lead/m^3 ambient concentrations) had significantly elevated PbBs (13.4 μg/dL) compared with children from the same locale whose parents did not work in the electronics plant (7.1 μg/dL) (Kaye et al. 1987). Based upon data collected from 1987–1994, children aged 1–5 years (n=139) of workers whose occupation resulted in lead exposure had a geometric mean PbB of 9.3 μg/dL as compared to a U.S. population geometric mean of 3.6 μg/dL (Roscoe et al. 1999). Of this group, 52% of the children had PbBs ≥10 μg/dL compared to 8.9% of the U.S. population and 21% had PbBs ≥20 μg/dL compared to 1.1% of the U.S. population (Roscoe et al. 1999). Exposures of lead workers' families have been identified in nearly 30 different industries and occupations. Industries in which exposure of family members has been reported most often include lead smelting, battery manufacturing and recycling, radiator repair, electrical components manufacturing, pottery and ceramics, and stained glass making (NIOSH 1995). Children of lead-exposed construction workers may also be at increased risk (Whelan et al. 1997).

Children may be exposed to lead because of activities associated with certain hobbies and artistic activities practiced by adults in the home. Some of the more obvious hobbies and activities involving use of lead-containing materials (casting, stained glass, pottery, painting, glassblowing, screenprinting) are discussed in Section 6.5. Activities involving use of lead-containing materials should always be done in an area well-ventilated with outdoor air and should never be done with children in the same room or in

close proximity. Recent data by Maas et al. (2005) indicate that high levels of lead are prevalent in inexpensive cosmetic jewelry that is sold to the general public at retail stores (see Section 6.4.5).

Children may be exposed to lead from other hobby or recreational activities that are not as obviously dangerous. For example, two case studies (one in North Carolina and one in Arizona) of lead poisoning in children from homes in which environmental surveys indicated no identifiable lead hazards have been reported. More extensive investigations revealed that both children had been observed on several occasions with pool cue chalk in their mouths. Subsequent chemical analysis of 23 different types of pool cue chalk identified three types as having lead concentrations in excess of 7,000 mg/kg (Miller et al. 1996).

Accidental or intentional ingestion of folk remedies containing lead (discussed in Section 6.4.5) represents another source for potential lead-poisoning in children. Acute lead encephalopathy in early infancy has been reported in a Middle Eastern study for 14 infants following the use of *Bint al Thahab*, a traditional medicine containing 91% lead monoxide, and for 5 infants following application of lead-containing *kohl/surma*, a preparation used as eye makeup (Al Khayat et al. 1997a). Hair dyes formulated with lead acetate represent a potential source for lead-poisoning both by accidental ingestion and by hand-to-mouth activity following contact with lead-contaminated surfaces, including dyed hair of adults (Mielke et al. 1997b).

Children may be exposed to lead through the inhalation of second-hand smoke. Mannino et al. (2003) employed data from the NHANES III and analyzed PbBs of children aged 4–16 who were exposed to high, low, and intermediate levels of second-hand smoke. Serum levels of the nicotine biomarker cotinine were used to classify the children into one of the three second-hand smoke exposure categories. The geometric mean PbBs were 1.5, 1.9, and 2.6 μg/dL for children with low (≤0.050–0.104 ng/mL), intermediate (0.105–0.562 ng/mL), and high (0.563–14.9 ng/mL) serum cotinine levels, respectively (Mannino et al. 2003).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to workers exposed to lead in the workplace, several other population groups at risk for potential exposure to high levels of lead can be identified: preschool-age children and fetuses (see Section 6.6), individuals living near sites where lead was produced or sites where lead was disposed, and individuals living near one of the 1,272 NPL hazardous waste sites where lead has been detected in some

environmental media (EPA 1986b; HazDat 2006; Murgueytio et al. 1998) also may be at risk for exposure to high levels of lead. Since lead is often detected in tobacco and tobacco smoke, persons who use chewing tobacco or smoke, may have higher PbB levels than persons that do not use these products (Bonanno et al. 2001).

General population exposure is most likely to occur through the ingestion of food and water that are contaminated with lead; however, some individuals and families may be exposed to additional sources of lead in their homes. This is particularly true of older homes that may contain lead-based paint. In an attempt to reduce the amount of exposure due to deteriorating leaded paint, the paint is commonly removed from homes by burning (gas torch or hot air gun), scraping, or sanding. These activities have been found to result, at least temporarily, in higher levels of exposure for families residing in these homes. In addition, those individuals involved in the paint removal process (i.e., do-it-yourself renovators and professionals who remove lead) can be exposed to such excessive levels that lead poisoning may occur (Chisolm 1986; Fischbein et al. 1981; Rabinowitz et al. 1985).

Special populations at risk of high exposure to tetraethyl lead include workers at hazardous waste sites and those involved in the manufacture and dispensing of tetraethyl lead (Bress and Bidanset 1991). Populations living near any of the 1,272 NPL sites that were identified as having lead present in the environmental media may be at risk for exposure to high levels of lead (HazDat 2006). However, the available data are insufficient to allow characterization of the sizes of these populations or intake levels of lead to which they may be exposed.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of lead is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of lead.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean

that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of lead and its compounds are sufficiently characterized to permit an estimation of the environmental fate of lead to be made (Howe 1981; Lide 1996; Budavari et al. 1989; Sax 1984; Sax and Lewis 1987). Availabilities of the various forms need to be modeled and the connectivities to bioaccessabilities and bioavailabilities determined.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2004, became available in May of 2006. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Lead is produced and imported for widespread use in the United States. Therefore, the potential for human exposure in the workplace, the home, the environment, and at waste sites may be substantial.

Lead is produced from both primary (i.e., mined ore) and secondary (i.e., scrap metal and wastes) sources, and is imported by the United States. In 1997, production from primary and secondary sources was 343,000 metric tons and 1.1 million metric tons, respectively (Smith 1998), and imports reached 265,000 metric tons (Larrabee 1998; Smith 1998). Approximately 1.6 million metric tons of lead were consumed in the United States in 1997 (Smith 1998). Of lead used in 1997, 86.9% was used for storage batteries, 7.8% was used in metal products, and 5.3% was used in miscellaneous applications (Smith 1998). Because of the adverse health effects associated with exposure to lead, its use in paints, ceramic products, gasoline additives (now banned), and solder has declined dramatically in recent years. In 1997, exports of lead metal totaled 37,400 metric tons, and exports of lead waste and scraps totaled 88,400 metric tons (Larrabee 1998; Smith 1998). Exports of lead in ore and concentrates and lead materials, excluding scrap, rose from 93,500 and 103,000 metric tons in 1999 to 253,000 and 123,000 metric tons, respectively, in 2003. In 2003, 92,800 metric tons of lead scrap were exported (USGS 2003).

Although certain uses of lead preclude recycling (e.g., use as a gasoline additive), lead has a higher recycling rate than any other metal (Larrabee 1998). An estimated 90–95% of the lead consumed in the United States is considered to be recyclable. In the United States, 77.1% of the lead requirements were satisfied by recycled lead products (mostly lead-acid batteries) in 1996. This compares to 69.5% in 1990 and 55.2% in 1980 (Larrabee 1997, 1998).

Industrial wastes, as well as consumer products, containing lead are disposed of in municipal and hazardous waste landfills. Current information on the amounts being disposed of is needed to evaluate the potential for exposure to lead.

The federal government regulates the release and disposal of lead. EPA has established national ambient air quality standards for lead. Under the Safe Drinking Water Act, EPA limits the level of lead in drinking water. Industrial emissions are regulated by the Clean Water Act. Lead and certain of its compounds are designated hazardous substances; CERCLA requires that the person in charge of a vessel or facility notify the National Response Center immediately when there is a release of a hazardous substance in an amount equal to or greater than the reportable quantity for that substance. Such data should be useful in determining potential for exposure and relating it to health effects.

Environmental Fate. Lead released to the atmosphere partitions to surface water, soil, and sediment (EPA 1986a; NAS 1980; Nielsen 1984; NSF 1977). Lead is transported in the atmosphere and in surface water. Organolead compounds are transformed in the atmosphere by photodegradation (DeJonghe and Adams 1986); however, the atmospheric transformation of inorganic lead compounds is not completely understood (EPA 1986a). Organolead compounds are transformed in surface waters by hydrolysis and photolysis (EPA 1979). Inorganic lead compounds are strongly adsorbed to minerals and organic matter in soils and sediments (Chaney et al. 1988; Chuan et al. 1996; EPA 1986a; Gerritse et al. 1981; Sauve et al. 1997). Some work has been conducted to assess the speciation of lead in air, water, and soil (Chaney et al. 1988; Corrin and Natusch 1977; EPA 1986a; Long and Angino 1977; Nerin et al. 1999; Spear et al. 1998). Lead is a naturally occurring element and is extremely persistent in the environment. Additional information on the atmospheric transformations of organic and inorganic lead compounds in the atmosphere would provide a basis for determining the lead compounds to which humans are most likely to be exposed. Additional data regarding the chemical speciation and the transformation pathways of lead in soils and water with varying properties such as pH, oxygen content and salinity are necessary to fully understand the environmental fate of lead in soils and water.

Bioavailability from Environmental Media. Available pharmacokinetic data indicate that lead is absorbed by humans following inhalation of particulate lead in ambient air and ingestion of contaminated foods, drinking water, and soil (Chamberlain et al. 1978; EPA 1986a; Morrow et al. 1980). In addition, children may ingest paint chips that contain lead (MPCA 1987). The bioavailability of lead from soil or dust on the hand after mouthing activity needs to be modeled. Absorption following dermal exposure is much more limited, although absorption of organolead compounds through the skin occurs (Kehoe and Thamann 1931; Laug and Kunze 1948; Moore et al. 1980). Dermal absorption models of lead would be useful in modeling total exposure pathways of lead.

Food Chain Bioaccumulation. Lead is bioaccumulated by terrestrial and aquatic plants and animals (Eisler 1988). However, lead is not biomagnified in terrestrial or aquatic food chains (Eisler 1988). No additional information is needed.

Exposure Levels in Environmental Media. Environmental monitoring data are available for lead in ambient air, indoor air, surface water, groundwater, drinking water, sediments, soils, and foodstuffs (Eckel and Jacob 1988; EPA 1982c, 1986a, 1988b, 1989d, 1989e, 1990; Lee et al. 1989; Maenhaut et al. 1979; Mielke 1993; Mielke et al. 1983, 1984/1985, 1989). More current data (1995–1996) on lead in ambient and indoor air, drinking water, and foodstuffs for residents in Arizona, EPA Region V (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin), and Maryland are available through the NHEXAS (Bonanno et al. 2001; Clayton et al. 2002; O'Rourke et al. 1999; Pellizzari et al. 1999; Ryan et al. 2000; Thomas et al. 1999). Estimates of human intake from inhalation of ambient air and ingestion of contaminated foods and drinking water are available (Dabeka et al. 1987; EPA 1986a, 1991d; Gartrell et al. 1986b; Gunderson 1988). Additional information on the concentrations of lead compounds in environmental media, particularly at hazardous waste sites, and an estimate of human intake would be helpful in establishing human exposure to lead. Absorption of lead through the skin may be a significant exposure pathway (Stauber et al. 1994) and may be deserving of further study. Lead has been found in tobacco and tobacco smoke and higher levels of lead have been detected in indoor air of the homes of smokers when compared to non smokers (Bonanno et al. 2001; Mannino et al. 2003). It is unclear whether the source of this lead is from plant uptake, atmospheric deposition of lead compounds to the surface of tobacco plants, or from tobacco plants being grown in soils that had previously been treated with arsenate pesticides. A study to determine the source of this lead in tobacco is needed in order to help reduce the risk of lead exposure to smokers and those that may inhale second hand smoke.

Reliable monitoring data for the levels of lead in contaminated media at hazardous waste sites are needed so that the information obtained on levels of lead in the environment can be used in combination with the known body burden of lead to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Lead can be measured in human blood, hair, perspiration, teeth, bones, feces, and urine (Aguilera de Benzo et al. 1989; Batuman et al. 1989; Blakley and Archer 1982; Blakley et al. 1982; Christoffersson et al. 1986; Delves and Campbell 1988; Ellen and Van Loon 1990; Exon et al. 1979; Hu et al. 1989, 1990, 1991; Jason and Kellogg 1981; Manton and Cook 1984; NIOSH 1977b, 1977c; Que Hee and Boyle 1988; Que Hee et al. 1985a; Wielopolski et al. 1986). The most common method of assessing human exposure involves measurement of lead in blood (PbB) (Aguilera de Benzo et al. 1989; Delves and Campbell 1988; Manton and Cook 1984; NIOSH 1977b, 1977c; Que Hee et al. 1985a). PbBs have been correlated with ambient air exposure levels and dust, and dietary intake levels (Rabinowitz et al. 1985). In their critical evaluation of reports of historic occupational aerosol exposure to lead, Vincent and Werner (2003) recommended that exposure measurements be made using sampling techniques and strategies that relate to the health effects underlying the need for exposure assessment. Additionally, sufficient detail must be included so that the quality and value of the data can be judged. This is necessary so the data can be pooled for broad hazard surveillance purposes. Additional information on the biological monitoring of populations living in the vicinity of hazardous waste sites would be helpful in estimating exposure of these populations to lead compounds. The relationships between the major biological monitoring media should be determined. Alkyl lead compounds can be measured in exhaled breath and the diethyllead metabolite of tetraethyl lead can be measured in urine. The most recent NHANES Report, containing data from 1999 to 2002 and released in 2005, contains blood lead levels for the U.S. population (CDC 2005a, 2005b). The data pertaining to lead levels in the U.S. population are summarized in Tables 6-12 and 6-13. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Estimates are available for intake by children through ingestion of contaminated soils, dust, paint chips (EPA 1989c), and breast milk (Wolff 1983). However, some of these estimates are not current or well understood. To better understand the sensitivity of the nursing infant to chemicals such as lead, epidemiological studies, chemical monitoring, and model development and application are needed (Byczkowski et al. 1994). The bioavailability of lead from soil or dust on the hand after mouthing activity needs to be modeled. Lead levels in blood (CDC 2005a, 2005b) and urine

(CDC 2003, 2005b) of children are available from the NHANES monitoring data, and have been summarized in Tables 6-12 and 6-13.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for lead were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2005) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-17.

Table 6-17. Ongoing Research Regarding the Environmental Fate and Exposure of Humans to Lead

Investigator	Affiliation	Research description	Sponsor
Blum CB	Columbia University, New York, New York	The estimation of bioavailability to lead and arsenic from soil currently use assumptions based on bioavailability data from animal or *in vitro* models. Using the technique of stable Pb isotope dilution, a method was developed for estimating soil Pb bioavailability in humans. This model examines changes in the ratio of ^{206}Pb to ^{207}Pb in blood, following the ingestion of trace quantities of Pb-contaminated soils.	National Institute of Environmental Health Sciences
Cochran JK and Veron A	SUNY at Stony Brook, Stony Brook, New York	This three-year award for United States-France collaboration in environmental geochemistry involves State University of New York at Stony Brook and the Centre Europeen de Recherche et d'Enseignement de Geosciences in Marseilles, France. The investigators will determine the history of input rates and sources of stable lead to coastal areas.	National Science Foundation
Basta NK and Lower SK	Ohio State University, Columbus, Ohio	The goals of this project are to: (1) determine the ability of chemical speciation methods that measure heavy metal bioavailability; (2) estimate ecotoxicity of contaminated soil; (3) determine the effect of soil chemical properties on chemical speciation and heavy metal bioavailability in contaminated soil and the ability of soil chemical properties to define ecotoxicity categories in development of ecological soil screening levels; (4) determine the ability of diammonium phosphate to reduce bioavailable chemical species of heavy metal contaminants in soil.	Department of Agriculture
Spraks DL	University of Delaware, Newark, Delaware	The goals of this project are to (1) determine the effect of reaction conditions and residence time on sorption/release of important metals/metalloids (Cu, Cd, Cr, Ni, Pb, As) on soil components and Delaware soils; and (2) ascertain metal/metalloid reaction mechanisms on soil components/soils using molecular level spectroscopic (e.g., x-ray absorption fine structure [XAFS] and microscopic [atomic force microscopy (AFS]) techniques. Metal/metalloid sorption studies will be examined as a function of residence time, pH, and total metal loading on soil components/soils, using a pH-stat batch method.	Department of Agriculture

Source: FEDRIP 2005

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring lead, its metabolites, and other biomarkers of exposure and effect to lead. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Blood, Urine, Serum, Cerebrospinal Fluid. Several analytical methods are available to analyze the level of lead in biological samples. The most common methods employed are flame atomic absorption spectrometry (AAS), graphite furnace atomic absorption spectrometry (GFAAS), anode stripping voltametry (ASV), inductively coupled plasma-atomic emission spectroscopy (ICP/AES), and inductively coupled plasma mass spectrometry (ICP/MS). According to Grandjean and Olsen (1984) and Flegal and Smith (1995), GFAAS and ASV are the methods of choice for the analysis of lead. In order to produce reliable results, background correction, such as Zeeman background correction that minimizes the impact of the absorbance of molecular species, must be applied. Limits of detection for lead using AAS are on the order of μg/mL (ppm) for flame AAS measurements, while flameless AAS measurements can detect blood lead levels at about 1 ng/mL (Flegal and Smith 1995). A detection limit of 0.05 ng/mL has been achieved for lead in blood samples analyzed by GFAAS (Flegal and Smith 1995). ICP/MS is also a very powerful tool for trace analysis of lead and other metals. Although ICP/MS instruments are more costly than GFAA instruments, their ability to analyze multiple metals from a single sample, low detection limits, reliability, and ease of use have increasingly made them popular for trace metal analysis. Other specialized methods for lead analysis are x-ray fluorescence spectroscopy (XRFS), neutron activation analysis (NAA), differential pulse anode stripping voltametry, and isotope dilution mass spectrometry (IDMS). The most reliable method for the determination of lead at low concentrations is IDMS (EPA 1986a; Grandjean and Olsen 1984), but due to the technical expertise required and high cost of the equipment, this method is not commonly used. It is primarily used for the development of certified standard reference materials by which other methods can determine their reliability since results of lead

analyses from numerous laboratories often do not agree (Fell 1984). Details of several methods used for the analysis of lead in biological samples are presented in Table 7-1.

Concentrations of lead in blood, urine, serum, and cerebrospinal fluid have been used as indicators of exposure to lead. Measurement of lead in blood is the most common method of assessing exposure. OSHA mandates biological monitoring of blood as a measure of workplace exposure to lead (Goyer 2001). Blood lead is also considered the most useful tool for screening and diagnostic testing (Moore 1995); the half-life of lead in blood is approximately 36 days (Todd et al. 1996). A second half-life is generally considered to be approximately 4 years (Graziano 1994) and reflects the replenishment of lead in the blood from the bone storage compartment. Sample preparation usually consists of wet ashing (digesting) the sample with strong acid and heat, and redissolving the residue in dilute acid prior to analysis so that all lead species are converted quantitatively to the same lead compound (NIOSH 1977c). Preparation methods not requiring wet ashing have also been used with good results (Aguilera de Benzo et al. 1989; Delves and Campbell 1988; Manton and Cook 1984; NIOSH 1977b; Que Hee et al. 1985a; Zhang et al. 1997). For samples analyzed by ICP/MS, ASV, AAS, and GFAAS, sensitivity is in the low- to sub-ppb (0.1–15 ppb) with good accuracy and precision (Aguilera de Benzo et al. 1989; Delves and Campbell 1988; NIOSH 1977b, 1977c; Que Hee et al. 1985a; Zhang et al. 1997). The presence of phosphate, ethylenediaminetetraacetic acid (EDTA), and oxalate can sequester lead and cause low readings in flame AAS (NIOSH 1994c). A comparison of IDMS, ASV, and GFAAS showed that all three of these methods can be used to reliably quantify lead levels in blood (Que Hee et al. 1985a). ACGIH recommends quantification of blood lead by GFAAS. ESA, Inc. has introduced a simple to use, portable device for performing blood lead measurements using a finger stick or a venous sample (ESA 1998). Results can be obtained in about 3 minutes. For analysis of urine, chelation and solvent extraction, followed by atomic absorption for quantification is the recommended method (ACGIH 1986). Estimated accuracy reported for an IDMS technique was excellent (Manton and Cook 1984). Sensitivity and precision were not reported by the authors, but they are generally considered to be excellent (EPA 1986a; Grandjean and Olsen 1984).

An indirect fluorescent method to quantify the level of Pb^{+2} in intracellular fluids has been published (Dyatlov et al. 1998). Although there are no commercially available fluorescent probes specific to Pb^{2+}, the fluorescent probe (fluo-3) frequently used to quantify levels of Ca^{2+} was employed as a means to estimate Pb^{2+} levels in calcium containing solution. The presence of Pb^{2+} depresses the fluorescent signal

Table 7-1. Analytical Methods for Determining Lead in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Blood	Dilution with Triton X-100®; addition of nitric acid and diammonium phospate	GFAAS	2.4 µg/L	93–105	Aguilera et al. 1989
Blood	Dilution of sample with ammonium solution containing Triton X-100	ICP/MS	15 µg/L	96–111	Delves and Campbell 1988
Blood	Dilution of sample in 0.2% Triton X-100 and water	GFAAS	≈15 µg/L	97–150	Que Hee et al. 1985a
Blood	wet ashing, dilution	ICP/MS	0.1 ppb	94–100	Zhang et al. 1997
		GFAAS	4 ppb	90–108	
Blood and urine	Mixing of urine sample with HNO_3; filtration, chelation of lead in whole blood or filtered urine with APDC, extraction with MIBK	AAS (NIOSH Method 8003)	0.05 µg/g (blood) or 0.05 µg/mL (urine)	99 (±10.8%)	NIOSH 1994e
Blood and urine	^{206}Pb addition and sample acid digestion; lead coprecipitation by addition of $Ba(NO_3)_2$, followed by electrodeposition on platinum wire	IDMS	No data	98–99	Manton and Cook 1984
Blood and tissue	Digestion of sample with $HNO_3/HClO_4/H_2SO_4$; heat	ICP/AES (Method 8005)	0.01 µg/g (blood) 0.2 µg/g (tissue)	113	NIOSH 1994b
Blood	Addition of 50 µL of blood into reagent, mixing, and transferring to sensor strip (commercial test kit)	Gold electrode sensor	1.4 µg/dL	No data	ESA 1998
Urine	Collect 50 mL urine sample and add 5 mL concentrated HNO_3 as preservative. Extraction-filter samples through cellulose membrane, adjust pH to 8, ash filters and resins in low temperature oxygen plasma for 6 hours	ICP/AES (Method 8310)	0.1 µg/ sample (50–200 mL sample volume)	100	NIOSH 1994f
Serum blood, and urine	Filtration of sample if needed; blood requires digestion in a Parr bomb; dilution of serum or urine with acid or water	ICP/AES	10B50 µg/L	85 (serum) >80 (urine, blood)	Que Hee and Boyle 1988

Table 7-1. Analytical Methods for Determining Lead in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Urine (δ-amino-levulinic acid)	Dilution of sample; reaction with ethylacetoacetate and ethylacetate to form δ-amino-levulinic acid-pyrrole; reaction with Erhlich's reagent	Spectrophotometry	No data	No data	Tomokuni and Ichiba 1988
Urine (δ-amino-levulinic acid)	Acidification of sample; separate δ-aminolevulinic acid on HPLC; reaction with formaldehyde and acetylacetone	HPLC/FL	10 µg/L	No data	Tabuchi et al. 1989
Plasma, Urine (δ-amino-levulinic acid)	Derivatization of δ-aminolevulinic acid with formaldehyde and acetylacetone to form fluorescent compounds; separation using HPLC	HPLC/FL	3 µg/L	No data	Oishi et al. 1996
Serum and cerebro-spinal fluid	^{206}Pb addition and sample acid digestion; lead isolation by ion-exchange, elution, and deposition onto platinum wire	IDMS	No data	80–120	Manton and Cook 1984
Feces	Dessication and pulverization of sample; digestion with hot acid in Paar bomb	ICP/AES	10–50 µg/L	>86	Que Hee and Boyle 1988
Testes, liver, spleen, kidney	Dicing of sample and digestion in hot acid in a Paar bomb; evaporation; redissolution in HCl/HNO_3	ICP/AES	10–50 µg/L	>80	Que Hee and Boyle 1988
Spleen, liver, and kidney; Liver, kidney, muscle	Wet digestion of sample with HNO_3-$HClO_4$ mixture; Bomb digestion of sample with acid and heat or digestion with acid and dry ashing; dissolution in acid; dilution with water	GFAAS GFAAS DPASV	No data 20 µg/g (bomb); 5 µg/g (dry ashing) No data	No data 85–107 (bomb); 75–107 (dry ashing) 82–120	Blakley and Archer 1982; Ellen and Van Loon 1990
Tissues (brain, heart, lung, kidney, liver, and testes)	Dry ashing of sample; dissolution in HNO_3	AAS	No data	No data	Exon et al. 1979
Tissues	Freeze drying of samples; subjection to thermal neutron irradiation; chemical separation of elements	NAA	No data	No data	Hewitt 1988
Brain	Wet ashing of sample with mixture of acids, mixing with Metex® and analysis	ASV	No data	No data	Jason and Kellogg 1981

Table 7-1. Analytical Methods for Determining Lead in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Bone	Partially polarized photon directed at second phalanx of left forefinger (noninvasive technique)	K-XRF	20 µg/g	No data	Christoffersson et al. 1986
Bone	Partially polarized photon directed at anteromedial skin surface of mid-tibia (non-invasive technique)	L-XRF	20 µg/g	No data	Wielopolski et al. 1986
Teeth	Cleaning and sectioning of tooth; digestion with HNO_3; evaporation; redissolution in buffer solution	ASV	No data	83–114	Rabinowitz et al. 1989
Teeth	Dry ashing of sample; crushing; dry ashing again; dissolution in HNO_3	AAS	No data	90–110	Steenhout and Pourtois 1981
Hair	Cleaning of sample with acetone/ methanol; digestion with acid mixture and heat; diammonium phosphate addition as matrix modifier	GFAAS	0.16 µg/g	99	Wilhelm et al. 1989
Bone	^{109}Cd gamma-ray irradiation with source at 2.5 cm from skin of proximal tibia	K-XRF	2 µg/g	No data	Hu et al. 1989, 1990, 1991
Hair	Cleaning of sample with hexane, ethanol, and water; wet ashing with HNO_3 and H_2O_2	ICP/AES	No data	No data	Thatcher et al. 1982

AAS = atomic absorption spectroscopy; APDC = ammonium pyrrolidine dithiocarbamate; ASV = anode stripping voltammetry; $Ba(NO_3)_2$ = barium nitrate; ^{109}Cd = cadmium 109 radioisotope; DPASV = differential pulse anodic stripping voltammetry; GFAAS = graphite furnace atomic absorption spectroscopy; H_2O_2 = hydrogen peroxide; HCl = hydrogen chloride; H_2SO_4 = sulfuric acid; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; HPLC/FL = high performance liquid chromatography/fluorimetry; ICP/AES = inductively coupled plasma/atomic emission spectroscopy; ICP/MS = inductively coupled plasma-mass spectrometry; IDMS = isotope dilution mass spectrometry; K-XRF = K-wave X-ray fluorescence; L-XRF = L-wave X-ray fluorescence; MIBK = methyl isobutyl ketone; NAA = neutron activation analysis; NaOH = sodium hydroxide; NIOSH = National Institute for Occupational Safety and Health; ^{206}Pb = lead 206

observed in the emission spectrum of the fluo-3 Ca^{2+} complex at 530 nm, and the concentration of Pb^{2+} in solution was correlated with the observed decrease of intensity in the emission spectra.

Several biomarkers exist for monitoring exposure to lead. A number of biochemical assays are available for the assessment of lead exposure and toxicity in the human body using standard clinical laboratory techniques. Details of such assays are reported in several reviews (EPA 1986a; Grandjean and Olsen 1984; Stokinger 1981) and are also available in standard clinical laboratory methods manuals. The commonly used assays are coproporphyrin, 1,25-dihydroxyvitamin D, ALA (δ-aminolevulinic acid), and EP (erythrocyte protoporphyrin) concentrations and ALAD (ALA dehydratase) activity. All of these assays are sensitive, reliable, and well established; however, erythrocyte protoporphyrin and ALAD activity appear to be the most useful and sensitive for determining exposure to lead. A recent review (Porru and Alessio 1996) indicated that ALAD activity was proportional to blood lead concentration ranging from 10 to 40 μg/dL, and EP concentration was proportional to blood lead over the range of 30–80 μg/dL. The EP concentration was said to be useful for assessing exposure experienced over the past 3 to 4 months. Urinary ALA, however, was not proportional to blood lead until the blood concentrations reached 60–70 μg/dL, a concentration too high to be of use for early screening since other clinical symptoms should already be evident. A colorimetric method for detection of ALA in urine, in which the pyrrole from ALA is formed and reacted with Ehrlich's reagent to form a colored end product, has been used successfully (Tomokuni and Ichiba 1988). ALA has also been determined in urine using high-performance liquid chromatography (HPLC) followed by quantification of a fluorescent end product (Tabuchi et al. 1989). A similar approach to ALA determination in blood and urine was described by Oishi et al. (1996) and was more sensitive than the method of Tabuchi et al. (1989). Erythrocyte protoporphyrin bound to zinc has been quantified using hemofluorimetry (Braithwaite and Brown 1987). An HPLC/fluorescent method has been reported for determination of coproporphyrin in urine (Tomokuni et al. 1988). Other biological assays that have been used as indicators of lead exposure are serum immunoglobulins and salivary IgA (Ewers et al. 1982). While all of these biological assays are reliable and have been verified for clinical laboratory use, they are not specific for lead.

Tissues. Lead has been quantified in a variety of tissues, including liver, kidney, brain, heart, lung, muscle, and testes. Techniques for measuring lead in tissues are similar to those used for blood and urine. When AAS, GFAAS, or ASV are used for analysis, the samples may be wet ashed, digested with acid, or bomb digested (Blakley and Archer 1982; Blakley et al. 1982; Ellen and Van Loon 1990; Exon et al. 1979; Jason and Kellogg 1981; Que Hee and Boyle 1988). The information located did not allow an adequate comparison between these methods. Parr bomb digestions are recommended for estimation of

metals in biological tissues (Que Hee and Boyle 1988). Sensitivities reported for GFAAS and ICP/AES are in the low ppm range (5–20 ppm) (Ellen and Van Loon 1990) and are probably comparable for the other techniques. Differential anodic stripping pulse voltametry (DPASV) and NAA have also been used to analyze tissues for lead. Sample preparation for DPASV is the same as those for AAS, GFAAS, and ASV. Its accuracy and precision are comparable to results using GFAAS, and its sensitivity is slightly greater (Ellen and Van Loon 1990). Determination of lead in tissue samples following freeze drying, neutron irradiation, and chemical separation has been reported. An advantage of this method is that the sample does not have to be dissolved. No further information was reported for the method (Hewitt 1988).

Hair, Teeth, and Bone. Noninvasive methods using x-ray fluorescence can be used for the determination of lead concentration in bones. Lead accumulates over a lifetime in bones, so these measurements represent a metric cumulative dose, whereas measurements of lead in blood represent a more recent dose. Typical analyses encompass L x-rays of the tibia produced using an x-ray generator (Wielopolski et al. 1986); K x-rays in the second phalanx of the index finger using a cobalt source and a germanium silicon detector (Christoffersson et al. 1986); and *in vivo* bone K x-ray fluorescence (Batuman et al. 1989; Hu et al. 1989, 1990, 1991, 1998). The K x-ray fluorescence technique has been more widely used and validated than the L x-ray method, which has limitations regarding its utility for the determination of lead levels in bone (Hu et al. 1998; Preiss and Tariq 1992). The more energetic K x-rays penetrate the cortical bone deeper (2 cm) than the soft L x-rays, and are therefore more suitable for determining the average lead content over the whole bone thickness (Wedeen 1990). The better penetration also alleviates errors resulting from the measurement of overlying skin and makes the method relatively insensitive to movement of the subject during the 15-minute sampling period (Landrigan and Todd 1994). The level of lead in bone has been reported to be a good indicator of stored lead in body tissue (Ahlgren et al. 1976; Bloch et al. 1976; Rosen et al. 1987; Skerfving et al. 1993). The sensitivity of the technique is in the low ppm range and the precision is acceptable. Advantages are that no sample preparation is required and the technique can safely and easily be done on live subjects. A limitation of x-ray fluorescence measurements is that its precision is dependent upon the mass of the bone being studied (Hu et al. 1998). Therefore, thin bones of children have greater measurement errors than mature bones found in adults. Teeth have been analyzed for lead using AAS and ASV (Rabinowitz et al. 1989; Steenhout and Pourtois 1981). Samples must be dry ashed or digested with acid prior to analysis. Precision and accuracy of both AAS and ASV are good. Detection limits were not reported by the authors. A detection limit in the sub-ppm range (0.16 ppm) and high accuracy were reported for GFAAS analysis of hair samples (Wilhelm et al. 1989). ICP/AES has also been used to analyze hair for lead, but lack of data prevents a comparison with the AAS method (Thatcher et al. 1982).

The isotopic distribution of lead (IDMS) in shed teeth from children has been shown to be useful in studies of the history of exposure to lead, including the definition of the source of the exposure, e.g., mine dust vs. food (Gulson and Wilson 1994), so IDMS certainly has important applicability, if not for routine determinations. ICP/MS, however, is easier, more sensitive, allows for multi-element analysis, and provides isotopic data.

7.2 ENVIRONMENTAL SAMPLES

The primary methods of analyzing for lead in environmental samples are AAS, GFAAS, ASV, ICP/AES, and XRFS (EPA 1993). Less commonly employed techniques include ICP/MS, gas chromatography/photoionization detector (GC/PID), IDMS, DPASV, electron probe x-ray microanalysis (EPXMA), and laser microprobe mass analysis (LAMMA). The use of ICP/MS for the analysis of trace metals (including lead) has increased in recent years due to its high sensitivity and ease of sample preparation. ICP/MS is generally 3 orders of magnitude more sensitive than ICP/AES; however, it is more costly than other spectroscopic methods and is not universally available (Al-Rashdan et al. 1991; California Department of Fish and Game 2004). Chromatography (GC, HPLC) in conjunction with ICP/MS can also permit the separation and quantification of organometallic and inorganic forms of lead (Al-Rashdan et al. 1991). In analyzing lead concentrations in the atmosphere, a distinction between the levels of inorganic lead, which exists predominantly in the particulate phase, and alkyl lead, which occurs predominantly in the vapor phase, is necessary. Particulate-phase lead can be separated from the gas phase using a filter technique. The filter collects the particulate matter and allows the dissolved material to pass through for separate analysis of each form. As with the analysis of biological samples, the definitive method of analysis for lead is IDMS. Table 7-2 summarizes several methods for determining lead in a variety of environmental matrices.

Air. Various methods have been used to analyze for particulate lead in air. The primary methods, AAS, GFAAS, and ICP/AES are sensitive to levels in the low $\mu g/m^3$ range (0.1–20 $\mu g/m^3$) (Birch et al. 1980; EPA 1988b; NIOSH 1981, 1994a, 1994c, 2003; Scott et al. 1976). Accuracy and precision are generally good. GFAAS is considered to be more sensitive than AAS; however, AAS is not subject to as much interference from matrix effects as GFAAS (NIOSH 1977a, 1977d). Detection of particulate lead by generation of the lead hydride has been used to increase the sensitivity of the AAS technique (Nerin et al. 1989). Excellent accuracy and precision was reported for this method. ASV has a wide range as well as high sensitivity. It is relatively inexpensive compared to other methods (NIOSH 1977a).

Table 7-2. Analytical Methods for Determining Lead in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Air (particulate lead)	Collection of particulate matter onto membrane filter; digestion with HNO_3/H_2O_2; dilution with distilled water	GFAAS (NIOSH Method 7105)	0.02 µg/ sample (1–1,500 L sample)	85–115	NIOSH 1994d
Air (particulate lead)	Collection of particulate matter onto membrane filter; wet ashing with HNO_3	AAS flame (Method 7082)	2.6 µg/sample (200–1,500 L sample)	97–100	NIOSH 1994c
Air (particulate lead)	Collection of particulate matter onto cellulose acetate membrane filter; wet ashing with $HNO_3/HClO_4$	ICP/AES (NIOSH Method 7300)	25 ng/mL	101–109	NIOSH 2003
Air (particulate lead)	Collection of particulate matter onto filter; extraction with HNO_3/HCl, heat, and sonication	ICP/AES	No data	No data	EPA 1988a
Air (particulate lead)	Collection of particulate matter onto filter; dry ashing; extraction with HNO_3/HCl; dilution with HNO_3	AAS AES	0.1 µg/m^3 0.15 µg/m^3	93 102	Scott et al. 1976
Air (particulate lead)	Collection of sample onto cellulose acetate filter; dissolution in HNO_3 with heat; addition of HCl/H_2O_2 and reaction in hydride generator with sodium borohydride to generate lead hydride	AAS	8 ng/L	100–101	Nerin et al. 1989
Air (particulate lead)	Collection of sample onto filter; addition of ^{206}Pb to filter; dissolution of filter in NaOH; acidification; separation of lead by electro-deposition; dissolution in acid	IDMS	0.1 ng/m^3	No data	Volkening et al. 1988
Air (particulate PbS)	Collection of particles onto filter, suspension in THF, recollection onto silver filter	XRD	60 µg/m^3	102.6	NIOSH 1994a
Air (particulate lead)	Collection of sample onto nucleopore polycarbonate filter; coating of filter sections with carbon	EPXMA LAMMA	No data No data	No data No data	Van Borm et al. 1990

Table 7-2. Analytical Methods for Determining Lead in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Air (tetramethyl and tetraethyl lead)	Adsorption of volatile compounds in filtered sample onto XAD-2 resin, desorption with pentane	GC/PID (NIOSH Method 2534 [TML] and 2533 [TEL])	0.4 µg/sample (15–100 L sample) (TML); 0.1 µg/ sample (30–200 L sample) (TEL)	97	NIOSH 1994g; 1994h
Air (particulate and organo-lead)	Collection of particulate matter collected onto glass fiber filter; passage of filtered gases through iodine monochloride bubblers; wet ashing of particulate matter; conversion of lead compounds in bubbler solution to dithiazone complex in presence of EDTA-salts and extraction with carbon tetrachloride solution followed by acid extraction	GFAAS	No data (particulate); 0.25 ng/m^3 (gaseous)	No data (particulate); 95–99 (gaseous)	Birch et al. 1980
Air (particulate and organo-lead)	Collection of particulate matter collected onto nucleopore filters; filtered gases cryogenically trapped and thermally desorbed	XRF (particulate) GC/GFAAS (gaseous)	0.3 µg/m^3 0.2 ng/m^3	46–>90 90–100	De Jonghe et al. 1981
Surface contamination (lead and its compounds)	Wiping of defined area surface using a moistened gauze pad; digestion of sample using nitric acid; dilution.	ICP/AES GFAAS	2 µg/sample 0.1 µg/sample	No data	NIOSH 1994a
Water (particulate and dissolved lead)	Filtration of water through a 0.45 µm membrane filter (dissolved lead); particulate material dissolved by wet ashing (insoluble lead)	ICP/AES (EPA Method 200.7)	42 µg/L	94–125	EPA 1983
Water (TAL)	Extraction with hexane	GC/AAS	0.5 µg/L	88–90	Chau et al. 1979
Water (TAL)	Purging of sample with gas followed by cryogenically trapping volatile species onto solid sorbent GC column	GC/AAS	0.5 ng/g	No data	Chau et al. 1980
Water (alkyl lead)	Complexation of sample with diethyldithiocarbamate; extraction with pentane; removal of water; butylation; extraction with nonane	GC/AAS	1.25 ng/L	90–108	Chakraborti et al. 1984

Table 7-2. Analytical Methods for Determining Lead in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Water (particulate and dissolved lead)	Filtration of water through a 0.45 µm membrane filter (dissolved lead); particulate material dissolved by wet ashing (insoluble lead)	AAS (EPA Method 239.1) GFAAS (EPA Method 239.2)	0.1 mg/L 1 µg/L	99.8–125.7 88–95	EPA 1983
Water (total lead)	Digestion of sample with acid and heat; dilution with water	AAS	1.0 ng/g	No data	Chau et al. 1979
Water (dissolved or total)	Acidification, addition of ammoniacal citrate-cyanide reducing solution; extraction with chloroform containing dithizone.	(Standard Method 3500-PbB)	No data	No data	NEMI 2005b
Water	Filtration, acidification, aspiration into a flame	AAS (Standard Method 3111B)	0.5 mg/L	No data	NEMI 2005a
Water	Digestion, analysis	GFAAS (Standard Method 3113B)	1 µg/L	101%	NEMI 2005c
Water and waste water (dissolved, total)	Filtration/acidification and analysis for dissolved; digestion followed by analysis for total	ICP/AES (Standard Method 3120B)	10 µg/L	109%	NEMI 2005d
Water, extracts or digests of waste	Filtration or digestion as appropriate (depends on matrix, dissolved or total, acid leachable, etc.)	ICP/MS (EPA Method 6020)	No data	71–137% (11–23% RSD) for aqueous solutions; 90B104% (6B28% RSD) for solid samples	EPA 1994d
Water	Filtration; addition of $Ni(NO_3)_2$ and $NH_4H_2PO_4$matrix modifiers	ETAAS	0.14 µg/L	89–101	Xu and Liang 1997
Water (total lead)	Filtration of sample followed by analysis; digestion of filter with acid	ICP/AES	10B50 µg/L	>80	Que Hee and Boyle 1988
Soil	Drying of soil sample followed by sieving; digestion with HNO_3; centrifugation	ICP/AES	0.09 µg/g	97–103	Schmitt et al. 1988

Table 7-2. Analytical Methods for Determining Lead in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Dust	Wiping of hard surface of known dimension; acid digestion	ICP/AES AAS GFAAS	Varies	No data	ASTM 1998f (ASTM E 1728); ASTM 1998b (ASTM E 1644); ASTM 1998a (ASTM E 1613)
Soil	Drying of soil followed by homogenization, digestion with nitric acid and hydrogen peroxide, dilution	ICP/AES AAS GFAAS	Varies	No data	ASTM 1998e (ASTM E 1727) ; ASTM 1998d (ASTM E 1726) ; ASTM 1998a (ASTM E 1613)
Soil	Drying of soil sample followed by sieving, digestion with HNO_3, filtration	AAS	No data	No data	Mielke et al. 1983
Soil	Drying of sample and sieving for XRF; digestion of sieved sample with HNO_3 and heat for AAS	XRF AAS	No data No data	65–98 63–68	Krueger and Duguay 1989
Soil	Drying of sample, dry ashing, digestion with acid, and dilution with water	AAS	2 µg/g	79–103	Beyer and Cromartie 1987
Soil	Digestion with HNO_3 and H_2O_2; evaporation; redissolution with HNO_3; filtration	FI-HG-AAS	2 µg/L	98–101	Samanta and Chakraborti 1996.
Soil, wastes, and ground-water	Acid digestion of sample, dilution with water, and filtration	AAS (EPA method 7420) GFAAS (EPA method 7421)	0.1 mg/L 1 µg/L	No data No data	EPA 1986c
Soil, dust, and paint	Digestion of sample with hot acid; evaporation of water; redissolution in HNO_3	AAS	12 ng/g	>80	Que Hee et al. 1985b

Table 7-2. Analytical Methods for Determining Lead in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Sediment	Digestion of sample with hot HNO_3/H_2SO_4	GFAAS	No data	92–95	Bloom and Crecelius 1987
Sediment, fish (TAL)	Homogenization of fish; addition of EDTA to sample; extraction with hexane; centrifugation; isolation off organic layer for analysis	GC/AAS	0.01 µg/g (sediment) 0.025 µg/g	81–85 72–76	Chau et al. 1979
Sediment, (fish), vegetation (TAL)	Purging of sample with gas followed by cryogenically trapping volatile species onto solid sorbent GC column	GC/AAS	0.1 ng/g (solid)	No data	Chau et al. 1980
Sediment, fish, vegetation (total lead)	Digestion of sample with acid and heat; dilution with water	AAS	50 ng/g (sediment) 10 ng/g (fish and vegetation)	No data No data	Chau et al. 1980
Dried paint	Sample collection using heat gun, cold scraping, or coring methods; microwave digestion with nitric acid and hydrochloric acid	ICP/AES AAS GFAAS	Varies	No data	ASTM 1998g (ASTM E 1729); ASTM 1998c (ASTM E 1645); ASTM 1998a (ASTM E 1613)
Milk	Addition of 50 µL $(C_2H_5)_4NOH$ in ethanol to 25 µL milk followed by heating and dilution with water to 125 µL	GFAAS	No data	No data	Michaelson and Sauerhoff 1974
Evaporated milk	Dry ashing of sample; dissolution in HNO_3	ASV	0.005 µg/g	99	Capar and Rigsby 1989
Mussel, tomato	Digestion of sample with acid or acid plus catalyst; generation of lead hydride	GFAAS	4 ng/g	94–95	Aroza et al. 1989
Agricultural crops	Dry ashing of sample with H_2SO_4 and HNO_3; dilution with water	DPASV	0.4 ng/g	85–106	Satzger et al. 1982

Table 7-2. Analytical Methods for Determining Lead in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Grains, milk mussel, fish	Bomb digestion of sample with acid and heat or digestion with acid and dry ashing; dissolution in acid; dilution with water	GFAAS	20 µg/g (bomb); 5 µg/g (dry ash)	85–107	Ellen and Van Loon 1990
			No data	75–107	
		DPASV		82–120	
Edible oils	Microwave digestion with acid mixture; $(NH_4)_2PO_4$ added as matrix modifier	ICP/AES	50 ng/g	75–107	Allen et al. 1998
		GFAAS	30 ng/g	78–117	
Citrus leaves and paint	Chopping or pulverization of sample; digestion with hot acid; evaporation of water; redissolution in acid	ICP/AES	10–50 µg/L	75–82 (citrus leaves); 89–96 (paint)	Que Hee and Boyle 1988
Feathers	Clean feathers with non ionic detergent; rinse with deionized water for 2–3 minutes.	ICP/MS	10 ppb	No data	California Department of Fish and Game 2004

AA = atomic absorption; AAS = atomic absorption spectroscopy; AES = atomic emissions spectroscopy; ASV = anode stripping voltammetry; $(C_2H_5)_4NOH$ = tetraethylammonium hydroxide; DPASV = differential pulse anodic stripping voltammetry; EDTA = ethylenediamine tetraacetic acid; EPA = Environmental Protection Agency; EPXMA = electron probe X-ray micro-analysis; ETAAS = electrothermal atomic absorption spectroscopy; GC = gas chromatography; GFAAS = graphite furnace atomic absorption spectrometry; HCl = hydrochloric acid; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; H_2O_2 = hydrogen peroxide; H_2SO_4 = sulfuric acid; ICP/AES = inductively coupled plasma-atomic emission spectroscopy; ICP/MS = inductively coupled plasma-mass spectrometry; IDMS = isotope dilution mass spectrometry; LAMMA = laser microprobe mass analysis; MS = mass spectrometry; NaOH = sodium hydroxide; NG = nanogram; NIOSH = National Institute for Occupational Safety and Health; ^{206}Pb = lead 206; PID = photoionization detector; TAL = tetraalkyl leads; TEL = tetraethyl lead; THF = tetrahydrofuran; TML = tetramethyl lead; XRD = X-ray diffraction; XRF = X-ray fluorescence

Advantages of ICP/AES are that it has a wide range and allows analysis of several elements at once. However, the technique is expensive in terms of equipment and supplies (NIOSH 1981). XRFS has been used to analyze for particulate lead in air (DeJonghe et al. 1981). While sensitivity was good, recovery was highly variable and relatively low compared to other methods. The highest sensitivity was obtained with IDMS, as expected (Volkening et al. 1988). As previously stated, this is the definitive method for determining lead in environmental, as well as biological samples. Two sophisticated methods, EPXMA and LAMMA, have been used to determine the inorganic lead species present in particulate matter in air (Van Borm et al. 1990).

Determination of lead vapor in air requires prior filtering of the air to exclude particulate lead, and trapping of the gaseous components. Gaseous lead is also referred to as organic lead or alkyl lead, the most common being the tetraalkyl species. Organic lead species may be trapped by liquid or solid sorbents, or cryogenically (Birch et al. 1980; DeJonghe et al. 1981; NIOSH 1978b). Gas chromatography (GC) is used to separate the different alkyl species. Detection by GFAAS and PID has been reported (DeJonghe et al. 1981; NIOSH 1978b). GFAAS detection is more sensitive than PID, but both have good accuracy.

Water. As with air, water can be analyzed for both particulate and dissolved (organic) lead. Particulate lead collected on a filter is usually wet ashed prior to analysis. Comparison of the GFAAS and AAS methods for particulate lead showed the former technique to be about 100 times more sensitive than the latter, although both offer relatively good accuracy and precision (EPA 1983). ICP/MS has been used to determine lead in water (EPA 1994d). Chelation/extraction can also be used to recover lead from aqueous matrices (APHA 1998). GC/AAS has been used to determine organic lead, present as various alkyl lead species, in water (Chakraborti et al. 1984; Chau et al. 1979, 1980). Sample preparation for organic lead analysis was either by organic solvent extraction (Chakraborti et al. 1984; Chau et al. 1979) or purge-and-trap (Chau et al. 1980). Sensitivity was in the ppb to ppt range and reliability was similar for all three methods. Total lead can be determined by digesting samples with acid and analyzing by either AAS or the more sensitive GFAAS (EPA 1986c).

Dusts, Sediments, and Soil. Both total and organic lead have been determined in dusts, sediments, and soils. In most cases, the sample must be digested with acid to break down the organic matrix prior to analysis (ASTM 1998b, 1998d; Beyer and Cromartie 1987; Bloom and Crecelius 1987; EPA 1986c; Krueger and Duguay 1989; Mielke et al. 1983; Que Hee and Boyle 1988; Que Hee et al. 1985b; Samanta and Chakraborti 1996; Schmitt et al. 1988); however, organic extraction (Chau et al. 1979) and purge-

and-trap (Chau et al. 1980) have also been used. The primary detection methods are ICP/AES, AAS, or GFAAS (GFAAS being more sensitive, but also more susceptible to interference). When quantification of organic lead is desired, GC is employed to separate the alkyl lead species (Chau et al. 1979, 1980). Precision and accuracy are acceptable for these atomic absorption-based methods (Beyer and Cromartie 1987; Bloom and Crecelius 1987; Chau et al. 1979; EPA 1986c; Krueger and Duguay 1989; Que Hee et al. 1985b). ICP/AES is reported to be more sensitive and reliable than atomic absorption techniques (Schmitt et al. 1988), but sample collection and preparation methods have been shown to strongly influence the reliability of the overall method (Que Hee et al. 1985b). Sampling of house dust and hand dust of children requires special procedures (Que Hee et al. 1985b). XRFS appears to provide a simpler method of measuring lead in soil matrices; however, the available data do not permit an assessment of the techniques sensitivity and reliability for soil analysis (Krueger and Duguay 1989). XRFS has been shown to permit speciation of inorganic and organic forms of lead in soil for source elucidation (Manceau et al. 1996).

Other Matrices. Lead has been determined in several other environmental matrices, including paint, fish, vegetation, agricultural crops, and various foods. As with soil, the methods of choice are ICP/AES, AAS, or GFAAS. Samples may be prepared using one of the methods described for sediment and soil or by wet or dry ashing (Aroza et al. 1989; ASTM 1998d; Capar and Rigsby 1989; Que Hee and Boyle 1988; Que Hee et al. 1985b; Satzger et al. 1982). ASV and DPASV have also been used with good sensitivity (ppb) and reliability to analyze for lead in other environmental media (Capar and Rigsby 1989; Ellen and Van Loon 1990; Satzger et al. 1982).

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of lead is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of lead.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean

that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods are available for measuring inorganic lead in blood, serum, urine, cerebrospinal fluid, tissues, bone, teeth, and hair (Aguilera de Benzo et al. 1989; Batuman et al. 1989; Blakley and Archer 1982; Blakley et al. 1982; Christoffersson et al. 1986; Delves and Campbell 1988; Ellen and Van Loon 1990; Exon et al. 1979; Hu et al. 1989, 1990, 1991; Jason and Kellogg 1981; Manton and Cook 1984; NIOSH 1977b, 1977c, 1994c, 2003; Que Hee and Boyle 1988; Que Hee et al. 1985a; Wielopolski et al. 1986; Zhang et al. 1997). Available methods for determining lead in body fluids are sensitive and reliable for measuring background exposure levels, as well as exposure levels at which health effects have been observed to occur. Blood lead levels have been found to correlate best with exposure concentrations (Moore 1995; Rabinowitz et al. 1985). Methods of quantifying lead in tissues, bone, teeth, and hair are generally reliable, but are only sensitive at relatively high exposure concentrations. Since the elimination half-time of lead in blood is approximately 30 days, PbBs generally reflect relatively recent exposures. Lead in bone is considered a biomarker of cumulative exposure to lead because lead accumulates in bone over the lifetime and most of the lead body burden resides in bone. There is a need for more sensitive methods of detection for matrices so that correlations between lead levels in these media and exposure concentrations can be more reliably determined. Several nonspecific biomarkers are used to assess exposure to lead. These include ALAD activity and ALA, EP, coproporphyrin, and 1,25-dihydroxyvitamin D concentrations (Braithwaite and Brown 1987; EPA 1986a; Grandjean and Olsen 1984; Oishi et al. 1996; Porru and Alessio 1996; Stokinger 1981; Tabuchi et al. 1989; Tomokuni and Ichiba 1988; Tomokuni et al. 1988). Lead interferes with the conversion of zinc protoporphyrin (ZPP) to heme by the enzyme ferrochelatase and a correlation has been observed between lead blood levels and ZPP; therefore, levels of ZPP can also be used as a biomarker of lead exposure (Goyer 2001). The methods for determining these biomarkers are generally sensitive and reliable. No additional research for these biomarkers appears to be needed. There is a need to identify and quantify those molecules responsible for lead transport within the body; the measurement of lead associated with these compounds could provide additional information about exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Numerous analytical methods are available for measuring inorganic and organic lead

compounds in air, water, sediments, dust, paint, soil, fish, agricultural products, and foodstuffs (NEMI 2005a, 2005b, 2005c, 2005d; Eckel and Jacob 1988; EPA 1982a, 1986a, 1988b, 1989d, 1989e, 1990, 1994d; Lee et al. 1989; Maenhaut et al. 1979; Mielke 1993; Mielke et al. 1983, 1984/1985, 1989). Most of these are sensitive and reliable for determining background concentrations of lead compounds in the environment and levels at which health effects might occur. The most frequently used methods are AAS, GFAAS, ASV, and ICP/AES, the methods recommended by EPA and NIOSH (ASTM 1998a; Birch et al. 1980; EPA 1988b; NIOSH 1981, 1994c, 2003; Scott et al. 1976). The definitive method is IDMS, which is used to produce reference standards by which laboratories can determine the reliability of their analyses (Volkening et al. 1988). No additional analytical methods for determining low levels of lead compounds in environmental media are needed. Additional method development work is needed if individual lead species in environmental media are to be accurately determined. ICP/MS based methods should be critically examined.

7.3.2 Ongoing Studies

Ongoing studies regarding analytical methods for lead were reported in the Federal Research in Progress database (FEDRIP 2005), and are summarized in Table 7-3.

Table 7-3. Ongoing Research Regarding the Analytical Methods for Lead in Environmental and Biological Samples

Investigator	Affiliation	Research description	Sponsor
Chillrud S	Columbia University, New York, New York	Core-Geochemistry Laboratory: A laboratory is being developed to support several ongoing research projects, including projects involving the analytical measurement of lead in environmental samples and human tissue. The instrumentation that will be used includes a VG sector 54-30 Thermal Ionization Mass Spectrometer (TIMS), a Hitachi Z8200 Graphite Furnace Atomic Absorption Spectrophotometer (GFAAS), a VG High-Resolution inductively coupled plasma-mass spectrometry (ICP-MS).	National Institute of Environmental Health Sciences
Mutti A	University of Parma, Parma Italy	Metals in exhaled breath condensate as chronic obstructive pulmonary disease (COPD) biomarkers: Develop biomarkers for COPD involving the analysis of exhaled breath condensate for the presence of lead by electro-thermal atomic absorption spectroscopy (ETAAS) and ICP-MS.	National Heart, Blood, and Lung Institute
Parsons PJ	New York State Department of Health, Human Toxicology and Molecular Epidemiology	Bone Lead Standardization Program: The aim of this proposal is to create a Standardization Program for Bone Lead measurements (BLSP) obtained via reference methods and via *in vivo* x-ray fluorescence (XRF).	National Institute of Environmental Health Sciences

Source: FEDRIP 2005

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8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines regarding lead and lead compounds in air, water, and other media are summarized in Table 8-1.

ATSDR has not derived MRLs for lead. The EPA has not developed a reference concentration (RfC) for lead. EPA has also decided that it would be inappropriate to develop a reference dose (RfD) for inorganic lead (and lead compounds) because some of the health effects associated with exposure to lead occur at blood lead levels as low as to be essentially without a threshold (IRIS 2005).

EPA has assigned lead a weight-of-evidence carcinogen classification of B2, probable human carcinogen, based on inadequate information in humans and sufficient data in animals (IRIS 2005). The International Agency for Research on Cancer (IARC) has classified inorganic lead compounds as probably carcinogenic to humans (Group 2A) based on limited evidence of carcinogenicity in humans and sufficient evidence in animals (IARC 2004). IARC also determined that organic lead compounds are not classifiable as to their carcinogenicity to humans (Group 3) based on inadequate evidence of carcinogenicity in humans and animals (IARC 2004). The Department of Health and Humans Services (DHHS) has determined that lead and lead compounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from studies in experimental animals (NTP 2005). The American Conference of Governmental Industrial Hygienists (ACGIH) has categorized elemental lead and certain inorganic lead compounds, assessed as lead, as A3 carcinogens: carcinogenic in experimental animals at a relatively high dose not considered relevant to worker exposure. The data obtained from epidemiologic studies suggest that, except for uncommon routes or levels of exposure, these substances are unlikely to cause cancer in humans (ACGIH 2004). ACGIH has categorized lead chromate, assessed on the basis of both lead and chromium, as an A2 carcinogen. Although substances in this category are carcinogenic in experimental animals at dose levels that are considered relevant to worker exposure, the data from epidemiologic studies are insufficient to confirm an increased risk of cancer in exposed humans (ACGIH 2004).

OSHA requires employers of workers who are occupationally exposed to a toxic or hazardous substance to institute engineering controls and work practices that maintain or reduce their exposure to a level that is at or below the permissible exposure limit (PEL) established for the substance. For occupational exposures to lead, the employer must use engineering controls and work practices to achieve an

Table 8-1. Regulations and Guidelines Applicable to Lead and Lead Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2004
	Lead compounds, inorganic	Group 2A[a]	
	Lead compounds, organic	Group 3[b]	
WHO	Air quality guidelines	0.5 µg/m^3	WHO 2000
	Drinking water quality guidelines	0.01 mg/L	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (TWA)		ACGIH 2004
	Lead, inorganic	0.05 mg/m^3	
EPA	Hazardous air pollutant	Yes	EPA 2004b 42 USC 7412
	National primary and secondary ambient air quality standards[c]	1.5 µg/m^3	EPA 2005b 40 CFR 50.12
NIOSH	REL (TWA)[d]	0.05 mg/m^3	NIOSH 2005
	IDLH	100 mg/m^3	
OSHA	PEL (8-hour TWA) for toxic and hazardous substances for lead	50 µg/m^3	OSHA 2005d 29 CFR 1910.1025
	PEL (8-hour TWA) for general industry for tetraethyl lead[e]	0.075 mg/m^3	OSHA 2005c 29 CFR 1910.1000
	PEL (8-hour TWA) for construction industry for tetraethyl lead[e]	0.1 mg/m^3	OSHA 2005b 29 CFR 1926.55
	PEL (8-hour TWA) for shipyard industry for tetraethyl lead[e]	0.1 mg/m^3	OSHA 2005a 29 CFR 1915.1000
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2005a 40 CFR 116.4
	Lead acetate, lead chloride, lead fluoroborate, lead iodide, lead nitrate, lead sulfate, lead sulfide, and tetraethyl lead		
	National primary drinking water standards		EPA 2002
	MCLG	Zero	
	MCL	Treatment technique[f]	
	Action level	0.015 mg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	10 pounds	EPA 2005c 40 CFR 117.3
	Lead acetate, lead chloride, lead fluoroborate, lead iodide, lead nitrate, lead sulfate, lead sulfide, and tetraethyl lead		

Table 8-1. Regulations and Guidelines Applicable to Lead and Lead Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Residential lead hazards standards – TSCA Section 403		EPA 2005l
	Floors	40 µg/ft^2	
	Interior window sills	250 µg/ft^2	
	Bare soil in children's play areas	400 ppm	
	Bare soil in rest of yard	1,200 ppm average	
c. Food			
FDA	Action level (µg/mL leaching solution)		FDA 2000
	Ceramicware		
	Flatware (average of 6 units)	3.0 µg/mL	
	Small hollowware (other than cups and mugs) (any 1 of 6 units)	2.0 µg/mL	
	Large hollowware (other than pitchers) (any 1 of 6 units)	1.0 µg/mL	
	Cups and mugs (any 1 of 6 units) and pitchers (any 1 of 6 units)	0.5 µg/mL	
	Silver-plated hollowware		
	Product intended for use by adults (average of 6 units)	7 µg/mL	
	Product intended for use by infants and children (any 1 of 6 units)	0.5 µg/mL	
	Bottled drinking water	0.005 mg/L	FDA 2004 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2004
	Lead	A3[g]	
	Biological exposure indices (lead in blood)[h]	30 µg/100 mL	
ATSDR	Action level for children	10 µg/dL	Agency for Toxic Substances and Disease Registry 1997
EPA	Carcinogenicity classification	Group B2[i]	IRIS 2005
	Oral slope factor	Not available	
	Inhalation unit risk	Not available	
	RfC	Not available	
	RfD	Not applicable[j]	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	10 pounds	EPA 2005d 40 CFR 302.4
	Reportable quantity		
	Lead, lead acetate, lead chloride, lead fluoroborate, lead iodide, lead nitrate, lead phosphate, lead sulfate, lead sulfide, and tetraethyl lead		

Table 8-1. Regulations and Guidelines Applicable to Lead and Lead Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Superfund, emergency planning, and community right-to-know		
	Effective date of toxic chemical release reporting for lead	01/01/87	EPA 2005g 40 CFR 372.65
	Extremely hazardous substances		EPA 2005e 40 CFR 355, Appendix A
	Tetraethyl lead		
	Reportable quantity	10 pounds	
	Threshold planning quantities	100 pounds	
	Superfund, emergency planning, and community right-to-know		
	Threshold amounts for manufacturing (including importing), processing, and otherwise using such toxic chemicals	100 pounds	EPA 2005f 40 CFR 372.28
NTP	Carcinogenicity classification	Reasonably anticipated to be human carcinogens	NTP 2005

[a]Group 2A: probably carcinogenic to humans
[b]Group 3: not classifiable as to carcinogenicity to humans
[c]National primary and secondary ambient air quality standards for lead and its compounds, measured as elemental lead by a reference method based on Appendix G to 40 CFR 50.12, or by an equivalent method, are: 1.5 µg/m^3, maximum arithmetic mean averaged over a calendar quarter.
[d]The REL also applies to other lead compounds (as Pb), including metallic lead, lead oxides, and lead salts (including organic salts such as lead soaps but excluding lead arsenate). The NIOSH REL for lead (10-hour TWA) is 0.050 mg/m^3; air concentrations should be maintained so that worker blood lead remains less than 0.060 mg Pb/100 g of whole blood.
[e]Skin designation
[f]Treatment Technique: lead is regulated by a Treatment Technique that requires systems to control the corrosiveness of their water. If more than 10% of tap water samples exceed the action level, water systems must take additional steps. For lead, the action level is 0.015 mg/L.
[g]A3: confirmed animal carcinogen with unknown relevance to humans
[h]BEI: Women of child-bearing potential, whose blood exceeds 10 µg/dL, are at risk of delivering a child with a blood Pb over the current CDC guideline of 10 µg/dL. If the blood Pb of such child remains elevated, they may be at increased risk of cognitive deficits.
[i]Group B2: probable human carcinogen
[j]See IRIS record for complete oral RfD discussion (IRIS 2005).

ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BEI = biological exposure indices; CDC = Centers for Disease Control and Prevention; CERCLA = Comprehensive Environmetnal Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TSCA = Toxic Substances Control Act; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

occupational exposure of 50 μg/m^3 (0.006 ppm) or lower, based on an 8-hour TWA (OSHA 2005d). When employee exposures to lead cannot be maintained ≤50 μg/m^3 through engineering and work practice controls, the employer is required to provide the employees with respirators as a means of supplemental control. The specifications for different types of respirators and the conditions for their use are provided in the Code of Federal Regulations at 29 CFR 1910.1025. OSHA specifies 30 μg/m^3 of air as the action level for employee exposure to airborne concentrations of lead (OSHA 2005d). Under the requirements for medical surveillance and biological monitoring, the blood lead level (PbB) of employees exposed to lead above the action level for >30 days/year must be monitored at least every 6 months. The frequency for sampling an employee's PbB increases to once every 2 months if the results of his or hers previous blood analysis indicated a PbB ≥40 μg/dL (OSHA 2005d). OSHA requires continuing the 2-month sampling protocol until the employee's PbB is below 40 μg/dL for two consecutive samplings. If an employee is working in an area where exposure to lead is at or above the action level, and the employee's periodic blood test or a follow-up test indicates a PbB ≥50 μg/dL, the employer is required to remove the employee from that work area (OSHA 2005d). The relocation of an employee may also be instituted if the average of the three most recent blood tests or the average of all blood tests given over the most recent 6-month period indicates a PbB ≥50 μg/dL. If however, the last single blood test taken during this period indicates a PbB ≤40 μg/dL, relocation of the employee may not be required (OSHA 2005d). Except for the construction industry and certain aspects of the agricultural industry, more detailed requirements for limiting all occupational exposures to lead, including shipyard employment (OSHA 2005f), can be found in 29 CFR 1910.1025 (OSHA 2005d). On May 4, 1993, OSHA published an interim final rule, which reduced the permitted level of occupational exposure to lead for construction workers from an 8-hour TWA of 200 μg/m^3 to an 8-hour TWA of 50 μg/m^3 (OSHA 1993). As with other industries, the action level for occupational exposure to lead in the construction industry is 30 μg/m^3 (OSHA 2005e). More detailed requirements for protecting construction workers from occupational exposures to lead can be found in 29 CFR 1926.62 (OSHA 2005e).

The EPA regulates lead under the Clean Air Act (CAA) and has designated lead as a hazardous air pollutant (HAP) (EPA 2004b). In the early 1970s, after determining that lead additives would impair the performance of emission control systems installed on motor vehicles and that lead particle emissions from motor vehicles presented a significant health risk to urban populations, the EPA began regulating the lead content in gasoline (EPA 1996a). In 1973, EPA instituted a phase-down program designed to minimize the lead content of leaded gasoline over time. By 1988, the total lead usage in gasoline had been reduced to <1% of the amount of lead used in the peak year of 1970 (EPA 1996a). The EPA defined unleaded gasoline as gasoline produced without the use of any lead additive and containing not more than 0.05 g of

lead per gallon and not more than 0.0005 g of phosphorous per gallon. The 0.05 g per gallon criterion was allowed because EPA determined that this maximum trace level would provide adequate protection for catalyst emission control devices (i.e., prevent deterioration in emission control systems) and would be practicable for the petroleum industry. In 1990, Congress added Section 211(n) to the CAA and provided that after December 31, 1995, it would be unlawful to offer, sell, dispense, or transport, for use as fuel in any motor vehicle, any gasoline that contains lead or lead additives. The effective date for this prohibition was January 1, 1996 (EPA 1996a). On February 2, 1996, the EPA published a direct final rule revising its regulation for consistency with the CAA prohibitions; however, EPA's definition of unleaded gasoline still allowed the sale of gasoline containing trace amounts of lead up to 0.05 g/gallon. The current definition, however, expressly prohibits the use of any lead additive in the production of unleaded gasoline. The term "lead additive" was defined to include pure lead as well as lead compounds (EPA 1996a).

Lead is regulated by the Clean Water Effluent Guidelines and Standards, which are promulgated under the authority of the Clean Water Act (CWA). The regulations provide limitations on pollutant concentrations in waste water discharges from point source categories and represent the degree of reduction in pollutant concentration that is attainable through demonstrated technologies for new and existing sources. The regulations also provide standards of performance for new sources as well as pretreatment standards for new and existing sources. The effluent limitations establish the maximum discharge of pollutants allowed for 1 day and for a monthly average. The CWA establishes the basic structure for regulating the discharge of pollutants to waterways and is designed to ensure that all waters are sufficiently clean to protect public health and/or the environment. However, if waters and their sediments become contaminated from sources such as atmospheric deposition and discharges from industrial, municipal, or agricultural operations, toxic substances could concentrate in the tissue of fish and wildlife. Advisories have been developed and issued to warn people about the health risks of consuming lead-contaminated fish, shellfish, or wildlife and provide guidance as to the amount of fish or wildlife that can be safely consumed. Each state, Native American Tribe, or U.S. Territory establishes its own criteria for issuing fish and wildlife advisories. A fish or wildlife advisory will specify which waters (lake, rivers, estuaries, or coastal areas) or hunting areas have restrictions. The advisory provides information on the species and size range of the fish or wildlife of concern. The advisory may completely ban eating fish and shellfish, or recommend consumption limits (numbers of fish meals per specified time period) considered to be safe to eat. For example, an advisory may recommend that a person eat a certain type of fish no more than once a month. Advisories may specify the tissues of the fish or wildlife that can be safely eaten or proper preparation and cooking practices to help decrease exposure to lead. The fish or

wildlife advisory is typically more restrictive to protect pregnant women, nursing mothers, and young children. Published information in the form of brochures on fish and wildlife advisories is available from state public health departments, natural resources departments, or fish and game departments. Signs may be posted in certain fishing and hunting areas frequently used by recreational fishers and hunters to warn them about specific contamination problems (EPA 1995b). Currently, 10 advisories are in effect in five states (Hawaii, Louisiana, Missouri, Ohio, and Tennessee), and one U.S. Territory (American Samoa) restricting the consumption of lead-contaminated fish and shellfish (EPA 2004d). No advisories were issued for wildlife.

In an effort to protect human health by reducing the lead levels in drinking water at consumers' taps to as close to the maximum contaminant level goal (MCLG) of zero, water system authorities are required to: (1) install or improve corrosion control to minimize lead levels at the tap while ensuring that treatment does not cause the water system to violate any national primary drinking water regulation; (2) install treatment to reduce lead in source water entering the distribution system; (3) replace lead service lines when >10% of targeted tap samples exceed 0.015 mg/L lead in drinking water if corrosion control and/or source water treatment does not bring lead levels below the lead action level; and (4) conduct public education programs if lead levels are above the action level (EPA 1991a).

The EPA also regulates the lead content in hazardous wastes as prescribed by the Resource Conservation and Recovery Act (RCRA). A solid waste may be defined as hazardous if it exhibits any of the four characteristics (ignitability, corrosivity, reactivity, and toxicity) used to identify hazardous wastes. A solid waste containing lead or lead compounds may be defined as a hazardous waste if it exhibits the characteristic of toxicity. The waste is said to exhibit the toxicity characteristic if the lead concentration in the extract obtained by subjecting a sample of the waste to the Toxicity Characteristic Leaching Procedure (TCLP) exceeds 5.0 mg/L (EPA 1990). On December 18, 1998, EPA issued a proposed rule under the Toxic Substances Control Act (TSCA) to provide new standards for the management and disposal of lead-based paint debris generated by individuals involved in abatements, renovations, and demolition of target housing and from lead removal and demolition of public and commercial buildings (EPA 1998a). As a result of the proposed rule and to avoid duplication and inconsistency in the management of lead-based paint debris, EPA also issued, on the same day a proposed rule that would temporarily suspend the applicability of the toxicity characteristic to these types of debris (EPA 1998b).

The Lead-Based Paint Poisoning Prevention Act, as amended by the National Consumer Information and Health Promotion Act of 1976, mandates that the use of lead-based paint in residential structures

constructed or rehabilitated by any federal agency or with federal assistance in any form be prohibited (HUD 1998). By definition, residential structures include non-dwelling facilities operated by the owner and commonly used by children under 6 years old, such as childcare centers. The Act also authorized the Department of Housing and Urban Development (HUD) to promulgate regulations to eliminate lead-based paint from HUD-associated housing built prior to 1978. The regulatory definition of lead-based paint is "any paint or other surface coating that contains lead equal to or in excess of 1.0 mg/cm^2 or 0.5 percent by weight" (HUD 1997, 1998). For paints manufactured after June 22, 1977, however, Section 501(3) of the Act defines lead-based as any paint where the nonvolatile content contains 0.06% lead by weight. Purchasers and tenants of HUD-associated housing constructed before 1978 must be notified that the dwelling was constructed prior to 1978 and may contain lead-based paint. Information concerning the hazards of lead-based paint, the symptoms and treatment of lead-based paint poisoning, the precautions to be taken to avoid poisoning, and maintenance and removal techniques must also be provided (HUD 1998). The Residential Lead-Based Paint Hazard Reduction Act of 1992 (also known as Title X of the Housing and Community Development Act) requires sellers, landlords, and agents to provide the same type of information to potential purchasers or tenants of other "target housing" (i.e., constructed prior to 1978). Exceptions to these requirements include housing for elderly or disabled persons, unless a child <6 years of age is expected to reside in the dwelling; and dwellings without bedrooms such as studio/efficiency apartments, individual room rentals, dormitories, and military barracks (HUD 1998). Title IX also mandates a broad range of interrelated lead exposure activities, some of which require inter-agency collaboration.

In addition to HUD, the primary federal agencies responsible for promulgating regulations implementing the mandates of Title X are the EPA, the Department of Health and Human Services (DHHS) and the Department of Labor's Occupational Safety and Health Administration (OSHA). Title X amends TSCA by adding Title IV, entitled "Lead Exposure Reduction". Title IV provides the authority for developing standards that reduce lead-based paint hazards in housing and environmental media (EPA 1998a). Section 402 of Title IV requires the EPA to promulgate regulations for accrediting training programs and certification of persons engaging in "lead-based paint activities" such as for lead abatement and renovation. The aim of the ruling is to ensure that individuals conducting these activities are properly trained and certified. The EPA/HUD training and certification program provides for five categories of lead-based paint professionals: supervisors, workers, inspectors, risk assessors, and project designers; and three categories of activities: inspection, risk assessment, and abatement. Section 403 of Title IV requires EPA to develop standards for lead-based paint hazards in most pre-1978 housing and child-occupied facilities and to address by regulation(s) the definition of "lead-based paint hazards", "lead-

contaminated dust", and “lead-contaminated soil”. On June 3, 1998, EPA issued several proposed standards in a notice of proposed rulemaking. It was proposed that lead-based paint hazards be described as “paint in poor condition” and defined as >10 ft^2 of deteriorated paint on exterior surface areas and >2 ft^2 on interior surface areas (EPA 1998b). The proposed standard for a lead-dust hazard is an average level of lead in dust of ≥40 $\mu g/ft^2$ on uncarpeted floors and ≥250 $\mu g/ft^2$ on interior window sills (EPA 2005l). For soils, an average concentration of 400 ppm/yard was the proposed standard at which the public should be made aware of the risk associated with exposure to lead (EPA 1998b).

Section 404 of Title IV concerns the authorization requirements for state and tribal programs. States and Native American tribes can seek authorization from EPA to implement their own lead training, accreditation, and certification programs. On August 26, 1996, EPA published the final rule establishing the requirements that state or tribal programs must meet for authorization to administer and enforce the standards and regulations promulgated in accordance with Title IV (EPA 1998c). According to “The Lead Listing” provided by the National Lead Service Providers Listing System, as of July 1, 1998, 22 states have established operational lead programs that actively certify lead service providers. Local, certified (licensed) lead-based paint inspectors, risk assessors, and laboratories can be located by calling the National Lead Information Center and Clearinghouse (1-800-LEAD-FYI [1-800-532-3394]) or through the Internet at http://www.leadlisting.org (HUD 1997). The Lead Listing is operated by a private entity for HUD’s Office of Lead Hazard Control.

Section 406 of Title IV directs the EPA to develop consumer information concerning the hazards of exposure to lead and procedures to be followed during housing renovations or remodeling. On June 1, 1998, the EPA issued its final rule on the requirements for lead hazard education prior to conducting renovations in target housing (EPA 1998a). It is important to note that while the federal disclosure program requires property owners to make others aware of the potential lead hazards in or on their property, the program does not require the property owner to conduct inspections or risk assessments prior to selling or leasing property. Regulations responding to the mandates of Title IV are codified at 40 CFR 745; Lead-Based Paint Poisoning Prevention in Certain Residential Structures.

Lead also appears on the FDA’s list of poisonous and deleterious substances, which was established to control levels of contaminants in human food and animal feed. The action levels established for these substances represent limits at or above which the FDA will take legal action to remove the affected consumer products from the market (FDA 2000). In 1993, the FDA has established an action level for lead in fruit beverages (80 $\mu g/kg$) packaged in lead-soldered cans (FDA 1998b); in 1995, the use of lead-

soldered cans was banned by the FDA. Lead solders are alloys of metals that contain lead and are used in the construction of metal food cans. The FDA considers any food packaged in containers that use lead in can solders to be adulterated and in violation of the Federal Food, Drug, and Cosmetic Act (FDA 1995). As of February 8, 1996, the FDA considers wine in bottles capped with tin-coated lead foil capsules to be adulterated (FDA 1996). Tin-coated lead foil has been used as a covering applied over the cork and neck areas of wine bottles to prevent insect infestations, as a barrier to oxygen, and for decorative purposes. Because it can be reasonably expected that lead could become a component of the wine, the use of these capsules is also a violation of the Federal Food, Drug, and Cosmetic Act (FDA 1996). The FDA has reviewed several direct human food ingredients and has determined them to be "generally recognized as safe" when used in accordance with current good manufacturing practices. Some of these ingredients contain allowable concentrations of lead ranging from 0.1 to 10 ppm (FDA 1998a).

The Lead Contamination Control Act of 1988 mandates that the Consumer Product Safety Commission (CPSC): (1) require the repair or recall of drinking water coolers containing lead in parts that come in contact with drinking water; (2) prohibit the sale of drinking water coolers that are not lead-free; (3) require that states establish programs to assist educational agencies in testing and remediating lead contamination of drinking water in schools; and (4) require that EPA certify testing laboratories and provide for coordination by the CDC of grants for additional lead screening and referral programs for children and infants (Congressional Record 1988). The CPSC has declared paints and similar surface coating having a lead content that exceeds the 0.06% by weight limit to be "banned hazardous products" (CPSC 1977). Paints and surface coatings with lead concentrations exceeding the 0.06% limit are defined as "lead-containing paint". Except for applications to motor vehicles and boats, once lead-containing paints are applied to toys or other articles intended for use by children and articles of furniture manufactured for consumer use, these items also become "banned hazardous products" (CPSC 1977). These products may be exempt from the ban if, at a minimum, the main label on the product includes the single word "Warning" and the statement: "Contains Lead. Dried Film of This Paint May Be Harmful If Eaten or Chewed" (CPSC 1977).

The CDC determined in 1991 that PbBs >10 μg/dL in children were to be considered elevated (CDC 1991). In its annual publication of threshold limit values (TLVs) and biological exposure indices (BEIs), the ACGIH notes that women of child-bearing age who have a PbB exceeding the CDC guideline value are at risk of delivering children with a PbB >10 μg/dL (ACGIH 1998). In its report to Congress, NIOSH summarizes occupational exposure information and provides recommendations for workers (NIOSH 1997b).

The ACGIH also notes that if a child's PbB remains elevated, the child may be at increased risk of cognitive deficits (ACGIH 1998). The ACGIH has adopted BEIs for various substances. The BEI for a substance is an industrial hygiene reference value to be used in evaluating potential health hazards. It is important to note that BEIs are guideline values, and that they are not intended for use as measures of adverse effects or for diagnosis of occupational illness (ACGIH 1998). They represent the level of substance most likely to be observed in specimens (e.g., blood or urine) collected from a healthy worker who has been exposed to a chemical at its TLV. The TLV refers to the airborne concentration of a substance at which nearly all workers may be repeatedly exposed, day after day, without adverse health affects. BEIs apply to 8-hour exposures occurring 5 days/week. The BEI for lead is 30 μg/dL (ACGIH 2004). The recommended exposure level (REL) for lead in the air adopted by the NIOSH is 0.05 mg/m^3 (NIOSH 2005). NIOSH also recommends maintaining air concentrations so that worker blood lead remains at <60 μg/dL (NIOSH 1997a).

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar

ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

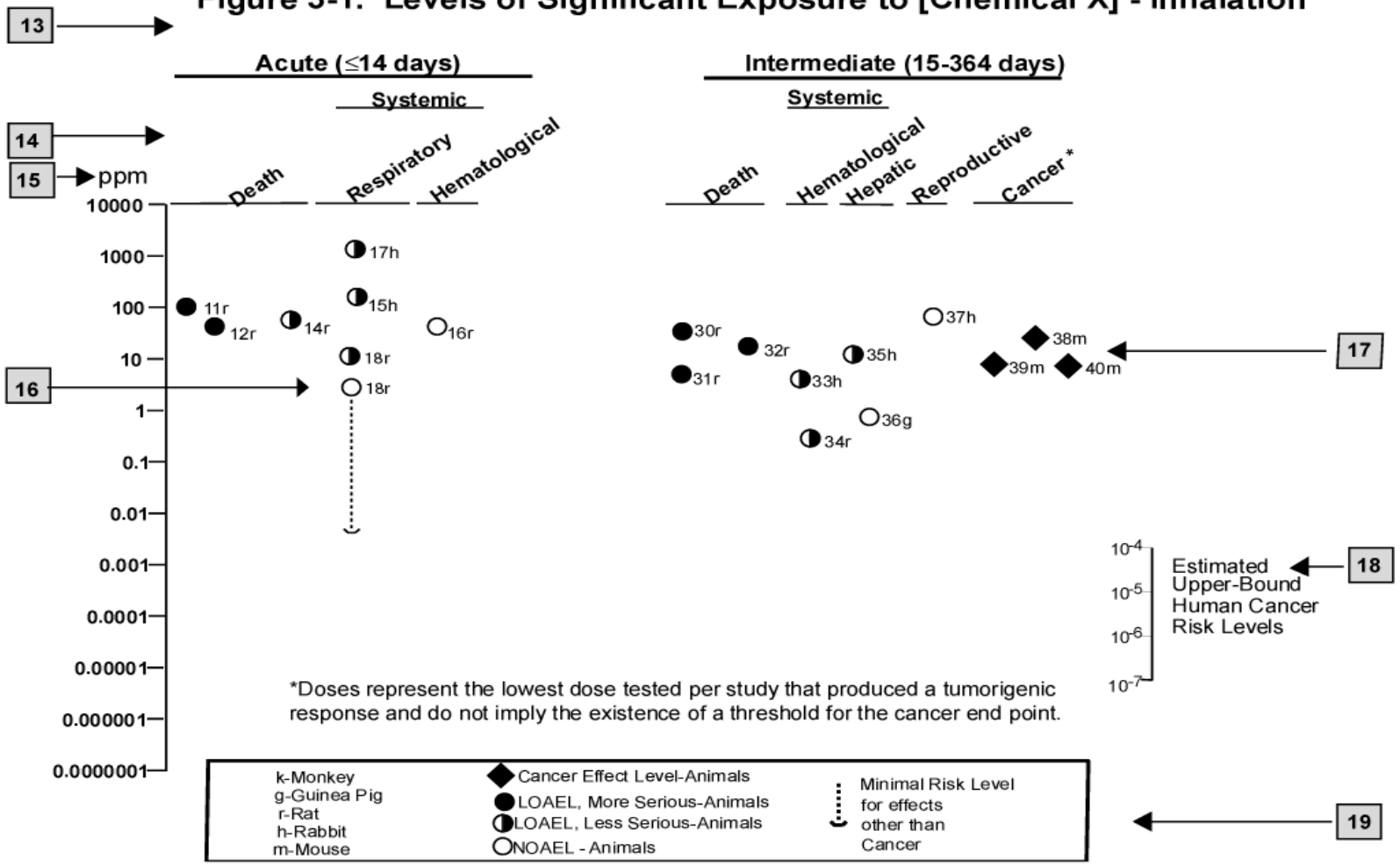
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. A FRAMEWORK TO GUIDE PUBLIC HEALTH ASSESSMENT DECISIONS AT LEAD SITES

ABSTRACT

The Agency for Toxic Substances and Disease Registry (ATSDR) provides health consultations and assessments at hazardous waste sites. Many of these sites have potentially significant levels of lead contamination for which the Agency must assess the health implications of exposure. Typically, environmental data are used to predict blood lead (PbB) levels in order to determine at which sites, if any, follow-up action is needed. Estimating blood lead levels from environmental lead concentrations, however, can be problematic. Several approaches have been developed, including classical ingestion rate determinations and comparison to animal studies, prevalence studies extrapolated to comparable sites, regression analysis of known exposure followed by slope factor estimates of similar levels of exposure, and the Environmental Protection Agency's (EPA) Integrated Exposure Uptake Biokinetic Model (IEUBK). Uncertainty is attendant to each of these approaches due, in part, to the limited nature of the environmental sampling data and the various site-specific factors. In this manuscript we describe an approach ATSDR developed to utilize regression analysis with multi-route uptake parameters to estimate blood lead levels.

The profound toxicity of lead has been acknowledged for many years. Developmental effects associated with female lead workers and wives of lead workers were well known during the 18th and 19th centuries, and much of what is taken for granted today regarding lead poisoning in children has been known for more than ninety years. None the less, production of lead compounds, mining and smelting of lead ore and secondary lead sources, and widespread use of lead-containing products continued to increase during the 20th century. These manufacturing, mining, and smelting activities resulted in the contamination of many industrial and residential areas. In addition, leaded gasoline and lead-based paint contributed to the dispersal of lead throughout the environment. During the 1970s and 1980s, federal agencies targeted programs and resources to reduce lead exposure in the United States. These primary prevention activities resulted in regulations governing air emissions, drinking water standards, the phase-out of lead in gasoline, and the banning of lead-based paint and leaded solder. Although these efforts have all contributed to reducing lead exposure to the general population, past uses have resulted in the contamination of many areas, many of which still have the potential for adversely affecting the public health.

Introduction

One of the mandates of the Agency for Toxic Substances and Disease Registry (ATSDR) (under the Comprehensive Environmental Response, Compensation, and Liability Act, Section 104(i)(3), or Superfund) is to address the potential for adverse effects on public health resulting from lead exposure. Lead has been identified as a contaminant in at least 1,026 of the National Priorities List (NPL) sites and is currently ranked first on the Priority List of Hazardous Substances (ATSDR 1996a). Consequently, ATSDR must address public health concerns regarding lead exposure at hazardous waste sites. ATSDR's specific responsibilities related to blood lead screening at lead-contaminated hazardous waste sites include: (1) evaluation of site-specific environmental lead exposure information, (2) identification of populations potentially exposed to lead, (3) decision about whether or not to conduct blood lead screening, (4) evaluation of blood lead screening results, and (5) determination of whether the U.S. Environmental Protection Agency's (EPA) proposed site remediation plans are sufficient to protect public health.

Evaluation of these environmental data is associated with a high level of biomedical judgment regarding appropriate public health actions. In this manuscript, we describe a framework developed to guide such judgment and one that can be used to evaluate the need for a site-specific public health action, which may include blood lead screening. This approach utilizes regression analysis along with uptake parameters and potential results of exposure in an effort to estimate blood lead levels in at-risk populations.

Superfund specifically directs ATSDR to ascertain significant human exposure levels for hazardous substances. Minimal risk levels (MRLs) were developed as part of the strategy to address this mandate. An MRL is "an estimate of the daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse, noncancerous effects over a specified duration of exposure" (ATSDR 1996b) and is analogous to the reference doses and the reference concentrations developed by EPA. MRLs are derived from no-observed-adverse-effect levels or lowest-observed-adverse-effect levels and are intended to assist in determining the safety of communities near hazardous waste sites. For example, an exposure level below the MRL suggests that there is little likelihood of adverse, noncancer human health effects occurring, whereas an exposure level exceeding the MRL alerts the health assessor that a more detailed evaluation using site-specific and chemical-specific information is required. Although the database for lead is large, empirical data from which to obtain a threshold for the effects of lead are lacking. With no observable threshold yet identified, the derivation of conventional health assessment tools such as MRLs is not feasible (De Rosa et al. 1991). In addition, a great deal of the human health effects data are expressed in terms of blood lead (PbB) levels rather than exposure dose, the usual comparison value. Using more traditional methodologies would overlook this significant body of literature, as well as the Centers for Disease Control (CDC, now the Centers for Disease Control and Prevention) guidelines[1]. A predictive tool relating environmental levels to PbBs is needed.

In response to this mandate, the Agency has been seeking ways to further refine the tools necessary for assessing the public health implications from exposure to hazardous substances. MRLs provide a guidance for single routes of exposure to a single substance. But, clearly, multi-route, multi-substance exposure considerations are needed not only for lead but for other substances. To this end, a framework for determining significant human exposure levels was developed (Mumtaz et al. 1995). The development of health-based guidance for lead is consistent with this concept. It should be noted that this effort and others to associate environmental levels with PbBs and consequently make health decisions are simply screening tools. Many issues must be considered on a site-by-site basis and used in conjunction with this guidance. Some of these issues are outlined below.

Exposure and Bioavailability Issues. Primary routes of exposure to lead are via inhalation and ingestion. Lead exposure occurs through inhalation of airborne lead particles with deposition rates in adults of 30%–50% depending on factors such as particle size and ventilation rate (EPA 1986). Once deposited in the lower respiratory tract, lead appears to be almost completely absorbed (Morrow et al. 1980).

Oral intake of lead is a more important route of exposure for children and can occur from ingestion of contaminated food, soil, dust, water, or lead-based paint chips. For young children (1–6 years of age), soil and dust are important pathways for exposure. Ingestion of soil and dust can occur through normal hand-to-mouth activity. Lead-based paint, often found in older homes, and flaking or peeling off walls, can also contribute significantly to exposure in young children. Through normal aging and weathering, intact lead-based paint can contribute to the contamination of dust or soil

The extent and rate of gastrointestinal absorption of lead is mediated by several factors including fasting, physical and chemical form of lead, and dietary status of the individual (Aungst et al. 1981; Grobler et al. 1988; Baltrop and Meek 1979; Chamberlain et al. 1978; Mahaffey et al. 1982; Rabinowitz et al. 1976).

Animal studies indicate that nutritional deficiencies in a number of essential elements (e.g., calcium, iron, zinc, copper, phosphorus) may impact the toxicokinetic and toxicological behavior of lead (ATSDR 1993; Chaney et al. 1989). In infants and children, lead retention has been shown to be inversely correlated with calcium intake (Johnson and Tenuta 1979; Sorrell et al. 1977; Ziegler et al. 1978). Zinc has been

[1]The weight of evidence suggests that PbBs of "10–15 µg/dL and possibly lower" are the levels of concern (ATSDR 1993; Davis 1990; EPA 1986). The Department of Health and Human Services (DHHS) has determined that primary prevention activities should begin at blood lead levels of 10 µg/dL in children (CDC 1991).

shown to have a protective effect against lead toxicity in a number of animal species (Goyer 1986; Haeger-Aronsen et al. 1976; Brewer et al. 1985; Cerklewski and Forbes 1976).

The physical and chemical characteristics of the lead/soil matrix and the particular lead species have also been shown to affect the bioavailability of lead. Studies measuring lead concentration at various soil and dust particle sizes have shown that higher lead concentrations are often found in the smaller-sized fractions. The results of these studies have been summarized by Duggan and Inskip (1985). This is particularly important for young children because smaller particles (<100 µm in diameter) also tend to adhere more readily to hands. Additionally, lead from smaller particles is more readily absorbed from the gastrointestinal tract (Baltrop and Meek 1979). It has been suggested that lead at mining waste sites is less bioavailable and therefore poses less of a human health hazard than lead found at smelter sites or in urban areas (Hemphill et al. 1991; Steele et al. 1990). These differences in bioavailability have been attributed to these biochemical/ biophysical differences of the lead source. Lead particles at mining sites are typically of larger size and consist of the less soluble lead sulfides. However, recent data suggest that this may not always be the case and that a site-by-site evaluation is necessary to determine the lead hazards to the surrounding populations (Gulson et al. 1994; Mushak 1991). See Mushak (1991) for a review of physical/chemical issues regarding lead bioavailability.

Age is also an important factor in that young children absorb lead more efficiently than adults (50% versus 15%) (Chamberlain et al. 1978). Fasting has a significant effect on absorption of lead. Retention of ingested lead is about 60% under fasting conditions compared with 4% when lead is ingested with a balanced meal (James et al. 1985).

Behavioral factors must also be considered. The normal hand to mouth activity of young children results in an increase in lead intake from hand soil/dust particles. In addition, children who exhibit pica behavior are at increased risk because they may ingest more lead-contaminated soil/dust. Health assessors should also be aware of distinct sources of lead within a household or community, such as certain hobbies that would expose one to lead (e.g. using molten lead for casting ammunition, leaded solder for making stained glass, leaded glazes for pottery), the use of folk remedies or lead-glazed pottery, or eating imported canned foods that might contain elevated lead from lead solder used in the can seams.

Approach

Numerous longitudinal and cross-sectional studies have attempted to correlate environmental lead levels with blood lead levels (Table 1). These studies have provided a number of regression analyses and corresponding slope factors (δ) for various media including air, soil, dust, water, and food. The specifics of each of these have been extensively discussed and evaluated elsewhere (Brunekreef 1984; Duggan and Inskip 1985; EPA 1986; Reagan and Silbergeld 1990; Xintaras 1992). In an attempt to use this valuable body of data, ATSDR has developed an integrated exposure regression analysis (Abadin and Wheeler, 1993). This approach utilizes slope values from select studies to integrate all exposures from various pathways, thus providing a cumulative exposure estimate expressed as total blood lead.

Table 1. Summary of blood slope factors from various environmental media.

Population	Slope	Comments	Reference
Air Slope Factors	µg/dL per µg Pb/m^3		
Adults; N = 43	1.75 ± 0.35	Experimental study; EPA analysis	Griffin et al. 1975
Adults; N=5	1.59–3.56	Experimental study; EPA analysis	Rabinowitz et al. 1976
Adults; N=10	2.7	Experimental study; EPA analysis	Chamberlain et al. 1978
Children; 1–18 years of age; N=831; 1,074 blood samples	1.92 ± 0.60	Omaha cross-sectional study; smelter	Angle et al. 1984
Children; N=148	2.46 ± 0.58	Belgium cross-sectional study; smelter; EPA analysis	Roels et al. 1980
Children; N=880	1.53 ± 0.064	Kellogg/Silver Valley cross-sectional study; EPA analysis; smelter	Yankel et al. 1977
Adult males; 5 groups, 30/group	2.57 ± 0.04	Cross-sectional study; air concentrations of 1 µg/m^3	Azar et al. 1975
Adult males; 5 groups, 30/group	1.12	Reanalysis of Azar 1975 by Snee 1982; at air concentration of 1 µg/m^3	Azar et al. 1975
Adult males; 5 groups, 30/group	1–2.39	Analysis of Azar 1975 by EPA; at 1 µg/m^3	Azar et al. 1975
Adults; N=44	1.14	Occupational longitudinal study over 30 months; air concentration <30 µg/m^3	Hodgkins et al. 1992

Table 1. Summary of blood slope factors from various environmental media (continued).

Population	Slope	Comments	Reference
Water Slope Factors	µg/dL per µg Pb/L		
Infants, N=131	0.26 at <15 µg/L 0.04 at >15 µg/L	Scottish study of infants; EPA analysis	Lacey et al. 1985
Children, N=495	0.16 at <15 µg/L 0.03 at >15 µg/L	Scottish study; EPA analysis	Laxen et al. 1987
Adult males, N=7,735	0.06	24 British towns sampled; water lead levels <100 µg/L	Pocock et al. 1983
Adult Females, N=114	0.03	Duplicate diet study; Ayr, Scotland; EPA analysis	Sherlock et al. 1982
Diet Slope Factors:	µg/dL per µg Pb/day		
Infants and toddlers; N=29	0.24	Breast-fed and formula-fed; EPA analysis	Ryu et al. 1983; EPA 1990
Adults; N=31	0.034--females	Duplicate diet study; Ayr, Scotland	Sherlock et al. 1982
Adults; N=15	0.014–0.017--males 0.018–0.022--females	Experimental study; blood leads were not allowed to equilibrate	Stuik et al. 1974
Adult males; N=15	0.027	Experimental study	Cools et al. 1976

Table 1. Summary of blood slope factors from various environmental media (continued).

Population	Slope	Comments	Reference
Soil Slope Factors	µg/dL per µg Pb/kg		
Mixed	0.002–0.016	Review of the literature	Reagan and Silbergeld 1990
Children; 1–18 years of age; N=831; 1,074 blood samples	0.0068 ± 0.00097	Omaha study; urban/suburban	Angle et al. 1984
Children; 1–72 months of age; N=377; 926 blood leads	-0.00016–0.00223 (near house) 0.00073–0.0023 at curb)	New Haven, CT; EPA analysis. The largest slopes were from the children under 1 year	Stark et al. 1982
Children; N=880	0.0011 (avg. for all ages) 0.0025 (for 2–3 year olds)	Kellogg/Silver Valley cross-sectional study; smelter; EPA analysis	Yankel et al. 1977
U.S. males age 18–65 years old (NHANES III)	0.001–0.003	Slope derived from Monte Carlo analysis	Stern 1996
Dust Slope Factors:	µg/dL per mg Pb/kg		
Children; 1–18 years of age; N=831; 1074 blood samples	0.00718 ± 0.00090	Omaha study; urban/suburban; housedust	Angle et al. 1984
Children; 1–6 years of age; N=32	0.008	Homes of lead workers; housedust	Baker 1977
Children; 2 years of age; N=82	0.004	Area of high lead soil; housedust	Baltrop et al. 1974
Adults and children; N=80	0.0086–0.0096 (housedust); 0.0021–0.0067 (outside dust)	Smelter	Roberts et al. 1974
Children; N=377; 1–72 months of age; 926 blood lead levels	0.00402 ± 0.0017 (0–1 year old); 0.00182 ± 0.00066 (2–3 years old) 0.00022±0.00077 (4–7 years old)	New Haven, CT; EPA analysis	Stark et al. 1982

Source: adapted from Duggan and Inskip 1985; EPA 1986, 1989

The general form of the model is:

$PbB = \delta_S TPb_S + \delta_D TPb_D + \delta_W TPb_W + \delta_{AO} TPb_{AO} + \delta_{AI} TPb_{AI} + \delta_F TPb_F$

where,

Pb_S=soil lead concentration
Pb_D=dust lead concentration
Pb_W=water lead concentration
Pb_{AO}=outside air lead concentration
Pb_{AI} = inside air concentration
Pb_F=food lead concentration
T=relative time spent
δ=the respective slope factor for specific media

A worktable that can be used to calculate a cumulative exposure estimate on a site-specific basis is provided in Table 2. To use the table, environmental levels for outdoor air, indoor air, food, water, soil, and dust are needed. In the absence of such data (as may be encountered during health assessment activities), default values can be used. In most situations, default values will be background levels unless data are available to indicate otherwise. Based on the U.S. Food and Drug Administration's (FDA's) Total Diet Study data, lead intake from food for infants and toddlers is about 5 µg/day (Bolger et al. 1991). In some cases, a missing value can be estimated from a known value. For example, EPA (1986) has suggested that indoor air can be considered 0.03 x the level of outdoor air. Suggested default values are listed in Table 3.

Empirically determined and/or default environmental levels are multiplied by the percentage of time one is exposed to a particular source and then multiplied by an appropriate regression slope factor. This assumes slope factor studies were based upon continuous exposure. The slope factors can be derived from regression analysis studies that determine PbBs for a similar route of exposure. Typically, these studies identify standard errors describing the regression line of a particular source of lead exposure. These standard errors can be used to provide an upper and lower confidence limit contribution of each source of lead to PbB. The individual source contributions can then be summed to provide an overall range estimate of PbB. While it is known that such summing of standard errors can lead to errors of population dynamics, detailed demographic analysis (e.g., Monte Carlo simulations) would likely lead to a model without much utility. As a screening tool, the estimates provided here have much greater utility than single value central tendency estimates, yet still provide a simple-to-use model that allows the health assessor an easy means to estimate source contributions to PbB.

As an example, Table 4 provides environmental monitoring data for a subset of data from the Multisite Lead and Cadmium Exposure Study (ATSDR 1995). Default values are used for air and dietary lead. The data are input as described in equation 1 with suggested slope factors from Table 2. The resulting media-specific contributions to PbB, the range of predicted PbBs, and the actual PbBs are given in Table 5.

The purpose of screening tools, such as MRLs or estimates derived from this approach, is to alert health assessors to substances that may pose risk to the exposed population. In addition, these approaches economize the use of resources by eliminating substances for which there is little likelihood of human

Table 2. Worktable for calculation of PbB from environmental and dietary lead.

Media	Concentration	Relative Time Spent	Slope Factor	Blood Lead	
				Low	High
Outdoor Air					
Indoor Air					
Food					
Water					
Soil					
Dust					
			Total		

Table 3. Suggested default values to be used for missing data.

Media	Default	Reference
Outdoor Air	0.1–0.2 µg/m^3	Eldred and Cahill 1994
Indoor Air	0.03–0.06 µg/m^3 (0.3 x outdoor concentration)	EPA 1986
Food	5 µg/day	Bolger et al. 1991
Water	4 µg/L	EPA 1991
Soil	10–70 mg/kg	Shacklette and Boerngen 1972
Dust	10–70 mg/kg	Shacklette and Boerngen 1972

Table 4. Media concentrations for three sites: A, B, and C.			
	SITE		
Media	A	B	C
Soil (mg/kg)	290	768	580
Dust (mg/kg)	383	580	560
Air (μg/m^3)	0.06-0.2	0.06-0.2	0.06-0.2
Water (μg/L)	1	1	1
Food (μg/day)	5	5	5

Table 5. Contribution of environmental lead to blood lead for three sites: A, B, and C.			
	SITE		
Media	**A** contribution to PbB (μg/dL)	**B** contribution to PbB (μg/dL)	**C** contribution to PbB (μg/dL)
Soil	1.1-2.8	3-7.4	2.3-5.6
Dust	1.7-3.8	2.6-5.7	2.5-5.5
Air	0.1-0.2	0.1-0.2	0.1-0.2
Water	0.26	0.26	0.26
Food	1.2	1.2	1.2
Predicted range of PbB (μg/dL)	4.4-8.3	7-14.8	6.4-12.8
Actual PbB	4.8	10.6	13.1

Slope values used were based on Angle et al. (1984): soil = 0.0068 ± 3SE; dust = 0.00718 ± 3SE; air = 1.92 ± 3SE.
Slope value for water was 0.26, based on Lacey et al. 1985 (reanalyzed by EPA 1986).
Slope value for food was 0.24, based on Ryu et al. 1983 (reanalyzed by Marcus in EPA 1990).
Default concentrations were used for air and food.

health effects so that efforts can be concentrated on those compounds of importance. Interpretation of the results from Table 5 would indicate that the potential exists that children at sites B and C have elevated PbBs as defined by the CDC guidelines. Further action on these sites would, therefore, be warranted based on the individual site-specific demographic information and the CDC recommended follow-up services. These might include education, follow-up testing, and social services (CDC 1997). Results from site A, however, would indicate to the health assessor that the environmental data would not likely adversely affect PbBs of resident children; resources can then be shifted to the other substances at the site.

Summary and Discussion

A number of methods and models have been used at sites to estimate potential risks from exposure to lead. One method is the use of prevalence data for estimating PbBs. In this case, PbB measurements can be made at a site and extrapolated to other sites with similar environmental and demographic data. Limitations of this method include site-to-site variability with respect to, among other things, children's behavioral patterns, age, and bioavailability issues. Estimation of past exposures can be problematic because of redistribution of Pb out of the blood compartment since PbB is only an indicator of recent exposure (<90 days).

More traditional approaches have calculated exposure doses from a particular medium via a specific route (ATSDR, 1992). Such exposure doses can then be compared with a reference value derived for the same substance via the same route of exposure. Usual assumptions are ingestion rates of 100 mg dust/day and 200 mg soil/day, child body weight of 15 kg, and continuous exposure scenarios. This approach assumes a threshold for the effects of lead and does not reflect the fullest possible use of the wealth of human data on PbBs.

Pharmacokinetic models have been developed that attempt to relate environmental levels to PbBs (Leggett 1993; O'Flaherty 1995). The Integrated Exposure Uptake Biokinetic Model (IEUBK) developed by EPA is one of the most extensive efforts to date to make population-based predictions of PbBs based upon environmental data. The model incorporates both exposure/uptake parameters and a biokinetic component to estimate the PbB distribution in the exposed population (EPA 1994).

The framework described here provides a useful screening tool. Preliminary efforts to test its predictive power have shown promise (unpublished data). The framework's strengths lie in its simplicity and flexibility to take into consideration environmental and biological variability between sites through the selection of slope factors from similar sites. For example, slope factors from a lead mining study can be used to address concerns at a mining community or, as more refined regression coefficients become available, they can be used in a site-specific manner to assist in making appropriate decisions. The framework also offers a simple approach that allows the health assessor to readily identify factors that may be contributing to elevated PbBs. In this manner, it provides for multi-media evaluation of all source contributions and utilizes a basic approach for determining significant human effect levels. This helps the health assessor determine source contributions of most significance and suggests plausible remediation avenues. These insights, coupled with biomedical judgment, can serve as valuable screening tools to identify those sites meriting further evaluation.

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DRAFT
TOXICOLOGICAL PROFILE FOR
MANGANESE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2008

DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Manganese was released in 2000. This present edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-32
Atlanta, Georgia 30333

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

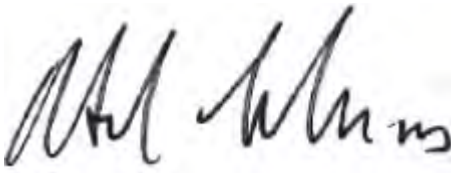
Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mail Stop F-32
Atlanta, Georgia 30333

Background Information

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99 499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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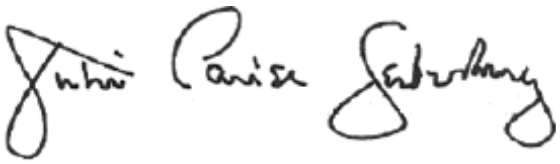

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QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone:	1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)	***Fax:***	(770) 488-4178
E-mail:	cdcinfo@cdc.gov	***Internet***:	http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for manganese. The panel consisted of the following members:

1. David Dorman, D.V.M., Ph.D., Associate Dean for Research and Graduate Studies, College of Veterinary Medicine, Professor of Toxicology, Department of Molecular Biomedical Sciences, North Carolina State University, Raleigh, North Carolina 27606,

2. Donald Smith, Ph.D., Professor of Environmental Toxicology, University of California, Santa Cruz, California 95064, and

3. Wei Zheng, Ph.D., Director of Graduate Studies, School of Health Sciences, Purdue University, West Lafayette, Indiana 47907.

These experts collectively have knowledge of manganese's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about manganese and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Manganese has been found in at least 869 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which manganese is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to manganese, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS MANGANESE?

Description	Manganese is a naturally occurring substance found in many types of rocks and soil. Pure manganese is a silver-colored metal; however, it does not occur in the environment as a pure metal. Rather, it occurs combined with other substances such as oxygen, sulfur, and chlorine. Manganese is a trace element and is necessary for good health.
Uses • **Manufacturing**	Manganese is used principally in steel production to improve hardness, stiffness, and strength. It is used in carbon steel, stainless steel, high-temperature steel, and tool steel, along with cast iron and superalloys.
• **Consumer products**	Manganese occurs naturally in most foods and may be added to food or made available in nutritional supplements. Manganese is also used in a wide variety of other products, including: • fireworks • dry-cell batteries • fertilizer • paints • a medical imaging agent • cosmetics It may also be used as an additive in gasoline to improve the octane rating of the gas. Small amounts of manganese are used in a pharmaceutical product called mangafodipir trisodium (MnDPDP) to improve lesion detection in magnetic resonance imaging of body organs.

Chapters 4, 5, and 6 have more information on the properties and uses of manganese and how it behaves in the environment.

1.2 WHAT HAPPENS TO MANGANESE WHEN IT ENTERS THE ENVIRONMENT?

Sources	Manganese is a normal constituent of air, soil, water, and food. Additional manganese can be found in air, soil, and water after release from the manufacture, use, and disposal of manganese-based products.
Breakdown	As with other elements, manganese cannot break down in the environment. It can only change its form or become attached or separated from particles. The chemical state of manganese and the type of soil determine how fast it moves through the soil and how much is retained in the soil. In water, most of the manganese tends to attach to particles in the water or settle into the sediment. The manganese-containing gasoline additive may degrade in the environment quickly when exposed to sunlight, releasing manganese.

For more information on manganese in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO MANGANESE?

Food – primary source of exposure	The primary way you can be exposed to manganese is by eating food or manganese-containing nutritional supplements. Vegetarians who consume foods rich in manganese such as grains, beans and nuts, as well as heavy tea drinkers, may have a higher intake of manganese than the average person.
Workplace air	Certain occupations like welding or working in a factory where steel is made may increase your chances of being exposed to high levels of manganese.
Water and soil	Because manganese is a natural component of the environment, you are always exposed to low levels of it in water, air, soil, and food. Manganese is routinely contained in groundwater, drinking water and soil at low levels. Drinking water containing manganese or swimming or bathing in water containing manganese may expose you to low levels of this chemical.
Air	Air also contains low levels of manganese, and breathing air may expose you to it. Releases of manganese into the air occur from: • industries using or manufacturing products containing manganese • mining activities • automobile exhaust

See Chapter 6 for more information on how you might be exposed to manganese or its compounds.

1.4 HOW CAN MANGANESE ENTER AND LEAVE MY BODY?

Enter your body • **Inhalation**	When you breathe air containing manganese, a small amount of the manganese will enter your body through your lungs and the remainder can become trapped in your lungs. Some of the manganese in your lungs can also be trapped in mucus which you may cough up and swallow into your stomach.
• **Ingestion**	Manganese in food or water may enter your body through the digestive tract to meet your body's needs for normal functioning.
• **Dermal contact**	Only very small amounts of manganese can enter your skin when you come into contact with liquids containing manganese.
Leave your body	Once in your body, manganese-containing chemicals can break down into other chemicals. However, manganese is an element that cannot be broken down. Most manganese will leave your body in feces within a few days.

For more information on how manganese enters and leaves the body, see Chapter 3.

1.5 HOW CAN MANGANESE AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in human and animal studies.

General population	Manganese is an essential nutrient, and eating a small amount of it each day is important to stay healthy.
Workers **• Inhalation**	The most common health problems in workers exposed to high levels of manganese involve the nervous system. These health effects include behavioral changes and other nervous system effects, which include movements that may become slow and clumsy. This combination of symptoms when sufficiently severe is referred to as "manganism." Other less severe nervous system effects such as slowed hand movements have been observed in some workers exposed to lower concentrations in the work place. The inhalation of a large quantity of dust or fumes containing manganese may cause irritation of the lungs which could lead to pneumonia. Loss of sex drive and sperm damage has also been observed in men exposed to high levels of manganese in workplace air. The manganese concentrations that cause effects such as slowed hand movements in some workers are approximately twenty thousand times higher than the concentrations normally found in the environment. Manganism has been found in some workers exposed to manganese concentrations about a million times higher than normal air concentrations of manganese.
Laboratory animals **• Inhalation**	Respiratory effects, similar to those observed in workers, have been observed in laboratory monkeys exposed to high levels of manganese.
Laboratory animals **• Oral**	Manganese has been shown to cross the blood-brain barrier and a limited amount of manganese is also able to cross the placenta during pregnancy, enabling it to reach a developing fetus. Nervous system disturbances have been observed in animals after very high oral doses of manganese, including changes in behavior. Sperm damage and adverse changes in male reproductive performance were observed in laboratory animals fed high levels of manganese. Impairments in fertility were observed in female rodents provided with oral manganese before they became pregnant. Illnesses involving the kidneys and urinary tract have been observed in laboratory rats fed very high levels of manganese. These illnesses included inflammation of the kidneys and kidney stone formation.
Cancer	The EPA concluded that existing scientific information cannot determine whether or not excess manganese can cause cancer.

Further information on the health effects of manganese in humans and animals can be found in Chapters 2 and 3.

1.6 HOW CAN MANGANESE AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in children	Studies in children have suggested that extremely high levels of manganese exposure may produce undesirable effects on brain development, including changes in behavior and decreases in the ability to learn and remember. In some cases, these same manganese exposure levels have been suspected of causing severe symptoms of manganism disease (including difficulty with speech and walking). We do not know for certain that these changes were caused by manganese alone. We do not know if these changes are temporary or permanent. We do not know whether children are more sensitive than adults to the effects of manganese, but there is some indication from experiments in laboratory animals that they may be.
Birth defects	Studies of manganese workers have not found increases in birth defects or low birth weight in their children. No birth defects were observed in animals exposed to manganese In one human study where people were exposed to very high levels of manganese from drinking water, infants less than 1 year of age died at an unusually high rate. It is not clear, however, whether these deaths were attributable to the manganese level of the drinking water. The manganese toxicity may have involved exposures to the infant that occurred both before (through the mother) and after they were born.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO MANGANESE?

Avoid inhalation of manganese at work	High levels of airborne manganese are observed in certain occupational settings such as steel factories or welding areas. You should take precautions to prevent inhalation of manganese by wearing an appropriate mask to limit the amount of manganese you breathe.
Avoid wearing manganese dust-contaminated work clothing in your home or car	Workers exposed to high levels of airborne manganese in certain occupational settings may accumulate manganese dust on their work clothes. Manganese-contaminated work clothing should be removed before getting into your car or entering your home to help reduce the exposure hazard for yourself and your family.
Avoid inhalation of welding fumes at home	If you weld objects around your home, do so in a well-ventilated area and use an appropriate mask to decrease your risk of inhaling manganese-containing fumes. Children should be kept away from welding fumes.
Diet	Children are not likely to be exposed to harmful amounts of manganese in the diet. However, higher-than-usual amounts of manganese may be absorbed if their diet is low in iron. It is important to provide your child with a well-balanced diet.
Water	While tap and bottled water generally contain safe levels of manganese, well water may sometimes be contaminated with sufficiently high levels of manganese to create a potential health hazard. If drinking water is obtained from a well water source, it may be wise to have the water checked for manganese to ensure the level is below the current guideline level established by the EPA.
Smoking	Manganese is a minor constituent of tobacco smoke. Avoiding tobacco smoke may reduce your family's exposure to manganese.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO MANGANESE?

Detecting exposure	Several tests are available to measure manganese in blood, urine, hair, or feces. Because manganese is normally present in our body, some is always found in tissues or fluids. Normal ranges of manganese levels are about 4–15 µg/L in blood, 1–8 µg/L in urine, and 0.4–0.85 µg/L in serum (the fluid portion of the blood).
Measuring exposure	Because excess manganese is usually removed from the body within a few days, past exposures are difficult to measure with common laboratory tests. A medical test known as magnetic resonance imaging, or MRI, can detect the presence of increased amounts of manganese in the brain. However, this type of test is qualitative, and has not been shown to reliably reflect or predict toxicologically meaningful exposures.

Information about tests for detecting manganese in the body is given in Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for manganese include the following:

Drinking water	The EPA has established that exposure to manganese in drinking water at concentrations of 1 mg/L for 1 or 10 days is not expected to cause any adverse effects in a child. The EPA has established that lifetime exposure to 0.3 mg/L manganese is not expected to cause any adverse effects.
Bottled water	The FDA has established that the manganese concentration in bottled drinking water should not exceed 0.05 mg/L.
Workplace air	OSHA set a legal limit of 5 mg/m^3 manganese in air averaged over an 8-hour work day.

For more information on regulations and advisories, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO MANGANESE IN THE UNITED STATES

Manganese is a naturally occurring element and an essential nutrient. Comprising approximately 0.1% of the earth's crust, it is the twelfth most abundant element and the fifth most abundant metal. Manganese does not exist in nature as an elemental form, but is found mainly as oxides, carbonates, and silicates in over 100 minerals with pyrolusite (manganese dioxide) as the most common naturally-occurring form. As an essential nutrient, several enzyme systems have been reported to interact with or depend on manganese for their catalytic or regulatory function. As such, manganese is required for the formation of healthy cartilage and bone and the urea cycle; it aids in the maintenance of mitochondria and the production of glucose. It also plays a key role in wound-healing.

Manganese exists in both inorganic and organic forms. An essential ingredient in steel, inorganic manganese is also used in the production of dry-cell batteries, glass and fireworks, in chemical manufacturing, in the leather and textile industries and as a fertilizer. The inorganic pigment known as manganese violet (manganese ammonium pyrophosphate complex) has nearly ubiquitous use in cosmetics and is also found in certain paints. Organic forms of manganese are used as fungicides, fuel-oil additives, smoke inhibitors, an anti-knock additive in gasoline, and a medical imaging agent.

The erosion of crustal rocks to create soil results in average manganese soil concentrations in the United States of 40–900 mg/kg. Its presence in soil results in vegetable and animal foods reliably containing varying amounts of the mineral. As an essential nutrient, manganese is added to certain foods and nutritional supplements. Vegetarians often have diets richer in manganese than those who select omnivorous diets.

The most important source of manganese in the atmosphere results from the air erosion of dusts or soils. The mean concentration of manganese in ambient air in the United States is 0.02 $\mu g/m^3$; however, ambient levels near industrial sources can range from 0.22 to 0.3 $\mu g/m^3$. Manganese is released into waterways mainly through the erosion of rocks and soils, mining activities, and industrial waste, or by the leaching of manganese from anthropogenic materials discarded in landfills or soil, such as dry-cell batteries. Surface waters in the United States contain a median manganese level of 16 µg/L, with 99^{th} percentile concentrations of 400–800 µg/L. Groundwater in the United States contains median

manganese levels of 5 to 150 µg/L, with the 99th percentile at 2,900 or 5,600 µg/L in rural or urban areas, respectively.

The general population is exposed to manganese through consumption of food and water, inhalation of air, and dermal contact with air, water, soil, and consumer products that contain manganese. The primary source of manganese intake is through diet. The Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) has set adequate intake (AI) levels for manganese for humans. These levels are presented in Table 2-1.

The inhalation of air contaminated with particulate matter containing manganese is the primary source of excess manganese exposure for the general population in the United States. Populations living in close proximity to mining activities and industries using manganese may be exposed by inhalation to high levels of manganese in dust. Workers in these industries are especially vulnerable to exposure to manganese dust. Manganese concentrations in soil may be elevated when the soil is in close proximity to a mining source or industry using manganese and may therefore pose a risk of excess exposure to children who ingest contaminated soil. Manganese is ubiquitous in drinking water in the United States. Although certain water sources in the United States are contaminated with excess manganese, there is little risk of excessive exposure to manganese through ingestion of fish or shellfish emanating from contaminated waters, unless the manganese levels in the fish are extremely high and/or the fish are eaten as subsistence. Although many forms of manganese are water-soluble, there is little evidence that dermal contact with manganese results in significant absorption through the skin. Thus, dermal contact with manganese is not generally viewed as an important source of exposure to the population at large.

Excess exposure to manganese may be revealed by tests to detect heightened levels in body fluids as well as in hair samples. Normal ranges of manganese levels in body fluids are 4–15 µg/L in blood, 1–8 µg/L in urine, and 0.4–0.85 µg/L in serum. Excess manganese in the body characteristically accumulates in the brain region known as the basal ganglia. This accumulation can be revealed by magnetic resonance imaging (MRI) as a distinctive symmetrical high-signal lesion in the globus pallidus region of the basal ganglia on T1- but not T2-weighted MRI.

Table 2-1. Adequate Intake (AI) for Manganese

Life stage	Age	Males (mg/day)	Females (mg/day)
Infants	0–6 Months	0.003	0.003
Infants	7–12 Months	0.6	0.6
Children	1–3 Years	1.2	1.2
Children	4–8 Years	1.5	1.5
Children	9–13 Years	1.9	1.6
Adolescents	14–18 Years	2.2	1.6
Adults	19 Years and older	2.3	1.8
Pregnancy	All ages	—	2.0
Lactation	All ages	—	2.6

Source: FNB/IOM 2001

2.2 SUMMARY OF HEALTH EFFECTS

Although low levels of manganese intake are necessary for human health, exposure to high manganese levels are toxic. Reports of adverse effects resulting from manganese exposure in humans are associated primarily with inhalation in occupational settings. Inhaled manganese is often transported directly to the brain before it is metabolized by the liver. The symptoms of manganese toxicity may appear slowly over months and years. Manganese toxicity can result in a permanent neurological disorder known as manganism with symptoms that include tremors, difficulty walking, and facial muscle spasms. These symptoms are often preceded by other lesser symptoms, including irritability, aggressiveness, and hallucinations. Some studies suggest that manganese inhalation can also result in adverse cognitive effects, including difficulty with concentration and memory problems. Although the workplace is the most common source of excess inhalation of manganese, frequent inhalation of fumes from welding activities in the home can produce a risk of excess manganese exposure leading to neurological symptoms. Environmental exposures to airborne manganese have been associated with similar preclinical neurological effects and mood effects as are seen in occupational studies. Acute or intermediate exposure to excess manganese also affects the respiratory system. Inhalation exposure to high concentrations of manganese dusts (specifically manganese dioxide [MnO_2] and manganese tetroxide [Mn_3O_4]) can cause an inflammatory response in the lung, which, over time, can result in impaired lung function. Lung toxicity is manifested as an increased susceptibility to infections such as bronchitis and can result in manganic pneumonia. Pneumonia has also been observed following acute inhalation exposures to particulates containing other metals. Thus, this effect might be characteristic of inhalable particulate matter and might not depend solely on the manganese content of the particle.

Many reports indicate that oral exposure to manganese, especially from contaminated water sources, can produce significant health effects. These effects have been most prominently observed in children and are similar to those observed from inhalation exposure. An actual threshold level at which manganese exposure produces neurological effects in humans has not been established. However, children consuming the same concentration of manganese in water as adults are ultimately exposed to a higher mg/kg-body weight ratio of manganese than adults (as a consequence of the lower body weight of children as well as their higher daily consumption volume and greater retention of manganese). Children are also potentially more sensitive to manganese toxicity than adults. A study conducted in infant monkeys suggests that soy-based infant formula, which contains a naturally higher concentration of manganese than human or cow's milk, may produce mild effects on neurological development, although such effects have not been documented in humans. While many of the studies reporting oral effects of

excess manganese have limitations that preclude firm conclusions about the potential for adverse effects, these studies collectively suggest that ingestion of water and/or foodstuffs containing increased concentrations of manganese may result in adverse neurological effects.

There is indirect evidence that reproductive outcomes might be affected (decreased libido, impotence, and sexual dysfunction have been observed in manganese-exposed men). The available studies on the effect that manganese has on fertility (as measured by birthrate) is inconclusive. Two studies in men occupationally exposed to manganese show adverse effects on reproductive parameters: one found increased sexual dysfunction and the other found reduced sperm quality, but neither measured birthrate in wives of affected workers. Impaired sexual function in men may be one of the earliest clinical manifestations of manganese toxicity, but no dose-response information is currently available, so it is not possible to define a threshold for this effect. There is a lack of information regarding effects in women since most data are derived from studies of male workers. Developmental data in humans exposed to manganese by inhalation are limited and consist mostly of reports of adverse pulmonary effects from inhaling airborne manganese dust and adverse neurological effects in offspring following ingestion exposure. Animal studies indicate that manganese is a developmental toxin when administered orally and intravenously, but inhalation data concerning these effects are scarce and not definitive. Some studies in children suggest that routine exposures to high levels of manganese from contaminated drinking water may ultimately impair intellectual performance and behavior.

The few available inhalation and oral studies in humans and animals indicate that inorganic manganese exposure does not cause significant injury to the heart, stomach, blood, muscle, bone, liver, kidney, skin, or eyes. However, if manganese is in the (VII) oxidation state (as in potassium permanganate), then ingestion may lead to severe corrosion at the point of contact. Studies in pigs have revealed a potential for adverse coronary effects from excess manganese exposure.

There is no evidence that manganese causes cancer in humans. Although no firm conclusions can be drawn from the mixed results in animal studies, there are little data to suggest that inorganic manganese is carcinogenic. The EPA has provided manganese with a weight-of-evidence classification D—not classifiable as to human carcinogenicity.

It should be noted that individuals with cirrhosis of the liver, as well as children with a congenital venous anomaly known as a portosystemic shunt, may be at heightened risk of health deficits from exposure to dietary and environmental sources of manganese. Manganese is ordinarily eliminated from the body

through bile, but cirrhosis and portosystemic shunts impair the normal functioning of the liver and thus limit the ability of the body to excrete manganese, which then can accumulate in the blood and, eventually, the brain.

A more detailed discussion of the critical targets of manganese toxicity (i.e., the nervous system, respiratory system, reproductive system, and development), follows.

Neurological Effects. There is clear evidence from studies of humans exposed to manganese dusts in mines and factories that inhalation of high levels of manganese can lead to a series of serious and ultimately disabling neurological effects in humans. This disease, termed manganism, typically begins with feelings of weakness and lethargy. As the disease progresses, a number of other neurological signs may become manifest. Although not all individuals develop identical signs, the most common are a slow and clumsy gait, speech disturbances, a masklike face, and tremors. The neurological symptoms may improve when exposure ceases; however, in most cases, the symptoms are found to persist for many years post-exposure. In addition, a syndrome of psychological disturbances (hallucination, psychosis) frequently emerges, although such symptoms are sometimes absent. As the disease progresses, patients develop severe muscle tension and rigidity and may be completely and permanently disabled. Workplace inhalation exposure levels producing overt symptoms of manganism have been on the order of 2–22 mg manganese/m^3. Subclinical neurological effects have been observed in several occupational studies. These effects include decreased performance on neurobehavioral tests; significantly poorer eye-hand coordination, hand steadiness, and reaction time; poorer postural stability; and lower levels of cognitive flexibility. Manganese air concentrations producing these effects in chronically exposed workers range from about 0.07 to 0.97 mg manganese/m^3. In addition, a study on environmental manganese sources indicated that both men and women were adversely affected by non-occupational exposure to manganese as evidenced by performance on neurobehavioral tests and increased neuropsychiatric disturbances. In these studies, a blood manganese level-age interaction was observed, with the poorest performance occurring among those older than 50 years who had the highest blood manganese levels. While manganese neurotoxicity has clinical similarities to Parkinson's disease, it can be clinically distinguished from Parkinson's. Manganism patients present a hypokinesia and tremor that is different from Parkinson's patients. In addition, manganism patients sometimes have psychiatric disturbances early in the disease, a propensity to fall backward when pushed, less frequent resting tremor, more frequent dystonia, a "cock-walk", and a failure to respond to dopaminomimetics.

While there is limited evidence that oral exposure to manganese leads to neurological effects similar to those reported for inhalation exposure, an accumulating body of evidence suggests that when children are exposed to excess levels of manganese in drinking water (≥0.2 mg/L), subtle learning and behavioral deficits may follow (see developmental effects below). Other studies have revealed cases of apparent manganism in both children and adults where exposures to high levels of manganese in drinking water were implicated as the probable cause. The symptoms in these cases are similar to those of individuals inhaling high levels of the mineral.

Respiratory Effects. Inhalation exposure to manganese dusts often leads to an inflammatory response in the lungs of both humans and animals. This generally leads to an increased incidence of cough and bronchitis and can lead to mild-to-moderate injury of lung tissue along with minor decreases in lung function. In addition, susceptibility to infectious lung disease may be increased, leading to increased pneumonitis and pneumonia in some manganese-exposed worker populations. These effects have been reported primarily in workers exposed to fairly high concentrations of manganese dusts in the workplace, although there are some data that indicate that, in populations living and attending school near ferromanganese factories, there was an increased prevalence of respiratory effects. The risk of lung injury in people exposed to the levels of manganese typically found in the general environment is expected to be quite low. However, exposure to manganese-containing dusts from factories, mining operations, automobile exhaust, or other sources may be of concern. It should be noted that these effects on the lung are not unique to manganese-containing dusts but are produced by a variety of inhalable particulate matter. On this basis, it seems most appropriate to evaluate the risk of inflammatory effects on the lung in terms of total suspended particulate matter (TSP) or particulate matter <10 μm in diameter (PM_{10}), as well as the concentration of manganese in the air. Studies involving controlled inhalation exposures in humans or animals to methylcyclopentadienyl manganese tricarbonyl (MMT), a gasoline additive that improves combustion efficiency, are not available because the compound breaks down readily in light to form inorganic manganese compounds. Rats exposed to high concentrations of car exhaust containing oxidation products from MMT-containing fuel exhibited labored breathing.

Reproductive Effects. Impotence and loss of libido are common symptoms in male workers afflicted with clinically identifiable signs of manganism. These symptoms could lead to reduced reproductive success in men. Impaired fertility (measured as a decreased number of children/married couple) has been observed in male workers exposed for 1–19 years to manganese dust (0.97 mg/m^3) at levels that did not produce frank manganism. This suggests that impaired sexual function in men may be one of the earliest clinical manifestations of manganese toxicity, but no dose-response information is

available; therefore, it is not possible to define a threshold for this effect. Evidence obtained in laboratory mammals indicates that exposure to high levels of manganese may adversely effect sperm quality, produce decreased testicular weights, and impair development of the male reproductive tract.

No direct effect of manganese toxicity has been observed on fertility in women. Although many studies in laboratory mammals have attempted to detect effects of manganese on female fertility, only one study demonstrated the possibility that excess manganese exposure outside of pregnancy may impair future fertility (decreased number of offspring).

Developmental Effects. There is evidence to suggest that children exposed to high levels of manganese in drinking water may develop a variety of adverse developmental effects, particularly relevant to their behaviors and ability to learn and remember. Some studies suggest that children exposed to particularly high levels of manganese over a long period of time (months or years) will eventually develop one or more symptoms, including diminished memory, attention deficit, aggressiveness, and/or hyperactivity. However, it is not clear from any of these studies whether other factors, perhaps environmental or genetic, are responsible for these changes in the presence of manganese, or whether manganese along can produce these effects.

A potentially serious developmental effect of manganese was suggested by the results of a study where high infant mortality in a Bangladesh community was reported in conjunction with the presence of a local drinking water supply containing high levels of manganese (concentration up to 8.31 mg/L). Infants exposed to levels of manganese equal to or greater than those recommended by the World Health Organization (WHO) were at the highest risk of mortality prior to 1 year of age. The nature of this epidemiological study, with nutritional deficits in the population anticipated but not documented, prevents a determination that manganese alone was responsible for the high rate of infant mortality.

Developmental studies involving the use of laboratory animals have detected subtle changes in growth; (e.g., diminished body weight, in animals provided with relatively high doses of manganese). These changes have been observed both when the animals were exposed while *in utero* or postpartum when the animals have already been born.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for manganese. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Inhalation MRLs for Inorganic Manganese

Acute and Intermediate Inhalation Exposure. MRL values were not derived for acute- or intermediate-duration inhalation exposures to manganese. The available data on the toxicity of inhaled manganese were considered inadequate for derivation of acute- or intermediate-duration inhalation MRLs. Data are lacking on whether exposure to inhaled manganese across these durations has any significant adverse effects on numerous end points including reports on developmental and reproductive effects.

Reports of human exposure at acute and intermediate durations (i.e., 15–364 days) indicate adverse respiratory and neurological effects, but these reports consist of anecdotal case studies and lack quantitative exposure values.

A few animal studies for these durations also evaluated respiratory effects in rodents and monkeys and reported no-observed-adverse-effect levels (NOAELs). Inhalation of particulate manganese compounds such as manganese dioxide or manganese tetroxide leads to an inflammatory response in the lungs of animals, although inhalation of $MnCl_2$ did not cause lung inflammation in rabbits (Camner et al. 1985). Several acute- and intermediate-duration studies in animals report various signs of lung inflammation following periods ranging from 1 day to 10 months at manganese concentrations ranging from 0.7 to 69 mg/m^3 (Bergstrom 1977; Camner et al. 1985; Shiotsuka 1984; Suzuki et al. 1978; Ulrich et al. 1979a, 1979b). Bergstrom (1977) and Ulrich et al. (1979a, 1979b) determined NOAELs, which are reported in the levels of significant exposure (LSE) table and figure. Increased susceptibility to lung infection by bacterial pathogens following inhalation of manganese dusts has been noted in acute animal studies (Maigetter et al. 1976). Conversely, Lloyd Davies (1946) reported no increase in the susceptibility of manganese-treated mice to pneumococci or streptococci.

More recently, reversible inflammation (pleocellular inflammatory infiltrates and fibrinonecrotic debris) in the nasal respiratory epithelium (but not the olfactory epithelium) was observed in young adult male Crl:CD(SD)BR rats following 13 weeks of inhalation exposure to 0.5 mg manganese/m^3 as manganese sulfate, but not in rats exposed to 0.1 mg manganese/m^3 as manganese sulfate or manganese phosphate (hureaulite) (Dorman et al. 2004b). The lesions were not apparent in groups of rats assessed 45 days after the end of exposure, indicating their transient nature. In studies with young male rhesus monkeys exposed to 0, 0.06, 0.3, or 1.5 mg manganese/m^3 as manganese sulfate 6 hours/day, 5 days/week for 65 days, no nasal histological effects were found in exposed monkeys, but the high exposure level induced lesions in the lower respiratory tract (mild subacute bronchiolitus, alveolar duct inflammation, and proliferation of bronchus-associated lymphoid tissue) (Dorman et al. 2005b). The lower airway lesions from intermediate-duration exposure appear to have been transient, because they were not found in monkeys assessed 45 days after the end of exposure (Dorman et al. 2005b). These findings in rats and monkeys are consistent with the understanding that inflammation of respiratory tissues from high-level exposure to inhaled manganese particulates is likely a consequence of the inhaled particulate matter.

Bredow et al. (2007) reported that nose-only inhalation exposure to 2 mg manganese/m^3 as manganese chloride aerosols 6 hours/day for 5 consecutive days did not cause lung lesions in female GVB/N mice, but induced a 2-fold increase in pulmonary levels of mRNA for vascular endothelial growth factor (VGEF), a regulator of proliferation, migration, and formation of new capillaries. Elevated levels of VGEF have been associated with respiratory diseases, but current understanding is inadequate to understand if this pulmonary gene expression response to manganese is adverse or benign.

There are limited evaluations of neurological end points in animals following intermediate-duration inhalation exposure to manganese. Neurological effects comparable to those observed in humans have been reported in monkeys exposed to manganese by parenteral routes (intravenous) for intermediate duration (Newland and Weiss 1992), but no reports of the application of sensitive neurobehavioral test batteries to animals following acute or intermediate-duration inhalation exposure to inorganic manganese were located.

In monkeys exposed to manganese oxide aerosol concentrations as high as 1.1 mg manganese/m^3 24 hours/day for 9 months, no exposure-related effects on limb tremor or electromyograms were observed, even though blood manganese levels were 5-fold higher in exposed compared with control monkeys (Ulrich et al. 1979a, 1979b, 1979c). No gross signs of neurological impairment were observed in rats exposed by the same protocol to manganese oxide aerosol concentrations as high as 1.1 mg manganese/m^3 (Ulrich et al. 1979a, 1979b, 1979c).

More recent studies of monkeys exposed to concentrations up to 0, 0.06, 0.3, or 1.5 mg manganese/m^3 as manganese sulfate 6 hours/day for 65 days reported: (1) no obvious signs of gross toxicity in the exposed monkeys; (2) about 2-fold higher manganese concentrations in most brain regions at 1.5 mg manganese/m^3, except for the globus pallidus which showed manganese concentrations 6-fold greater than control concentrations; and (3) a spectrum of exposure-related changes in biochemical markers of neurotoxicity in various regions of the exposed monkeys, compared with control monkeys (Dorman et al. 2006a, 2006b; Erikson et al. 2007). No published accounts of the application of sensitive neurobehavioral test batteries to these animals are available and there are no studies in monkeys reporting NOAELs and lowest-observed-adverse-effect level (LOAELs) for neurological effects following chronic-duration exposure.

Increased locomotor activity has been observed in Sprague-Dawley rats exposed for 90 days (6 hours/day, 5 days/week) to a manganese phosphate/manganese sulfate mixture at concentrations ≥0.03 mg manganese/m^3 (Salehi et al. 2003) and to manganese sulfate at concentrations ≥0.009 mg manganese/m^3 (Tapin et al. 2006), but this effect was not observed with exposure to hureaulite (manganese phosphate) at aerosol concentrations as high as 1 mg manganese/m^3 (Normandin et al. 2002). Significant neuronal cell loss in the globus pallidus and caudate putamen was also observed in Sprague-Dawley rats exposed for 90 day (6 hours/day, 5 days/week) to the manganese phosphate/manganese sulfate mixture at an aerosol

concentration of 3 mg manganese/m^3; these changes, however, were not accompanied with signs of tremor as assessed with electromyographic techniques (Salehi et al. 2006).

MRL values for acute or intermediate durations based on animal studies were not derived, because an MRL based on animal data would be lower than the proposed chronic-duration inhalation MRL that is based on effects observed in humans. It is uncertain if this is due to species differences in susceptibility to the neurotoxic properties of inhaled manganese or to the testing of humans with sensitive neurobehavioral tests that have not been applied to animals following inhalation exposures to manganese.

- An MRL of 0.0003 mg manganese/m^3 (manganese in respirable dust; 0.3 µg manganese/m^3) has been derived for chronic inhalation exposure (365 days or more) to manganese.

The study chosen to derive the MRL is from an investigation of an occupational cohort involving 92 male workers in a dry alkaline battery plant (Roels et al. 1992). They and the 101 age- and area-matched controls (with no industrial exposure to manganese) were observed for performance on a battery of neurobehavioral tests. Manganese workers were exposed for an average (geometric mean) of 5.3 years (range: 0.2–17.7 years) to a respirable dust concentration of 215 µg manganese/m^3 and a total dust concentration of 948 µg manganese/m^3. Manganese concentrations were measured with personal samplers, with respirable dust being <5 microns in diameter. The authors noted that plant exposure conditions had not changed considerably in the last 15 years, suggesting that past exposures were consistent with those measured at the time of the study. Performance in measured neurobehavioral tests, especially on measures of simple reaction time, eye-hand coordination, and hand steadiness, was significantly worse in manganese-exposed workers than in the comparison group.

Manganese-exposed workers performed significantly worse than the controls on the neurobehavioral tests, with particular differences in simple reaction time, eye-hand coordination, and hand steadiness. Dr. Harry Roels provided the data on the manganese-exposed group evaluated in this study. These data included individual exposure levels and whether the individual had an abnormal performance in the neurobehavioral tests (scores below the 5^{th} percentile score of the control group). Percent precision score in the eye-hand coordination test was the most sensitive end point among the end points showing statistically significantly elevated incidences of abnormal scores and was selected as the basis of the MRL. Average exposure concentration for each worker was calculated by dividing the individual lifetime integrated respirable concentration (LIRD; calculated by Dr. Roels from occupational histories and measurements of workplace air manganese concentrations) by the individual's total number of years working in the factory. Individuals were grouped into eight exposed groups and the control group, and

the average of the range in each group was used in benchmark modeling of the incidence data for number of workers with abnormal percent precision eye-hand coordination scores (see Table A-1 in Appendix A).

Available dichotomous models in the EPA Benchmark Dose Software (version 1.4.1c) were fit to the incidence data for abnormal eye-hand coordination scores in workers exposed to respirable manganese (Roels et al. 1992, Table A-1). Results from the modeling are shown in Table A-2 in Appendix A. Based on the chi-square and Akaike Information Criterion (AIC) measures of fit, all of the models provided adequate and comparable fits to the data (the quantal linear and Weibull models had the same parameter values). The model with the lowest AIC, the logistic model, was selected as the best fitting model, and the $BMCL_{10}$ from the logistic model, 142 µg respirable manganese/m^3, was selected as the point of departure for the chronic inhalation MRL. An alternative approach to selecting a point of departure (averaging $BMCL_{10}$ values across all models in Table A-2) arrived at a similar point of departure of 105 µg respirable manganese/m^3, which would yield an identical MRL value.

The MRL of 0.3 µg manganese/m^3 was derived by adjusting the point of departure to a continuous exposure basis (142 x 5/7 x 8/24) and dividing by an uncertainty factor of 100:

- 10 for uncertainty about human variability including possibly enhanced susceptibility of the elderly, infants, and children; individuals with chronic liver disease or diminished hepatobiliary function; and females and individuals with iron deficiency; and

- 10 for limitations/uncertainties in the database including the lack of epidemiological data for humans chronically exposed to soluble forms of manganese and the concern that the general population may be exposed to more soluble forms of manganese than most of the manganese-exposed workers in the principal and supporting studies and the uncertainty that a factor of 10 for human variability will provide enough protection for manganese effects on brain development in children. In addition, data on developmental toxicity for this route and duration of exposure are lacking. There is limited information on reproductive effects in females (one study in rat dams) and reported effects on male reproductive organs have not been clearly associated with decreased reproductive function. Though it is clear that the neurological system is the target organ for effects from chronic-duration inhalation exposure to manganese, data are lacking to fully characterize the potential risk for all organ systems from chronic inhalation exposure.

Neurological effects from repeated inhalation exposure to manganese are well recognized as effects of high concern based on case reports and epidemiological studies of groups of occupationally exposed people and results from animal inhalation studies. A number of epidemiological studies have used batteries of neurobehavioral tests of neuromotor, cognition, and mood states to study the psychological or neurological effects of exposure to low levels of manganese in the workplace (Bast-Pettersen et al. 2004; Beuter et al. 1999; Blond and Netterstrom 2007; Blond et al. 2007; Bouchard et al. 2003, 2005, 2007a, 2007b; Chia et al. 1993a, 1995; Crump and Rousseau 1999; Deschamps et al. 2001; Gibbs et al. 1999;

Iregren 1990; Lucchini et al. 1995, 1999; Mergler et al. 1994; Myers et al. 2003a, 2003b; Roels et al. 1987a, 1992, 1999; Wennberg et al. 1991) or in environmental media close to manganese-emitting industries (Lucchini et al. 2007; Mergler et al. 1999; Rodríguez-Agudelo et al. 2006). Some of these studies have found statistically significant differences between exposed and non-exposed groups or significant associations between exposure indices and neurological effects (Bast-Pettersen et al. 2004; Chia et al. 1993a; Iregren 1990; Lucchini et al. 1995, 1999; Mergler et al. 1994; Roels et al. 1987a, 1992; Wennberg et al. 1991), whereas others have not found significant associations (Deschamps et al. 2001; Gibbs et al. 1999; Myers et al. 2003a, 2003b; Young et al. 2005). Table A-3 in Appendix A summarizes results from these studies. The neurological effects associated with prolonged low-level manganese exposure generally have been subtle changes including deficits in tests of neuromotor or cognitive functions and altered mood states; they have been referred to by various authors as preclinical or subclinical neurological effects. Manganese air concentrations associated with these effects in chronically exposed workers range from about 0.07 to 1.59 mg manganese/m^3 (manganese in total or inhalable dust measurements; values for manganese in respirable dust are noted in parentheses in Table A-3). Comparison of the effect levels in these studies provides support for selection of the Roels et al. (1992) as the basis of the MRL; the advantage of the Roels et al. (1992) study is that individual worker data were available to support a benchmark dose analysis.

Several benchmark analyses of results from other epidemiological data for neurobehavioral deficits in manganese-exposed workers provide support for the MRL.

Dr. Anders Iregren provided ATSDR with individual worker data on total dust manganese exposure and performance on neurobehavioral tests for the occupational cohort that participated in his study (Iregren 1990; Wennberg et al. 1991). A benchmark analysis was also performed with these data (Clewell and Crump 1999) and the $BMCL_{10}$ value derived from this evaluation was 0.071 mg manganese/m^3 based upon the reported observation that the respirable fraction ranged upwards to 80% of the total dust measured. This $BMCL_{10}$ value is similar to that estimated for the Roels et al. (1992) study (0.105 mg manganese/m^3), thus giving support to the value obtained for the current MRL study.

Clewell et al. (2003) conducted benchmark analyses on data from three neuromotor tests in the Roels et al. (1992) study (visual reaction time, eye-hand coordination, and hand steadiness) and from five neuromotor tests in the Gibbs et al. (1999) study (hole 6 of the hand steadiness test, percent precision of the eye-hand coordination test, reaction time in the complex reaction test, RMS amplitude in the steady test, and tap time). Exposure measures in these analyses were recent measures of manganese

concentrations in respirable dust. $BMCL_{10}$ values were 0.257, 0.099, and 0.202 mg manganese/m^3, respectively, for the visual reaction time, eye-hand coordination, and hand steadiness data from the Roels et al. (1992) study. $BMCL_{10}$ values from the analyses of outcomes from the Gibbs et al. (1999) study ranged from 0.09 to 0.27 mg manganese/m^3 (averaging the BMCLs within end points across different benchmark dose models applied to the data). Clewell et al. (2003) did not have individual worker data from the Iregren (1990) or Mergler et al. (1994) studies, but, based on some assumptions about exposures (e.g., all exposed workers were exposed to average concentrations for the facilities and respirable manganese concentrations were calculated for the Iregren workers based on an assumption that 50% of total dust manganese was respirable), they calculated $BMCL_{10}$ values for six end points from the Mergler et al. (1994) study and the simple reaction time end point in the Iregren (1990) study. $BMCL_{10}$ values ranged from 0.1 to 0.3 mg manganese/m^3 from the Mergler et al. (1994) study end points to 0.1 mg manganese/m^3 for the reaction time end point in the Iregren (1990) study.

Health Canada (2008) recently prepared a draft document in which benchmark dose analyses were conducted on data for neurobehavioral end points from the study of manganese alloy workers by Lucchini et al. (1999). Using the average manganese concentrations in respirable dust over the 5-year period before testing as the dose metric, dose-response data for six tests of fine motor control, two aspects of memory tests, and one test of mental arithmetic were fit to linear models, which were used to calculate $BMCL_{05}$ values ranging from about 0.019 to 0.0588 mg manganese/m^3. After adjustment to convert from occupational exposure (5 days/week, 8 hours/24 hours) to continuous exposure, adjusted $BMCL_{05}$ values were divided by a total uncertainty factor of 100 to arrive at prospective reference concentrations. The uncertainty factor was comprised of a factor of 10 to account for interindividual variability in response to manganese to protect possibly enhanced susceptibility of the elderly, infants and children, individuals with asymptomatic pre-parkinsonism, individuals with chronic liver disease or parenteral nutrition, and females and individuals with iron deficiency and a second factor of 10 to account for limitations/ uncertainties in the database including: (1) the general population may be exposed to more soluble forms of manganese than most of the manganese-exposed workers; (2) the lack of extensive studies of the effect of prenatal exposure to manganese; and (3) the potential effects that manganese exposure early in life may have on health outcomes later in life. The prospective reference concentrations ranged from about 0.05 to 0.08 μg manganese/m^3.

Oral MRLs for Inorganic Manganese

Overview. No oral MRLs were derived for acute-, intermediate-, or chronic-duration oral exposure to manganese, even though the limited human data and extensive animal data clearly identify neurobehavioral changes as the most sensitive effect from intermediate- and chronic-duration oral exposure to excess inorganic manganese. However, inconsistencies in the dose-response relationship information across studies evaluating different neurological end points under different experimental conditions in different species, as well as a lack of information concerning all intakes of manganese (e.g., dietary intakes plus administered doses), make it difficult to derive intermediate- or chronic-duration MRLs using standard MRL derivation methodology from the animal studies. New reports of neurobehavioral effects in children associated with elevated concentrations of manganese in drinking water were evaluated as the possible basis of an oral MRL for intermediate and/or chronic durations of exposure. However, the data were assessed to be unsuitable for MRL derivation due to uncertainties about other possible confounding exposures to neurotoxic agents in the drinking water or via food, and the lack of information about dietary intakes of manganese by the children. An interim guidance value of 0.16 mg manganese/kg/day, based on the Tolerable Upper Intake Level for 70 kg adults of 11 mg manganese/day (established by the U.S. Food and Nutrition Board/Institute of Medicine [FNB/IOM 2001]) is recommended to be used for ATSDR public health assessments of oral exposure to inorganic forms of manganese.

Acute Oral Exposure. Quantitative data are not available to derive acute-duration oral MRLs. The only new acute-duration study reported that a single dose of 50 mg manganese chloride/kg (13.9 mg manganese/kg) to a group of 10 white rats caused worsened acquisition of an avoidance reaction in response to unconditioned and condition stimuli, increased latent period of a conditioned reflex activity, and increased numbers of errors and time taken to navigate a maze (compared with controls), beginning on day 5 after dose administration and lasting until day 10–15 (Shukakidze et al. 2003). Although neurobehavioral impairment from acute oral exposure to manganese is plausible based on results from studies of manganese-exposed workers and repeatedly exposed animals, there are no corroborating data from other acute-duration studies to confirm this finding of impaired neurobehavior following a single oral dose of 13.9 mg manganese/kg.

Other acute-duration oral studies found only decreased liver and body weight and decreased leukocyte and neutrophil counts in rats at dietary doses of 1,300 mg manganese/kg/day and no effects in mice at dietary doses up to 2,600 (males) or 3,900 (females) mg manganese/kg/day after 14 days of exposure to

manganese sulfate in the diet (NTP 1993). No signs of developmental or maternal toxicity were observed in a standard developmental toxicity study of pregnant rats given daily gavage doses of 2,200 mg manganese/kg/day as manganese chloride on gestation days 6–17 (Grant et al. 1997a). With intermediate-duration, no exposure-related effects on fetal body weight or skeletal development or anomalies were found in pregnant rabbits exposed to 33 mg manganese/kg/day on gestation days 6–20, but some evidence for delayed fetal skeletal development was found in pregnant Sprague-Dawley rats exposed to the same dose of manganese chloride on gestation days 0–21 (Szakmáry et al. 1995).

Intermediate Oral Exposure. With intermediate-duration oral exposure, effects on neurobehavior are expected to be the most sensitive effects from excessive manganese, particularly during early developmental periods, based on findings for subtle neurobehavioral effects in epidemiological studies on manganese-exposed workers (see Section 3.1), higher brain manganese levels and altered brain dopamine levels in neonatal rats, compared with adult rats, due to immaturity of the blood-brain barrier and the lack of biliary excretion in preweanling rats (Aschner et al. 2005; Dorman et al. 2000, 2005a; Kontur and Fechter 1985, 1988), and results from studies of the effects of intermediate-duration oral exposure on systemic toxicity end points and neurobehavioral, neurochemical, and neurodevelopmental end points in adult and young laboratory animals (Calibresi et al. 2001; Reichel et al. 2006; Tran et al. 2002a, 2002b).

The discussion that follows provides evidence that, while systemic effects of manganese are not typically the most sensitive end point of action, some evidence exists to support adverse cardiovascular effects of manganese at relatively low dose levels, followed by a review of the large number of studies that most consistently support neurobehavior effects as the most sensitive effects from excessive oral manganese exposure.

In standard toxicity studies of intermediate-duration oral exposure to inorganic manganese, marginal evidence for systemic toxicity was found in rats at doses ≥33 mg manganese/kg/day (increased neutrophil count and decreased liver weight in males; decreased body weights at higher doses) and in mice at the highest administered dose of 1,950 mg manganese/kg/day (decreased hemoglobin, mild hyperplasia of forestomach, decreased liver and body weight) (NTP 1993). Corroborative evidence comes from reports of decreased red blood cell counts and body weight in mice following 100 days of dietary exposure to one of several forms of inorganic manganese (manganese acetate, carbonate, oxide, or chloride) at a dose level of 284 mg manganese/kg/day (Komura and Sakamoto 1991).

However, other animal studies indicate that excessive oral intake of manganese may present a cardiovascular hazard. Under magnesium deficiency conditions (4.1 mmol Mg/kg diet), swine fed moderately elevated levels of manganese (about 500 mg manganese/kg diet) died suddenly within 5 weeks and showed necrosis and mineralization of the heart (Miller et al. 2000). This finding was supported with subsequent findings of myocardial necrosis and mitochondrial swelling in magnesium-deficient pigs fed a diet high in manganese (500 mg manganese/kg diet) for 8 weeks (Miller et al. 2004) and of depressed heart muscle mitochondrial O_2 consumption and decreased red blood cells in rats consuming a high manganese diet (250 mg manganese/kg diet) under marginal magnesium dietary conditions; the manganese-induced effects on hematological end points in rats were absent when adequate dietary magnesium was provided (Miller et al. 2006). In another study involving rats supplied with adequate and excessive Mn in the diet (10–15 and 45–50 mg manganese/kg diet), aortas from rats with excessive dietary manganese showed less expression and sulfation of heparin sulfate glycosaminoglycans, compared with the adequate condition (Kalea et al. 2006). The results from these studies suggest that excessive intermediate-duration oral intake of manganese may present a cardiovascular hazard, especially under magnesium-deficient dietary conditions, but their use as the basis of an intermediate-duration oral MRL for inorganic manganese is limited due to the lack of reported information to accurately calculate daily intakes. Myocardial lesions were not found in rats or mice provided manganese sulfate in the diet for 2 years at dose levels up to 232 or 731 mg manganese/kg/day, respectively (NTP 1993).

Numerous studies support the sensitivity of neurobehavioral end points to intermediate-duration oral doses of manganese. In humans and nonhuman primates exposed orally for intermediate durations, neurobehavioral end points have been examined in healthy adult female subjects given low (0.01 mg manganese/kg/day) or high (0.3 mg manganese/kg/day) manganese diets for 8 weeks (Finley et al. 2003) and in infant monkeys fed either a commercial cow's milk formula (17.5 mg manganese/kg/day), a commercial soy formula (107.5 mg manganese/kg/day), or a soy formula with added magnesium chloride (328 mg manganese/kg/day) for 4 months with monkeys tested through 18 months of age (Golub et al. 2005). No differences between the low and high dietary-intake states were found in the adult females on scores for hand-steadiness and self-reported traits such as assertiveness and anger (Finley et al. 2003). Monkeys provided the highest manganese dose level showed no marked differences from the cow's milk controls in gross motor maturation, growth, cerebrospinal fluid levels of dopamine or serotonin metabolites, or performance on tests of cognitive end points, but showed decreased activity during sleep at 4 months and decreased play activity between 1 and 1.5 months. These results suggest that daily intakes of 328 mg manganese/kg/day (but not 107.5 mg manganese/kg/day) during neonatal periods may cause subtle neurobehavioral changes in primates.

In neurobehavioral assessments of rodents orally exposed to inorganic manganese for intermediate durations during neonatal periods, subtle neurobehavioral effects have been observed at supplemental dose levels as low as about 10–20 mg manganese/kg/day (Brenneman et al. 1999; Dorman et al. 2000; Kristensson et al. 1986; Pappas et al. 1997; Reichel et al. 2006; Tran et al. 2002a, 2002b). Although there are some inconsistencies in the results obtained in these studies (e.g., Brenneman et al. [1999] found increased motor activity with exposure to 22 mg manganese/kg/day after exposure on postnatal days 1–49, but Dorman et al. [2000] found no effects of the same dose level on motor activity after exposure on postnatal days 1–21), the weight of evidence suggests that subtle neurobehavioral effects can occur in rats with intermediate-duration neonatal exposures at doses ≥10–20 mg manganese/kg/day.

Findings for histopathological changes in the rat brain following intermediate-duration oral exposure to inorganic manganese during neonatal periods are less consistent than the findings for subtle neurobehavioral effects. Chandra and Shukla (1978) reported neuronal degeneration in cortical and cerebellar sections from the brains of young rats orally exposed to 0.3 mg manganese/kg/day as manganese chloride between postnatal days 21 and 51. In contrast, Kristensson et al. (1986) reported no adverse histological changes in cerebellum or hippocampus in rats exposed to a much higher dose level of manganese chloride (150 mg manganese/kg/day) between postnatal days 3 and 44. Pappas et al. (1997) reported a decreased cortical thickness in the offspring of rat dams exposed to 120 or 650 mg manganese/kg/day from gestation day 1 through postnatal day 30, but found no immunohistological evidence for increased glial fibrillary acidic protein in the cortex, caudate, or hippocampus. Dorman et al. (2000) reported that no adverse histological changes were found in sections of the following brain regions in Sprague-Dawley rats exposed to 11 or 22 mg manganese/kg/day on postnatal days 1–21: olfactory bulbs, cerebral cortex, hippocampus, basal ganglia, thalamus, hypothalamus, midbrain, and cerebellum. The weight of evidence from these studies indicates that subtle neurobehavioral effects in neonatally exposed rats are not consistently associated with histological changes in the brain.

Neurobehavioral effects have also been observed in adult rats orally exposed to inorganic manganese for intermediate durations. In several studies, doses inducing these effects were higher than those inducing subtle neurobehavioral effects after neonatal exposure (Calabresi et al. 2001; Centonze et al. 2001; Torrente et al. 2005), but in two other studies, neurobehavioral effects were observed at doses as low as 5.6 mg manganese/kg/day (Shukakidze et al. 2003) and 6.5 mg manganese/kg/day (Vezér et al. 2005, 2007). Increased open field activity, increased interest in a novel object, and increased signs of fear were observed in adult male Wistar rats exposed to drinking water containing 20 mg manganese chloride/L for

10 weeks (estimated doses of 1,310 mg manganese/kg/day), but no effects on radial maze performance, numbers of neuronal cells or levels of glial fibrillary acidic protein in striatum, or intrinsic electrophysiological membrane properties of striatal neurons with the exception of a manganese-induced increase in the frequency and amplitude of spontaneous excitatory postsynaptic potentials (Calabresi et al. 2001; Centonze et al. 2001). In an earlier study of adult male Wistar rats exposed to 20 mg manganese chloride/L for 13 weeks, no neuronal loss or gliosis was evident in the globus pallidus by either histological or immunohistochemical examination (Spadoni et al. 2000). Decreased open field activity and impaired spatial learning were observed in restraint stressed adult male Sprague-Dawley rats exposed to 153 mg manganese/kg/day (but not 76 mg manganese/kg/day) as manganese chloride in drinking water for 19 weeks (Torrente et al. 2005). No changes in motor activity or performance in a passive avoidance test were observed in adult male Sprague-Dawley rats exposed to 11 or 22 mg manganese/kg/day for 21 days; these doses induced increased pulse-elicited acoustic startle response with neonatal exposure, but exposure during adulthood did not (Dorman et al. 2000). The lowest intermediate-duration daily dose associated with neurobehavioral effects in adult rats is 5.6 mg manganese/kg/day for severely impaired cognitive performance in a maze test following a 30-day exposure of white rats to manganese chloride in the diet (strain not otherwise indicated) (Shukakidze et al. 2003). In another study, decreased open-field locomotor activity and acoustic startle response and impaired performance in maze learning (a test of spatial memory) were observed in male adult Wistar rats exposed to gavage doses of 6.5 or 25.9 mg manganese/kg/day for 10 weeks, compared with controls (Vezér et al. 2005, 2007). Decreased acoustic startle response and impaired spatial memory were still evident in exposed rats, compared with controls, after 5–7 weeks without exposure (Vezér et al. 2005, 2007).

Several types of reproductive effects have been reported for manganese. A study by Hafeman et al. (2007) reported a high mortality rate among infants <1 year of age in a Bangladesh community where manganese levels in drinking water were high, but the actual association between the manganese levels in drinking water and infant mortality is difficult to make with certainty. The average level of manganese intake was calculated to be 0.26 mg manganese/kg/day. Other reproductive effects reported for manganese in intermediate-duration animal studies include 25% decreased pregnancy rate in Long-Evans rats (males and females) exposed to manganese oxide in the diet at 180 mg manganese/kg/day (but not 55 mg manganese/kg/day) for 100–224 days (Laskey et al. 1982), increased incidence of testicular degeneration in male Sprague-Dawley rats exposed to manganese acetate at gavage doses of 137 (but not 69) mg manganese/kg/day for 63 days (Ponnapakkam et al. 2003c), and delayed growth of testes and sex accessory glands in CD-1 mice exposed to manganese oxide in the diet at 205 mg manganese/kg/day (Gray and Laskey 1980). In Swiss mice exposed for 12 weeks to manganese chloride in drinking water,

impaired fertility was observed in males at 309 mg manganese/kg/day (but not a 154 mg manganese/kg/day) and in females at 277 mg manganese/kg/day (Elbetieha et al. 2001). Decreased sperm motility and sperm counts were observed in CD-1 mice exposed to 4.8 or 9.6 mg manganese/kg/day as manganese acetate, but no effects on the ability of exposed males to impregnate unexposed female mice were found at these doses (Ponnapakkam et al. 2003a). The results from the intermediate-duration animal studies suggest that oral exposure to manganese may produce adverse effects on reproduction, but at much higher doses than those inducing subtle neurobehavioral effects in adult or neonatal rats.

In summary, results from animal studies identify subtle neurobehavioral effects as the critical effect in rodents from intermediate-duration oral exposure to inorganic manganese. Potential points of departure for an intermediate-duration oral MRL include LOAEL values of 5.6 mg manganese/kg/day for severely impaired cognitive performance in a maze test following 30-day dietary exposure of adult white rats (Shukakidze et al. 2003); 6.5 mg manganese/kg/day for decreased open-field locomotor activity and acoustic startle response and impaired performance in maze learning (a test of spatial memory) in male adult Wistar rats exposed for 10 weeks by gavage (Vezér et al. 2005, 2007); and 11 mg manganese/kg/day for increased pulse-initiated acoustic startle response in Sprague-Dawley rats exposed (orally by pipette) on postnatal days 1–21 (Dorman et al. 2000). In contrast, hand steadiness or self-reported scales for assertiveness or anger were not different in adult female subjects following 8 weeks of exposure to dietary doses of 0.01 or 0.3 mg manganese/kg/day (Finley et al. 2003). In young monkeys, decreased activity during sleep at 4 months and decreased play activity between 1 and 1.5 months were observed following daily intakes of 328 mg manganese/kg/day (but not 107.5 mg manganese/kg/day), but no effects on gross motor maturation or performance in cognitive tests were observed at either dose level compared with controls (Golub et al. 2005).

The effects noted in the rat study by Shukakidze et al. (2003) are much more severe than effects noted in adult rats at reportedly higher dose levels of 1,310 mg manganese/kg/day (Calabresi et al. 2001; Centonze et al. 2001) or 153 mg manganese/kg/day (Torrente et al. 2005) or in adult rats at comparable reported doses of 6.5 mg manganese/kg/day (Vezér et al. 2005, 2007). Shukakidze et al. (2003) reported that the exposed rats “showed increased aggresivity, frequently fell from the platform in the maze, and were unable to perform the maze test.” Because the reporting of the experimental conditions in the Shukakidze et al. (2003) study is sparse and the severity of effects is so unusual, the results are considered to be outlying results that are not consistent with the rest of the database and not appropriate as the basis of an MRL.

If the LOAEL of 6.5 mg manganese/kg/day for decreased open-field locomotor activity and acoustic startle response and impaired performance in maze learning in male adult Wistar rats exposed for 10 weeks by gavage (Vezér et al. 2005, 2007) was used as the point of departure for the intermediate-duration oral MRL, a value of 0.007 mg manganese/kg/day would be derived if an uncertainty factor of 1,000 were used (10 for use of a LOAEL, 10 for extrapolating across species, and 10 for human variability). However, this rodent-based value of 0.007 mg manganese/kg/day would be about 4-fold below the FNB/IOM (2001) recommended AI of 1.8 and 2.3 mg manganese/day for women and men, respectively (approximately 0.03 mg manganese/kg/day) and about 23-fold below the FNB/IOM (2001) recommended Tolerable Upper Intake Level (UL) of 11 mg/day for adults ≥19 years of age (approximately 0.16 mg manganese/kg/day). Part of the apparent discrepancy between this prospective MRL and the recommended dietary intakes is that the MRL is based only on manganese intakes above the normal dietary intakes. Unfortunately, the dietary intakes of manganese by the rats in the Vezér et al. study (2005, 2007) cannot be estimated from the information provided in the published report.

Alternatively, using the monkey NOAEL of 107 mg manganese/kg/day for decreased activity during sleep at 4 months and decreased play activity between 1 and 1.5 months in formula-fed infant monkeys provided soy-based formula from birth to 4 months of age (Golub et al. 2005), a value of 1 mg manganese/kg/day would be derived if an uncertainty factor of 100 were used (10 for extrapolating across species and 10 for human variability). The monkey-based value would be about 6-fold higher than the FNB/IOM (2001) UL of 11 mg manganese/day for adults (0.16 mg manganese/kg/day assuming a 70-kg body weight). The formulas fed to the infant monkeys in this study are expected to have been the principal source of manganese.

For children and adolescents, FNB/IOM (2001) scaled the adult UL values according to reference body weights for children and adolescents, noting that there were no reports of manganese toxicity in children and adolescents and that it was not possible to establish UL values for infants (0–12 months).

Based on several surveys, FNB/IOM (2001) reported that average intakes of adults with typical "Western-type" and vegetarian diets ranged from 0.7 to 10.9 mg/day (0.01–0.156 mg manganese/kg/day, assuming a 70-kg body weight). WHO (2004b) recently calculated an estimated daily intake of about 0.0003 mg manganese/kg/day for 70-kg subjects drinking 2 L of water per day at a concentration of 0.010 mg manganese/L, the median of a survey of manganese in drinking water.

Chronic Oral Exposure. Data on the effects of manganese following chronic oral exposure are less extensive than intermediate-duration data, but these reports do suggest that neurological effects similar to those seen after intermediate-duration exposure may be anticipated following chronic oral exposure to excess manganese. In the reports of neurological effects in humans following chronic oral exposure, there is either uncertainty regarding the exposure level (He et al. 1994; Zhang et al. 1995) or uncertainty that the effects observed were solely attributable to manganese (Bouchard et al. 2007c; Holzgraefe et al. 1986; Kawamura et al. 1941; Kilburn 1987; Kondakis et al. 1989; Wasserman et al. 2006; Wright et al. 2006). However, there is no clear understanding of the threshold for manganese deficiency/sufficiency or toxicity. Males consuming 0.35 and 0.11 mg manganese/day exhibited symptoms of manganese deficiency (Doisy 1973; Friedman et al. 1987, respectively). But Davis and Greger (1992) did not report any deficiency symptoms among female subjects, 20% of whom consumed <1 mg manganese/day and Finley et al. (2003) did not observe signs of manganese deficiency or toxicity in adult females with dietary intakes of 0.8 or 20 mg manganese/day for 8 weeks. Authors of a case study suspected abuse of vitamin and mineral preparations to be the source for excess manganese and neurological symptoms observed in their patient (Banta and Markesbery 1977).

Four reports of manganese neurotoxicity in children have been published recently including: (1) severe manganism-like neurotoxic symptoms (inability to stand independently, tendency to fall backward, and development of a “cock-like” walk) in a previously healthy 6-year-old female that were associated with elevated drinking water concentrations of manganese (1.7–2.4 mg manganese/L), pica, a diet high in manganese-rich foods, and elevated levels of plasma manganese (Sahni et al. 2007); (2) inattentiveness and lack of focus in the classroom and low-percentile performance in tests of memory in a 10-year-old male with no history of learning problems associated with elevated manganese in drinking water (1.21 mg manganese/L) (Woolf et al. 2002); (3) a statistically significant relationship for decreasing intelligence scores with increasing manganese levels in drinking water in a cross-sectional epidemiological study of 142 10-year-old children in Bangladesh (Wasserman et al. 2006); and (4) a statistically significant relationship between increased levels of oppositional behaviors and hyperactivity and increased levels of manganese in drinking water in an epidemiological study of 46 children (ages 6–15 years) in Quebec, Canada (Bouchard et al. 2007c). Although these recent reports cannot causally link the observed neurotoxic effects to excessive manganese intakes, they provide added weight to the evidence for the neurotoxic potential of excessive manganese in children.

As shown in the chronic exposure section of the oral LSE table and figure in Chapter 3, estimated daily intakes from drinking water were calculated as 0.103 mg manganese/kg/day for the 6-year-old female

(Sahni et al. 2007), 0.06 mg manganese/kg/day for the 10-year-old male (Woolf et al. 2002), 0.11 mg manganese/kg/day based on the mean manganese drinking water concentration for the fourth quartile group of Bangladesh 10-year-old children (1.923 mg manganese/L), reference daily water intakes (1.3 L/day) and average body weights (22.4 kg) (Wasserman et al. 2006), and 0.02 mg manganese/kg/day for the high-manganese intake children in Quebec (0.5 mg manganese/L), reference daily water intakes (1.3 L/day) and reference body weights (37.2 kg) (Bouchard et al. 2007c).

To derive an oral MRL for intermediate and chronic durations, an average of the drinking water LOAELs for neurobehavioral effects in the two case reports (Sahni et al. 2007; Woolf et al. 2002), the cross-sectional study of 10-year-olds in Bangladesh (Wasserman et al. 2006), and the study of children in Quebec (Bouchard et al. 2007c) could potentially serve as a point of departure for the MRL. However, the following uncertainties associated with these studies of children preclude their use as the basis for an intermediate- or chronic-duration MRL: (1) whether or not the observed effects were solely due to excess manganese alone or could have been influenced by other drinking water or dietary components; (2) the lack of information about manganese levels in food and air; and (3) the small sample sizes.

Interim Guidance Value for Oral Exposure to Inorganic Manganese. As discussed in the preceding sections, no oral MRLs were derived for acute-, intermediate-, or chronic-duration exposure to inorganic manganese, but it is recommended that an interim guidance value of 0.16 mg manganese/kg/day be used for ATSDR public health assessments. The interim guidance value is based on the Tolerable Upper Intake Level for adults of 11 mg manganese/day established by the U.S. Food and Nutrition Board/Institute of Medicine (FNB/IOM 2001) based on a NOAEL for Western diets (0.16 mg manganese/kg/day assuming an adult body weight of 70 kg). The interim guidance value is well above the FNB/IOM Adequate Intake (AI) value for manganese for men and women of 2.3 and 1.8 mg manganese/day, respectively (for 70-kg individuals, this would result in exposures of 0.033 and 0.026 mg manganese/kg/day, respectively). The interim guidance value is necessary because of the prevalence of manganese at hazardous waste sites and the fact that manganese is an essential nutrient. It is recommended that this value be used until more information on actual intake levels across environmental media can be obtained.

MRLs for MMT

Inhalation and oral MRL values for acute, intermediate, or chronic exposures to MMT have not been derived. There are currently insufficient data regarding the systemic toxicity and carcinogenicity of this

compound via inhalation or oral exposures and no reliable data concerning current environmental or occupational exposures with appropriate dose-response information.

MRLs for Mangafodipir

MRL values for mangafodipir are not believed to be warranted. This compound is used in a clinical environment, is administered intravenously only, and is restricted to a very limited population. Thus, it is believed unlikely that this compound would be found at hazardous waste sites or other environmental settings.

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of manganese. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Manganese is a naturally occurring element found in rock, soil, water, and food. In humans and animals, manganese is an essential nutrient that plays a role in bone mineralization, protein and energy metabolism, metabolic regulation, cellular protection from damaging free radical species, and formation of glycosaminoglycans (Wedler 1994). Manganese acts as both a constituent of metalloenzymes and an enzyme activator. Enzymes that contain manganese include arginase, pyruvate carboxylase, and manganese-superoxide dismutase (MnSOD) (Keen and Zidenberg-Cher 1990; NRC 1989; Wedler 1994). Manganese, in its activating capacity, can bind either to a substrate (such as adenosine triphosphate, ATP), or to a protein directly, thereby causing conformational changes (Keen and Zidenberg-Cher 1990). Manganese has been shown to activate numerous enzymes involved with either a catalytic or regulatory function (e.g., transferases, decarboxylases, hydrolases) (Wedler 1994). The nutritional role of manganese is discussed in Section 3.4. Although manganese is an essential nutrient, exposure to high levels via inhalation or ingestion may cause some adverse health effects.

It has been suggested that these adverse health effects, especially neurologic effects, are occurring on a "continuum of ...dysfunction" that is dose-related (Mergler et al. 1999). In other words, mild or unnoticeable effects may be caused by low, but physiologically excessive, amounts of manganese, and these effects appear to increase in severity as the exposure level or duration of exposure increases. Case reports and occupational studies address this continuum of nervous system dysfunction and help to characterize the apparent dose-response relationship. It is clear that chronic exposure to manganese at very high levels results in permanent neurological damage, as is seen in former manganese miners and smelters. Chronic exposure to much lower levels of manganese (as with occupational exposures) has been linked to deficits in the ability to perform rapid hand movements and some loss of coordination and balance, along with an increase in reporting mild symptoms such as forgetfulness, anxiety, or insomnia.

Chemical Forms of Concern. Manganese can exist in both inorganic and organic forms. This profile will discuss key manganese compounds in both forms, with inorganic compounds discussed first.

The inorganic forms include manganese chloride ($MnCl_2$), manganese sulfate ($MnSO_4$), manganese acetate (MnOAc), manganese phosphate ($MnPO_4$), manganese dioxide (MnO_2), manganese tetroxide (Mn_3O_4), and manganese carbonate ($MnCO_3$). Emphasis has been placed on the health effects of compounds containing inorganic manganese in the Mn(II), Mn(III), or Mn(IV) oxidation states, since these are the forms most often encountered in the environment and the workplace. There is evidence in animals and humans that adverse neurological effects can result from exposure to different manganese compounds; much of this information on toxicity differences between species of manganese is from reports and experiments of acute exposures to very high doses. Results from animal studies indicate that the solubility of inorganic manganese compounds can influence the bioavailability of manganese and subsequent delivery of manganese to critical toxicity targets such as the brain; however, the influence of manganese oxidation state on manganese toxicity is not currently well understood. Manganese in the form of permanganate produces toxic effects primarily through its oxidizing capacity. However, because of its tendency to oxidize organic material, the permanganate ion is not stable in the environment; thus, the probability of exposure to this species around waste sites is considered very low. For this reason, data on exposures to permanganate are only briefly discussed.

The organic compounds that will be discussed are methylcyclopentadienyl manganese tricarbonyl (MMT) and mangafodipir. The latter is a chelate of Mn(II) and an organic ligand, dipyridoxyl diphosphate (MnDPDP; Mn(II) *N,N'*-dipyridoxylethylenediamine-*N,N'*-diacetate 5,5'bis(phosphate)). These compounds were chosen for this profile because their toxicity is expected to be mediated by excess exposure to elemental manganese. Organic fungicides containing manganese, such as maneb, were not chosen for discussion in this profile, because their critical toxic effects are expected to be mediated by the organic moities of their chemical structure, not by excessive elemental manganese.

MMT is a fuel additive developed in the 1950s to increase the octane level of gasoline and thus improve the antiknock properties of the fuel (Davis 1998; Lynam et al. 1999). Additional information on the chemical, physical, and environmental properties of MMT is included in Chapter 4. Exposure to MMT is expected to be primarily through inhalation or oral pathways, although occupational exposure for gasoline attendants or mechanics may be more significant via dermal absorption. Engines using MMT-containing gasoline and equipped with catalytic converters primarily emit manganese in inorganic phosphate and sulfate forms and smaller amounts of manganese dioxides can be detected (Mölders et al. 2001; Ressler et

al. 2000; Zayed et al. 1999a, 1999b). These findings and observations that MMT is very unstable in light and degrades quickly in air (Garrison et al. 1995) suggest that human exposure to manganese from the use of MMT in gasoline is most likely to occur in inorganic forms as a result of the combustion of MMT, with the exception of people occupationally exposed to uncombusted gasoline containing MMT. However, despite this evidence, there are some reports that MMT levels in the environment increase with traffic density (Garrison et al. 1995; Zayed et al. 1999a, 1999b); therefore, inhalation and/or ingestion exposures to the parent compound are possible. Exposure and resultant toxicity from MMT's inorganic combustion products are covered under the inorganic subsections, while toxicity attributable to MMT is covered under the organic subsections.

Mangafodipir is a contrast agent for magnetic resonance imaging (MRI) used primarily (after intravenous administration) to detect and characterize neoplastic liver lesions; it has also been found to aid in the identification of kidney and pancreatic tumors (Federle et al. 2000; Grant et al. 1997a, 1997b; Ni et al. 1997). The compound is only used in the diagnosis of organ-specific cancers and is found exclusively in a clinical setting. Mangafodipir is injected intravenously; therefore, inhalation, oral, and dermal pathways of exposure are not a concern. Because exposure to this compound is pathway-specific and the exposure population is inherently limited, toxicity arising from exposure to mangafodipir will be discussed in a separate subsection to Section 3.2.4, Diagnostic Uses.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a

considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL and that, in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Inorganic manganese compounds are not volatile, but they can exist in the air as aerosols or suspended particulate matter. Table 3-1 and Figure 3-1 summarize the available quantitative information on the health effects that have been observed in humans and animals following inhalation exposure to various inorganic manganese compounds. All exposure levels are expressed as milligrams of manganese per cubic meter (mg manganese/m^3).

Many of the studies, especially those dealing with occupational exposures, make the distinction between respirable and total manganese dust. Respirable dust is usually defined by a particular dust particle size that varies from study to study. It is typically defined as those particles ≤5 microns; these smaller dust particles can enter the lower areas of the lungs, including the bronchioles and the alveoli. These particles can be absorbed by the lung and will enter the bloodstream immediately, thus avoiding clearance by the

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Rat (Sprague-Dawley)	10 d 6 hr/d	Resp			43 (pneumonitis and increased lung weight)	Shiotsuka 1984 MnO2	
			Hemato	138				
2	Mouse (CD-1)	2 hr	Resp	2.8 F			Adkins et al. 1980b Mn3O4	
3	Mouse (FVB/N)	5 d 6 h/d	Resp	2 F			Bredow et al. 2007 (MnCl2)	No significant treatment-related histopathic lesions in lungs.
4	Gn Pig (NS)	1 hr 24 hr/d	Resp	14			Bergstrom 1977 MnO2	
Immuno/ Lymphoret								
5	Mouse (CD-1)	1-4 d 3 hr/d			69 M (increased susceptibility to pneumonia)		Maigetter et al. 1976 MnO2	
Neurological								
6	Rat (Sprague-Dawley)	Gd 9-10 or pnd 37-47 or Gd 9-10 and pnd 37-47			0.71 (decreased APP, COX-2, nNOS, GFAP, TGF-beta mRNA in the brain)		HaMai et al. 2006 (MnSO4)	Increased transcription of genes related to oxidative stressor inflammation in brain of rats exposed during gestation or early adulthood.

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
Developmental								
7	Rat (Sprague-Dawley)	Gd 9-10 or pnd 37-47 or Gd 9-10 and pnd 37-47			0.71 (decreased APP, COX-2, nNOS, and GFAP mRNA)		HaMai et al. 2006 (MnSO4)	Increased transcription of genes related to oxidative stressor inflammation in brain of rats exposed during gestation or early adulthood.
INTERMEDIATE EXPOSURE								
Systemic								
8	Monkey (Rhesus)	90 d 6 h/d 5 d/wk	Resp	0.3 M	1.5 M (increased incidence of subacute bronchiolitis/alveolar duct inflammation)		Dorman et al. 2005b (MnSO4)	
9	Monkey	90 d 6 h/d 5 d/wk	Resp	1.5 M			Dorman et al. 2006a (MnSO4)	Only absolute and relative organ weights were examined for the pituitary, liver, lung, kidney, heart, pancreas, hemotocrit.
			Cardio	0.3 M	1.5 M (17% decrease in relative heart weight 90 days post-exposure)			
			Hemato	0.3 M	1.5 M (decreased total bilirubin concentrations)			
			Hepatic	1.5 M				
			Renal	1.5 M				
			Endocr	1.5 M				
			Bd Wt	1.5 M				

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
10	Monkey (Rhesus)	10 mo 22 hr/d	Resp		0.7 F (mild inflammation)		Suzuki et al. 1978 MnO2	
11	Monkey (NS)	9 mo (continuous)	Resp	1.1			Ulrich et al. 1979a Mn3O4	No histopathological changes in lung or brain and no pulmonary function changes.
12	Rat (CD)	13 wk 6 h/d 5 d/wk	Resp	0.1 M	0.5 M (transient inflammatory changes in the nasal respiratory epithelium)		Dorman et al. 2004b (MnSO4)	Inflammatory changes were no longer present 45 days after exposure period was over.
13	Rat (CD)	13 wk 6 h/d 5 d/wk	Resp	0.1 M			Dorman et al. 2004b MnPO4	There were no lesions or inflammation observed in the nasal respiratory epithelium of rats.
14	Rat (Sprague-Dawley)	12 wk 6 h/d 5 d/wk	Bd Wt		0.11 M (12% decreased body weight)		El-Rahman 2004 hureaulite	
15	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d	Bd Wt	0.03 M	0.3 M (10% decreased body weight)		Salehi et al. 2003 manganese phosphate/sulfate mixture	
16	Rat (Sprague-Dawley)	90 d 5 d/wk 6 h/d	Bd Wt	0.9 M			Tapin et al. 2006 manganese sulfate dihydrate	

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
17	Rat (NS)	9 mo (continuous)	Resp	1.1			Ulrich et al. 1979b Mn3O4	
			Hemato	1.1				
			Hepatic	1.1				
18	Rabbit (NS)	4 wk 5 d/wk 6 hr/d	Resp	3.9 M			Camner et al. 1985 MnCl2	
19	Pigeon	5 d/wk 5, 9, or 13 wk (IC)	Hemato		0.167 (decrease in total blood proteins (p<= 0.05) at 13 weeks of exposure that persisted 2 weeks after exposure ended)		Sierra et al. 1998 Mn3O4	
Neurological								
20	Monkey	90 d 6 h/d 5 d/wk		1.5 M			Dorman et al. 2006a (MnSO4)	Only absolute and relative brain weight were examined.
21	Monkey (Rhesus)	90 d 6 h/d 5 d/wk			0.06 M (altered levels of GS, GLT-1 mRNA, GLAST, TH mRNA, GLT-1 mRNA, GLAST mRNA, and TH mRNA in the brain)		Erikson et al. 2007 (MnSO4)	
22	Monkey (NS)	9 mo (continuous)		1.1			Ulrich et al. 1979a Mn3O4	

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
23	Rat (CD)	13 wk 6 h/d 5 d/wk		0.5 M			Dorman et al. 2004b (MnSO4)	No changes in GFAP levels in the olfactory bulb, cerebellum, and striatum.
24	Rat (CD)	13 wk 6 h/d 5 d/wk		0.1 M			Dorman et al. 2004b MnPO4	No changes in GFAP levels in the olfactory bulb, cerebellum, and striatum.
25	Rat (Sprague-Dawley)	12 wk 6 h/d 5 d/wk			0.11 M (increased free amino acid contents; focal glial cell proliferation; astrocytic nodules)	1.1 M (neuronal degeneration)	El-Rahman 2004 MnPO4	
26	Rat (CD)	Gd 0-19, pnd 1-18 6 h/d 7 d/wk			0.05 (decreased brain GS mRNA, MT mRNA and GHS levels in F1 females and decreased brain MT mRNA and GSH levels F1 males)		Erikson et al. 2005 (MnSO4)	

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
27	Rat (CD)	Gd 0-19, pnd 1-18 6 h/d 5 d/wk			0.05 (decreased brain GS and TH protein and mRNA, MT, and GSH and increased GSSG levels in F1 rats)		Erikson et al. 2006 (MnSO4)	
28	Rat (Sprague-Dawley)	90 d 5 d/wk 6 h/d		1 M			Normandin et al. 2002 hureaulite	No differences in neuronal cell counts compared to controls, and no changes in locomotor and tremor assessments.
29	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d			0.03 M (increased locomotor activity)		Salehi et al. 2003 manganese phosphate/sulfate mixture	There was a significant increase in distance traveled, but not in rest time; increased exposure did not result in increased response.
30	Rat (Sprague-Dawley)	90 d 5 d/wk 6 h/d			3 M (significant neuronal cell loss in the globus pallidus and caudate putamen)		Salehi et al. 2006 manganese phosphate/sulfate mixture	
31	Rat (Sprague-Dawley)	90 d 5 d/wk 6 h/d			0.009 M (increased locomotor activity)		Tapin et al. 2006 manganese sulfate dihydrate	

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
32	Rat (NS)	9 mo (continuous)		1.1			Ulrich et al. 1979b Mn3O4	
33	Mouse (Swiss ICR)	18 wk 5 d/wk 7 hr/d			61 F (decreased maternal pup retrieval latency)		Lown et al. 1984 MnO2	
34	Mouse (Swiss ICR)	16-32 wk 5 d/wk 7 hr/d			72 M (increased open-field behavior)		Morganti et al. 1985 MnO2	
Reproductive								
35	Monkey (Rhesus)	90 d 6 h/d 5 d/wk		1.5 M			Dorman et al. 2006a (MnSO4)	Only testes weight was examined.
36	Mouse (Swiss ICR)	18 wk 5 d/wk 7 hr/d		61 F			Lown et al. 1984 MnO2	No effect on number of pups born.
Developmental								
37	Rat (CD)	Gd 0-19, pnd 1-18 6 h/d 7 d/wk			0.05 (decreased brain GS mRNA, MT mRNA and GHS levels in F1 females and decreased brain MT mRNA and GSH levels F1 males)		Erikson et al. 2005 (MnSO4)	

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
38	Rat (CD)	Gd 0-19, pnd 1-18 6 h/d 5 d/wk			0.05 (decreased brain GS and TH protein and mRNA, MT, and GHS and increased GSSG levels in F1 rats)		Erikson et al. 2006 (MnSO4)	
CHRONIC EXPOSURE								
Systemic								
39	Human	7.5 yr (average duration in Mn mine) (occup)	Resp		90 M (increased respiratory symptoms and prevalence of subjects with impaired pulmonary function)		Boojar and Goodarzi 2002	
40	Human	NS (occup)	Resp			3.6 M (pneumonia)	Lloyd Davies 1946 MnO2	
41	Human	1-19 yr (occup)	Resp			0.97 M (cough, decreased lung function)	Roels et al. 1987a Mn salts and oxides	
			Hemato	0.97 M				
42	Human	5.3 yr (occup)	Resp	0.18			Roels et al. 1992 MnO2	
			Endocr	0.18				

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m^3)	LOAEL Less Serious (mg/m^3)	LOAEL Serious (mg/m^3)	Reference Chemical Form	Comments
43	Monkey (Rhesus)	66 wk	Hemato	0.1			EPA 1977 Mn3O4	
Neurological								
44	Human	24 yr (median employment in steel plant) (occup)			0.07 M (longitudinal analysis showed impaired ability to perform fast pronation/supination of the hands and fast finger tapping compared with controls)		Blond and Netterstrom 2007	No impairments of slow hand and finger movements or increased tremor intensity were observed compared with controls.
45	Human	24 yr (median employment in steel plant)		0.07 M			Blond et al. 2007	Cognitive function could not be distinguished between Mn-exposed steel workers and controls.
46	Human	19.3 yr (average employment in Mn alloy plant) (occup)			0.23 M (increased Mn impairment with age in 1/9 neuromotor tests, 3/12 cognitive tests, and 1 or 4 sensory tests)		Bouchard et al. 2005	

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
47	Human	15.7 yr (average employment) (occup)			0.23 M (significantly higher scores for 2 [depression, anxiety] of 9 neuropsychiatric symptoms)		Bouchard et al. 2007a	
48	Human	15.3 yr (average employment) (Occup)			0.23 M (impaired performance on 1/5 neuromotor tests and enhanced score for 1 [confusion-bewilderment] of 6 mood states)		Bouchard et al. 2007b	Follow-up to Mergler et al. 1994; no significant ($p<0.05$) differences between exposed and controls in 9 cognitive tests.
49	Human	1.1-15.7 yr (occup)			1.59 M (postural sway with eyes closed)		Chia et al. 1995 MnO2	
50	Human	NS (occup)				22 M (bradykinesia, mask-like face)	Cook et al. 1974 NS	
51	Human	19.87 yr; mean (SD±9) employment in enamels production (occup)		2.05			Deschamps et al. 2001	No significant effects on blood levels of Mn or tests of cognition. Tests of neuromotor functions were not conducted.

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
52	Human	12.7 yr (mean) (occup)		0.051			Gibbs et al. 1999 NS	
53	Human	1-35 yr (2.6 median) (occup)			0.14 M (decreased reaction time, finger tapping)		Iregren 1990 MnO2	
54	Human	1-28 yr			0.149 M (decreased neurobehavioral performance finger tapping, symbol digit, digit span, additions)		Lucchini et al. 1995 (primarily MnO2) (MnOx - Mn oxides)	
55	Human	11.5 yr (mean) (occup)			0.0967 M (decreased performance on neurobehavioral exams)		Lucchini et al. 1999 MnO2, Mn3O4	
56	Human	16.7 yr (mean) (occup)			0.032 M (decreased motor function)		Mergler et al. 1994 NS	

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
57	Human	10.8 yr (mean employment in Mn mines) (occup)		0.21			Myers et al. 2003a	No associations between measures of exposure and neurobehavioral endpoints were found: 3 motor function and 3 cognitive tests.
58	Human	18.2 yr; mean (SD 7.6) employment in a Mn smelter (occup)		0.85			Myers et al. 2003b	Neurobehavioral test batteries showed significant effects, only in a few endpoints and little evidence of positive exposure-response relationships.
59	Human	1-19 yr (occup)			0.97 M (altered reaction time, short-term memory, decreased hand steadiness)		Roels et al. 1987a Mn salts and oxides	
60	Human	5.3 yr (occup)			0.179[b] (impaired visual time, eye-hand coordination, and hand steadiness)		Roels et al. 1992 MnO2	
61	Human	NS (occup)				2.6 M (tremor, decreased reflexes)	Saric et al. 1977 NS	

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
62	Human	1-9 yr (occup)				6 M (psychomotor disturbances, weakness, pain)	Schuler et al. 1957 MnO2	
63	Human	NS (occup)				5 M (weakness, ataxia, pain)	Tanaka and Lieben 1969 NS	
64	Human	1 yr (occup)				3.5 M (weakness, anorexia, ataxia)	Whitlock et al. 1966 NS	
65	Monkey (Rhesus)	2 yr 5 d/wk 6 hr/d			30 F (altered DOPA levels)		Bird et al. 1984 MnO2	
66	Monkey (Rhesus)	66 wk		0.1			EPA 1977 Mn3O4	
Reproductive								
67	Human	1-19 yr (occup)				0.97 M (decreased fertility in males as assessed by number of observed vs expected children)	Lauwerys et al. 1985 Mn salts and oxides	
68	Human	at least 1 yr (occup)				2.82 M (abnormal sperm)	Wu et al. 1996 (MnO2)	

Table 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
69	Human	at least 1 yr (occup)				44.4 M (abnormal sperm)	Wu et al. 1996 (Mn fumes)	

All doses expressed as mg manganese/m3.

a The number corresponds to entries in Figure 3-1.

b The chronic-duration inhalation minimal risk level (MRL) of 0.0003 mg manganese/m3 was derived by using a benchmark dose analysis BMDL10 (surrogate NOAEL) of 0.142 mg manganese/m3 for performance deficits in several neurobehavioral tests. This value was adjusted using the following uncertainty and modifying factors: 10 for human variability, 5/7 for intermittent exposure (5 days/week), 8/24 for intermittent exposure (8 hours/day), and 10 for potential differences in toxicity due to the different forms of manganese and other limitations in the database.

APP = amyloid precursor protein; Bd Wt = body weight; Cardio = cardiovascular; COX = cyclooxygenase; d = day(s); DOPA = dihydroxyphenylalanine; Endocr = endocrine; F = Female; Gd = gestational day; GFAP = glial fibrillary acidic protein; GLAST = glutamate/aspartate transporter; GLT-1= glutamate transporter-1; Gn pig = guinea pig; GS = glutamine synthetase; GSH = reduced glutathione; GSSG = oxidized glutathione; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); mRNA = messenger ribonucleic acid; MT = metallothionein; nNOS = neuronal nitric oxide synthase; NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; pnd = post-natal day; Resp = respiratory; TGF-beta = transforming growth factor beta; TH = tyrosine hydroxylase; wk = week(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation

Acute (≤14 days)

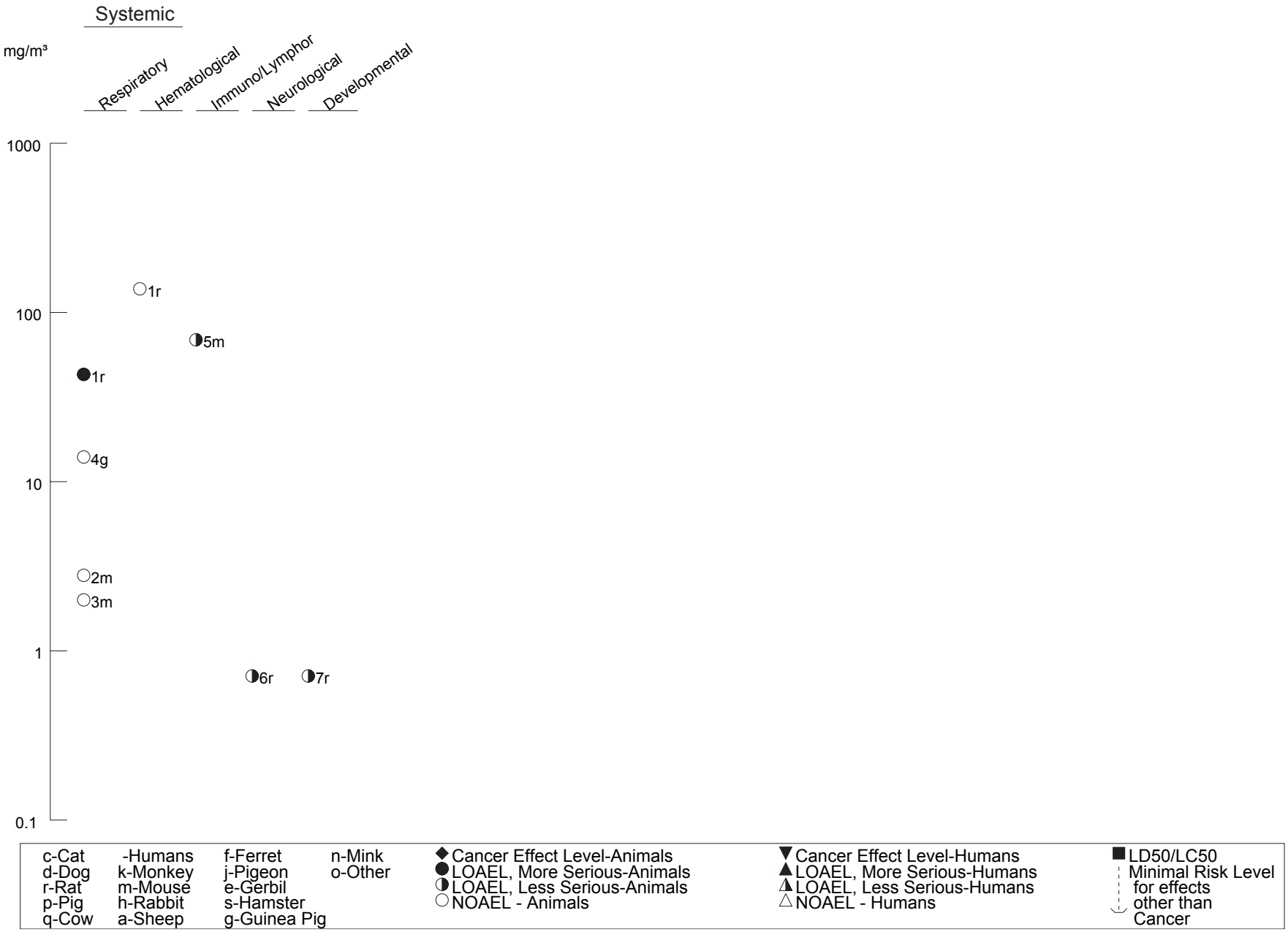


Figure 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation *(Continued)*

Intermediate (15-364 days)

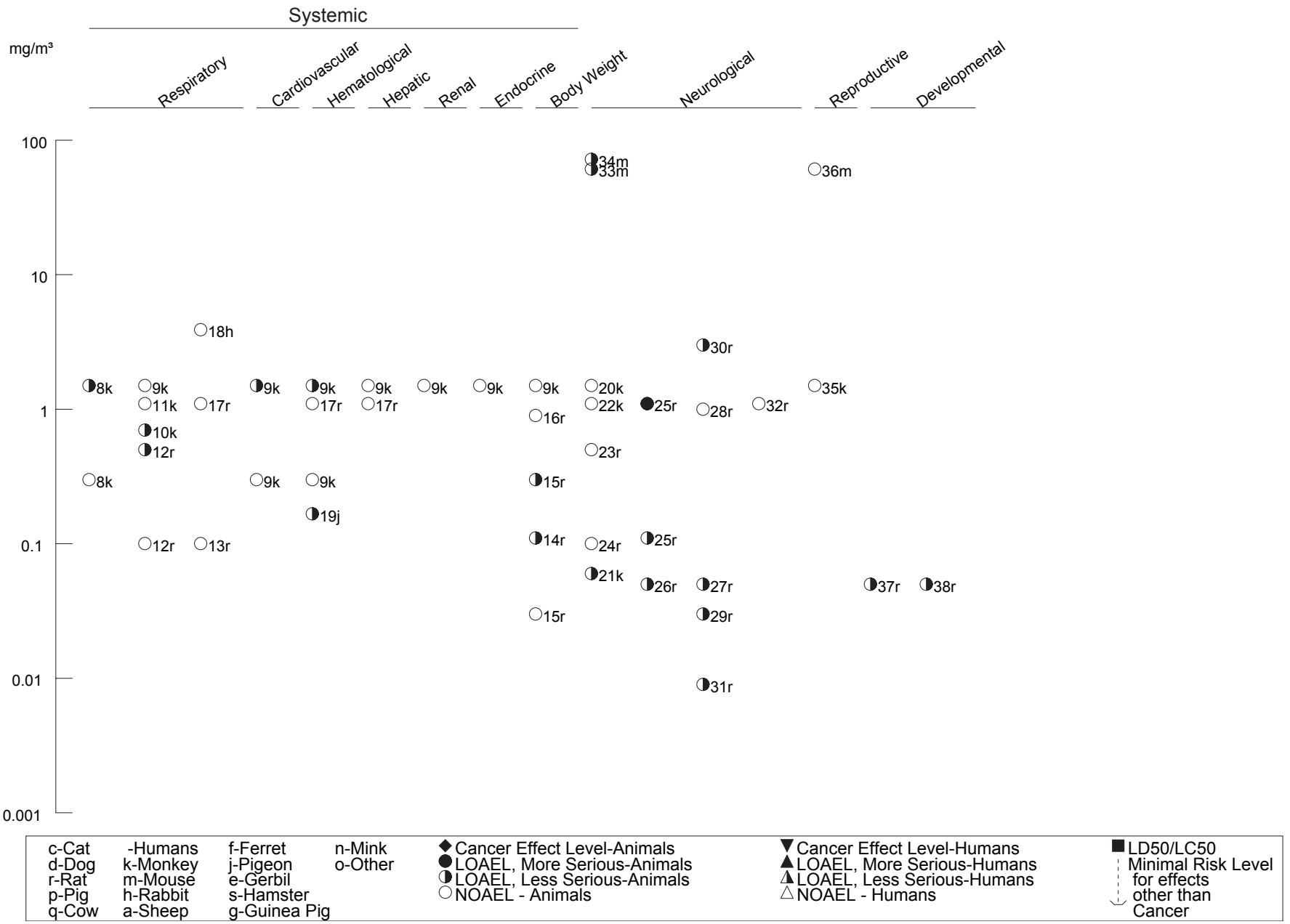
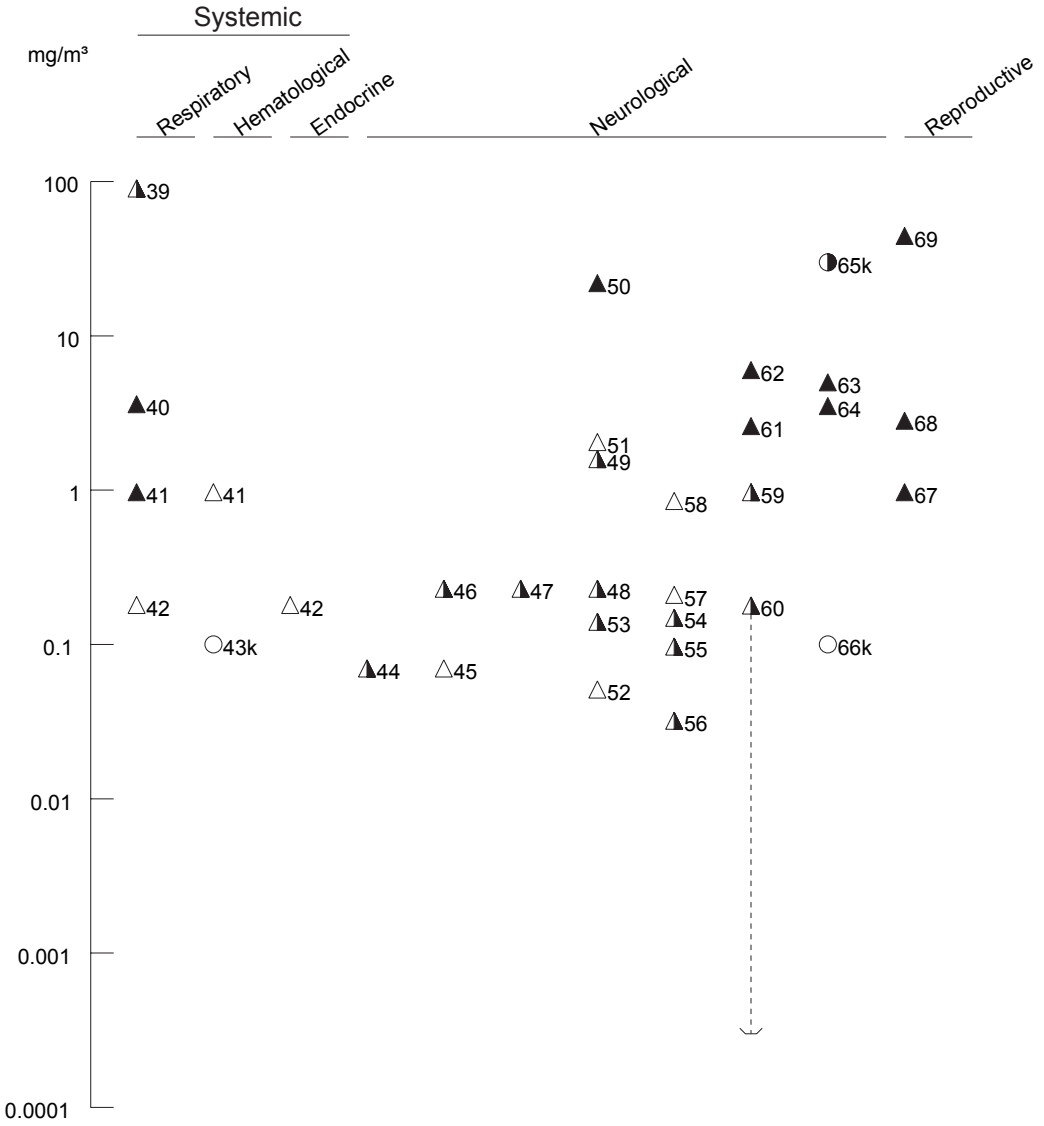


Figure 3-1 Levels of Significant Exposure to Inorganic Manganese - Inhalation *(Continued)*

Chronic (≥365 days)



liver. Total dust represents larger particles that cannot travel as deeply into the lungs as respirable dust, and will largely be coughed up and swallowed. Although many of the recent occupational studies have provided information on the size of the respirable particles that are associated with the exposure levels documented, some of the occupational studies and historical studies in miners only measure total dust. The profile provides, where possible, the different exposure levels in terms of respirable and total dust, but does not make a further distinction between particle sizes of the respirable dust.

3.2.1.1 Death

No conclusive studies have been located that show inhalation exposure of humans to manganese resulting in death. Hobbesland et al. (1997a) investigated nonmalignant respiratory diseases as a cause of death in male ferromanganese and silicomanganese workers. The authors found a slight excess in the numbers of deaths caused by pneumonia for manganese furnace workers, but could not discount other work-related exposures as potential causes of the pneumonia.

In analyses performed several years ago, MMT in gasoline was found to combust primarily to manganese tetroxide, but in the low levels currently used in gasolines, it is primarily combusted to manganese phosphate and manganese sulfate (Lynam et al. 1999). Therefore, inhalation exposures to exhaust from gasoline containing MMT will be discussed with inorganic manganese exposures. No deaths were observed in male outbred albino rats and male golden hamsters exposed to the exhaust (either irradiated or non-irradiated) from automobiles that were fueled with MMT-containing gasoline (Moore et al. 1975).

No other studies were located regarding death in humans or animals after inhalation exposure to inorganic manganese.

MMT has been used in very few inhalation studies due to the photolability of the compound; its short half-life in air makes it a very difficult compound to administer to laboratory animals in exposure chambers or nose-cones. Hinderer (1979) evaluated the toxicity of various unspecified MMT concentrations administered to 10 male Sprague-Dawley rats per exposure group during 1- and 4-hour exposure periods. The inhalation LD_{50} was determined to be 62 mg manganese/m^3 (247 mg MMT/m^3*55 mg manganese/218.1 mg MMT=62 mg manganese/m^3) for a 1-hour exposure and 19 mg manganese/m^3 for a 4-hour exposure. No mention was made in the report of steps taken to prevent MMT photodegradation during the experiment.

3.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for (systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. In humans, inhalation of particulate manganese compounds such as manganese dioxide or manganese tetroxide can lead to an inflammatory response in the lung. This is characterized by an infiltration of macrophages and leukocytes, which phagocytize the deposited manganese particles (Lloyd Davies 1946). Damage to lung tissue is usually not extensive, but may include local areas of edema (Lloyd Davies 1946). Symptoms and signs of lung irritation and injury may include cough, bronchitis, pneumonitis, and minor reductions in lung function (Abdel-Hamid et al. 1990; Akbar-Khanzadeh 1993; Boojar and Goodarzi 2002; Lloyd Davies 1946; Roels et al. 1987a); occasionally, pneumonia may result (Lloyd Davies 1946). These effects have been noted mainly in people exposed to manganese dust under occupational conditions, although there is some evidence that respiratory effects may also occur in residential populations near ferromanganese factories (Kagamimori et al. 1973; Nogawa et al. 1973; WHO 1987). The frequency of effects has been shown to decrease in at least one population when concentrations of total manganese in falling dust declined (Kagamimori et al. 1973). It is likely that the inflammatory response begins shortly after exposure and continues for the duration of the exposure.

It is important to note that an inflammatory response of this type is not unique to manganese-containing particles, but is characteristic of nearly all inhalable particulate matter (EPA 1985d). This suggests that it is not the manganese *per se* that causes the response, but more likely the particulate matter itself.

An increased prevalence of pneumonia has also been noted in some studies of workers with chronic occupational exposure to manganese dust (Lloyd Davies 1946) and in residents near a ferromanganese factory (WHO 1987). It seems likely that this increased susceptibility to pneumonia is mainly secondary to the lung irritation and inflammation caused by inhaled particulate matter, as discussed above.

Inhalation of particulate manganese compounds such as manganese dioxide or manganese tetroxide also leads to an inflammatory response in the lungs of animals, although inhalation of manganese chloride did not cause lung inflammation in rabbits (Camner et al. 1985). Several acute- and intermediate-duration studies in animals report various signs of lung inflammation following periods ranging from 1 day to 10 months at manganese concentrations ranging from 0.7 to 69 mg/m^3 (Bergstrom 1977; Camner et al.

1985; Shiotsuka 1984; Suzuki et al. 1978; Ulrich et al. 1979a, 1979b). Bergstrom (1977) and Ulrich et al. (1979a, 1979b) determined NOAELs, which are reported in Table 3-1. Increased susceptibility to lung infection by bacterial pathogens following inhalation of manganese dusts has been noted in acute animal studies (Maigetter et al. 1976). Conversely, Lloyd Davies (1946) reported no increase in the susceptibility of manganese-treated mice to pneumococci or streptococci. Bredow et al. (2007) reported that nose-only inhalation exposure to 2 mg manganese/m^3 as manganese chloride aerosols 6 hours/day for 5 consecutive days did not cause lung lesions in female GVB/N mice, but induced a 2-fold increase in pulmonary levels of mRNA for vascular endothelial growth factor (VGEF), a regulator of proliferation, migration, and formation of new capillaries. Elevated levels of VGEF have been associated with respiratory diseases, but current understanding is inadequate to know if this pulmonary gene expression response to manganese is adverse or benign.

Moore et al. (1975) exposed male golden hamsters and outbred albino rats to automobile exhaust from a car that burned MMT-containing fuel. The animals were exposed to non-irradiated exhaust or irradiated exhaust; the irradiation served to convert hydrocarbon gases and vapors to particulate form. Controls for each species were exposed to clean air. The animals were exposed for 8 hours/day for 56 consecutive days. While the hamsters were fed a diet containing an adequate amount of manganese for normal development, the rats were divided into two groups: one group was fed a manganese-sufficient diet (42.2 µg manganese/g diet) and the other group was fed a manganese-deficient diet (5 µg manganese/g diet). After the exposure, the authors observed a thickening of the cuboidal epithelium at the level of the terminal bronchiole in the golden hamsters. The lesion was not classified as severe and only affected one to two sites per lung section. Further, the lesions did not increase with length of exposure to the exhaust products (from 1 to 9 weeks). The incidence of lesions in the lung was 21% after exposure to irradiated exhaust, 14% after exposure to non-irradiated exhaust, and 6% after exposure to clean air.

More recently, reversible inflammation (pleocellular inflammatory infiltrates and fibrinonecrotic debris) in the nasal respiratory epithelium (but not the olfactory epithelium) was observed in young adult male Crl:CD(SD)BR rats following 13 weeks of inhalation exposure to 0.5 mg manganese/m^3 as manganese sulfate, but not in rats exposed to 0.1 mg manganese/m^3 as manganese sulfate or manganese phosphate (hureaulite) (Dorman et al. 2004b). The lesions were not apparent in groups of rats assessed 45 days after the end of exposure, indicating their transient nature. In studies with young male Rhesus monkeys exposed to 0, 0.06, 0.3, or 1.5 mg manganese/m^3 as manganese sulfate 6 hours/day, 5 days/week for 65 days, no nasal histological effects were found in exposed monkeys, but the high exposure level induced lesions in the lower respiratory tract (mild subacute bronchiolitus, alveolar duct inflammation,

and proliferation of bronchus-associated lymphoid tissue) (Dorman et al. 2005b). The lower airway lesions from intermediate-duration exposure appear to have been transient, because they were not found in monkeys assessed 45 days after the end of exposure (Dorman et al. 2005b). These findings in rats and monkeys are consistent with the understanding that inflammation of respiratory tissues from high-level exposure to inhaled manganese particulates is likely a consequence of the inhaled particulate matter.

No studies were located concerning respiratory effects in humans following inhalation exposure to MMT.

Male rats exposed to high concentrations of MMT (exposure doses not reported) via inhalation exhibited labored breathing during and after 1- and 4-hour exposures (Hinderer 1979). Gross necropsy or histopathological analyses on these animals were not performed.

Cardiovascular Effects. Three studies reported adverse cardiovascular effects after occupational exposure to manganese. Saric and Hrustic (1975) observed a lower mean systolic blood pressure in male workers at a ferromanganese plant. Manganese concentrations in the plant ranged from 0.4 to 20 mg/m^3, but specific data on exposure levels were lacking. More recently, Jiang et al. (1996a) studied the potential cardiotoxicity of manganese dioxide exposure in 656 workers (547 males, 109 females) involved in manganese milling, smeltering, and sintering. The authors took 181 samples of airborne manganese (not specified if respirable or total dust), with a geometric mean of 0.13 mg/m^3. The workers, whose work tenure ranged from 0 to 35 years, had a greater incidence of low diastolic blood pressure. The incidence of this effect was highest in young workers with the lowest tenure in the plant. There was no increase of abnormal electrocardiograms between workers and their matched controls. The authors surmised that manganese's ability to lower the diastolic blood pressure weakens with age as the elasticity of the blood vessels deteriorates.

Hobbesland et al. (1997b) reported a significantly increased incidence in sudden death mortality for workers in ferromanganese/silicomanganese plants during their employment period (standardized mortality ratio [SMR]=2.47). The sudden deaths included cardiac deaths and other natural causes. More specifically, among furnace workers, who are more likely to be exposed to manganese fumes and dusts than non-furnace workers, the mortality during active-person time was statistically significantly elevated (38.7%) compared to non-furnace workers (23.3%; $p<0.001$). However, the authors caution that the association of increased death and manganese exposure is speculative and the increase in sudden death could also be caused by common furnace work conditions (heat, stress, noise, carbon monoxide, etc.).

No studies on cardiovascular effects from inhalation exposure to MMT in humans or animals were located.

Gastrointestinal Effects. There are no reports of gastrointestinal effects following inhalation exposure to inorganic manganese in humans or animals.

There are no reports concerning the gastrointestinal effects following inhalation exposure to MMT in humans or animals.

Hematological Effects. Examination of blood from persons chronically exposed to high levels of manganese in the workplace has typically not revealed any significant hematological effects (Mena et al. 1967; Roels et al. 1987a; Smyth et al. 1973; Whitlock et al. 1966). The effect of manganese exposure on erythrocyte superoxide dismutase activity remains inconsistent; some investigators observed increased activity among male manganese smelters (Yiin et al. 1996), while others reported decreased activity in male welders (Li et al. 2004). However, an increased plasma malondialdehyde level is consistent between manganese-exposed smelters (Yiin et al. 1996) and welders (Li et al. 2004). Malondialdehyde is a product of lipid peroxidation; lipid peroxidation is believed to be a mechanism for cell toxicity. The authors observed that plasma malondialdehyde and manganese levels were strongly correlated in exposed workers and interpreted this response to be an indicator of manganese toxicity via lipid peroxidation.

No studies on hematological effects from inhalation exposure to MMT in humans or animals were located.

Hepatic Effects. Even though the liver actively transports manganese from blood to bile (see Section 3.4.4), there is no information to indicate that the liver is adversely affected by manganese; however, there are few specific studies on this subject. In a study by Mena et al. (1967), workers chronically exposed to manganese dust in the workplace exhibited no abnormalities in serum levels of alkaline phosphatase. Of 13 patients who were hospitalized with chronic manganese poisoning, 1 had a 20% sulfobromophthalein (SBP) retention and 1 had a 12% SBP retention, although histological examination of a liver biopsy from the latter revealed no abnormal tissue (Mena et al. 1967). No significance was ascribed to the elevated SBP retention.

Rats exposed to manganese tetroxide dusts for 9 months exhibited no adverse effects or histopathological lesions; however, slight increases in liver weights were noted (Ulrich et al. 1979b). These data, although limited, indicate that the liver is not significantly injured by manganese.

No studies on hepatic effects from inhalation exposure to MMT in humans or animals were located.

Musculoskeletal Effects. No studies were located concerning musculoskeletal effects from inhalation exposure to inorganic manganese.

No studies were located concerning musculoskeletal effects from inhalation exposure to MMT in humans or animals.

Renal Effects. The kidney is not generally considered to be a target for manganese, but specific studies are rare. No abnormalities in urine chemistry were detected in workers chronically exposed to manganese dusts in the workplace (Mena et al. 1967), but other more sensitive tests of renal function were not performed.

No studies were located regarding renal effects in animals after inhalation exposure to inorganic manganese.

No studies on renal effects from inhalation exposure to MMT in humans or animals were located.

Endocrine Effects. Few studies have measured endocrine effects in humans exposed to inorganic manganese. Two studies measured hormonal levels after exposure to manganese. The first study (Alessio et al. 1989) involved chronic exposure of foundry workers to manganese for approximately 10 years. The exposure levels were reported as 0.04–1.1 mg manganese/m^3 (particulate matter) and 0.05–0.9 mg/m^3 as fumes. These levels overlap the current American Congress of Governmental Industrial Hygiene (ACGIH) threshold limit value-time weighted average (TLV-TWA) of 0.2 mg/m^3 for particulate, but are less than the limit of 1 mg/m^3 for manganese fumes. The study reported both elevated prolactin levels and elevated cortisol levels; however, no changes in the levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) were noted.

Smargiassi and Mutti (1999) reported effects in a group of workers from a ferroalloy plant who were exposed occupationally to elevated levels of airborne manganese. Serum prolactin levels in these workers

were evaluated in a 1992 study and again in a 1997 study. Serum prolactin levels, which were significantly elevated in the earlier analysis, had also increased significantly over the earlier measurement ($p<0.001$). This difference was especially noticeable in those with abnormally high prolactin levels. During the five year period between studies, exposure levels were consistent and were not reduced; therefore, it is unclear whether prolactin levels reflect current or cumulative exposure.

Other elements of endocrine function (reproductive function, etc.) are discussed elsewhere in the text.

No studies were located regarding endocrine effects in animals after inhalation exposure to inorganic manganese.

No studies on endocrine effects from inhalation exposure to MMT in humans or animals were located.

Dermal Effects. No studies have been located concerning dermal effects in humans or animals following inhalation exposure to inorganic or organic manganese.

Ocular Effects. No studies have been located concerning ocular effects in humans or animals following inhalation exposure to inorganic manganese.

There are no studies reporting ocular effects following inhalation exposure of humans to MMT. One- and 4-hour exposures to doses of MMT used in lethality studies resulted in conjunctivitis in rats (Hinderer 1979).

Body Weight Effects. No studies were located regarding body weight effects in humans following exposures to inorganic manganese.

No studies were located regarding body weight effects in humans following inhalation exposure to MMT. Hinderer (1979) observed a decrease in weight gain in Sprague-Dawley rats during the first 7 days following a 1- or 4-hour exposure to unspecified MMT concentrations in an acute toxicity test. The rats resumed their normal weight gain by 14 days post-exposure.

Metabolic Effects. No studies were located concerning metabolic effects from inhalation of inorganic manganese in humans or animals.

No studies were located concerning metabolic effects following inhalation exposure to MMT in humans or animals.

3.2.1.3 Immunological and Lymphoreticular Effects

One study on immunological effects in humans following inhalation to inorganic manganese was located. Male welders exposed to manganese (0.29–0.64 mg/m^3 for an unspecified duration), vibration, and noise exhibited suppression of the T and B lymphocytes characterized by reductions in serum immunoglobin G (IgG) and total E-rosette-forming cells (Boshnakova et al. 1989). However, the welders in this study were exposed to numerous other compounds, including cobalt, carbon dioxide, and nitric oxide. Therefore, it is impossible to determine whether exposure to manganese caused the effects. It is not known whether any of these changes are associated with significant impairment of immune system function. No studies were located on lymphoreticular effects in humans exposed to manganese by the inhalation route.

No studies were located on immunological or lymphoreticular effects in animals exposed to inorganic manganese by the inhalation route.

As noted above, inhalation exposure to particulate manganese compounds can lead to an inflammatory response in the lung (i.e., pneumonitis), and this is accompanied by increased numbers of macrophages and leukocytes in the lung (Bergstrom 1977; Lloyd Davies 1946; Shiotsuka 1984; Suzuki et al. 1978). However, this is an expected adaptive response of the immune system to inhaled particulates, and these data do not indicate that the immune system is injured. Conflicting data are reported concerning increased susceptibility to bacterial infection after exposure to airborne manganese. Lloyd Davies (1946) indicated that manganese exposure did not increase the susceptibility of mice to bacterial infection, whereas Maigetter et al. (1976) reported that exposure to aerosolized manganese dioxide altered the resistance of mice to bacterial and viral pneumonias.

No studies on immunological or lymphoreticular effects from inhalation exposure to MMT in humans or animals were located.

3.2.1.4 Neurological Effects

Neurological effects from repeated inhalation exposure to manganese are well recognized as effects of high concern based on case reports and epidemiological studies of groups of occupationally exposed

people and results from animal inhalation studies. The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Manganism from High Level Occupational Exposure to Inorganic Manganese. There is conclusive evidence from studies in humans that inhalation exposure to high levels of manganese compounds (usually manganese dioxide, but also compounds with Mn(II) and Mn(III)) can lead to a disabling syndrome of neurological effects referred to as 'manganism'. Manganism is a progressive condition that usually begins with relatively mild symptoms, but evolves to include dull affect, altered gait, fine tremor, and sometimes psychiatric disturbances. Some of these symptoms also occur with Parkinson's disease, which has resulted in the use of terms such as "Parkinsonism-like disease" and "manganese-induced Parkinsonism" to describe those symptoms observed with manganese poisoning. Despite the similarities, significant differences between Parkinsonism and manganism do exist (Barbeau 1984; Calne et al. 1994; Chu et al. 1995). Barbeau (1984) reported that the hypokinesia and tremor present in patients suffering from manganism differed from those seen in Parkinson's disease. Calne et al. (1994) noted other characteristics that distinguish manganism from Parkinson's disease: psychiatric disturbances early in the disease (in some cases), a "cock-walk," a propensity to fall backward when displaced, less frequent resting tremor, more frequent dystonia, and failure to respond to dopaminomimetics (at least in the late stages of the disease).

Manganism and Parkinson's disease also differ pathologically. In humans and animals with chronic manganese poisoning, lesions are more diffuse, found mainly in the pallidum, caudate nucleus, the putamen, and even the cortex with no effects on the substantia nigra and no Lewy bodies (Pal et al. 1999; Perl and Olanow 2007). In people with Parkinson's disease, lesions are found in the substantia nigra and other pigmented areas of the brain (Barbeau 1984). Moreover, Lewy bodies are usually not found in substantia nigra in manganism cases, but are almost always found in cases of Parkinson's disease (Calne et al. 1994; Perl and Olanow 2007). Manganese appears to affect pathways that are post-synaptic to the nigrostriatal system, most likely the globus pallidus (Chu et al. 1995). MRI of the brain reveals accumulation of manganese in cases of manganism, but few or no changes in people with Parkinson's disease; fluorodopa positron emission tomography (PET) scans are normal in cases of manganism, but abnormal in people with Parkinson's disease (Calne et al. 1994). Other studies suggest that manganese produces a syndrome described as parkinsonism, distinct from Parkinson's Disease or manganism (Lucchini et al. 2007, Racette et al. 2005). It is likely that the terms Parkinson-like-disease and manganese-induced-Parkinsonism will continue to be used by those less knowledgeable about the

significant differences between the two. Nonetheless, comparison with Parkinson's disease and the use of these terms may help health providers and health surveillance workers recognize the effects of manganese poisoning when encountering it for the first time.

Typically, the clinical effects of high-level inhalation exposure to manganese do not become apparent until exposure has occurred for several years, but some individuals may begin to show signs after as few as 1–3 months of exposure (Rodier 1955). The first signs of the disorder are usually subjective, often involving generalized feelings of weakness, heaviness or stiffness of the legs, anorexia, muscle pain, nervousness, irritability, and headache (Mena et al. 1967; Nelson et al. 1993; Rodier 1955; Tanaka and Lieben 1969; Whitlock et al. 1966). These signs are frequently accompanied by apathy and dullness along with impotence and loss of libido (Abdel-Hamid et al. 1990; Emara et al. 1971; Mena et al. 1967; Nelson et al. 1993; Rodier 1955; Schuler et al. 1957). Early clinical symptoms of the disease include a slow or halting speech without tone or inflection, a dull and emotionless facial expression, and slow and clumsy movement of the limbs (Mena et al. 1967; Nelson et al. 1993; Rodier 1955; Schuler et al. 1957; Shuqin et al. 1992; Smyth et al. 1973; Tanaka and Lieben 1969). In a study by Wolters et al. (1989), 6-fluorodopa (6-FD) and ^{18}F-2-fluoro-2-deoxyglucose (FDG) PET were used to investigate the neurochemistry of four patients with "early manganism." FDG PET demonstrated decreased cortical glucose metabolism. No anomalies were noted in the 6-FD scans. This led the authors to suggest that, in early manganism, damage may occur in pathways that are postsynaptic to the nigrostriatal system, and most likely involve striatal or pallidal neurons.

As the disease progresses, walking becomes difficult and a characteristic staggering gait develops. Muscles become hypertonic, and voluntary movements are accompanied by tremor (Mena et al. 1967; Rodier 1955; Saric et al. 1977a; Schuler et al. 1957; Smyth et al. 1973). Few data are available regarding the reversibility of these effects. They are thought to be largely irreversible, but some evidence indicates that recovery may occur when exposure ceases (Smyth et al. 1973). Manganism has been documented in welders and in workers exposed to high levels of manganese dust or fumes in mines or foundries. Extreme examples of psychomotor excitement have been observed in manganese miners and, to a lesser extent, in industrial workers (Chu et al. 1995; Mena et al. 1967; Nelson et al. 1993). The behavior, known as "manganese madness" (Mena 1979) includes nervousness, irritability, aggression, and destructiveness, with bizarre compulsive acts such as uncontrollable spasmodic laughter or crying, impulses to sing or dance, or aimless running (Emara et al. 1971; Mena et al. 1967; Rodier 1955; Schuler et al. 1957). Patients are aware of their irregular actions, but appear incapable of controlling the behavior.

The reports of frank manganism (Rodier 1955; Schuler et al. 1957; Smyth et al. 1973) observed in manganese miners clearly indicate that the onset of manganism results from chronic exposure to high concentrations of the metal. Documented cases indicate that the most important route of exposure is inhalation of manganese dusts or fumes, while other pathways such as ingestion of the metal from mucociliary transport of larger particles and hand-to-mouth activity, may contribute a smaller amount. Based on the data provided by Rodier (1955) and Schuler et al. (1957), it appears that the frequency of manganism cases increased with prolonged exposure, suggesting that the seriousness of the symptoms presented increases with cumulative exposure. For example, Rodier (1955) reports that the highest percentage of manganism cases (28, or 24.4%) occurred in miners with 1–2 years experience. Only six cases of manganism (5.2%) were reported in males with 1–3 months exposure, and 68% of the cases reported occurred after exposures >1–2 years in length. Rodier did not present statistics on the number of men in the mine who were employed for comparable durations who did not suffer from manganism. Schuler et al. (1957) studied fewer manganism cases, but showed that the number of men with manganism increased with time spent mining, with the average time delay before onset of the disease being 8 years, 2 months. In fact, the minimum duration of exposure to the metal was 9 months before signs of manganism became recognizable, and the maximum exposure was 16 years. However, Schuler et al. (1957) point out that their study was not intended to "suggest incidence rates" and of the 83 miners selected for examination of potential manganism, only 9 were chosen as actually suffering from manganese poisoning. As with the Rodier (1955) study, the Schuler et al. (1957) study did not discuss the exposure duration or symptomatology of those men not displaying "frank manganism;" therefore, these collective data, although suggestive of a cumulative effect of manganism neurotoxicity, must be interpreted with caution.

Huang et al. (1998) documented the progression of clinical symptoms of manganism in five surviving workers (from an original six) chronically exposed to manganese in a ferroalloy plant. These men were exposed from 3 to 13 years and were examined 9–10 years after manganese exposure had ceased. Neurologic examination revealed a continuing deterioration of health exhibited in gait disturbance, speed of foot tapping, rigidity, and writing. The men had high concentrations of manganese in blood, urine, scalp, and pubic hair at the time of the original neurologic evaluation. Follow-up analyses revealed a drastic drop in manganese concentrations in these fluids and tissues (e.g., 101.9 μg/g manganese in blood from patient 1 in 1987; 8.6 μg/g manganese in blood in 1995). Further, T1-weighted MRI analysis did not reveal any high-signal intensity areas. These data support the progression and permanence of clinical effects from excess manganese exposure, even when tissue levels of the metal had returned to normal. Further, it shows that this neurotoxicity can continue in the absence of continuing manganese exposure

and that a spectrum of responses to excess manganese exposure can be seen depending upon dose, duration of exposure, and timing of the observation. While some subclinical manifestations of manganese neurotoxicity will resolve, once neuropathology has occurred (in the form of loss of dopaminergic neurons), then reversal becomes more limited and is restricted to functional compensation.

As shown in Table 3-1 and Figure 3-1, cases of frank manganism have been associated with workplace exposure levels ranging from about 2 to 22 mg manganese/m^3 (Cook et al. 1974; Rodier 1955; Saric et al. 1977; Schuler et al. 1957; Tanaka and Lieben 1969; Whitlock et al. 1966). For example, Tanaka and Lieben (1969) reported that no cases of frank manganism were diagnosed in 38 workers from Pennsylvania industrial plants in which estimated air concentrations were below 5 mg manganese/m^3, whereas 7 cases were diagnosed in 117 workers from plants with air concentrations exceeding 5 mg/m^3. Whitlock et al. (1966) reported on two cases of frank manganism in workers who were exposed to estimated air concentrations ranging from 2.3 to 4.7 mg manganese/m^3.

Neurological Assessments of Workers Exposed to Low Levels of Inorganic Manganese. Studies estimating the impact of low-level exposure to manganese on neurological health have employed a number of sensitive tests designed to detect signs of neuropsychological and neuromotor deficits in the absence of overt symptoms (Iregren 1990, 1994, 1999). These analyses allow the comparison of discrete performance values that are associated with either biological levels of manganese or approximations of exposure levels. Thus, they allow for the comparison of one exposure group to another without the subjective description of neurological symptoms that were prevalent in the studies with miners and others with frank manganism. A number of epidemiological studies have used these techniques to study the psychological or neurological effects of exposure to low levels of manganese in the workplace (Bast-Pettersen et al. 2004; Beuter et al. 1999; Blond and Netterstrom 2007; Blond et al. 2007; Bouchard et al. 2003, 2005, 2007a, 2007b; Chia et al. 1993a, 1995; Crump and Rousseau 1999; Deschamps et al. 2001; Gibbs et al. 1999, Iregren 1990; Lucchini et al. 1995, 1999; Mergler et al. 1994; Myers et al. 2003a, 2003b; Roels et al. 1987a, 1992, 1999; Wennberg et al. 1991) or in environmental media close to manganese-emitting industries (Lucchini et al. 2007; Mergler et al. 1999; Rodríguez-Agudelo et al. 2006). Some of these studies have found statistically significant differences between exposed and non-exposed groups or significant associations between exposure indices and neurological effects (Bast-Pettersen et al. 2004; Chia et al. 1993a; Iregren 1990; Lucchini et al. 1995, 1999; Mergler et al. 1994; Roels et al. 1987a, 1992; Wennberg et al. 1991), whereas others have not found significant associations (Deschamps et al. 2001; Gibbs et al. 1999, Myers et al. 2003a, 2003b; Young et al. 2005). The neurological effects associated with prolonged low-level manganese exposure generally have been subtle changes, including

deficits in tests of neuromotor or cognitive functions and altered mood states; they have been referred to by various authors as preclinical or subclinical neurological effects. As shown in Table 3-1 and Figure 3-1, manganese air concentrations associated with these effects in chronically exposed workers range from about 0.07 to 0.97 mg manganese/m^3 (manganese in total or inhalable dust measurements). For several of these work environments, values of concentrations of manganese in respirable dust (generally particulate diameters <10 µm) represented <20–80% of the total dust values.

In a cross-sectional epidemiological study of 141 male workers in a manganese dioxide and salt producing plant, Roels et al. (1987a) detected preclinical neurological effects (alterations in simple reaction time, audioverbal short-term memory capacity, and hand tremor) in workers exposed to 0.97 mg manganese (median concentration in total dust)/m^3 as manganese dioxide, manganese tetroxide, manganese sulfate, manganese carbonate, and manganese nitrite for a group average of 7.1 years. End points in exposed workers were compared with end points in a matched control group of 104 non-exposed male workers from a nearby chemical plant. The prevalences of subjective symptoms were similar in exposed and control workers, except for the elevation of nonspecific symptoms (such as fatigue, tinnitus, trembling of fingers, and increased irritability) in the exposed workers. Statistically significant mean deficits were found in exposed workers (compared with controls) in tests of simple reaction time (visual), audioverbal short-term memory capacity, eye-hand coordination, and hand steadiness. The prevalence of abnormal values in the neurological tests were not statistically significantly correlated with manganese levels in blood or urine or duration of employment, with the exception that blood levels of manganese were correlated with prevalence of abnormal responses in tests of eye-hand coordination and hand steadiness.

Iregren (1990) used neurobehavioral tests (simple reaction time, digit span, finger tapping, verbal ability, hand dexterity, and finger dexterity tests from the Swedish Performance Evaluation System, SPES) to study adverse effects in 30 male workers from two different manganese foundries exposed to an estimated median concentration of 0.14 mg manganese (in total dust)/m^3 as manganese dioxide for 1–35 years (mean, 9.9 years). The exposed workers had below-average scores on a number of the tests, such as reaction time and finger tapping, when compared to matched controls with no occupational manganese exposure.

Roels et al. (1992) provided similar results to these earlier reports. Workers in a dry alkaline battery factory exhibited impaired visual reaction time, hand-eye coordination, and hand steadiness when exposed to concentrations of manganese dioxide in total dust ranging from 0.046 to 10.840 mg

manganese/m^3 and in respirable dust from 0.021 to 1.32 mg manganese/m^3 (exposure ranged from 0.2 to 17.7 years). A lifetime integrated exposure (LIE) for both total manganese dust and respirable manganese was estimated for each of the exposed workers ($LIE=\sum((C_{job\ 1} \times T_1) + (C_{job\ 2} \times T_2) + ... (C_{job\ n} \times T_n))$, where C is concentration, T is years of exposure, and LIE is expressed as mg manganese/m^3 times year). Based on the analysis of data by a logistic regression model, it was suggested that there was an increased risk (odds ratio [OR]=6.43, 95% confidence interval [CI]=0.97–42.7) of decreased hand steadiness at a lifetime integrated exposure level of 3.575 mg/m^3*year for total dust or 0.730 mg/m^3*year for respirable dust. It should be noted that the LIE at which an increased risk of abnormal neurological function occurs is based on exposures in an occupational setting. Therefore, periods of exposures would be followed by periods that would be relatively free of manganese inhalation. Presumably, during these "rest" periods the homeostatic mechanism would excrete excess manganese to maintain the manganese concentration within physiologic limits. Further, the LIE for deleterious neural effects may be biased in favor of a higher concentration due to the "healthy worker effect" (i.e., the most susceptible individuals are not incorporated into the study).

Crump and Rousseau (1999) performed a follow-up study of 213 men occupationally exposed to manganese, 114 of whom were subjects in the Roels et al. (1987a, 1987b) studies. Exposure data were unavailable during the 11 years of study (1985–1996) during which blood and urine samples were taken and neurological tests (short-term memory, eye-hand coordination, and hand steadiness) were administered as in the Roels studies. Yearly blood and urine manganese levels remained fairly consistent throughout the study period, and were comparable to the levels reported in the previous studies. The authors suggest that the consistency of these data on manganese levels indicates that the airborne manganese concentrations to which the subjects were exposed during the study period were likely comparable to those at the time of the Roels studies. The average age and exposure duration of the subjects increased from 36 and 7 years, respectively, in 1985, to 41 and 14 years, respectively, in 1996. Variations in year-to-year test results were observed that were not attributable to age of the subject or exposure to manganese. The authors observed decreases in errors in the short-term memory test (number of repeated words and number of errors). During 1987, 1988, and 1989, the average number of words remembered on the memory test was lower than in any other year. However, there was a progressive improvement in percent precision and percent imprecision on the eye-hand coordination test during 1985–1988 (after 1991, the design of the test was modified and percent imprecision was lower in that year and all subsequent testing years). The authors suggest several reasons for the inter-year variability in test results (Crump and Rousseau 1999), including variations in test conditions, different groups of workers being tested in different years, the mood of the workers following a plant restructuring, and increased

caution on the part of the subjects when answering test questions. When data analysis was controlled for year of testing, older workers performed significantly worse than younger workers on total words recalled in the memory test, and on percent precision and percent sureness in the eye-hand coordination test. Further, blood and urine manganese levels were not significantly associated with performance on memory or eye-hand coordination tests, but blood manganese was negatively associated with performance on the hand steadiness test ($p<0.05$). Age was not a factor in hand steadiness when the year of test was controlled for in the analysis. Crump and Rousseau (1999) investigated whether individual test scores worsened with time by studying the group of 114 men from the original Roels et al. (1987a, 1987b) studies and a subset of 44 long-term employees who had been given both memory and hand steadiness tests on two occasions, 8 years apart. These analyses revealed decreases in performance over time for a particular hole in the hand steadiness test and improvements in repetitions and errors on the memory test, both of which were statistically significant. The authors suggest that the improvements in the memory test were likely the result of increased caution on the part of the subject. The changes in performance over time could not be attributed solely to manganese exposure because it was impossible to control for age and year of testing in all of the analyses. The authors noted the lack of an age-matched control group with which to compare test results and the absence of data caused by workers ending their terms of employment. Some have questioned whether inter-year variability in test results, potentially caused by different test administrators over time, would affect interpretation of the findings. While this may contribute to the changes in performance over time seen in the Crump and Rousseau (1999) study, this factor will potentially impact any study of this type. The lack of a control group precludes the determination of a reliable NOAEL or LOAEL based on the results of this study.

A study by Mergler et al. (1994) also supports the work of Iregren and Roels. This epidemiologic study included 115 (95% of the total) male workers from a ferromanganese and silicomanganese alloy factory who were matched to other workers from the region with no history of exposure. The groups were matched on the following variables: age, sex, educational level, smoking, and number of children. These workers were exposed to both manganese dioxide dusts and manganese fumes. Environmental levels of manganese in total dust were measured at 0.014–11.48 mg/m^3 (median, 0.151 mg/m^3; arithmetic mean, 1.186 mg/m^3, geometric mean, 0.225 mg/m^3), while manganese levels in respirable dust were 0.001–1.273 mg/m^3 (median, 0.032 mg/m^3; arithmetic mean, 0.122 mg/m^3; geometric mean, 0.035 mg/m^3), and mean duration of exposure was 16.7 years. The exposed workers had significantly greater blood manganese levels, but urinary manganese did not differ between groups. Manganese workers showed decreased performance on tests of motor function (including those from the SPES) as compared to matched control workers with no manganese exposure. Using test results obtained from performance of

the groups on the Luria-Nebraska Neuropsychological Battery and other tests, the authors reported that manganese-exposed workers performed more poorly than controls on tests of motor function, particularly on tests that required alternating and/or rapid hand movements and hand steadiness. The exposed workers also differed significantly from the controls in cognitive flexibility and emotional state. They also exhibited significantly greater levels of tension, anger, fatigue, and confusion. Further, these workers had a significantly lower olfactory threshold than controls; this is the first study to report this effect following inhalation exposure to manganese. Several follow-up studies of the workers from this manganese alloy plant are described later in this section (Bouchard et al. 2005, 2007a, 2007b).

Similar effects to those observed in the Mergler et al. (1994) study were observed by Chia et al. (1993a). Workers in a manganese ore milling plant exposed to 1.59 mg manganese (mean concentration in total dust)/m^3 exhibited decreased scores in several neurobehavioral function tests including finger tapping, digit symbol, and pursuit aiming. Further, the workers exhibited an increased tendency for postural sway when walking with their eyes closed (Chia et al. 1995).

An epidemiologic study (Lucchini et al. 1995) also supports findings of these studies concerning the preclinical neurological effects of manganese exposure. This study, which evaluated performance on neuromotor tests (seven tests from the SPES, including simple reaction time, finger tapping, digit span, additions, symbol digit, shapes comparison, and vocabulary) involved 58 male workers from a ferroalloy plant. The workers had been exposed for 1–28 years (mean, 13; standard deviation [SD], 7) to geometric mean airborne concentrations of manganese, as manganese dioxide, in total dust as high as 0.070–1.59 mg/m^3 (geometric means in different areas). These concentrations had decreased in the last 10 years to a range of 0.027–0.270 mg manganese (in total dust)/m^3. At the time of the study, the exposed workers were undergoing a forced cessation from work of 1–48 days. Blood and urine manganese levels were analyzed. A cumulative exposure index (CEI) was calculated for each subject by multiplying the average annual airborne manganese concentration in respirable dust characteristic of each job by the number of years for which this activity was performed. Significant correlations were found between the log value of blood manganese concentrations in exposed workers and the tests of additions, digit span, finger tapping, and symbol digit (log values for the last two tests); between the log value of urinary manganese levels and the performance on the additions test; and between the log value of the CEI and the log value of the symbol digit score. Further, a significant correlation on an individual basis was found between external exposure, represented by CEI, and blood and urine manganese levels. These results are unique in that they are the first to suggest that blood and urine manganese concentrations are indicative of exposure on an individual basis. As suggested by Lucchini et al. (1995), the correlations may be observable in this

study, when they have not existed in past studies (Roels et al. 1987a, 1992), because the workers were assessed at a time when they were not currently being exposed to manganese. In support of this possibility, the correlation coefficients between the urine and manganese levels and the CEI increased with time elapsed since the last exposure to airborne manganese (Lucchini et al. 1995).

Roels et al. (1999) performed an 8-year prospective study with 92 subjects exposed to manganese dioxide at a dry-alkaline battery plant (Roels et al. 1992) to determine if poor performance on tests measuring visual reaction time, eye-hand coordination, and hand steadiness could be improved if occupational manganese exposure were decreased. The workers were divided into "low" (n=23), "medium" (n=55), and "high" (n=14) exposure groups depending on location within the plant and job responsibility. At the end of the 1987 study, technical and hygienic improvements had been implemented within the plant to decrease atmospheric manganese concentrations. Yearly geometric mean values for airborne total manganese dust (MnT) in the "low," "medium," and "high" exposure areas decreased in the following manner, respectively: ~0.310–~0.160; ~0.900–~0.250; and ~3–~1.2 mg/m^3. The cohort decreased from 92 subjects in 1987 to 34 subjects in 1995 due to turnover, retirement, or dismissal, but no worker left due to neurological signs or symptoms. A separate group of workers was selected who had prior manganese exposure (ranging from 1.3 to 15.2 years). These subjects had left the manganese processing area of the plant prior to the end of 1992, and therefore, their exposure to manganese had ceased at that time; these workers were still employed in other areas of the plant. The control group consisted of 37 workers employed at the same polymer factory that had provided the control population in the previous study (Roels et al. 1992). This group, with an average age of 38.5 (range, 32–51 years) allowed for the analysis of age as a confounder. Exposure data (respirable manganese and total manganese dust, MnT) were taken with personal air samplers. Time-trend analysis of air sampler data revealed a significant decrease in total manganese from 1987 to 1995, with a more pronounced decline from 1992 forward. From 1987 to 1990, the authors observed that the precision of the hand-forearm movement (PN1) in the eye-hand coordination test for the whole cohort worsened, but then got progressively better. Hand steadiness and visual simple reaction time variables were inconsistent over time, and time-trends were not observed. When the cohort was divided into exposure groups, and analyzed for performance on the eye-hand coordination test, it was revealed that in general, the performance on the PN1 aspect of the test improved from 1987 to 1995, especially after 1991. The performance of the "low-dose" group was comparable to that of the control group in 1987 (Roels et al. 1992) and to that of the control group in 1997. The performance of the "medium-dose" group was intermediate between the "low-dose" and "high-dose" group. The only significant differences in performance were in the "high-dose" group as compared to the "low-dose" group during the years 1988–1990 (test scores of 49–51 for the high-dose group and 63–65 for the "low-

dose" group). However, it was noted that performance on the eye-hand coordination test for the "medium" and "high-dose" groups was considerably poorer than the controls.

Significant differences were noted in variables in the hand steadiness test between the exposure groups during 1987–1992 (data not reported), when manganese concentrations were at their highest. However, no readily identified temporal changes in performance among the groups on this test was found, nor with the visual reaction time test. When the authors performed separate time-trend analysis on MnT levels and PN1 (eye-hand coordination test) values, a significant time effect was present for each variable. An analysis of covariance was performed for each exposure group (low, medium, and high) in which log MnT was considered as covariate in order to adjust for estimation of PN1 variations as log MnT changed over time. The resultant data suggested that a reduction in log MnT was associated with an improvement in PN1 for each group. The authors also found that when time was also considered with log MnT as an interaction term, it did not influence PN1 variations over the years and the effect of time on PN1 values disappeared when log MnT was maintained as an ordinary covariate. The authors interpreted this to mean that performance on the eye-hand coordination tests were only related, and inversely so, to the exposure to manganese. In other words, when manganese exposure was increased, test performance decreased and vice versa (Roels et al. 1999). However, in the high-exposure group, the performance increased from 71 to 83% of that of the control group, and leveled off at this point, despite decreased manganese exposure occurring from 1991/1992 with most dramatic improvements occurring in 1994. The authors suggest that this leveling off of performance by the high-exposure group may be indicative of a permanent effect of manganese on eye-hand coordination. The authors tested PN1 values in exposed subjects 3 years following a cessation of exposure. They found that in 20/24, the PN1 values were below the mean PN1 values of the control group, but 16 of these individuals showed an improvement in 1996 (percent improvement unspecified). The remaining four subjects (three "low-exposure" and one "medium-exposure" subjects) had PN1 values that exceeded the mean value of the control group. However, these data indicate that although there was improvement in performance on the coordination test, the vast majority of the exposed group still could not perform to the level of an unexposed worker 3 years after manganese exposure ceased. In addition, the exposed workers who did perform as well or better than the control subjects were among the least exposed workers while at the plant. As discussed previously, performance of the "low-exposure" group on eye-hand coordination tests during 1992–1995 was comparable to that of the control groups from 1987 and 1997, indicating that manganese exposure of these individuals during that time did not severely impact their ability to perform this neurobehavioral test. Comparable performance on the tests by the same control group in 1987 and 10 years later, in 1997, indicates that age was not a confounder in this study. None of the variables except visual reaction time

was significantly correlated with age, and the existing correlation in the visual reaction time test only represented a 3% difference (Roels et al. 1999).

Lucchini et al. (1999) also investigated differences in neurobehavioral test performance over time as exposure to manganese (manganese dioxide and manganese tetroxide) decreased. The study group consisted of 61 men who worked in different areas of a ferroalloy plant. The plant was divided into three exposure areas with total manganese dust (geometric mean) values decreasing from 1981 to 1995: "high-exposure" values decreased from 1.6 to 0.165 mg/m^3; "medium-exposure" values decreased from 0.151 to 0.067 mg/m^3; and "low-exposure" values decreased from 0.57 to 0.012 mg/m^3. The authors estimated that the annual average manganese concentration in the "medium-exposure" group was 0.0967 mg manganese in total dust/m^3. Respirable dust constituted 40–60% of the total dust value. Control subjects consisted of 87 maintenance and auxiliary workers from a nearby hospital who had not been exposed to neurotoxins. The study and control groups were well matched except for years of education and the percentage of subjects working night shifts. The study groups answered a questionnaire concerning neuropsychological and Parkinsonian symptoms and underwent testing to determine the effect of manganese on neuromotor performance. Four tests were from the SPES (addition, digit span, finger tapping, symbol digit) and five timed tasks were from the Luria Nebraska Neuropsychological Battery (open-closed dominant hand--Luria 1, open-closed non-dominant hand—Luria 2, alternative open-closed hands—Luria 3, thumb-fingers touch dominant hand—Luria 4, and thumb-fingers touch non-dominant hand—Luria 5). Individual scores were taken from these subtests, and the sum of the Luria tests was taken (Luria sum). Postural tremor was also measured, as was visual reaction time and coordination ability via the hand pronation/supination test. Manganese levels in blood and urine, as well as blood lead levels were analyzed prior to each neurobehavioral test. Manganese levels in both blood and urine were significantly elevated in exposed workers compared to controls ($p<0.0001$). Blood lead levels were also significantly higher in the ferroalloy workers ($p=0.0002$). The authors noted that the study groups did not report as many complaints as those reported in the Mergler et al. (1994) study.

After correcting for age, education, alcohol, smoke, coffee, shift work, and blood lead levels, an analysis of test results indicated that performance of the exposed workers was significantly different than that of controls on all tests except for Luria 5 and Luria sum (Lucchini et al. 1999). A comparison of SPES test results from workers tested in 1990 or 1991 and those from this study did not indicate any difference in paired t-test values; this indicates that performance did not improve over time or with decreasing exposure to manganese. CEI values were calculated (in the same manner as in Lucchini et al. [1995]) for each exposure group and performance on the neurobehavioral tests was analyzed for correlation to these

values and to manganese levels in body fluids. Significant differences were found between those with low CEI values of <0.5 mg/m^3*years, mid CEI values of 0.5–1.8 mg/m^3*years, and high CEI values of >1.8 mg/m^3*years and performance on the following tests: symbol digit, finger tapping, dominant and non-dominant hand, and digit span. A positive correlation was observed between the log CEI value and these tests, indicating that performance decreased as exposure increased. No correlations were found between CEI values and manganese levels in blood and urine; these results differ from the correlation between CEI and manganese levels in fluids from the previous study (Lucchini et al. 1995). Lucchini et al. (1995) estimated a manganese dose (total dust) that would represent the annual airborne manganese concentration indicative of neurobehavioral deficit in this study by dividing the geometric mean CEI of the mid-exposure subgroup, 1.1 mg/m^3*years, by the geometric mean value of years of exposure for this same subgroup, 11.51, yielding a value of 0.096 mg/m^3. A comparable respirable dust value would be 0.038 mg/m^3 (0.096*0.40).

Gibbs et al. (1999) studied a population of workers in a U.S. plant that produces electrolytic manganese metal. These 75 workers and a well-matched group of control workers with no manganese exposure were administered a computerized questionnaire concerning neurological health issues (including mood, memory, fatigue, and other issues) and were analyzed for performance on several neurobehavioral tests including hand steadiness (Movemap steady, Movemap square, and tremor meter), eye-hand coordination (orthokinisimeter), and rapidity of motion (four-choice reaction time and finger tapping). The Movemap test is a relatively recent test that has not undergone widespread use, and it has not been validated by other researchers. Further, although technically sophisticated, the test has not been observed to discriminate between exposure groups any better than simpler current methods (Iregren 1999). Airborne levels of total and respirable manganese were obtained using personal samplers and were not available for years prior to 1997. Using the arithmetic mean of samples collected in 12 different job categories, exposure was estimated for the years prior to 1997. Cumulative exposure values for each worker were estimated for the 30-day and 12-month exposure periods just prior to neurobehavioral testing. Multiple regressions of the test scores were performed using age and each of the following manganese exposure variables individually as explanatory variables: duration of exposure; 30-day cumulative exposure; 1-year cumulative exposure; and cumulative occupational exposure to either respirable or total manganese. Shift work was also used as a variable in conjunction with age and cumulative 30-day exposure to respirable or total manganese. The authors threw out outlying data points if they were >3 times the SD of the residual after a model fit. Exposures to respirable and total dust were highly correlated (r^2, 0.62–0.75), as were cumulative exposures over the previous 30 days and the previous year (r^2, 0.72–0.82); however, lifetime integrated exposure was not correlated with either 30-day or 12-month exposure values. The average

exposure value for manganese-exposed workers was estimated at 0.066±0.059 mg/m^3 (median, 0.051 mg/m^3) for respirable dust, and 0.18±0.21 mg/m^3 for total dust.

Responses to the questionnaire and performance on the neurobehavioral tests did not differ significantly between exposed and control groups (Gibbs et al. 1999). Cumulative years of exposure had an effect on tapping speed—speed increased with increased exposure, but only when outliers were included in the analysis. The authors also reported an inverse correlation between age and performance on tests measuring eye-hand coordination but positively correlated between age and complex reaction time. The study by Gibbs et al. (1999) is the first to report a lack of poorer performance on neurobehavioral tests by workers chronically exposed to manganese. Interestingly, the median exposure estimates for respirable dust in this population (0.051 mg/m^3) is slightly higher than the lowest level of respirable dust at which preclinical neurological effects have been seen (0.032 mg/m^3) as reported by Mergler et al. (1994).

Gorell et al. (1999) noted a high OR of 10.51 for the development of Parkinson's disease in individuals >50 years old who were occupationally exposed to manganese for >20 years, but not for those exposed for <20 years. However, the numbers of individuals with a >20-year exposure was rather small (n=4), and occupational exposures to other metals (copper, and lead-iron, lead-copper, and iron-copper combinations) for >20 years were also associated with increased risk for the disease.

In a cross-sectional study of 138 (114 male and 34 female) enamels-production workers, Deschamps et al. (2001) administered a questionnaire about neurological symptoms; evaluated performance on psychological tests of similarity recognition, vocabulary (oral word association), geometrical figure recognition (visual gestalts), and short-term memory (digit span); and measured levels of manganese in blood samples. Results were compared with a control group of 137 nonexposed workers matched for age, educational level, and ethnic group. Exposed workers were employed for a mean duration of 19.87 years (SD±9) in enamels production. Mean manganese levels in 15 personal air samples and 15 stationary air samples collected at the plant during the year preceding the tests were 2.05 mg manganese/m^3 (SD 2.52; range 0.5–10.2) for total dust and 0.035 mg manganese/m^3 for respirable manganese (SD 0.063; range 0.01–0.293). Symptoms of asthenia, sleep disturbance, and headache were significantly elevated in exposed workers, compared with controls, but no significant differences in blood levels of manganese or performance on the administered tests were found between the exposed and control groups of workers. Clinical examination of the exposed subjects revealed no cases of obvious neurological impairment, but sensitive psychomotor tests of simple reaction times and motor functions were not administered in this study.

In a cross-sectional study, Myers et al. (2003a) evaluated results from a health questionnaire and a battery of neurobehavioral tests administered to 489 workers employed as office workers, miners, surface processors, engineers, and other service workers from two South African manganese mines. Cumulative exposure indices for each subject were calculated based on total dust measurements and job history. Workers were employed in the mines for a mean of 10.8 years (SD=5.5 years; range 1–41 years), had an average cumulative exposure index of 2.2 (mg manganese/m^3 per year, SD=2.2; range=0–20.8), an average exposure intensity of 0.21 mg manganese/m^3 (SD=0.14; range, 0–0.99), and an average blood manganese concentration of 8.5 µg/L (SD=2.8; range, 2.2–24.1). Neurobehavioral end points included three tests of motor function in the Luria-Nebraska battery (tests 1, 2, and 23), mean reaction time in the SPES, and three cognitive tests (forward and backward digit span and digit-symbol score). Multiple linear regression analysis revealed no significant ($p<0.05$) associations between any measure of exposure and questionnaire or test battery outcomes.

In another cross-sectional study, Myers et al. (2003b) evaluated neurobehavioral end points in a group of 509 workers at a South African manganese smelter, compared with a group of unexposed workers from an electrical fittings assembly plant (remote from the manganese smelter). Workers were employed for a mean of 18.2 years (SD 7.6), compared with 9.4 years (SD 7.0) in the control group. Exposure was assessed from manganese determinations in dust from personal air samples, blood samples, and urine samples. Cumulative exposure indices were calculated for each exposed worker based on manganese concentrations in "inhalable" dust from personal air samples and job histories. Mean values for exposed workers were 16.0 mg manganese/m^3 per year (SD 22.4) for cumulative exposure index, 0.82 mg manganese/m^3 (SD 1.04) for average intensity of exposure, 12.5 µg manganese/L (SD 5.6) for blood manganese, and 10.5 µg manganese/L (SD 20.3) for urine manganese. Control workers had mean values of 6.4 µg manganese/L (SD 1.7) for blood manganese and 0.96 µg manganese/L (SD 0.81) for urine manganese. Neurobehavioral end points included the Swedish nervous system questionnaire and the following neurobehavioral test batteries: World Health Organization (WHO) neurobehavioral core test battery, SPES, Luria-Nebraska tests, and Danish product development tests (tests of hand steadiness, tremor, and body sway). Information collected for potential confounders included age, educational level, alcohol and tobacco consumption, neurotoxic exposures in previous work, past medical history, and previous head injury. Multiple linear and logistic regression analyses were conducted to examine possible exposure-response relationships. Several tests showed significant ($p<0.05$) differences between exposed and control workers, but no evidence of exposure-response relationships including the following: the Santa Ana, Benton and digit span WHO tests; hand tapping and endurance tapping SPES tests; one

Luria-Nebraska test (item 2L); several self-reported symptoms (e.g., tiredness, depressed, irritated); and increased sway under two conditions (eyes open with or without foot insulation). Results from two other tests (WHO digit-symbol test and Luria-Nebraska item 1R) showed differences between exposed and control groups and some evidence for increased deficits with increasing exposure, but the change with increasing exposure was greater at lower exposure levels than at higher exposure levels. Results from all of the remaining tests showed no significant adverse differences between the exposed and control groups. The authors concluded that "the most likely explanation for few, weak and inconsistent findings with implausible or counterintuitive exposure-response relationships is chance, and it is concluded that this is essentially a negative study."

Young et al. (2005) reanalyzed the data collected by Myers et al. (2003b) on the basis of estimated exposures to manganese in "respirable" dust. Exposure estimates for each worker (cumulative exposure indices in mg manganese/m^3 per year and average intensity of exposure in mg manganese/m^3) were recalculated based on manganese determinations in personal air samplings of respirable dust (collected on 37 mm, 5 µm MCEP membrane filters, as opposed to inhalable dusts of larger particle sizes used to estimate exposure in the earlier analyses by Myers et al. [2003b]). Results from comparisons of mean performances of exposed and control groups in the neurobehavioral tests and regression analyses to assess exposure-response relationships were similar to results from the earlier analyses by Myers et al. (2003b) based on manganese determinations in inhalable dust. The authors concluded that the results did not provide evidence that exposure estimates based on respirable dust provide a more sensitive method to detect manganese neurobehavioral effects.

Bast-Pettersen et al. (2004) cross-sectionally examined neurobehavioral end points in a group of 100 male workers in manganese alloy plants and a group of 100 control workers (paired matched for age) from two plants, one producing silicon metal and microsillica and another titanium oxide slag and pig iron. Manganese alloy workers were employed for a mean of 20.2 years (SD 8.6; range 2.1– 41.0 years); comparable statistics were not reported for the control workers. Exposure was assessed from manganese determinations in dust from personal air samples (collected on 3 days for each subject closely before the neurobehavioral assessment), blood samples, and urine samples. Arithmetic means for manganese workers were 0.753 mg manganese/m^3 inhalable dust for work room air (geometric mean 0.301; range 0.009–11.5 mg manganese/m^3), 189 nmol manganese/L in blood (range 84–426 nmol/L), and 3.9 nmol manganese/mmol urine creatinine (range 0.1–126.3). The Institute of Occupational Medicine (IOM) personal samplers used in this study are expected to provide estimates that are approximately 2-fold higher than estimates using 25- or 37-mm plastic Millipore personal air samplers used in many earlier

studies to measure "total dust". Mean levels of manganese in blood (166 nmol manganese/L) and urine (0.9 nmol manganese/mmol creatinine) of control workers were significantly lower than levels in exposed workers. Neurobehavioral end points included: two self-administered neuropsychiatric questionnaires; six tests of cognitive functions (Weschlers adult intelligence scale, digit symbol, trail making test, Stroop color-word recognition, digit span, and Benton visual retention); and eight tests of motor functions (static hand steadiness, "TREMOR" test, finger tapping, foot tapping, supination/pronation of hand, Luria-Nebraska thumb/finger sequential touch, simple reaction time, and hand-eye coordination). Information collected for potential confounders included age, years of education, alcohol and tobacco consumption, and prevalence of previous brain concussions. Multiple linear regression analyses were conducted to examine the influence of potential confounders and exposure-response relationships for test results. No significant ($p<0.05$) effect of exposure was found in tests for cognitive functions, reaction time, or symptom reporting. No statistically significant ($p<0.05$) differences were found in tests of motor speed, grip strength, or reaction time. Postural tremor as measured in the hand steadiness test was significantly ($p<0.05$) increased in the exposed group compared with the controls and showed an exposure-response relationship when the exposed group was regrouped into three groups of increasing duration of employment. Results from an alternative test of tremor ("TREMOR") did not distinguish between the manganese alloy group and the control group. The results indicate that the manganese-exposed group of workers had increased hand tremor compared with the control group, but were indistinguishable from the control group in other tests of motor function, cognitive function, or symptom reporting.

Bouchard et al. (2005) reanalyzed results from neurobehavioral tests administered by Mergler et al. (1994) to 74 male workers in a manganese alloy plant to examine the influence of age on the tests. At the time of testing, workers had been employed an average of 19.3 years (range 1–27 years) and 71 of the workers were employed for >10 years. Based on personal air and stationary air samples 8-hour time-weighted average manganese concentrations ranged from 0.014 to 11.48 mg manganese/m^3 total dust (geometric mean=0.225 mg manganese/m^3) and from 0.001 to 1.273 mg manganese/m^3 respirable dust (geometric mean=0.035 mg manganese/m^3). The referent group contained 144 workers with no history of occupational exposure to neurotoxicants who were matched for age, educational level, smoking status, and number of children. Mean blood manganese levels were 11.9±5.3 µg/L (range 4.4–25.9 µg/L) in exposed workers and 7.2±0.3 µg/L (range 2.8–15.4 µg/L) in controls. Paired differences between exposed and control workers increased significantly ($p<0.05$) with age for one of nine tests of neuromotor domain (nine-hole hand steadiness test); 3 of 12 tests of cognitive domain (trail making B [test of visual conception and visuomotor tracking], delayed word recall [test of learning, recall and attention], and cancellation H [test of visuomotor tracking and concentration]); and 1 of 4 sensory domain tests

(vibratometer–vibrotactile perception of the index and toe). The results suggest that older workers may be more slightly more susceptible to the neurological effects of low-level manganese exposure than younger workers.

Bouchard et al. (2007a) examined neuropsychiatric symptoms in a group of 71 male workers in a manganese alloy plant, 14 years after cessation of exposure, and in a group of 71 unexposed referents of similar age and education levels from the same geographical region. Based on personal air and stationary air samples during the operation of the plant, 8-hour time-weighted average manganese concentrations were 0.014–11.48 mg manganese/m^3 total dust (geometric mean=0.225 mg manganese/m^3) and 0.001–1.273 mg manganese/m^3 respirable dust (geometric mean=0.035 mg manganese/m^3). The mean number of years of occupational exposure to manganese was 15.7 (range, 7.4–17.3 years). The exposed workers were participants in the earlier study by Mergler et al. (1994). Neuropsychiatric symptoms were assessed by a self-administered questionnaire, the Brief Symptom Inventory, from which scores were determined for somatization (psychological distress from perception of bodily dysfunction), obsessive-compulsive behavior, interpersonal sensitivity (feeling of personal inadequacy), depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Former, manganese workers showed significantly ($p<0.05$) higher scores (after adjustment for age, education, and alcohol consumption) for two of the nine neuropsychiatric symptoms (depression, anxiety), compared with controls.

In a follow-up to the Mergler et al. (1994) study, Bouchard et al. (2007b) evaluated neurobehavioral end points in a group of 77 male former workers in a manganese alloy plant, 14 years after cessation of employment, and in a group of 81 nonexposed referents group-matched for age, education and alcohol consumption. The groups were initially assessed in 1990 and, for the present study in 2004, in five neuromotor tests, nine cognitive tests, and six mood state tests. Based on personal air and stationary air samples during the operation of the plant, 8-hour time-weighted average manganese concentrations were 0.014–1.48 mg manganese/m^3 total dust (geometric mean=0.225 mg manganese/m^3) and 0.001–1.273 mg manganese/m^3 respirable dust (geometric mean=0.035 mg manganese/m^3). Mean years of occupational exposure to manganese was reported as 15.3 years (maximum=17.3 years). In the 1994 assessment, significant ($p<0.05$) differences between exposed and control workers were found in scores for one of five neuromotor tests (Luria Motor Scale), three of nine cognitive tests (cancellation H, digit span, color-word test), and one (tension-anxiety) of six mood state tests. In 2004, significant ($p<0.05$) differences between the exposed and control workers persisted for one (Luria Motor Scale) of five neuromotor tests, none of the nine cognitive tests, and one (confusion-bewilderment) of the six mood states. These results

indicate that exposure-related effects observed initially in the manganese alloy workers did not progress in a 14-year period following cessation of employment.

Neurological Assessments of Environmentally Exposed Populations Exposed to Inorganic Manganese. Mergler et al. (1999) studied environmental exposure to manganese and its possible effect on mood (Bowler et al. 1999), neuromotor function (Beuter et al. 1999), and levels of the metal in biological fluids (Baldwin et al. 1999). The study group was a community in southwest Quebec, Canada, near which a former manganese alloy production plant served as a point source for environmental manganese pollution. Due to the presence of MMT in gasoline in Canada, inhaled manganese from car exhaust is a potential contributor to manganese exposures experienced in the population studied. A total of 273 persons comprised the test population. These individuals were selected using a stratified random sampling strategy from the Quebec Health Plan Register, which includes all residents. This strategy helped to ensure that no selection bias was introduced. These individuals were administered a test battery including a computerized neuromotor test, blood sampling, visual function tests from the Neurobehavioral Evaluation System-2, an extensive neuropsychological test battery, and diverse tests covering such areas as olfactory threshold, finger tapping, digit span, and postural sway. Blood sampling data for the study subjects (Baldwin et al. 1999) indicated that manganese levels in women (geometric mean=7.5 μg/L) were significantly higher than in men (6.75 μg/L). No relationship was found between the overall level of manganese in blood and those of lead or iron in serum. However, blood manganese levels were negatively correlated with serum iron in women and had a tendency to decrease with increasing age. Serum iron levels in men were higher than in women. The authors analyzed manganese in drinking water from the study subjects' residences and analyzed air samples from four different locations for total manganese particulates and PM_{10} values. The geometric mean value for manganese in drinking water was 4.11 μg/L; there was no correlation between individual values in drinking water manganese and manganese blood levels. Intersite differences in manganese values in total particulate were not observed in the air samples, but intersite differences did exist for manganese in PM_{10} values. Two geographical areas were identified where manganese in air contributed to blood manganese levels; serum iron was negatively related to blood manganese levels in this analysis (Baldwin et al. 1999).

The Profile of Moods State and Brief Symptom Inventory self-report scales were used to assess condition of mood in the study population (Bowler et al. 1999). The results from these analyses indicated that men who are older (>50 years) and have higher blood manganese levels (≥7.5 μg/L) showed significant disturbances in several mood symptoms with significantly increased values for anxiety, nervousness, and irritability; emotional disturbance; and aggression and hostility when compared to those with lower levels

of blood manganese. Neuromotor, neurological, and neurobehavioral analyses revealed that subjects with higher blood manganese levels (≥7.5 μg/L) performed significantly worse on a test for coordinated upper limb movements, with poorest performance in older men (Mergler et al. 1999). Also in men, proximal events on the qualified neurological examination, involving arm movements were significantly slower for those with higher blood manganese, and hand movements (distal events) tended to be in the same direction. No correlation was observed in women. Other measures of motor performance (e.g., hand-arm tremor and tapping movements) were not related to blood manganese levels, although a significant decrease in tremor frequency dispersion was observed with log MnB (manganese blood level). For both men and women, performance on the learning and memory tests was inversely correlated with manganese blood level values, although performance on individual portions of the overall test varied significantly with gender. For men, higher levels of manganese in blood were associated with poorer performance on list acquisition, delayed auditory recall, and visual recognition following a distracter. Females, in contrast, tended to recall fewer geometric shapes, made more errors on the visual reproduction test, but remembered more numbers on the digit span forward test. This study is unique in that it is the first to study both males and females in an exposed population, and it shows an association between elevated manganese blood levels linked to elevated environmental manganese and poor performance on neurobehavioral and neuropsychiatric tests. This study also reported that neurological effects associated with higher levels of blood manganese were more likely to be observed in persons >50 years of age. In contrast, Roels et al. (1999) reported that age was a significant factor only in performance of the visual reaction time test, but not for the eye-hand coordination test or the measure of hand steadiness used in their longitudinal studies. However, Crump and Rousseau (1999) reported that older age was a significant factor in poor performance in tests of short-term memory and eye-hand coordination. Although there were no statistically significant neurological effects associated with manganese exposure among workers of a metal-producing plant evaluated by Gibbs et al. (1999), these investigators also noted that test performance in eye-hand coordination and reaction time decreased with increasing age.

Rodriquez-Agudelo et al. (2006) examined neurobehavioral end points in 168 women and 120 men from eight communities at various distances from manganese extraction or processing plants in the district of Molango, Mexico. Manganese levels in PM_{10} dust in air samples collected from 28 houses were determined, and the values obtained from the closest monitor were assigned to each of the 288 participants (values ranged from 0 to 5.86 μg manganese/m^3). Concentrations of manganese in samples of drinking water and maize grain were mostly below detection limits, whereas soil concentrations ranged from about 6 to 280 mg manganese/kg, with the largest concentrations noted in samples collected close to the manganese industrial sites. Blood samples were collected from each

participant and used for manganese and lead determinations. Neuromotor tests (which were a Spanish adaptation of Luria diagnostic procedures) were administered, and odds ratios (ORs) were calculated for 24 different end points involving hand motor functions using dichotomous assessments of performance (e.g., normal and poor) after grouping the participants based on associated manganese concentrations in air or blood manganese levels. No associations were found between neuromotor performance and blood levels of manganese or lead. After grouping the participants into those associated with air concentrations between 0 and 0.1 µg manganese/m^3 and those with concentrations between 0.1 and 5.86 µg manganese/m^3 (approximate midpoint=3 µg manganese/m^3), significantly ($p<0.05$) elevated ORs for poor performance were calculated for only 3 of the 24 neuromotor end points (two movement coordination, left hand performance [OR=1.99, 95% CI 1.15–3.43]; change of hand position, left hand performance [OR=1.98, 95% CI 0.99–3.95], and conflictive reaction, a test of verbal regulation of movement [OR=2.08. 95% CI 1.17–3.71]). Although the authors concluded that the results indicate that "there is an incipient motor deficit in the population environmentally exposed to large manganese levels," a more likely explanation for the few and inconsistent findings is chance. This explanation is supported by the finding that no statistically significant associations were found between any neuromotor function end points and blood manganese levels. In addition, the lack of air monitoring data for individual participants in the study precludes assigning the "high" air concentration exposure level as a reliable LOAEL or NOAEL.

In a community-based study, Lucchini et al. (2007) examined possible associations between prevalence of Parkinsonian disorders and levels of manganese in settled dust collected from communities in the vicinities of manganese ferroalloy industrial plants in the province of Brescia, Italy. Parkinsonian patients were identified from clinical registers from local hospitals, area neurologists, and records of exemption from prescription payments, as well as from records of L-Dopa prescriptions; a total of 2,677 Parkinsonian cases were identified among 903,997 residents. SMRs for each of 206 municipalities were calculated based on national rates standardized for age and gender. Municipalities with the highest SMRs were located within 20 km and/or downwind of three manganese alloy industrial plants in the Valcamonica region of Brescia. An average standardized prevalence of 492 cases/100,000 residents was observed in the 37 municipalities of the Valcamonica region. Crude and standardized prevalence rates for the Valcamonica municipalities were significantly ($p<0.05$) higher than rates for the other 169 municipalities of Brescia. Municipality-based SMRs for Parkinsonian disorders were significantly ($p<0.05$) associated with manganese levels in settled dust, and manganese levels in settled dust samples from the 37 municipalities in Valcamonica were significantly ($p<0.05$) higher than levels in samples for the other 169 municipalities. The results suggest that prolonged environmental exposure to excessive

manganese in the Valcamonica region of Brescia may increase the risk for Parkinsonian disorders, but the results do not identify a reliable NOAEL or LOAEL that can be expressed in units of manganese air concentrations. The authors speculated that, even though manganese-induced and Parkinsonian neurological disorders are expected to have two distinct target areas in the brain (the globus pallidus and the substantia nigra, respectively), structural and chemical interconnections between the brain areas may interact to cause increased risk for Parkinsonian disorders as suggested by Weiss (2006).

Neurological Studies of Animals Exposed by Inhalation to Inorganic Manganese. In several early animal studies, intermediate or chronic inhalation exposure of monkeys and rats to manganese dusts has not produced neurological signs similar to those seen in humans (Bird et al. 1984; EPA 1983c; Ulrich et al. 1979a, 1979b). For example, Ulrich et al. (1979a) reported that monkeys continually exposed for 9 months to aerosols of manganese dioxide at concentrations as high as 1.1 mg manganese/m^3 showed no obvious clinical signs of neurotoxicity, no histopathological changes in brain tissues, and no evidence for limb (leg) tremor or electromyographic effects on flexor and extensor muscles in the arm. However, in a chronic study with Rhesus monkeys, decreased levels of dopamine were found in several regions of the brain (caudate and globus pallidus) (Bird et al. 1984). Behavioral tests detected signs of neurological effects in mice (increased open-field activity and decreased maternal pup retrieval latency), although these are only seen at relatively high exposure levels (60–70 mg manganese/m^3) (Lown et al. 1984; Morganti et al. 1985).

Several studies provide evidence for associations between decreased neuronal cell counts in the globus pallidus and neurobehavioral changes (increased locomotor activity) in rats exposed by inhalation for 13 weeks to a mixture of manganese phosphate/sulfate (at 1.05 mg manganese/m^3) or manganese sulfate alone (at concentration between 0.009 and 0.9 mg manganese/m^3), but not to manganese phosphate alone at concentrations up to 1.1 mg manganese/m^3 (Normandin et al. 2002; Salehi et al. 2003, 2006; Tapin et al. 2006). Other 13-week rat inhalation exposure studies reported increased brain manganese concentrations and increased locomotor activity after exposure to 3.75 mg manganese/m^3 as metallic manganese (St-Pierre et al. 2001) and increased brain manganese concentrations with no increases in olfactory bulb, cerebellar, or striatal concentrations of glial fibrillary acidic protein (GFAP) after exposure to 0.5 mg manganese/m^3 as manganese sulfate or 0.1 mg manganese/m^3 as manganese phosphate (Dorman et al. 2004b). GFAP is a widely acknowledged marker of damage to astrocytes.

In male Sprague-Dawley rats, increased locomotor activity (increased distance traveled, but no change in resting time) was observed after up to 13 weeks of exposure to 0.03 or 3 mg of a manganese

phosphate/sulfate mixture/m^3 (6 hours/day, 5 days/week), but not at 0.3 mg/m^3 (Salehi et al. 2003). These exposure concentrations correspond to 0.01, 0.11, and 1.05 mg manganese/m^3. Assessment of brain manganese levels, hind limb tremor, and neuropathology of the brain (counts of neuronal cells) found no evidence for tremor at any exposure level, but rats at the highest exposure level showed significantly ($p<0.05$) increased concentrations of manganese in the frontal cortex, globus pallidus, and caudate putamen, as well as significantly ($p<0.05$) decreased neuronal cell counts in the globus pallidus and caudate putamen, compared with control values or to values for rats in the lower exposure groups (Salehi et al. 2006).

In similar experiments with male Sprague-Dawley rats exposed to 0, 0.03, 0.3, or 3 mg manganese sulfate/m^3 (Tapin et al. 2006) or 0, 0.03, 0.3, or 3 mg manganese phosphate/m^3 (Normandin et al. 2002) for 13 weeks by the same exposure protocol, some differences in results were obtained. These exposure levels correspond to 0.009, 0.09, or 0.9 mg manganese/m^3 for manganese sulfate and 0.01, 0.11, or 1.1 mg manganese/m^3 for manganese phosphate. With exposure to manganese phosphate, manganese levels were significantly ($p<0.05$) elevated (at 3 mg/m^3) in the olfactory bulb, frontal cortex, globus pallidus, caudate putamen, and cerebellum regions of the brain, but no exposure-related effects were found on neuronal cell counts or locomotor activity (Normandin et al. 2002). In contrast, manganese sulfate exposure significantly ($p<0.05$) increased manganese levels in all regions of the brain, and decreased neuronal counts in the globus pallidus at 0.3 and 3 mg manganese sulfate/m^3, compared with controls (Tapin et al. 2006). In addition, the two highest exposure levels of manganese sulfate were associated with significantly ($p<0.05$) increased locomotor activity (distance traveled), increased resting time, and decreased total ambulatory counts; the lowest exposure level, 0.03 mg manganese sulfate/m^3 also increased the distance traveled end point of locomotor activity (Tapin et al. 2006). As with the manganese phosphate/sulfate mixture, neither manganese phosphate nor manganese sulfate exposure was associated with hind limb tremors in the rats. Earlier studies by the same research group, found that Sprague-Dawley rats exposed to 3.75 mg aerosols of metallic manganese/m^3 (6 hours/day, 5 days/week for 13 weeks) showed significantly ($p<0.05$) higher manganese concentrations in various regions of the brain, and higher distance traveled and lower resting time in locomotor tests, compared with controls; neuronal counts were not assessed in this earlier study (St-Pierre et al. 2001).

Several studies have examined the influence of inhalation exposure to manganese sulfate on biochemical end points associated with oxidative stress or inflammation in the brain of rats (Erikson et al. 2005, 2006; HaMai et al. 2006; Taylor et al. 2006) and monkeys (Erikson et al. 2007). Erikson et al. (2005, 2006) exposed neonatal rats to manganese sulfate (0, 0.05, or 1 mg manganese/m^3) during gestation and

postnatal days (PNDs) 1–18 and examined five brain regions for several biochemical end points associated with oxidative stress either on PND 19 (Erikson et al. 2006) or after 3 weeks without exposure (Erikson et al. 2005). End points included levels of glutamine synthase (GS) protein and mRNA, metallothionein (MT) mRNA, tyrosine hydroxylase (TH) protein and mRNA, and total reduced glutathione. At PND 9, increased manganese concentrations in the striatum (the most consistently affected region) were associated with decreases in GS, MT, and TH mRNA, and significantly decreased levels of glutathione (Erikson et al. 2006), but these were not apparent 3 weeks after cessation of exposure (Erikson et al. 2005). However, other end points (such as decreased GS protein) were changed, compared with control values, 3 weeks after cessation of exposure (Erikson et al. 2005). Similar end points, as well as levels of mRNA and protein for glutamate transporters, were examined in six brain regions of young male Rhesus monkeys exposed to 0, 0.06, 0.3, or 1.5 mg manganese/m^3 as manganese sulfate for 65 days (Erikson et al. 2007). Exposure-related changes included decreased MT mRNA in most regions, decreased TH protein levels in the caudate and globus pallidus, increased GSH in the frontal cortex, and decreased GSH in the caudate. In another study, HaMai et al. (2006) exposed three groups of rats to 0 or 0.71 ng manganese/m^3 (2 hours/day) as manganese sulfate on gestation days (GDs) 9 and 10, on PNDs 37–47, or on GDs 9 and 10 plus PNDs 37–47 and measured brain levels of mRNA for gene products related to oxidative stress or inflammation. Gestational exposure was associated with decreased mRNA for amylid precurson (APP), cyclooxygenase-2 (COX-2), neuronal nitric oxide synthetase (nNOS), and GFAP, whereas adult exposure was associated with greater transcriptional decreases for the same gene products as well as transcriptional growth factor beta (HaMai et al. 2006). The results from these studies indicate that acute- or intermediate-duration inhalation exposure to manganese sulfate concentrations ranging from about 0.1 to 1 mg manganese/m^3 can differentially affect brain biochemical markers of neurotoxicity, but understanding of the neurotoxic mechanism of manganese is inadequate to confidently define any one of the observed changes as biologically adverse.

No studies on neurological effects from inhalation exposure to MMT in humans or animals were located.

3.2.1.5 Reproductive Effects

As discussed earlier (see Section 3.2.1.4), impotence and loss of libido are common symptoms in male workers afflicted with clinically identifiable signs of manganism attributed to occupational exposure to manganese for 1–21 years (Emara et al. 1971; Mena et al. 1967; Rodier 1955; Schuler et al. 1957). These symptoms could lead to reduced reproductive success in men. Impaired fertility (measured as a decreased number of children/married couple) has been observed in male workers exposed for 1–19 years to

manganese dust (0.97 mg/m^3) at levels that did not produce frank manganism (Lauwerys et al. 1985). This suggests that impaired sexual function in men may be one of the earliest clinical manifestations of manganism, but no dose-response information was presented so it is not possible to define a threshold for this effect. Jiang et al. (1996b) performed a reproductive epidemiological study on 314 men in a manganese plant. The men, from six different factories, performed milling, smeltering, and sintering duties for up to 35 years. The geometric mean airborne manganese concentration (assumed to be total dust) was 0.145 mg/m^3 as manganese dioxide. The researchers found no significant differences in reproductive outcomes between exposed and control workers (controls were matched for several factors, including age, smoking, personal hygiene, living habits, and cultural background). The incidences of sexual dysfunction were evaluated through researchers' questions and judged by the occurrence of two positive responses to three potential conditions: impotence, abnormal ejaculation (early ejaculation or nonejaculation), and lack of sexual desire. Impotence and lack of sexual desire were higher in the exposed group than in the controls (Jiang et al. 1996b). Wu et al. (1996) reported increased semen liquefaction time and decreased sperm count and viability in three groups of men occupationally exposed to manganese: 63 miners or ore processors, 38 electric welders in mechanical fields, and 110 electric welders in shipbuilding. Matched controls consisted of 99 men who were employed in the same occupation and from the same area, but were not exposed to manganese or other reproductive toxins. The men had been exposed to manganese for ≥1 year. Geometric means of total manganese dust (as manganese dioxide) ranged from 0.14 mg/m^3 for mining operations to 5.5 mg/m^3 for manganese powder processing. Manganese fume concentrations varied; the mechanical welders were exposed to a concentration of 0.25 mg/m^3 (geometric mean), while the shipbuilding area concentrations ranged from geometric means of 6.5–82.3 mg/m^3, depending on the location within the ship. The miners had a significant percentage (14.3%; $p<0.01$) of samples with increased liquefaction time, decreased sperm count (34.9%; $p<0.01$), and decreased percentage of total viable sperm (33.3% had abnormal counts; $p<0.01$) compared to controls. Welders in shipbuilding had decreased sperm viability levels that were significantly different from controls ($p<0.01$). Manganese concentrations in semen were significantly increased compared to controls in the mechanical welders; copper, nickel, chromium, and iron concentrations were also elevated in semen in welders in both mechanical and shipbuilding careers. Further, stepwise regression analysis of the impact of these other metals on the measured reproductive parameters indicated that the higher the nickel concentration, the lesser the semen volume and the greater the number of deformed sperm. Copper in the seminal fluid was also positively linked with the viable sperm percentage, sperm viability and number of sperm. Although this study indicates that manganese exposure can cause sperm toxicity, the presence of other metals prevents any conclusive statements concerning its importance. Gennart et al. (1992) performed a reproductive study on 70 male workers

exposed to manganese dioxide at a median concentration of 0.71 mg manganese/m^3 in total dust for an average of 6.2 years in a dry alkaline battery plant. Results from a questionnaire answered by the workers and controls in the study and from analysis of birthrates of exposed and control workers revealed no difference in birthrates between the groups.

These results in human studies reveal conflicting evidence for whether occupational exposure to manganese causes adverse reproductive effects. Effects reported may occur as a secondary result of neurotoxicity but do not provide information on any direct effect manganese may have on the reproductive organs. No information was found regarding reproductive effects in women.

Intratracheal instillation studies in rabbits indicate that single high doses of manganese (158 mg/kg, as manganese dioxide) can cause severe degenerative changes in the seminiferous tubules and lead to sterility (Chandra et al. 1973; Seth et al. 1973). This effect did not occur immediately, but developed slowly over the course of 4–8 months following the exposure. Direct damage to the testes has not been reported in humans occupationally exposed for longer periods, suggesting that this effect may not be of concern under these exposure circumstances. However, it is unclear if specific studies to investigate possible testicular damage have been performed.

None of the studies located reported adverse effects in female animals following inhalation exposure to manganese. In a study with female mice (Lown et al. 1984), the average number of pups born to exposed females was increased when dams were exposed to manganese dioxide before conception through gestation. In a report of a study of tissue manganese concentrations in lactating rats and their offspring following exposure to manganese sulfate aerosols at 0, 0.05, 0.5, or 1 mg manganese/m^3 starting 28 days prior to breeding through PND 18, no mention was made of reproductive performance variables such as the percentage of dams that delivered or the number of pups per litter (Dorman et al. 2005a).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

No studies were located concerning reproductive effects following inhalation exposure to organic manganese compounds in humans or animals.

3.2.1.6 Developmental Effects

Very little information is available on the developmental effects of inorganic manganese from inhalation exposure. The incidences of neurological disorders, birth defects, and stillbirths were elevated in a small population of people living on an island where there were rich manganese deposits (Kilburn 1987). However, no conclusions could be reached on the causes of either the neurological effects or the increased incidence of birth defects and stillbirths because there were insufficient exposure data. Control data were not provided, and the study population was too small for meaningful statistical analysis. Although inhalation exposure was not ruled out, the route of exposure was assumed to be primarily oral.

Lown et al. (1984) evaluated the developmental effects of inhaled manganese in mice. The study involved exposing dams and non-pregnant female mice to either filtered air or manganese at an average concentration of 61 mg/m^3 (as manganese dioxide) 7 hours/day, 5 days/week, for 16 weeks prior to conception. The authors then exposed the mice to either air or manganese post-conception, irrespective of preconception exposure. Once delivered, six pups (three of each sex) were distributed to foster mothers and then nursed in the absence of exposure to manganese. The pups were then evaluated on postpartum day 7 for weight gain and gross locomotor activity and on day 45 for different behavioral parameters and learning performance. The authors observed that pups raised by foster mothers that had been exposed to manganese preconception and filtered air postconception had reduced weights compared to pups raised by foster mothers exposed only to filtered air. The activity data indicated that there were no observable differences in activity between pups who had been exposed to manganese *in utero* and those that had not. Therefore, the data did not provide evidence that manganese exposure resulted in adverse neurological developmental effects.

No studies were located concerning developmental effects in humans or animals following inhalation exposure to organic manganese.

3.2.1.7 Cancer

No studies were located regarding carcinogenic effects in humans or animals after inhalation exposure to inorganic or organic manganese.

3.2.2 Oral Exposure

Although humans are often exposed to significant quantities of inorganic manganese compounds in food and water (see Sections 6.4 and 6.5), reports of adverse effects in humans from ingestion of excess manganese are limited. Most information on the effects of oral exposure to inorganic manganese is derived from studies in animals. These studies are summarized in Table 3-2 and Figure 3-2, and the findings are discussed below. All doses are expressed as mg manganese/kg/day.

Health effects following oral exposure to the organic manganese compound, MMT, were observed in animals. Studies involving oral exposure of animals to MMT are summarized in Table 3-3 and Figure 3-3. As discussed previously, because inhalation, oral, and dermal pathways are not a concern regarding exposure to mangafodipir, this compound's studies are not presented in an LSE table or figure; instead, they are discussed in Section 3.2.4.

3.2.2.1 Death

Two studies have been located in which death in humans may have been caused by the ingestion of manganese-contaminated water (Hafeman et al. 2007; Kawamura et al. 1941). Kawamura et al. (1941) reported death from "emaciation" in two adults who ingested drinking water contaminated with high levels of manganese. Hafeman et al. (2007) reported high mortality among infants <1 year of age in a Bangladesh population where the drinking water supplied by certain local wells contained high levels of manganese. As discussed in detail in Sections 3.2.2.4 (Kawamura et al. 1941) and 3.2.2.5 (Hafeman et al. 2007), several aspects of these two reports suggest that factors other than, or in addition to, high levels of manganese in drinking water may have been responsible for the deaths.

In animals, most studies indicate that manganese compounds have low acute oral toxicity when provided in feed. In rats, daily doses of 1,300 mg manganese/kg/day (as manganese sulfate in the feed) for 14 days did not affect survival (NTP 1993). Survival was decreased in male rats fed 200 mg manganese/kg/day (as manganese sulfate) for 2 years (NTP 1993). The cause of death was attributed to increased severity of nephropathy and renal failure; however, female rats fed 232 mg manganese/kg/day (as manganese sulfate) for 2 years were not affected in this manner (NTP 1993). Similarly, doses as high as 2,251 mg manganese/kg/day (as manganese chloride) in the diet were tolerated by male mice (females were not tested) for 6 months without lethality (Gianutsos and Murray 1982). The survival of both male and female mice was also unaffected by feeding as much as 731 mg manganese/kg/day (as manganese sulfate) for 2 years (NTP 1993).

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (GW)				412 M (LD50)	Holbrook et al. 1975 MnCl2	
2	Rat (albino)	once (GW)				351 M (LD50)	Kostial et al. 1978 MnCl2	
3	Rat (Wistar)	once (GW)				342 M (LD50) 331 F (LD50) 275 (LD50 - pups)	Kostial et al. 1989 MnCl2	
4	Rat (Swiss albino)	once (G)				642 M (LD50)	Singh and Junnarkar 1991 MnCl2	
5	Rat (Swiss albino)	once (G)				782 M (LD50)	Singh and Junnarkar 1991 MnSO4	
6	Rat (Wistar)	once (GW)				1082 (LD50)	Smyth et al. 1969 MnOAc	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
7	Rat (F344/N)	14 d (F)	Resp	1300			NTP 1993 MnSO4	
			Cardio	1300				
			Hemato	650 M 1300 F	1300 M (decreased leukocyte and neutrophil counts)			
			Hepatic	650 M 1300 F	1300 M (reduced liver weight)			
			Renal	1300				
			Endocr	1300				
			Bd Wt	650	1300 (57% decreased body weight in males; 20% in females)			

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
8	Mouse (B6C3F1)	14 d (F)	Resp	2600 M 3900 F			NTP 1993 MnSO4	
			Cardio	2600 M 3900 F				
			Hemato	2600 M 3900 F				
			Hepatic	2600 M 3900 F				
			Renal	2600 M 3900 F				
			Endocr	2600 M 3900 F				
Neurological								
9	Rat (Wistar)	6 d (GW)			22 M (increase in dihydroxyphenylacetic acid and uric acid in striatum)		Desole et al. 1994 MnCl2	
10	Rat (Wistar)	2 x/d 6 d 1 x (d 7) (GW)			8.8 M (decrased concentrations of dopamine in brainstem; glutathione depletion potentiated Mn effects on dopamine as well as concentrations of DOPAC and HVA)		Desole et al. 1997 MnCl2	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
11	Rat (F344/N)	14 d (F)		1300			NTP 1993 MnSO4	
12	Rat (albino)	1 d (GW)			13.9 (decreased acquisition of an avoidance reaction)		Shukakidze et al. 2003 MnCl2*4H2O	
Reproductive								
13	Rat (Sprague-Dawley)	Gd 6-17 (GW)		2200 F			Grant et al. 1997 MnCl2	
14	Rat (Fischer- 344)	14 d (F)		1300 M			NTP 1993 MnSO4	
Developmental								
15	Rat (Sprague-Dawley)	Gd 6-17 (GW)		2200			Grant et al. 1997 MnCl2	
INTERMEDIATE EXPOSURE								
Death								
16	Rat (Long- Evans)	21 d (GW)				225 (LD50 - 21 days)	Rehnberg et al. 1980 Mn3O4	
Systemic								
17	Rat (Long- Evans)	224 d (F)	Hemato	180 M			Carter et al. 1980 Mn3O4	
18	Rat (Wistar)	1 x/d 28 d (F)	Bd Wt			6 M (rats gained only 44% of amount gained by control rats with normal food consumption)	Exon and Koller 1975 Mn3O4	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
19	Rat (F344/N)	13 wk (F)	Resp		40 F (reduced lung weight)		NTP 1993 MnSO4	
			Cardio	520 M				
				618 F				
			Gastro	520 M				
				618 F				
			Hemato		33 M (increased neutrophil count)			
					155 F (decreased leukocyte count)			
			Hepatic		33 M (decreased liver weight)			
					618 F (decreased liver weight)			
			Renal	520 M				
				618 F				
			Endocr	520 M				
				618 F				
			Bd Wt	77 F	155 F (11% decrease in body weight)			

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
20	Rat (Sprague-Dawley)	63 d (GW)	Renal		87 M (increased incidence of glomerulosclerosis/ glomerulonephritis or urolithiasis [i.e., bile stone formation] in males)		Ponnapakkam et al. 2003b MnOAc	Rats sacrificed immediately after last day of dosing. No urolithiasis observed in females of any treatment group.
21	Rat (Sprague-Dawley)	Gd 0-21 (GW)	Endocr	33 F			Szakmary et al. 1995 MnCl2	No effect on secretion or peripheral blood levels of progesterone or 17b-estradiol.
			Metab		11 F (increased cytochrome P450)			
22	Rat (white)	10 wk (W)	Hepatic	12 M			Wassermann and Wassermann 1977 MnCl2	Only ultrastructural changes in liver cells were noted.
23	Mouse Swiss	12 wk (W)	Bd Wt	277 F			Elbetieha et al. 2001 MnCl2	
24	Mouse (CD-1)	90 d (F)	Hepatic	205 M			Gray and Laskey 1980 Mn3O4	No clinical signs or changes in body, kidney or liver weights.
			Renal	205 M				

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
25	Mouse (ddY)	100 d (F)	Hemato		284 M (decreased red blood cell count and white blood cell count)		Komura and Sakamoto 1991 MnOAc	
			Bd Wt		284 M (10% decrease in body weight gain)			
26	Mouse (ddY)	100 d (F)	Hemato		284 M (decreased hematocrit)		Komura and Sakamoto 1991 MnCO3	
27	Mouse (ddY)	100 d (F)	Hemato		284 M (decreased white blood cell count)		Komura and Sakamoto 1991 MnO2	
28	Mouse (ddY)	100 d (F)	Hemato		284 M (decreased red blood cell count and white blood cell count)		Komura and Sakamoto 1991 MnCl2	
			Bd Wt		284 M (10% decrease in body weight gain)			

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Mouse (B6C3F1)	13 wk (F)	Resp	1950			NTP 1993 MnSO4	
			Cardio	1950				
			Gastro	975 M 1950 F	1950 M (mild hyperplasia and hyperkeratosis of the forestomach)			
			Hemato	975	1950 (decreased hematocrit, hemoglobin, and erythrocyte count)			
			Hepatic	975 M 1950 F	1950 M (reduced liver weight)			
			Renal	1950				
			Endocr	1950				
			Bd Wt	975 M 1950 F	1950 M (13% lower body weight compared to controls)			
30	Gn Pig	30 d; 1 d (G)	Gastro		4.4 M (patchy necrosis, decreased ATPase, GTPase in stomach and small intestine)		Chandra and Imam 1973 MnCl2	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
31	Rat (F344/N)	13 wk (F)			33 M (increased neutrophil count)		NTP 1993 MnSO4	
					155 F (decreased leukocyte count)			
Neurological								
32	Human	1 x/d 8 wk varying dose (IN)		0.3 F			Finley et al. 2003 MnSO4	The high Mn diet did not influence neuropsychological variables (interpersonal behavior survey and state-trait anger expression) or handsteadiness.
33	Monkey (Rhesus)	4 mo during infancy (F)			107.5 M (minimally adverse behavioral effects in soy and soy+Mn groups: decreased activity during sleep at 4 months and decreased play activity between 1-1.5 months)		Golub et al. 2005 MnCl2	No marked differences from controls in gross motor maturation, growth, or cognitive tests. No effect of Mn on CSF DA, HVA or 5-HIAA.
34	Rat (Sprague-Dawley)	6 wk (W)			71.1 (decreased Fe levels in caudate putamen and substantia nigra; decreased GABA uptake activity in striatal synaptosomes)		Anderson et al. 2007a MnCl2	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
35	Rat (Sprague-Dawley)	2 mo (W)			594 M (increased gamma-aminobutyric acid levels)		Bonilla 1978b MnCl2	
36	Rat (Sprague-Dawley)	8 mo (W)			392.5 M (increased L-tyrosine hydroxylase activity in neostriatum, midbrain, hippocampus, and hypothalamus)		Bonilla 1980 MnCl2	
37	Rat (Sprague-Dawley)	8 mo (W)			13 M (decreased norepinephrine levels)		Bonilla and Prasad 1984 MnCl2	
38	Rat (CD)	pnd 1-49 (GW)		11	22 (increased spontaneous motor activity)		Brenneman et al. 1999 MnCl2	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
39	Rat (Wistar)	10 wk (W)			1310 M (significantly increased open field activity, significantly elevated, continued interest in a novel object and increased fear; enhanced dopaminergic inhibitory control of corticostriatal excitatory transmission)		Calabresi et al. 2001 MnCl2	No effects on radial maze performance, neuronal numbers in striatum, levels of GFAP and TH in striatum, or membrane properties of striatal neurons.
40	Rat (Wistar)	10 wk (W)			1310 M (increased frequency and amplitude of spontaneous excitatory membrane potentials in corticostriatal slices from Mn-treated rats compared with control rats)		Centonze et al. 2001 MnCl2	
41	Rat (albino)	30 d (W)			146.7 M (increased activity and aggression, turnover of striatal dopamine, tyrosine and homovanillic acid, altered neurotransmitter levels)		Chandra 1983 MnCl2	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
42	Rat (ITRC albino)	60 d (GW)				0.31 M (increased monoamine oxidase activity in the brain, neuronal degeneration in cerebral and cerebellar cortex and caudate nucleus)	Chandra and Shukla 1978 MnCl2*4H2O	No evidence of behavioral changes or locomotor disturbances; exposure started at 21 days of age.
43	Rat (ITRC albino)	360 d (W)			40 M (increase of dopamine, norepinephrine, and homovanillic acid above control levels in striatum observed at 15-60 days of treatment, followed by a decrease of all three compounds below control levels at 300-360 days of treatment)		Chandra and Shukla 1981 MnCl2	
44	Rat (CD Neonatal)	24 d (GW)		1 M	10 M (decreased dopamine levels in the hypothalamus, significant decrease in hypothalamic tyrosine hydroxylase activity, significant increase in hypothalamic monoamine oxidase activity)		Deskin et al. 1980 MnCl2	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
45	Rat (CD)	pnd 0-24 (GW)		15	20 M (increased serotonin in hypothalamus, decreased acetylcholinesterase in striatum)		Deskin et al. 1981 MnCl2	
46	Rat	21 d 1 x/d (GW)			11 (significant increase in pulse elicited startle reflex at pnd 21)		Dorman et al. 2000 MnCl2	
47	Rat	100-265 d (W)			390 M (increased dopamine and dopamine metabolite levels)		Eriksson et al. 1987a MnCl2	
48	Rat (Sprague-Dawley)	Gd 7- pnd 21 (F)			8 (hematological changes indicative of Fe deficiency in dams and pups; increased levels of the inhibitory neurotransmitter, GABA, in pup brains)		Garcia et al. 2006 NS	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
49	Rat (Long- Evans)	20 d Gd 0-20 (W)		1248			Kontur and Fechter 1985 MnCl2	No effect on dopamine or norepinephrine turnover in the forebrain or hiindbrain and no effect on development of acoustic startle response.
50	Rat (Long- Evans)	14-21 d (GO)		13.8			Kontur and Fechter 1988 MnCl2	No effect on monoamine levels or their metabolites in the striatum, hypothalamus or nucleus accumbens.
51	Rat	44 d (GW)				150 (ataxia)	Kristensson et al. 1986 MnCl2	
52	Rat (Sprague-Dawley)	30 d (GW)			2.2 M (redistribution of iron in body fluids associated with upregulation of transferritin receptor mRNA and downregulation of ferritin mRNA from the choroid plexus and striatum)		Li et al. 2006 MnCl2	Observed effects likely to be marginally to minimally adverse.

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
53	Rat (Sprague-Dawley)	30 d (GO)		10 M	20 M (significant [p < 0.05] body weight decrease [~9%] and significant [p < 0.05] increase in aspartate, glutamate, glutamine, taurine and GABA in the cerebellum [~20-50%, depending upon the amino acid] of adult rats)		Lipe et al. 1999 MnCl2	
54	Rat (Wistar)	4 wk (W)		15.1 M	26.7 M (increases in striatal Mn levels in cirrhotic rats, striatal neurotransmitter [dopamine or homovanillic acid] increased with or without cirrhosis)		Montes et al. 2001 MnCl2*4H2O	No effect on bilirubins, alanine aminotransferase or collagen at either dose with or without bile duct ligation.
55	Rat (Wistar)	13 wk (W)			611 M (33% reduction in immunoreactive cells with glutamine synthetase in the globus pallidus)		Morello et al. 2007 MnCl2*4H2O	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
56	Rat (F344/N)	13 wk (F)		520 M 618 F			NTP 1993 MnSO4	
57	Rat (Sprague-Dawley)	Gd 1- pnd 30 (W)			120 M (significant decrease in cortical thickness; with high dose rats demonstrating evidence of hyperactivity [significantly increased locomotor activity and increased rearing in an open field] on pnd 17)		Pappas et al. 1997 MnCl2	
58	Rat (Sprague-Dawley)	50 d (NS)			74.9 M (increased serum levels of dopamine sulfate, L-Dopa, and L-p-tyrosine and decreased levels of dopamine)		Ranasinghe et al. 2000 MnSO4	
59	Rat (Sprague-Dawley)	21 d (NS)		4.4 M	13.1 M (subtle behavioral effects [altered balance in the neonatal period and diminished locomotor response to cocaine in adulthood] and neurochemical effects in adulthood [decreased dopamine binding sites in the striatum])		Reichel et al. 2006 MnCl2	No change in negative geotaxis performance; no change in motor activity, coordination, or olfactory orientation tasks.

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
60	Rat (albino)	30 d (F)				5.6 (severely impaired cognitive performance in maze)	Shukakidze et al. 2003 MnCl2*4H2O	
61	Rat (Wistar)	13 wk (W)			3311 M (impaired ability of globus pallidus neurons to survive mechanical dissociation)		Spadoni et al. 2000 (NS)	No neuronal loss or gliosis (GFAP accumulation) was evident in globus pallidus by either histological or immunohistochemical examination).
62	Rat (albino)	90 d (W)			11.8 M (altered brain regional dopamine and serotonin levels and monoamine oxidase activity)		Subhash and Padmashree 1991 MnCl2	
63	Rat (Sprague-Dawley)	21 wk (GW, W)		76 M	153 M (significantly decreased open field activity among restrained rats, impaired spatial learning with or without restraint in a water maze)		Torrente et al. 2005 MnCl2*4H2O	All MnCl2*4H2O rats received 38 mg Mn/kg/d for the first 2 weeks. Other groups at these doses were restrained 2 hours/day.

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
64	Rat (Sprague-Dawley)	20 d (GO)		3.8	7.5 (olfactory discrimination [homing test], and performance on a passive avoidance task; striatal dopamine concentrations were about 50% lower than control values)		Tran et al. 2002a MnCl2	No significant ($p < 0.05$) exposure-related effects on righting test conducted on pnd 6.
65	Rat (Sprague-Dawley)	20 d (GO)		7.5 M			Tran et al. 2002b MnCl2	No statistically significant effects in either burrowing detour task or passive avoidance task.
66	Rat (Wistar)	22 wk (GW)			6.5 M (significant decreases in spatial memory performance, open field locomotor activity and acoustic startle responses; increased latency of sensory evoked potentials)		Vezér et al. 2005, 2007 MnCl2*4H2O	Impairment of spatial memory performance and acoustic startle response persisted through 5-7 weeks without exposure.
67	Rat (CD)	21 d (IN)		13.8			Weber et al. 2002 MnCl2*4H2O	No important changes observed on endpoints of oxidative stress in the brain.

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
68	Mouse (CD-1)	6 mo (F)			2250.7 M (decreased dopamine levels)		Gianutsos and Murray 1982 MnCl2	
69	Mouse (CD-1)	90 d (F)			205 M (decreased locomotor activity)		Gray and Laskey 1980 Mn3O4	
70	Mouse (ddY)	100 d (F)			284 M (decreased motor activity)		Komura and Sakamoto 1991 MnCl2, MnOAc, MnCO3, MnO2	
71	Mouse (C57BL/6N)	1 x/d 8 wk (GW)			43.7 F (increased locomotor activity in Mn-treated mice; increased Mn content of striatum and substantia nigra; decreased striatal dopamine; increased apoptotic neurons expressing nitric oxide synthase, choline acetyltransferase and enkephalin in striatum and globus pallidus; increased astrocytes expressing evidence of nitric oxide formation)		Liu et al. 2006 MnCl2	
72	Mouse (B6C3F1)	13 wk (F)		1950			NTP 1993 MnSO4	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
73	Rat (Long- Evans)	20 d Gd 0-20 (W)		624 F	1248 F (decreased litter weight)		Kontur and Fechter 1985 MnCl2	
74	Rat (Long- Evans)	100-224 d (F)		20 M 55 F	55 M (significantly decreased testicular weight with low-Fe diet)	180 F (significantly decreased [~25%] pregnancy rate)	Laskey et al. 1982 Mn3O4	No effect on litter size, ovulations, resorptions, preimplantation deaths or mean fetal weights. No effect on testosterone or LH levels.
75	Rat (Sprague-Dawley)	Gd 1- pnd 30 (W)		620 F			Pappas et al. 1997 MnCl2	Mn exposure of pregnant dams did not affect litter sizes or sex ratios of pups at delivery.
76	Rat (Sprague-Dawley)	63 d (GW)		68.6 M	137.2 M (increased incidences of testicular degeneration in male rats)		Ponnapakkam et al. 2003c MnOAc*4H20	
77	Rat (Sprague-Dawley)	Gd 0-21 (GW)			22 F (increase in relative weight of liver, thymus, and brain)	33 F (post implantation loss)	Szakmary et al. 1995 MnCl2	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
78	Mouse Swiss	12 wk (W)		154 M		309 M (statistically significantly impaired male fertility)	Elbetieha et al. 2001 MnCl2	
79	Mouse Swiss	12 wk (W)			44 F (increased uterine weights relative to body weight)	277 F (implantation number reduced by 17% and the number of viable fetuses reduced by 19% from the control value)	Elbetieha et al. 2001 MnCl2	
80	Mouse (CD-1)	90 d (F)			205 M (delayed growth of testes and sex accessory glands)		Gray and Laskey 1980 Mn3O4	
81	Mouse (B6C3F1)	13 wk (F)		1950			NTP 1993 MnSO4	
82	Mouse (CD-1)	1 x/d 43 d (GW)		2.4 M	4.8 M (decreased sperm motility and sperm counts)		Ponnapakkam et al. 2003a MnOAc	No effects on fertility at 9.6 mg/kg/day when treated males were mated with unexposed females.
83	Mouse (CD-1)	1 x/d 43 d (GW)		9.6 M			Ponnapakkam et al. 2003a MnOAc	Fertility endpoints were not affected at 9.6 mg Mn/kg/day. Fertility was not affected when exposed males mated with nonexposed females.

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
84	Rabbit (New Zealand)	Gd 6-20 (GW)		33 F			Szakmary et al. 1995 MnCl2	
Developmental								
85	Monkey (Rhesus)	4 mo (F)			107.5 M (minimally adverse effects in soy and soy+Mn groups: decreased activity during sleep at 4 months and decreased play activity between 1-1.5 months)		Golub et al. 2005 MnCl2	No marked differences from controls in gross motor maturation, growth, or cognitive tests. No effect of Mn on CSF DA, HVA or 5-HIAA.
86	Rat (CD)	pnd 1-49 (W)		11	22 (~20% decrease in body weight at pnd 49)		Brenneman et al. 1999 MnCl2	
87	Rat (CD)	pnd 1-49 (GW)		11	22 (increased spontaneous motor activity)		Brenneman et al. 1999 MnCl2	
88	Rat	21 d 1 x/d (GW)			11 (significant increase in pulse elicited startle reflex at pnd 21)		Dorman et al. 2000 MnCl2	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
89	Rat (Sprague-Dawley)	Gd 7- pnd 21 (F)			8 (hematological changes indicative of Fe deficiency in dams and pups; increased levels of the inhibitory neurotrnasmitter, GABA, in pup brains)		Garcia et al. 2006 NS	
90	Rat (Sprague-Dawley)	17 d (F)		8			Garcia et al. 2007 NS	
91	Rat	44 d (GW)				150 (ataxia)	Kristensson et al. 1986 MnCl2	
92	Rat (Sprague-Dawley)	Gd 1- pnd 30 (W)		120 M	620 M (transient decrease (~20%) in pup body weight on pnd 9-24; difference not apparent on pnd 90)		Pappas et al. 1997 MnCl2	No maternal toxicity from Mn; brain Mn not significantly elevated at 120 mg/kg/day; no effects on brain levels of serotonin or 5-HIAA.
93	Rat (Sprague-Dawley)	21 d (NS)		4.4 M	13.1 M (subtle behavioral effects [altered balance in the neonatal period and diminished locomotor response to cocaine in adulthood] and neurochemical effects in adulthood [decreased dopamine binding sites in the striatum])		Reichel et al. 2006 MnCl2	No change in negative geotaxis performance; no change in motor activity, coordination, or olfactory orientation tasks.

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
94	Rat (Sprague-Dawley)	Gd 0-21 (GW)			33 (increased retardation in skeletal/organ development)		Szakmary et al. 1995 MnCl2	
95	Rat (Sprague-Dawley)	20 d (GO)		3.8	7.5 (decreased performance in the olfactory discrimination [homing test] and passive avoidance task; striatal dopamine concentrations were about 50% lower than control values)		Tran et al. 2002a MnCl2	
96	Rat (Sprague-Dawley)	20 d (GO)		7.5 M			Tran et al. 2002b MnCl2	No statistically significant ($p < 0.05$) effects in either burrowing detour task pnd 50-56) or passive avoidance task (pnd 60-69).
97	Rat (CD)	21 d (IN)		13.8			Weber et al. 2002 MnCl2*4H2O	No obvious effect of oral exposure during pnd 1-21 on biochemical measures related to oxidative stress in cerebrocortical or cerebellar regions.

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
98	Rabbit (New Zealand)	Gd 6-20 (GW)		33			Szakmary et al. 1995 MnCl2	No effect on fetal body weights or skeletal anomalies in fetuses.
CHRONIC EXPOSURE								
Death								
99	Human	</= 1 yr (W)				0.26 (increased fatality among children <1 year of age)	Hafeman et al. 2007 NS	
100	Rat (F344/N)	2 yr (F)				200 M (14% survival compared to 49% in controls)	NTP 1993 MnSO4	
Systemic								
101	Rat (F344/N)	2 yr (F)	Resp	200 M 232 F			NTP 1993 MnSO4	
			Cardio	65 M				
			Gastro	200 M 232 F				
			Hemato	65 M				
			Renal		200 M (increased severity of chronic progressive nephropathy)			
			Bd Wt		200 M (body weight 10% lower than controls)			

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
102	Mouse (B6C3F1)	2 yr (F)	Resp	585 M 731 F			NTP 1993 MnSO4	
			Cardio	585 M 731 F				
			Gastro	177 M 226 F	585 M (hyperplasia, erosion)	732 F (ulceration and inflammation of the forestomach)		
			Hemato	177 M 731 F	585 M (increased hematocrit, hemoglobin, and erythrocyte counts)			
			Musc/skel	585 M 731 F				
			Hepatic	585 M 731 F				
			Renal	585 M 731 F				
			Endocr		585 M (thyroid follicular hyperplasia and dilatation) 64 F (thyroid follicular hyperplasia)			
			Dermal	584 M 732 F				
			Bd Wt	584 M 223 F	732 F (13% lower body weight than controls)			

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
103	Rat (F344/N)	2 yr (F)		200 M 232 F			NTP 1993 MnSO4	
104	Mouse (B6C3F1)	2 yr (F)		585 M 731 F			NTP 1993 MnSO4	
Neurological								
105	Human	50 yr (W)		0.0048	0.059 (mild neurological signs)		Kondakis et al. 1989 NS	
106	Human	~68 d intermittently x 5 yr (W)				0.103 F (pica, emotional lability, personality changes, speech impairments, loss of balance and coordination, inability to walk)	Sahni et al. 2007 NS	
107	Human	10 yr or more (W)		0.009			Vieregge et al. 1995 NS	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
108	Human	10 yr (W)		0.04	0.07 (significantly reduced performance on Full-Scale IQ test, performance and verbal tests in children)		Wasserman et al. 2006 NS	No statistically significant effects on Full-Scale IQ testing, performance or verbal tests.
109	Human	5 yr (W)			0.06 M (Mn possibly producing deficit in free retrieval skills, affecting general, verbal and visual memory and learning skills; inattentiveness; lack of focus in classroom)		Woolf et al. 2002 NS	
110	Monkey (Rhesus)	18 mo (GW)				6.9 M (weakness, rigidity, neuronal loss and depigmentation of the substantia niagra)	Gupta et al. 1980 MnCl2	
111	Rat (Wistar)	2 yr (W)			40 (altered neurotransmitter uptake)		Lai et al. 1984 MnCl2	
112	Rat (Sprague-Dawley)	65 wk (W)			40 M (increased activity)		Nachtman et al. 1986 MnCl2	
113	Mouse (ddY)	3 gen (W)				10.6 (altered gait)	Ishizuka et al. 1991 MnCl2*4H2O	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
114	Mouse (ddY)	12 mo (F)			275 M (decreased locomotor activity)		Komura and Sakamoto 1992a MnOAc	
115	Mouse (ddY)	12 mo (F)			275 M (decreased locomotor activity)		Komura and Sakamoto 1992a MnCO3	
116	Mouse (ddY)	12 mo (F)			275 M (decreased dopamine and increased homovanilic acid in brain; decreased norepinephrine and epinephrine; decreased locomotor activity)		Komura and Sakamoto 1992a MnO2	
117	Mouse (ddY)	12 mo (F)			275 M (decreased locomotor activity)		Komura and Sakamoto 1992a MnCl2	
118	Mouse (ddY)	12 mo (F)			45 M (significant [p < 0.05] decreases in dopamine and homovanillic acid levels in the corpus striatum)		Komura and Sakamoto 1994 MnCl2	

Table 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral (continued)

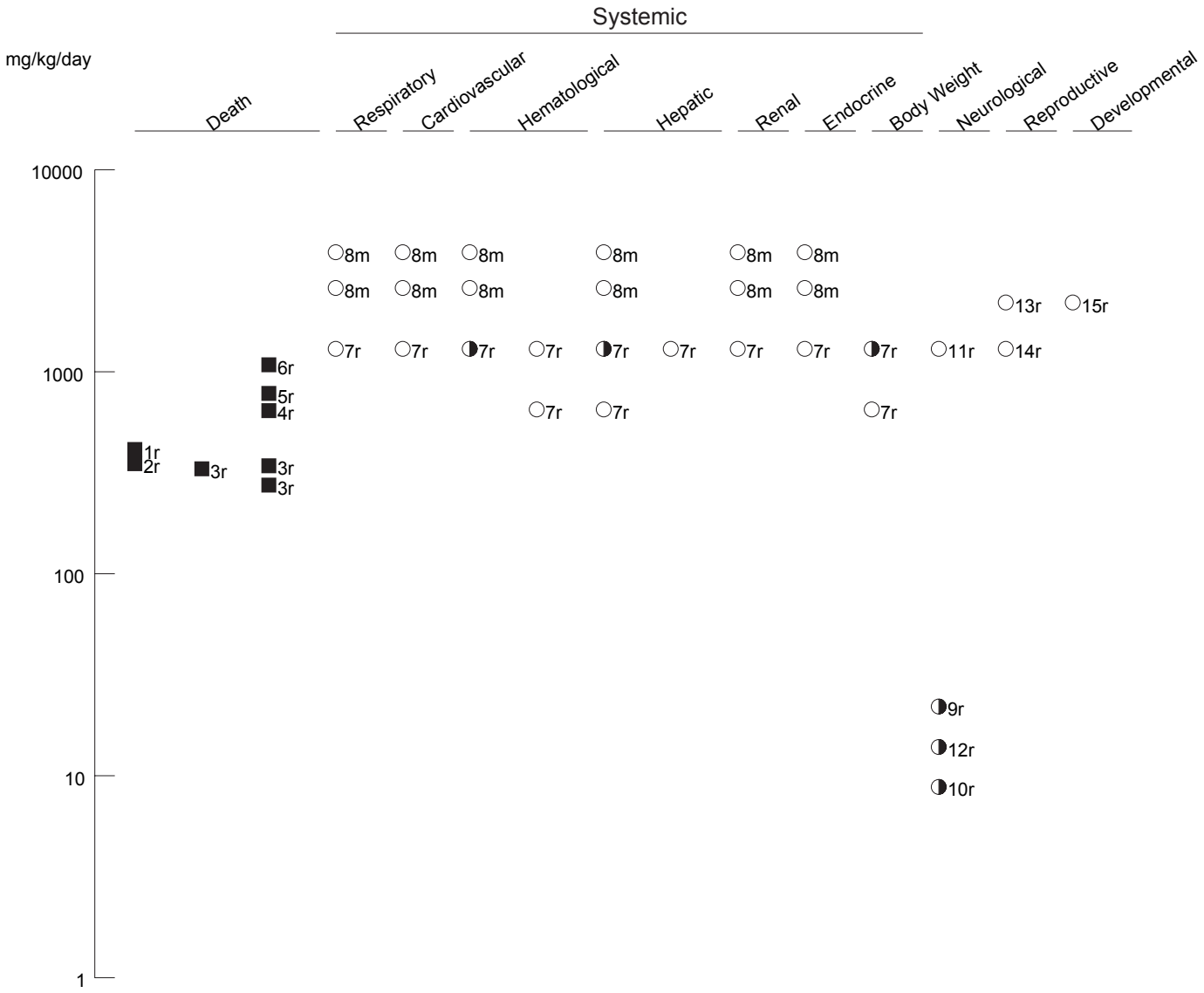
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
119	Mouse (B6C3F1)	2 yr (F)		585 M 731 F			NTP 1993 MnSO4	
Reproductive								
120	Rat (F344/N)	2 yr (F)		200 M 232 F			NTP 1993 MnSO4	
121	Mouse (B6C3F1)	2 yr (F)		585 M 731 F			NTP 1993 MnSO4	
Developmental								
122	Rat (ITRC)	1 gen (W)			420 M (altered neurotransmitter levels)		Ali et al. 1985 MnCl2*4H2O	

a The number corresponds to entries in Figure 3-2.

ATPase = adenosine triphosphatase; Bd Wt = body weight; Cardio = cardiovascular; CSF = cerebrospinal fluid; d = day(s); DA = dopamine; DOPAC = dihydroxyphenylacetic acid; Endocr = endocrine; F = Female; (F) = feed; (G) = gavage; GABA = gamma-aminobutyric acid; Gastro = gastrointestinal; Gd = gestational day; GFAP = glial fibrillary acidic protein; Gn pig = guinea pig; (GO) = gavage in oil; (GW) = gavage in water; GTPase = glucose-6-phosphatase; Hemato = hematological; 5-HIAA = 5-hydroxy-indoleacetic acid; HVA = homovanillic acid; Immuno/Lymphoret = immunological/lymphoreticular; (IN) = ingestion; LD50 = lethal dose, 50% kill; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; TH = tyrosine hydroxylase (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral

Acute (≤14 days)



c-Cat d-Dog r-Rat p-Pig q-Cow
-Humans k-Monkey m-Mouse h-Rabbit a-Sheep
f-Ferret j-Pigeon e-Gerbil s-Hamster g-Guinea Pig
n-Mink o-Other

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◮ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral *(Continued)*

Intermediate (15-364 days)

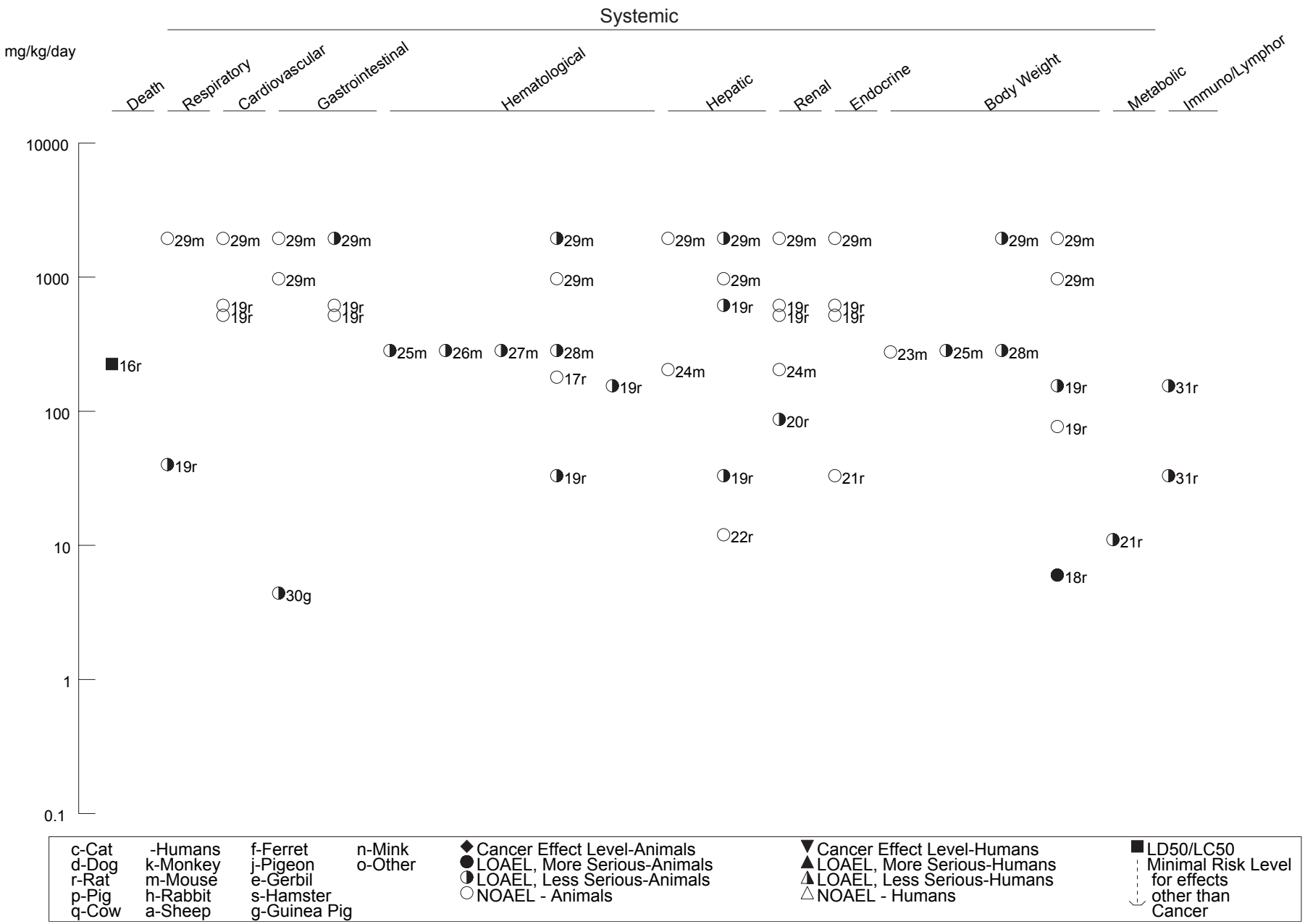


Figure 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral *(Continued)*

Intermediate (15-364 days)

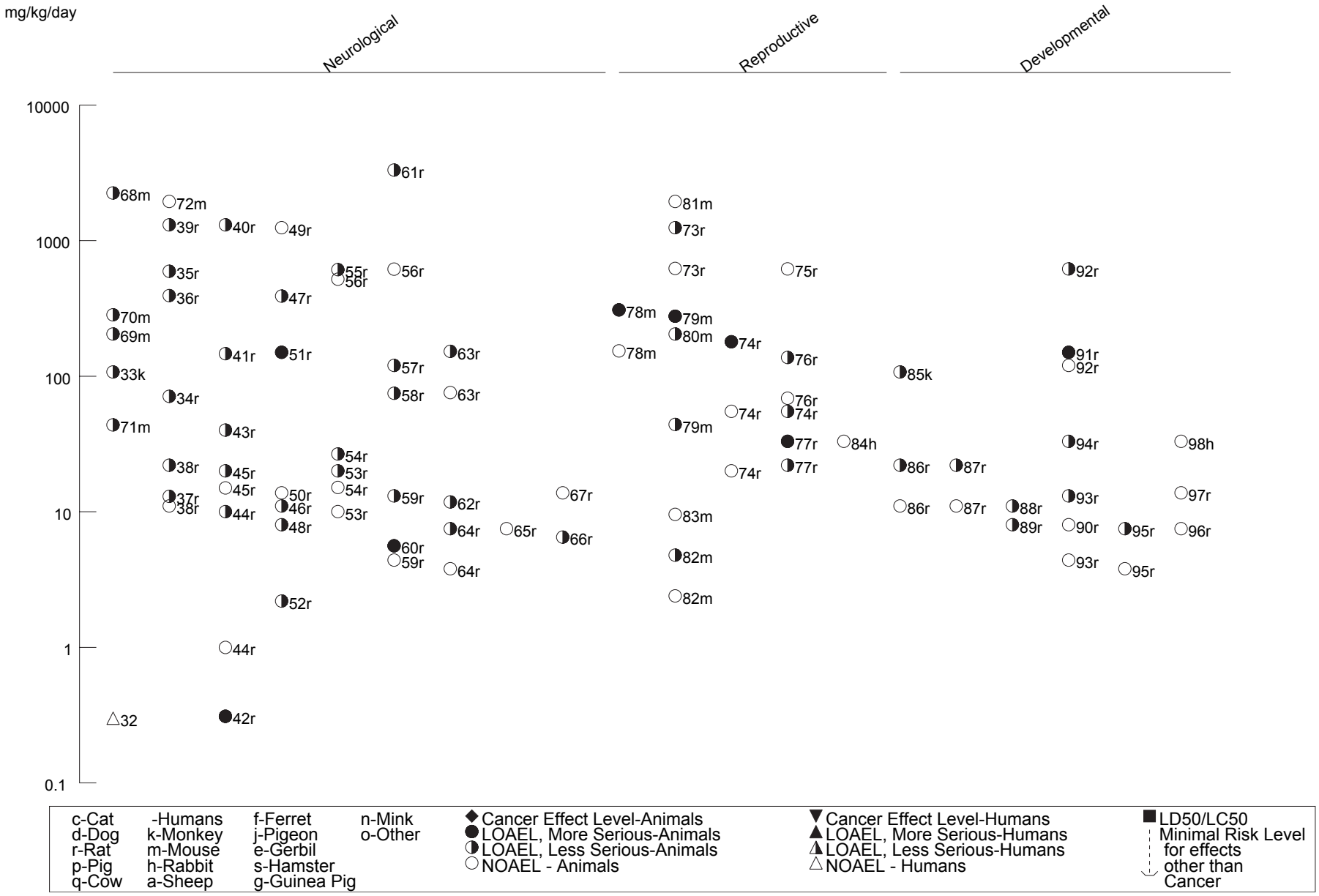


Figure 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral *(Continued)*

Chronic (≥365 days)

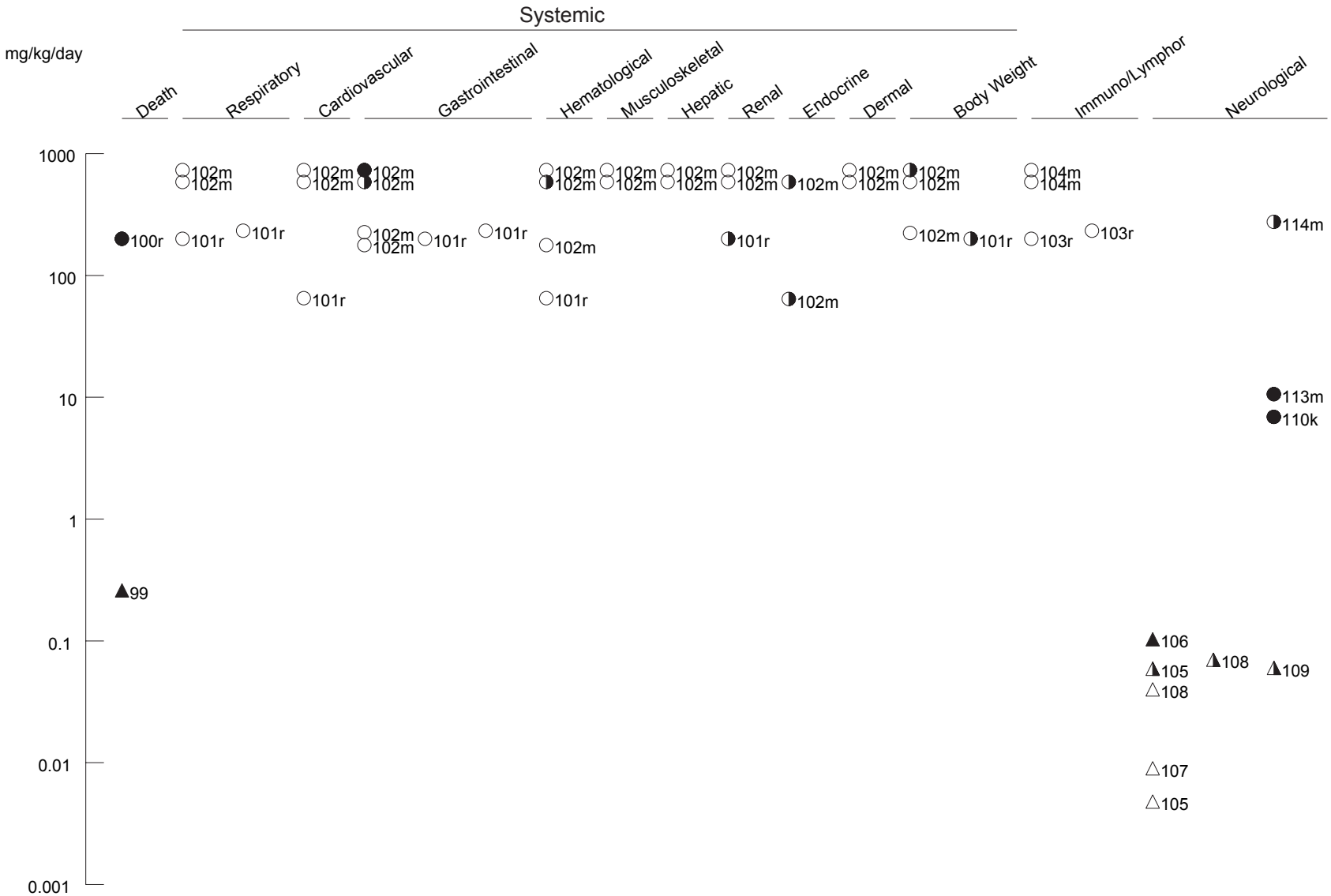


Figure 3-2 Levels of Significant Exposure to Inorganic Manganese - Oral *(Continued)*

Chronic (≥365 days)

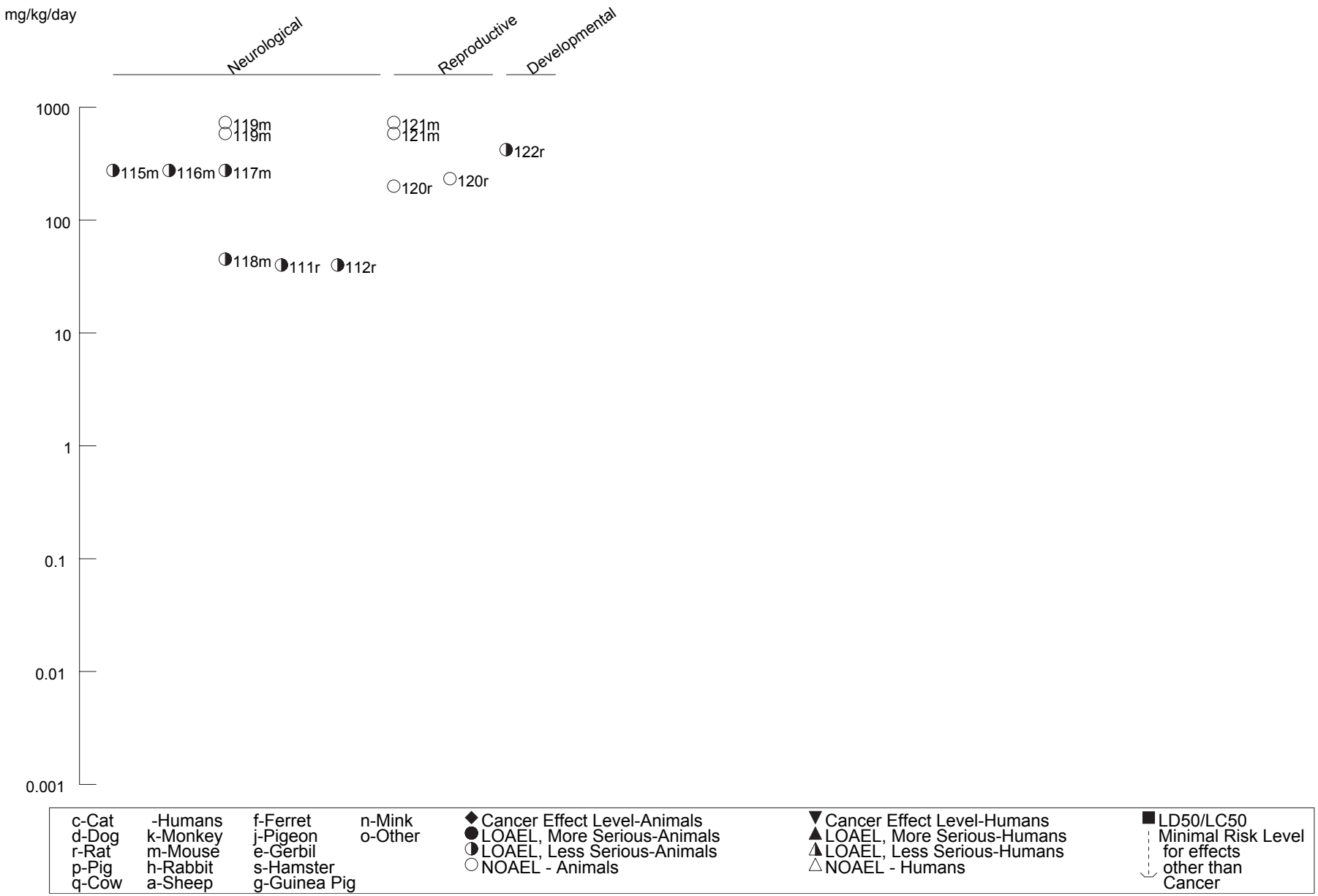


Table 3-3 Levels of Significant Exposure to MMT - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (GO)				12.5 M (increase in mortality, LD50=50 mg MMT/kg or 13 mg Mn/kg)	Hanzlik et al. 1980a	
2	Rat (Sprague-Dawley)	1 x				15 (LD50)	Hinderer 1979	
3	Rat (COBS)	1 x (GO)				14.6 (LD50)	Hysell et al. 1974	
4	Mouse (CD-1)	1 x (GO)				58 F (LD50)	Hinderer 1979	
Systemic								
5	Rat (Sprague-Dawley)	once (GO)	Resp			30 M (distended lungs with bloody fluid, hemorrhage, perivascular and alveolar edema)	Hanzlik et al. 1980a	
6	Rat (COBS)	1 x (GO)	Resp	7.6		11.3 (severe fibrinopurulent pneumonia with prominent macrophage infiltrate of lungs)	Hysell et al. 1974	All rats from 3.8 and 7.6 mg Mn/kg bw/d groups survived and appeared normal 14 days post-exposure.
			Hepatic	7.6		11.3 (hepatic parenchymal necrosis and leukocytic infiltration)		

Table 3-3 Levels of Significant Exposure to MMT - Oral (continued)

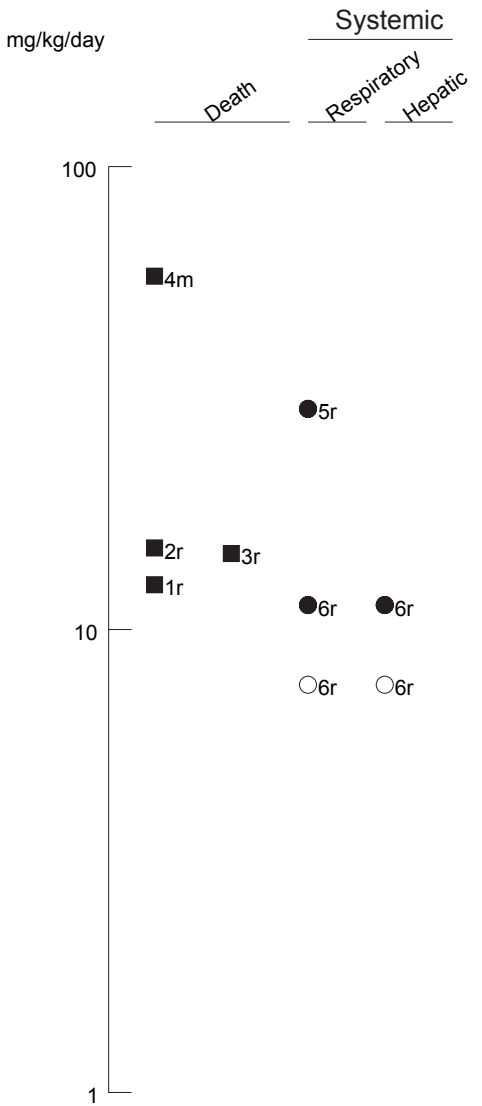
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
7	Mouse (ddY)	1 x/d 12 mo (F)	Bd Wt		11 M (>10% decrease in body weight in exposed group)		Komura and Sakamoto 1992b	
Neurological								
8	Mouse (ddY)	1 x/d 12 mo (F)			11 M (increase in spontaneous motor activity on day 80)		Komura and Sakamoto 1992b	
9	Mouse (ddY)	12 mo (F)			11 M (changes in brain neurochemistry)		Komura and Sakamoto 1994	

a The number corresponds to entries in Figure 3-3.

Bd Wt = body weight; d = day(s); (F) = feed; F = Female; GO) = gavage in oil; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; pnd = post-natal day; Resp = respiratory; x = time(s)

Figure 3-3 Levels of Significant Exposure to MMT - Oral

Acute (≤14 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

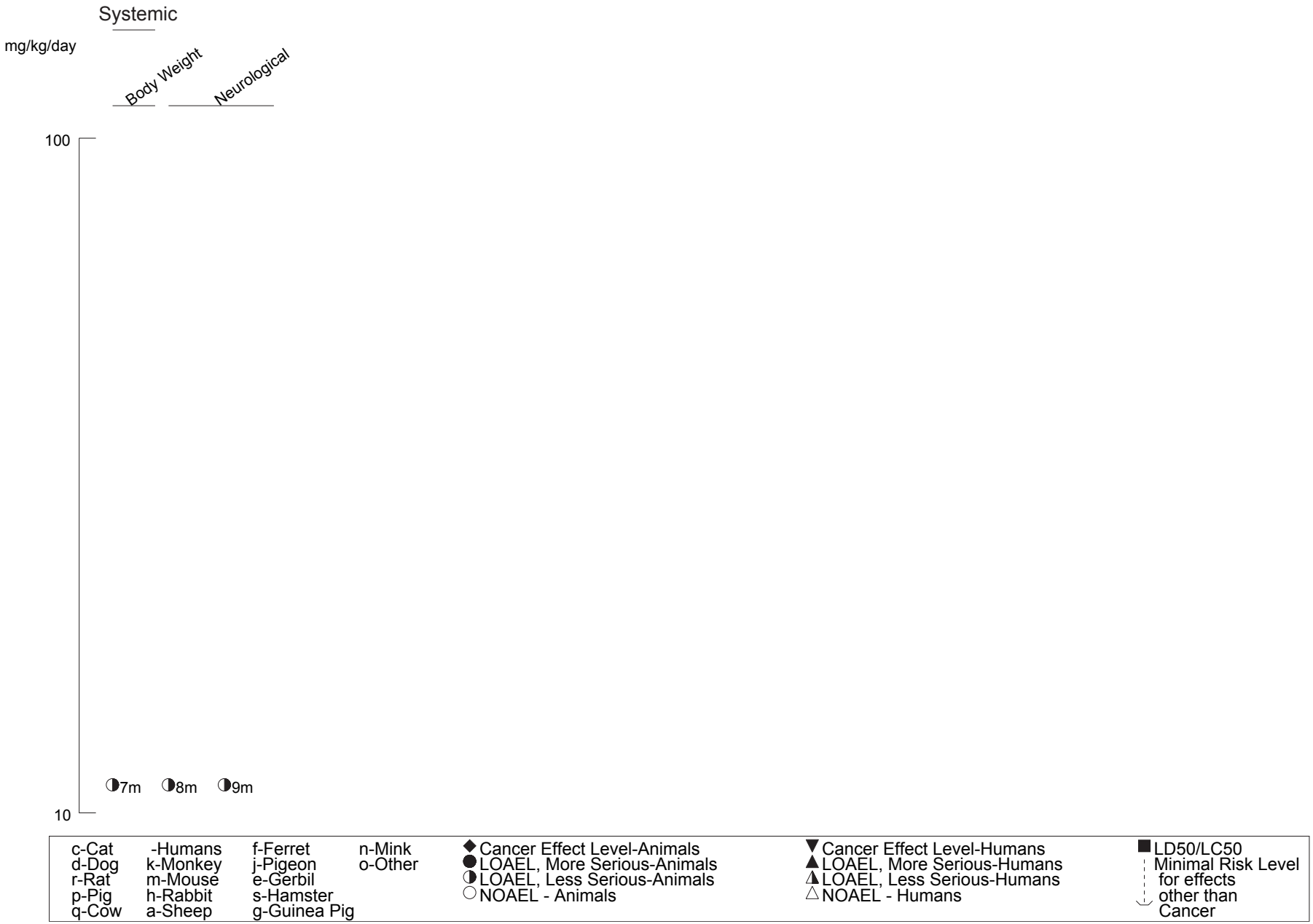
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-3 Levels of Significant Exposure to MMT - Oral *(Continued)*

Chronic (≥365 days)



In contrast to these studies, when exposure is by gavage (usually as highly concentrated solutions of manganese chloride in water), measured LD_{50} values for 1–21 days of exposure range from 225 to 1,082 mg manganese/kg/day in mice and rats (Holbrook et al. 1975; Kostial et al. 1978, 1989; Rehnberg et al. 1980; Singh and Junnarkar 1991; Smyth et al. 1969). These results suggest that gavage dosing with a bolus of a concentrated soluble manganese compound in water may not be a good model for determining the toxic effects of manganese ingested by humans from environmental sources. Bolus dosing produced death in animals at concentrations near the daily dose levels tolerated in food or drinking water by the same strains and species of animals subjected to longer durations of exposure. It is possible that bolus dosing circumvents the homeostatic control of manganese absorption. It should be noted that the concentrations used in the bolus dosing studies are much higher than even excess levels to which certain humans are typically exposed.

In a study where young pigs were fed a diet moderately high (1.7 mg manganese/kg/day) in manganese but deficient in magnesium, all eight pigs consuming the high manganese diet died within 5 weeks following convulsive seizures; only two of the pigs in a group without supplemental manganese died (Miller et al. 2000). Further studies suggested that high dietary manganese could exacerbate magnesium deficiency in heart muscle, thus creating a complicating factor in the deaths of the magnesium-deficient pigs (Miller et al. 2000).

In conclusion, route of exposure and animal species and strain differences, as well as sex, may account for some of the observed variations in the lethality of manganese. In addition, deficiencies in certain essential nutrients, such as magnesium, may increase the lethal potential of excess manganese.

No studies were located concerning death in humans following ingestion of MMT.

MMT, dissolved in oil and administered by gavage, was found to have LD_{50} values of 15 mg manganese/kg in the male and female Sprague-Dawley rat and 58 mg manganese/kg in the adult female CD-1 mouse (Hinderer 1979).

Hysell et al. (1974) administered via gavage increasing amounts of MMT (dissolved in oil) to adult COBS rats, 10 animals/group. No lethality was observed at the lowest two doses of 3.8 and 7.5 mg manganese/kg, but 5/10 rats died within 2–6 days postdosing at a dose of 11.3 mg manganese/kg. Increasing numbers of rats died at higher doses, with decreasing times of death post-dosing; complete

mortality occurred at the highest dose of 37.5 mg manganese/kg. The survivors appeared normal by 14 days. The LD_{50} (14-day) was estimated at 14.6 mg manganese/kg.

Hanzlik et al. (1980a) determined the 14-day LD_{50} for purified MMT administered in corn oil via gavage to adult male Sprague-Dawley rats to be 12.5 mg manganese/kg (95% confidence interval, 9.5–16.8 mg manganese/kg). The animals survived similar times post-dosing as those in the Hysell et al. (1974) study.

All LD_{50} values from each reliable study for death in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

3.2.2.2 Systemic Effects

In general, there is a lack of data concerning systemic toxic effects in humans who have ingested manganese. This is likely due to the strong homeostatic control the body exerts on the amount of manganese absorbed following oral exposure; this control protects the body from the toxic effects of excess manganese. Studies in humans and animals provide limited data regarding the effects of manganese ingestion on systemic target tissues. This information is discussed below and is organized by target tissue. Table 3-3 and Figure 3-3 present the highest NOAEL and all LOAEL values from each reliable study for these effects for each species and each duration category.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to inorganic manganese.

No respiratory effects were reported in mice fed up to 3,900 mg manganese/kg/day (as manganese sulfate) or rats fed 1,300 mg manganese/kg/day (as manganese sulfate) for 14 days (NTP 1993). Male rats fed manganese sulfate for 13 weeks showed no respiratory effects at 520 mg manganese/kg/day; however, females exhibited decreased lung weight at 40–618 mg manganese/kg/day (NTP 1993). No respiratory effects were noted in mice of either sex fed 122–1,950 mg manganese/kg/day (as manganese sulfate) for 13 weeks (NTP 1993), in rats fed up to 232 mg manganese/kg/day (as manganese sulfate), or in mice fed up to 731 mg manganese/kg/day (as manganese sulfate) for 2 years (NTP 1993).

The lungs of adult male Sprague-Dawley rats administered one dose of MMT via gavage in corn oil (31.25 mg manganese/kg) showed signs of hemorrhage and alveolar and perivascular edema, with an accumulation of proteinaceous material in the alveoli. As early as 12 hours following gavage

administration of this same dose, the lung/body weight ratio increased to 2.5 times the control value (Hanzlik et al. 1980). Hinderer (1979) observed dark red lungs in Sprague-Dawley rats and CD-1 mice administered sublethal doses (values unspecified) of MMT in an acute toxicity study. Gross necropsy of the lungs of COBS rats administered one dose of MMT in Wesson oil (dose range, 20–37.5 mg manganese/kg) revealed severe congestion and the release of a serosanguinous fluid upon sectioning; histopathology of lungs from rats dying within 24 hours post-exposure showed severe congestion, perivascular and alveolar edema, and alveolar hemorrhage (Hysell et al. 1974). Sections of lungs from rats surviving until 14 days post-exposure revealed extensive areas of consolidation, thickened alveolar septa and focal areas of alveolar macrophage activity.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to inorganic manganese.

In a 1993 National Toxicology Program (NTP) study, no cardiovascular effects (pathological lesions) were observed in mice or rats fed 3,900 or 1,300 mg manganese/kg/day, respectively, for 14 days. No cardiovascular effects were observed in rats or mice exposed for 13 weeks to doses as high as 1,950 mg manganese/kg/day (as manganese sulfate) or for 2 years to doses as high as 731 mg manganese/kg/day (as manganese sulfate) (NTP 1993).

In a study of weanling male Sprague-Dawley rats provided with a diet supplemented with 55 mg manganese/kg/day for 14 weeks, Kalea et al. (2006) found that the level of uronic acid in aortas of the manganese-supplemented group was significantly ($p<0.05$) higher than in a group of rats fed a diet with adequate manganese (5.5 mg manganese/kg/day). Among heparan sulfate glycosaminoglycans, aortas from manganese-supplemented rats contained higher concentrations of total galactosaminoglycans and decreased concentration of hyaluronan and heparan sulfate (50% less heparan sulfate) when compared to aortas from rats consuming diets with adequate manganese. Heparan sulfate chains of aortas from manganese-supplemented rats contained 41% higher concentration of non-sulfated units compared to those of rats fed the adequate manganese diet (Kalea et al. 2006). These results raise concern about the potential for manganese to influence vascular chemistry in deleterious ways, creating increased vulnerability to cardiovascular events.

In the course of investigating a mechanism to explain the sudden deaths in pigs from high doses of manganese (Miller et al. 2000), studies were conducted in which pigs were fed either low (3.4 mg/kg/day) or adequate dietary magnesium (6.8 mg/kg/day) along with high (55 mg/kg/day) or low doses

(5.5 mg/kg/day) of manganese (Miller et al. 2004). No differences in heart muscle ultrastructure were observed; however, marked myocardial necrosis and mitochrondrial swelling were observed in pigs fed high dietary manganese in combination with low magnesium (13.9 mg magnesium/kg/day; Miller et al. 2004). In pigs fed high manganese and adequate magnesium, no swelling of myocardial mitrochondria was observed. These results suggest that high manganese, when fed in combination with low magnesium, disrupts mitochondrial ultrastructure (Miller et al. 2004). In another related study, when rats were provided with high dietary manganese (13.8 mg manganese/kg/day as manganese carbonate) for 8 weeks, heart muscle oxygen consumption was depressed, although no effects of manganese on hematologic variables were observed (Miller et al. 2006). No effects of manganese were observed on heart muscle activities for Ca^{+2} ATPase, liver glutathione peroxidase, or brain glutathione peroxidase at doses as high as 55 mg manganese/kg/day (Miller et al. 2006). The depression in heart muscle oxygen consumption produced by high dietary manganese presents yet another possible mechanism by which high doses of manganese can produce adverse cardiovascular events.

No studies were located regarding the cardiotoxic effects of MMT in either humans or animals following oral exposure.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to manganese, except for one case report of a child who accidentally ingested some potassium permanganate (Southwood et al. 1987). This led to severe local corrosion of the mouth, esophagus, and stomach due to the caustic effects of potassium permanganate on the tissue, but there was no evidence of systemic toxicity.

Adverse gastrointestinal effects have been reported in guinea pigs and mice but not in rats. Guinea pigs administered 4.4 mg manganese/kg/day (as manganese chloride by gavage) did not suffer any gross abnormalities in either the stomach or small or large intestines as a result of treatment but did have patchy necrosis and decreased adenosine triphosphatase and glucose 6-phosphatase levels in both the stomach and small intestine (Chandra and Imam 1973). This study differs from the others in its delivery of manganese (by gavage); the gavage treatment may have partially or completely contributed to the adverse effects seen in the stomach and small intestine of the guinea pigs. No gastrointestinal effects were observed in female mice fed 1,950 mg manganese/kg/day (as manganese sulfate in food) or rats fed up to 618 mg manganese/kg/day (as manganese sulfate in food) for 13 weeks, but male mice exhibited mild hyperplasia and hyperkeratosis of the forestomach at 1,950 mg manganese/kg/day, also in food (NTP 1993).

In a 1993 NTP study, rats fed as much as 232 mg manganese/kg/day (as manganese sulfate) for 2 years showed no gastrointestinal effects; however, mice treated with manganese sulfate for 2 years exhibited hyperplasia, erosion, and inflammation of the forestomach at 585 mg manganese/kg/day for males and 731 mg manganese/kg/day for females. The acanthosis was judged by the authors to be a result of direct irritation of the gastrointestinal epithelium and to be of minor consequence.

No studies were located concerning gastrointestinal effects following oral exposure to MMT in humans. Hinderer (1979) observed discolored intestinal tracts in Sprague-Dawley rats and fluid-filled intestines and spotting of the intestine in CD-1 mice dosed by gavage with high concentrations (values not provided) of MMT in a 14-day toxicity study. Hysell et al. (1974) observed that single lethal doses of 20–37.5 mg manganese/kg (as MMT, given by gavage) produced small intestines that were distended with clear watery contents and thin, friable walls.

Hematological Effects. In a dietary study with female subjects (Davis and Greger 1992), no changes in hematocrit, serum transferrin, or serum ferritin were reported following supplementation with 0.25 mg manganese/kg/day for 119 days. Vieregge et al. (1995) found no effects on hemoglobin, ceruloplasmin, or copper and iron levels in serum for a population of 40-year-old people who had ingested at least 0.3 mg manganese/L in drinking water for a minimum of 10 years. These data indicate that exposure to increased manganese in water did not result in observable hematological toxicity.

Alterations in hematological parameters have been reported in rats and mice, although they were found to vary depending on species, duration, and the form of manganese administered. No conclusive evidence regarding a significant functional deficit has been reported. In mice fed 284 mg manganese/kg/day for 100 days, red blood cell count was decreased by manganese acetate and manganese chloride; white blood cell count was decreased by manganese acetate, manganese chloride, and manganese dioxide; and hematocrit was decreased by manganese carbonate (Komura and Sakamoto 1991). However, manganese carbonate had no effect on red blood cells or white blood cells, manganese dioxide had no effect on red blood cells or total hematocrit, and manganese acetate and manganese chloride had no effect on total hematocrit. It has been suggested that the manganese-related effects on red blood cells may be related to the displacement of iron by manganese. The significance of the other hematological effects was not noted. In a study in rats and mice dosed with manganese sulfate for 14 days, 13 weeks, or 2 years, minor changes in hematology parameters were reported; these changes varied depending on species, dose, and duration, and the study authors did not consider them to be clearly related to compound administration

(NTP 1993). No significant hematological effects were observed in mice exposed to 180 mg manganese/kg/day (as manganese tetroxide) for 224 days (Carter et al. 1980). In a study where male Sprague-Dawley rats were fed 55 mg manganese/kg/day as manganese carbonate for 8 weeks, significantly decreased hematocrit and hemoglobin levels were observed (Miller et al. 2006). However, an even lower level of dietary manganese carbonate (35.8 mg manganese/kg/day) fed to male Sprague-Dawley rats in a diet containing a relatively low concentration of magnesium (200 mg magnesium/kg feed/day) for 4 weeks also produced significantly decreased hematocrit and hemoglobin levels (Miller et al. 2006). Thus, the potential for dietary manganese to produce adverse effects on red blood cells may be further modulated by the relative availability of magnesium in the diet.

No studies were located concerning hematological effects following oral exposure to MMT in humans or animals.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to inorganic manganese.

In young rats, high concentrations of manganese chloride in the diet (218–437 mg manganese/kg/day) led to rickets (Svensson et al. 1985, 1987); however, this was found to be due to a phosphate deficiency stemming from precipitation of manganese phosphate salt ($MnHPO_4$) in the intestine rather than to a direct biological effect of manganese on bone formation. No significant musculoskeletal effects were observed in mice or rats fed up to 731 mg manganese/kg/day for 2 years (NTP 1993).

No studies were located concerning musculoskeletal effects following oral exposure to MMT in humans or animals.

Hepatic Effects. A single study of human oral exposure of manganese investigated potential hepatotoxicity by analyzing liver enzymes in serum. Vieregge et al. (1995) reported no effects on bilirubin, alkaline phosphatase, glutamic pyruvic transaminase, glutamic oxalacetic transaminase, or gamma glutamyl transferase in humans, ≥40 years old, who had ingested well water containing ≥0.30 mg/L for at least 10 years. These limited data indicate that chronic exposure to elevated levels of manganese did not result in observable liver toxicity in this population.

In animals, a variety of histological changes in subcellular organelles (e.g., rough and smooth endoplasmic reticulum, Golgi apparatus) were observed in the livers of rats exposed to 12 mg

manganese/kg/day for 10 weeks (as manganese chloride) (Wassermann and Wassermann 1977). However, these changes were not considered to be adverse but to be adaptive, possibly in response to increased manganese excretion in the bile (see Section 3.4.4). Reductions in liver weight have also been reported in male Fischer 344 rats fed 1,300 mg manganese/kg/day (as manganese sulfate) for 14 days. However, these effects were not seen in $B6C3F_1$ mice fed dosages up to 3,900 mg manganese/kg/day (as manganese sulfate) for 14 days (NTP 1993). In rats fed up to 618 mg manganese/kg/day (as manganese sulfate) for 13 weeks, decreased liver weights were reported in males at $\geq$33 mg manganese/kg/day and females at 618 mg manganese/kg/day (NTP 1993). When mice were fed 122–1,950 mg manganese/kg/day (as manganese sulfate) for 13 weeks, the females showed no hepatic effects; however, the males exhibited both relative and absolute reduced liver weights at 1,950 mg manganese/kg/day (NTP 1993). In CD-1 mice, no hepatic changes were seen in males fed 205 mg manganese/kg/day (as manganese tetroxide) (Gray and Laskey 1980). No significant hepatic histological changes were observed in either mice or rats exposed for 2 years, with rats fed up to 232 mg manganese/kg/day (as manganese sulfate), and mice fed up to 731 mg manganese/kg/day (as manganese sulfate) (NTP 1993).

There are no studies concerning hepatic effects following oral exposure to MMT in humans.

Hinderer (1979) observed mottling of the liver in CD-1 mice administered high doses (unspecified) of MMT via gavage in a 14-day acute toxicity study. Histological evaluation of livers of adult male Sprague-Dawley rats administered 31.3 mg manganese/kg/day (as MMT) revealed scattered hepatocytes throughout the lobule that contained cytoplasmic vacuoles (Hanzlik et al. 1980b). Twelve hours after administration of the same dose, no changes in plasma glutamic pyruvic transaminase (GPT) or liver glucose 6-phosphatase (G6P) activities were observed. After the death of 8/14 animals at this dose level (24 hours post-dosing), there were still no changes in plasma GPT, liver G6P, or hepatic triglycerides (Hanzlik et al. 1980b). Hysell et al. (1974) observed that COBS rats that were gavage-dosed with 20–37.5 mg manganese/kg (as MMT) once and died within 24 hours post-dosing had livers with acute centrolobular passive congestion. This damage progressed to hepatic parenchymal necrosis and leukocytic infiltration in those rats surviving 48–72 hours (15–37.5 mg manganese/kg/day), and extensive cytoplasmic vacuolar change in rats surviving to 14 days.

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to inorganic manganese.

In animal studies, no significant renal histopathological changes were observed in any of the following: mice and rats fed up to 3,900 or 1,300 mg manganese/kg/day (as manganese sulfate) for 14 days (NTP 1993); mice exposed to 205 mg manganese/kg/day (as manganese tetroxide) in their diet for 90 days (Gray and Laskey 1980); mice or rats fed up to 1,950 mg manganese/kg/day for 13 weeks (NTP 1993); or mice fed up to 731 mg manganese/kg/day for 2 years and female rats fed 232 mg manganese/kg/day (as manganese sulfate) (NTP 1993). Contrary to these findings, increased severity of chronic progressive nephropathy was noted in male rats fed 200 mg manganese/kg/day (as manganese sulfate) for 2 years (NTP 1993). In addition, glomerulosclerosis/nephritis and urolithiasis (kidney stones) were observed in male, but not female, Sprague-Dawley rats exposed to dietary doses ≥87 mg manganese/kg/day for 63 days (Ponnapakkam et al. 2003b).

No studies were located concerning renal effects in humans following oral exposure to MMT.

Hanzlik et al. (1980b) observed occasional vacuolar degeneration of proximal convoluted tubules of the kidney in Sprague-Dawley rats administered a single gavage dose of 31.3 mg manganese/kg (as MMT). Histopathologic renal effects observed within 24 hours of a gavage dose of 20–37.5 mg manganese/kg (Hysell et al. 1974) included hyaline droplet change, cytoplasmic vacuolation of the proximal convoluted tubules, and distention of the glomerular space and tubule lumens with a finely granular material that stained lightly basophilic. Within 48 hours post-dosing, there was severe tubular degeneration in the form of nuclear pyknosis and cell lysis. Animals surviving the administration of 3.75–25 mg manganese/kg did not have any adverse renal effects.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to inorganic manganese; however, other elements of endocrine function (e.g., reproductive effects) following oral exposure to inorganic manganese are discussed elsewhere.

In mice fed up to 3,900 mg manganese/kg/day (as manganese sulfate) and rats fed 1,300 mg manganese/kg/day (as manganese sulfate) for 14 days, no endocrine effects (pathological lesions) were observed (NTP 1993). The adrenal gland was assessed for atypical cells and hyperplasia. In the pituitary gland, the pars distalis was assessed for cyst, hyperplasia, and hypertrophy. The pars intermedia was checked for cysts. C-cells and hyperplasia were examined in the thyroid gland. No endocrine effects were observed in mice or rats fed up to 1,950 mg manganese/kg/day (as manganese sulfate) for 13 weeks. A 2-year study in rats fed up to 232 mg manganese/kg/day (as manganese sulfate) reported no endocrine effects (NTP 1993). However, in a 2-year mouse study, thyroid follicular hyperplasia and dilatation were

observed in males fed 584 mg manganese/kg/day, and thyroid follicular hyperplasia was observed in females fed 64 mg manganese/kg/day (NTP 1993).

No studies were located regarding endocrine effects in humans or animals following oral exposure to MMT.

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to inorganic manganese.

In animals, no significant dermal histopathological changes were observed in mice or rats exposed for 2 years to doses up to 731 or 232 mg manganese/kg/day, respectively, (NTP 1993).

No studies were located regarding dermal effects following oral exposure to organic manganese.

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to inorganic manganese.

In animals, no significant ocular histopathological changes were observed in mice or rats exposed for 2 years to average oral doses of 731 or 232 mg manganese/kg/day (as manganese sulfate), respectively (NTP 1993).

No studies were located regarding ocular effects in humans or animals after oral exposure to organic manganese.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to inorganic manganese.

In some animal studies, lower body weights were observed in rats and mice in manganese-dosed groups. For example, an NTP study (1993) reported decreases in body weight gain of 57% in male rats and 20% in female rats fed 1,300 mg manganese/kg/day (as manganese sulfate in food) for 14 days. Exon and Koller (1975) reported that rats fed daily doses of manganese tetroxide as low as 6 mg manganese/kg/day (mean ingestion value over the duration of the experiment) for 28 days gained only 44% as much weight over the course of the study as control rats. No changes in eating habits in this lowest dose group were observed, although rats in the highest dose group at 4,820 mg manganese/kg/day did exhibit decreased

weight gain due to starvation and the effects of the manganese. No histopathological changes were reported in the exposed animals. The authors suggested that the decrease in weight gain might have been due to manganese interference in metabolism of calcium, phosphorous, and iron.

In chronic studies, a similar sex-related difference in the response to this effect was reported. By the end of a 2-year exposure to the maximum daily dose of 200 mg manganese/kg/day (as manganese sulfate in food), male rats had a final mean body weight that was 10% lower than that of controls; however, females' mean body weights were not significantly different from those of controls throughout the study at all dose levels (232 mg manganese/kg/day was the maximum dose for female rats) (NTP 1993). Food intake (as mg/kg/day) was similar for exposed groups and control groups and for males and females (NTP 1993).

Laskey et al. (1982) investigated body weight changes in a study of adverse reproductive toxicity in male and female Long-Evans rats exposed to manganese. Pregnant dams were fed 0, 350, 1,050, and 3,500 mg manganese/kg/day (in conjunction with a low-iron diet [20 mg iron/kg/day] or a diet adequate in iron [200 mg iron/kg/day]); the pups were continued on their respective diets from day 14 to 15 postpartum to the end of the study (224 days). Manganese treatment did not have any effect on body weight, in either sex fed adequate iron. In iron-deficient male rats, however, body weights were significantly decreased from controls at 24 days postpartum in the 1,050 mg manganese/kg/day diet and at all doses at 40- and 60-day time points. Interestingly, body weight was not significantly different in iron-deficient male rats fed manganese at 350 mg/kg/day at 100 days and at 224 days (no dose group had weight values significantly different from control at day 224). Female body weights were only significantly different in the highest dose at day 24 and in the remaining two manganese doses at day 60. Body weights were not significantly different from controls for the remainder of the study. Significant mortality in both sexes from the highest manganese group fed an iron-deficient diet limited the available data.

No studies were located concerning body weight effects following oral exposure to MMT in humans. Hanzlik et al. (1980b) observed no significant differences in acutely exposed rats at a dose of 31.3 mg manganese/kg as MMT. Hinderer (1979) also observed normal weight gain in surviving Sprague-Dawley rats and CD-1 mice administered doses of MMT ranging from 7 to 159 mg manganese/kg in a one-dose 14-day lethality study.

In a chronic study, Komura and Sakamoto (1992b) administered 11 mg manganese/kg/day (as MMT) in chow to male ddY mice for 12 months. A 12% decrease in weight gain was observed at 9 months

between exposed mice and mice fed unmodified chow, increasing to a 17% difference at 12 months. All differences in these time points were statistically significant. There was no observed difference in food intake between the exposed and control groups.

Metabolic Effects. No studies were located regarding metabolic effects following oral exposure to inorganic manganese in humans or animals.

No studies were located regarding metabolic effects following oral exposure to MMT in humans or animals.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to inorganic manganese.

Alterations in white blood cell counts have been reported in rats and mice following oral exposure to manganese. One NTP study reported immunological effects in rodents treated for 13 weeks, but not in those treated for 2 years (NTP 1993). Mice were fed 122–1,950 mg manganese/kg/day (as manganese sulfate) for 13 weeks. Males exhibited decreased leukocyte counts at ≥975 mg manganese/kg/day; however, these effects may not have been treatment-related; females were unaffected. For 13 weeks, rats were fed 33–520 mg manganese/kg/day (males) and 40–618 mg manganese/kg/day (females); neutrophil counts were increased in males at ≥33 mg manganese/kg/day, lymphocytes were decreased in males at ≥130 mg manganese/kg/day, and total leukocytes were decreased in females at ≥155 mg manganese/kg/day (NTP 1993). Rats fed up to 232 mg manganese/kg/day (as manganese sulfate) and mice fed up to 731 mg manganese/kg/day (as manganese sulfate) for 2 years exhibited no gross or histopathological changes or organ weight changes in the lymph nodes, pancreas, thymus, or spleen (NTP 1993). Komura and Sakamoto (1991) reported decreased white blood cell counts in mice following dosing at 284 mg manganese/kg/day with manganese acetate, manganese chloride, or manganese dioxide for 100 days. It is not known if any of these changes are associated with significant impairment of immune system function.

No studies were located regarding immunological or lymphoreticular effects following oral exposure to MMT in humans or animals.

3.2.2.4 Neurological Effects

Although inhalation exposure to high levels of manganese is known to result in a syndrome of profound neurological effects in humans (see Section 3.2.1.4, above), there is only limited evidence that oral exposure leads to neurological effects in humans.

An outbreak of a disease with manganism-like symptoms was reported in a group of six Japanese families (about 25 people) exposed to high levels of manganese in their drinking water (Kawamura et al. 1941). Noted symptoms included a masklike face, muscle rigidity and tremors, and mental disturbance. Five people were severely affected (2 died), 2 were moderately affected, 8 were mildly affected, and 10 were not affected. These effects were postulated to be due to the contamination of well water with manganese (14 mg/L) that leached from batteries buried near the well. Although many of the symptoms reported were characteristic of manganese toxicity, several aspects of this outbreak suggest that factors in addition to manganese may have contributed to the course of the disease. First, symptoms appeared to have developed very quickly. For example, two adults who came to tend the members of one family developed symptoms within 2–3 weeks. Second, the course of the disease was very rapid, in one case progressing from initial symptoms to death in 3 days. Third, all survivors recovered from the symptoms even before the manganese content of the well had decreased significantly after removal of the batteries. Thus, while there is no doubt that these people were exposed to manganese, there is considerable doubt that all of the features of this outbreak (particularly the deaths) were due to manganese alone.

A manganism-like neurological syndrome has been noted in an aboriginal population living on an island near Australia where environmental levels of manganese are high (Kilburn 1987). Symptoms included weakness, abnormal gait, ataxia, muscular hypotonicity, and a fixed emotionless face. Although it seems likely that excess manganese exposure is an etiologic factor in this disease (based on occupational exposure data from a study where exposure was assumed to be primarily by inhalation although oral exposure was not ruled out), absence of data on dose-response correlations and absence of data from a suitable control group preclude a firm conclusion on the precise role of manganese (Cawte et al. 1987). It is possible that other factors besides manganese exposure may have contributed to the neurological effects, including genetic factors, dietary deficiencies in antioxidants and calcium, and excess alcohol consumption (Cawte et al. 1989). Also, it should be noted that if manganese intake is a causal factor for neurological damage, exposure of the population evaluated in this study could occur not only through the oral route (e.g., food, water, soil), but also by inhaling manganese-containing dusts in environmental or workplace air (Cawte et al. 1987).

In another study, Kondakis et al. (1989) reported that chronic intake of drinking water containing elevated levels of manganese (1.8–2.3 mg/L) led to an increased prevalence of neurological signs in the elderly residents (average age, 67 years) of two small towns in Greece. Effects in these residents were compared with effects in similarly aged residents in a town where manganese levels were 0.004–0.015 and 0.082–0.25 mg/L. These levels are within and slightly above levels found in U.S. drinking water, respectively (see Section 6.4.2). Over 30 different neurological signs and symptoms were evaluated, each being weighted according to its diagnostic value for Parkinsonism. Based on this system, the average neurological scores for the residents of the control town (0.004–0.015 mg manganese/L), the town with mid-range levels (0.08–0.25 mg manganese/L), and the town with elevated manganese (1.8–2.3 mg manganese/L) were 2.7, 3.9, and 5.2, respectively. Results from this study suggest that higher-than-usual oral exposure to manganese might contribute to an increased prevalence of neurological effects in the aged population.

However, there are a number of limitations to this study that make this conclusion uncertain. First, no details were reported regarding which neurological signs or symptoms were increased, so it is difficult to judge if the differences were due to effects characteristic of manganism or to nonspecific parameters. Second, the weighting factors assigned to each neurological symptom were based on the symptom's diagnostic value for Parkinsonism; however, there are clinically significant differences between manganism and Parkinsonism. Therefore, the weighting scheme should have placed more weight on those symptoms (e.g., sleep disorders, emotional lability, weakness, fatigue, and irritability) reported in humans with manganism, such as manganese-exposed miners. The report does not indicate whether efforts were made to avoid bias in the examiner or in the study populations. Nonetheless, the use of the weighting scheme does strengthen the authors' assertion of an association between elevated manganese concentration in the water source and increased susceptibility to neurological symptoms in older populations. Although the subjective parameters included in this scoring are indicative of alterations in mood or emotional state, and affective disorders often accompany other more objective nervous system effects, the authors did not state whether individuals who experienced neurological signs did, in fact, ingest higher levels of manganese than unaffected individuals. The authors reported that the populations in the towns were very similar to each other, but they provided few data to substantiate this. In this regard, even small differences in age, occupational exposures, or general health status could account for the small differences observed. Thus, this study suggests, but does not prove, that chronic oral intake of high levels of manganese can lead to neurological changes in humans.

A study by Vieregge et al. (1995) reported no difference in performance on neurological function studies by people who had ingested well water with high concentrations of manganese. These individuals (high-exposure group), ages ≥40 years, were exposed to manganese at a minimum concentration of 300 μg manganese/L in water for at least 10 years. The controls consisted of a matched group of people who ingested well water with a manganese concentration no higher than 0.05 mg/L. Mean blood manganese concentrations in the high-concentration group were 8.5±2.3 μg/L compared to the control value of 7.7±2.0 μg/L. Performance on motor coordination tests in the 'high-exposure' group was no different than the performance of the control group. The authors noted that they could not control for the ingestion of water from sources other than the wells described. Ingestion of manganese in food is also a major contributor, but the authors did not report an estimate of manganese levels ingested from foodstuffs. However, these possible confounders were considered negligible because no differences between groups were revealed in a risk factor analysis for nutritional factors performed by the authors and because manganese concentrations in the blood were not statistically different between the two groups. Manganese drinking water levels for the 'control group' in this study were within the range of levels reported in U.S. drinking water (see Section 6.4.2). As with the report by Kondakis et al. (1989), a limitation of this study is the use of a neurological assessment scale for 'Parkinsonian signs' rather than an evaluation of symptoms associated with manganism, though the authors observed no 'detectable' neurological impairment.

Goldsmith et al. (1990) investigated a cluster of Parkinson's disease in the southern region of Israel. They reported an increased prevalence of Parkinsonism particularly among those 50–59 years old, which suggested early onset of the disease. The authors believed that a potential environmental cause was the water source common to residents in the region where the cluster of Parkinson's disease was observed. Although the authors reported that the water samples examined showed a "substantial excess of aluminum and a smaller excess of iron and manganese," the concentrations were not reported. Soil samples were reported to contain excess concentrations of manganese as well as beryllium, chromium, europium, and ytterbium, though no quantitative values were provided. The residents were connected to a national water system, so it could not be determined when the water supply may have become contaminated with excess levels of manganese and other metals. Moreover, there was no clear evidence that persons living in the region were actually exposed to a contaminated water supply. Although identified as a cluster of Parkinson's disease rather than manganism, the authors suggested that the disease cluster might be related to an environmental source. However, the limitations in this study make it difficult to make any clear association between chronic oral intake of excess levels of manganese and the prevalence of neurological disease.

Iwami et al. (1994) studied the metal concentrations in rice, drinking water, and soils in Hohara, a small town on the Kii peninsula of Japan. This town reportedly had a high incidence of motor neuron disease. The researchers observed that a significantly increased manganese content in local rice and a decreased concentration of magnesium in drinking water were positively correlated with the incidence of motor neuron disease in Hohara (r^2=0.99).

Evidence of neurological effects following oral manganese exposure has been noted in case studies of adults, as well. For example, in a case report of a man who accidentally ingested low doses of potassium permanganate (about 1.8 mg manganese/kg/day) for 4 weeks, the man began to notice weakness and impaired mental capacity after several weeks (Holzgraefe et al. 1986). Although exposure was stopped after 4 weeks, the authors reported that a syndrome similar to Parkinson's disease developed after about 9 months. Though suggested by the appearance of a syndrome resembling Parkinsonism, it is difficult to prove that these neurological effects were only caused by exposure to the manganese compound. The authors speculated that the ingested MnO_4^- was reduced to Mn(II) or Mn(III); however, while this would be expected, it was not measured. Since MnO_4^- is a corrosive agent, it seems likely that it may have caused significant injury to the gastrointestinal tract (the patient did experience marked stomach pain), perhaps leading to a larger-than-normal gastrointestinal absorption of manganese.

In another study, Banta and Markesbery (1977) reported on a case involving a 59-year-old man with no occupational or environmental exposure to manganese. The man exhibited dementia and neuromuscular deficiencies including bradykinesia, shuffling gait, retropulsion, and rigidity in the upper extremities. Masked faces with infrequent blinking and stooped posture were also observed. Manganese concentrations were significantly elevated in serum, urine, hair, feces, and cerebrum. Although the authors posit that the man may have had Alzheimer’s disease as well as manganese toxicity, they question how the individual could build up significant body stores of manganese in the absence of occupational exposure or any other known source of excess manganese. The authors suggest that the manganese overload may have been caused by abuse of vitamins and minerals.

Several studies have documented the potential for adverse neurological outcomes from childhood exposure to manganese-contaminated drinking water and/or food. Two studies (He et al. 1994; Zhang et al. 1995) have reported adverse neurological effects in children (aged 11–13) who were exposed to excess manganese in well water and in foods fertilized with sewage water. However, these two studies have several flaws that preclude their use as substantial support for the link between ingestion of excess

manganese and the incidence of preclinical neurological effects in children. These studies utilized a group of 92 children pair-matched to 92 controls who lived in a nearby region. The pairs were matched for age, sex, grade, family income level, and parental education level; in addition, all children lived on farms. Although the groups were well matched, the duration and amount of manganese uptake from the flour (from wheat fertilized with sewage) and drinking water containing excess levels was not well characterized. Moreover, the studies did not indicate if nutritional status, such as low iron or calcium intake, which could greatly enhance manganese uptake, were evaluated as potential confounding factors.

The exposed population drank water with average manganese levels of 0.241 mg/L (He et al. 1994; Zhang et al. 1995). The control group drank water containing 0.04 mg manganese/L. These values were measured over 3 years, although it was not stated if the children were exposed during the entire 3 years, or what the children's daily manganese intakes were. The exposed children performed significantly more poorly ($p<0.01$) in school and on neurobehavioral exams than control students. School performance was measured as mastery of the native language and other subjects; neurobehavioral performance was measured using the WHO core test battery. However, the report did not state what measures, if any, were taken to ensure that the individuals administering the tests were blind to the exposure status of the subject. Such safeguards would be necessary to prevent the introduction of bias in measurement and analysis of the performance data of the subjects. The exposed children's hair, blood, and urine manganese levels were significantly increased relative to controls. A simple correlation analysis indicated the performance of exposed children on five of the six of the neurobehavioral tests administered (digit span, Santa Ana manual dexterity, digit symbol, Benton visual retention test, and pursuit aiming test) was inversely correlated with hair manganese levels. Although the authors reported that iron, copper, and zinc were measured in blood and hair, no other metals were measured in these tissues. Because the exposed group presumably ingested food from sources irrigated with sewage, the children may have been exposed to increased levels of other metals, such as lead or mercury. The authors indicate that the children were exposed to increased manganese in their diet from excess levels in foodstuffs and drinking water. Of the foodstuffs evaluated (cabbage, spinach, potatoes, eggplant, sorghum, and flour), only wheat flour contained excess manganese compared to that from the control area. Although the total amount of manganese ingested from the wheat flour and drinking water was not estimated, the authors suggest that the elevated manganese level in drinking water was the key factor contributing to the observed effects. The authors report that children ingesting food and water containing elevated manganese showed poor performance in neurobehavioral tests and poorer school performance when compared to children from a control area. Because exposure levels and duration were not well defined, these studies as reported are not rigorous enough to establish causality between ingestion of excess manganese and preclinical

neurological effects in children. Nonetheless, these studies are strongly suggestive that subclinical neurobehavioral effects often seen in industrial workers exposed to excess manganese via inhalation are observed in children.

In a recent study, a cross-sectional investigation of intellectual function was conducted on 142 10-year-old children in Araihazar, Bangladesh, who had consumed tube-well water with an average concentration of 793 µg manganese/L and 3 µg arsenic/L (Wasserman et al. 2006). The children received a medical examination and their weight, height, and head circumferences were measured. Intellectual function was assessed on tests drawn from the Wechsler Intelligence Scale for Children, version III, by summing weighted items across domains to create verbal, performance, and full-scale raw scores (the tests were adapted for use in this particular population). Maternal intelligence was assessed with Raven's Standard Progressive Matricies, a non-verbal test considered relatively free of cultural influences. Children provided urine specimens for measuring urinary arsenic and creatinine and provided blood samples for measuring blood lead, arsenic, manganese, and hemoglobin concentrations. To assess the dose-response relationship between manganese in well water and intellectual function, children were stratified into four approximately equal sized groups, based on well water manganese levels. The results of the intelligence tests are displayed in Table 3-4.

The results indicated that, unadjusted for other contributors, children in group 1 (i.e., those with estimated mean dose of 0.006 mg manganese/kg bw/day), when compared with the other three groups, had higher full-scale scores; groups 2 (estimated mean dose of 0.02 mg manganese/kg bw/day) and 4 (estimated mean dose of 0.07 mg manganese/kg bw/day) were significantly different. The unadjusted result for performance scores revealed that group 2 had a significantly lower score than group 1. In the verbal test, group 4 had a significantly lower unadjusted score than group 1.

After adjustment for sociodemographic factors, groups 1 and 4 were significantly different on all three tests, with group 4 performing more poorly (Table 3-4). Although groups 2 and 3 (estimated mean dose of 0.04 mg manganese/kg bw/day) performed more poorly on average than group 1, the averages from groups 2 and 3 were not statistically significantly different from group 1. Therefore, children consuming the largest amounts of manganese from well water, estimated to be on average 0.07 mg manganese/kg bw/day, did show significant decrements in all forms of intellectual performance tested.

There are also individual case reports that supply further evidence of potential neurological effects from exposure to manganese-contaminated drinking water. Sahni et al. (2007) report a case history of a

Table 3-4. Scores on Intelligence Tests

	Quartiles by mean calculated dose of manganese (mg/kg bw/day)[a]			
Test type	0.006	0.02	0.04	0.07
Full-scale	81.7±3.1	73.0±4.1	74.0±3.7	60.7±5.2[b]
Performance	64.6±2.7	56.4±3.2	56.9±2.8	45.6±4.8[b]
Verbal	17.6±0.8	16.6±0.9	17.0±1.0	14.3±1.3[b]

[a]Adjusted scores by four groups of water manganese for full-scale, performance, and verbal raw scores. In each case, adjustments were made for maternal education and intelligence, type of housing, child height, head circumference, and access to TV. Scores represent mean ± standard error on the mean.
[b]Adjusted score significantly different from lowest dose group, $p<0.05$.

Source: Wasserman et al. 2006

previously healthy Canadian 6-year-old girl who lived with her family in an urban center in Canada. Since 2000, the child's family had spent summers at their nearby cottage, characterized as weekend visits in June, followed by full-time residence in July and August. While the municipal water used at the primary residence of the family had non-detectable levels of manganese, the cottage well used between 2000 and 2003 was found to have manganese concentrations of 1.7–2.4 mg/L. A neighboring cottage well used in 2004 had 1.7–2.2 mg manganese/L, while spring water used in 2004 had non-detectable levels. The child's estimated intake from well water exposure was 0.103 mg manganese/kg/day. In 2005, municipal water was brought to the cottage for drinking, but well water was used for washing and cooking. A food history demonstrated that the family consumed more manganese-rich foods, such as pineapples and leafy green vegetables, than a typical Canadian family. However, the family was not vegetarian. The patient and her 7-year-old, asymptomatic sister had very similar diets, with the exception that the sister consumed soy milk due to lactose intolerance. No inhalation exposures to manganese were identified. No industrial releases of manganese were reported in the vicinity of either residence. No other possible source of manganese involving occupational exposures, hobbies among family members, etc., was identified. The patient presented with pica and emotional lability in August 2004. Over the following months, she developed progressive behavioral and neurologic symptoms. She became withdrawn and less verbal, with stuttered and slurred speech. Her balance, coordination, and fine motor skills declined; eventually (in November 2004), she could no longer stand independently, tended to fall backward, and demonstrated a high steppage "cock-like" gait. An MRI indicated hyperintensity in the basal ganglia, indicative of high manganese accumulation. The patient demonstrated high levels of manganese in whole blood (39.7 µg/L). The patient also had severe iron deficiency and polycythemia, which was attributed to elevated cobalt. Her blood levels of lead were normal. While her liver manganese was elevated, her liver function was normal, as was her blood copper level. Other members of the family had elevated blood levels of manganese (1.9–2.8 µg/L) when tested between March and June 2005. The patient's symptoms abated to a large degree when she was treated with phlebotomies for the polycythemia and ethylene-diamine tetraacetic acid chelation for the manganese overload and iron therapy. These treatments occurred from November 2004 through July 2005, when her iron supplementation stopped. By August 2005, the patient's condition had deteriorated, with her pica returning; she fell frequently and needed assistance where she was previously independent. Phlebotomies and oral iron therapy were resumed in October 2005. The authors concluded that a metabolic disorder involving divalent metals (manganese, iron, and cobalt) interacting with environmental exposures was the most likely explanation for the patient's symptoms.

Woolf et al. (2002) describe the case of a 10-year-old boy whose sole source of drinking water at home over a 5-year period was from a well on the family's property in a Boston, Massachusetts suburb. The well water tested after 5 years of use had a manganese concentration of 1.21 ppm (estimated intake: 0.06 mg manganese/kg/day). The child had elevated blood levels of manganese (serum concentration of 0.90 µg/100 mL, compared to reference normal of <0.265 µg/100 mL) and whole-blood manganese concentration of 3.82 µg/100 mL (reference normal: <1.4 µg/100 mL). The child's urinary excretion of manganese was found to be 8.5 µg/L over a 24-hour period (reference normal: <1.07 µg/L). Although no other member of the family exhibited elevated blood concentrations of manganese, the child and his brother each had elevated manganese levels in hair samples (the patient's level was 3,091 ppb; the brother's was 1,988 ppb; reference normal: <260 ppb hair). At this time, the family switched to bottled drinking water, but continued to use the well water for other purposes (bathing, etc.). The child exhibited no evidence of illness or tremors. A detailed neurologic examination was normal. His balance with his eyes closed was good, but he did not coordinate rapid alternating motor movement well. His fine motor skills were normal and he had no sensory deficits. A battery of neuropsychologic tests revealed that while the child's global cognitive skills were intact, he had striking difficulties in both visual and verbal memory (14^{th} and 19^{th} percentiles, respectively), suggesting a deficit in free retrieval skills, and had a general memory index at the 13th percentile and learning index at the 19th percentile. The child was in 5^{th} grade at the time of testing and had no history of learning problems, although teachers had persistently reported difficulties with listening skills and following directions. The authors report that the findings from the neuropsychological testing are consistent with the toxic effects of manganese, although the authors indicate that a causal relationship cannot be inferred in this case.

Though limited, these case reports also provide further evidence for a link between ingestion of elevated levels of manganese and learning problems. Other studies have found that manganese levels in hair are higher in learning-disabled children than in normal-functioning children (Collipp et al. 1983; Pihl and Parkes 1977). The route of excess exposure is not known, but is presumed to be mainly oral. These observations are consistent with the possibility that excess manganese ingestion could lead to learning or behavioral impairment in children as suggested by the results of He et al. (1994) and Zhang et al. (1995). However, an association of this sort is not sufficient to establish a cause-effect relationship because a number of other agents, including lead, might also be involved (Pihl and Parkes 1977). Moreover, other potentially confounding factors (e.g., health and nutritional status) must be taken into consideration in interpreting such studies.

However, a pilot study conducted by Bouchard et al. (2007c) found significant associations between hair levels of manganese and certain behavioral end points. The study involved a group of children (24 boys and 22 girls) from Quebec, Canada whose homes received drinking water from one of two wells; one well provided water with a relatively high level of manganese (610 µg/L; W1) and the second well provided water with a much lower level of manganese (160 µg/L; W2). The children, aged 9–13, had estimated average exposure levels of 0.02 mg manganese/kg/day (W1) and 0.007 mg manganese/kg/day (W2). The children with exposure to water from the high-manganese well had significantly higher ($p<0.05$) levels of manganese in their hair than those children exposed to water from the low-manganese well. Moreover, the children with high concentrations of manganese in their hair demonstrated significantly more ($p<0.05$) oppositional behaviors (e.g., breaking rules, getting annoyed or angered) and more hyperactivity than children with lower manganese hair concentrations (after adjustment of scores for age, sex, and income). No manganese-related differences were observed for tests related to cognitive problems (disorganization, slow learning, lack of concentration). Although this report is a pilot study, it nonetheless suggests the possibility that exposure to relatively high levels of manganese in water can influence behavior in children.

Several studies report the link between hepatic encephalopathy and an increased manganese body burden following chronic liver disease in adults (Hauser et al. 1994; Pomier-Layrargues et al. 1998; Spahr et al. 1996) and children (Devenyi et al. 1994) and in individuals with surgically-induced portacaval shunts (PCS) (Hauser et al. 1994). The manganese exposure in these studies was assumed to originate from a normal diet. Hepatic encephalopathy comprises a spectrum of neurological symptoms commonly occurring in individuals with chronic liver disease; these symptoms include varying degrees of mental dysfunction, although extrapyramidal symptoms may also be identified during a clinical examination (Spahr et al. 1996). In the Hauser et al. (1994) study, two men aged 49 and 65 years, both with chronic liver disease, and one 56-year-old man with cirrhosis of the liver and a portacaval shunt, showed a variety of neurological symptoms including bradykinesia, postural tremor of the upper extremities, and gait disturbances, as well as a decrease in cognitive function. These men all had significant elevations ($p<0.05$) in blood manganese as compared to healthy male and female controls, and had hyperintense signals in the basal ganglia bilaterally as measured by T1-weighted MRI. Similar elevations of blood manganese were reported in a population of 57 cirrhotic patients with an absence of clinical encephalopathy (Spahr et al. 1996). Blood manganese was elevated in 67% of the patients and was significantly higher in those patients with previous portacaval anastomoses or transjugular intrahepatic portosystemic shunt. MRI signal hyper intensity was observed in the globus pallidus; the elevated blood manganese levels were significantly correlated with the intensity of the signal in affected patients.

Neurological evaluation of extrapyramidal symptoms using the Columbia rating scale indicated a significant incidence of tremor, rigidity, or akinesia in ~89% of the patients, although there was no significant correlation between blood manganese level and these symptoms.

Similar results were observed in a young girl with Alagille's syndrome (involving neonatal cholestasis and intrahepatic bile duct paucity) with end-stage cholestatic liver disease who exhibited several neurological dysfunctions including dystonia, dysmetria, propulsion, retropulsion, and poor check response bilaterally (Devenyi et al. 1994). The girl had elevated blood manganese (27 μg/L compared to normal value of ~9.03 μg/L) and exhibited hyperintense MRI signal in the basal ganglia. After a liver transplant, the MRI signal abated and the blood manganese level returned to normal. This study and those in adults indicate that the increased manganese body burden (as evidenced by increased manganese blood and brain levels) may contribute to the resultant neurological symptoms and encephalopathy in individuals with cirrhosis or chronic liver disease.

Rose et al. (1999) evaluated brain manganese levels in 12 autopsied cirrhotic individuals who died from hepatic coma and 12 control subjects with no history of hepatic, neurological, or psychiatric disorders at time of death. Neutron activation analysis of the brain tissue revealed an increase in manganese content in the cirrhotic individuals, particularly in the globus pallidus, which had 186% more manganese than that of controls (significant at a level of $p<0.001$). Significant, although less extreme, increases in manganese were also found in the putamen and caudate nucleus from cirrhotic patients. However, the increased brain manganese did not correlate with patient age, the etiology of the cirrhosis, or the history of recurrent hepatic encephalopathy (reported in 6 patients).

An association has been suggested between violent behavior and excess manganese exposure; this was investigated by measuring the correlation between the manganese content in hair and violent behavior in prison subjects and controls (Gottschalk et al. 1991). The prisoners did have significantly higher hair manganese content than controls, but further research was indicated to determine whether manganese was a causative factor in violent behavior. The highest concentrations of manganese demonstrated in the hair samples (1.8–2.5 ppm) were, however, within the control ranges reported by Kondakis et al. (1989) (0–13 ppm) and Huang et al. (1989) (0.1–2.2 ppm for scalp and 0.3–9.8 ppm for pubic hair). Another factor to be considered in the interpretation of these results is the hair color composition within the samples evaluated. At least one study (Cotzias et al. 1964) has reported that manganese content was greater in dark hair when compared to that found in lighter colored hair. Another study showed that manganese accumulated in melanin-containing tissues including the melanin from human hair (Lydén et al. 1984). In

their study of inhabitants living in Angurugu on Groote Eylandt, Australia, Stauber et al. (1987) found that samples of grey hair from one elderly Aborigine participant had the same manganese content as the individual's black hair. The white hairs of a local dog also had the same manganese content as the dog's black hairs. Based on this evidence, these investigators stated that there was no evidence to support previous reports that dark colored hair concentrated more manganese than light hair. The average manganese content in scalp hair among male and female Aborigine residents was 3.5–5-fold greater than the average scalp hair manganese in male and female Caucasian residents, respectively. The authors cautioned that interpretation of data on manganese content in scalp hair should take into consideration endogenous as well as potential exogenous sources. Moreover, long-term manganese exposure that may be associated with adverse effects may not be represented by manganese content in hair growth from only a few months (Stauber et al. 1987). Thus, further investigations are needed to determine whether manganese content can vary significantly due to hair color pigment alone.

Manganese has also been associated with amyotrophic lateral sclerosis (ALS). In a human study, spinal cord samples from ALS patients were found to have higher manganese concentrations in the lateral fasciculus and anterior horn than in the posterior horn (Kihira et al. 1990). Also, ALS patients exhibited a positive correlation between manganese and calcium spinal cord content, whereas controls exhibited a negative correlation. It was suggested that an imbalance between manganese and calcium in ALS patients plays a role in functional disability and neuronal death. There was also some indication from previous studies that an excess intake of manganese in drinking water may have caused this imbalance, although data to support this were not presented. While this is suggestive of an association between manganese and ALS, it is equally plausible that ALS leads to an imbalance in manganese-calcium metabolism.

No neuropsychological effects were found in a recent study by Finley et al. (2003) of healthy, nonsmoking, premenopausal women were studied in a research project using a crossover design to determine the combined effects of very low or high dietary manganese with foods containing either saturated or unsaturated fats on measures of neuropsychological and basic metabolic function. Women were fed for 8 weeks at one of two doses of manganese (0.01 or 0.3 mg manganese/kg/day), with one-half of the subjects receiving 15% energy as cocoa butter and the other half receiving 15% energy as corn oil. Blood draws and neuropsychological tests (involving tests of steadiness and ability to control muscular tremor, signs of Parkinson's and related neurologic diseases, as well as tests to determine a range of components related to hostility and anger) were given at regular intervals during the dietary periods. Manganese intake did not affect any neurological measures and only marginally affected psychologic variables.

There are significantly more studies on the neurological effects of manganese ingestion in animals as compared to humans. A few of these report observed effects that were comparable to clinical signs seen in people. Gupta et al. (1980) reported that monkeys given 25 mg manganese/kg/day (as manganese chloride) for 18 months developed weakness and muscular rigidity (however, no data were provided to support these observations).

Rats dosed with 150 mg manganese/kg/day (as manganese chloride) developed a rigid and unsteady gait after 2–3 weeks, but this was a transient condition that was not apparent by 7 weeks (Kristensson et al. 1986). In addition, in two separate studies, the authors reported a decrease in spontaneous activity, alertness, muscle tone, and respiration in mice dosed once with 58 mg manganese/kg/day by gavage (Singh and Junnarkar 1991) and staggered gait and histochemical changes in two third-generation mice treated with 10.6 mg manganese/kg/day (as manganese chloride) in drinking water (Ishizuka et al. 1991). As shown in Table 3-3 and Figure 3-3, changes of this sort have been reported at oral exposure levels that ranged from 1 to 2,270 mg manganese/kg/day (as manganese chloride, manganese acetate, or manganese tetroxide) (e.g., Bonilla 1978b; Bonilla and Prasad 1984; Chandra 1983; Eriksson et al. 1987a; Gianutsos and Murray 1982; Gray and Laskey 1980; Komura and Sakamoto 1991, 1992b; Lai et al. 1984; Nachtman et al. 1986; Subhash and Padmashree 1991). Thus, the database on neurological effects in adult animals ingesting high levels of manganese does not provide a clear picture of manganese-induced effects and the significance of these results is difficult to interpret.

Rose et al. (1999) reported the effects on manganese body burden (exclusively from the diet) in rats with either induced cirrhosis of the liver, acute liver failure (induced by portacaval anastomosis followed by hepatic artery ligation), or a surgically-administered portacaval shunt (PCS). Brain manganese levels in these three groups of rats were compared to control rats and sham-operated rats. PCS and sham-operated rats were evaluated 4 weeks following surgery, while cirrhotic rats were studied 6 weeks following surgery. Rats with acute liver failure were studied 15–18 hours following devascularization at coma stage of encephalopathy. Manganese levels were statistically significantly increased as compared to non-treated controls and sham-operated controls in both cirrhotic and PCS rats in the frontal cortex, globus pallidus, and caudate/putamen; manganese levels were highest in the globus pallidus. For example, in the globus pallidus, brain manganese was increased 57% in the PCS rats as compared to the control rats ($p<0.0001$). However, the level of manganese in the globus pallidus in the PCS rats was significantly elevated as compared to cirrhotic rats, indicating that shunting is a strong determinant of manganese deposition in the brain.

Montes et al. (2001) also explored the potential for hepatic disease to potentiate the toxic effects of manganese by observing effects on levels of specific neurotransmitters. Groups of male Wistar rats were assigned to one of six treatments: (1) sham operated; (2) bile duct ligated (BDL); (3) sham operated with 15.1 mg manganese/kg/day supplied as manganese chloride in drinking water; (4) BDL with 15.1 mg manganese/kg/day in drinking water; (5) sham operated with 26.7 mg manganese/kg/day in drinking water; or (6) BDL with 26.7 mg manganese/kg/day in drinking water. The BDL condition models a cirrhotic-type condition in the rats. Rats received this treatment for 4 weeks beginning at surgery. At the end of treatment, rats were weighed and killed. Total bilirubins (as well as conjugated and unconjugated forms) increased over control in all BDL groups, but there was no significant effect of manganese treatment. There was also no effect of manganese on alanine aminotransferase levels or on collagen, although these measures were significantly increased by BDL. However, the combination of BDL and manganese exposure produced 2- and 4-fold increases ($p<0.001$) of striatal manganese content at the 15.1 and 26.7 mg manganese/kg/day doses, respectively, while BDL alone did not produce changes. Striatal DA content was significantly decreased compared to control in BDL rats; the addition of 26.7 mg manganese/kg/day to BDL produced an approximate 33% increase in dopamine (DA) content over BDL alone. The highest dose of manganese produced 2-fold striatal homovanillic acid (HVA) increases over control in both sham-operated and BDL rats. BDL and manganese treatment at 15.1 mg manganese/kg/day each individually produced 2-fold increases over control levels in striatal DA turnover, measured as HVA/DA; the combination of BDL with manganese at 15.1 mg manganese/kg/day produced the same result as each condition individually. The sham-operated and BDL high dose rats each had HVA/DA levels of nearly 3 times the control level; all of these differences were significant ($p<0.05$). These results suggest that hepatic dysfunction can, indeed, potentiate the neurotoxicity of manganese.

In another study, Montes et al. (2006) explored the potential role of hepatic dysfunction as a potentiator of the toxic effects of manganese on neuronal damage produced by oxidative stress. Groups of male Wistar rats were assigned to one of four treatments (n=6–9 in each group): (1) sham operated; (2) BDL; (3) sham operated with 26.7 mg manganese/kg/day (as manganese chloride) in drinking water; or (4) BDL with 26.7 mg manganese/kg/day in drinking water. Rats received this treatment for 4 weeks beginning at time of surgery. Compared with sham-operated controls, BDL treatment with or without manganese caused significant ($p<0.05$) increases (>2-fold) in gamma glutamyltranspeptidase and alanine aminotransferase activities, collagen, and glycogen levels, but manganese alone did not increase these indices of liver damage. Manganese or BDL treatments alone caused moderate, statistically significant ($p<0.05$) increases (~20%) in manganese content in the striatum and globus pallidus. Manganese contents

in both regions were further and markedly increased by the BDL and manganese treatment (300–400% increase). Levels of nitric oxide (NO) were not consistently changed in either brain region in manganese-alone or BDL plus manganese-treated rats compared with sham-operated controls, with the exception that the NO levels in the globus pallidus were decreased ($p<0.05$) by ~25% in BDL and BDL plus manganese rats. Constitutive nitric oxide synthetase (NOS) activities in the globus pallidus were decreased (but not to a statistically significant degree) in BDL and BDL plus manganese-treated rats.

Many studies in animals have explored the interplay between iron deficiency and manganese supplementation and its ultimate potential for modulating neurotransmission in the brain. In a study by Li et al. (2006) groups of 7–8-week-old male Sprague-Dawley rats were dosed by gavage with sterile saline (control) or manganese chloride dissolved in sterile saline at 2.2 or 6.6 mg manganese/kg/day; rats were dosed daily for 5 consecutive days/week (weekdays only) for 30 days. The study was conducted to determine the mechanism by which iron is regulated at the blood-brain barrier and the blood-cerebrospinal fluid (B-CSF) barrier and how manganese may alter these processes. Serum iron concentrations were found to be significantly decreased ($p<0.05$) at 2.2 and 6.6 mg manganese/kg/day (50 and 66% of control value, respectively. In contrast, iron concentrations in the cerebrospinal fluid (CSF) were significantly ($p<0.05$) increased at 2.2 and 6.6 mg manganese/kg/day (136 and 167% of control values). Manganese produced a dose-dependent increase of binding of IRP1 to iron-responsive element-containing RNA in (percentage increase of high-dose group over control indicated in parentheses): the choroid plexus (+70%); in capillaries of striatum (+39%), hippocampus (+56%), and frontal cortex (+49%); and in brain parenchyma of striatum (+67%), hippocampus (+39%), and cerebellum (+28%). Manganese exposure significantly increased the expression of TfR mRNA in choroid plexus and striatum with a reduction in the expression of Ft mRNA. The results indicate that intermediate-duration oral exposure to excess manganese decreased serum iron concentrations and increased iron concentrations in the CSF. These changes were associated with: (1) increased binding of iron regulatory proteins and mRNA containing iron responsive element in several brain regions and (2) upregulation of transferritin receptor mRNA and down-regulation of ferritin mRNA in choroid plexus and striatum.

In a recent study by Anderson et al. (2007a), male and female PND 1 Sprague-Dawley rats were divided into groups receiving either a control diet (35 mg iron/kg, 10 mg manganese/kg diet and drinking water) or a diet with manganese supplementation (same as control diet with 1 g/L of manganese chloride added to drinking water for a final dose of 71.1 mg manganese/kg/day). Rats were sacrificed after 6 weeks of treatment. Additional females and males (n=6 per group) were provided with an iron-deficient diet

(4 mg/kg iron, 10 mg manganese/kg diet and drinking water) and an iron deficient/manganese supplemented diet (same iron-deficient diet plus 1 g manganese chloride/L water). Manganese exposure significantly ($p<0.05$) reduced iron concentrations in the caudate putamen and the substantia nigra from male and female rats. In female rats, manganese exposure also significantly reduced iron levels in the caudate putamen. The largest decrease was seen in the female caudate putamen, where iron levels dropped by approximately 66% compared to controls and the female substantia nigra, where iron levels dropped by approximately 75% compared to controls. Manganese concentrations in the brain were seen to increase over controls most prominently in the female globus pallidus (approximately 60%). A significant negative correlation ($p<0.05$) was observed between synaptosomal manganese concentration and 3H-GABA uptake in rats of both sexes. 3H-GABA levels were significantly reduced from controls in both males and females (by approximately 50%). In rats provided with an iron-deficient diet, few differences were observed between the iron-deficiency condition and the iron-deficiency plus manganese condition. In males, iron levels were approximately 10 times higher in the caudate putamen of iron-deficient animals than in the animals that were iron-deficient and manganese-supplemented.

Some studies have explored the relation between high dietary manganese and nitrous oxide synthesis as a means of exploring the impact of manganese on oxidative stress and, hence, neuronal injury.

Liu et al. (2006) studied 12-week-old female C57Bl/6 mice, paired as littermates from timed pregnant dams, that received by gavage either water or 43.7 mg manganese/kg/day as manganese chloride for 8 weeks prior to sacrifice. Manganese-treated mice had significantly ($p<0.05$) increased levels of manganese in the striatum and decreased locomotor activity and striatal dopamine content. Neuronal injury in the striatum and globus pallidus was observed, especially in regions proximal to the microvasculature. Neuropathological assessment revealed marked perivascular edema, with hypertrophic endothelial cells and diffusion of serum albumin into the perivascular space. Immunofluorescence studies revealed the presence of apoptotic neurons expressing neuronal NOS choline acetyltransferase, and enkephalin in both the striatum and globus pallidus. Soma and terminals of dopaminergic neurons were morphologically unaltered in either the substantia nigra or striatum. Regions with neuronal injury contained increased numbers of reactive astrocytes that coexpressed inducible NOS2 and localized with areas of increased neuronal staining for 3-nitrotyrosine protein adducts, a marker of NO formation. The data suggest a possible role for astrocyte-derived NO in injury to striatal-pallidal interneurons from manganese intoxication.

In a study by Weber et al. (2002), Charles River CD rat pups were dosed (by mouth with micropipette) according to average pup weight for each litter starting on PND 1 and continuing until PND 21 at doses of 0 (nanopure water vehicle), 6.9, or 138 mg manganese/kg/day. Pups were sacrificed on PND 21, and samples of cerebellum and cerebral cortex were collected and frozen in liquid nitrogen, with manganese concentrations evaluated in brain tissue. Also evaluated were cerebrocortical and cerebellar metallothionein (MT) mRNA levels, glutamine synthetase (GS) activity, GS protein levels, and total glutathione (GSH) levels. High-dose manganese exposure significantly increased ($p<0.05$) total cerebrocortical GSH when compared to control without changes observed in any of the other measures. The same change was apparent with the high-dose manganese exposure on cerebellar GSH, although slight differences in the standard error of the mean prevented reaching statistical significance. However, it should be noted that these measures actually decreased with respect to the control in the low dose manganese group. Overall, data do not appear to support an effect of manganese exposure on measured biochemical variables indicative of oxidative stress.

In a study by Lipe et al. (1999), groups of 30-day-old and 90-day-old male Sprague-Dawley rats were exposed to10 or 20 mg manganese/kg/day as manganese chloride for 30 days. A dose-dependent decrease in body weight gain was found in the adult, but not the weanling rats. Significant ($p<0.05$) increases were observed in concentrations of aspartate, glutamate, glutamine, taurine, and gamma-aminobutyric acid (GABA) in the cerebellum of the adult rats dosed with 20 mg manganese/kg/day; this increase also appeared to be dose dependent. A significant ($p<0.05$) decrease in the concentration of glutamine was observed in caudate nucleus and hippocampus of weanling rats dosed with 10 mg manganese/kg/day. A significant ($p<0.05$) increase in GABA concentration in the caudate nucleus of weanlings was observed in the 20 mg manganese/kg/day group. A significant ($p<0.05$) decrease in the concentration of glutamine in the caudate nucleus and hippocampus was found in weanlings of the 10 mg manganese/kg group.

In a study by Morello et al. (2007), groups of adult male Wistar rats had free access to either normal drinking water or to a water solution providing 611 mg manganese/kg/day as manganese chloride, with treatment lasting for 13 weeks. A significant reduction in the number of immunoreactive cells for glutamine synthetase was observed in the globus pallidus for manganese-treated animals compared to controls (33% reduction). No effect of manganese was observed in the sensorimotor cortex or striatum, nor was there any effect observed for other manganoproteins tested.

In a study by Ranasinghe et al. (2000), groups of male Sprague-Dawley rats were provided daily with 0 (n=2), 74.9 (n=4), or 149.8 mg (n=4) mg manganese/kg/day, administered as manganese sulfate; another control group of two rats received 20 mg sodium/day. All animals were treated for 50 days. Mean manganese concentrations in liver, brain, heart, and kidney were elevated in the low- and high-dose groups, compared with untreated sodium controls, but statistical analyses of these data were not performed. A decrease was observed in dopamine serum levels in manganese-treated rats compared to controls; the sulfated form was increased in both dose groups compared to controls (12–13 times; from 0.014 nmol/mL in controls to 0.179 nmol/mL in the 20 mg manganese group). Increases were also observed in L-dopa and L-dopa sulfate in both treatment groups. No treatment-related differences were observed in serum levels of L-P tyrosine or its L-P tyrosine sulfate.

In a study by Desole et al. (1997), groups of 3-month-old male Wistar rats were given gavage doses of 0 or 8.8 mg manganese/kg/day as manganese chloride in water for 6 days. Other groups of control or manganese-treated rats received 20 mg/kg buthionine (S,r) sulfoximine0ethyl ester (BSO-E) by intraperitoneal injection twice daily (1 hour before gavage treatment) on days 4, 5, 6, and 7. Rats were sacrificed on day 7, and brainstem samples were extracted for determination of concentrations of dopamine, dihydroxyphenylacetic acid (DOPAC), HVA, and noradrenaline (NA), as well as concentrations of reduced glutathione, ascorbic acid, dehydroascorbic acid, and uric acid (the latter being indicators of oxidative stress potential). Compared with controls, manganese treatment alone increased concentrations of GSH (10–14%) and uric acid (28–45%) in striatum and brainstem, without affecting ascorbic acid concentrations, increased concentrations of DOPAC and HVA in striatum, without affecting dopamine, and decreased brainstem concentrations of dopamine. As expected, BSO-E treatment alone decreased GSH concentrations in striatum (23%) and brainstem (35%), without affecting striatal or brainstem concentrations of ascorbic acid, dehydroasocrbic acid, or uric acid or striatal concentrations of dopamine, DOPAC, or HVA; however, brainstem concentrations of dopamine were decreased by this treatment. Compared with controls, manganese plus BSO-E treatment decreased concentrations of GSH and ascorbic acid in striatum (42 and 22%, respectively) and brainstem (23 and 22%, respectively) and increased concentrations of dihydroxyascorbic acid and uric acid; these results are indicative of a heightened oxidative stress condition. In addition, manganese plus BSO-E treatment decreased striatal concentrations of dopamine, DOPAC, and HVA and brainstem concentrations of dopamine and noradrenaline. The magnitude of the manganese plus BSO-E treatment changes were mostly larger than changes seen in all other experimental groups. The results indicate that the manganese treatment decreased brainstem concentrations of dopamine without affecting neurochemical indicators of oxidative

stress and that a glutathione depleted condition potentiated the effects of manganese on brainstem and striatal concentrations of dopamine, DOPAC, and HVA.

The effects of manganese on a variety of behavioral assessments in rats have been conducted; these studies have found changes in measures related to fear, locomotor activity, and cognitive performance (Calabresi et al. 2001; Shukakidze et al. 2003; Torrente et al. 2005; Vezér et al. 2005, 2007). In some of these studies, electrophysiological changes in the brain have been associated with the behavioral changes (Calabresi et al. 2001; Spadoni et al. 2000; Vezér et al. 2005, 2007).

Measures of locomotor activity, fear, and learning and memory were made on male Wistar rats treated with either tap water as drinking water or a solution of magnesium chloride (1,310 mg manganese/kg/day) as drinking water for 10 weeks (Calabresi et al. 2001). Brain manganese levels ranged from 3 to approximately 4 times higher than controls. Manganese-treated rats were significantly ($p<0.001$) more active than control rats in the open field. Manganese-treated rats showed progressively and significantly more interest in the "novel" object over three trials than the control rats ($p<0.001$; an average of four contacts for manganese-treated animals compared to an average of <2 for controls on the third trial). Manganese-treated animals also produced significantly ($p<0.05$) more fecal boluses (indicative of heightened fearfulness) in the open field than control rats over the three trials. No major differences were observed between treatment groups in the eight-arm radial maze test, with the manganese-treated animals taking significantly ($p<0.01$) more 45 degree angle turns than the control rats. An enhanced dopaminergic inhibitory control of the corticostriatal excitatory transmission via presynaptic D2-like dopamine receptors in corticostriatal slices obtained from the manganese-treated rats was observed. The use of agonists acting on presynaptic purinergic, muscarinic, and glutamatergic metabotropic receptors revealed normal sensitivity. Membrane responses recorded from single dopaminergic neurons following activation of D2 dopamine autoreceptors were also unchanged following manganese intoxication. The authors suggest that the behavioral symptoms described in the "early" clinical phase of manganism may be produced by an abnormal dopaminergic inhibitory control on corticostriatal inputs (Calabresi et al. 2001).

Spadoni et al. (2000) studied groups of male, PND 20 Wistar rats provided with either access to drinking water or 3311 mg manganese/kg/day in drinking water, with treatment lasting for 13 weeks. No neuronal loss or gliosis was detected in the globus pallidus with either treatment. However, the majority of GP neurons from manganese-treated rats died following brief incubation in standard dissociation media. Patch-clamp recordings in the whole-cell configuration were not tolerated by surviving GP neurons from

manganese-treated rats. Manganese-treated GP cells, but not striatal cells, demonstrated an unusual response to glutamate, since repeated applications appeared to produce irreversible cell damage.

Another factor that could potentiate the neurotoxicity of manganese was explored by Torrente et al. (2005), with rats subjected to restraint stress along with manganese exposure. Groups of 15 adult male Sprague-Dawley rats (250–300 g) were dosed for 2 weeks with either plain drinking water or drinking water providing 38.2 mg manganese/kg/day as manganese chloride. The manganese chloride group was then split into two groups, with drinking water doses of 76 and 153 mg manganese/kg/day provided for another 19 weeks. One-half of the animals in each group were subjected to restraint stress for 2 hours daily by placing them in metacrilate cylindrical holders. Animals treated with 153 mg manganese/kg/day with restraint traveled a significantly shorter distance than control restraint animals (38% decrease; $p<0.05$). Manganese concentrations in brain and cerebellum were significantly elevated in exposed groups, compared with controls. Body weight and food consumption were significantly decreased ($p<0.05$) in the exposed groups, compared with control values. Terminal body weights were 86 and 51% of control values in the low- and high-dose unrestrained groups and 90 and 56% in the respective restrained groups. Open field activity was significantly decreased ($p<0.05$) in the high-dose restrained groups. Spatial learning was also impaired in high-dose rats with or without restraint); for example, unrestrained high-dose rats showed significantly ($p<0.05$) increased latency to find a hidden platform in the water maze test on days 1, 2, 3, 4, and 5 of testing.

In a study by Shukakidze et al. (2003), groups of white rats were tested for cognitive performance in a multipath maze. Group I served as a control group, which was trained in the maze for 10 days, fed normal feed for 30 days, and then retested. Groups II and III, instead of receiving normal feed, received dosed feed at 5.6 or 13.9 mg manganese/kg/day (as manganese chloride). Groups IV and V were dosed the same doses as Groups II and III, respectively, but received the doses for 30 days prior to maze training. Groups II and III received normal feed for the next 90 days prior to retesting for 10 days. An additional group of animals received a single dose (undefined route) prior to 10 days of training in the maze. Both groups of rats dosed after training (Groups II and III) showed moderate disruption of their acquired skill in the maze compared to controls. Group III also demonstrated increased "aggressivity". Both groups that were exposed prior to training (Groups IV and V) were entirely unable to learn the maze. When these rats were reassessed after a 3-month period without excess manganese, they remained unable to learn the maze. After training, 8/12 rats in the group with the single dose (Group VI) mastered the maze; 4/12 required assistance from the experimenter to orient themselves. Groups of 9 (control) and 10 (manganese-treated) rats were tested in an active avoidance of conditioned and unconditioned stimuli

paradigm. Manganese-treated rats received by mouth 13.9 mg manganese/kg/day (as manganese chloride) in water 1 hour prior to the experiment on day 1. Rats were tested over 16–17 days. Manganese treatment resulted in significant and reversible behavioral change, with manganese exposure leading to worsened acquisition of the avoidance reaction in response to unconditioned and conditioned stimuli, increased latent period of conditioned reflex activity, and increased numbers of errors and time taken to navigate a maze, beginning on day 5 of the experimental period and lasting until day 10–15, depending on the end point.

Tran et al. (2002b) studied Sprague-Dawley rat pups that received dietary supplementation in the form of 0, 0.7, 3.8, or 7.5 mg manganese/kg/day (as manganese chloride). Male and female pups were sacrificed during infancy and at weaning (18–24 per treatment group) for tissue analyses of trace elements. Twenty-four rats were sacrificed at PND 35 for dopamine analysis (Tran et al. 2002a). The 32 remaining rats, all males, no longer received treatment. Behavioral testing began with a burrowing detour test (PNDs 50–56) and ended with a passive avoidance test (PNDs 60–64). No statistically significant results for any individual treatment group for any behavioral task or striatal dopamine levels. A statistically significant positive trend was observed for passive avoidance (approximately 50% more footshocks in highest dose group compared with control). The control had approximately 2 times the striatal dopamine levels of the two highest dose groups on animals sacrificed on PND 65. Striatal dopamine increase observed in Tran et al. (2002a) at an earlier timepoint (PND 40).

Vezér et al. (2005, 2007) examined neurobehavioral end points in young adult male Wistar rats treated by water gavage with 0, 6.5, or 25.9 mg manganese/kg/day for 10 weeks. Rats were tested in an eight-arm radial maze test (spatial learning and memory test) and an open field test (locomotor ability). Rats were also tested for amphetamine-induced locomotor activity, acoustic startle response, and prepulse inhibition. At 5 and 10 weeks of treatment, as well as at the end of the post-treatment period 8 weeks later, electrophysiological testing was performed, including recording of cortical evoked potentials as well as spontaneous electrical activity in the hippocampus. Immunohistochemistry was performed to detect changes in density of glial fibrillary acid protein (GFAP) immunoreactive structures in the hippocampal CA1region. Blood and tissue samples (from the cortex and hippocampus) were collected in the 5th and 10th treatment and 12 post-treatment week. Blood and tissue levels of manganese were determined. Manganese accumulation was first seen in blood and then in brain of high-dose rats. Decreased short- and long-term spatial memory performance (at least $p<0.05$) and decreased spontaneous open field activity ($p<0.05$) were observed in both low- and high-dose groups compared with controls. The number of acoustic startle responses, as well as their associated prepulse inhibition of the acoustic startle

responses, were decreased in manganese-treated animals. The latency of sensory evoked potentials increased and their duration decreased. Manganese levels returned to normal at the end of the post-treatment period, but impairment of long-term spatial memory remained, as well as the decrease in number of acoustic startle responses in high-dose rats. Prepulse inhibition responses returned to normal. Open field activity returned to normal at the end of post-treatment, but a residual effect could be observed under the influence of D-amphetamine. The electrophysiological effects partially returned to normal during post-treatment. Significantly ($p<0.05$) high percentages of area showing GFAP immunoreactivity were observed in the dentate gyrus (but not in the striatum radiatum or striatal oriens) in the low- and high-dose groups, compared with controls.

No studies regarding neurological effects following oral exposure to MMT by humans were identified.

Komura and Sakamoto (1992b) administered 11 mg manganese/kg/day (as MMT) to ddY mice in food for 12 months. To measure differences in behavior between exposed and control mice that were fed normal chow, spontaneous motor activity was measured at regular intervals during exposure to determine differences in behavior between exposed and control mice fed normal chow. The authors observed a significant increase in spontaneous activity at day 80; no other significant differences were noted. In a separate study (Komura and Sakamoto 1994), the authors analyzed brain levels of different neurotransmitters and metabolites after identical MMT treatment. MMT resulted in a 66% decrease in dopamine (DA; $p<0.05$) and a 95% decrease in normetanephrine (NMN; $p<0.01$) in the hypothalamus; in the hippocampus, DA was unchanged, while the level of 3,4-dihydroxyphenylacetic acid (DOPAC) was reduced 41% ($p<0.05$), and the 3-methoxytyramine (3MT) level increased 3.5-fold ($p<0.01$). In the midbrain, the only significant changes noted were an almost 6-fold increase in 3MT ($p<0.01$) and a 1.75-fold increase of homovanillic acid (HVA), a metabolite of DOPAC via conjugation by catechol-o-methyl transferase ($p<0.05$). In the cerebral cortex, HVA was decreased by 61%, norepinephrine (NE) by 64%, and epinephrine by 43% (all were $p<0.05$) due to MMT administration. In the cerebellum, DOPAC was decreased 51% ($p<0.05$), while NMN was increased 7.7-fold ($p<0.01$). Finally, in the medulla oblongata, DOPAC was decreased by 45% ($p<0.05$), HVA was decreased by 55% ($p<0.01$), and serotonin (5HT) was decreased 81% ($p<0.01$); metanephrine was increased approximately 2.75-fold in the medulla ($p<0.05$).

Through analysis of the distribution of manganese in the different brain regions of the mice, the authors observed relationships between manganese content and neurotransmitter levels. For example, a weak relationship was found between the manganese level in the corpus striatum and the level of NE. There

was no relationship between the increase in HVA and the manganese levels in this same region. The relationship between the increase in 3MT and manganese levels in the midbrain was weak, as was the relationship between DOPAC and manganese levels in the cerebellum. There were no relationships between amines and manganese levels in the hippocampus, cerebral cortex, or medulla oblongata, although some changes were found. A significant correlation was found between the level of NMN and manganese in the cerebellum. As discussed more fully in Section 3.4.2, the cerebellum contained the most manganese of any brain region following MMT administration (Komura and Sakamoto 1994).

3.2.2.5 Reproductive Effects

Potential reproductive effects of manganese were suggested by the results of a study by Hafeman et al. (2007), where high infant mortality in a Bangladesh community was reported in conjunction with the presence of a local drinking water supply containing high levels of manganese. The Health Effects of Arsenic Longitudinal Study (HEALS) was conducted on 11,749 participants 18–70 years of age living in Araihazar, Bangladesh. Data on the reproductive history of the 6,707 women in this population were collected and samples were taken of drinking water from all of the wells in the study region. Manganese concentrations were determined for a total of 1,299 wells, representing the drinking water supply of 3,824 infants <1 year old. Eight-four percent of infants were exposed, directly or through maternal intake, to water manganese levels above 0.4 mg/L with manganese concentrations ranging from 0 to 8.61 mg/L, for an average calculated daily intake of 0.26 mg manganese/kg/day. Of the 3,837 children born to women who reported to drink from the same well for most of their childbearing years, 335 of them died before reaching 1 year of age. Infants exposed to greater than or equal to the 0.4 mg/L WHO (2004b) standard for manganese in drinking water had an elevated mortality risk during the first year of life compared to unexposed infants (OR=1.8; 95% CI, 1.2–2.6). Adjustment for water arsenic indicators of social class and other variables and potential confounders did not appreciably alter the results. When the population was restricted to infants born to recently married parents (marriage year 1991 or after), the elevation was larger (OR=3.4; 95% CI, 1.5–7.9). Although the results of the study suggest that the presence of high levels of manganese in the water may be responsible for the high infant mortality observed here, information provided by the authors on mechanism of manganese exposure suggests that infant exposure to the high levels of manganese in the water may be complex (i.e., would likely require direct rather than indirect or fractionated exposure, such as that occurring through breast milk or by *in utero* exposure). The authors also indicate that it is not possible to infer that the manganese is solely responsible for the high rate of infant mortality documented in this study

In a 14-day study in rats, no changes in testicular weight were reported at 1,300 mg manganese/kg/day (NTP 1993). However, several intermediate-duration studies in rats and mice indicate that manganese ingestion can lead to delayed maturation of the reproductive system in males. One study investigated the effect of 1,050 mg manganese (as manganese tetroxide)/kg/day, provided to weanling mice and their dams starting when the pups were 15 days old (Gray and Laskey 1980). On day 30, the mice were weaned and maintained on the high-manganese diet until killed for analysis at 58, 73, or 90 days old. The growth and general appearance of the weanling rats appeared normal. At time of death, preputial gland, seminal vesicle, testes, and body weights were measured. The high-manganese diet resulted in a significant decrease in growth of these reproductive tissues but no growth retardation of the body and no change in liver or kidney weights.

A later study by Laskey et al. (1982) evaluated the reproductive functioning of male and female Long-Evans rats that had been exposed to 0, 350, 1,050, and 3,500 mg manganese/kg/day (in conjunction with a low-iron diet [20 mg iron/kg/day] or a diet adequate in iron [200 mg iron/kg/day]) while *in utero* (dams were fed the described diets during gestation) and from day 14 to 15 postpartum. The rats were maintained on the diet throughout the remainder of the study (224 days). The rats were mated at 100 days postpartum and the reproductive success of these matings was evaluated.

In males, manganese treatment resulted in decreased testes weights (testes weights analyzed with body weight as a covariable) observed at 40 days (at the 1,050 and 3,500 mg manganese/kg/day dose levels) and 100 days (at the 1,050 mg manganese/kg/day dose level) of age, only when administered with the low-iron diet. Hormone levels in male rats were also evaluated. No treatment-related effect was seen in 40-day-old males. At 60 and 100 days of age, however, dose-related decreases in serum testosterone were observed, while serum LH (luteinizing hormone) levels remained relatively unchanged. Luteinizing hormone (LH) is secreted by the pituitary to stimulate testosterone production in the Leydig cells. Testosterone levels control LH production through a negative feedback loop. An increase in testosterone would normally be associated with a subsequent decrease in LH. The decrease in testosterone simultaneous with a stable LH levels suggests that manganese is targeting the Leydig cells. Manganese treatment in both iron regimens prevented the normal decrease in serum follicle-stimulating hormone (FSH) from 60 to 100 days. In addition, manganese only negatively affected epididymal sperm counts at 100 days in the iron-deficient group. When serum concentrations of LH, FSH, and testosterone and epididymal sperm counts from the 60- and 100-day-old rats were used to predict the reproductive age of the males, the 60-day old animals were predicted correctly. Of the 100-day-old animals, 2/12 controls, 7/12 at 350 mg manganese/kg, and 12/12 at 1,050 mg manganese/kg were classified as 60 days old.

These data indicate that manganese induced a significant maturational delay in the reproductive organs of the male rat (Laskey et al. 1982).

To further assess the mechanism of toxicity of manganese in the pre-weanling rat, Laskey et al. (1985) dosed rats from birth to 21 days of age with particulate manganese tetroxide in 50% sucrose solution by gavage at doses of 0, 71, or 214 mg manganese/kg/day. They then assessed the hypothalamic, pituitary, and testicular functions in the rat by measuring the endogenous or stimulated serum concentrations of FSH, LH, and testosterone at 21 or 28 days of age. LH-releasing hormone (LH-RH) was used to stimulate the pituitary-testicular axis to secrete FSH, LH, and subsequently testosterone; human chorionic gonadotropin (hCG) was used to stimulate acutely (2-hour time period) the testicular secretion of testosterone and repeatedly (7-day time period) to assess the ability of the Leydig cells to maintain maximal testosterone synthesis and secretion. Some rats from both control and manganese-dosed groups were castrated to determine the effect this would have on the study end points. Manganese treatment had only a slight effect on body and testes weights, while no effects were observed on unstimulated or stimulated FSH or LH serum levels. In addition, manganese did not affect endogenous or acute hCG-stimulated serum testosterone concentrations, but did decrease serum testosterone level following repeated hCG stimulation. Liver manganese at the 71 mg/kg/day manganese dose was significantly elevated over controls in both castrated (8.42±7.23 mg/kg for treated vs. 1.96±0.22 mg/kg for controls) and noncastrated (3.36±0.91 mg/kg for treated vs. 1.81±0.11 mg/kg for controls) rats. In addition, hypothalamic manganese concentrations were significantly increased at the 71 mg/kg/day dose in both castrated (6.10±3.0 mg/kg in treated vs. 0.59±0.11 mg/kg in controls) and noncastrated (3.73±1.18 mg/kg in treated vs. 0.65±0.057 mg/kg in controls) rats. The authors speculate that since their earlier results had shown changes in male reproductive development in postpubertal animals with minimal manganese concentrations in tissues (Gray and Laskey 1980; Laskey et al. 1982), it seemed likely that the changes in this later study (Laskey et al. 1985) would result from high manganese concentrations in the hypothalamus, pituitary, or testes, with the tissue with the highest manganese concentration being the site of the toxic reproductive effect. However, the results from this latest study reveal that manganese had no effect on the hypothalamus or pituitary to produce LH or FSH in pre-weanling rats, despite the increased manganese concentrations. Rather, the data indicate that it is delayed production of testosterone, shown by the inability of the Leydig cells to maintain maximum serum concentrations of the hormone, which results in the delayed sexual maturation. This delay in testosterone was not significant enough, however, to impair rodent fertility at manganese doses as high as 1,050 mg/kg/day (Laskey et al. 1982).

A slight decrease in pregnancy rate was observed in rats exposed to 3,500 mg manganese/kg/day (as manganese tetroxide) in the diet for 90–100 days prior to breeding (Laskey et al. 1982). Since both sexes were exposed, it is not possible to conclude whether the effect was in males, females, or both. However, this exposure regimen did not have significant effects on female reproductive parameters such as ovary weight, litter size, ovulations, or resorptions (Laskey et al. 1982).

Manganese was found to affect sperm formation and male reproductive performance in other intermediate-duration oral studies (Elbetieha et al. 2001; Joardar and Sharma 1990; Ponnapakkam et al. 2003a, 2003c). Joardar and Sharma (1990) administered manganese to mice, as potassium permanganate or manganese sulfate, at 23–198 mg/kg/day by gavage for 21 days. The treatment resulted in sperm head abnormalities, and the percentage of abnormal sperm was significantly elevated in all exposed mice as compared to controls. Increased incidences of testicular degeneration occurred in male Sprague-Dawley rats exposed for 63 days to doses ≥137.2 mg manganese/kg/day as manganese acetate, but not at 68.6 mg/kg/day (Ponnapakkam et al. 2003c). Impaired male fertility was observed in male mice exposed to manganese chloride in drinking water for 12 weeks before mating with unexposed females at a daily dose level of 309 mg manganese/kg/day, but not at doses ≤154 mg manganese/kg/day (Elbetieha et al. 2001). In the 309-mg/kg/day group, 17 pregnancies occurred in 28 mated females, compared with 26 pregnancies out of 28 females mated with controls. At lower dose levels in another study, decreased sperm motility and sperm counts were observed in male CD-1 mice after 43 days of exposure to manganese acetate at doses of 4.6 or 9.6 mg manganese/kg/day, but these doses did not impair the ability of these males to impregnate unexposed females (Ponnapakkam et al. 2003a).

In another intermediate feeding study, Jarvinen and Ahlström (1975) administered varying doses of manganese sulfate, from nutritionally deficient levels to excess amounts, to Sprague-Dawley female rats for 8 weeks prior to mating. The rats were continued on manganese diet (0.75, 4.5, 10, 29, 94, or 187 mg manganese/kg/day) until GD 21. The authors found no effect of manganese on maternal weight gain, implantation number, resorptions, or percentage of dead fetuses. The authors did observe that manganese doses of 94 mg manganese/kg/day and higher resulted in significant increases in liver manganese concentrations, whereas nonpregnant females had liver manganese concentrations that were unchanged, irrespective of dose. These data suggest that pregnancy allows the female to develop significant liver manganese stores, and it is possible these stores may be mobilized during gestation or at a future time. The authors also noted that pregnant rats had consistent liver iron concentrations, whereas nonpregnant rats developed a dose-dependent decrease in liver iron concentrations. Further, the highest dose in dams caused a significant increase in fetal manganese content.

Szakmáry et al. (1995) studied the reproductive effects of manganese chloride, administered by gavage to pregnant rabbits and rats at concentrations of 0, 11, 22, and 33 mg manganese/kg/day on GDs 6–20 in the rabbit and throughout gestation in the rat. Manganese did not result in any reproductive effect in the rabbit, but the highest manganese dose did cause an increase in postimplantation loss in the rat. In 13-week dietary studies, no gross or histopathological lesions or organ weight changes were observed in reproductive organs of rats fed up to 618 mg manganese/kg/day or mice fed 1,950 mg manganese/kg/day, but the reproductive function was not evaluated (NTP 1993).

More recent oral studies indicate that ingested manganese does not result in female reproductive toxicity when rat dams were exposed during pregnancy, but impaired female fertility was observed when female mice were exposed to manganese in drinking water for 12 weeks before mating with unexposed males. The first study involved a dose of 22 mg manganese/kg/day administered as manganese chloride by gavage to female rats on days 6–17 of gestation (Grant et al. 1997a). No treatment-related mortality, clinical signs, changes in food or water intake, or body weights were observed in the dams. In the second study (Pappas et al. 1997), manganese chloride was provided to pregnant rats in drinking water at doses up to 620 mg manganese/kg/day throughout gestation. The manganese did not adversely affect the health of the dams, litter size, or sex ratios of the pups. More extensive analyses of female reproductive organs were not performed. Similarly, Kontur and Fechter (1985) found no significant effect on litter size in female rats exposed to manganese chloride in drinking water except at concentrations so high (1,240 mg manganese/kg/day) that water intake by the dams was severely reduced. In contrast, Elbetieha et al. (2001) reported that decreased numbers of implantations and viable fetuses were observed in female Swiss mice exposed to manganese chloride in drinking water at a dose level of 277 mg manganese/kg/day for 12 weeks before mating with unexposed males.

In a 2-year NTP study, no adverse reproductive effects (lesions in reproductive organs) from manganese sulfate exposure were reported for rats at up to 232 mg manganese/kg/day or mice at up to 731 mg manganese/kg/day (NTP 1993).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

No studies were located regarding reproductive effects in humans or animals following oral exposure to MMT.

3.2.2.6 Developmental Effects

Very little information is available on the developmental effects of manganese in humans. The incidences of neurological disorders and the incidences of birth defects and stillbirths were elevated in a small population of people living on an island where there were rich manganese deposits (Kilburn 1987); however, the lack of exposure data, the small sample sizes, and the absence of a suitable control group preclude ascribing these effects to manganese. The route of exposure was assumed to be primarily oral, but inhalation exposure was not ruled out.

As discussed in Section 3.2.2.4, two studies have evaluated adverse neurological results in children exposed to increased manganese concentrations in both water and food. The first study (He et al. 1994), evaluated 92 children, aged 11–13, who drank water containing manganese at average levels of at least 0.241±0.051 mg/L for 3 years or more and who also ate foodstuffs (wheat flour) with excess manganese (due to the high concentration of the metal in sewage water used to irrigate/fertilize the fields). These children were compared to 92 children from a nearby village whose manganese concentration in water did not exceed 0.040±0.012 mg/L (controls). The children who consumed higher manganese concentrations performed more poorly on the WHO neurobehavioral core tests (the emotional status test was omitted) than the control children. Further, the blood and hair manganese concentrations of exposed children were significantly higher than those of the control population. The negative results on the tests were correlated with hair manganese concentration. Zhang et al. (1995) reported that the children with increased manganese exposure also performed more poorly in school (as measured by mastery of their native language, mathematics, and overall grade average), and their serum levels of serotonin, norepinephrine, dopamine, and acetylcholinesterase were significantly decreased compared to controls. In the second study, Wasserman et al. (2006) cross-sectionally evaluated intellectual function in 142 10-year old children in Bangladesh who had been consuming well water with an average concentration of 793 µg manganese/L and 3 µg arsenic/L. Intellectual function was assessed using Weschler's Intelligence Scale for Children, from which raw scores for verbal, performance, and full scale were calculated. After grouping children into four groups based on manganese concentrations in the wells (<200, 200–499, 500–999, and ≥1,000 µg/L), regression analyses indicated that children in the highest exposure group (with estimated daily intakes of 0.07 mg manganese/kg/day in drinking water) had statistically significantly lower verbal, performance, and full scale scores compared with children in the lowest exposure group.

In animals, classical developmental toxicity studies have not found distinct effects on fetal survival, gross fetal malformations, or skeletal or visceral malformations or alterations. For example, acute administration of manganese chloride by gavage to pregnant rats at a dose of 22 mg manganese/kg/day on GDs 6–17 resulted in no adverse fetal developmental effects, measured as weight gain, gross malformations, or skeletal malformations (Grant et al. 1997a). In another study, Szakmáry et al. (1995) studied the developmental toxicity of manganese in the rabbit and rat. The metal, as manganese chloride, was administered by gavage during the whole period of gestation in the rat, and during organogenesis (day 6–20) in the rabbit at concentrations of 0, 11, 22, and 33 mg/kg/day. In the rabbit, manganese treatments did not result in decreases in fetal weights, skeletal retardation, or extra ribs, or in an increase in fetuses afflicted with major anomalies. In the rat, the highest dose resulted in retardation of development of the skeleton and internal organs. In addition, manganese at the highest dose caused a significant increase in external malformations, such as clubfoot. However, when pups from dams treated at the same dose were allowed to grow for 100 days after birth, no external malformations were observed, indicating that these effects were self-corrected. No significant differences were found in any of the groups concerning the development of the ears, teeth, eyes, forward motion, clinging ability, body posture correction reflex, or negative geotaxis reflex.

Many developmental toxicity studies in animals orally exposed to excessive manganese have focused on possible effects on development of reproduction functions and neurological functions.

Several animal studies of the effects of manganese on reproductive development show developmental effects.

One study involved pre-weanling mice (Gray and Laskey 1980) that were fed 1,050 mg manganese/ kg/day (as manganese tetroxide) beginning on PND 15. On days 58, 73, and 90, mice were sacrificed and reproductive organ (preputial gland, seminal vesicle, and testes) weights and body weights were measured. The manganese decreased the growth of these reproductive organs, but had no effect on body growth or liver or kidney weights.

In another study, Laskey et al. (1982) evaluated the effect of dietary manganese exposure on rats during gestation and continued during nursing and after weaning at doses of 0, 350, 1,050 or 3,500 mg manganese/kg/day. The manganese was given in combination with either 20 or 200 mg iron/kg/day (the former is deficient in iron, the latter is adequate). Manganese treatment was lethal at the highest dose in the iron-deficient diet, but had no effect on male or female body weight at any age in animals receiving an

iron-sufficient diet. In the iron-poor diet, body weights of males were significantly depressed ($p<0.05$) through day 100 of the study, whereas the females' body weights were depressed only through day 60. Select females and males were mated at day 90–100 of the study and the reproductive outcomes were analyzed. The manganese treatment did not have any significant adverse effects at any dose except to significantly decrease the number of pregnancies at the highest dose ($p<0.05$). Litter size, ovulations, resorptions, preimplantation deaths, and fetal weights were unaffected by the metal. Testes weights in males were significantly decreased from controls only when administered manganese in conjunction with an iron-poor diet: at day 40 at 1,050 and 3,500 mg manganese/kg/day and at day 100 at 1,050 mg/kg/day. Hormone levels in male rats were also evaluated. No effect was seen from manganese treatment in 40-day-old male rats. At 60–100 days of age, however, dose-related decreases in serum testosterone were observed, when age-related increases were expected and no increase in serum LH was observed. Manganese given in both iron regimens prevented the normal decrease in serum follicle-stimulating hormone (FSH) from 60 to 100 days. Manganese decreased epididymal sperm count only when given with the iron-poor diet as measured at 100 days.

A third study involved gavage administration of 0, 71, or 214 mg manganese/kg/day (as manganese tetroxide) to pre-weanling rats from birth to 21 days of age (Laskey et al. 1985). Functioning of the hypothalamus, pituitary, and testicular tissues were measured by assaying endogenous or stimulated serum concentrations of FSH, LH, and testosterone at days 21 or 28. No manganese-related effects were observed on unstimulated or stimulated FSH or LH serum levels. In addition, manganese did not affect endogenous or acute hCG-stimulated serum testosterone concentrations but did decrease serum testosterone level following chronic hCG stimulation. Liver and hypothalamic manganese concentrations were significantly increased in treated rats given the 71 mg/kg/day dose over controls. The authors hypothesized that the manganese had an unknown affect on the testicular Leydig cell that resulted in the delayed production of testosterone. This delayed production was presumably causing the delayed reproductive maturation seen in the earlier study (Gray and Laskey 1980), but was not enough to affect fertility outcomes at doses as high as 1,050 mg/kg/day (Laskey et al. 1982).

Many animal studies have examined neurological end points in animals repeatedly exposed during gestations and/or neonatal or juvenile stages of life. End points evaluated have included brain chemistry, neurobehaviors, and neuropathology.

Studies of manganese in Rhesus monkeys by Golub et al. (2005) were prompted by the observation that soy-based formulas provided to human infants contain relatively high levels of manganese and thus may

pose a potentially toxic hazard to early neurological development. Groups of eight male infant Rhesus monkeys were fed a commercial cow's milk based formula (Similac containing 50 µg manganese/L as control, providing 17.5 mg manganese/kg/day), a commercial soy protein based formula (soy containing 300 µg manganese/L, providing 107.5 mg manganese/kg/day), or the same soy formula with added manganese chloride for a final concentration of 1,000 µg manganese/L (soy plus manganese, providing 328 mg manganese/kg/day). Formulas were exclusively fed to infants starting on the day of birth and extending through 4 months of age, at which time monkeys were transitioned to standard laboratory diet. A behavioral test battery was administered over an 18-month period. The battery included measures of motor, cognitive, and social skills, as well as tests related to the dopamine system (reward delay, fixed interval dopamine drug response). Infants that did not generate sufficient data in each test to permit evaluation were excluded from data analyses. Growth and levels of the dopamine metabolite HVA and the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) in CSF at 4, 10, and 12 months of age were also measured. No significant differences between groups were observed for body weights and levels of dopamine and serotonin metabolites in cerebrospinal fluid.

Monkeys fed soy supplemented with manganese were consistently more active during 12 weekly 7-minute observation periods, compared with control and soy monkeys. "Motor behaviors" were observed in seven of eight soy plus manganese monkeys, compared with three of eight in soy monkeys and three of eight in control monkeys. Assessment of gross motor maturation during these observation periods did not detect clear differences between the groups. Both soy and soy plus manganese groups showed some changes in activity/sleep patterns. Compared with controls at 4 months, the 4-month monkeys fed soy plus manganese showed 50% less activity ($p<0.05$) during the sleep portion of the sleep/wake cycle (this change was not seen at 8 months). At 8 months (but not at 4 months), both soy and soy plus manganese monkeys showed significantly ($p<0.05$) longer sleep periods and shorter longest time inactive during awake periods than controls. Social interactions were assessed during 16 sessions in which each monkey was paired with another monkey in the study. In these sessions, both soy and soy plus manganese monkeys demonstrated ~66% less time ($p<0.05$) in chase or rough play and more time in clinging activity compared with control monkeys.

Significant group differences were not consistently observed in more highly structured tests to assess cognitive functions including learning, memory, and attention than controls ($p<0.05$ for 328 mg manganese/kg/day and $p<0.01$ for 107.5 mg manganese/kg/day). For example, a response latency decrease was observed in a reward delay response task in the soy group by 50% compared to control, but no significant difference (although a 20% reduction) was observed in the soy plus manganese group. The

authors noted that more formal tests of cognitive functions would be most appropriately administered at more mature ages.

Other studies in neonatal animals have detected neurostructural and neurochemical changes at doses similar to or slightly above dietary levels (1–10 mg manganese/kg/day) (Chandra and Shukla 1978; Deskin et al. 1980), suggesting that young animals might be more susceptible to manganese than adults.

Kristensson et al. (1986) investigated the developmental effects of manganese chloride on 3-day-old male rat pups. The authors dosed the pups with 150 mg manganese/kg/day by gavage in water for 41 days. The pups developed a transient ataxia on days 15–22, which was resolved by the end of the dosing period. The exposed pups also had increased levels of manganese in the blood and the brain (7–40-fold increase in 15- and 20-day-old rats, with cortex and striatum concentrations being relatively equal). In 43-day-old rats, the increases in brain manganese levels were less than those observed in younger rats (i.e., approximately 3 times the control levels), but the striatal levels were higher than in the cortex. Manganese treatment decreased the concentration of homovanillic acid (metabolite of dopamine) in the striatum and the hypothalamus, but not in other brain regions. No other monoamines and metabolites were affected. In a similar study, neonatal rats given bolus doses of manganese chloride in water of 0.31 mg manganese/kg/day for 60 days suffered neuronal degeneration and increased brain monoamine oxidase on days 15 and 30 of the study, but did not show any clinical or behavioral signs of neurotoxicity (Chandra and Shukla 1978).

Deskin et al. (1980, 1981) also found changes in brain chemistry in rat pups dosed with manganese. In the first study, male rat pups were administered 0, 1, 10, or 20 mg manganese/kg/day (as manganese chloride) via gavage in 5% sucrose solution for 24 days postnatal. The authors observed that the two highest doses resulted in decreased dopamine levels in the hypothalamus, while the highest dose resulted in a significant decrease in brain tyrosine hydroxylase activity and a significant increase in monoamine oxidase activity in the hypothalamus. Hypothalamic norepinephrine was unaffected by any manganese dose, and no significant changes in neurochemistry were noted in the corpus striatum. The authors suggested that the observed effects were probably due to decreased activity of tyrosine hydroxylase and increased levels of monoamine oxidase.

The second study (Deskin et al. 1981) involved dosing male rat pups with 0, 10, 15 or 20 mg manganese/kg/day (as manganese chloride) via gavage in 5% sucrose solution, for 24 days starting at birth. The authors performed neurochemical analyses of hypothalamus and corpus striatum as before and

observed that serotonin was increased in the hypothalamus at the highest dose, but was not elevated significantly in the striatum. Acetylcholinesterase levels were significantly decreased in the striatum at the highest dose, but were unchanged in the hypothalamus. The authors believed that the decrease in acetylcholinesterase to be of minor functional significance given that other mechanisms can also regulate acetylcholine metabolism.

Lai et al. (1984) studied the effect of chronic dosing of 40 mg manganese/kg/day (as manganese tetroxide given in drinking water) to neonatal rats that were exposed from conception, throughout gestation, and up to 2 years of age. The authors found that manganese treatment led to small decreases in choline acetyltransferase activities in cerebellum and midbrain of 2-month-old rats. The regional distribution of glutamic acid decarboxylase or acetylcholinesterase was unchanged.

An intermediate drinking water study in pregnant rats (Pappas et al. 1997) investigated the developmental neurotoxicity of manganese chloride doses of either 120 or 620 mg manganese/kg/day given on GDs 1–21. Following birth, the dams were continued on manganese until weaning at PND 22. When the dams were removed, the pups were continued on the same manganese doses until PND 30. Male pups were observed on several days subsequent to exposure in a number of behavioral tests that measured spontaneous motor activity, memory, and cognitive ability. The manganese-treated rats' performance was not significantly different from control rats. Pups from the highest-dose group exhibited a significantly decreased weight gain on several days post-dosing, as well as an increased activity level on PND 17 that was no longer evident by PND 30. The high-dose rats were not overactive on other days, and the decreased weight gain was resolved by PND 90. Neurochemical analyses of the brains from treated pups indicated that brain manganese concentrations were significantly elevated in the high-dose group, as compared to controls. Brain enzyme and dopamine concentrations were not significantly different between groups, but cortical manganese concentrations were significantly elevated in the high-dose group. Cortical thickness was significantly different in several areas of the brains of pups in the high-dose group but was only found to be significantly different in one area of the low-dose group. The significance of the cortical thinning is not clear.

While the Szakmáry et al. (1995) and Pappas et al. (1997) studies did not observe any changes in behavior due to manganese, many other studies have explored the potential for oral manganese exposure during early development to produce effects on later behavior and have frequently observed subtle changes in behavior attributable to manganese exposure (Ali et al. 1983a; Kontur and Fechter 1988; Reichel et al. 2006; Tran et al. 2002a).

A study by Kontur and Fechter (1988) reported no difference in levels of monoamines and related metabolites in neonatal rats at 22 mg manganese/kg/day as manganese chloride (14–21 days), although Dorman et al. (2000) reported elevated striatal DA and DOPAC in 21-day-old rats administered the same high daily dose used by Kontur and Fechter (1988) from PND 1 to 21. Effect of manganese treatment on neurobehavior was also evaluated in this study. There was a significant decrease in body weight gain in pups at the highest manganese exposure dose. Although there were no statistically significant effects on motor activity or performance in the passive avoidance task in the neonates, manganese treatment induced a significant increase in amplitude of the acoustic startle reflex at PND 21. However, in adult rats, the amplitude of the acoustic startle reflex was significantly decreased compared to the control at the lowest dose tested.

Reichel et al. (2006) studied the effects of manganese in male Sprague-Dawley rats that were born and dosed daily with an oral dose of 0, 4.4 or 13.1 mg manganese/kg/day as manganese chloride on postpartum days 1–21. Locomotor activity was assessed (distance traveled horizontally; PNDs 10–14), as was olfactory orientation (PNDs 9–13), negative geotaxis (PNDs 8–12) and balance and coordination (PND 90). Day of eye opening, pinna detachment, and incisor eruptions was also evaluated. Mean body weights at PND 21 were decreased by about 2 and 3% in the low- and high-dose groups, respectively, compared with controls. Manganese concentrations in striatum were elevated in the high dose group, compared with control, at PND 14 (~4-fold) and PND 21 (~2-fold), but not at PND 90. Manganese levels were not measured in the low-dose group. No exposure-related effects were noted on developmental landmarks (eye opening, pinna detachment, incisor eruption), basal motor activity during the neonatal period (PNDs 10–14) and adulthood (PND 90), or olfactory discrimination of home cage bedding during the neonatal period. The only behavioral end point affected during the neonatal period was a significant ($p<0.05$) increase in mean latencies to rotate 180° on the inclined plane of a negative geotaxis task. At PND 90, dopamine transporter binding sites in the striatum were decreased by about 20 and 60% in the low- and high-dose groups, respectively; only the high-dose value was significantly different ($p<0.05$) from the control. At PND 90, the locomotor activating effects of 20 mg/kg cocaine were significantly ($p<0.05$) decreased in the neonatally exposed manganese high dose group, compared with controls. The results indicate that neonatal exposure of rats to excess manganese caused subtle behavioral effects (altered balance in the neonatal period and diminished locomotor response to cocaine in adulthood) and neurochemical effects in adulthood (decreased dopamine binding sites in the striatum).

In a study by Tran et al. (2002a), Sprague-Dawley PND 1 litters were culled to 10–12 pups per dam and then were supplemented from PNDs 1–20 with 0, 0.7, 3.8, or 7.5 mg manganese/kg/day as manganese chloride provided by mouth. Male and female pups were used. Righting test (PND 6), homing test (olfactory discrimination; PND 10), and passive avoidance (PND 32) were performed. Striatal dopamine levels were also determined after sacrifice on PND 40. Tissue analyses (on brain, liver, kidneys, spleen, and small intestine) for iron, copper, zinc, and manganese content were performed on animals sacrificed on PNDs 14, 21, and 40. Animals were not dosed after PND 20. The two highest dose groups of rats took approximately twice as long (2 seconds) as control and 0.7 mg manganese/kg/d (approximately 1 second) to right themselves; this result was not statistically significant. In the homing test of olfactory discrimination, the 7.5 mg manganese/kg/day group took significantly longer to reach their goal compared to controls and the 3.8 mg manganese/kg/day group (the 0.7 mg manganese/kg/day group performed similarly to the control). The control group required approximately 40 seconds; the high-dose group required 75 seconds (an 88% increase in the high-dose group over the control). In the passive avoidance task, there was a positive linear trend, with the highest dose group showing a 3-fold increase in the number of footshocks received over the control. The 3.8 mg manganese/kg/d group showed a 2-fold increase in the number of footshocks over the control. A negative linear relationship was also observed in striatal dopamine concentrations, with the high-dose group having approximately half the dopamine concentration of the control. No dose-related trends over time points were observed in manganese content of tissues. The highest dose group showed some statistically significant ($p<0.05$) increases in manganese in body tissues (brain, small intestine, kidney) at different time points. An increase ($p<0.05$) was observed in the high dose group for iron in the small intestine on PND 40. No changes were seen in copper or zinc tissue concentration. Both males and females were used in behavioral tests since ANOVAs showed no interactive effects of treatment or sex.

Ali et al. (1983a) conducted a gestational study investigating the neurological effects of excess manganese in drinking water on rats maintained on either a normal or low-protein diet. Manganese exposure originated 90 days prior to mating and continued throughout gestation and nursing. The offspring of rats who drank the equivalent of 240 mg manganese as manganese chloride/kg/day had pups with delayed air righting reflexes. No treatment-related effects were observed in body weight or brain weight in pups from dams fed the normal amount of protein. Significant delays in age of eye opening and development of auditory startle were observed only in the pups of dams fed protein-deficient diets. In a recent study, Dorman et al. (2000) evaluated the effects of oral manganese treatment in neonatal CD rats. Pups were administered manganese chloride in water at 11 or 22 mg manganese/kg for 21 days by mouth with a micropipette and were dosed starting after birth (PND 1) until weaning (PND 21). At PND 21, the

effect of manganese treatment on motor activity, learning and memory (passive avoidance task), evoked sensory response (acoustic startle reflex), brain neurochemistry, and brain pathology was evaluated. Manganese treatment at the highest dose was associated with decreased body weight gain in pups, although the authors indicated that absolute brain weight was not significantly altered. There were no statistically significant effects on motor activity or performance in the passive avoidance task. However, manganese treatment induced a significant increase in amplitude of the acoustic startle reflex. Significant increases in striatal DA and DOPAC concentrations were also observed in the high-dose treated neonates. No pathological lesions were observed in the treated pups. The authors indicated that these results suggest that neonatal rats are at greater risk than adults for manganese-induced neurotoxicity when compared under similar exposure conditions.

In a longer-duration intermediate study, Jarvinen and Ahlström (1975) fed female rats up to 187 mg manganese/kg/day (as manganese sulfate) for 8 weeks prior to conception. The rats were continued on manganese treatment until the 21st day of gestation. The unborn pups from dams administered 94 mg manganese/kg/day had significantly decreased weights as compared to the other groups. No gross malformations were observed in the fetuses, and alizarin-stained bone preparations revealed no abnormalities in any dose group. However, fetuses from dams fed the highest manganese dose had significantly higher concentrations of manganese in their bodies than fetuses from the other groups. These data indicate that a level of 187 mg manganese/kg/day overwhelmed the rat's homeostatic control of manganese and the metal accumulated in the fetus. The highest manganese dose also resulted in a significant decrease in the iron content of the fetuses.

Garcia et al. (2006, 2007) studied the relationship between dietary manganese and dietary iron on brain chemistry and neurotransmission. In one study, groups of 5–7 dams were fed diets containing 35 ppm iron (control) or 8 mg manganese/kg/day and 35 ppm iron (manganese-supplemented) from GD 7 through PND 7 (Garcia et al. 2006). On PND 4, pups born to control dams were pooled and randomly cross-fostered to dams fed one of the two diets such that initial mean litter weights were equivalent. Pups were exposed to each of these diets via maternal milk from PND 4 to 21 as well as via direct ingestion of chow (beginning around PND 11) and were euthanized on PND 21. In the dams, the high manganese diet induced changes in hematological parameters similar to those seen with iron-deficiency: 50% decrease in plasma iron (without significant decreases in hemoglobin) and increased plasma transferrin and total iron binding capacity. Compared with controls, manganese-exposed pups showed decreased hemoglobin (about 20%), decreased plasma levels of iron (about 70%), increased plasma tranferrin and total iron binding capacity (about 10%), increased brain concentrations of manganese, chromium, and zinc,

decreased brain iron levels, increased protein expression of divalent metal transporter-1 (DMT-1) and transferrin receptor (TfR) in all brain regions, increased GABA concentrations, and increased ratios of GABA to glutamate concentrations. Because GABA is an inhibitory amino acid and glutamate is an excitatory amino acid, the authors suggested that the manganese treatment induced enhanced inhibitory transmission in the brain of the pups. The results indicate that manganese treatment altered transport and distribution of iron in developing rat pups and induced perturbations in brain levels of the neurotransmitter, GABA.

In a further study by Garcia et al. (2007), groups of 5–7 GD7 timed–pregnant Sprague-Dawley rats were fed one of three experimental diets: control (35 mg Fe/kg diet; 10 mg manganese/kg diet), low iron (3 mg Fe/kg diet; 10 mg manganese/kg diet), or low iron with supplemented manganese (3 mg Fe/kg diet, 100 mg manganese/kg diet). On PND 4, pups born to the control dams were pooled and randomly cross-fostered to dams fed one of the two iron-deficient diets, such that initial mean litter weights were approximately equivalent. The pups received these diets via maternal milk from PND 4 to 21, at which time the pups were sacrificed. Levels of essential metals in the brain were measured (in cerebellum, cortex, hippocampus, striatum, and midbrain) by inductively coupled plasma-mass spectrometry. Increases in brain levels in low iron/manganese-treated rats (compared to control and low iron) were seen for the following metals: copper, manganese (~50%), chromium (~150%), cobalt (~150%), molybdenum (~25%), zinc (~130%), aluminum (~130), and vanadium (~150%). A decrease in brain iron levels was observed for low iron animals; low iron/manganese-treated rats had iron levels significantly higher than the low iron animals.

No studies of developmental effects following oral exposure to MMT in humans or animals were located.

3.2.2.7 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to inorganic manganese.

Chronic (2-year) feeding studies in rats and mice have yielded equivocal evidence for the carcinogenic potential of manganese. For example, rats exposed to up to 232 mg manganese/kg/day as manganese sulfate for 2 years showed no increases in tumor incidence (NTP 1993). Mice fed up to 731 mg manganese/kg/day as manganese sulfate for 2 years had a marginally increased incidence of thyroid gland follicular cell adenomas (high-dose animals) and a significantly increased incidence of follicular cell

hyperplasia (NTP 1993); this was considered by NTP to be "equivocal evidence of carcinogenic activity of Mn(II) sulfate monohydrate in male and female B6C3F_1 mice" (there was "no evidence of carcinogenic activity" in rats in this study).

No studies were located regarding carcinogenic effects in humans or animals following oral exposure to MMT.

3.2.3 Dermal Exposure

For inorganic manganese compounds, dermal exposure is not a typical pathway of exposure because manganese does not penetrate the skin readily. For organic manganese, dermal exposure is a possibility with all compounds discussed in this profile. This exposure pathway is most likely, however, with MMT, where occupational workers (mechanics, workers in the gasoline industry, pesticide manufacturers and sprayers) are likely to handle large quantities of these compounds.

No studies were located regarding the any health effects in humans or animals after dermal exposure to inorganic manganese.

3.2.3.1 Death

No studies were located regarding death in humans from dermal exposure to MMT.

Hinderer (1979) reported LD_{50} values for rabbits (strain and sex were unreported) that were administered varying doses of “neat” commercial MMT on abraded skin in the trunk area for 24 hours. These values, generated by four different laboratories, ranged from 140 to 795 mg/kg. Although this dose range is wide, the author reported that it was analogous to the wide oral LD_{50} range given for the compound in other reports.

3.2.3.2 Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans or animals following dermal exposure to MMT.

Cardiovascular Effects. No studies concerning cardiovascular effects following dermal exposure to MMT in humans or animals were located.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following dermal exposure to MMT. Hinderer (1979) observed bloody diarrhea in rabbits exposed dermally to MMT; the compound was obtained as commercial grade, "neat," and applied to shaved skin for 24 hours. No histopathology was performed to ascertain the presence of lesions on the gastrointestinal tract.

Hematological Effects. No studies were located regarding hematological effects in humans or animals following dermal exposure to MMT.

Musculoskeletal Effects. No studies regarding musculoskeletal effects in humans or animals following dermal exposure to MMT were located.

Hepatic Effects. Hinderer (1979) observed that rabbits that underwent dermal application of a commercial "neat" solution of MMT for 24 hours on shaved skin had discoloration of the liver and swollen liver. No histopathology was performed.

Renal Effects. Hinderer (1979) observed that rabbits that underwent dermal application of a commercial "neat" solution of MMT for 24 hours on shaved skin had discoloration of the kidneys and swollen and congested kidneys. No histopathology was performed.

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals following dermal exposure to MMT.

Dermal Effects. No studies were located regarding dermal effects in humans following dermal exposure to MMT. Hinderer (1979) observed that rabbits exposed dermally to commercial "neat" MMT on shaved skin for 24 hours developed edema and erythema. Further dermal irritation tests performed showed that MMT is a moderate skin irritant. Campbell et al. (1975) exposed male albino rats dermally to MMT for 24 hours on closely clipped dorsolateral aspects of the trunk that were either abraded or allowed to remain intact; skin reactions were evaluated and scored at 24 hours and again 48 hours later. By comparing skin reactions following exposure to a test rating that categorized irritancy levels, MMT was determined to be safe for intact or abraded skin contact. However, the authors note that MMT in concentrated form is absorbed through the skin, and dermal absorption or interactions with other materials or factors were not incorporated into their study.

Ocular Effects. No studies were located regarding ocular effects in humans or animals following dermal exposure to inorganic manganese.

Hinderer (1979) performed a standard Draize irritation test with commercial “neat” MMT in rabbits and found the compound not to be an eye irritant.

Body Weight Effects. No studies were located regarding body weight effects in humans or animals following dermal exposure to inorganic manganese.

Rabbits exposed dermally to commercial “neat” MMT exhibited slight body weight loss, although the actual amount was not reported (Hinderer 1979).

Metabolic Effects. No studies were located regarding metabolic effects in humans or animals following dermal exposure to inorganic manganese.

No studies were located regarding metabolic effects in humans or animals following dermal exposure to MMT.

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects following dermal exposure to inorganic manganese in either humans or animals.

No studies regarding immunological and lymphoreticular effects following dermal exposure to MMT in humans or animals were located.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects following dermal exposure to inorganic manganese in either humans or animals.

Rabbits exposed to “neat” commercial grade MMT on shaved areas of their trunks for 24 hours experienced the following reported symptoms: polypnea, vocalization, excitation, ataxia, tremors, cyanosis, and convulsions (Hinderer 1979).

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following dermal exposure to inorganic manganese.

No studies were located regarding reproductive effects in humans or animals following dermal exposure to organic manganese.

3.2.3.6 Developmental Effects

No studies were located regarding reproductive effects in humans or animals after dermal exposure to inorganic manganese.

No studies were located in humans or animals concerning developmental effects following dermal exposure to MMT.

3.2.3.7 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to inorganic manganese.

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to MMT.

3.2.4 Diagnostic Uses

Manganese is a paramagnetic element that can contain up to five unpaired electrons in its ionic form. The unpaired electrons can facilitate T1 relaxation (in MRI) by interacting with hydrogen nuclei of water molecules (Earls and Bluemke 1999). This T1 relaxation provides a contrast in signal during MRI from normal cells and tumor cells because normal cells will take up the metal, whereas the cancerous cells take up little or no manganese (Toft et al. 1997a). The Mn^{2+} ion is the ion of choice because it is most readily found in the body. However, because increased amounts of other sources of Mn^{2+}, especially manganese chloride, were found to have a high acute toxicity (as discussed in the previous sections), it is necessary to chelate the Mn^{2+} ion with another molecule that might decrease the toxic nature of the free ion. One such

chelate is the fodipir molecule, or dipyridoxal diphosphate. The result is mangafodipir, Mn(II)-*N*,*N*'-di-pyridoxylethylendiamino-*N*,*N*;-diacetate-5,5'-bis(phosphate), or manganese dipyridoxal diphosphate (MnDPDP). This clinical imaging agent is primarily used in the detection of hepatobiliary tumors, as it is preferentially taken up by parenchymatous cells. However, as other organs have parenchymatous cells, the compound is also useful in the detection of kidney, pancreas, and adrenal gland tumors (Earls and Bluemke 1999).

This section will discuss the adverse effects of administration of mangafodipir. This section will not discuss the efficacy of mangafodipir as a contrast agent in the identification of abdominal cancer. Because this compound is used primarily in the detection of liver and other parenchymatous tumors, it is found exclusively in hospitals and other clinical settings. It is only administered intravenously; therefore, all subsequent studies discussed entail an intravenous exposure route. Because the toxicity of mangafodipir is mediated by manganese, the doses will be in mg manganese/kg body weight, rather than in terms of the parent compound.

3.2.4.1 Death

There are no reports of lethality in humans following administration of mangafodipir.

Administration of mangafodipir can occur either all at once (bolus) or over a specific timed period necessary to give the entire amount of a precalculated dose (slow infusion). The latter method has been found to be better tolerated in a clinical setting (Bernardino et al. 1992; Lim et al. 1991; Padovani et al. 1996).

Mangafodipir was found to cause lethality in both sexes of Swiss-Webster mice with an LD_{50} of 2,916 mg manganese/kg after slow infusion of 15 seconds (Larsen and Grant 1997). The compound had an LD_{50} of 103 mg/kg in both sexes of the same rodent when administered in a bolus dose (Larsen and Grant 1997), showing the increased toxicity in the bolus administration. When given as a slow infusion over 5 minutes in both sexes of the CD-1 mouse, the compound had an LD_{50} value of 157 mg/kg, and when given at a rate of 1.2 mL/second in BOM:NMRI male mice, the LD_{50} was 211 mg/kg. In another study, the LD_{50} in both sexes of the Swiss-Webster mouse was found to be 290 mg/kg, when given as a slow infusion over approximately 2.5 minutes (Elizondo et al. 1991). One male and one female beagle dog given a single slow infusion (lasting ~110 seconds) of 160 mg/kg mangafodipir, as well as the one male given 120 mg/kg, died prior to the second day of the experiment; the remaining female given 120 mg/kg was

sacrificed due to a moribund condition on day 3 of the experiment (Larsen and Grant 1997). Dogs of both sexes given 83 or 99 mg/kg survived the 14-day observation period. A single slow infusion (lasting 5 minutes) at a dose of 160 mg/kg did not result in lethality in the Sprague-Dawley rat (Larsen and Grant 1997).

Death was not observed in Sprague-Dawley rats administered nine doses of 16 mg manganese/kg/day (as mangafodipir) given over 3 weeks (Elizondo et al. 1991; Larsen and Grant 1997). Moribund condition prompted the sacrifice of one male and one female beagle dog on days 12 and 21, respectively, of a 21-day exposure period in which the animals were administered 5.4 mg/kg/day manganese (as mangafodipir), whereas a lower dose of 1.6 mg/kg/day did not result in death or sacrifice of any treated dogs (Larsen and Grant 1997). Moribund condition also prompted the sacrifice of a single male Cynomolgus monkey on day 18 of a mangafodipir-dosing regimen involving 16 mg manganese/kg/day doses also given 3 times/week for 3 weeks (Larsen and Grant 1997). The authors did not indicate the precise cause of lethality in the sacrificed dogs; however, they noted the dogs' livers showed histological signs of cholangiohepatitis, fibroplasia, bile duct proliferation, and hepatocyte necrosis, with cortical tubular necrosis in the kidneys. The sacrificed monkey had a serum chemistry profile indicative of renal failure and associated liver toxicity.

3.2.4.2 Systemic Effects

Respiratory Effects. No reports were located concerning respiratory effects in humans following dosing with mangafodipir.

A single dose of 160 mg manganese/kg as mangafodipir in Sprague-Dawley rats of both sexes resulted in dyspnea (Larsen and Grant 1997).

Cardiovascular Effects. Mangafodipir, when administered to humans in timed doses in clinical studies has resulted in transient facial flushing and increased blood pressure at doses as low as 0.2 mg manganese/kg (facial flushing) (Bernardino et al. 1992; Lim et al. 1991; Padovani et al. 1996; Wang et al. 1997).

Slow infusion of mangafodipir at doses of 16.5 mg manganese/kg resulted in no cardiotoxicity in mongrel dogs of either sex (Karlsson et al. 1997). The dogs suffered from medically-induced acute ischaemic heart failure; cardiotoxicity was measured as the depression of cardiovascular function, with specific

measured end points being aortic pressure, pulmonary artery pressure, right atrial pressure, cardiac output, and heart rate (Karlsson et al. 1997). Sprague-Dawley rats suffered no cardiotoxicity (as measured by histomorphological evaluation) after a single administration of mangafodipir at doses as high as 63 mg/kg (Larsen and Grant 1997).

Rats administered nine doses (3 times/week for 3 weeks) of 16 mg manganese/kg did not suffer any adverse cardiovascular effects as measured by histomorphological analyses (Larsen and Grant 1997). Twenty-one days of daily administration of 5.4 mg manganese/kg in beagle dogs resulted in reduced heart rate by the end of the treatment (Larsen and Grant 1997). Cynomolgus monkeys administered 16 mg/kg for 3 days/week for 3 weeks resulted in flushing of the face, but no other measured cardiovascular effects (Larsen and Grant 1997).

Gastrointestinal Effects. Incidences of gastrointestinal effects in humans following injection with mangafodipir have been limited to rare complaints of nausea or vomiting that are short-lived (15 seconds to 5 minutes in length) and not dose- or administration rate-dependent (bolus vs. infusion) (Bernardino et al. 1992; Lim et al. 1991; Padovani et al. 1996; Wang et al. 1997). A dose of 81 mg manganese/kg as mangafodipir in beagle dogs of both sexes resulted in vomiting, diarrhea, and decreased food consumption (Larsen and Grant 1997).

Vomiting was observed in Cynomolgus monkeys of both sexes after administration of nine doses of 16 mg manganese/kg, given 3 times/week for 3 weeks (Larsen and Grant 1997). No other gastrointestinal effects in animals were reported.

Hematological Effects. No hematological changes (versus pretreatment values) were noted in three different studies that included 13 healthy males (Wang et al. 1997), 54 healthy males (Lim et al. 1991), or 96 human volunteers of both sexes with known or suspected focal liver tumors (Bernardino et al. 1992) administered up to 1.4 mg manganese/kg as mangafodipir (either via bolus or slow infusion).

A single dose of 63 mg manganese/kg as mangafodipir in both sexes of Sprague-Dawley rats resulted in no adverse hematological effects (Larsen and Grant 1997). Intermediate studies of adverse effects were also negative. Doses as high as 16 mg/kg given 3 times/week for 3 weeks to Sprague-Dawley rats (Elizondo et al. 1991; Larsen and Grant 1997) or Cynomolgus monkeys, or 5.4 mg/kg in beagle dogs dosed daily for 21 days, failed to induce any adverse hematological effects (Larsen and Grant 1997).

Musculoskeletal Effects. No reports of musculoskeletal effects in humans or animals following mangafodipir administration were located.

Hepatic Effects. Blood chemistry analyses revealed no significant changes in liver enzymes in several volunteers, either with or without tumors, given mangafodipir at doses up to 1.4 mg manganese/kg (Bernardino et al. 1992; Lim et al. 1991; Wang et al. 1997). Three individuals dosed with 0.55 mg manganese/kg and one dosed with 1.4 mg/kg had increased serum alanine aminotransferase; however, there was no dose response with these results and the maximum increase in the enzyme was to 70 International Units (IU)/l (the upper limit of the normal range is 45 IU/l) (Lim et al. 1991).

A single dose of up to 63 mg manganese/kg administered to both sexes of Sprague-Dawley rats did not produce any adverse hepatic effects as observed by histomorphological analyses (Larsen and Grant 1997). The administration of nine total doses of mangafodipir, three per week, at 16 mg manganese/kg/day per dose, resulted in an increased incidence (relative amount unreported) in hepatic microgranulomas in female Sprague-Dawley rats, but no effect on liver enzymes as measured by serum chemistry (Elizondo et al. 1991; Larsen and Grant 1997). Twenty-one daily doses of 1.6 mg/kg/day resulted in an increase in serum enzymes (alanine aminotransferase, ornithine carbamyl transferase, glutamine dehydrogenase, alkaline phosphatase, gamma-glutamyl transferase), as well as bilirubin and cholesterol, in both sexes of beagle dogs, while a higher dose of 5.5 mg/kg/day resulted in increased liver enzymes and liver weight and changes in liver pathology (cholangiohepatitis, fibroplasia, bile duct proliferation, and hepatocyte necrosis) (Larsen and Grant 1997). The authors noted that altered serum albumin:globulin ratios and increased prothrombin time were indicative of decreased liver protein synthesis. When dogs at this high dose were allowed a 4-week recovery period, healing of the liver was observed; specific measures of healing were not provided, although resolution of lesions in other affected organs, such as the kidneys, was mentioned. The authors also noted that increased serum levels of liver enzymes and decreased liver protein synthesis were reversible effects in dogs allowed a recovery period. Doses of 0.54 mg/kg/day did not have any effect on the liver (Larsen and Grant 1997). In both sexes of the Cynomolgus monkey, nine total doses of 16 mg/kg/day given 3 times/week for 3 weeks, resulted in increases in liver enzymes (alanine aminotransferase, gamma-glutamyl transferase), as well as increases in bilirubin and relative liver weights in males, and focal hepatitis/cholangiolitis in one male at the end of the dosing period. When the monkeys were given a 2-week recovery period following a 3-week administration of the highest dose, only one male had a liver lesion, which was in the process of healing. Doses of 1.6 mg/kg/day in this primate did not cause any adverse hepatic effects (Larsen and Grant 1997).

Renal Effects. Administration of mangafodipir at up to 1.4 mg manganese/kg in a few human studies has not resulted in any adverse renal effects as measured by blood chemistry or urinalysis (Bernardino et al. 1992; Wang et al. 1997).

Single doses of mangafodipir up to 63 mg manganese/kg given to Sprague-Dawley rats did not cause renal effects as measured by blood chemistry, urinalysis, gross necropsy, and histopathology (Larsen and Grant 1997). Sprague-Dawley rats of both sexes given nine doses (thrice weekly for 3 weeks) of 16 mg/kg manganese did not show any adverse renal effects as measured by urinalysis, blood chemistry, and histomorphological analysis (Elizondo et al. 1991; Larsen and Grant 1997). Daily administration of mangafodipir over 21 days in both sexes of the beagle dog at concentrations up to 6 mg/kg resulted in cortical tubular necrosis of the kidneys at this highest dose, as well as decreased glomerular filtration rate, as indicated by high serum carbamide and creatinine levels. There were no measurable effects at ≤1.6 mg/kg (Larsen and Grant 1997). Administration of nine doses of mangafodipir, also given thrice weekly for 3 weeks, at individual concentrations of 16 mg manganese/kg to Cynomolgus monkeys of both sexes resulted in increased kidney weights and enzymes, as well as creatinine, urea, and other inorganic ions. Doses of 1.6 mg/kg over the same time period did not result in any adverse effect (Larsen and Grant 1997).

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals following administration of mangafodipir.

Dermal Effects. No studies were located regarding dermal effects in humans or animals following intravenous administration of mangafodipir.

Ocular Effects. No studies were located concerning ocular effects in humans following administration of mangafodipir.

Cynomolgus monkeys administered nine individual doses at 16 mg/kg over 3 weeks and beagle dogs given up to 6 mg/kg daily for 21 days did not have any adverse ocular effects from the mangafodipir treatment (Larsen and Grant 1997).

Body Weight Effects. No reports were located concerning body weight effects in humans following mangafodipir dosing.

Mice given acute doses of mangafodipir as high as 275 mg manganese/kg and rats administered a dose of 160 mg/kg did not suffer any body weight effects (Larsen and Grant 1997).

Rats (Elizondo et al. 1991; Larsen and Grant 1997) and monkeys (Larsen and Grant 1997) administered nine doses of mangafodipir over 3 weeks at doses as high as 16 mg manganese/kg did not have any treatment-related effects on body weight. Dogs administered 21 daily doses of the compound suffered decreased body weight (unspecified decrease) at 5.4 mg/kg, but no effect at 1.6 mg/kg (Larsen and Grant 1997). There were no significant treatment-related adverse effects on body weight of male and female rats or female rabbits used in reproductive studies with mangafodipir (Blazak et al. 1996; Grant et al. 1997a; Treinen et al. 1995), except for a transient decrease in body weight during weeks 2–5, 9, and 10 in male rats administered 6 mg manganese/kg/day for 85 days (Grant et al. 1997a). The authors noted that the decrease was significant when compared to controls, but did not report actual data.

Metabolic Effects. No studies were located regarding metabolic effects in humans or animals following administration of mangafodipir.

3.2.4.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans following exposure to mangafodipir.

Injection of mangafodipir 3 times/week for 3 weeks in Sprague Dawley rats at doses of 1.6, 6.3, or 16 mg manganese/kg resulted in eosinophilia in females only at the highest dose, but had no effect in males. The authors stated they are unsure of the clinical importance of this effect as it was only seen at repeated high doses (Larsen and Grant 1997). Daily dosing of mangafodipir in beagle dogs of both sexes at doses of 1.6 mg manganese/kg for 21 days resulted in a decrease in eosinophils and an increase in toxic neutrophils (absolute amounts not reported) (Larsen and Grant 1997). A lower dose of 0.54 mg/kg had no immunological effect.

3.2.4.4 Neurological Effects

No statistically significant increases in adverse neurological effects in humans following mangafodipir administration were reported. In one study, four subjects given doses ranging from a low of 0.17 mg/kg to a high of 1.4 mg/kg complained of light-headedness or dizziness (Lim et al. 1991). Five of 96 patients administered mangafodipir complained of a headache following dosing; only two of these five, given

varying doses of mangafodipir ranging from 0.17 to 1.4 mg manganese/kg, could be attributed to the contrast agent (Bernardino et al. 1992). No other neurological effects were reported in human studies.

Single doses of mangafodipir ranging from 8.3 to 275 mg manganese/kg in mice and a single dose of 160 mg/kg in rats, resulted in decreased activity and abnormal gait and stance (Larsen and Grant 1997). Mongrel dogs infused once with mangafodipir at doses of 0.55, 3.3, or 16.5 mg manganese/kg did not have any treatment-related changes in plasma catecholamines or physiological signs of sympathetic activation as compared to the undosed controls (Karlsson et al. 1997). In a separate study, beagle dogs receiving either single doses ranging from 83 to 160 mg/kg or 21 daily doses at 5.4 mg manganese/kg suffered decreased appetite as measured by decreased food consumption; when the dogs were allowed a recovery period following the repeated dosing, the food consumption normalized within the first 2–3 days (Larsen and Grant 1997).

Rats and monkeys administered nine doses of up to 16 mg/kg each did not have any observable neurotoxic effects (Larsen and Grant 1997).

Grant et al. (1997a) did observe behavioral changes in the pups of Sprague-Dawley dams exposed to 0, 0.6, 1.1, or 2.2 mg manganese/kg on GDs 6–17. Although no significant effects were observed at the lowest dose, the exposed pups suffered a significant decrease in grasp/holding time and a 10–11% decrease in body weight at PNDs 4 and 7 at the 1.1 mg/kg dose. At the highest dose, pup weight was significantly decreased at PNDs 4, 7, 14, and 21; performance on grasp/holding, negative geotaxis, and surface righting tests was also significantly impaired. In addition, postnatal survival was decreased on days 0–4 (56 vs. 95.9% in the control group) and 4–21 (78.9 vs. 100% in the control group) at the highest dose (Grant et al. 1997a).

Current studies do not provide evidence on the potential for neurotoxicity following clinical exposure to mangafodipir. In general, studies on neurological effects in humans or animals following mangafodipir exposure did not involve a long observation period. Because deposition of manganese in the brain can be significantly delayed following exposure, it is possible that the studies to date were terminated prior to the onset of potential neurotoxicity. However, neurotoxicity in humans or animals has not been reported following single exposures to manganese, even at high doses. Studies on toxicokinetics of other manganese compounds also indicate that a single exposure is not likely to result in significant neurological effects. For further information on distribution, refer to Section 3.4 Toxicokinetics.

3.2.4.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following administration of mangafodipir.

A single dose of 160 mg/kg in male Sprague-Dawley rats resulted in no adverse effects in testes as measured by organ weight and histomorphological analysis (Larsen and Grant 1997).

Male Sprague-Dawley rats dosed nine times in 3 weeks with 16 mg manganese/kg as mangafodipir suffered a decrease in absolute testes weights, but no relative decrease in weight and no histomorphological effects (Larsen and Grant 1997).

Injection of pregnant Sprague-Dawley rats with up to 4.4 mg manganese/kg as mangafodipir, on GDs 6–8, 9–11, 12–14, or 15–17 (all during organogenesis) resulted in no evidence of reproductive toxicity as measured by pregnancy rate, numbers of corpora lutea, implantations or resorptions (Treinen et al. 1995). Further, daily intravenous administration of doses up to 2.2 mg manganese/kg throughout GDs 6–17 did not result in any significant changes in pregnancy rate, corpora lutea, implantations, or resorptions (Treinen et al. 1995). However, Grant et al. (1997a) observed a >50% rate of post-implantation loss in pregnant Sprague-Dawley rats administered 2.2 mg manganese/kg as mangafodipir during GDs 6–17. Doses of 0.6 and 1.1 mg/kg resulted in postimplantation loss rates that were similar to that of the control group. There were no obvious differences in compound administration or animal husbandry between the two studies that would indicate why such disparate results would occur. Intravenous dosing of New Zealand white rabbits with up to 1.1 mg manganese/kg/day on GDs 6–17 did not cause reproductive toxicity in one study (Grant et al. 1997a), but a dose of 3.3 mg manganese/kg/day during GDs 6–18 in the same species resulted in a significant increase (3-fold) in post-implantation loss (Blazak et al. 1996). This latter dose corresponds to a 12-fold increase over the one-time human clinical dose (Earls and Bluemke 1999).

Mangafodipir dosing in female Sprague-Dawley rats for 22 total days, starting prior to conception and ending on the 7^{th} day of gestation at a dose of up to 6 mg manganese/kg, did not result in any adverse reproductive effects (Grant et al. 1997a).

Male Sprague-Dawley rats dosed for 84–85 days with 0, 0.6, 2, or 6 mg manganese/kg as mangafodipir did not show any signs of reproductive toxicity as measured by histomorphological analyses. Although

absolute testes weights in the intermediate dose group were reduced compared to controls, relative weights were not, and in the absence of histopathological findings, this reduction is not considered an adverse effect. The treated rats were bred with females to determine if mangafodipir dosing had any effect on fertility. Pregnancy rates, and the number of corpora lutea, implantations, or resorptions were unaffected by parental treatment (Grant et al. 1997a).

3.2.4.6 Developmental Effects

No studies were located regarding developmental effects in humans following intravenous exposure to mangafodipir.

Treinen et al. (1995) tested the sensitivity of different gestational periods to the administration of mangafodipir in Sprague-Dawley rats. Pregnant rats were dosed with 0, 1.1, 2.2, or 4.4 mg manganese/kg on 3 consecutive days: GDs 6–8, 9–11, 12–14, or 15–17. The 1.1 mg/kg dose given on days 15–17 resulted in a significant increase in skeletal malformations in fetuses (10/113 fetuses vs. 0/106 in the control group; $p<0.05$). A higher dose of 2.2 mg/kg also caused a significant increase in malformations when given on GDs 12–14 (10 out of 104 fetuses affected) and days 15–17 (21/143) (both $p<0.05$), and the 4.4 mg/kg dose caused increases in malformations when given on days 9–11(5/83), 12–14 (45/128), and 15–17 (98/129) (all $p<0.05$). The malformations seen in this study included angulated or irregularly shaped clavicle, femur, fibula, humerus, ilium, radius, tibia, ulna, and/or scapula (Treinen et al. 1995).

The offspring of Sprague-Dawley rats dosed with 0, 0.1, 0.3, or 1 mg manganese/kg as mangafodipir daily throughout GDs 6–17 had a significant increase ($p<0.05$) in abnormal limb flexures (38/270 fetuses affected) and skeletal malformations (141/270 fetuses affected) only at the highest dose (Treinen et al. 1995). These malformations included the same ones listed for the segmented teratology study above. In a separate experiment evaluating the teratology of mangafodipir administration on GDs 6–17 in pregnant Sprague-Dawley rats, Treinen et al. (1995) observed a significant increase ($p<0.05$) in skeletal malformations in offspring of rats dosed with 2.2 mg manganese/kg (86/92 fetuses affected) compared to controls. In both the segmented and continuous teratology studies, no maternal toxicity was observed.

Fetuses from Sprague-Dawley females dosed with 0, 0.6, 1.1, or 2.2 mg manganese/kg on GDs 6–17 exhibited a statistically significant increase in wavy ribs at 0.6 mg/kg (20.5% of the viable fetuses impacted vs. 0.7% at the control dose; $p<0.05$). At the intermediate dose, there was a statistically significant increase in the number of fetuses with abnormalities (20 out of 159 viable fetuses) including

distortion or misshaping of one or more of the following bones: humerus, radius, ulna, scapula, clavicle, femur, tibia, and fibula; in addition, 56.6% of the viable fetuses had wavy ribs and the fetuses weighed 14% less than controls ($p<0.05$). At 2.2 mg/kg, there was a significant decrease in fetal viability (56% decrease; $p<0.05$), a greater increase in fetuses with abnormalities (45 out of 64 viable fetuses,) and a greater percentage (85.9%) with wavy ribs (Grant et al. 1997a). These effects were observed in the absence of maternal toxicity. By contrast, when the mangafodipir was administered for 22 days prior to conception and up to GD 7 in the same species at doses of 0, 0.6, 2, and 6 mg manganese/kg/day, no adverse effects on the number of viable fetuses, fetal weight, or the number of fetuses with abnormalities were reported (Grant et al. 1997a). These teratogenic studies indicate that developmental toxicity resulting from mangafodipir dosing is highly dependent on the time-frame of administration.

Grant et al. (1997a) also observed behavioral changes in the offspring of Sprague-Dawley dams administered 0, 0.6, 1.1, or 2.2 mg manganese/kg on GDs 6–17. The exposed pups suffered a significant decrease in grasp/holding time and a 10–11% decrease in body weight at PNDs 4 and 7 at the 1.1 mg/kg dose, but no significant effects at the lower dose (Grant et al. 1997a). At the highest dose, pup weight was significantly decreased at PNDs 4, 7, 14, and 21, and performance on grasp/holding, negative geotaxis, and surface righting tests was significantly impaired. In addition, postnatal survival was decreased on days 0–4 (56 vs. 95.9% in the control group) and 4–21 (78.9 vs. 100% in the control group) at the highest dose (Grant et al. 1997a). These effects occurred at doses that did not cause observable maternal toxicity.

Mangafodipir administration in New Zealand white rabbits at doses of 0, 0.3, 0.55, or 1.1 mg manganese/kg on GDs 6–18 resulted in incomplete ossification of the sternebrae at 1.1 mg/kg in one study (Grant et al. 1997a), but no significant effects on fetotoxicity or fetal weight; this dose did not result in any maternal toxicity. In a separate study, mangafodipir at doses as high as 3.3 mg manganese/kg in the same strain of rabbit for the same period of exposure did not result in any significant increases in external, skeletal, or visceral malformations in a separate teratology study (Blazak et al. 1996). This dose did result in an 11% decrease in fetal weight (although this value was not statistically significant in the study, it is considered a significant developmental effect) and a 20% decrease in the number of viable fetuses (also not statistically significant). It is not readily apparent why two studies with similar dosing regimens would obtain such conflicting results. A comparison between rat and rabbit gestational studies indicates that the rabbit is a much less sensitive model for reproductive and developmental toxicity induced by mangafodipir.

3.3 GENOTOXICITY

There is some evidence from a study on occupationally exposed welders that manganese may cause chromosomal aberrations; the welders were exposed to other potentially toxic compounds including nickel (known to cause chromosomal aberrations) and iron; therefore, the observed increase in chromosomal aberrations cannot be attributed solely to manganese (Elias et al. 1989). Mutagenicity studies in both bacteria and mammalian strains are equivocal. While manganese sulfate was shown to not be mutagenic to *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537 either in the presence or absence of S9 from Aroclor 1254-induced liver from rats or Syrian hamsters (Mortelmans et al. 1986), it was shown to be mutagenic to strain TA97 elsewhere (Pagano and Zeiger 1992). In yeast (*Saccharomyces cerevisiae* strain D7), a fungal gene conversion/reverse mutation assay indicated that manganese sulfate was mutagenic (Singh 1984). Manganese chloride was reportedly not mutagenic in *S. typhimurium* strains TA98, TA100, and TA1535, but it was mutagenic in strain TA1537, and conflicting results were obtained for TA102 (De Méo et al. 1991; Wong 1988).

In vitro assays in mammalian cells also gave conflicting results concerning manganese mutagenicity. Manganese chloride produced gene mutations in cultured mouse lymphoma cells (Oberly et al. 1982). Manganese chloride caused DNA damage *in vitro* using human lymphocytes at a concentration of 25 µm without metabolic activation, but not at the lower tested concentrations of 15 and 20 µm (Lima et al. 2008). The compound also caused DNA damage in human lymphocytes using the single-cell gel assay technique in the absence of metabolic activation, but caused no DNA damage when S9 was present (De Méo et al. 1991). Manganese sulfate induced sister chromatic exchange in Chinese hamster ovary (CHO) cells in both the presence and absence of S9 from Aroclor 1254-induced rat liver (Galloway et al. 1987). In a separate assay, manganese sulfate also induced chromosomal aberrations in CHO cells in the absence of S9 but not in its presence (Galloway et al. 1987). Manganese chloride caused chromosome aberrations in human lymphocytes without metabolic activation, but only when treated in the G2 phase of the cell cycle; treatment in the G1, G1/S, and S1 phases of the cell cycle did not result in chromosome aberrations (Lima et al. 2008). The compound was also found to be clastogenic in root tip cells of *Vicia faba* (Glass 1955, 1956), but not in cultured FM3A cells in the absence of metabolic activation (Umeda and Nishimura 1979). Potassium permanganate caused chromosomal aberrations in FM3A cells (Umeda and Nishimura 1979), but not in a primary culture of cells from Syrian hamster embryos when tested in the absence of metabolic activation (Tsuda and Kato 1977). Manganese chloride caused cell transformation in Syrian hamster embryo cells (Casto et al. 1979). A list of *in vitro* study results is given in Table 3-5.

Table 3-5. Genotoxicity of Manganese *In Vitro*

Species (test system)	Compound	End point	Strain	Results: With activation	Results: Without activation	Reference
Inorganic manganese compounds						
Prokaryotic organisms:						
Salmonella typhimurium (plate incorporation assay)	$MnCl_2$	Gene mutation	TA98	–	–	Wong 1988
			TA102	–	–	
			TA1535	–	–	
			TA1537	–	+	
	$MnSO_4$	Gene mutation	TA98, TA100, TA1535, TA1537, TA97	–	–	Mortelmans et al. 1986
S. typhimurium (preincubation assay)	$MnSO_4$	Gene mutation	TA97	No data	+	Pagano and Zeiger 1992
	$MnCl_2$	Gene mutation	TA102	No data	+	DeMéo et al. 1991
			TA100	No data	–	DeMéo et al. 1991
	$MnCl_2$	Gene mutation	TA102	No data	+	DeMéo et al. 1991
			TA100	No data	–	DeMéo et al. 1991
Photobacterium fischeri (bioluminescence test)	$MnCl_2$	Gene mutation (restored luminecence)	Pf-13 (dark mutant)	No data	+	Ulitzur and Barak 1988
Escherichia coli	$MnCl_2$	Gene mutation	KMBL 3835	No data	+	Zakour and Glickman 1984
Bacteriophage (*E. coli lysis*)	$MnSO_4$	Gene mutation	T4	No data	+	Orgel and Orgel 1965
Bacillus subtilis (recombination assay)	$MnCl_2$	Inhibition of growth in recombination deficient mutant (Rec^-) compared to wild type (Rec^+)	M45 (Rec^-)	No data	+	Nishioka 1975
	$Mn(NO_3)_2$				+	
	$MnSO_4$			+		
	$Mn(CH_3C00)_2$				+	
	$KmnO_4$				–	
B. subtilis (recombination assay)	$MnCl_2$	Inhibition of growth in recombination deficient mutant (Rec^-) compared to wild type (Rec^+)	M45 (Rec^-)	No data	–	Kanematsu et al. 1980
	$Mn(NO_3)_2$				–	
	$Mn(CH_3C00)_2$			–		

Table 3-5. Genotoxicity of Manganese *In Vitro*

Species (test system)	Compound	End point	Strain	Results		Reference
				With activation	Without activation	
Eukaryotic organisms:						
Fungi:						
Saccharomeyces cervisiae	$MnSO_4$	Gene conversion, reverse mutation	D7	No data	+	Singh 1984
Mammalian cells:						
Mouse lymphoma cells	$MnCl_2$	Gene mutation	L5178Y TK+/-	No data	+	Oberly et al. 1982
Syrian hamster embryo cells	$MnCl_2$	Enhancement of SA7 transformation		No data	+	Casto et al. 1979
Human lymphocytes (Single-cell gel assay)	$MnCl_2$	DNA damage	lymphocyte	–	+	DeMéo et al. 1991
Chinese hamster ovary cells	$MnSO_4$	Chromosomal aberrations/ sister chromatid exchange		+	+	NTP 1993
Human lymphocytes	$MnCl_2$	Chromosomal aberrations (G2 phase)		No data	+	Lima et al. 2008
Human lymphocytes	$MnCl_2$	DNA damage		No data	+	Lima et al. 2008
Organic manganese compounds						
Prokaryotic organisms:						
E. coli and *S. typhimurium*	MnDPDP	Gene mutation	*E. coli*: WP_2uvrA^- *S. typhimurium*: TA100, TA1535, TA98, TA1537	–	–	Larsen and Grant 1997
Eukaryotic organisms:						
CHO cells	MnDPDP	Forward mutation		–	–	Larsen and Grant 1997
	MnDPDP	Chromosomal aberration		–	–	Larsen and Grant 1997

– = negative result; + = positive result; ± = weakly positive result; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; $Mn(CH_3COO)_2$ = manganese acetate; $MnCl_2$ = manganese chloride; MnDPDP = mangafodipir; $Mn(NO_3)_2$ = manganese nitrate; $MnSO_4$ = manganese sulfate; Rec = recombination

Manganese chloride did not produce somatic mutations in *Drosophila melanogaster* fruit flies in one study (Rasmuson 1985), and manganese sulfate did not induce sex-linked recessive lethal mutations in germ cells of male *D. melanogaster* (Valencia et al. 1985).

In vivo assays in mice showed that oral doses of manganese sulfate or potassium permanganate caused micronuclei and chromosomal aberrations in bone marrow (Joardar and Sharma 1990). In contrast, oral doses of manganese chloride did not cause chromosomal aberrations in the bone marrow or spermatogonia of rats (Dikshith and Chandra 1978). A list of *in vivo* study results is given in Table 3-6.

The results of *in vitro* studies show that at least some chemical forms of manganese have mutagenic potential. However, as the results of *in vivo* studies in mammals are inconsistent, no overall conclusion can be made about the possible genotoxic hazard to humans from exposure to manganese compounds.

Genotoxicity data concerning MMT was not available.

One study was located regarding genotoxic effects in humans following inhalation exposure to manganese. In this study, the incidences of chromosomal aberrations in three groups of welders with occupational exposures (10–24 years) to metals including manganese, nickel, and chromium were examined (Elias et al. 1989). An increase in chromosomal aberrations was found in the group working with the metal active gas welding process; however, since their exposures included nickel as well as manganese, the authors could not attribute the results to any one metal exposure (nickel is known to cause chromosomal aberrations by the inhalation route). The median manganese concentrations during the survey were 0.18 mg/m^3 for respirable dust and 0.71 mg/m^3 for total dust. No information was available regarding the genotoxicity of manganese alone.

No studies were located regarding genotoxic effects in humans after oral exposure to inorganic manganese.

In male Swiss albino mice, manganese sulfate and potassium permanganate have both been found to be clastogenic, and their effects were found to be dependent primarily on the concentration (not duration) of exposure (Joardar and Sharma 1990). In this *in vivo* study, oral doses were administered at varying levels over a 3-week period. The manganese sulfate doses were 10.25, 20.25, and 61 mg/100 g body weight, and the potassium permanganate doses were 6.5, 13, and 38 mg/100 g body weight. Sperm head

Table 3-6. Genotoxicity of Manganese *In Vivo*

Species (test system)	Compound	End point	Route	Results	Reference
Inorganic manganese compounds					
Nonmammalian systems:					
Drosophila melanogaster	$MnSO_4$	Sex-linked recessive lethal	Feeding injection	–	Valencia et al. 1985
D.melanogaster	$MnCl_2$	Somatic mutation	Soaking larvae	–	Rasmuson 1985
Mammalian systems:					
Albino rat (bone marrow cells) (spermatogonial cells)	$MnCl_2$	Chromosomal aberrations	Oral	–	Dikshith and Chandra 1978
Albino mouse	$MnSO_4$	Chromosomal aberrations	Oral	+	Joardar and Sharma 1990
Albino mouse	$KMnO_4$	Chromosomal aberrations	Oral	+	Joardar and Sharma 1990

– = negative result; + = positive result; $KMnO_4$ = potassium permanganate; $MnCl_2$ = manganese chloride; $MnSO_4$ = manganese sulfate

abnormalities and the frequency of chromosomal aberrations in bone marrow cells and micronuclei were significantly increased. In male rats, repeated oral doses of 0.014 mg manganese/kg/day (as manganese chloride) for 180 days did not produce any significant chromosomal damage in either bone marrow or spermatogonial cells (Dikshith and Chandra 1978).

No studies were located regarding genotoxic effects in animals after inhalation exposure to inorganic manganese.

No studies were located concerning genotoxic effects in humans or animals following inhalation or exposure to MMT.

3.4 TOXICOKINETICS

Manganese is required by the body and is found in virtually all diets. As discussed in Chapter 6, adults consume between 0.7 and 10.9 mg of manganese per day in the diet, with higher intakes for vegetarians who may consume a larger proportion of manganese-rich nuts, grains, and legumes than non-vegetarians (WHO 2004b). Manganese intake from drinking water is substantially lower than intake from food. Exposure to manganese from air is considered negligible as compared to intake from diet, although persons in certain occupations may be exposed to much higher levels than the general public (see Section 6.7).

Even though daily dietary intake of manganese can vary substantially, adult humans generally maintain stable tissue levels of manganese through the regulation of gastrointestinal absorption and hepatobiliary excretion (Andersen et al. 1999; Aschner and Aschner 2005; Aschner et al. 2005; Roth 2006). Following inhalation exposure, manganese can be transported into olfactory or trigeminal presynaptic nerve endings in the nasal mucosa with subsequent delivery to the brain, across pulmonary epithelial linings into blood or lymph fluids, or across gastrointestinal epithelial linings into blood after mucociliary elevator clearance from the respiratory tract (Aschner and Dorman 2006; Dorman et al. 2006a; Roth 2006). Manganese is found in the brain and all other mammalian tissues, with some tissues showing higher accumulations of manganese than others. For example, liver, pancreas, and kidney usually have higher manganese concentrations than other tissues (Dorman et al. 2006a). The principal route of elimination of manganese from the body is fecal elimination via hepatobiliary excretion; contributions from pancreatic, urinary, and lactational elimination are expected to be small (Dorman et al. 2006a). Excess manganese is expected to be eliminated from the body rapidly. For example, following the intravenous bolus injection of

manganese chloride in rats, manganese concentrations in plasma return to normal levels within 12 hours (Zheng et al. 2000).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding the absolute amount of manganese that is absorbed by humans or animals after inhalation exposure to manganese dusts.

In general, the extent of inhalation absorption is a function of particle size, because size determines the extent and location of particle deposition in the respiratory tract. Manganese from smaller particles that are deposited in the lower airway is mainly absorbed into blood and lymph fluids, while manganese from larger particles or nanosized particles deposited in the nasal mucosa may be directly transported to the brain via olfactory or trigeminal nerves. Alternatively, particles deposited in the upper or lower respiratory tract may be moved by mucociliary transport to the throat, where they are swallowed and enter the stomach. The latter process is thought to account for clearance of a significant fraction of manganese-containing particles initially deposited in the lung. Thus, manganese may be absorbed in the nasal mucosa, in the lung, and in the gastrointestinal tract following inhalation of manganese dust. However, the relative amounts absorbed from each site are not accurately known.

Absorption of manganese deposited in the lung is expected to be higher for soluble forms of manganese compared with relatively insoluble forms of manganese (Aschner et al. 2005). Evidence in support of this hypothesis comes from studies in which 3-month-old male Sprague-Dawley rats were given intratracheal doses (1.22 mg manganese/kg) of relatively soluble (manganese chloride) or insoluble (manganese dioxide) forms of manganese (Roels et al. 1997). Peak concentrations of manganese in blood were observed earlier after manganese chloride intratracheal administration (0.5 hour) compared with manganese dioxide (168 hours after administration). Peak concentration of manganese in blood were about 4-fold higher in rats exposed to manganese chloride than in rats exposed to manganese dioxide (Roels et al. 1997). Confirmatory evidence has been presented by Dorman et al. (2001a, 2004b). For example, rats exposed to manganese sulfate (0.1 mg manganese/m^3, 6 hours/day, 5 days/week for 13 weeks) showed higher olfactory bulb and striatum manganese concentrations than rats exposed to 0.1 mg manganese/m^3 manganese phosphate (hureaulite) (Dorman et al. 2004b).

Results consistent with nasal uptake of manganese and transport to the brain along neuronal tracts have been obtained in several animal studies (Brenneman et al. 2000; Dorman et al. 2001a, 2002a; Elder et al. 2006; Fechter et al. 2002; Henriksson et al. 1999; Lewis et al. 2005; Normandin et al. 2004; Tjälve and Henriksson 1999; Tjälve et al. 1996; Vitarella et al. 2000). For example, following intranasal administration of 4 μg/kg ^{54}Mn (as manganese chloride) to weanling Sprague-Dawley rats, whole-body autoradiography showed that the olfactory bulb contained the vast majority of measured manganese at 1, 3, and 7 days post-dosing (90, 69, and 47%, respectively) with values decreasing to a low of 16% at 12 weeks (Tjälve et al. 1996). Significant uptake of manganese by other brain regions was not observed until the third day, when the basal forebrain, cerebral cortex, hypothalamus, and striatum had 21, 2, 3, and 1% of the measured label, respectively (Tjälve et al. 1996). Subsequent experiments with varying doses of manganese chloride showed that the uptake of manganese into the olfactory epithelium and the transfer to the brain olfactory bulb leveled off at the highest doses, indicating that these are saturable processes (Henriksson et al. 1999). Following single, 90-minute, nose-only inhalation exposures of 8-week old male CD rats to aerosols of manganese chloride (0.54 mg ^{54}Mn/m^3; Brenneman et al. 2000) or manganese phosphate (0.39 mg ^{54}Mn/m^3; Dorman et al. 2002a), peak concentrations of radioactivity in the brain olfactory bulb (at 1–3 days after exposure) were about 20- or 4-fold higher, respectively, than peak concentrations in the striatum at 21 days after exposure. Results consistent with transport of manganese to the brain along olfactory neurons have also been obtained in rats exposed to manganese phosphate aerosols in inhalation chambers (0, 0.03, 0.3, or 3 mg manganese/m^3) 6 hours/day for up to 14 days (Vitarella et al. 2000). Elevated concentrations of manganese were observed in the olfactory bulb, striatum, and cerebellum at the 0.3 and 3 mg manganese/m^3 exposure levels, compared with control levels, and concentrations in the olfactory bulb were about 1.4–2.4-fold higher than concentrations in the striatum (Vitarella et al. 2000). Elevated manganese concentrations were also found in the olfactory bulb, striatum, and cerebellum, following 90 days of inhalation chamber exposure (6 hours/day, 5 days/week) of young (6 weeks old at start) male or female CD rats or aged (16 months old at start) male CD to aerosols of either manganese sulfate or manganese phosphate ("hureaulite") at an exposure concentration of 0.1 mg manganese/m^3 (Dorman et al. 2004b). Regardless of age or gender, the olfactory bulb showed the highest elevation in manganese concentration, compared with other brain tissues, and concentrations in the olfactory bulb were higher in rats exposed to soluble manganese than in rats exposed to relatively insoluble manganese phosphate (Dorman et al. 2004a). Following 12 days of inhalation exposure of rats to ultrafine manganese oxide particles (30 nm diameter; about 0.5 mg manganese dioxide/m^3), Elder et al. (2006) reported that manganese concentrations in the olfactory bulb were increased by 3.5-fold over controls, compared with 2-fold increased concentrations in lungs. Lung lavage analysis showed no signs of pulmonary inflammation following 11 days of exposure, but several markers of inflammation were

noted in the olfactory bulb including increase tumor necrosis factor-α mRNA and protein. Elder (1996) argued that these results are consistent with the direct transport of the nanosized particles from the nasal mucosa via the olfactory neuronal tract to the olfactory bulb, noting that when the right nares were occluded, manganese only accumulated in the left olfactory bulb.

Elevated concentrations of manganese have also been observed in the trigeminal ganglia of rats and mice at 0, 7, and 14 days following nose-only inhalation exposure to aerosols of manganese chloride at a concentration of about 2 mg manganese/m^3, 6 hours/day, 5 days/week for 2 weeks (Lewis et al. 2005). The latter results are consistent with uptake of manganese in the nasal respiratory epithelium and subsequent transport to the brain via trigeminal neurons. In Rhesus monkeys exposed to 1.5 mg manganese/m^3 manganese sulfate for 65 days, olfactory epithelium, olfactory bulb, and trigeminal nerve manganese concentrations were increased by about 17-, 8-, and 2-fold over concentrations in air control monkeys (Dorman et al. 2006a). These results are consistent with the hypothesis that the nasal olfactory transport route may be more important than the trigeminal neuron transport route in nonhuman primates. The relative importance of the nasal route of manganese absorption (and delivery to the brain) in humans has not been quantified, but it may be less important in humans than in rats because the olfactory bulb accounts for a larger part of the central nervous system and the olfactory epithelium accounts for a larger proportion of the nasal mucosa in rats compared with humans (Aschner et al. 2005; Dorman et al. 2002a). Using a pharmacokinetic model describing the olfactory transport and blood delivery manganese in rats, Leavens et al. (2007) calculated that 21 days or 8 days following acute inhalation exposure of rats to $^{54}MnCl_2$ or $^{54}MnHPO_4$, respectively direct olfactory transport accounted for the majority of label in the olfactory bulb, but only a small percentage (≤3%) of the label in the striatum.

Absorption of manganese deposited in the lung or nasal mucosa of rats is expected to be influenced by iron status, with enhanced absorption under iron-deficient conditions and diminished absorption under iron-excess conditions. Following intratracheal administration of ^{54}Mn-manganese chloride, ^{54}Mn blood concentrations were lower in male Sprague-Dawley rats fed a high-iron diet (about 10,000 ppm Fe), compared with concentrations in rats fed a control iron (210 ppm Fe) diet (Thompson et al. 2006). These results are consistent with diminished pulmonary absorption of manganese under iron-loaded conditions. Supporting this interpretation, 4 hours after ^{54}Mn administration, levels of ^{54}Mn (expressed as a percentage of the instilled dose) were higher in the lungs of high-iron rats, compared with control rats, but generally lower in other tissues in high-iron versus control rats (Thompson et al. 2006). In rats fed the high-iron diet, mRNA levels for divalent metal transporter 1 (DMT1—a transport protein that facilitates membrane transport of divalent iron and manganese) were decreased in the bronchus-associated

lymphatic tissue of high-iron rats, compared with control rats (Thompson et al. 2006). In Belgrade rats, homozygous (b/b) for a mutation in DMT1 that impairs transport function and fed 500 ppm Fe in the diet, ^{54}Mn blood levels following intranasal administrations of ^{54}Mn-manganese chloride were markedly (2–5-fold) lower than those in blood of anemic heterozygous (+/b) rats fed a 20 ppm Fe diet (Thompson et al. 2007). For example, levels of ^{54}Mn remaining in the blood 4 hours after administration were 0.022 and 0.115% of the instilled dose in the homozygous (b/b) and anemic heterozygous (+/b) rats, respectively (a 5-fold difference). Intermediate levels of ^{54}Mn in blood were found in heterozygous (+/b) rats fed the 500 ppm Fe diet (Thompson et al. 2007). In Sprague-Dawley rats, levels of DMT1 protein in the olfactory epithelium were 1.5- to 2.5-fold greater under anemic conditions (20 ppm Fe in diet for 3 weeks), compared with iron-sufficient conditions, 200 ppm Fe in diet for 3 weeks (Thompson et al. 2007). These results are consistent with the hypothesis that up- and down-regulation of DMT1 plays a role in enhanced nasal absorption of manganese under iron-deficient conditions and diminished absorption under iron-excess conditions, respectively.

No studies were located regarding the absorption of organic manganese compounds following inhalation exposure in either humans or animals.

3.4.1.2 Oral Exposure

The amount of manganese absorbed across the gastrointestinal tract in humans is variable, but typically averages about 3–5% (Davidsson et al. 1988, 1989a; Mena et al. 1969). Data were not located on the relative absorption fraction for different manganese compounds, but there does not appear to be a marked difference between retention of manganese ingested in food (5% at day 10) or water (2.9% at day 10) (Davidsson et al. 1988, 1989a; Ruoff 1995). In humans, manganese absorption tends to be greater from manganese chloride (in demineralized water) than from foods (labeled intrinsically or extrinsically with ^{54}Mn); however, the biological half-life of manganese from either manganese chloride or food is the same (EPA 1995b; Johnson et al. 1991). In human adults, supplementation of the diet with manganese sulfate for 12–35 weeks at a level approximately 2 times the normal dietary intake caused a 30–50% decrease in absorption of a tracer dose of $^{54}MnCl_2$ (Sandstrom et al. 1990).

Results from animal studies indicate that the gastrointestinal absorption of manganese is rapid and expected to be higher for soluble forms of manganese compared with relatively insoluble forms of manganese. Following a single gavage dose of 6 mg manganese/kg as manganese chloride to rats, maximal plasma concentrations were attained rapidly (T_{max}=15 minutes) (Zheng et al. 2000). From

analysis of time course of plasma concentrations following oral and intravenous administration, the oral bioavailability for manganese was calculated to be 13.9% (Zheng et al. 2000). Roels et al. (1997) noted that in 3-month-old male rats, gavage administered manganese chloride (24.3 mg manganese/kg) reached a maximal level in blood, 7.05 µg/100 mL, within the first 30 minutes post-dosing (first time point measured), whereas manganese from manganese dioxide, administered in the same fashion, did not reach a maximal level in blood of 900 ng/100 mL until 144 hours (6 days) post-dosing. Following four weekly gavage doses of manganese chloride at 24.3 mg manganese/kg per dose, significant increases in manganese concentration were observed in blood and the cerebral cortex, but not cerebellum or striatum, as compared to controls; for identical doses of manganese dioxide, manganese levels were significantly increased only in blood. The lack of significant increase in manganese levels in any brain region following administration of the dioxide is likely due to the delayed uptake of manganese in the blood.

One study showed that, in full-term infants, manganese is absorbed from breast milk and cow's milk formulas that were either unsupplemented or supplemented with iron, copper, zinc, and iodine (Dorner et al. 1989). Manganese intake was greater in the formula-fed infants than in the breast-fed infants due to the higher manganese content of the formula. However, breast-fed infants retained more of their daily intake of manganese (40%) than did the formula-fed infants (20%). It must be noted that the full-term infants evaluated in this study were 2–18 weeks old, and the data did not stratify intake and retention amounts by age. Further, the data did not indicate if there were similar proportions of manganese taken up from breast milk as compared to the formulas. A study by Davidson and Lönnerdal (1989) demonstrated the *in vitro* receptor-mediated uptake of manganese from lactoferrin; the authors speculated that this may lead to the absorption of manganese from breast milk in human infants.

There is some evidence to suggest that gastrointestinal absorption of manganese is age-dependent. Dorner et al. (1989) have shown that infants, especially premature infants, retain a higher proportion of manganese than adults. Animal studies also support this finding. For example, Rehnberg et al. (1980, 1981, 1982) dosed 1-day-old rat pups with up to 214 mg manganese/kg/day (as manganese tetroxide) for up to 224 days, then measured manganese concentrations in tissues. The authors noted that intermediate and chronic exposure of rats to manganese tetroxide in water or food resulted in much larger increases in tissue levels in young rats (1–15 days in intermediate studies, 24–40 days in chronic study) than in older rats. These increases in neonates were judged to be due to the neonates' greater absorption of manganese as a result of a slower rate of transport through the gut (Rehnberg et al. 1985). Similar results have been reported in rats exposed to manganese chloride (Kostial et al. 1978). However, such age-dependent differences in tissue retention of manganese could also be due to differences in excretory ability (Cotzias

et al. 1976; Miller et al. 1975) or to age-related changes in dietary intake levels of iron and manganese (Ballatori et al. 1987). Dorner et al. (1989) found that both pre-term and full-term infants had active excretion of manganese; in fact, some infants had negative manganese balances. Animal studies show that absorption and/or retention of manganese is higher in neonates, but returns to the level of older animals at approximately post-GD 17–18 (Kostial et al. 1978; Lönnerdal et al. 1987; Miller et al. 1975; Rehnberg et al. 1981). Available studies (Dorner et al. 1989) do not provide adequate data to determine when this transition takes place in human infants.

One of the key determinants of absorption appears to be dietary iron intake, with low iron levels leading to increased manganese absorption. Mena et al. (1969) administered oral ^{54}Mn and ^{39}Fe to subjects with iron-deficiency anemia (ranging in age from 13 to 44 years old) and measured manganese and iron uptake with whole-body autoradiography. The uptake of manganese by anemic subjects was 7.5% while in non-anemic subjects, it was 3.0%. This is probably because both iron and manganese are absorbed by the same transport system in the gut. The activity of this system is inversely regulated by dietary iron and manganese intake levels (Chandra and Tandon 1973; Diez-Ewald et al. 1968; Rehnberg et al. 1982; Thomson et al. 1971). Interaction between iron and manganese occurs only between nonheme iron and manganese. Davis et al. (1992a) demonstrated that increasing dietary intakes of nonheme iron, but not heme iron, depressed biomarkers of manganese status (i.e., serum manganese concentrations and lymphocyte manganese-dependent superoxide dismutase activity).

Studies of oral absorption of manganese in animals have yielded results that are generally similar to those in humans. Manganese uptake in pigs, which have similar gastrointestinal tracts to humans, has been measured using labeled manganese administered orally (Finley et al. 1997). The mean absorption rates for different times post-dosing were 5% 1–6 hours post-dosing, 7% 6–12 hours post-dosing, and 3.8% 12–24 hours post-dosing. Gastrointestinal uptake of manganese chloride in rats has been estimated to be 2.5–8.2% (Davis et al. 1993; Pollack et al. 1965). Uptake is increased by iron deficiency (Pollack et al. 1965) and decreased by preexposure to high dietary levels of manganese (Abrams et al. 1976a; Davis et al. 1992b). In a rat study, the intestinal transfer of the calcium ion and manganese ion was found to be competitive, and the authors suggested that there is a common mechanism for their transfer in the intestines (Dupuis et al. 1992). High dietary intakes of phosphorus (Wedekind et al. 1991) and calcium (Wilgus and Patton 1939) have also been demonstrated to depress manganese uptake in chicks.

Manganese absorption has also been found to vary according to manganese intake; in rats with manganese-deficient diets, absorption was at least 2-fold higher than in rats whose diets contained an adequate amount of manganese (as manganese carbonate) (Davis et al. 1992b).

Two studies in suckling rat pups found differing absorptions of manganese from different milks and formulas. The first study (Lönnerdal et al. 1987) found that the percent of ^{54}Mn (added to the food source as an extrinsic label) retained (measured as whole-body retention) in 14-day-old pups fed breast milk, cow milk, cow milk formula, and soy formula, was 82, 90, 77, and 65%, respectively.

The latter study (Lönnerdal et al. 1994) found that 13-day-old rat pups fed ^{54}Mn (from manganese chloride that was incubated with the food for at least 24 hours prior to feeding) in breast milk, cow milk, and several different manufacturers' cow milk formulas had similar absorption values. These pups absorbed (measured as whole-body retention) 80% of the label from breast milk, 83% from cow milk, and 63–90% from the cow milk formulas, with the two lowest retention values being significantly lower than the others. In this latter study, manganese absorption from soy formulas was significantly lower than the other milks and formulas tested, ranging from 63 to 72%.

The inherent concentration of manganese in each of these food sources from the first study was 0.01, 0.04, 0.05, and 0.30 μg/mL, respectively (Lönnerdal et al. 1987). Therefore, when the retention of the label was multiplied by the actual manganese concentration of the food, the total amounts of absorbed manganese were 0.004, 0.018, 0.019, and 0.097 μg/dose fed, respectively. These data indicate that infants fed cow milk formula may retain 5 times more manganese, and infants fed soy formula may retain 25 times more manganese than breast-fed infants. Although the latter results differ significantly from those observed earlier, the researchers report that the similar relative values for manganese absorption were indicative of significant efforts made to optimize both the relative concentrations and the bioavailability of minerals and trace elements in the manufactured formulas.

No studies were located regarding absorption of manganese following oral exposure to MMT in humans. Several studies (Hanzlik et al. 1980a, 1980b; Hinderer 1979; Hysell et al. 1974; Komura and Sakamoto 1992a, 1992b) indicate that absorption is occurring because toxicity is observed following MMT exposure; however, no absorption rates or relative amounts were provided in these studies. The plasma temporal pattern of manganese following oral administration of MMT has been studied in male Sprague-Dawley rats (Zheng et al. 2000). Following oral gavage of 20 mg MMT/kg, manganese appears in the plasma with a C_{max} between 2 and 12 hours after dosing. When nearly equivalent oral doses of MMT

(5.6 mg manganese/kg) or manganese chloride (6 mg manganese/kg) were administered, the C_{max} (0.93 mg manganese/mL) following oral MMT was about 3-fold higher than that following oral manganese chloride (0.30 mg manganese/mL) (Zheng et al. 2000).

3.4.1.3 Dermal Exposure

The only available human study regarding dermal exposure to manganese discussed a case report of a man burned with a hot acid solution containing 6% manganese. The authors speculated that manganese absorption had occurred across the burn area (Laitung and Mercer 1983) because the man had slightly elevated urinary manganese levels (11–14 vs. 1–8 mg/L). In most cases, manganese uptake across intact skin would be expected to be extremely limited.

No studies were located regarding absorption of organic manganese in humans or animals following dermal exposure.

3.4.2 Distribution

Manganese is a normal component of human and animal tissues and fluids. In humans, most tissue concentrations range between 0.1 and 1 μg manganese/g wet weight (Sumino et al. 1975; Tipton and Cook 1963), with the highest levels in the liver, pancreas, and kidney and the lowest levels in bone and fat (see Table 3-7). Manganese levels in the blood, urine, and serum of healthy, unexposed subjects living in the Lombardy region of northern Italy were 8.8±0.2, 1.02±0.05, and 0.6±0.014 μg/L, respectively (Minoia et al. 1990). Serum manganese concentrations in healthy males and females in Wisconsin were 1.06 and 0.86 μg/L, respectively (Davis and Greger 1992; Greger et al. 1990). Although precise inhalation exposure data were not available for humans, chronic occupational exposure studies have shown that higher levels of inhalation exposure generally correspond with higher blood or urine manganese levels for groups, but that individual measurements may not correspond to individual exposure or be reliable exposure predictors (Abdel-Hamid et al. 1990; Alessio et al. 1989; Jarvisalo et al. 1992; Roels et al. 1992; Siqueira et al. 1991).

Studies investigating manganese levels in human fetal tissues or fluids are very few. Widdowson et al. (1972) measured manganese in fetal livers from 29 unborn infants (ranging in gestational age from 20 to 41 weeks) and from 5 adults. The fetal manganese levels ranged from 0.09 to 0.23 mg/100 g wet weight with a mean of 0.14 mg/100g wet weight, while the mean of the five adults was 0.18 mg/100 g wet weight (range of values not reported). The highest fetal manganese value of 0.23 mg/100 g wet weight

Table 3-7. Manganese Levels in Human and Animal Tissues

	Tissue concentrations (µg manganese/g wet weight)			
	Humans		Rats	Rabbits
Tissue	Tipton and Cook (1963)	Sumino et al. (1975)	Rehnberg et al. (1982)	Fore and Morton (1952)
Liver	1.68	1.2	2.6–2.9	2.1
Pancreas	1.21	0.77	No data	1.6
Adrenals	0.20	0.69	2.9	0.67
Kidney	0.93	0.56	0.9–1.0	1.2
Brain	0.34	0.30[a]	0.4	0.36
Lung	0.34	0.22	No data	0.01
Heart	0.23	0.21	No data	0.28
Testes	0.19	0.20	0.4	0.36
Ovary	0.19	0.19	No data	0.60
Muscle	0.09	0.09	No data	0.13
Spleen	0.22	0.08	0.3	0.22
Fat	No data	0.07	No data	No data
Bone (rib)	No data	0.06	No data	No data
Pituitary	No data	No data	0.5	2.4

[a]Average of cerebrum and cerebellum

was from one of the two infants at 41 gestational weeks of age when analyzed. The data indicate that fetal liver manganese levels throughout the latter half of gestation are comparable to those in the adult.

Concentrations of manganese also have been measured in the blood of pregnant women, as well as in the plasma of cord blood of preterm and full-term infants (Wilson et al. 1991). Manganese concentrations in full-term (37–42 weeks gestation) infants were 5.5±1.5 μg/L, slightly higher than the preterm (27–36 weeks gestation) infants' values of 5.0±1.1 μg/L, but the difference was not statistically significant. There were no correlations between the levels in infants and mothers. The higher manganese levels in cord blood of gestationally older infants, along with the higher manganese level in the oldest fetus from the Widdowson et al. (1972) study, suggest that manganese levels may rise slightly as the fetus approaches birth; however, there are inadequate data points to make a strong argument for this possibility. Serum manganese values of 180 healthy Venezuelan infants decreased consistently from a high value of 0.45 μg/L (mean of 22 infants) at 5 days of age to a low value of 0.29 μg/L (mean of 40 infants) at 12 months of age (Alarcón et al. 1996). The level of manganese at 12 months was the only measurement that was statistically different than the 5-day value. The values were not statistically different between the sexes. Rükgauer et al. (1997) obtained very different results in their analyses of serum manganese levels in German children, adolescents, and adults. The authors evaluated 137 children (aged 1 month–18 years); the mean serum manganese level for all children was 1.4 μg/L (range 0.17–2.92 μg/L). When the children were separated by age, the serum manganese values were found to decrease from a mean value of 2.12 μg/L (age 0–1 year) to a minimum of 0.98 μg/L (age 14–18 years). Adults (age 22–75 years) had a mean value of 0.79 μg/L. These data indicate that children had much higher manganese levels in serum than those levels shown by the other studies. It is unknown why this latter study indicates results that are vastly different from those reported in the earlier studies. Rükgauer et al. (1997) took precautions to prevent manganese contamination of their experimental materials during sampling and analysis. Also, the authors reported that the subjects were healthy and were not suffering from nutritional diseases or metabolic disorders and were not taking medicines containing trace elements. However, the children and adolescent subjects were chosen from a pediatric hospital after seeking medical attention on non-nutrition related matters. Therefore, this population may not be a representative sample of the general population. Animal studies, by contrast, suggest that distribution of manganese in the infant and young child may be very different from the adult.

Levels in tissues from animals fed a normal diet are generally similar but, perhaps are slightly higher than those in humans (Fore and Morton 1952; Rehnberg et al. 1982). Levels of manganese in the milk of rats

fed a normal diet averaged 0.054 µg/g (Miller et al. 1975). Data on changes in tissue levels following acute exposures to excess manganese are presented in exposure-specific subsections later in this chapter.

Manganese is also found in breast milk for the continuing metabolic nutrition of the infant. One study reported manganese concentrations from 82 normal, healthy French women of 12±5.6 µg/L at postpartum day 2 in human colostrum decreasing to 3.4±1.6 µg/L at postpartum day 6 in breast milk (Arnaud and Favier 1995). Another study reported an average manganese concentration in breast milk of 6.2 µg/L using 2,339 samples from mothers of 20 full-term and 6 preterm infants (Dorner et al. 1989). Collipp et al. (1983) have reported concentrations of manganese in breast milk of 10 µg/L. These reports, however, did not address the dietary manganese intake of the nursing mothers. It is unknown whether mothers exposed to increased concentrations of manganese have higher-than-usual levels of the metal in breast milk.

Manganese is distributed throughout all cells in the body; therefore, it is present in germ cells. However, existing studies in humans and animals are not sufficient to predict if distribution of excess manganese into germ cells might result in heritable genetic changes. Manganese is constantly present in human tissues and, therefore, is able to enter germ cells. One human study involving inhalation exposure to nickel and manganese observed chromosomal aberrations in welders working with these metals (Elias et al. 1989). However, the presence of nickel is a confounding factor, as it is known for causing chromosomal changes. Studies in animals are equivocal; there are not enough data to make predictions as to the likelihood for excess exposures of manganese to cause heritable genetic changes.

Concentrations of manganese in select human and animal tissues are presented in Table 3-7 and concentrations of manganese in plasma and serum in infants of differing ages and adults are presented in Table 3-8.

3.4.2.1 Inhalation Exposure

Following inhalation exposure of mice to manganese dust, for a short period of time the concentration of manganese in the lung is approximately proportional to the concentration of manganese in the air (Adkins et al. 1980c). However, as noted earlier, some of the particles that are deposited in the lung are transported to the gastrointestinal tract (Mena et al. 1969). The rate of particle transport from the lungs has not been quantified in humans, but half-times of elimination in animals range from 3 hours to 1 day (Adkins et al. 1980c; Bergstrom 1977; Newland et al. 1987).

Table 3-8. Manganese Levels in Human Serum/Plasma

	Concentration (µg/L) (mean±2 standard deviations)	
Age	Serum[c]	Plasma
5 Days[a]	0.45±0.12 (22)	
1 Month	0.41±0.11 (20)	
3 Months	0.39±0.13 (22)	
5 Months	0.39±0.10 (14)	
7 Months	0.38±0.09 (20)	
10 Months	0.37±0.11 (20)	
11 Months	0.36±0.12 (22)	
12 Months	0.29±0.10 (40)	
1 Month–18 years[b]	1.4±1.25	
22–75 Years		0.79±0.63

[a]Data from infants 5 days–12 months in age are from Alarcón et al. (1996). Data are from mixed-sex groups. No statistically significant differences in manganese concentrations were found between sexes.
[b]Data from Rükgauer et al. (1997).
[c]Value in parentheses is the number of subjects.

The relative increases in tissue levels of manganese following inhalation exposure to inorganic forms of manganese have received considerable investigation in animals.

Increases of 20–60% in manganese levels in the kidney and spleen were noted in mice 24–48 hours after exposure to manganese dioxide (Adkins et al. 1980c). Rats exposed to an aerosol containing 0.0003 mg $^{54}Mn/m^3$ for 1 hour had manganese levels in the liver, lung, kidney, and brain of 0.0495, 0.1366, 0.0141, and 0.0014 ng ^{54}Mn/organ, respectively, 5 days after exposure (Wieczorek and Oberdörster 1989b). Sheep exposed to welding fumes for 3 hours exhibited a 40-fold increase in lung manganese content (Naslund et al. 1990). Preferential accumulation of manganese in specific locations of the brain (including the caudate nucleus, globus pallidus, and substantia nigra) was noted in one monkey exposed to an aerosol of manganese chloride (20–40 mg/m^3) several hours/day for 3–5 months (Newland et al. 1989). This preferential uptake could play a role in the characteristic neurological effects of manganese (see Section 3.5).

Roels et al. (1997) investigated the distributional differences in rats exposed to manganese in two forms (manganese chloride and manganese dioxide) administered via intratracheal injection (intended to simulate inhalation), by gavage (oral administration) and via intraperitoneal injection. When administered intratracheally once a week for 4 weeks, 1.22 mg manganese/kg as manganese chloride resulted in a 68% steady-state increase in blood manganese concentration after the dosing period. This dose also resulted in significantly increased concentrations of manganese in the rat cerebellum (27% increase that approached statistical significance), striatum (205% increase), and cortex (48% increase), compared with control rats.

When rats were administered the same amount of manganese under the same dosing regimen, with manganese in the form of manganese dioxide, similar, but less striking, results were observed (Roels et al. 1997). Manganese concentrations in the blood were increased by 41%, and in the cerebellum, striatum, and cortex by 31, 48, and 34%, respectively, over the control rats.

Tjälve et al. (1996) investigated the distribution of manganese in brain tissues, liver, and kidneys of young male rats following intranasal injection of $^{54}MnCl_2$. Radiography data indicated that 1 day after dosing, the olfactory bulb contained 90% of the manganese (measured as µg/100g wet weight) in the measured tissues, while the basal forebrain contained 6% of the manganese. Concentrations of manganese in the basal forebrain increased to 21 and 28% of the measured total at 3 and 7 days post-

dosing, respectively. Manganese in the cerebral cortex, hypothalamus, striatum, and hippocampus were also maximal at 7 days post-dosing. Manganese values in liver and kidneys were approximately 1% of the total measured for the first 7 days, and then decreased steadily until 12 weeks. These results were compared to distribution of manganese following intraperitoneal injection, in which no brain region showed preferential distribution at 1, 7, or 21 days post-dosing (Tjälve et al. 1996). In another study, Gianutsos et al. (1997) found a dose-dependent accumulation of manganese in the olfactory bulb and tubercle following intranasal injection of manganese chloride into one nostril. Injection of 200 μg manganese resulted in maximally elevated levels in the olfactory bulb (400% higher than the uninjected side), with levels in the tubercle half that in the bulb within 12 hours post-exposure; these levels remained elevated for 3 days. Two injections of 200 μg manganese doubled the level of manganese in the striatum compared to saline-injected controls; single doses did not increase tissue manganese levels. No other brain regions were noted and blood manganese levels were not changed with any treatment. These data indicate that the olfactory mucosa is an important pathway for distribution of manganese into the brain.

Vitarella et al. (2000) exposed adult rats to airborne doses of particulate manganese, as manganese phosphate, at 0, 0.03, 0.3, 3 mg manganese/m^3. The particles had a mean diameter of 1.5 μm. Exposures lasted for 6 hours/day for either 5 days/week (10 exposures) or 7 days/week (14 exposures). The following tissues were analyzed for manganese content using neutron activation analysis: plasma, erythrocytes, olfactory bulb, striatum, cerebellum, lung, liver, femur, and skeletal muscle. Increased manganese concentrations were reported in olfactory bulb, lung, femur, and skeletal muscle following exposure to 3 mg/m^3 (after either dosing regiment); a lower dose of 0.3 mg/m^3 resulted in increased manganese concentrations in olfactory bulb, and lung (14-day dose regimen only). Striatal manganese levels were increased at the two highest doses only after 14 days of exposure. However, concentrations in the cerebellum were similarly elevated, which was interpreted by the authors to indicate that accumulation of manganese was not selective for the striatum. Red blood cell and plasma manganese levels were increased only in rats exposed to the highest dose for the 10-day exposure period. These data indicate that even at lower doses manganese can accumulate in the olfactory bulb and that the neuronal pathway to the brain is significant for inhaled manganese in rodents.

Although the results from the studies by Tjälve et al. (1996) and Vitarella et al. (2000) indicate that manganese can be transported via the olfactory neural pathway from the nasal mucosa to the olfactory bulb of the brain and, to a limited degree, to other brain regions in rodents, the relative importance of this pathway to the delivery of manganese to basal ganglia sites of neurotoxicity is uncertain. Statistical mapping of functional olfactory connections in rat brains using MRI following nasal administration of

manganese chloride could readily detect connections to the olfactory bulb, but could not detect connections to other brain regions (Cross et al. 2004). Mainstream manganese entry into the brain from blood occurs through capillary endothelial cells of the blood-brain barrier and through the cerebral spinal fluid via the choroid plexuses (Bock et al. 2008; Crossgrove and Yokel 2005). A number of transport mechanisms (including facilitated diffusion, active transport, transferrin-mediated transport, divalent metal transporter-1 mediation, store-operated calcium channels) have been proposed to transport manganese across the blood barrier, but current understanding is inadequate to determine the predominant mechanism of transport (Aschner et al. 2005; 2007; Crossgrove and Yokel 2004, 2005; Roth 2006).

A concern that inhaled manganese, compared with ingested manganese, may more readily result in manganese accumulation in the brain, a principal toxicity target of manganese, has led to recent detailed investigations of manganese concentrations in various brain regions and in other tissues following inhalation exposure of animals to environmentally relevant forms of manganese. These studies have investigated manganese concentrations in tissues of young male and female CD rats exposed by inhalation to manganese sulfate or manganese tetroxide for 14 days at concentrations of 0, 0.03, 0.3, or 3 mg manganese/m^3 (Dorman et al. 2001a), young male CD rats given low- (2 ppm), sufficient- (10 ppm), or high-manganese (100 ppm) diets for 67 days, followed by inhalation exposure to manganese sulfate for 14 days at concentrations of 0, 0.092, or 0.92 mg manganese/m^3 (Dorman et al. 2001b), young male and female CD rats or aged male CD rats after 90 days of inhalation exposure to manganese sulfate at 0.01, 0.1, or 0.5 mg manganese/m^3 or manganese phosphate at 0.1 mg manganese/m^3 (Dorman et al. 2004a), maternal CD rats and offspring after inhalation exposure to manganese sulfate at 0, 0.05, 0.5, or 1.0 mg manganese/m^3 starting 28 days prior to breeding through PND 18 (Dorman et al. 2005a, 2005b), and young male Rhesus monkeys after inhalation exposure to manganese sulfate at 0.06, 0.3 or 1.5 mg manganese/m^3 for 15, 33, or 65 exposure days (Dorman et al. 2006a).

The results from these animal studies indicate that tissue manganese concentrations in the brain depended on aerosol concentration, exposure duration, and brain region. Tissue manganese concentrations generally increased with increasing air concentrations and durations of exposure. With repeated exposures at the highest air concentrations ($\geq$0.92 mg manganese/m^3), manganese concentrations in brain regions were elevated, compared with control animals, showing the following order: olfactory bulb>striatum>cerebellum. Illustrative data for maternal CD rats (Dorman et al. 2005a) and young Rhesus monkeys (Dorman et al. 2006a) exposed to manganese sulfate are shown in Tables 3-9 and 3-10, respectively. Comparison of manganese concentrations across tissues shows the following order in exposed maternal rats: liver > pancreas > olfactory bulb > lung > striatum $\approx$ femur > milk > cerebellum

Table 3-9. Terminal Mean (±Standard Error on the Mean) Tissue Manganese Concentrations (µg Manganese/g Tissue Wet Weight) in Maternal CD Rats Exposed to Aerosols of Manganese Sulfate 6 Hours/Day, 7 Days/Week Starting 28 Days Prior to Breeding Through Postnatal Day 18

	Exposure concentration (mg manganese/m^3)			
Tissue	0	0.05	0.5	1.0
Whole blood	0.08±0.04	0.06±0.02	0.06±0.01	0.05±0.01
Olfactory bulb	0.56±0.05	0.71±0.04[a]	1.40±0.07[a]	1.73±0.07[a]
Striatum	0.51±0.02	0.54±0.02	0.74±0.02[a]	0.89±0.02[a]
Cerebellum	0.50±0.02	0.52±0.02	0.60±0.01[a]	0.61±0.03[a]
Lung	0.22±0.03	0.37±0.02	0.86±0.07[a]	1.05±0.06[a]
Liver	3.21±0.15	3.04±0.09	3.37±0.15	4.28±0.76[a]
Femur	0.62±0.07	0.61±0.04	077±0.05	0.89±0.06[a]
Pancreas	1.66±0.13	1.80±0.19	1.29±0.28	1.91±0.23
Milk	0.21±0.08	0.20±0.06	0.47±0.06	0.77±0.10[a]
Group size (n)	8	10	9	8

[a]Significantly ($p<0.05$) different from control mean value.

Source: Dorman et al. 2005a

Table 3-10. Mean (±Standard Error on the Mean) Tissue Manganese Concentrations (µg Manganese/g Tissue Wet Weight) in Young Male Rhesus Monkeys Exposed to Aerosols of Manganese Sulfate (1.5 mg Manganese/m^3) 6 Hours/ Day, 5 Days/Week for Up to 65 Days

Exposure to air	1.5 mg manganese/m^3					
Exposure (days)	65	15	33	65	65 (+45)[a]	65 (+90)[a]
Tissue						
Olfactory tissues						
Olfactory epithelium	0.49±0.01	6.10±0.39[b]	7.34±0.70[b]	7.10±2.01[b]	0.65±0.04	0.69±0.11
Olfactory bulb	0.31±0.01	2.19±0.44[b]	2.29±0.26[b]	2.40±0.18[b]	0.35±0.02	0.31±0.02
Olfactory tract	0.30±0.06	0.77±0.19[b]	0.84±0.11[b]	1.12±0.08[b]	0.18±0.02	0.22±0.02
Olfactory cortex	0.19±0.01	0.43±0.04[b]	0.45±0.01[b]	0.42±0.01[b]	0.26±0.01	0.21±0.01
Brain						
Globus pallidus	0.48±0.04	1.92±0.40[b]	2.41±0.29[b]	2.94±0.23[b]	1.09±0.03[b]	0.59±0.12
Putamen	0.36±0.01	1.01±0.08[b]	1.50±0.14[b]	1.81±0.14[b]	0.58±0.03[b]	0.44±0.02
Caudate	0.34±0.02	0.93±0.11[b]	1.37±0.13[b]	1.72±0.10[b]	0.57±0.03	0.43±0.02
Frontal cortex	0.25±0.03	0.36±0.01[b]	0.52±0.03[b]	0.47±0.02[b]	0.26±0.01	0.23±0.01
Cerebellum	0.44±0.01	0.85±0.06[b]	0.96±0.05[b]	1.10±0.11[b]	0.66±0.04	0.61±0.10
Pituitary	0.84±0.12	3.79±0.38[b]	5.60±0.33[b]	6.19±0.61[b]	3.01±0.91[b]	1.54±0.18
Trigeminal nerve	0.17±0.05	0.27±0.02	0.51±0.14[b]	0.42±0.08[b]	0.18±0.01	0.17±0.02
Organs						
Femur	0.13±0.02	0.27±0.04[b]	0.13±0.03	0.20±0.03	0.12±0.02	0.09±0.01
Heart	0.16±0.03	0.25±0.05	0.50±0.03[b]	0.62±0.05[b]	0.23±0.3	0.27±0.01
Kidney	1.14±0.12	2.65±0.14[b]	3.04±0.09[b]	2.61±0.30[b]	1.38±0.13	1.27±0.14
Liver	2.49±0.09	2.96±0.34	3.28±0.22	3.52±0.45[b]	2.88±0.27	2.04±0.06
Lung	0.15±0.03	0.39±0.06[b]	0.35 ±0.02[b]	0.33±0.04b	0.09±0.01	0.06±0.01
Pancreas	1.59±0.11	2.89±0.14[b]	2.38±0.34[b]	2.95±0.24[b]	1.41±0.270.	1.53±0.10
Skeletal muscle	0.15±0.03	0.22±0.03	0.22±0.02	0.58±0.19[b]	19±0.02	0.12±0.01
Parietal bone	0.08±0.04	0.48±0.16[b]	0.56±0.18[b]	0.25±0.04	0.17±0.03	0.16±0.04
Testis	0.26±0.03	0.41±0.06	0.50±0.04[b]	0.39±0.07	0.36±0.04	0.31±0.02
Fluids						
Bile	0.89±.22	7.38±.78[b]	4.40±.89[b]	7.60±1.68[b]	1.17±0.28	0.77±0.13
Blood	0.010±.001	0.016±.06	0.022±.002[a]	0.026±0.003[b]	0.021±0.002[b]	0.013±.001
Urine	0.000±.000	0.000±.000	0.001±.000	0.005±0.001[b]	0.000±0.000	0.000±.000
Group size (n)	6	4	4	4	4	4

[a]These monkeys were sacrificed 45 or 90 days after the 65-day exposure period.
[b]Significantly ($p<0.05$) greater than mean value for air control rats.

Source: Dorman et al. 2006a

>> whole blood (Table 3-9). In young Rhesus monkeys after 65 days of exposure, the order was: bile > olfactory epithelium > pituitary > liver > pancreas ≈ globus pallidus > olfactory bulb > kidney > putamen > caudate > cerebellum > heart >skeletal muscle > frontal cortex > lung > parietal bone ≈ femur >> blood (Table 3-10).

Brain tissues from the monkeys were dissected into more regions than the rat brains and, immediately following 65 days of exposure to the highest exposure concentration, showed the following order of elevated manganese concentrations: pituitary>globus pallidus>olfactory bulb>putamen>caudate> cerebellum>frontal cortex>trigeminal nerve (see Table 3-10). These results are consistent with the evidence that the human striatum, globus pallidus, and substantia nigra are the primary neurotoxicity target for manganese (Aschner et al. 2005; Pal et al. 1999). Three- to 5-fold increases (over air control values) in mean manganese tissue concentrations were found in the globus pallidus, putamen, and caudate in monkeys exposed to 1.5 mg manganese/m^3 manganese sulfate for 65 days, but levels were <3-fold increased in the frontal cortex and cerebellum, two brain regions not generally associated with manganese neurotoxicity (Dorman et al. 2006a; Table 3-10).

Comparison with the rat results in Table 3-9 suggests that rodents do not accumulate manganese in the basal ganglia (i.e., the collection of deep regions of the brain including the striatum [comprised of the caudate and putamen]) to the same relative degree as primates, a difference that may be related to findings that overt signs of manganese neurotoxicity are more readily detected in nonhuman primates than rodents (Aschner et al. 2005; Bock et al. 2008; Newland 1999). Recent corroborative findings showed that marmosets, a nonhuman primate, accumulated more manganese in the brain (especially in the basal ganglia and the visual cortex) than rats following intravenous injection of equivalent mg/kg body weight doses of manganese chloride (Bock et al. 2008). The mechanisms by which manganese accumulates in the basal ganglia of primates are poorly understood (Aschner et al. 2005; Bock et al. 2008; Brenneman et al. 1999; Dorman et al. 2006b), but Bock et al. (2008) have hypothesized that primates may accumulate relatively more manganese in the basal ganglia than rodents because of a relatively larger cerebral spinal fluid space in lateral ventricles adjacent to the basal ganglia.

The high concentrations of manganese in bile sampled from manganese-exposed monkeys (compared with air control values in Table 3-10) are reflective of the hepatobiliary excretion of manganese. It is currently unknown whether or not the high manganese concentrations attained in the pituitary glands of these monkeys has any effect on normal pituitary function; in this study, exposed monkeys showed no

difference in serum levels of luteinizing hormone (LH), a hormone that stimulates production of testosterone by the Leydig cells of the testes (Dorman et al. 2006a).

In pregnant rats repeatedly exposed to inhaled manganese, the placenta appears to partially limit the transport of manganese to the developing fetus (Dorman et al. 2005b). After inhalation exposure to manganese sulfate at 0, 0.05, 0.5, or 1.0 mg manganese/m^3 starting 28 days prior to breeding through PND 18, samples of maternal tissues (whole blood, lung, pancreas, liver, brain, femur, and placenta) and fetal tissues (whole blood, lung, liver, brain, and skull cap) were collected and analyzed for manganese concentrations. Elevated ($p<0.05$) manganese concentrations were observed in exposed maternal rats (compared with air control rats) in the following tissues: brain and placenta at 0.5 and 1.0 mg manganese/m^3 and lung at 0.05, 0.5, and 1.0 mg manganese/m^3. In contrast, statistically significant elevations of manganese concentrations in sampled fetal tissues were observed only in the liver at 0.5 and 1.0 mg manganese/m^3. In pups born and allowed to live up to PND 19 (and sampled for tissue evaluations at PNDs 1, 14, and 19), statistically significant ($p<0.05$) elevated manganese concentrations (compared with air control values) were observed in blood, liver, and bone samples from exposed neonatal rats at concentrations ≥0.05 mg manganese/m^3, starting at PND 1 (Dorman et al. 2005a). As shown in Table 3-11, elevated brain manganese concentrations were observed in exposed neonates starting at PND 14 (but not at earlier time points); tissue concentrations increased with increasing exposure concentration (Dorman et al. 2005a). At PND 19, mean manganese concentration in the striatum was about 2.6-fold higher in offspring exposed to 1 mg manganese/m^3, compared with air control means (Table 3-11). In contrast, the mean striatum concentration at PND 19 in maternal rats exposed to 1 mg manganese/m^3 was about 1.7-fold increased, compared with controls (Table 3-11). The results from this study suggest that the brain in developing fetuses is partially protected from excess manganese by the placenta, and that the neonatal period, compared with adulthood, is relatively more susceptible to increased manganese concentration in brain tissues with inhalation exposure to manganese sulfate aerosol concentrations between 0.05 and 1 mg manganese/m^3.

In an examination of the distribution of manganese in young adult male and female CD rats (28 days at start) and aged male CD rats (16 months at start) following 90-day inhalation exposure to manganese sulfate or manganese phosphate, no evidence was found for a gender or age effect on delivery of manganese to the striatum or on the order of manganese concentrations in tissues (pancreas> olfactory bulb > femur > testes), but gender or age-related differences in tissue manganese concentrations in other brain regions, as well as in the lung, pancreas, femur, and testis, were noted (Dorman et al. 2004a). Following a 90-day inhalation exposure to 0.5 mg manganese/m^3 manganese sulfate, young adult male

Table 3-11. Manganese Concentrations in Brain Tissues of Lactating CD Rats and Offspring Exposed to Aerosols of Manganese Sulfate

	Mean maternal concentrations at PND 18 (µg manganese/g)[b]			Mean offspring concentrations (µg manganese/g)[c]				
				Brain/striatum			Cerebellum	Olfactory bulb
Air level[a] (mg manganese/m^3)	Striatum	Cerebellum	Olfactory bulb	PND 1	PND 14	PND 19	PND 19	PND 19
0	0.51±0.02	0.50±0.02	0.56±0.04	0.39	0.19	0.37	0.34	0.36
0.05	0.54±0.02	0.52±0.02	0.71±0.04[d]	0.42	0.35[d]	0.63[d]	0.51[d]	0.52[d]
0.5	0.74±0.02[d]	0.60±0.01[d]	1.40±0.07[d]	0.45	0.59[d]	0.83[d]	0.64[d]	0.70[d]
1	0.89±0.02[d]	0.61±0.03[d]	1.73±0.07[d]	0.50	0.55[d]	0.97[d]	0.72[d]	0.76[d]

[a]Rats were exposed for 6 hours/day starting 28 days prior to breeding through postnatal day (PND) 18 as reported by Dorman et al. (2005a, 2005b).
[b]Mean±SEM from Table 3 in Dorman et al. (2005a).
[c]Means from Figure 4 in Dorman et al. (2005a). Bar graphs were digitized to obtain numerical estimates of means for male and female offspring combined. At PNDs 1 and 14, whole brain tissues were analyzed. At PND 19, brains were dissected into striatum, cerebellum, and olfactory bulb before analysis.
[d]Significantly ($p<0.05$) different from air control mean.

PND = postnatal day; SEM = standard error of the mean

rats had significantly ($p<0.05$) higher olfactory bulb, blood, femur, and pancreas manganese concentrations than aged male rats, and aged male rats had significantly higher testis manganese concentrations than young male rats. Young male rats exposed to 0.5 mg manganese/m^3 had significantly higher olfactory bulb, blood, and lung manganese concentrations than similarly exposed female rats, and female rats exposed to 0.5 mg manganese/m^3 had significantly higher cerebellum manganese concentrations than control females. Young male and female rats exposed to 0.5 mg manganese/m^3 for 90 days had increased ^{54}Mn clearance rates than air-exposed controls, but similarly-exposed aged male rats did not display increased ^{54}Mn clearance rates, compared with controls (Dorman et al. 2004a). No age-related effects were observed on the order of manganese concentrations in the various tissue.

No studies were located regarding distribution of manganese in human or animals following inhalation exposure to MMT or mangafodipir.

3.4.2.2 Oral Exposure

Excess manganese uptake has occurred in humans following oral exposure, presumably via the diet, when the individuals suffered from chronic liver disease or some other liver dysfunction (cirrhosis, portacaval shunt, etc.). In these instances, excess manganese was shown to accumulate in certain regions of the brain, as determined by T1-weighted MRI or neutron activation analysis (Devenyi et al. 1994; Fell et al. 1996; Hauser et al. 1994, 1996; Pomier-Layrargues et al. 1998; Rose et al. 1999; Spahr et al. 1996). These studies show that manganese preferentially accumulates in the basal ganglia, especially the globus pallidus, and the substantia nigra.

Rats given a single oral dose of 416 mg manganese/kg body weight (as manganese chloride tetrahydrate) exhibited little tissue accumulation of manganese 14 days later (Holbrook et al. 1975). Studies in animals indicate that prolonged oral exposure to manganese compounds results in increased manganese levels in all tissues, but that the magnitude of the increase diminishes over time (Kristensson et al. 1986; Rehnberg et al. 1980, 1981, 1982). Table 3-12 provides illustrative data based on rats exposed to 214 mg manganese/kg(body weight)/day (as manganese tetroxide) for up to 224 days. As the data reveal, large increases in tissue levels of manganese compared to the controls occurred in all tissues over the first 24 days, but levels tended to decrease toward the control levels as exposure was continued. This pattern is thought to be due to a homeostatic mechanism that leads to decreased absorption and/or increased excretion of manganese when manganese intake levels are high (Abrams et al. 1976a; Ballatori et al. 1987; Mena et al. 1967). Davis et al. (1992b) and Malecki et al. (1996b) demonstrated that rats fed

Table 3-12. Manganese Levels in Rat Tissue After Oral Exposure

	Tissue concentrations (percent of control)[a]		
Tissue	24 days	60 days	224 days
Liver	810	137	138
Kidney	430	102	128
Brain	540	175	125
Testes	260	125	100

[a]Values presented are the ratio (expressed as a percentage) of tissue levels of manganese in animals receiving 3,550 ppm manganese in the diet (as manganese tetroxide) compared to animals receiving a normal diet (50 ppm).

Source: Rehnberg et al. 1980

elevated levels of manganese for several weeks had increased tissue manganese concentrations, despite increased gut endogenous losses of manganese, as biliary manganese. This reflected several factors. Although the percentage of manganese absorbed decreased, the total amount of manganese absorbed increased when higher levels of manganese were fed. Moreover, although the total amount of manganese lost in bile increased when manganese intake increased, the percentage of manganese intake lost in bile remained constant at ~1% of manganese intake (Malecki et al. 1996b). Table 3-9 contains a summary of manganese levels measured in rat tissue.

A study measuring the retention of a single oral dose of radiolabeled manganese in adult and neonatal rats indicated that retention of the label 6 days after exposure was much greater in pups (67%) than in adults (0.18%); the addition of manganese to the animals' drinking water decreased radiolabel retention in pups and adults (Kostial et al. 1989).

The distributional differences in rats exposed to either manganese chloride or manganese dioxide by gavage were investigated by Roels et al. (1997). After administration of 24.3 mg manganese/kg body weight (as manganese chloride) once weekly for 4 weeks, the authors analyzed blood and brain concentrations of the metal. Manganese concentrations were significantly elevated in the blood (approximately 83% increase over controls) and the cortex of the brain (approximately 39% increase over controls). Gavage administration of manganese dioxide, by contrast, did not significantly increase the amount of manganese in blood or any section of the brain. In addition, administration of manganese as manganese chloride by gavage caused roughly the same amount of increased manganese in the blood as intratracheal administration of manganese in the same form; it did not cause as significant an increase of manganese in the cortex (Roels et al. 1997). These data indicate that inhalation exposure to manganese in the form of manganese chloride or manganese dioxide causes accumulation of manganese in the brain more readily than oral exposure.

Acute manganese exposure in drinking water was found to alter brain regional manganese levels in neonatal rats; after 5 days of exposure, the highest level was in the striatum (12.05 μg/g wet weight) and the lowest level was in the cerebral cortex (0.85 μg/g wet weight) (Chan et al. 1992). After 10 days, the highest concentrations were in the pons and medulla and the lowest were in the hypothalamus. Regional manganese differences were less pronounced in weanling and adult rats. A study by Lai et al. (1991) confirms that intermediate exposure to manganese in drinking water increases brain manganese concentrations; rats exposed from conception to 120 days at 0.04 or 0.4 mg manganese/kg/day had mean

brain manganese levels of 0.36–0.72 μg/g in the low-dose animals and 0.62–1.35 μg/g in the high-dose animals, compared to 0.21–0.38 μg/g in controls.

In a dietary study, elevated manganese levels were found in the organs of male mice fed manganese chloride, manganese acetate, manganese carbonate or manganese dioxide at 284 mg manganese/kg/day for 100 days; levels of manganese in the liver and kidney were significantly higher in the animals exposed to manganese acetate or manganese carbonate than in those exposed to manganese chloride or manganese dioxide (Komura and Sakamoto 1991). In a 1993 NTP study, mice and rats chronically fed manganese sulfate generally exhibited elevated tissue levels of manganese; the manganese levels in the liver and kidney were higher than the levels in the brain.

No studies were located concerning disposition of manganese in humans or animals following oral exposure to MMT or mangafodipir.

3.4.2.3 Dermal Exposure

No studies were located regarding tissue distribution of manganese in humans or animals after dermal exposure to inorganic manganese.

No studies were located regarding tissue distribution of manganese in humans or animals after dermal exposure to organic manganese.

3.4.2.4 Other Routes of Exposure

No studies were located regarding tissue distribution of inorganic manganese in humans after exposure via other routes of exposure.

A number of studies have been conducted that investigated various facets of the distribution of inorganic manganese in animal models. The studies utilized a number of routes of administration, and the results suggested that route may play an important role in distribution. In an intraperitoneal study performed in monkeys, manganese was reported in all tissues studied. The highest levels were found in the pancreas, liver, and kidney, and the lowest levels were found in the blood; levels in the central nervous system were found to decrease more slowly than those in other tissues (Dastur et al. 1971). Calves injected intravenously with ^{54}Mn were found to have 3-fold higher liver manganese concentrations and 13-fold higher pancreatic manganese concentrations than calves fed manganese (Carter et al. 1974). Davis et al.

(1993) observed that rats injected intraportally with free ^{54}Mn or ^{54}Mn complexed with transferrin and rats injected intraperitoneally with free ^{54}Mn accumulated more manganese in the pancreatic tissue and less in the liver than those rats that were either fed ^{54}Mn or injected intravenously in the portal vein with an albumin-^{54}Mn complex. The similarity in the distribution of the injected manganese-albumin complex and the free manganese in the diet when compared to the distribution of manganese when it was administered by other routes or complexed with other proteins suggests that the route of administration and type of complexed protein may cause differences in the transport of manganese in the sera.

Roels et al. (1997) studied the effect of intraperitoneal administration of manganese chloride and manganese dioxide on distributional differences of manganese in rats. Doses of 1.22 mg manganese/kg as manganese chloride given once per week for 4 weeks resulted in significant increases (when compared to controls) in blood (approximately 60%), striatum (34%), and cortex (36%) concentrations of manganese; no changes were observed in the cerebellum. Identical dosing of rats with manganese dioxide resulted in significant increases in manganese levels in blood (79%), cerebellum (40%), striatum (124%), and cortex (67%) over those in controls. These data indicate that administration of manganese dioxide by this route resulted in greater accumulation of manganese in the brain than did manganese chloride.

The distribution of manganese in the brain was investigated using Cebus (Newland and Weiss 1992; Newland et al. 1989) and Macaque (Newland et al. 1989) monkeys given intravenous injections of manganese chloride that reached a cumulative dose of 10–40 mg manganese/kg. Magnetic resonance images indicated hyper-intensity of the globus pallidus and substantia nigra consistent with an accumulation of manganese in these areas (Newland and Weiss 1992; Newland et al. 1989). Substantial accumulation of manganese was also noted in the pituitary at low cumulative doses (Newland et al. 1989). London et al. (1989) reported a rapid localization of manganese in the choroid plexus observed on MRI; similarly, radiotracer studies of manganese injected into the intracerebroventricular space revealed that radiolabeled manganese was located in the choroid plexus within 1 hour and was located in the rat dentate gyrus and CA3 of the hippocampus 3 days post-dosing (Takeda et al. 1994).

No studies were located regarding disposition of MMT in humans following other routes of exposure, but toxicokinetics of MMT following parenteral administration has received some research attention in animals.

Young adult male rats were administered MMT dissolved in propylene glycol via subcutaenous injection at a dose of 1 mg manganese/kg (McGinley et al. 1987). Control rats received vehicle alone. The rats were sacrificed 1.5, 3, 6, 12, 24, 48, or 96 hours post-injection. Levels of manganese in the control animals were measured in the blood (0.09±0.01 mg/kg), lung (1.51±0.22 mg/kg), liver (2.49±0.36 mg/kg), kidney (1.29±0.23 mg/kg), and brain (0.45±0.01 mg/kg). These values were assumed by the authors to originate from the feed given to the rats and were subtracted from similar values analyzed for MMT-treated rats to determine the amount of manganese in these tissues and fluids that originated from MMT. Maximum accumulation of MMT-derived manganese was measured 3 hours after dosing and was found primarily in the following four tissues: lung (~9 mg/kg); kidney (3.9 mg/kg); liver (2.75 mg/kg); and blood (~0.75 mg/kg). Concentrations of manganese in these four tissues was still elevated (~1 mg/kg) at 96 hours post-dosing. Brain manganese concentrations were not significantly elevated over control levels in MMT-treated animals (McGinley et al. 1987).

Gianutsos et al. (1985) administered 0, 11, or 22 mg manganese/kg as MMT (dissolved in propylene glycol) to male adult mice via subcutaneous injection to determine distribution of manganese. Control mice received vehicle alone. Mice were sacrificed at different time points after dosing. The experiment was divided into an acute study (one dose) or a "chronic study" (ten doses). The brain manganese level 24 hours after the single dose of MMT at 11 mg/kg was 0.93±0.07 μg/g; the value after 22 mg/kg was 1.35±.09 μg/g. Both values were significantly different from the control value of 0.61±0.08 μg/g. The brain manganese level in the mice administered 10 doses of 11 mg/kg each was 1.37±0.27 μg/g; after 10 doses of 22 mg/kg, the value was 3.33±0.15 μg/g; both were significantly greater than the control value of 0.64±0.06 μg/g, and were significantly different than the levels reported after the acute exposure. Manganese levels in the brains of mice given a single dose of MMT at 22 mg manganese/kg were compared with those following injection of the same manganese dose as manganese chloride; mice were sacrificed at different time points from 1–24 hours post-dosing. The brain manganese levels following MMT exposure increased from a low at 1 hour to a maximum at 24 hours of ~1.4 μg/g wet weight. The manganese level in brain after manganese chloride exposure followed the same increasing trend over the 24 hour analysis period, but was higher at each time point, with a maximum value of >2.0 μg/g wet weight (Gianutsos et al. 1985).

Clinical studies involving cancer patients or healthy volunteers have analyzed the usefulness of mangafodipir as a contrast agent for the identification of certain abdominal tumors. Although these studies do not necessarily quantify the amount of manganese, or mangafodipir, in particular tissues, they

are useful tools in identifying the location of the metal; also relative proportions of manganese among two or more tissues that contain the metal can be observed by differences in signal from these imaging studies.

Several studies have shown the qualitative presence of manganese in the liver due to increased signal in that organ following mangafodipir administration of 0.17–0.83 mg manganese/kg upon T1-weighted MRI (Bernardino et al. 1992; Lim et al. 1991; Padovani et al. 1996; Wang et al. 1997). Two studies show that the human liver takes up more of the manganese from mangafodipir than any other organ: the signal from the liver was roughly 2 times the amount from the spleen after dosing with 0.55 mg manganese/kg (Lim et al. 1991); the liver signal after dosing with 0.55 mg manganese/kg had reached a 100% increase over baseline signal by 20 minutes following post-dosing, whereas the maximal signal from other organs was only 80% in the pancreas, ~30% in the spleen, ~90% in the renal medulla, and 50% in the choroid plexus, all at the same dose. The renal cortex was the only other tissue to reach a 100% increase over baseline signal at 0.55 mg manganese/kg. Dosing with 0.25 mg manganese/kg (the clinically used dose for current MRI testing of patients) resulted in a similar distribution pattern, although the signal was decreased compared to the higher dose. The signal from the renal cortex at the lower dose had a maximum of 80% over baseline, whereas the signal in the liver at this dose was ~75% of the baseline value (Wang et al. 1997).

Several studies have determined the distribution of manganese in tissues of animals following intravenous administration of mangafodipir. Grant et al. (1994) reported that in rats injected with 2 times the clinical dose of [^{54}Mn] mangafodipir (0.55 mg manganese/kg), the carcass retained 8% of the label and the tissues retained 7% of the label; individual tissue concentrations of manganese were not reported.

Gallez et al. (1997) injected adult male mice once with 0.25 mg manganese/kg as [^{54}Mn] mangafodipir (clinical dose) and determined the tissue manganese content at time points ranging from 15 minutes to 3 months post-dosing. Brain concentration of ^{54}Mn did not reach a maximum value of 0.26±0.04 (value is the percent of injected dose/g tissue) until 24 hours post-dosing; this value was not different than the brain manganese content of mice injected with manganese chloride. This maximum value was still observed in the brain 2 weeks post-dosing, but measurements taken at 1 and 3 months post-dosing were below the detection limit. By contrast, manganese from manganese chloride was still detectable, although not at maximal levels, at 3 months' time. Liver manganese reached a maximum value of 7.5±1.4 (percent dose/g tissue) 15 minutes post-dosing and then decreased to below the detection limit 1 month later.

Male and female Sprague-Dawley rats injected with [^{54}Mn] mangafodipir at a dose of 5.5 mg manganese/kg had the following distribution of labeled manganese 30 minutes post-dosing (values are given in percent injected dose/g tissue): liver, 1.3; kidney, 1.2; heart, 0.25; spleen, 0.2; blood, 0.3; small bowel, 1.3; large bowel, 0.5; muscle, 0.1; and brain, negligible. Distribution of manganese in tissues of rats injected with labeled manganese chloride was compared to the previous results, and for all tissues, the label was greater after administration with the chloride than from the mangafodipir, with the exception of kidney and large bowel, but these differences were not significant (Elizondo et al. 1991).

The distribution of label in male and female Sprague-Dawley rats injected with either [^{54}Mn] or [^{14}C] mangafodipir at a dose of 0.39 or 0.55 mg manganese/kg, respectively, was studied by Hustvedt et al. (1997). The plasma concentration of labeled manganese reached a peak of 10.2 μg/mL at 5 minutes post-dosing and was quickly distributed into the following organs (values given as μg equivalents of compound/g): pancreas, 10.2; liver, 4.0; kidneys, 3.6; testes/ovaries, 1.7; spleen, 1.0; heart, 0.9; and brain, 0.69. When the bile duct was cannulated, the distribution of an equivalent dose of mangafodipir showed an increased retention of labeled manganese in all organs but the brain (0.62): pancreas, 17.2; liver, 12.3; kidneys, 10.1; testes/ovaries, 5.6; small intestine, large intestine and heart, 2.1; and spleen, 1.9. By contrast, tissue retention of ^{14}C from radiolabeled mangafodipir was very low: pancreas, 0.016; liver, 0.045; kidneys, 0.067; testes/ovaries, 0.015; spleen, 0.023; small intestine, 0.012; large intestine, 0.019; heart, 0.017; and brain, 0.009. These data indicate that manganese dissociates from the fodipir moiety after mangafodipir administration and partitions into the tissues listed above.

The tissue distribution of normal and bile-cannulated dogs following administration of [^{54}Mn] or [^{14}C] mangafodipir was also studied (Hustvedt et al. 1997). Doses of 0.55 manganese/kg were used except for the normal dogs when the manganese was labeled; the dose in this case was 0.38 mg/kg. The general pattern of distribution of manganese and carbon was similar to that seen with rats, except the concentrations were increased in the dog. The values for normal dogs were taken 168 hours post-dosing for both forms of labeled mangafodipir; the bile-cannulated dogs were analyzed 24 hours post-dosing. The maximum concentration of ^{54}Mn in the plasma following dosing was 13.1 μg/mL at the end of the infusion period. The plasma concentrations declined rapidly with a terminal half-life of approximately 15 minutes. In the normal dog and bile-cannulated dog, the tissue distribution was as follows (the values for the bile-cannulated dog are given in parentheses; all values are in μg equivalents of compound/g): liver, 8.7 (79.8); pancreas, 8.1 (2.5); kidneys, 6.6 (37.5); bile, 5.9 (no sample); testes/ovaries, 2.2 (3.2); brain, 0.79 (1.1); spleen, 0.65 (26.6); and heart, 0.62 (3.1). The distribution of labeled carbon in normal (or bile-cannulated dogs) was the following: kidneys, 0.79 (4.1); liver, 0.13 (0.48); bile, 0.059 (no

sample); testes/ovaries, 0.05 (0.079); pancreas, 0.015 (0.11); heart, 0.015 (0.035); spleen, 0.007 (0.15); and brain, not detected (not detected). These data indicate that in the dog, as in the rat, the manganese cation is retained by the tissues, but the fodipir moiety is not.

Distribution of ^{54}Mn and ^{14}C following mangafodipir administration was also studied in the pregnant rat (Hustvedt et al. 1997). Whole-body autoradiography of a section of the rat made at different time points revealed that the kidney had retained the highest amount of labeled manganese; later time points showed a distribution similar to those seen in the rat and dog studies mentioned previously with the pancreas and liver causing the most intense signal upon autoradiography. By 24 hours, fetal livers and bones were clearly seen, but placental radioactivity had decreased substantially. Fat deposits also contained a significant amount of the radioactivity at 24 hours. By contrast, radioactivity from labeled carbon in the mangafodipir was relatively uniformly distributed throughout the pregnant rat at 5 minutes and 1 hour post-dosing, with the highest levels in the kidneys. At 24 hours, virtually all tissues were indistinguishable from background.

The human distribution studies have involved much shorter observation times than the animal studies, with maximal increase in MRI signal in human studies observed in minutes following administration. These studies have shown the liver to accumulate the highest amount of manganese from the administered dose of mangafodipir. This is an important limitation since the brain, the primary target of manganese neurotoxicity, may not accumulate a significant amount of manganese until much later, possibly after the current experiments in humans and animals were truncated. Experiments in rats and dogs, both normal and bile-cannulated, indicate that the brain does not accumulate a significant amount of manganese following administration of mangafodipir at levels much higher than the recommended clinical dose of the agent (Hustvedt et al. 1997), even at 168 hours post-dosing in the dog. Gallez et al. (1997) reported that manganese accumulation in the brain of adult mice following injection of a clinical dose of mangafodipir did not reach maximal levels until 24 hours post-dosing. This would indicate that the human distribution studies were terminated prematurely. However, while brain accumulation of manganese following mangafodipir administration is similar to that from manganese chloride, the manganese is not present after 2 weeks, whereas manganese from the inorganic compound was present, although at a decreased amount, 3 months following dosing (Gallez et al. 1997). These data indicate that single, clinical doses of mangafodipir are not likely to cause persistent accumulation of manganese in the brain.

3.4.3 Metabolism

Manganese is capable of existing in a number of oxidation states, and limited data suggest that manganese may undergo changes in oxidation state within the body. Circumstantial support for this hypothesis comes from the observation that the oxidation state of the manganese ion in several enzymes appears to be Mn(III) (Leach and Lilburn 1978; Utter 1976), while most manganese intake from the environment is either as Mn(II) or Mn(IV) (see Chapter 6). Another line of evidence is based on measurements of manganese in tissues and fluids using electron spin resonance (ESR), which detects the unpaired electrons in Mn(II), Mn(III), and Mn(IV). When animals were injected with manganese chloride, levels of manganese increased in bile and tissues, but only a small portion of this was in a form that gave an ESR signal (Sakurai et al. 1985; Tichy and Cikrt 1972). This suggests that Mn(II) is converted to another oxidation state (probably Mn(III)), but it is also possible that formation of complexes between Mn(II) and biological molecules (bile salts, proteins, nucleotides, etc.) results in loss of the ESR signal without oxidation of the manganese ion.

Evidence by Gibbons et al. (1976) suggests that oxidation of manganese occurs in the body. It was observed that human ceruloplasmin led to the oxidation of Mn(II) to Mn(III) *in vitro*, and although the process was not studied *in vivo*, it is a likely mechanism for manganese oxidation in the blood. These authors also noted that manganese oxidation led to a shift in manganese binding *in vitro* from α_2-macroglobulin to transferrin and that *in vivo* clearance of Mn(II)-α_2-macroglobulin from cows was much more rapid than the clearance of Mn(III)-transferrin (Gibbons et al. 1976). This suggests that the rate and extent of manganese reduction/oxidation reactions may be important determinants of manganese retention and toxicity in the body.

As demonstrated in a study by Komura and Sakamoto (1991), tissue levels of manganese in rats were affected by the form in which the manganese was administered in the diet; levels of manganese were significantly higher in animals fed manganese acetate or manganese carbonate than in animals fed manganese chloride or manganese dioxide.

Reaney et al. (2006) compared brain concentrations of manganese, dopamine, and gamma amino butyric acid in female retired breeder Long Evans rats exposed to cumulative intraperitoneal doses of 0, 30, or 90 mg manganese/kg of Mn(II) chloride or Mn(III) pyrophosphate. Rats were given intraperitoneal doses of 0, 2, or 6 mg manganese/kg, 3 times/week for 5 weeks. In Mn(III)-treated rats, brain manganese concentrations (analyzed in the striatum, globus pallidus, thalamus, and cerebrum regions) and blood

concentrations were higher than brain concentrations in Mn(II)-treated rats. The only other marked changes in end points between the two treatment groups was that the highest Mn(III) exposure group showed a 60% increased dopamine level in the globus pallidus (compared with controls), whereas the comparably treated Mn(II) rats showed a 40% decrease in globus pallidus dopamine level. These results suggest that manganese valence state can influence tissue toxicokinetic behavior, and possibly toxicity.

MMT. Following intravenous administration in the male rat, MMT was metabolized to hydroxyl-methylcyclopentadienyl manganese tricarbonyl (CMT-CH_2OH) and carboxycyclopentadienyl manganese tricarbonyl (CMT-COOH), both of which are present in urine (Hanzlik et al. 1980a). Metabolites are also present in the bile, as indicated by the fecal recovery of ^3H from the ring structure in MMT following intravenous or intraperitoneal administration of radiolabeled compound to rats (Hanzlik et al. 1980a, 1980b). After intravenous dosing of MMT in rats, 11% of the radiolabel was recovered in feces within 30 minutes (Hanzlik et al. 1980b). These metabolites have not been characterized; however, the administration of phenobarbitol to the rat doubled the biliary excretion of the metabolite (Hanzlik et al. 1980a).

In vitro studies showed that rat liver microsomes activated with NADPH and molecular oxygen metabolized MMT (Hanzlik et al. 1980b). Preliminary studies with pooled liver microsomes from 5 to 6 normal or phenobarbital-induced rats showed that reaction rates of metabolism were linear for the first 20 minutes. MMT and aminopyrine, a positive control compound that is metabolized exclusively by cytochrome P450, showed parallel responses to changes in incubation conditions (i.e., NADPH dependence, inhibition by carbon monoxide, induction by phenobarbital). Liver microsomes metabolized MMT with an estimated K_M of 78 μM and a V_{max} of 3.12 nmol/mg protein/minute. When the studies were done with liver microsomes from phenobarbital-treated rats, the K_M remained the same, but the V_{max} doubled (Hanzlik et al. 1980b). Lung microsomes were equally capable of metabolizing MMT, but phenobarbital induction did not enhance the response.

In humans, an infusion of the clinical dose of MnDPDP (5 μmol/kg or 0.25 mg/kg) is rapidly dephosphorylated to manganese dipyridoxyl monophosphate (MnDPMP). This metabolite has been measured in human blood as quickly as 18 minutes after the beginning of infusion of the contrast agent, and is still measurable 1.3 hours after the start of the infusion (Toft et al. 1997a). MnDPMP was not observed in the blood after the first 18 minutes. The monophosphate is then fully dephosphorylated to manganese dipyridoxyl ethylenediamine (MnPLED); this compound has been isolated in blood from 18 minutes after the start of an infusion until 40 minutes after the start. Transmetallation of either

MnDPDP, MnDPMP, or MnPLED with zinc can occur, forming ZnDPDP, ZnDPMP, or ZnPLED. ZnDPDP has been identified in the bloodstream during the first 18 minutes of an infusion of 0.25 mg manganese/kg as MnDPDP. ZnDPMP has been detected in the blood from 18 to 40 minutes following the start of the infusion, and ZnPLED has been measured in the blood from 18 minutes to 8.33 hours following the start of the infusion. The major metabolite detected in urine was ZnPLED (Toft et al. 1997a). Figure 3-4 depicts the metabolism of mangafodipir in the human.

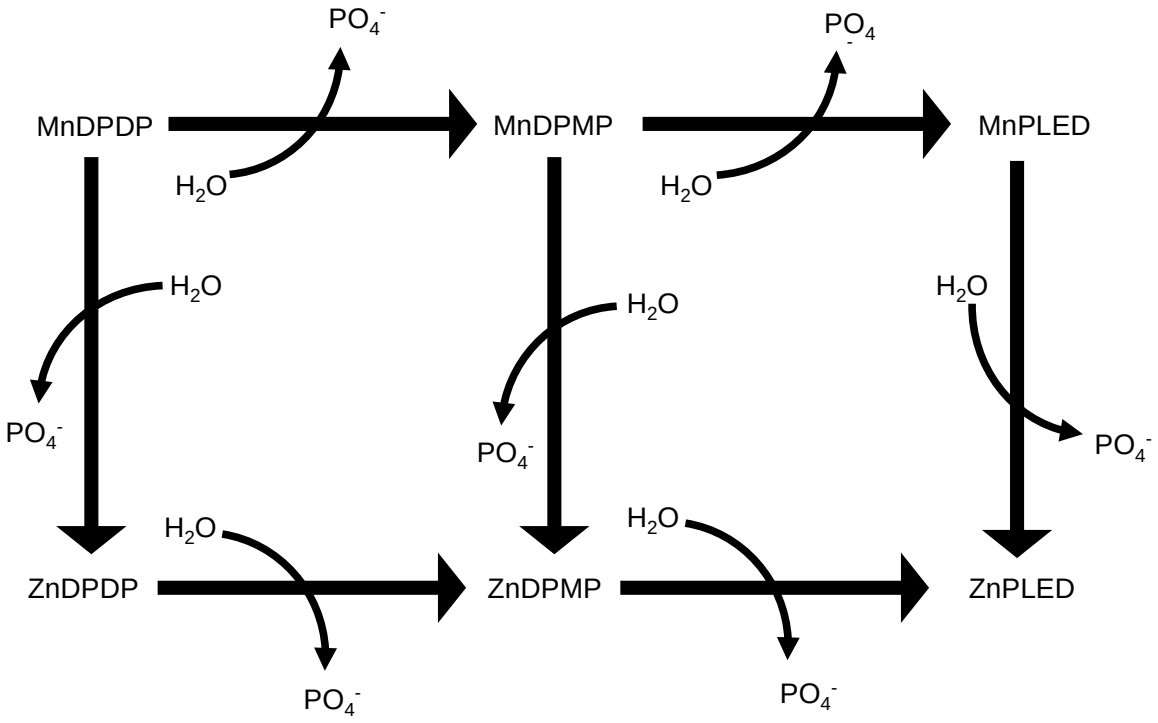
To study mangafodipir metabolism in the dog, Toft et al. (1997c) injected three male and female beagles with 0.55, 1.7, or 5.5 mg manganese/kg and took timed blood samples post-dosing to analyze for the presence of metabolites. Mangafodipir was rapidly metabolized by dephosphorylation and transmetallation at all three doses. After infusion with 0.55 mg/kg, MnPLED was the primary metabolite observed in the bloodstream 1 minute after the end of the infusion period, and MnDPDP was present at a concentration lower than the five metabolites. At 30 minutes post-dosing, ZnPLED was the main metabolite. However, at 5.5 mg/kg, MnPLED was the main metabolite at all sampling times (1, 5, and 30 minutes). The authors estimated that the ratios of manganese metabolites to zinc metabolites were 1, 2, and 3.5 at doses of 0.55, 1.7, or 5.5 mg manganese/kg, respectively; these data are consistent with the authors' hypothesis that the limited availability of free or loosely bound plasma zinc governs the initial transmetallation reaction (Toft et al. 1997c).

In vitro experiments with radiolabeled MnDPDP and whole blood or plasma from human donors indicate that mangafodipir undergoes a rapid transmetallation with zinc that is nearly complete within 1 minute after the start of incubation, followed by a relatively slow dephosphorylation process. The primary metabolite after a 90-minute incubation of whole blood with MnDPDP was MnDPMP, followed by CaDPDP/DPDP, Mn(III)DPDP (suggested as an artifact due to high pH and oxygen), and MnPLED. Experiments using ^{14}C-DPDP indicate that this chelate cannot enter red blood cells; therefore, the zinc contained within the cells is unavailable for binding to this compound. Binding of manganese ion to serum proteins was observed as well, indicating that dissociation of the metal from the chelate had occurred during incubation (Toft et al. 1997b).

3.4.4 Elimination and Excretion

In humans, absorbed manganese is removed from the blood by the liver where it conjugates with bile and is excreted into the intestine. Biliary secretion is the main pathway by which manganese reaches the intestines where most of the element is excreted in the feces (Bertinchamps et al. 1965; Davis et al. 1993;

Figure 3-4. Metabolism of MnDPDP



Source: Toft et al. 1997c

Malecki et al. 1996). However, some of the manganese in the intestine is reabsorbed through enterohepatic circulation (Schroeder et al. 1966).

Small amounts of manganese can also be found in urine, sweat, and milk (EPA 1993b). Urinary excretion of manganese by healthy males was 7.0 nmole/g creatinine (7.0 nmole=385 ng=0.385 μg) (Greger et al. 1990). Similarly, urinary manganese excretion by women was 9.3 nmole/day. Moreover, urinary excretion of manganese was not responsive to oral intake of manganese (Davis and Greger 1992). Dorner et al. (1989) showed that some infants fed breast milk and formula suffered negative manganese balances due to high fecal excretion. However, animal studies indicate that in the young, excretion is not well-developed and may result in increased retention of the element. For example, in mice, rats, and kittens, there is an almost complete absence of excretion during the neonatal period (Cotzias et al. 1976). However, data in neonatal rats indicate that manganese retention rates decrease to rates observed in adult animals. This is indirect evidence that excretion may mature during the end of the neonatal period though the exact time frame across species is unknown.

3.4.4.1 Inhalation Exposure

In humans who inhaled manganese chloride or manganese tetroxide, about 60% of the material originally deposited in the lung was excreted in the feces within 4 days (Mena et al. 1969). Chronically exposed male workers were reported to have urine manganese levels that were significantly higher than unexposed persons; for example, male foundry workers had a mean manganese level of 5.7 μg/L compared to 0.7 μg/L in unexposed controls (Alessio et al. 1989). Other studies have reported significantly increased levels of urinary manganese in men occupationally exposed to airborne manganese dusts and fumes (Lucchini et al. 1995; Roels et al. 1987a, 1992). Mergler et al. (1994) did not report a significant difference in urinary manganese levels between the exposed and control groups in their occupational study. The differences in urinary excretion may be due to differences in duration or extent of exposure. A listing of these occupational studies that measured exposure levels of manganese and the resultant levels of the metal in biological samples is provided in Table 3-13.

Rats exposed to either manganese chloride or manganese tetroxide by intratracheal instillation excreted about 50% of the dose in the feces within 3–7 days (Drown et al. 1986). Monkeys exposed to an aerosol of $^{54}MnCl_2$ excreted most of the manganese, with a half-time of 0.2–0.36 days (Newland et al. 1987). However, a portion of the compound was retained in the lung and brain. Clearance of this label was slower, occurring with half-times of 12–250 days. These data do not provide information on how much

Table 3-13. Levels of Manganese in Exposed and Non-Exposed Workers

Occupational study	Mean age (years)	Mn in air (mg/m^3)	Biological samples	
			Mn-blood µg/100 mL	Mn-urine µg/g creatinine
Roels et al. (1987b)				
Exposed	34.3±9.6	0.97[a] (total dust)	1.36[b]±0.64 (1.22)[c]	4.76[b] (0.4)[c]
Non-exposed	38.4±11.3		0.57[b]±0.27 (1.59)[c]	0.30[b] (0.15)[c]
Roels et al. (1992)				
Exposed	31.3±7.4	0.179[a] (respirable dust)	0.81[c]	0.84[c]
Non-exposed	29.3±8.0		0.68[c]	0.09[c]
Chia et al. (1993a)				
Exposed	36.6±12.2	1.59[b] (total dust)	2.53[c]	6.1[c] (µg/L)
Non-exposed	35.7±12.1		2.33[c]	3.9[c] (µg/L)
Mergler et al. (1994)				
Exposed	43.4±5.4	0.032[a] (respirable dust)	1.12[b] (1.03)[c]	1.07[b] (0.73)[c]
Non-exposed	43.2±5.6		0.72[b] (0.68)[c]	1.05 (0.62)[c]
Lucchini et al. (1999)				
Exposed	42.1±8.3	0.0967 (respirable dust) (CEI/years)	0.97[b] (0.92)[c]	1.81[b] (1.53)[c]
Non-exposed	42.6±8.8		0.6[b] (0.57)[c]	0.67[b] (0.40)[c]

[a]Median
[b]Arithmetic mean
[c]Geometric mean

CEI = cumulative exposure index

of the manganese excreted in the feces after inhalation exposure was first absorbed and then excreted via the bile versus the amount simply transported directly from the lung to the gastrointestinal tract where it may have been absorbed. In addition, because these investigators measured manganese using gamma spectrometry techniques, the relatively long elimination half-times from the brain may have been influenced by manganese present in skull bones. In monkeys exposed to 1.5 mg manganese/m^3 manganese sulfate for 65 days, manganese concentrations were elevated (compared with air control values) in many brain regions and other tissues; 45 days following cessation of exposure, concentrations remained elevated in the olfactory cortex, globus pallidus, putamen, pituitary gland, and blood, but returned to air control values by 90 days after exposure (Dorman et al. 2006a). Based on these data, Dorman et al. (2006a) calculated elimination half-lives of about 15–16 days for the globus pallidus and putamen, suspected neurotoxicity targets of manganese.

Rat studies have demonstrated that urinary excretion of manganese 1 day following inhalation exposure was increased 200- and 30-fold when the animals were treated with the chelating agents 1,2-cyclohexylene-aminetetraacetic acid (CDTA) and diethylene triamine pentaacetic acid (DTPA), respectively, but fecal excretion was not altered (Wieczorek and Oberdörster 1989b).

No studies were located regarding excretion of manganese in either humans or animals following inhalation exposure to organic manganese.

3.4.4.2 Oral Exposure

Humans who ingested tracer levels of radioactive manganese (usually as manganese chloride) excreted the manganese with whole-body retention half-times of 13–37 days (Davidsson et al. 1989a; Mena et al. 1969; Sandstrom et al. 1986). The route of manganese loss was not documented, but was presumed to be mainly fecal after biliary excretion. Serum manganese concentrations in a group of healthy men and women in Wisconsin were 1.06 and 0.86 µg/L, respectively (Davis and Greger 1992; Greger et al. 1990). Urinary excretion of manganese by men was 7.0 nmole/g creatinine (Greger et al. 1990). Similarly, urinary manganese excretion of women was 9.3 nmole/day. Moreover, urinary excretion of manganese was not responsive to oral intake of manganese (Davis and Greger 1992).

In a more recent study, young rats fed 45 mg manganese/kg/day were found to absorb 8.2% of the manganese ingested and to lose approximately 37% of the absorbed manganese through endogenous gut secretions (Davis et al. 1993).

The daily excretion of manganese from mice ingesting 11 mg manganese/kg as MMT in their daily diet was 5.4% of their daily intake (Komura and Sakamoto 1992b). In a comparison of plasma manganese kinetics following oral administration of MMT or manganese chloride in male rats, MMT-derived manganese was eliminated extremely slowly, having an average elimination half-time of 55.2 hours, compared with 4.56 hours for manganese chloride (Zheng et al. 2000). Rats receiving MMT showed an apparent oral clearance (CL/F) of 0.09 $L.hours^{-1}.kg^{-1}$, which was about 37-fold less than the oral clearance of manganese chloride (CL/F = 3.2 $L.hours^{-1}.kg^{-1}$). Accordingly, the AUC in MMT rats was about 37-fold higher than that in manganese chloride rats who received equivalent dose of manganese. A gender difference in manganese toxicokinetics following oral MMT exposure was also observed; female rats showed higher mean AUC and longer half times of plasma manganese than male rats (93.1 versus 51.8 mM hours and 68.4 versus 42.0 hours, respectively (Zheng et al. 2000).

No other studies were located regarding excretion of manganese from organic manganese compounds in either humans or animals.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of inorganic or organic manganese in humans or animals after dermal exposure to manganese.

3.4.4.4 Other Routes of Exposure

No studies were located regarding excretion of manganese by humans after exposure to inorganic manganese via other routes of exposure.

Rats exposed to manganese chloride by intravenous injection excreted 50% of the dose in the feces within 1 day (Klaassen 1974) and 85% by day 23 (Dastur et al. 1971), indicating that biliary excretion is the main route of manganese clearance. Only minimal levels were excreted in urine (<0.1% of the dose within 5 days) (Klaassen 1974). Direct measurement of manganese levels in bile revealed concentrations up to 150-fold higher than in plasma, indicating the existence of either an active transport system (Klaassen 1974) or some sort of trapping mechanism (Tichy and Cikrt 1972). Based on the difference in blood levels following portal or femoral injection, Thompson and Klaassen (1982) estimated that about 33% of the manganese burden in blood is removed in each pass through the liver. Apparently, some

manganese can cross directly from the blood to the bile (Bertinchamps et al. 1965; Thompson and Klaassen 1982), but most appears to be secreted into the bile via the liver (Bertinchamps et al. 1965).

The chemical state of manganese in bile is not known, but a considerable fraction is bound to bile components (Tichy and Cikrt 1972). This material is apparently subject to enterohepatic recirculation, since biliary manganese is reabsorbed from the intestine more efficiently than free Mn(II) (Klaassen 1974). The amount of manganese that contributes to total body burden following reabsorption from enterohepatic recirculation is not known.

While biliary secretion appears to be the main pathway by which manganese is excreted into the intestines, direct transport from blood across the intestinal wall may also occur (Bertinchamps et al. 1965; Garcia-Aranda et al. 1984). The relative amount of total excretion attributable to this pathway was not quantified by Bertinchamps, but it appears to be only a fraction of that attributable to biliary secretion (Bertinchamps et al. 1965).

Manganese originating from mangafodipir administered at clinical (0.25 mg/kg) and more than twice the clinical dose (0.55 mg/kg) is primarily excreted in the feces via the bile in both humans and animals (Grant et al. 1994; Hustvedt et al. 1997; Toft et al. 1997a; Wang et al. 1997). In contrast to the chelate, DPDP, manganese is incompletely cleared from the body 24 hours after administration, and roughly 7–8% of a dose is still retained in the body after 1 week (Hustvedt et al. 1997).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target

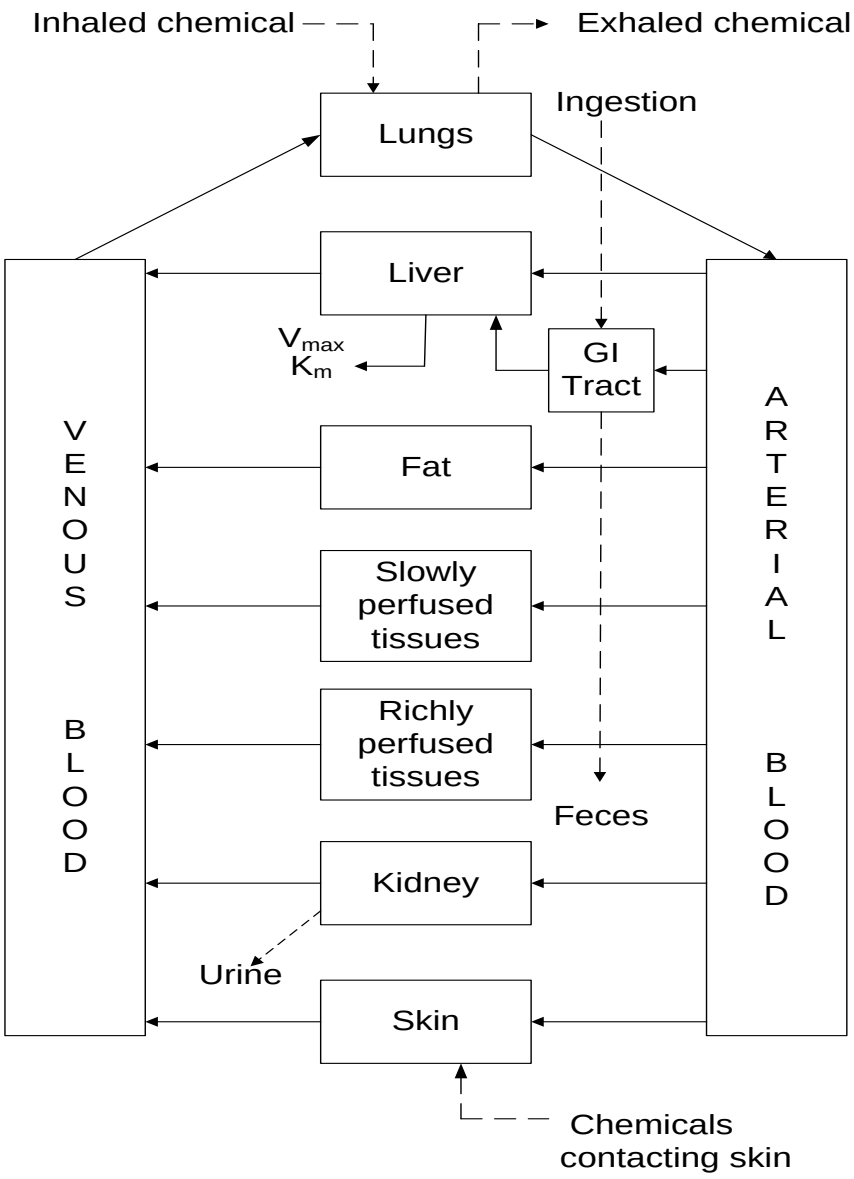
tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

If PBPK models for manganese exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

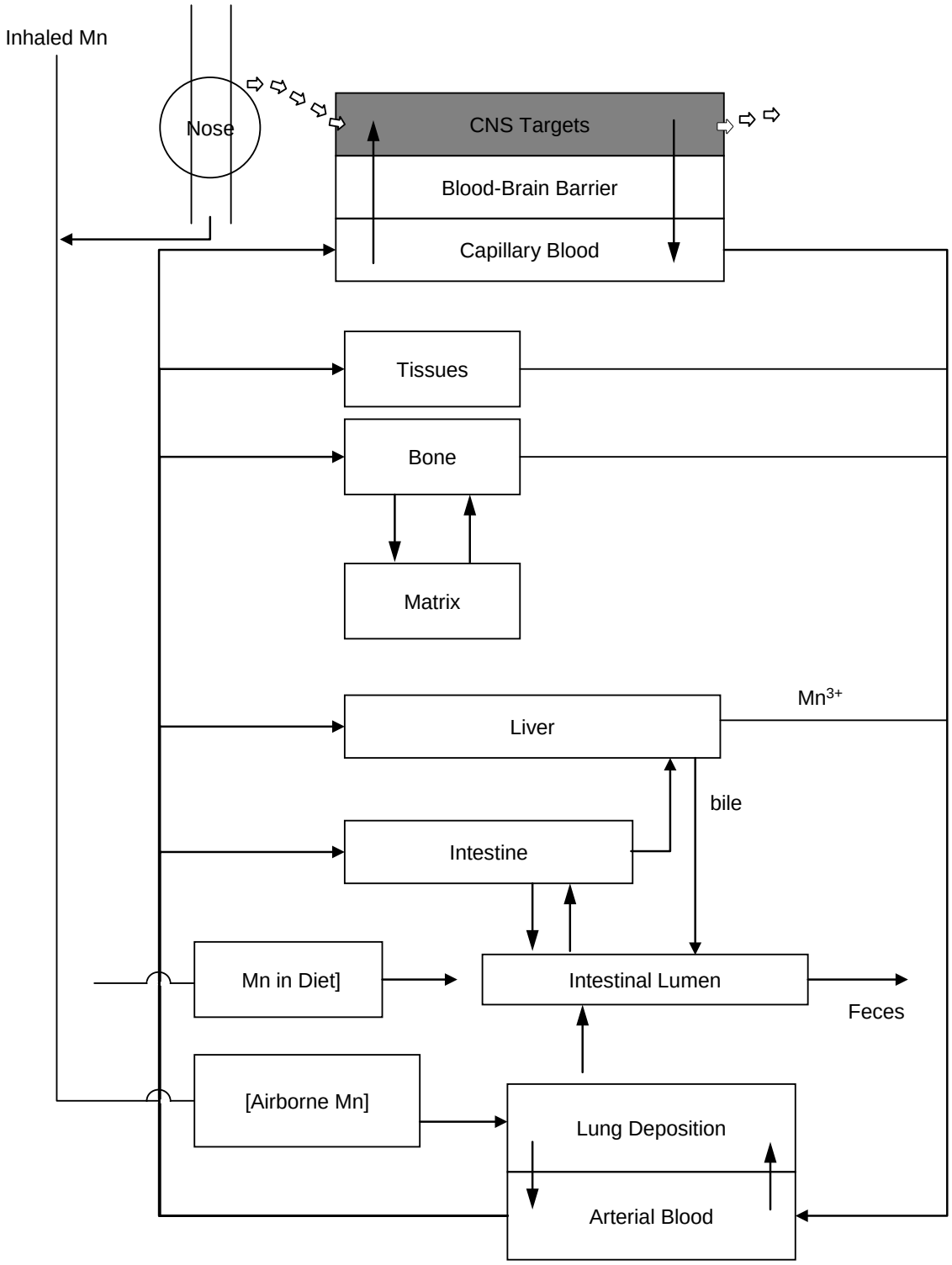
PBPK models for manganese are discussed below.

No PBPK models have been developed for manganese in humans, but several recent reports are available on the development of models for manganese in rats.

Initial Conceptual PBPK Model for Manganese (Andersen et al. 1999). A qualitative PBPK model for manganese disposition in humans and animals was initially developed by Andersen et al. (1999). This model represented the current understanding of manganese nutrition and toxicology, and because several data gaps existed concerning manganese pharmacokinetics, this model is anticipated to change with time (Andersen et al. 1999). The model, shown in Figure 3-6, was not designed to be quantitative in nature. The authors indicated that several data gaps prevented such an evaluation of manganese uptake, distribution, and excretion. For instance, there were inadequate data concerning oxidation rates for manganese in blood, uptake rates of protein-bound forms by the liver, neuronal transfer rates within the central nervous system, and quantitative data on systems controlling manganese uptake via the intestines and liver (such as transport mechanism in the intestines) (Andersen et al. 1999). Andersen et al. (1999) suggested that an approach to setting acceptable exposure levels for an essential, but neurotoxic, nutrient such as manganese could be based on predicting exposure levels by any route that would increase brain manganese concentrations to a small fraction (e.g., 10–25%) of the variation observed in the general human population. Reliable and validated multiple-route PBPK models for multiple species, including humans, are needed to take this approach to setting acceptable exposure levels. Efforts to develop such models in rats have been recently described (Leavens et al. 2007; Nong et al. 2008; Teeguarden et al. 2007a, 2007b, 2007c).

Whole-Body PBPK Models (Nong et al. 2008; Teeguarden et al. 2007a, 2007b, 2007c). Utilizing pharmacokinetic and tissue manganese concentration data from several published studies of manganese in rats and mice, recent efforts have developed PBPK models for manganese in rats that include processes involved in homeostatic regulation of tissue levels of manganese taken up by ingestion and by inhalation (Nong et al. 2008; Teeguarden et al. 2007a, 2007b, 2007c). Two PBPK model structures were developed and evaluated for their ability to account for kinetics of manganese in the liver and brain striatum following inhalation and dietary administration of soluble forms of inorganic manganese. The data sets

Figure 3-6. Qualitative PBPK Model for Manganese



Source: Andersen et al. 1999

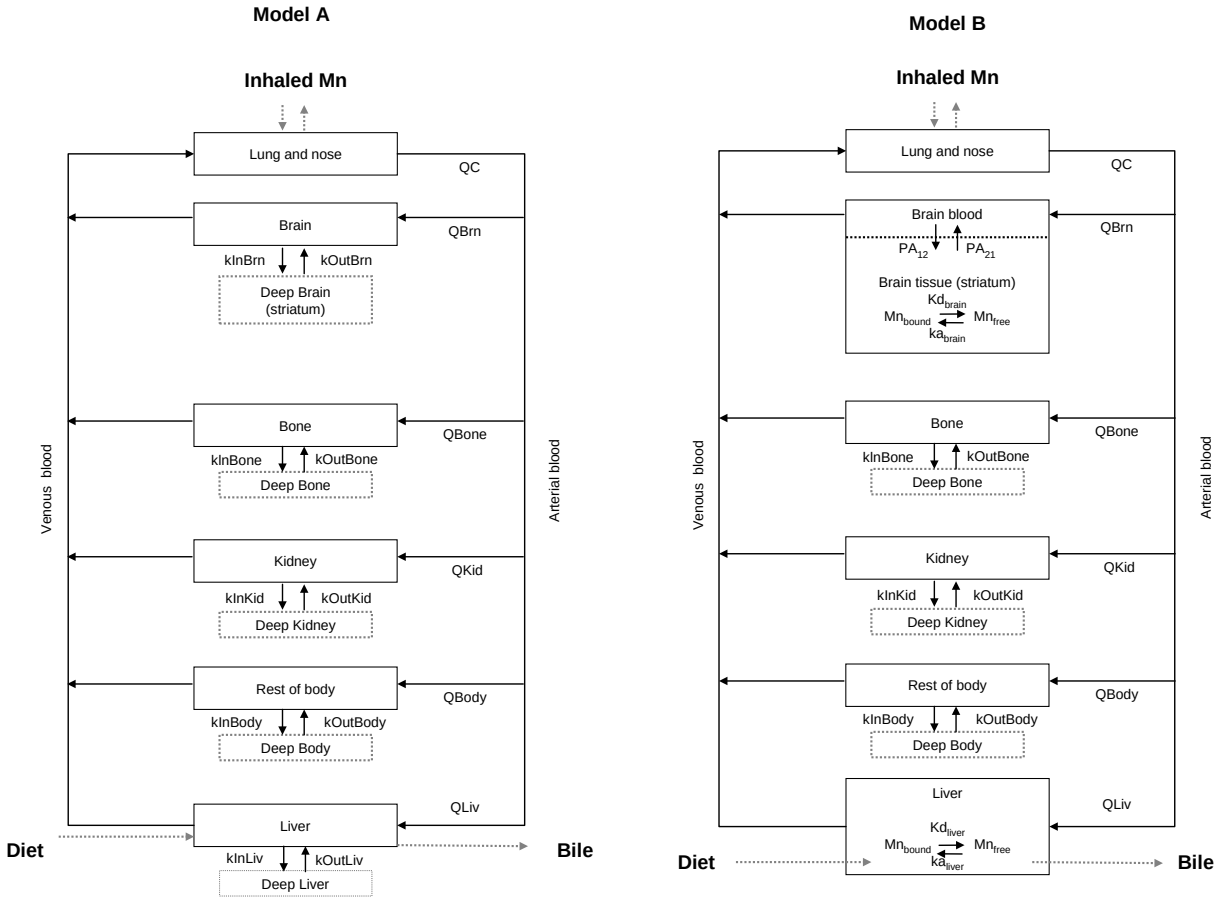
used to evaluate the models were: (1) tissue manganese concentrations in rats receiving diets containing 2, 10, or 100 ppm manganese for 13 weeks and elimination kinetics for an intravenous tracer dose of ^{54}Mn-manganese chloride (Dorman et al. 2001b); (2) tissue manganese concentrations and tracer kinetics in rats fed a 100-ppm diet and exposed to 0, 0.03, 0.3 or 3 mg manganese/m^3 manganese sulfate 6 hours/day for 14 consecutive days (Dorman et al. 2001a); and (3) tissue manganese concentrations (sampled at 0, 45, and 90 days after exposure) in rats fed a 10-ppm diet and exposed to 0, 0.1 or 0.5 mg manganese/m^3 for 6 hours/day, 5 days/week for 90 days (Dorman et al. 2004b).

Structures of the models are shown in Figure 3-7. Model A is based on regulation of tissue concentrations by simple partitioning with slow inter-compartmental transfer from free manganese in tissues to deeper tissue stores of manganese ("diffusion-controlled tissue partitioning"; Nong et al. 2008; Teeguarden et al. 2007a, 2007b, 2007c). Model B features saturable binding of manganese in liver and brain with equilibrium binding constants defined by slow association and dissociation rate constants (Nong et al. 2008). Both models contain a submodel for deposition and absorption in the nose and lung shown schematically in Figure 3-8 (Teeguarden et al. 2007c).

Nong et al. (2008) Model A Description and Development. Model A contains six compartments: the respiratory tract, brain striatum, liver, kidneys, bone, and slowly perfused tissues (Figure 3-7). The respiratory tract is divided into two subcompartments: nasopharyngeal tissues and lung (Figure 3-8). Table 3-14 lists parameters of Model A as described by Teeguarden et al. (2007c). Each of the six compartments is subdivided into a conventional flow-limited compartment connected to the blood and tissue stores that are not readily equilibrated with blood moving through the tissue compartment. First-order clearance rate constants (e.g., kInBrnC and koutBrnC) determine the transfer of manganese from the flow-limited compartment to the deep compartment of each tissue. The clearance rate constants, together with the blood flow to the tissue (e.g., QBrnC) and the tissue partition coefficients (e.g., PBrn), determine the steady-state concentrations and the rate of change manganese in each of the tissues, according to differential equations that are described in detail by Teeguarden et al. (2007c).

Physiological parameters were taken from the literature and included values for blood flows, organ volumes, and food intake rate (Table 3-14). The initial (basal) concentrations of manganese in the tissues (Table 3-14) were taken from literature values as described by Teeguarden et al. (2007c). Remaining model parameters were estimated by fitting the model to experimental data. Fractions of manganese in the shallow versus deep compartments of each tissue (e.g., fBrn and FDBrn, Table 3-14) were calibrated to obtain the best fit to intraperitoneal ^{54}Mn clearance data collected by Furchner et al. (1966). Partition

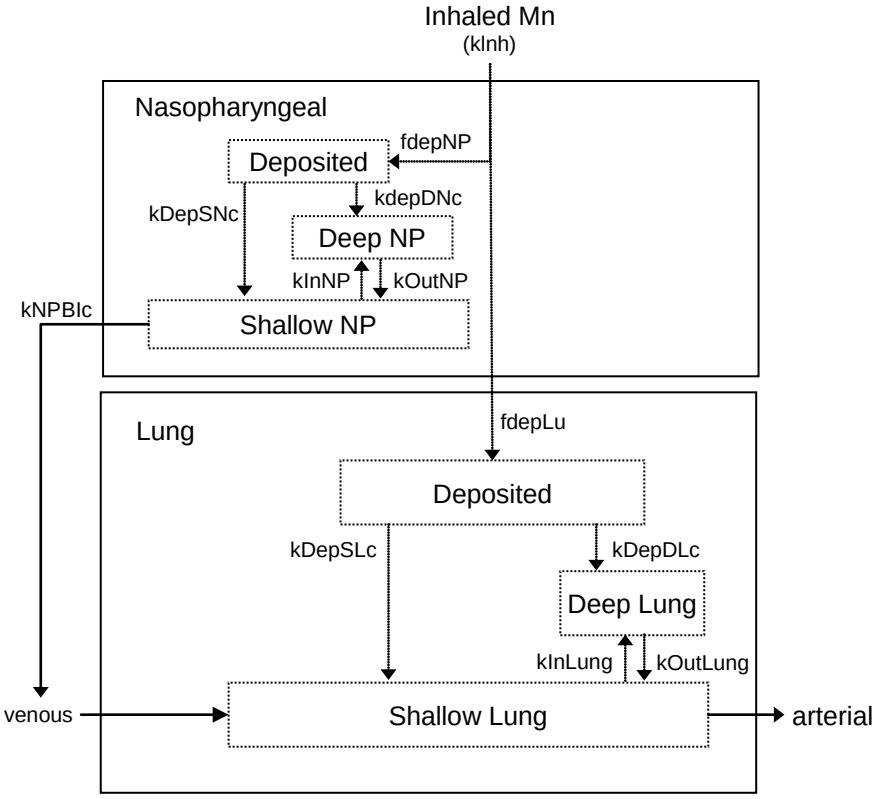
Figure 3-7. Schematic Structures of Nong et al. (2008) PBPK Models A and B for Manganese in CD Rats*



*Values and descriptions of model parameters are in Tables 3-14, 3-15, and 3-16.

Source: Nong et al. 2008

Figure 3-8. Schematic of Models for Nasopharyngeal and Lung Deposition of Manganese and Transport to Blood in the Nong et al. (2008) PBPK Models A and B for Manganese in CD Rats



Source: Teeguarden et al. 2007c

Table 3-14. Parameter Values in the Teeguarden et al. (2007c) PBPK Model for Manganese in CD Rats (Nong et al. 2008) Model A

Parameter		Value[a]
BW	Body weight (kg)	0.325[b]
QCC	Cardiac output (L/hour for 1-kg animal)	14.6
QPC	Alveolar ventilation (L/hour for 1-kg animal)	30.0
Blood flows (fraction of cardiac output)		
QSlowC	Slow	0.534
QBoneC	Bone	0.122
QBrnC	Brain	0.02
QKidC	Kidneys	0.141
QLivC	Liver	0.183
Tissue volumes (fraction of body weight)		
VArtC	Arterial blood	0.0224
VBldC	Blood	0.0676
VSlowC	Slow	0.738
VBoneC	Bone	0.021
VDBoneC	Bone deep compartment	0.052
VBrnC	Brain	0.006
VKidC	Kidneys	0.007
VLivC	Liver	0.034
VLungC	Lung	0.007
VNasPhaC[c]	Nasopharyngeal	0.0038
VTraBroC[c]	Tracheobronchial	0.01107
VPulmonC	Pulmonary	0.01107
VVenC	Venous blood	0.0452
Partition coefficients		
Pslow	Slow	0.4
PBone	Bone	30
PBrn	Brain	0.1
PKid	Kidneys	1.25
PLiv	Liver	5.0
PLung	Lung	0.3
Pnaspha	Nasopharyngeal	0.3
Clearance rates		
kBile0C	Biliary excretion (L/hour-kg body weight)	2.0
kFeces	Loss in feces (L/hour-kg body weight)	0.0001
Clearance rates (/h)		
kInSlowC	Into deep slow compartment	0.017
kInBoneC	Into deep bone compartment	0.105
kInBrnC	Into deep brain compartment	0.011
kInKidC	Into deep kidney compartment	0.146

Table 3-14. Parameter Values in the Teeguarden et al. (2007c) PBPK Model for Manganese in CD Rats (Nong et al. 2008) Model A

Parameter		Value[a]
kInLivC	Into deep liver compartment	0.621
kInNPC	Into deep nose compartment	0.035
kInLungC	Into deep lung compartment	0.035
kOutSlowC	Out of deep slow	0.0035
kOutBoneC	Out of deep bone	0.00085
kOutBrnC	Out of deep brain	0.00056
kOutKidC	Out of deep kidneys	0.0034
kOutLivC	Out of deep liver	0.007
kOutNPC	Out of deep nose	0.0035
kOutLungC	Out of deep lung	0.0035
Initial concentrations of manganese (µg/L)		
CArt0	Arterial blood	10.0
CBld0	Blood	10.0
CSlow0	Slow	110.0
CDSlow0	Deep slow	110.0
CBone0	Bone	650.0
CDBone0	Deep bone compartment	650.0
CBrn0	Brain	450.0
CDBrn0	Deep brain	450.0
CKid0	Kidneys	1000.0
CDKid0	Deep kidneys	1000.0
CLiv0	Liver	2600.0
CDLiv0	Deep liver	2600.0
CLung0	Lung	250.0
CDLung0	Deep lung	250.0
CNose0	Nose	0.0
CDNose	Deep nose	0.0
CVen0	Venous blood	10.0
Fractional coefficients		
fDepNP[c]	Particles deposited nasopharyngeal	0.2
fDepTB[c]	Particles deposited tracheobronchial	0.21
fDepPu[c]	Particles deposited pulmonary	0.07
Fraction of manganese in shallow versus deep tissue[d] (ratios of volumes; not separately estimated model parameters)		
fSlow	Slow	0.5
fDSlow	Deep slow	0.5
fBrn	Brain	0.05
fDBrn	Deep brain	0.95
fKid	Kidneys	0.25
fDKid	Deep kidneys	0.75

Table 3-14. Parameter Values in the Teeguarden et al. (2007c) PBPK Model for Manganese in CD Rats (Nong et al. 2008) Model A

Parameter		Value[a]
fLiv	Liver	0.4
fDLiv	Deep liver	0.6
fLung	Lung	0.1
fDLung	Deep lung	0.9
FDNose	Deep nose	0.9
fDBody	Body	0.5
Dosing parameters		
InFac1	Dietary intake factor for first diet	0.05
FDietUp	Fraction of manganese in diet that is absorbed	0.008

[a]Physiological parameters are consistent with those reported by Brown et al. (1997). Rate constants were fit to available experimental data on the kinetics of Mn in the various tissues. Rate constants fitted to the control steady-state Mn tissue concentrations reported by Furchner et al. (1966) and used to simulate ip and inhalation experiments are shown.
[b]Default body weight. Some body weights were lower (0.25) to represent study conditions.
[c]The deposition lung region of the lung is the sum of the tracheobronchial and pulmonary tissue (fDepLu=fDepTB+fDepPu; VDepLuC=VTraBroC+VPulmonC).
[d]This fraction is not an independently estimated variable. Instead, the fraction represents the ratio of the two rate constants, kin and kout, for each tissue.

Source: Teeguarden et al. 2007c

coefficients (e.g., PBrn, Table 3-14) and clearance rate constants into and out of deep compartments (e.g., kInBrnC, kOutBrnC) were calibrated with ^{54}Mn kinetic data collected by Furchner et al. (1966) and steady-state tissue manganese concentration data collected by Wieczorek and Oberdörster (1989c). The fraction of manganese absorbed from the gut (F_{DietUp}) was assumed to be 0.8%. The rate of biliary excretion from liver (kBile0C) was determined by matching the rate of manganese excreted from liver against the amount of manganese taken up from the diet, while maintaining steady-state levels of manganese in all tissues and matching the turnover of ^{54}Mn for each tissue (Teeguarden et al. 2007c). For inhaled manganese, fractional depositions in the nasopharyngeal (fDepNP = 0.2), tracheobronchial (fDepTB = 0.21), and pulmonary (fDeppu = 0.07) regions were taken from the EPA (1994a) respiratory tract deposition model for 1.1-µm aerosols. The model assumed that deposited aerosols dissolved immediately and that there was no clearance from the airway lumen to the gut via mucociliary transport; this assumption is valid for soluble manganese forms such as manganese chloride and manganese sulfate, but would not be valid for less-soluble forms of manganese such as manganese phosphate (Nong et al. 2008; Teeguarden et al. 2007c).

Nong et al. (2008) described further refinements to model A parameters shown in Table 3-15. Daily manganese dietary intake (F_{DietUp}) and biliary elimination rate constants (k_{BileC}) were first calibrated for different levels of manganese in the diet (2, 10, 100, and 125 ppm; Table 3-15) by fitting the model to the observed steady-state tissue manganese concentration data for rats exposed to 2, 10, or 100 ppm manganese in the diet for 13 weeks (Dorman et al. 2001b). After this refinement, clearance rates for the liver and brain striatum (kIn and kOut values shown in Table 3-15) were refined by fitting the model to tissue manganese concentration data from the 14-day inhalation study by Dorman et al. (2001a).

Nong et al. (2008) Model B Description and Development. Model B contains a similar structure to Model A, except that manganese concentrations in the liver and brain striatum are dependent on capacity-limited binding of manganese (Figure 3-7). In addition, uptake from striatal blood to striatal tissues is described with diffusion terms (PA_{12} and PA_{21}, Figure 3-7). The diffusion terms were included to account for observations of preferential increases in some brain regions compared with other tissues, such as liver or blood, following inhalation exposure to manganese (see Dorman et al. 2006a for review). The diffusion terms are thought to reflect movement of manganese across the blood-brain barrier (Nong et al. 2008). In Model B, the total amounts of manganese in the liver and brain striatum tissues are dependent on concentrations of free circulating manganese, the binding capacity of the tissue, and the concentrations of bound manganese in tissue stored (Nong et al. 2008). Differential equations to describe changes (with time) in amounts of free or bound manganese in the liver and the brain striatum are described in detail by

Table 3-15. Refined Parameter Values in Nong et al. (2008) Model A

Parameter[a]	Manganese level in diet	Biliary excretion (/h/kg)
k_{BileC}	2 ppm manganese	0.19
	10 ppm manganese	0.28
	100 ppm manganese	0.60
	125 ppm manganese	0.60
	Tissue clearance rates (/h/kg)	
kInLivC	Into deep liver compartment	0.621
kInBrnC	Into deep brain compartment	0.011
kOutLivC	Out of deep liver compartment	0.007
kOutBrnC	Out of deep brain compartment	0.00039
	Dosing parameters: diet level of manganese	Fraction of manganese in diet that is absorbed
F_{DietUp}	2 ppm manganese	0.044
	10 ppm manganese	0.018
	100 ppm manganese	0.004
	125 ppm manganese	0.003

[a]The remaining parameters are described in Teeguarden et al. (2007c). Clearance rates are scaled to the body weight ($BW^{-0.25}$).

Source: Nong et al. 2008

Nong et al. (2008). Table 3-16 lists binding rate constants (e.g., kaBrnC, kdBrnC), binding capacities ($B_{max,Brain}$, $B_{max.Liver}$), brain diffusion constants (PA_{12} and PA_{21}), and partition coefficients in Model B. Liver and brain striatum binding capacity levels were first determined by fitting the model to steady-state tissue concentration data from the 13-week dietary study by Dorman et al. (2001b), using starting values for the tissue binding parameters that were estimated based on clearance rate values (kIn and kout) for liver and brain striatum in Model A. Tissue binding parameters (e.g., kaBrnC, kdBrnC) and brain diffusion constants (PA_{12} and PA_{21}) were then refined by fitting the model to the 14-day-inhalation tissue concentration data from Dorman et al. (2001a).

Evaluation of Nong et al. (2008) Models A and B. Nong et al. (2008) compared the abilities of Models A and B to predict: (1) whole-body elimination kinetics of ^{54}Mn in rats fed a 100-ppm diet for 13 weeks (data from Dorman et al. 2001b); (2) liver and brain striatum manganese concentration data in rats exposed to 0.03, 0.3, or 3 mg manganese/m^3 for 6 hours/day for 14 consecutive days (Dorman et al. 2001a); (3) whole-body elimination kinetics of ^{54}Mn in rats following 14-day inhalation exposure to 3 mg manganese/m^3; and (4) liver and brain striatum manganese concentrations in rats during and following a 90-day inhalation exposure period to 0.1 or 0.5 mg manganese/m^3 (Dorman et al. 2004b). Both models adequately predicted observed ^{54}Mn elimination kinetics data, but Model B much more accurately predicted liver and brain striatum manganese concentration data during and following 14- or 90-day inhalation exposures. Model A consistently overestimated liver and brain striatum manganese concentration, particularly at concentrations of 0.1, 0.3, or 0.5 mg manganese/m^3 (as shown in Figures 4 and 7 of Nong et al. 2008). Nong et al. (2008) concluded that the evaluation of the models "highlighted the importance of tissue binding in maintaining relatively constant tissue concentrations across a wide range of inhaled concentrations." Nong et al. (2008) mentioned that the next steps in model development would be to extend tissue binding in Model B to all other tissues in the models for which appropriate data are available for calibrating tissue-specific binding rate constants.

PBPK Model for Manganese Transport from the Olfactory Mucosa to Striatum (Leavens et al. 2007). Leavens et al. (2007) developed a pharmacokinetic model describing the olfactory transport and blood delivery of manganese to the striatum in rats following acute inhalation exposure to manganese chloride or manganese phosphate. Figure 3-9 shows the structure of the model, which presumes that manganese undergoes axonal transport from the olfactory mucosa (OM) to the olfactory bulb (OB), followed by serial transport to the olfactory tract and tubercle (OTT) and then to the striatum (S). Tables 3-17 and 3-18 list values of the model parameters for soluble manganese chloride and relatively insoluble manganese phosphate, respectively. Each of the compartments in the model (containing a left and right

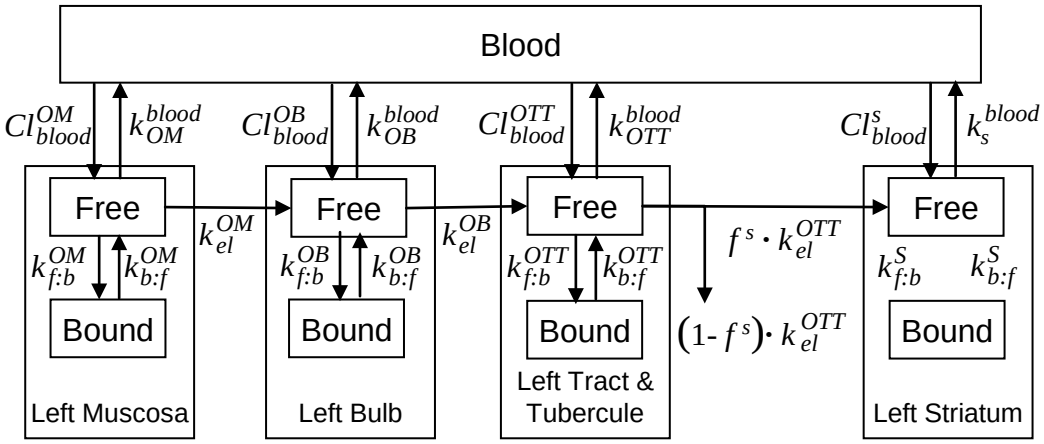
Table 3-16. Parameter Values in Nong et al. (2008) Model B

Parameters[a]		Values
Tissue binding rate constants[a]		
kaBrnC	Association striatum constant (/h/µg/kg)	0.000176
kaLivC	Association liver constant (/h/µg/kg)	0.06772
kdBrnC	Dissociation striatum constant (/h/kg)	0.00002
kdLivC	Dissociation liver constant (/h/kg)	0.0054196
Tissue binding constants (µg/kg)		
$B_{max,brain}$	Maximal binding striatum constant	3,300
$B_{max,liver}$	Maximal binding liver constant	1,000
Brain diffusion constants (/hour/kg)		
PA_{12}	Influx brain tissue constant	1
PA_{21}	Efflux brain tissue constant	0.16
Partition coefficient		
P_{brain}	Brain (striatum):blood	1.0
P_{liver}	Liver:blood	1.08

[a]The remaining parameters are described in Teeguarden et al. (2007c).
[b]Rate constants are scaled to the $BW^{-0.25}$ and maximal binding capacities are scaled to $BW^{-0.75}$.

Source: Nong et al. 2008

Figure 3-9. Schematic of the Leavens et al. (2007) Model to Describe Olfactory and Blood Delivery of Manganese to the Left Side of the Brain Isilateral to the Olfactory Mucosa (OM) in the Left Nasal Cavity*



*The model structure for the right side is identical. Values and descriptions of model parameters are in Tables 3-16, 3-17, and 3-18.

Source: Leavens et al. 2007

Table 3-17. Parameter Values for Manganese Chloride in the Leavens et al. (2007) PBPK Model for Olfactory Transport of Manganese in Rats

Parameter	Description	Value	Units	Source
Compartment volumes				
V^{L}_{OM}	Left OM	0.059	mL	Measured[a]
V^{L}_{OB}	Left OB	0.031	mL	Measured[a]
V^{L}_{OTT}	Left OTT	0.030	mL	Measured[a]
V^{L}_{S}	Left striatum	0.032	mL	Measured[a]
V^{R}_{OM}	Right OM	0.065	mL	Measured[a]
V^{R}_{OB}	Right OB	0.038	mL	Measured[a]
V^{R}_{OTT}	Right OTT	0.046	mL	Measured[a]
V^{R}_{S}	Right striatum	0.042	mL	Measured[a]
Blood clearance into olfactory compartments				
Cl^{OM}_{blood}	Influx to OM	$4x10^{-4}$	mL/hour	Estimated
Cl^{OB}_{blood}	Influx to OB	$1x10^{-5}$	mL/hour	Estimated
Cl^{OTT}_{blood}	Influx to OTT	$6x10^{-4}$	mL/hour	Estimated
Cl^{S}_{blood}	Influx to striatum	$3x10^{-5}$	mL/hour	Estimated
Rate constants for olfactory compartments efflux to blood				
k^{blood}_{OM}	Efflux from OM to blood	$1x10^{-6}$	$hour^{-1}$	Estimated
k^{blood}_{OB}	Efflux from OB to blood	$1x10^{-6}$	$hour^{-1}$	Estimated
k^{blood}_{OTT}	Efflux from OTT to blood	0.0	$hour^{-1}$	Estimated
k^{blood}_{S}	Efflux from striatum to blood	$1x10^{-6}$	$hour^{-1}$	Estimated
Olfactory transport rate constants				
k^{OM}_{el}	OM to OB	0.022	$hour^{-1}$	Estimated
k^{OB}_{el}	OB to OTT	0.037	$hour^{-1}$	Estimated
k^{OTT}_{el}	OTT to striatum	0.094	$hour^{-1}$	Estimated
f^{S}	Fraction of OTT loss rate to striatum	0.001	Unitless	Estimated
Binding rate constants in olfactory compartments				
$k^{OM}_{f:b}$	OM free to bound	0.006	$hour^{-1}$	Estimated
$k^{OB}_{f:b}$	OB free to bound	0.0047	$hour^{-1}$	Estimated
$k^{OTT}_{f:b}$	OTT free to bound	0.0043	$hour^{-1}$	Estimated
$k^{S}_{f:b}$	Striatum free to bound	0.0026	$hour^{-1}$	Estimated
$k^{OM}_{b:f}$	OM bound to free	$1x10^{-6}$	$hour^{-1}$	Constant[b]
$k^{OB}_{b:f}$	OB bound to free	$1x10^{-6}$	$hour^{-1}$	Constant[b]
$k^{OTT}_{b:f}$	OTT bound to free	$1x10^{-6}$	$hour^{-1}$	Constant[b]
$k^{S}_{b:f}$	Striatum bound to free	$1x10^{-6}$	$hour^{-1}$	Constant[b]

[a]Unpublished results measured in CD rats used in Brenneman et al. (2000) study. Plugged and unplugged exposure data were averaged together because they were not significantly different.
[b]Not possible to estimate both constants for the binding; therefore, the rate constants for the bound to free manganese were set to a low rate to allow slow removal of manganese tracer from the bound compartment.

Source: Leavens et al. 2007

Table 3-18. Parameter Values for Manganese Phosphate in the Leavens et al. (2007) PBPK Model for Olfactory Transport of Manganese in Rats

Parameter	Description	Value	Units	Source
Compartment volumes				
V^{L}_{OM}	Left OM	0.085	mL	Measured[a]
V^{L}_{OB}	Left OB	0.038	mL	Measured[a]
V^{L}_{OTT}	Left OTT	0.025	mL	Measured[a]
V^{L}_{S}	Left striatum	0.05	mL	Measured[a]
V^{R}_{OM}	Right OM	0.074	mL	Measured[a]
V^{R}_{OB}	Right OB	0.038	mL	Measured[a]
V^{R}_{OTT}	Right OTT	0.04	mL	Measured[a]
V^{R}_{S}	Right striatum	0.035	mL	Measured[a]
Blood clearance into olfactory compartments				
Cl^{OM}_{blood}	Influx to OM	0.0017	mL/hour	Estimated
Cl^{OB}_{blood}	Influx to OB	0.0018	mL/hour	Estimated
Cl^{OTT}_{blood}	Influx to OTT	0.0016	mL/hour	Estimated
Cl^{S}_{blood}	Influx to striatum	$1.8x10^{-5}$	mL/hour	Estimated
Rate constants for olfactory compartments efflux to blood				
k^{blood}_{OM}	Efflux from OM to blood	$3x10^{-6}$	$hour^{-1}$	Estimated
k^{blood}_{OB}	Efflux from OB to blood	0.0	$hour^{-1}$	Estimated
k^{blood}_{OTT}	Efflux from OTT to blood	$1x10^{-6}$	$hour^{-1}$	Estimated
k^{blood}_{S}	Efflux from striatum to blood	$1.5x10^{-5}$	$hour^{-1}$	Estimated
Olfactory transport rate constants				
k^{OM}_{el}	OM to OB	0.011	$hour^{-1}$	Estimated
k^{OB}_{el}	OB to OTT	0.036	$hour^{-1}$	Estimated
k^{OTT}_{el}	OTT to striatum	0.099	$hour^{-1}$	Estimated
f^{S}	Fraction of OTT loss rate to striatum	0.033	Unitless	Estimated
Binding rate constants in olfactory compartments				
$k^{OM}_{f:b}$	OM free to bound	0.00086	$hour^{-1}$	Estimated
$k^{OB}_{f:b}$	OB free to bound	0.0014	$hour^{-1}$	Estimated
$k^{OTT}_{f:b}$	OTT free to bound	0.0031	$hour^{-1}$	Estimated
$k^{S}_{f:b}$	Striatum free to bound	0.024	$hour^{-1}$	Estimated
$k^{OM}_{b:f}$	OM bound to free	$1x10^{-6}$	$hour^{-1}$	Constant[b]
$k^{OB}_{b:f}$	OB bound to free	$1x10^{-6}$	$hour^{-1}$	Constant[b]
$k^{OTT}_{b:f}$	OTT bound to free	$1x10^{-6}$	$hour^{-1}$	Constant[b]
$k^{S}_{b:f}$	Striatum bound to free	$1x10^{-6}$	$hour^{-1}$	Constant[b]

[a]Unpublished results measured in CD rats used in Dorman et al. (2000) study. Plugged and unplugged exposure data were averaged together because they were not significantly different.
[b]Not possible to estimate both constants for the binding; therefore, the rate constants for the bound to free manganese were set to a low rate to allow slow removal of manganese tracer from the bound compartment.

Source: Leavens et al. 2007

nasal cavity) is connected by blood and each is comprised of pools of free and bound manganese. The rates of transport between tissue compartments and between bound and free pools are modeled as first-order transport processes. Tables 3-17 and 3-18 show measured values for compartment volumes, values for blood clearance into olfactory compartments (e.g., $Cl^{OM/blood}$), values for rate constants for efflux from compartments to blood (e.g., $k^{blood/OM}$), values for transport rate constants between compartments (e.g., $k^{OM/el}$), and binding rate constants in the olfactory compartments (e.g., OM free to bound, $k^{OM/f.b}$ and OM bound to free, $k^{OM/b.f}$). Equations for mass balance, clearance, and free concentrations of manganese for each of the compartments are described in detail by Leavens et al. (2007).

Model parameters were estimated by optimization procedures using kinetics data from rats exposed nose-only for 90 minutes to ^{54}Mn-manganese chloride (Brenneman et al. 2000) or ^{54}Mn-manganese phosphate (Dorman et al. 2002a). In each experiment, one group was exposed with both nostrils unplugged, while a second group was exposed with the right nostril plugged. Blood concentrations were not measured in either of these studies, but ^{54}Mn concentrations in the kidney, liver, and pancreas were measured and reported. The mean concentration in these three organs is used to represent blood concentration in the model, and the data were used to obtain parameters for equations describing first-order absorption and elimination into a single compartment; values for the parameters under plugged and unplugged conditions, obtained through model optimization procedures, are listed in Table 3-19. The optimized model was used to predict the percentage of ^{54}Mn that was transported into each compartment either via direct olfactory transport or blood delivery. For manganese chloride, olfactory transport was predicted to deliver >97–99% of the tracer in the left or right olfactory bulbs, 40–76% of the tracer in the left or right olfactory tract and tubercle, and only 4–8% of the tracer in the left or right striatum under plugged or unplugged conditions. For manganese phosphate, the respective predictions were 38–59% in the olfactory bulbs, 86–90% in the olfactory tract and tubercle and 77–83% in the striatum. Leavens et al. (2007) cautioned against the predictions for the striatum, since the model overpredicted striatum concentrations at the later time points for the plugged exposures to manganese chloride or manganese phosphate and the unplugged exposures to manganese phosphate (Figures 4–7 in Leavens et al. 2007).

Table 3-19. Parameter Values for Describing Blood Concentrations in the Leavens et al. (2007) PBPK Model for Olfactory Transport of Manganese in Rats

Parameter[a]	Description	Value		Units	Source
		Plugged	Unplugged		
Manganese chloride exposures					
C_Θ	Initial deposited concentration[b]	261	791	ng/g	Estimated
k_a	First-order absorption	0.0068	0.005	$hour^{-1}$	Estimated
K	First-order elimination rate constant	0.057	0.063	$hour^{-1}$	Estimated
Manganese phosphate exposures					
C_Θ	Initial deposited concentration[b]	171	376	ng/g	Estimated
k_a	First-order absorption	0.0035	0.0034	$hour^{-1}$	Estimated
K	First-order elimination rate constant	0.083	0.124	$hour^{-1}$	Estimated

[a]Estimated pharmacokinetic parameters for mean of liver, kidney, and pancreas concentration reported in Brenneman et al. (2000). See text for equation and details.
[b]Equal to FX_0/V_b, where X_0 is initial dose, F is fraction dose bioavailable for absorption, and V_b is the blood volume.

Source: Leavens et al. 2007

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Manganese absorption occurs primarily through the diet; however, absorption via the lungs can be significant for occupationally exposed persons or for those exposed to excess levels of airborne manganese, such as downwind of a manganese point source. Manganese absorption through the gut may occur through a nonsaturable simple diffusion process through the mucosal layer of brush border membranes (Bell et al. 1989) or via an active-transport mechanism that is high-affinity, low-capacity, and rapidly saturable (Garcia-Aranda et al. 1983). Manganese particles that are too large to enter the alveoli (>10 microns in diameter) remain in the upper respiratory tract, where they are coughed up by mucociliary transport and swallowed. Differences in solubility of manganese compounds deposited in the alveolar regions may impact the rate at which manganese will be absorbed, but manganese is bioavailable when deposited in these regions (Drown et al. 1986).

Diets high in iron have been shown to suppress manganese absorption, and conversely, iron-poor diets increase manganese uptake (Lönnerdal 1997, Lönnerdal et al. 1994). Phosphorus (Wedekind et al. 1991) and calcium (Wilgus and Patton 1939) have also been found to decrease manganese uptake.

Distribution. Review articles by Aschner and Aschner (1991) and Aschner et al. (2005; 2007) summarize some of the available data regarding the distribution of manganese. Dietary manganese, thought to be absorbed as Mn(II), enters portal circulation from the gastrointestinal tract and is bound to α_2-macroglobulin or albumin in the plasma. After delivery to the liver, the major portion of Mn(II) is secreted in the bile, but some may be oxidized by ceruloplasmin to Mn(III). The Mn(III) enters systemic circulation conjugated with plasma transferrin; once this complex enters a neuron, it dissociates, and from there, the manganese is transported to axon terminals. For example, Sloot and Gramsbergen (1994) observed that radiolabeled manganese injected into the striatum or substantia nigra of rat brain is transported in an anterograde direction through both γ-amino-butyric acid-producing striato-nigral and dopaminergic nigro-striatal fibers.

Other studies, however, argue for the transport of Mn(II) into the brain. For example, Murphy et al. (1991) measured the kinetics of manganese transport in the brains of adult male rats using a perfusion technique. The rats were infused with increasing concentrations of $[^{54}Mn]Cl_2$; blood and brain samples were analyzed for manganese at varying time points. The data indicated a saturable mechanism for transporting Mn(II) into the choroid plexus, and influx into the cerebral cortex was also near saturation at

the highest plasma concentration of manganese used. Influx into other brain regions (e.g., caudate nucleus, hippocampus, hypothalamus) and cerebrospinal fluid (CSF) showed non-saturable transport of the cation. The authors suggested that the non-saturable transport into these brain regions resulted from passive diffusion of manganese down a concentration gradient from ventricular cerebrospinal fluid because some of these brain regions have components adjacent to the ventricles and manganese concentrations in these regions were below levels in the CSF. The authors also noted that at all plasma manganese concentrations tested (from 0.8 to 78 nmol/mL), the transfer coefficient for manganese uptake into the choroid plexus was significantly higher than in any other area of the central nervous system. For example, at 0.08 nmol/mL, the transfer coefficients for the CSF and the choroid plexus were $16.2 \pm 2.43 \times 10^{-6}$ mL/second*g and $23{,}800 \pm 2{,}910 \times 10^{-6}$ mL/second*g, respectively. Even after correcting for differences in compartment size, influx of manganese into the choroid plexus was an order of magnitude greater than influx into CSF.

Rabin et al. (1993) also measured transport of $[^{54}Mn]Cl_2$ in adult rats using a similar technique. In this study, the authors used three perfusates (whole blood, plasma/serum, and saline) to determine brain uptake in environments that facilitated or prevented protein binding of the metal. The authors reported that uptake of manganese into the cortex, hippocampus, caudate nucleus, and choroid plexus was greater and more rapid when saline was used rather than with whole blood. When EDTA-saline was used as the perfusate, uptake was not significantly different than zero, indicating that divalent manganese was the form taken up by the brain. The transfer coefficients of Mn(II) from saline in the different regions of the brain (frontal, parietal, and occipital cortex regions; hippocampus; caudate nucleus; and thalamus-hypothalamus) ranged from 5 to 10×10^{-5} mL/second*g, whereas that of the choroid plexus was 727×10^{-3} mL/second*g. The authors noted that the transfer coefficients were greater than that expected for passive diffusion and suggested a facilitated blood-brain barrier transport by a channel or carrier mechanism (Rabin et al. 1993). These findings of a rapid uptake mechanism and concentrated uptake into the choroid plexus are consistent with results reported by Murphy et al. (1991). Separate binding studies performed by the authors determined that albumin, transferrin, α_2-macroglobulin added to the manganese during perfusion significantly decreased brain uptake of the cation in all brain regions. The authors were uncertain whether Mn(II) in the form of low-molecular mass solutes was taken up at the blood-brain barrier. However, based on other literature and their own unpublished results, they suggest that the free ion is the species transported.

Other studies have also revealed the rapid appearance of manganese in the choroid plexus. Ingersoll et al. (1995) demonstrated that manganese levels in the lateral choroid plexus were 44 and 24 times higher than

levels in CSF, and blood, respectively, 4 hours after intraperitoneal injection of 10 mg manganese/kg. However, manganese concentration in the choroid plexus did not change significantly following intrathecal administration of this same dose. This demonstrated that manganese in the blood could be sequestered by the choroid plexus, whereas little to no transfer of manganese from CSF to the choroid plexus occurred. Intrathecal administration of manganese increased manganese concentrations in all brain regions examined while there were only slight changes in brain manganese concentrations after intraperitoneal administration. Moreover, intrathecal administration of manganese decreased spontaneous motor activity with no effect on motor activity following intraperitoneal dosing. The authors suggested that these results indicated that the brain is protected from high concentrations of manganese through sequestering in the choroid plexus, but this mechanism could become overwhelmed with rising levels of blood manganese such that manganese could then "leak' from the choroid plexus into CSF and thereby enter the brain. This interpretation appears to be consistent with the findings of London et al. (1989). In these studies, 50 and 100 mg/kg manganese was administered intraperitoneal doses 5 and 10 times that used by Ingersoll et al. (1995). Using MRI images, these doses were shown to concentrate in the ventricles, the pineal gland, and the pituitary gland and the authors indicated that this high concentration of manganese appeared in the ventricular CSF because it crossed the barrier of the choroid plexus. Takeda et al. (1994) used autoradiography to also show that manganese in selected brain regions was taken up via the CSF from the choroid plexus. Moreover, Zheng et al. (1998) observed that, in a subchronic manganese intoxication rat model, the increases in manganese concentrations observed in targeted brain regions were closely related in magnitude to that of CSF manganese, but not to that of serum manganese. The observations of Takeda et al. (1994) and Zheng et al. (1998) support the view that manganese in the CSF serves as the main source for manganese distribution in brain tissues.

Recent reviews of the state of the science have emphasized that manganese can enter the brain via three pathways: (1) from the nasal mucosa to the brain olfactory bulb via olfactory neural connections; (2) from the blood through capillary endothelial cells of the blood-brain barrier; and (3) from the blood through the cerebral spinal fluid via the choroid plexuses (Aschner et al. 2005; Bock et al. 2008; Crossgrove and Yokel 2005). Current understanding is inadequate to determine which of these pathways may predominate in cases of severe manganism or cases of subtle neurological impairment in nonhuman primates or humans. A number of transport mechanisms (including facilitated diffusion, active transport, transferrin-mediated transport, divalent metal transporter-1 mediation, store-operated calcium channels) have been proposed to transport manganese across the blood barrier or into the choroid plexus, but current understanding is inadequate to determine the predominant molecular mechanism of transport in either of the pathways (Aschner et al. 2005, 2007; Crossgrove and Yokel 2004, 2005; Roth 2006).

3.5.2 Mechanisms of Toxicity

The central nervous system is the primary target of manganese toxicity. Although it is known that manganese is a cellular toxicant that can impair transport systems, enzyme activities, and receptor functions, the principal manner in which manganese neurotoxicity occurs has not been clearly established (Aschner and Aschner 1991; Aschner et al. 2007).

Mn(III) has been found to be more cytotoxic to human neural cells as a manganese pyrophosphate complex (MnPPi) than as a manganese-transferrin complex (MnTf) (Suarez et al. 1995). Specifically, human neuroblastoma cells (cell line SH-SY5Y) grown in culture showed effects of cytotoxicity from 30 μM MnPPi but did not show the same signs of cytoxicity from MnTf (membrane damage and cell granulation and aggregation) until concentrations of 60 μM were reached (Suarez et al. 1995). Both manganese complexes inhibited mitochondrial enzyme activity, but MnTf was slightly more toxic than MnPPi in this respect (Suarez et al. 1995).

Neuropathological changes are detectable in the basal ganglia of humans with manganism, and the specific area of injury appears to be primarily in the globus pallidus; the substantia nigra is sometimes affected, but generally to a lesser extent (Katsuragi et al. 1996; Yamada et al. 1986). Studies in nonhuman primates have produced similar findings (Newland and Weiss 1992; Newland et al. 1989). Limited evidence suggests that dopamine levels in the caudate nucleus and putamen are decreased in manganism patients (Bernheimer et al. 1973). Similarities in the behavior of manganism patients to those with Parkinson’s disease have prompted some to refer to manganism as "manganese-induced Parkinsonism" or "Parkinson-like disease." Further, the two diseases do affect functional related regions of the brain, but Parkinsonism is believed to be due to the selective loss of subcortical neurons whose cell bodies lie in the substantia nigra and whose axons terminate in the basal ganglia (which includes the caudate nucleus, the putamen, the globus pallidus, and other structures). These nigral neurons use dopamine as their neurotransmitter, and treatment of Parkinson patients with levo-dopa (the metabolic precursor to dopamine) often relieves some of the symptoms of Parkinson's disease (Bernheimer et al. 1973). Some investigators have reported that oral levo-dopa can temporarily improve symptoms of manganese-induced neurotoxicity (Barbeau 1984). However, most studies show that manganism patients typically do not respond to levo-dopa treatment (Calne et al. 1994; Chu et al. 1995; Huang et al. 1989), indicating that they have likely suffered degeneration of the receptors and neurons that normally respond to this neurochemical (Chu et al. 1995).

The precise biochemical mechanism by which manganese leads to this selective destruction of dopaminergic neurons is not known, but many researchers believe that the manganese ion, Mn(II), enhances the autoxidation or turnover of various intracellular catecholamines, leading to increased production of free radicals, reactive oxygen species, and other cytotoxic metabolites, along with a depletion of cellular antioxidant defense mechanisms (Barbeau 1984; Donaldson 1987; Garner and Nachtman 1989b; Graham 1984; Halliwell 1984; Liccione and Maines 1988; Parenti et al. 1988; Verity 1999). Oxidation of catechols is more efficient with Mn(III), than with Mn(II) or Mn(IV) (Archibald and Tyree 1987). Formation of Mn(III) may occur by oxidation of Mn(II) by superoxide (O_2^-) In cases of exposure to Mn(VII), it is likely that a reduction to the Mn(II) or Mn (III) state occurs (Holzgraefe et al. 1986), but this has not been demonstrated.

Hussain et al. (1997) studied the effects of chronic exposure of manganese on antioxidant enzymes, including manganese superoxide dismutase (MnSOD). MnSOD is an antioxidant enzyme located primarily in the mitochondria that contains manganese as a functional component. MnSOD protects against oxidative injury by catalyzing the dismutation of O_2^-, Hussain et al. (1997) found that administration of 0, 1.1, and 2.2 mg manganese/kg/day (as manganese chloride), 5 days/week for 3 months, resulted in increased MnSOD in the hippocampus, cerebellum, and brainstem. Other areas of the brain were not affected and other antioxidant enzymes, such as Cu,ZnSOD and glutathione peroxidase (GPx), were not increased. The researchers suggest that since a critical role of MnSOD is to protect against oxidative injury, the increase of this enzyme after manganese exposure may reduce the risk of oxidative stress induced by that exposure. Thus, this protective mechanism would have to be overwhelmed in cases of manganese toxicity. Additionally, the authors suggest that, since MnSOD was altered while Cu,ZnSOD and Gpx were unchanged, manganese may not affect cytosolic enzymes like Cu,ZnSOD. In support of this point, the authors also mention other reports that suggest that these antioxidant enzymes are independently regulated (Mossman et al. 1996; Warner et al. 1993; Yen et al. 1996).

Supporting evidence for the hypothesis that high levels of manganese exert neurotoxicity through oxidation is provided by Desole et al. (1994). The authors observed that 22 mg manganese/kg/day (as manganese chloride) administered orally in 6-month-old rats resulted in increased concentrations of DOPAC (an oxidation product of DA) and uric acid, but left DA levels unchanged. Daily doses of 44 or 66 mg manganese/kg/day resulted in significantly decreased concentrations of DA, glutathione, ascorbic acid, and DOPAC, and increased concentrations of uric acid in the rat striatum when compared to

controls. The researchers also measured levels of these metabolites in the rat striatal synaptosomes, which were used as a model for neuronal terminals. Here, DA levels were unchanged at 22 mg manganese/kg/day but were decreased at the two highest doses. DOPAC levels remained constant at all three dose levels. Thus, the DOPAC/DA ratio was significantly increased at 44 and 66 mg manganese/kg/day in the synaptosomes. While the authors suggest that these data support other findings that manganese oxidizes dopamine (Segura-Aguilar and Lind 1989), the decrease in DA could be the result of decreased production or release of the chemical, rather than increased oxidation. Catabolism of adenosine triphosphate (ATP) forms xanthine and hypoxanthine, both of which are metabolized by xanthine oxidase. The products of this metabolism are uric acid and superoxide radical anion (Desole et al. 1994). The increase in uric acid production in rat striatum following oral dosing with 44 or 66 mg manganese/kg (as manganese chloride) suggests that manganese induces oxidative stress mediated by xanthine oxidase. Desole et al. (1995) expanded their studies to investigate the protective effect of allopurinol, a xanthine-oxidase inhibitor, to 3-month-old rats exposed to manganese. In this study, allopurinol was administered by gavage at a dose of 300 mg/kg/day for 4 days. Manganese (87 mg/kg/day) was also administered by gavage, for 7 days, either alone or with allopurinol; the allopurinol decreased the striatal ratio of DOPAC and homovanillic acid (HVA) to dopamine. When given in conjunction with manganese, allopurinol antagonized the manganese-induced increase in DOPAC levels and the (DOPAC + HVA)/DA ratio. Together, the two studies suggest that manganese-induced oxidative stress through the formation of reactive oxygen species may be a mechanism for manganese neurotoxicity, and allopurinol may protect against this oxidative stress in the striatum and brainstem of young rats.

Experiments such as the one by Desole et al. (1994) indicate that overexposure of rats to manganese results in increased dopamine turnover in the rat striatum. However, patients with basal ganglia dysfunction caused by manganese had normal striatal fluorodopa uptake on PET scan, indicating that the nigrostriatal pathway was intact (Wolters et al. 1989). Seven intravenous injections of manganese chloride into Rhesus monkeys resulted in an extrapyramidal syndrome characterized by bradykinesia, facial grimacing, and rigity, with gliosis of the globus pallidus and the substantia nigra par reticularis (Olanow et al. 1996). These intravenous injections, however, would have resulted in a highly elevated but transient increase in blood manganese levels. Striatal dopamine and homovanillic acid levels were within normal ranges; yet, there was clear evidence of manganese-induced neurotoxicity. Interestingly, none of the symptoms improved after levo-dopa administration, supporting findings in humans that manganism does not respond to levo-dopa treatment (Chu et al. 1995; Huang et al. 1989).

While there are a number of studies that support the hypothesis that manganese exerts its neurotoxicity through oxidation, a study by Sziráki et al. (1999) has demonstrated atypical antioxidative properties of manganese in iron-induced brain lipid peroxidation and copper dependent low density lipoprotein conjugation. However, the underlying mechanisms of the antioxidant effects are not clear. Brenneman et al. (1999) measured reactive oxygen species (ROS) in the brains of neonatal rats administered up to 22 mg manganese/kg/day for up to 49 days (dosing was only 5 days/week from day 22 to 49). On PND 21, no increase in ROS was seen in the striatum, hippocampus, or hindbrain of exposed rats at any dose, compared to controls administered water only. In the cerebellum, ROS levels were significantly increased to the same extent at both dose levels, as compared to controls. Manganese levels were not increased significantly in the cerebellum at any dose level, but were increased in the striatum, and the rest of the brain at the high dose level, when measured at PND 49. Mitochondrial manganese was not significantly elevated in the cerebellum or striatum, but was elevated in the rest of the brain at this high dose level, also at PND 49. These data do not support the hypothesis that oxidative damage is a mechanism of action in manganese-induced neurotoxicity in the rat.

As reviewed Taylor et al. (2006), the available literature contains results both in support of and inconsistent with oxidative stress involvement in manganese neurotoxicity. Recent support for oxidative stress involvement includes the finding that co-treatment of rats with the antioxidant, N-acetylcysteine, and intraperitoneal injections of high doses of manganese chloride (50 mg/kg, once or daily for 4 days) prevented the development of pathological changes observed following injection of manganese chloride alone (Hazell 2006). Likewise, mouse catecholaminergic cells (CATH.a) were protected from the cytotoxicity of 50–1000 µM manganese by supplementation of the culture media with 5 mM glutathione or 10 mM N-acetylcysteine (Stredrick et al. 2004). In contrast, in a series of studies of neonatal rats, adult male and female rats, or senescent male rats exposed by inhalation to manganese sulfate or manganese phosphate at concentrations up to 3 mg manganese/m^3 with acute exposure durations or 1 mg manganese/m^3 with subchronic exposure durations (Dorman et al. 2001a, 2004a, 2005a), no consistent exposure-related changes were found in the following markers of oxidative stress in various brain regions: glutathione, metallothionein, and glutamine synthetase (Taylor et al. 2006).

Mn(II) may also be involved in neurotoxicity. The neurotoxicity of Mn(II) has been linked to its ability to substitute for Ca(II) under physiological conditions (Aschner and Aschner 1991), and the intestinal transfers of Ca(II) and Mn(II) have been shown to be competitive *in vivo* (Dupuis et al. 1992). Although the mechanism for Mn(II) transport into brain cells is uncertain, Mn(II) preferentially accumulates in the mitochondria in the areas of the brain that are associated with manganism and neurological symptoms.

Manganese is taken up into mitochondria via the calcium uniporter, and once there, Mn(II) inhibits mitochondrial oxidative phosphorylation. Gavin et al. (1992) observed that Mn(II) can inhibit mitochondrial oxidative phosphorylation when incubating isolated mitochondria with Mn(II) at concentrations >1 μM. Recently, it has also been shown that intramitochondiral Mn(II) can inhibit the efflux of Ca(II), which may result in a loss of mitochondrial membrane integrity (Gavin et al. 1999). At the same time, intramitochondrial Mn(II) can also inhibit oxidative phosphorylation and decrease energy production. However, Brouillet et al. (1993) has suggested that the impaired oxidative metabolism induced by manganese is indirectly linked to an excitotoxic process that results in neuronal degeneration. Because manganese accumulates in the mitochondria and is associated with impaired energy production, these authors compared the effects of intrastriatal injection of manganese with effects produced by known mitochodral toxins, aminooxyacetic acid and 1-methyl-4-phenylpyridinium. Lesions produced by these compounds can be blocked through an inhibition of the glutamatergic *N*-methyl-*D*-aspartate (NMDA) receptor or by the removal of the cortical glutamatergic input into the striatum by decortication. Thus, these lesions are termed "excitotoxic lesions." It was shown that decortication or pre-treatment with the NMDA noncompetitive antagonist, MK-801, could reverse or ameliorate neurochemical changes induced by intrastriatal injection of manganese. These authors also showed that intrastriatal manganese treatment also interfered with energy metabolism, ATP concentrations were significantly reduced by 51% and lactate levels were increased by 97%. There is additional evidence that the glutamatergic excitatory system may play a role in manganese toxicity. Recent studies in genetically epilepsy-prone rats have suggested that there are abnormalities in manganese-dependent enzymes. Although the manganese-dependent enzymes are believed to be unrelated to seizure activity in these animals, it is suggested that there is a link between the low manganese concentrations in glial cells and elevated glutamate levels due to low glutamine synthetase activity (Critchfield et al. 1993).

Mn(II) (from manganese chloride) has also been shown to inhibit mitochondrial aconitase activity to a significant level in the frontal cortex of male rats dosed with 6 mg manganese/kg/day for 30 days (Zheng et al. 1998). Aconitase levels in striatum, hippocampus, and substantia nigra were decreased in treated rats, but not to a significant extent. Aconitase, which catalyzes the interconversion of L-citrate to isocitrate, via *cis*-aconitate, requires iron as a cofactor at its active center (Zheng et al. 1998). When the authors incubated brain mitochondrial fractions with Mn(II), aconitase activity was decreased; the addition of excess iron [Fe(II)] revived the enzyme activity. These data suggest that the similarity of manganese and iron facilitates their proposed interaction at the subcellular level; however, the data do not prove that Mn(II) is the form of manganese that is exerting the inhibitory effect.

Conversely, Suarez et al. (1995) did not observe cytotoxicity in cultured cells exposed to 100 μM Mn(II). The discrepancy noted in this study, and that of Gavin et al. (1992) may have occurred because of a protective effect of the cell membrane; if the cell membrane protects the cytosol, which typically has a low manganese concentration, then the Mn(II) concentration may be too low to affect the mitochondria through uniport uptake (Suarez et al. 1995). Another explanation is that mitochondrial uptake of Mn(II) occurs, but toxic effects require that cells be exposed much longer than isolated mitochondria (Suarez et al. 1995). It has also been established that manganese accumulation in the brain varies between regions, particularly in developing animals; this region-specific accumulation may alter the metabolism and homeostasis of manganese (Chan et al. 1992). In addition, it has been demonstrated that the manganese concentration in the central nervous system, in particular the ventral mesencephalon, can be reduced by cocaine, a dopamine reuptake inhibitor, or by reserpine, a dopamine depleting agent (Ingersoll et al. 1999). This suggests that the dopamine reuptake carrier is linked to a transport mechanism for manganese.

In vitro studies of rat brain mitochondria have demonstrated that there is no apparent mechanism for Mn(II) clearance other than the slow Na^+ independent mechanism; it is suggested that Ca(II) and Mn(II) may accumulate in the brain mitochondria during manganese intoxication (Gavin et al. 1990). Other theories regarding the mode of neurotoxicity for manganese (and other metal ions) include toxicity caused by the formation of hydroxyl radicals during the manganese-catalyzed autooxidation of hydrazines (Ito et al. 1992).

It has been suggested that the mechanism of manganese neurotoxicity may in part involve complex interactions with other minerals (Lai et al. 1999). In a developmental rat model of chronic manganese toxicity, administration of manganese in drinking water was associated with increased levels of iron, copper, selenium, zinc, and calcium in various regions of the brain. Moreover, the subcellular distribution of various minerals was differentially altered following manganese treatment. Iron deficiency is associated with increased manganese burden in the central nervous system of rats, while administration of excess iron significantly decreases manganese uptake (Aschner and Aschner 1990). The biochemical mechanisms underlying the interactions between manganese and other minerals are unclear.

Subtle deficits in fine motor and cognitive function in chronically exposed young adult male Cynomologus macaques monkeys have been associated with manganese impairment of *in vivo* amphetamine-induced dopamine release in the striatum, without detectable changes in markers of striatial dopamine terminal integrity, and with decreased cerebral cortex N-acetylaspartate/creatine ratio (Guilarte

et al. 2006a, 2006b; Schneider et al. 2006). In these studies, four monkeys (5–6 years old at the start) were given intravenous injections of manganese sulfate, 10–15 mg/kg or 3.26–4.89 mg manganese/kg, once per week for an average of 34.2 weeks. Three additional monkeys without excess manganese exposure or behavioral evaluations were used as a control group for post-mortem analyses of the brain (Guilarte et al. 2006a). Prior to manganese exposure, the monkeys were trained to perform tests for cognitive and motor function; overall behavior was assessed by ratings and videotaped analysis (Schneider et al. 2006). By the end of the exposure period, monkeys developed deficits in spatial working memory, showed modest decreases in spontaneous activity and manual dexterity, and showed increased frequency of compulsive-type behaviors such as compulsive grooming (Schneider et al. 2006). At study termination, mean manganese concentrations were elevated in exposed monkeys, compared with control monkeys, in the following brain regions: globus pallidus (3.30 versus 0.72 µg/g tissue); caudate (1.18 versus 0.38 µg/g tissue); putamen (1.5 versus 0.48 µg/g tissue); and frontal white matter (0.57 versus 0.17 µg/g tissue) (Guilarte et al. 2006b; Schneider et al. 2006). Positron emission tomography (PET) analysis found changes in amphetamine-induced release of dopamine in the striatum (up to 60% decrease compared with baseline values), but no significant changes in striatal dopamine receptor binding potentials (Guilarte et al. 2006a). Post-mortem chemical and immunohistochemical analysis of caudate and putamen tissue found no evidence for exposure-related changes to levels of D2-dopamine receptor (D2-DAR), dopamine receptor (DAT), tyrosine hydroxylase, or dopamine and its metabolite, homovanillic acid (Guilarte et al. 2006a). Using ^{1}H-magnetic resonance spectroscopy, concentrations of creatine (Cr), N-acetylaspartate (NAA), choline, and myo-inositol were measured. Decreases (relative to baseline) in the NAA/Cr ratio were measured in the parietal cortex and frontal white matter, but not in the striatum (Gulilarte et al. 2006b). Guilarte et al. (2006b) suggested that the changes in the NAA/Cr ratio are indicative of neuronal degeneration or dysfunction in the parietal cortex that may also be associated with the neurobehavioral changes noted in the monkeys. Subsequent gene expression profiling in the frontal cortex of these monkeys found changes consistent with cellular stress responses that the investigators proposed may help to explain the subtle cognitive effects noted (Guilarte et al. 2008). The collective results from these studies suggest that subtle neurobehavioral changes noted in epidemiological studies of chronically exposed workers (see Section 3.2.1.4 and Appendix A) may be similar to those noted in these monkeys and may be related to manganese-induced functional changes and gene expression changes noted in the striatum and the cerebral cortex.

As reviewed by Fitsanakis et al. (2006), most mechanistic research on manganese neurotoxicity has focused on perturbations of the dopaminergic system, but there is evidence to suggest that early consequences of manganese neurotoxicity may involve perturbations of other neurotransmitters including

GABA and glutamate in the basal ganglia and other brain regions. For example, there is evidence to suggest that manganese decreases the ability of astrocytes to clear glutamate from extracellular space (Erikson and Aschner 2002, 2003), increases the sensitivity of glutamate receptors to glutamate (see Fitsanakis and Aschner 2005 and Fitsanakis et al. 2006 for review), and perturbs glutamine-glutamate-GABA interconversions in frontal cortex and basal ganglia of rats (Zwingmann et al. 2004, 2007). When rat striatum was perfused with artificial cerebrospinal fluid with 200 nM manganese, GABA levels in the perfusate were decreased by about 60% compared with controls, but no effects on levels of glutamate, aspartate or glycine in the perfusate were observed (Takeda et al. 2003). In the perfused rat hippocampus, 200 nM manganese caused a 50% decrease in the levels of GABA, glutamate, and aspartate in the perfusate (Takeda et al. 2002). The results from the studies of Takeda et al. (2002, 2003) suggest that there are differential regional effects of manganese on the release of different neurotransmitters. Fitsanakis et al. (2006) concluded that additional research is needed to better understand the interdependence of neurotransmitters, including dopamine, glutamate, and GABA and their relationships to manganese neurotoxicity.

3.5.3 Animal-to-Human Extrapolations

As discussed in Section 3.2, the available literature on toxicological analysis of manganese in humans and animals is quite extensive. However, due to the wide dose ranges administered, the variety of responses, and the differences in measured end points, comparisons of effects across species is not straightforward.

Rodent models have primarily been used to study manganese neurotoxicity. These studies have reported mostly neurochemical, rather than neurobehavioral, effects (Brouillet et al. 1993; Chandra 1983; Chandra and Shukla 1978, 1981; Daniels and Abarca 1991; Deskin et al. 1980, 1981; Eriksson et al. 1987a; Gianutsos and Murray 1982; Parenti et al. 1986; Singh et al. 1979; Subhash and Padmashree 1991), as very few studies investigated neurobehavioral effects. It has been suggested that this focus may reflect difficulties in characterizing behavioral changes following basal ganglia damage in the rodent (Newland 1999). Other techniques, such as those used to identify basal ganglia damage as a result of exposure to neuroleptics (Newland 1999), may be refined to further exploit the rodent model as a predictor of neurobehavioral change in the human. The usefulness of the rat model for manganese neurotoxicity is also limited because the distribution of manganese in brain regions is dissimilar to that of the human (Chan et al. 1992; Brenneman et al. 1999; Kontur and Fechter 1988; Pappas et al. 1997). Studies to date have used exposure routes such as inhalation, intravenous, intraperitoneal, or subcutaneous, with few

exceptions (Brenneman et al. 1999; Dorman et al. 2000, 2002, 2004a, 2005a, 2006b; Lown et al. 1984; Morganti et al. 1985; Pappas et al. 1997).

The rabbit has also been used as a model for manganese toxicity in a few studies (Chandra 1972; Szakmáry et al. 1995). The only available neurotoxicity study using the rabbit (Chandra 1972) reported that the species, when dosed intratracheally with 253 mg manganese/kg body weight (inferred as a one-time dose), developed hindlimb paralysis (a response not typically observed in humans exposed to excess manganese) after an observation period of 18 months. The animals also exhibited wide-spread neuronal degeneration in the brain. This study suggests that rabbits and humans may be qualitatively similar in the manifestation of neurobehavioral effects. However, further studies are needed to determine if the two species manifest comparable symptoms within the same dose range.

The nonhuman primate has been a useful model for predicting neurotoxicity in the human as the monkey presents neurobehavioral responses to toxicants that are very similar to those observed in humans (Eriksson et al. 1987b; Golub et al. 2005; Gupta et al. 1980; Newland and Weiss 1992; Olanow et al. 1996). Further, the monkey also undergoes neurochemical changes (Bird et al. 1984) as a result of manganese exposure. Studies have shown that monkeys exposed to manganese injected either intravenously or subcutaneously exhibit symptoms very similar to those observed in miners and others exposed to manganese, including ataxia, bradykinesia, unsteady gait, grimacing, and action tremor (Eriksson et al. 1992a, 1992b; Newland and Weiss 1992; Olanow et al. 1996). In addition, monkeys exhibiting these effects show accumulation of manganese in the basal ganglia as observed by MRI (Eriksson et al. 1992b; Newland and Weiss 1992), as do humans who are either exposed to, or are unable to clear, excess manganese (Devenyi et al. 1994; Fell et al. 1996; Hauser et al. 1994; Ono et al. 1995; Pomier-Layrargues et al. 1998; Rose et al. 1999; Spahr et al. 1996). However, primate studies showing these neurobehavioral effects have involved routes of administration that do not mimic environmental exposures, and although the effects in monkeys are qualitatively similar, it is currently unknown whether the effects are seen at the same dose metric as those in humans. Newland (1999) proposes using MRI techniques to relate the administration of certain amounts of manganese with a corresponding MRI signal in the brain and the resultant neurobehavioral effects. This technique might be very useful in developing a true dose-response relationship for manganese neurotoxicity in both the monkey and human.

Mechanisms of manganese toxicity *in vivo* are likely to be comprised in part by unique characteristics of the exposed individual, as well as by general physiology and exposure route. Therefore, further studies are needed to develop appropriate animal models for human populations identified as susceptible (e.g.,

children, elderly adults, nutritionally-compromised children and adults) using appropriate animal modalities. Such techniques may lead to a more complete evaluation of the pathways and circumstances by which manganese exposure can result in toxicity. Additional research to further develop PBTK models in rats that have been recently described (Leavens et al. 2007; Nong et al. 2008; Teeguarden et al. 2007a, 2007b, 2007c) and extend them to populations of potentially susceptible individuals (in rodents, nonhuman primates, and primates) may be useful to increase understanding of interspecies differences in manganese neurotoxicity and provide support for extrapolations of dose-response relationships in animals to humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

The potential hazardous effects of certain chemicals on the endocrine system are of current concern because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering,

for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Studies of endocrine effects in humans following manganese exposure are very limited. Alessio et al. (1989) reported the elevation of serum prolactin and cortisol in chronically-exposed workers, while no changes in prolactin, FSH, or LH levels were observed in an occupational study involving shorter exposure periods (Roels et al. 1992). Lucchini et al. (1995) reported elevated serum prolactin levels in ferromanganese workers; 20 of those workers still showed elevated prolactin levels 5 years later after exposure to consistent levels of airborne manganese (Smargiassi and Mutti 1999). In fact, the serum prolactin levels had increased significantly over the previous values. Although these changes are minor, changes in prolactin secretion may have effects on different physiological functions, including loss of libido and impotence in men, and infertility and change in menstrual cycle in women.

No studies of endocrine effects in animals following airborne manganese exposure were located. Short-term animal studies and some of the long-term animal studies were negative for endocrine effects following oral exposure to manganese (NTP 1993). One intermediate study reported a decrease in circulating testosterone and a significant increase in substance P in the hypothalamus and neurotensin in the pituitary in rats dosed intraperitoneally with 6.6 mg manganese/kg/day as manganese chloride (Hong et al. 1984). Two other studies in rats reported that manganese tetroxide in food, given at a dose of 350 mg manganese/kg/day for 224 days (starting on day 1 of gestation and continuing for 224 days) (Laskey et al. 1982) and 214 mg manganese/kg/day given up to 28 days (Laskey et al. 1985), resulted in reduced testosterone levels in male rats. The biological significance of this effect is unknown because the decrease had no result on fertility in the latter study (Laskey et al. 1985), and there were no observed effects on the hypothalamus or pituitary.

A current interest in endocrine effects of manganese revolves around the possibility that developmental manganese exposure may influence the timing of puberty. One study performed on 23-day-old female rats in which manganese was provided by a single, intraventricular administration of 0, 0.01, 0.02, 0.04, or 0.17 mg manganese/kg as manganese chloride found that, at the three highest doses, manganese stimulated a dose-responsive increase in luteinizing hormone (LH) levels (Pine et al. 2005). A dose of 2 mg manganese/kg/day, provided to another group of female pups by daily gavage from PND 12 to 29 significantly advanced the average age of puberty (by approximately 1 day) as well as produced significant increases in serum levels of LH, follicule stimulating hormone (FSH), and estradiol (E_2) (Pine

et al. 2005). These results suggest a role for manganese in regulating the timing of puberty in female rats and suggests that excess manganese exposure may accelerate the onset of puberty. Manganese also appears to have pubertal effects in male rats; an oral gavage dose of 11 mg manganese/kg/day provided daily on PNDs 15–48 or 15–55 produced significantly increased LH, FSH, and testosterone at 55 days of age (Lee et al. 2006). Increases in both daily sperm production and efficiency of spermatogenesis were also observed, suggesting that manganese may be a stimulator of prepubertal LHRH/LH secretion and thus facilitate the onset of male puberty. *In vitro* experiments using medial basal hypothalamic implants from adult male Sprague-Dawley rats showed that manganese at 500 μM increased luteinizing hormone-releasing hormone (LHRH) release, nitric oxide synthase activity, and the content of cyclic cGMP in the medial basal hypothalamus (Prestifilippo et al. 2007). The inhibition of nitric oxide synthase with a competitive inhibitor prevented the manganese-induced increase in LHRH release. The results of these *in vitro* studies provide added evidence of the ability of manganese to modulate levels of LHRH, even in adult animals (Prestifilippo et al. 2007).

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates

because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Children as a group have typically not been studied for the adverse effects of overexposure to inorganic manganese. Manganese results in adverse respiratory effects, as well as neurological effects; the latter effects have been the most investigated. As discussed previously, manganism has typically been observed in occupational settings, as in manganese miners, or in isolated cases of extreme exposure to inhaled or ingested manganese. In general, these exposure scenarios do not pertain to children. Reports do exist, however, of incidences of overexposure to inorganic manganese resulting in respiratory illness. Two studies exist that investigated increased respiratory complaints and symptoms at a junior high school situated 100 m from a manganese alloy plant in Japan (manganese concentrations in total dust at a 200 meter perimeter around the plant were 0.004 mg/m^3 [3.7 $\mu g/m^3$]) (Kagamimori et al. 1973; Nogawa et

al. 1973). The initial study showed that the incidences of self-reported respiratory illnesses among children in the exposed school were much higher than those of a control school 7 km away from the plant (Nogawa et al. 1973). Further, evaluations of respiratory fitness showed significant decreases in several parameters. When the installation of dust catchers resulted in a decreased manganese concentration in total dust, complaints of illness decreased, and the test results improved (Kagamimori et al. 1973). These respiratory effects were not unique from those observed in adults exposed to airborne manganese. Further, it was not reported if other compounds were present in the dust generated by the plant, which might have contributed to or caused the reported illnesses. It is possible that these effects might have been triggered by the dust and were not specific to manganese.

Studies on potential neurological effects in children from inhalation exposure to excess inorganic manganese are limited. One study showed that a native population living on an island with rich manganese deposits suffered increased neurological disorders and incidences of birth defects (Kilburn 1987); their exposure was most likely via inhalation and oral routes. This study involved small sample sizes and lacked exposure concentrations and a suitable control group; these limitations preclude ascribing these effects to manganese alone.

Children who have been exposed to elevated levels of inorganic manganese presumably through diet (either a normally ingested diet or through total parenteral nutrition, TPN) have shown signs of motor disorders (e.g., dystonia, dysmetria, propulsion, retropulsion, poor check response bilaterally) similar to those observed in cases of frank manganism (Devenyi et al. 1994; Fell et al. 1996). In a few of the cases, the presence of liver dysfunction indicated a decreased ability to clear excess manganese (Devenyi et al. 1994; Fell et al. 1996), but some of the children with apparently normal livers also exhibited motor disorders (Fell et al. 1996). Several children also exhibited hyperintense signals on MRI resulting from increased exposure to manganese due to cholestatic end-stage liver disease (Devenyi et al. 1994) and from high concentrations of the element in TPN, either in the presence (Fell et al. 1996) or absence (Fell et al. 1996; Ono et al. 1995) of liver disease. The Ono et al. (1995) study involved a child on TPN for more than 2 years; although this child did have increased blood manganese and hyperintense signals in the basal ganglia as shown by MRI, the authors did not report any observable signs of neurotoxicity. A similar lack of observable neurotoxicity was reported in two siblings fed TPN with high manganese concentrations (0.2 mmol manganese/kg/day) for several months (the brother for 63 months total starting at age 4 months; the sister for 23 months total starting at age 1 month) (Kafritsa et al. 1998). Both children had elevated blood manganese levels and showed hyperintense signals in the basal ganglia (especially the globus pallidus and subthalamic nuclei) on MRI. Reduction of manganese concentration

in the TPN resulted in a gradual loss of signal on MRI analysis (becoming comparable to normal scans) and a decrease in blood manganese levels as measured in three subsequent annual exams. These equivocal results indicate that there are considerable differences in susceptibility to the neurotoxic effects of excess manganese in children.

Four reports of manganese neurotoxicity in children have been published recently including: (1) severe manganism-like neurotoxic symptoms (inability to stand independently, tendency to fall backward, and development of a "cock-like" walk) in a previously healthy 6-year-old female that were associated with elevated drinking water concentrations of manganese (1.7–2.4 mg manganese/L), pica, a diet high in manganese-rich foods, and elevated levels of plasma manganese (Sahni et al. 2007); (2) inattentiveness and lack of focus in the classroom and low-percentile performance in tests of memory in a 10-year-old male with no history of learning problems associated with elevated manganese in drinking water (1.21 mg manganese/L) (Woolf et al. 2002); (3) a statistically significant relationship for decreasing intelligence scores with increasing manganese levels in drinking water in a cross-sectional epidemiological study of 142 10-year-old children in Bangladesh (Wasserman et al. 2006); and (4) a statistically significant relationship between increased levels of oppositional behaviors and hyperactivity and increased levels of manganese in drinking water in an epidemiological study of 46 children (ages 6–15 years) in Quebec, Canada (Bouchard et al. 2007c). These results provide added weight to the evidence for the neurotoxic potential of excessive manganese in children, but the following uncertainties associated preclude the establishment of causal relationships between the observed effects and manganese exposure: (1) whether or not the observed effects were solely due to excess manganese alone or could have been influenced by other drinking water or dietary components; (2) the lack of information about manganese levels in food and air; and (3) the small sample sizes.

Two other earlier studies show that children who drank water containing manganese at average concentrations of at least 0.241 mg/L (Zhang et al. 1995) and ate food with increased manganese content (He et al. 1994) for 3 years performed more poorly in school (as shown by mastery of their native language, mathematics, and overall grade average) and on the WHO neurobehavioral core test battery than those students who drank water with manganese ≤0.04 mg/L. These neurobehavioral tests are among those administered to workers occupationally exposed to manganese to determine the presence of early neurological deficit (Chia et al. 1993a; Iregren 1990; Lucchini et al. 1995; Mergler et al. 1994; Roels et al. 1987a, 1992). These concentrations are much lower than the ones to which adults were exposed in the Kondakis et al. (1989) study. In this study, ingestion of drinking water with excess manganese (1.8–2.3 mg/L) was linked to the onset of unspecified neurological symptoms in an aged

population (average age, over 67 years). Though there are limitations, this and other environmental studies in adults (Baldwin et al. 1999; Beuter et al. 1999; Goldsmith et al. 1990; Kawamura et al. 1941; Kondakis et al. 1989; Mergler et al. 1999) and two studies in children (He et al. 1994; Zhang et al. 1995) indicate that both adults and children can manifest similar neurological deficits that are potentially linked to ingesting excess manganese. However, these reports are lacking well-characterized and quantitative exposure data that would indicate whether children and adults experience neurological effects at the same or different exposure levels. Existing studies do not allow estimations of the quantitative susceptibility of children to the preclinical effects of excess manganese exposure. They do indicate, though, that children can develop symptoms of neurotoxicity after oral exposure to manganese that are similar to those effects seen in adults environmentally or occupationally exposed to the metal. Further, these studies indicate that neurological effects may be a concern for children exposed to excess manganese from the environment or from a hazardous waste site.

The investigations by He et al. (1994) and Zhang et al. (1995) showed that children with poorer school performance had higher manganese hair content than children from the control area. Other studies have found that manganese levels in hair are higher in learning disabled children than in normal children (Collipp et al. 1983; Pihl and Parkes 1977). The route of excess exposure is not known, but it is presumed to be mainly oral. These observations are consistent with the possibility that excess manganese ingestion could lead to learning or behavioral impairment in children. However, an association of this sort is not sufficient to establish a cause-effect relationship since a number of other agents, including lead, might also be involved (Pihl and Parkes 1977).

Developmental studies in animals following inhalation exposure to manganese are sparse. One study exists (Lown et al. 1984) in which pregnant mice were exposed to a high concentration of airborne manganese or filtered air for 17 days preconception and then exposed to either the same concentration of manganese or filtered air postconception. Their pups were then fostered to adult females who had experienced the same inhalation exposures as the mothers (no manganese exposure, pre- or post-conception exposure, or both). The pups of exposed mothers had decreased body weight, but exhibited no differences in activity compared to pups from mothers exposed to air, irrespective of exposure history. In neonatal rats orally exposed to 25 or 50 mg manganese/kg/day from PNDs 1 through 21, manganese concentrations in various brain regions were about 2-fold higher than brain manganese concentrations in adult rats exposed to the same oral dose levels for 21 days (Dorman et al. 2000). At the highest dose level, neonatal rats showed an increased acoustic startle response, but exposure-related changes in other neurological end points (clinical signs, motor activity, and passive avoidance) were not found (Dorman et

al. 2000). In another recent study, inhalation exposure of female CD rats to manganese sulfate, starting 28 days prior to breeding through PND 18, caused elevated manganese concentrations in exposed maternal rats (compared with air control rats) in the following tissues: brain and placenta at 0.5 and 1.0 mg manganese/m^3 and lung at 0.05, 0.5, and 1.0 mg manganese/m^3 (Dorman et al. 2005a). In contrast, statistically significant elevations of manganese concentrations in sampled fetal tissues were observed only in the liver at 0.5 and 1.0 mg manganese/m^3, and elevated brain manganese concentrations were only observed in offspring after PND 14. The results from this study suggest that the brain in developing fetuses is partially protected from excess manganese by the placenta, and that the neonatal period is sensitive to increased manganese concentration in brain and other tissues under exposure to elevated airborne manganese concentrations.

Oral studies in animal models, whether involving the dosing of pregnant dams or sucklings, reveal a variety of neurochemical and physiological changes as a result of manganese exposure. The majority of studies have involved manganese chloride. One study in rats reported that pups exposed *in utero* 11 days during gestation to a relatively low concentration of manganese chloride (22 mg/kg; by gavage in water) did not have any observable decrease in weight gain, nor any gross or skeletal malformations upon necropsy (Grant et al. 1997a). Another study (Szakmáry et al. 1995) that also administered manganese chloride in water by gavage to pregnant rats at the slightly higher concentration of the 33 mg manganese/kg/day throughout the entire gestation period reported a delay of skeletal and organ development as well as an increase in skeletal malformations, such as clubfoot, in unborn pups. These malformations, however, were self-corrected in pups allowed to grow to 100 days of age. In addition, the same dose and route did not result in any observable developmental toxicity in the rabbit (Szakmáry et al. 1995). Rat pups exposed during gestation and after birth to manganese at relatively high concentrations of 120–620 mg/kg in drinking water suffered no observable adverse effects at the low dose and only transient adverse effects (decrease in weight and hyperactivity) at the high dose (Pappas et al. 1997). Similar transient body weight decreases and increases in motor activity were observed in neonatal rats administered 22 mg manganese/kg/day (as manganese chloride), by mouth or gavage, for up to 49 days (Brenneman et al. 1999; Dorman et al. 2000).

Rat pups from a generational study in which the male and female parents were exposed to 240–715 mg manganese/kg/day (as manganese chloride in drinking water) in either a diet adequate or deficient in protein (Ali et al. 1983a) suffered a delayed air righting reflex (independent of protein content of diet) and showed significant alterations in the age of eye opening and development of auditory startle when produced by parents fed low-protein diets with 240 mg manganese/kg/day in water. Kontur and Fechter

(1988) administered up to 1,240 mg manganese/kg/day as manganese chloride in drinking water to pregnant rats during days 0–20 of gestation. Although the authors found increased manganese levels in the fetus, there were no measurable effects on dopamine or norepinephrine turnover in the pup brain, or in the development of a startle response. In a more recent study, an increased amplitude in acoustic startle reflex was observed at PND 21 in neonatal rats administered 22 mg manganese/mg/day (as manganese chloride) by mouth from PND 1 to 21 (Dorman et al. 2000). Significant increases in brain dopamine and DOPAC concentrations in select brain regions in these animals as well as increased brain manganese concentrations were reported. This study demonstrated that neonates treated with manganese showed neurological changes, whereas no effects were observed in the adult animals treated similarly. Jarvinen and Ahlström (1975) fed pregnant rats varying doses of manganese sulfate in food for 8 weeks prior to and during gestation. Fetuses taken at 21 days did not show gross abnormalities, but did have significantly increased body burdens of manganese from mothers fed 187 mg/kg/day.

Neonatal rats given manganese chloride in drinking water for 44 days at a dose of 150 mg manganese/kg/day developed a transient ataxia on days 15–20 of the treatment and had decreased levels of homovanillic acid in the hypothalamus and striatum on day 15 but not day 60 (Kristensson et al. 1986). Neonatal rats given bolus doses of manganese chloride in water of 1 mg manganese/kg/day for 60 days suffered neuronal degeneration and increased monoamine oxidase on days 15 and 30 of the study, but did not show any clinical or behavioral signs of neurotoxicity (Chandra and Shukla 1978). Similarly, neonatal rats given bolus doses of manganese chloride in 5% sucrose at doses of 0, 1, 10 or 20 mg manganese/kg/day for 24 days after birth showed decreased levels of dopamine, but not norepinephrine, in the hypothalamus (Deskin et al. 1980); doses of 20 mg/kg/day caused a decrease of tyrosine hydroxylase activity and an increase in monoamine oxidase activity in the hypothalamus. In a follow-up study, Deskin et al. (1981) gave 0, 10, 15 and 20 mg manganese/kg/day (as manganese chloride in 5% sucrose by gavage) to neonatal rats from birth to age 24 days. The authors found that the highest dose resulted in increased serotonin in the hypothalamus and decreased acetylcholinesterase in the striatum. However, the authors did not indicate that the acetylcholinesterase decrease was important given other mechanisms involved in the metabolism of this neurochemical. Other recent findings from rat studies include increased locomotor activity when dosed with 10 mg/kg cocaine in adulthood (but no increased locomotor activity without cocaine challenge) following oral exposure to 13.1 mg manganese/kg/day (but not 4.4 mg manganese/kg/day) on PNDs 1–21 (Reichel et al. 2006); and impaired olfactory-mediated homing ability and passive avoidance of footshocks in male Sprague-Dawley rats exposed to oral doses of 17.2 mg manganese/kg/day (but not 8.6 mg manganese/kg/day) as manganese chloride on PNDs 1–20 (Tran et al. 2002a, 2002b).

Several studies evaluated the effects of manganese in the diet on reproductive development in the pre-weanling rodent. Gray and Laskey (1980) fed mice 1,050 mg manganese/kg/day (as manganese tetroxide) in the diet beginning on PND 15 and continuing for 90 days. The manganese caused decreased growth of the testes, seminal vesicles, and preputial gland. Later studies evaluated the effect of excess manganese via the diet and gavage on development of the rat (Laskey et al. 1982, 1985). These studies reported that 350 mg manganese/kg/day (as manganese tetroxide in food fed to pregnant rats and resulting male offspring for a total of 224 days) (Laskey et al. 1982) or 214 mg manganese/kg/day (as manganese tetroxide by gavage in water given for 28 days) (Laskey et al. 1985) reduced testosterone levels in developing rats.

Studies involving intravenous or subcutaneous exposure routes of pregnant dams indicate that doses of manganese chloride as low as 1.1 mg manganese/kg/day administered on GDs 6–17 in the rat (Grant et al. 1997a; Treinen et al. 1995) and 14 mg/kg/day administered on GDs 9–12 in the mouse (Colomina et al. 1996) can result in decreased fetal body weight and skeletal abnormalities.

The data indicate that animals may suffer adverse developmental effects after inhalation, oral, and intravenous exposures of their pregnant mothers, but results are mixed. Taken together, the evidence from environmental studies in humans and studies in animals suggests that younger children can be affected by exposures to excess manganese. Only one study is available that compared the incidence of adverse neurological effects in neonates and adults exposed to excess manganese (Dorman et al. 2000). Another recent study (Dorman et al. 2005b) showed that fetal brains were protected from excess manganese when their mothers were exposed to air concentrations as high as 1 mg manganese/m^3 manganese sulfate for 28 days before mating through PND 18, but increased brain manganese concentrations developed in the offspring by PND 14. Additional information may help to quantitatively characterize the potential differences in susceptibility to manganese-induced effects in young and adult animals.

No studies currently exist on the health effects arising in children as a result of exposure to organic manganese. Therefore, predictions concerning potential effects must be made from extrapolations from existing animal studies.

Weanling mice who ingested 11 mg manganese/kg/day as MMT for 12 months exhibited a significant increase in spontaneous activity at day 80, but no other behavioral differences throughout the exposure

period (Komura and Sakamoto 1992b). Concentrations of certain neurotransmitters and dopamine metabolites were modified in different brain regions, but the relationship to manganese levels in the affected regions was weak to none (Komura and Sakamoto 1994).

Developmental studies in rats involving intravenous exposure of pregnant dams to mangafodipir during organogenesis (days 6–17) indicate that the compound targets the skeletal system, resulting in irregularly shaped bones at doses as low as 1 mg manganese/kg/day (Grant et al. 1997a; Treinen et al. 1995). Further, application of specific doses of the compound during segmented time periods in organogenesis causes the same skeletal defects (Treinen et al. 1995). When the compound is administered from 22 days prior to conception until GD 7, at up to 6 mg manganese/kg/day, no developmental effects were observed (Grant et al. 1997a). These data further indicate that animals developing during organogenesis are particularly susceptible to developmental toxicity from mangafodipir exposure. Further, behavioral changes and significant decreases in body weight were observed in rat pups delivered from dams dosed with 1.1 mg manganese/kg/day, while decreased survival was observed in pups from dams given 2.2 mg manganese/kg/day on GDs 6–17.

In contrast to the rat, available studies suggest that the rabbit is far less susceptible to the developmental effects of mangafodipir. One study reported only decreased ossification in fetal sternebrae at 1.1 mg manganese/kg/day when given to dams on GDs 6–17 (Grant et al. 1997a); a similar study in the same species reported no observable developmental toxicity at 2.2 mg manganese/kg/day, but a significant decrease in fetal weight and viable fetuses, with no skeletal abnormalities, at a dose of 3.3 mg manganese/kg/day also given during organogenesis (Blazak et al. 1996).

In total, these developmental studies indicate that organic manganese can induce adverse developmental effects in the unborn and young, with effects ranging from slight biochemical changes in the brain to structural changes to changes in functional development. However, the majority of studies have involved very high exposure doses.

The developmental toxicity of elemental manganese has been shown in large part by comparison studies between manganese chloride and mangafodipir (Blazak et al. 1996; Grant et al. 1997a; Treinen et al. 1995). While these studies have provided much information as to the targeted teratogenicity of manganese during organogenesis, they have generally involved intravenous exposures, which are not particularly relevant to the general population. Further, it is likely that the majority of women who may be exposed to mangafodipir are beyond child-bearing age, since clinical subjects with suspected liver

tumors that merit use of the compound to assist in diagnosis are often over 50 years old (mean values; Bernardino et al. 1992). Should child-bearing women be exposed to the compound in a clinic environment, the doses required to induce developmental toxicity in animals greatly exceed the clinical dose (Blazak et al. 1996; Grant et al. 1997a; Treinen et al. 1995).

The pharmacokinetics of manganese in infants is known to be different than in adults. Balance studies, although limited, show that there is high retention of manganese during the neonatal period (Dorner et al. 1989). Formula-fed infants had an apparent manganese absorption of around 20% (Davidsson et al. 1988; 1989b), compared to absorption in adults, which is shown to be around 3–5% (Mena et al. 1969). The increased absorption may be a compensatory mechanism due to the low concentration of manganese in mother's milk (Collipp et al. 1983; Dorner et al. 1989; Lönnerdal et al. 1987) and to the increased metabolic needs of infants as compared to adults, since manganese is required for adequate bone mineralization, as well as for connective tissue synthesis (Hurley and Keen 1987). Alternatively, the increased absorption may be due to decreased excretion in the very young (Kostial et al. 1978; Lönnerdal et al. 1987; Miller et al. 1975; Rehnberg et al. 1981), although at least one study indicates that both pre-term and full-term infants actively excrete manganese (Dorner et al. 1989). Some studies have indicated that infants, who acquire all of their manganese in the first 4 months of life from human milk or milk formulas, ingest very different amounts of manganese due to the differing manganese content of these food sources. More specifically, studies showed that due to the low manganese concentration of human milk (4–10 μg/L) and its higher concentration in cow's milk formulas (30–75 μg/L) and soy formulas (100–300 μg/L) (Dorner et al. 1989; Lönnerdal et al. 1987), more manganese was absorbed from the formula (with absorption rate from all sources being roughly equal). Recent changes in nutritional status of infant formulas have resulted in a more nutritionally balanced absorption of manganese when compared to human milk and cow's milk formulas (~80–90%), with absorption of manganese from soy milk formulas being slightly lower (~70%; Lönnerdal et al. 1994). However, given the existing differences in inherent manganese concentrations between the different food sources, reports still suggest that infant intake of manganese from milk formulas is 10–50 times that of a breast-fed infant (Lönnerdal 1997). Animal studies show that absorption and/or retention of manganese is similar to that of older animals at approximately post-gestational day 17–18 (Kostial et al. 1978; Lönnerdal et al. 1987; Miller et al. 1975; Rehnberg et al. 1981). However, when this transition takes place in human infants has not been clearly defined.

Animal studies also show increased absorption of manganese in the young. For example, Kostial et al. (1989) found that rat pups retained a greater proportion (67%) of a single oral dose of radiolabeled

manganese than adult rats (0.18%). Bell et al. (1989) found that manganese absorption in rat pups (using isolated brush border membrane vesicles from the intestine) is nonsaturable and appears to occur primarily by diffusion. In the older rat, however, a high affinity, low capacity, active-transport mechanism for manganese absorption appears to be present (Garcia-Aranda et al. 1983).

Several elements, including iron (Davis et al. 1992a), phosphorus (Wedekind et al. 1991), and calcium (Wilgus and Patton 1939) are known to decrease manganese absorption in adults and animals. Iron-poor diets result in increased manganese absorption in humans (Mena et al. 1969) and in rats (Pollack et al. 1965). These interactions have not been studied in infants or children, but are expected to occur.

Manganese is known to cross the placenta and has been detected in cord blood in healthy full-term and pre-term infants. It is unknown whether mothers exposed to increased concentrations of manganese will pass on toxic amounts of the metal to their unborn children via the blood. However, as manganese is an essential nutrient and is part of the human body at all times, it is expected to be found in all tissues and fluids of the infant. Manganese is also naturally found in breast milk (typical concentrations in mature milk range from 4 to 10 µg/L) (Collipp et al. 1983). No studies exist concerning breast milk concentrations of mothers exposed to increased concentrations of manganese, but milk manganese concentrations increased with increasing exposure levels in lactating female rats exposed by inhalation to manganese sulfate at 0.05, 0.5, or 1 mg manganese/m^3 for 28 days before mating through PND 18 (Dorman et al. 2005a). The mean milk concentration was statistically significantly increased, compared with air control levels, however, only at the highest exposure level. It is unclear if manganese stored in the brain, bone, or in another depot, in excess amounts, could be mobilized to affect a developing fetus. However, one study by Jarvinen and Ahlström (1975) showed that pregnant rats fed 94 mg manganese/kg/day (as manganese sulfate) for 8 weeks accumulated the metal in their livers in contrast to non-pregnant females. Further, at a daily dose of 187 mg/kg/day, increased manganese concentrations were found in 21-day-old fetuses. These data suggest that homeostatic control of pregnant mothers regulated the distribution of the metal at lower concentrations, but this control was circumvented at high daily concentrations, resulting in liver excesses and distribution in the developing fetus. Although the fetuses in this study showed no physical abnormalities, no neurochemical or neurobehavioral studies were performed to determine potential adverse effects on these relevant end points.

Transferrin is one of the proteins responsible for binding and transporting both iron and manganese throughout the body. One study (Vahlquist et al. 1975) reported no correlation between infant cord blood and maternal blood transferrin levels. The same study reported an increase in plasma transferrin from

1.68±0.60 mg/mL in blood from infants at 6 weeks of age, to a peak of 2.60±0.27 mg/mL at 10 months, with values stabilizing at these adult levels throughout 16 years of age. The authors did not comment as to the statistical difference, if any, of these values.

There are no established biomarkers consistently used as indicators for overexposure to manganese in either adults or children. Elevated blood concentrations and hyperintense signals in the globus pallidus on T1-weighted MRI have been observed in children with increased exposure to manganese (Devenyi et al. 1994; Fell et al. 1996; Kafritsa et al. 1998; Ono et al. 1995). However, the same limitations of these indicators of overexposure in adults (wide range of blood manganese in normal populations, high cost and, hence, low availability of MRI) apply to children. Blood manganese has generally been poorly related to current levels of exposure or cumulative exposure index (Smargiassi and Mutti 1999). Elevated blood manganese alone does not constitute an adequate indicator of manganese overexposure. There are no pediatric-specific biomarkers of exposure or effect. See Section 3.8.1 for further information.

Studies suggest that children may differ from adults in their susceptibility to the toxic effects of manganese due to toxicokinetic differences (i.e., increased absorption and/or retention). Qualitative similarities exist between respiratory and neurological effects seen in adults and children suffering from extreme manganese exposure. While infant and animal studies indicate that the young have an increased uptake of manganese, and distribution of the element in certain tissues may differ with age, studies that reveal quantitative levels of manganese associated with discrete frank effects in both adults and children are lacking. The studies to date (namely absorption, distribution and excretion studies in animals) suggest a pharmacokinetic susceptibility to manganese that is different in children than in adults.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a

substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to manganese are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by manganese are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Manganese

Manganese can be measured with good sensitivity in biological fluids and tissues (see Section 7.1), and levels in blood, urine, feces, and hair have been investigated as possible biomarkers of exposure. As a group, workers exposed to a mean concentration of 1 mg manganese/m^3 had higher levels of manganese in the blood and the urine than unexposed controls (Roels et al. 1987b). The group average levels in blood appeared to be related to manganese body burden, while average urinary excretion levels were judged to be most indicative of recent exposures. A study by Lucchini et al. (1995) is the only evidence that suggests that blood and urine levels were correlated with manganese exposure on an individual basis. This study differed from others in that it involved exposure to manganese dioxide and measured adverse

effects in workers after exposure ceased, whereas other studies involved current exposures, and some, like Roels et al. (1987b) involved exposure to numerous manganese compounds (salts and oxides). The findings of Lucchini et al. (1995) suggest that blood and urine levels of manganese, on an individual basis, are positively correlated with exposure levels in the few weeks following cessation of exposure. In a study of chronically exposed workers who were evaluated while exposure was ongoing, Lucchini et al. (1999) found a positive correlation between manganese levels in total dust and in blood of exposed workers. This correlation did not exist for cumulative exposure index and blood levels of the metal.

Other studies have indicated that on an individual basis, the correlation between the level of workplace exposure and the levels in blood or urine is not a reliable predictor of exposure (Jarvisalo et al. 1992; Roels et al. 1987b, 1992; Smyth et al. 1973). However, two studies (Jarvisalo et al. 1992; Roels et al. 1992) suggest that blood and urinary manganese levels may be used to monitor group exposure, such as exposure in an occupational setting. Also, a study (Siqueira et al. 1991) of ferromanganese workers indicated that exposed workers had elevated levels of plasma and urinary urea and decreased levels of urinary calcium, HDL cholesterol, and plasma inorganic phosphate. The study authors concluded that measurement of these parameters may be useful in the early detection of manganese poisoning. Although manganese may play a role in a metabolic pathway or other biological function involving these products, it is unclear what physiological significance these parameters have as related to manganese toxicity. There was no significant correlation between fecal excretion of manganese and occupational exposure to the metal (Valentin and Schiele 1983). A recent study on environmental exposure to manganese (Baldwin et al. 1999) in southwest Quebec, Canada, indicates that significantly higher levels of blood manganese are correlated with high levels of airborne manganese. In this study, air samples were taken in four geographic areas around a former ferroalloy plant (point source for airborne manganese). The air samples, which were for total dust and PM_{10} levels, were taken for 3 consecutive days in the summer. Using a geometric algorithm, 297 blood manganese values from nearby residents in seven postal zones were separated into two geographical areas corresponding to the point source. Higher blood manganese values in men and women were located in the geographic area with the higher airborne manganese values. It is notable that the air samples taken were limited in number and were taken only in the summer. However, the authors mentioned that the data were consistent with samples taken in an adjacent urban area and were consistent with potential exposure sources. Further, at the time of sampling, the ferroalloy plant was not in use and exposure data indicated that airborne levels of manganese decreased dramatically at a point 25 km downwind of the plant after the plant closed (Zayed et al. 1994). Thus, manganese exposure of the population in the Baldwin et al. (1999) study is likely to have been greater in the past; current blood manganese levels may be analogous to those observed in occupational workers undergoing

a forced layoff (Lucchini et al. 1995). These data, combined with the occupational studies, indicate that there may be a plateau level of homeostatic control of the metal. At low levels, blood manganese concentrations would be related to intake from food, water, and air; large differences in individual blood manganese levels would be observed. At high exposure levels, such as in occupational environments, a higher but still non-toxic level of blood manganese may be maintained by homeostatic control (i.e., a plateau level is reached); alternatively, that level may be exceeded.

These data also indicate that blood manganese levels can be an indicator of exposure to environmental manganese. These data indicate that manganese in blood or urine may be useful in detecting groups with above-average current exposure, but that measurements of manganese in these body fluids in individuals may only be related to exposure dose after the exposure has ceased.

In addition to individual variability, another factor that limits the usefulness of measuring manganese in blood, urine, or feces as a measure of excess manganese exposure is the relatively rapid rate of manganese clearance from the body. As discussed in Section 3.4, excess manganese in blood is rapidly removed by the liver and excreted into the bile, with very little excretion in urine (Klaassen 1974; Malecki et al. 1996b). Thus, levels of manganese in blood or urine are not expected to be the most sensitive indicators of exposure.

Serum prolactin (PRL) has been shown to be a possible biomarker of manganese action of dopamine neurotransmission (Smargiassi and Mutti 1999). Manganese acts on the tuberoinfundibular dopaminergic system, which exerts tonic inhibition of PRL secretion. Serum PRL levels observed in workers occupationally exposed to manganese were shown to be consistent with mechanistic studies as they were distinctly higher than unexposed workers. It is still unclear whether or not serum PRL levels indicate recent or cumulative exposure. The value of PRL as a biomarker is called into question by the Roels et al. (1992) study in which serum PRL levels were not increased in workers chronically exposed to airborne manganese.

Lymphocyte manganese-dependent superoxide dismutase activity increases with increased manganese uptake (Yiin et al. 1996). It has been suggested that this enzyme, in conjunction with serum manganese levels, may be helpful in assessing low and moderate levels of manganese exposure (Davis and Greger 1992; Greger 1999). MnSOD has been shown to be elevated in women ingesting 15 mg of supplemental manganese/day, while levels have been shown to be depressed in the heart and liver of manganese deficient animals. MnSOD is important as a possible biomarker because its levels can be related to

oxidative damage. Its sensitivity as a biomarker depends on factors that induce oxidative stress or effect manganese bioavailability including diets high in polyunsaturated fatty acids and strenuous physical exercise (Greger 1999).

Brain MRI scans and a battery of specific neurobehavioral tests (Greger 1998) may be useful in assessing excessive manganese exposure even among industrial workers exposed to airborne manganese (Nelson et al. 1993). These scans also have been successfully used to identify accumulation of manganese in the brains of children exposed to excess manganese (Devenyi et al. 1994; Fell et al. 1996; Ihara et al. 1999; Kafritsa et al. 1998; Ono et al. 1995; Sahni et al. 2007). Levels in feces could be useful in evaluating relatively recent high-level exposures but would not be expected to be helpful in detecting chronic low-level exposures. These methods are potentially useful biomarkers, but require additional evaluation to determine their validity.

While it is well established that exposure to excess manganese can result in increased tissue levels in animals, the correlations among exposure levels, tissue burdens, and health effects have not been thoroughly investigated in humans or animals. Also, since homeostatic mechanisms largely prevent fluctuations of manganese concentration in whole blood and since manganese is mainly excreted by the biliary route, it is not believed possible to identify a biological marker to assess the intensity of exposure or concentration in the target organ (Lauwerys et al. 1992). As noted by Rehnberg et al. (1982), manganese levels in tissues are subject to homeostatic regulation via changes in absorption and/or excretion rates. While exposure to very high levels may overwhelm these mechanisms, continuous exposure to moderate excesses of manganese does not appear to cause a continuous increase in tissue levels (Rehnberg et al. 1982). Moreover, even if tissue levels are increased in response to above-average exposure, levels are likely to decrease toward the normal level after exposure ceases. For example, the level of manganese in the brain of a subject with severe manganism was not different from the normal level (Yamada et al. 1986). For these reasons, measurement of tissue levels of manganese at autopsy or possibly biopsy may be of some value in detecting current exposure levels but is not useful in detecting past exposures. Evaluation of manganese exposure by analysis of tissue levels is also not readily applicable to living persons except through the collection of biopsy samples.

MRI has been used to track manganese distribution in the brains of monkeys (Dorman et al. 2006b; Newland and Weiss 1992; Newland et al. 1989) and humans (Kafritsa et al. 1998; Klos et al. 2005; Nolte et al. 1998; Park et al. 2003; Rose et al. 1999; Uchino et al. 2007; Wolters et al. 1989). In addition, it has been used to assay hyperintense signaling in the globus pallidus and other brain areas of individuals with

chronic liver disease (Devenyi et al. 1994; Hauser et al. 1994, 1996; Klos et al. 2005; Nolte et al. 1998; Park et al. 2003; Pomier-Layrargues et al. 1998; Spahr et al. 1996; Uchino et al. 2007), individuals on chronically-administered TPN (Kafritsa et al. 1998; Nagatomo et al. 1999; Ono et al. 1995), and individuals with symptoms characteristic of manganism (Nelson et al. 1993). Although data addressing the sensitivity and specificity of MRI as an indicator for body burden or exposure are limited, the technique is being used to identify individuals who are likely to have increased stores of manganese in brain and potentially in other tissues, as well. For example, the hyperintense signaling in the brain is typically coincident with elevated blood manganese levels (Devenyi et al. 1994; Hauser et al. 1994, 1996; Kafritsa et al. 1998; Klos et al. 2005; Nagatomo et al. 1999; Nolte et al. 1998; Ono et al. 1995; Park et al. 2003; Pomier-Layrargues et al. 1998; Spahr et al. 1996; Uchino et al. 2007). Dorman et al. (2006b) evaluated the use of the pallidal index (PI—ratio of hyperintensities in the globus pallidus and the adjacent subcortical frontal white matter) and the T1 relaxation rate (R1) from MRI to reflect manganese concentrations determined by analytical chemistry in brain regions of monkeys repeatedly exposed by inhalation to aerosols of manganese sulfate at several concentrations ≥0.06 mg. Increases in the PI and R1 were correlated with the pallidal manganese concentration, but increased manganese concentrations in white matter confounded the PI measurements. Dorman et al. (2006b) suggested that R1 can be used to estimate regional brain manganese concentrations and that this technique may be used as a reliable biomarker of occupational manganese exposure.

Neutron activation has been shown to be a possible means of *in vivo* measurement of manganese in the liver and possibly other tissues and organs, including the brain (Arnold et al. 1999; Rose et al. 1999). Minimum detection levels are low enough to distinguish between normal and elevated concentrations.

Scalp hair has also been investigated as a possible biomarker of manganese exposure. While some studies have found a correlation between exposure level and manganese concentration in hair (Collipp et al. 1983), use of hair is problematic for several reasons. For example, exogenous contamination may yield values that do not reflect absorbed doses, and hair growth and loss limit its usefulness to only a few months after exposure (Stauber et al. 1987). Manganese has also been reported to have a strong affinity for pigmented tissues (Lydén et al. 1984), and Hurley and Keen (1987) and Sturaro et al. (1994) have reported that manganese concentrations in hair vary with hair color. Further, hair may be contaminated by dye, bleaching, or other materials. Thus, it is not surprising that other studies have found no correlation between individual hair levels and the severity of neurological effects in manganese-exposed persons (Stauber et al. 1987). A study that investigated the correlation between potentially toxic metal content in hair and violent behavior found an association between manganese and violent behavior, but it

was not conclusively established that manganese was the causative factor (Gottschalk et al. 1991). He et al. (1994) observed that poor performance in school and on neurobehavioral tests was inversely correlated with hair levels of manganese. The manganese exposure in this study was via drinking water and certain foods. Several studies have found that manganese levels in hair are higher in learning disabled children than in nondisabled children (Collipp et al. 1983; Pihl and Parkes 1977). The route of excess exposure is not known but is presumed to be mainly oral. However, an association of this sort is not sufficient to establish a cause-effect relationship since a number of other agents, including lead, might also be involved (Pihl and Parkes 1977). Other studies have found statistically significant associations between hair manganese levels and behavioral deficits (Bouchard et al. 2007c; Wright et al. 2006). These studies suggest that hair manganese levels can provide meaningful exposure assessments.

Clara cell protein CC16 is a potential biomarker for exposure to MMT, because the protein decreases in both BALF and serum following MMT exposure (Bernard and Hermans 1997; Halatek et al. 1998), possibly due to decreased synthesis and/or protein secretion due to loss of producing cells (Halatek et al. 1998). The protein can be quantified in serum or urine, but no dose-response studies on the potential biomarker have been performed.

There are no known biomarkers of exposure that are specific for children; any biomarkers applicable for use in adults should be applicable for children. For example, manganese-induced hyperintense signals on MRI have been seen in children (Devenyi et al. 1994; Kafritsa et al. 1998; Ono et al. 1995; Sahni et al. 2007) as well as adults (Hauser et al. 1994, 1996; Nagatomo et al. 1999; Pomier-Layrargues et al. 1998; Spahr et al. 1996).

3.8.2 Biomarkers Used to Characterize Effects Caused by Manganese

The principal adverse health effects associated with exposure to manganese are respiratory effects (lung inflammation, pneumonia, reduced lung function, etc.) and the neurological syndrome of manganism and preclinical neurological effects. Although the respiratory effects are similar in many different exposure studies (Kagamimori et al. 1973; Lloyd Davies 1946; Nogawa et al. 1973), there are no specific biomarkers of effect other than reduced lung function. The fully developed disease can be diagnosed by the characteristic pattern of symptoms and neurological signs (Mena et al. 1967; Rodier 1955), but the early signs and symptoms are not specific for manganese. Careful neurological and psychomotor examination in conjunction with known exposure to manganese may be able to detect an increased incidence of preclinical signs of neurological effects in apparently healthy people (Iregren 1990; Roels

et al. 1987a). However, these signs are not sufficiently specific for preclinical effects of manganese to reliably identify whether an individual has been exposed to excess levels for a prolonged period. In addition, no biochemical indicator is currently available for the detection of the early neurotoxic effects of manganese. There are no specific biomarkers that would clearly indicate long-term exposure to excess manganese.

Idiopathic Parkinsonism and manganism can be difficult to distinguish due to some similarity in the symptoms (Kim et al. 1999). Idiopathic Parkinsonism is marked by neurodegeneration in the dopaminergic nigrostriatal pathway, while manganism induced damage occurs postsynaptic to the nigrostriatal system. PET with ^{18}F-dopa afforded a differentiation between manganism and idiopathic Parkinsonism in isolated patients with manganese exposure by indexing the integrity of the dopaminergic nigrostriatal pathway.

Measurement of altered levels of dopamine and other neurotransmitters in the basal ganglia has proven to be a useful means of evaluating central nervous system effects in animals (e.g., Bonilla and Prasad 1984; Eriksson et al. 1987a, 1987b), and these changes are often observed before any behavioral or motor effects are apparent (Bird et al. 1984). No noninvasive methods are currently available to determine whether there are decreased dopamine levels in the brain of exposed humans, but decreased urinary excretion of dopamine and its metabolites has been noted in groups of manganese-exposed workers (Bernheimer et al. 1973; Siqueira and Moraes 1989). However, the relationship between manganese effects on peripheral versus central dopamine levels has not been clearly defined, and given the lack of change in dopamine content in substantia nigra of humans exposed to manganese, the relevance of the animal studies to central nervous system disorder is questionable.

Smargiassi et al. (1995) evaluated platelet monoamine oxidase (MAO) and serum dopamine β-hydroxylase (DBH) activities in 11 men occupationally exposed to manganese via inhalation in a ferroalloy plant. Exposed workers, in general, had lower MAO activities, but similar DBH activities, in comparison to 15 nonexposed control males. However, a positive dose-effect relationship was observed in the exposed group between a Cumulative Exposure Index (CEI) and DBH activity (r^2=0.40, $p<0.05$). The CEI took into account the average annual respirable or total manganese concentrations in dust, the ventilation characteristic of each working area, the number of years that each worker spent in a given area, and all of the areas that a worker had been during his job history. The authors proposed that DBH, which is an expression of catecholamine release, might be increasing dose-dependently in response to reduced turnover of MAO. The authors cautioned however, that while the data appear interesting, they

should be investigated in a larger study population, with careful analysis of possible confounding factors (Smargiassi et al. 1995).

Reduced urinary excretion of 17-ketosteroids (perhaps as a consequence of decreased testosterone production) has been noted in many patients with neurological signs of manganism (Rodier 1955), but it has not been determined whether this change is detectable prior to the occurrence of neurological effects. Although the urinary excretion of manganese is generally not related to oral manganese intake, Davis and Greger (1992) have suggested that the concentration of manganese in serum, combined with lymphocyte manganese-dependent superoxide dismutase activity, may be helpful in assessing low and moderate levels of manganese exposure. Manganese superoxide dismutase is activated by manganese, thus it is sensitive to the overall manganese balance. Therefore, increased manganese concentrations will affect an increased manganese superoxide dismutase level. There is no clear link between activity of superoxide dismutase and the harmful effects of manganese. Therefore, the potential usefulness of this technique as a biomarker of effect requires further evaluation.

The Clara cell protein CC16 is a potential biomarker for pulmonary effects from exposure to MMT (Bernard and Hermans 1997; Halatek et al. 1998). Damage of Clara cells by MMT causes a significant reduction in the levels of this protein in the BALF, but does not affect its level in serum. The protein can be quantified in serum or urine as well. However, no dose-response studies on the potential biomarker have been performed. Further, the protein has only been studied following intraperitoneal administration of MMT. It is unknown if CC16 levels will change following other exposure pathways.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (Agency for Toxic Substances and Disease Registry 1990) and for information on biomarkers for neurological effects see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

There is clear evidence from studies in animals that the gastrointestinal absorption (and hence the toxicity) of manganese is inversely related to dietary iron concentrations. That is, high levels of nonheme iron lead to decreased manganese absorption and toxicity, and low levels of iron lead to increased manganese absorption and toxicity (Chandra and Tandon 1973; Davis et al. 1992a, 1992b; Diez-Ewald et al. 1968; Rehnberg et al. 1982). Conversely, high levels of dietary manganese lead to decreased iron absorption (Davis et al. 1992b; Diez-Ewald et al. 1968; Garcia et al. 2006, 2007; Li et al. 2006;

Rossander-Hulten et al. 1991; Thomson et al. 1971). Short-term effects of this sort are believed to be the result of kinetic competition between iron and manganese for a limited number of binding sites on intestinal transport enzymes (Thomson et al. 1971), while longer-term effects of iron deficiency or excess are thought to be due to adaptive changes in the level of intestinal transport capacity (Cotzias 1958). The studies reporting competition between iron and manganese in absorption clearly indicate the impact an iron-poor diet will have on manganese uptake in the human (Chandra and Tandon 1973; Davis et al. 1992a, 1992b; Diez-Ewald et al. 1968; Mena et al. 1969; Rehnberg et al. 1982; Thomson et al. 1971). Further, competition between manganese and iron at the blood-brain barrier has been reported (Aschner and Aschner 1990), indicating that excesses of either metal will affect the brain distribution of the other. Johnson and Korynta (1992) found that, in rats, dietary copper can also decrease manganese absorption and increase manganese turnover; dietary ascorbate supplementation had minimal effects on manganese absorption. However, there is insufficient information to determine the significance of these observations for health effects in humans exposed to copper and manganese by the oral route.

Mn(II) pretreatment reduces Cd(II)-induced lethality (Goering and Klaassen 1985). Cadmium has been noted to have an inhibitory effect on manganese uptake (Gruden and Matausic 1989). In addition, manganese appears to be capable of increasing the synthesis of the metal-binding protein metallothionine (Waalkes and Klaassen 1985). Data from a study by Goering and Klaassen (1985) suggest that manganese pretreatment increases the amount of Cd^{+2} bound to metallothionine, thereby decreasing hepatotoxicity due to unbound Cd^{+2}. The significance of these observations for health effects in humans exposed to cadmium and manganese by the oral or inhalation routes is not clear.

High dietary intakes of phosphorus (Wedekind et al. 1991) and calcium (Wilgus and Patton 1939) were shown to depress manganese utilization in chicks. Low levels of calcium and iron may act synergistically to affect manganese toxicity by increasing absorption, but it is not known whether ensuring iron plus calcium sufficiency will reduce the toxic effects of manganese once it has been absorbed (Cawte et al. 1989). Thus, the importance of these observations to humans exposed to manganese by the oral or inhalation routes is not clear.

Ethanol has been suspected of increasing the susceptibility of humans to manganese toxicity (e.g., Rodier 1955), but evidence to support this is limited. Singh et al. (1979) and Shukla et al. (1976) reported that concomitant exposure of rats to ethanol and manganese (as manganese chloride in drinking water) led to higher levels of manganese in the brain and liver than if manganese were given alone; the higher levels were accompanied by increased effects as judged by various serum or tissue enzyme levels (Shukla et al.

1978). Although the authors referred to these effects as "synergistic," the data suggest that the effects were more likely additive. Based on the report in humans and evidence in animals, the effects of manganese on humans may be enhanced by the consumption of ethanol, but additional investigation is needed.

There is some evidence from a study in animals that chronic administration of drugs such as chlorpromazine (an antipsychotic) results in increased levels of manganese in the brain, including the caudate nucleus (Weiner et al. 1977). Chronic chlorpromazine treatment sometimes results in tardive dyskinesia, and manganese deposition in the brain might contribute to this condition. It has not been determined whether excess manganese exposure increases the risk of chlorpromazine-induced dyskinesia.

Intramuscular injection of animals with metallic nickel or nickel disulfide (Ni_3S_2) normally leads to a high incidence of injection-site sarcomas, but this increased incidence is reduced when the nickel is injected along with manganese dust (Sunderman et al. 1976). The mechanism of this effect is not clear, but natural killer cell activity normally undergoes a large decrease following nickel injection, and this is prevented by the manganese (Judde et al. 1987). However, the significance that these observations have for human health effects resulting from exposure to nickel and/or manganese by the oral or inhalation routes is not clear.

One study found that allopurinol, when administered orally to rats, antagonized the oxidative effects of manganese in the striatum and brainstem (Desole et al. 1994). The authors suggest that allopurinol, a xanthine oxidase inhibitor, may exert its protective effect by inhibiting both dopamine oxidative metabolism and xanthine oxidase-mediated production of reactive oxygen species.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to manganese than will most persons exposed to the same level of manganese in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of manganese, or compromised function of organs affected by manganese. Populations who are at greater risk due to their unusually high exposure to manganese are discussed in Section 6.7, Populations with Potentially High Exposures.

A number of researchers have observed that there is a wide range in individual susceptibility to the neurological effects of inhaled manganese dusts (Rodier 1955; Schuler et al. 1957; Smyth et al. 1973; Tanaka and Lieben 1969). For example, Rodier (1955) reported that the majority of manganism cases in miners occurred after 1–2 years of exposure to the metal, with only six cases observed occurring with 1–3 months exposure. Schuler et al. (1957) showed that in his group of miners, the average time for manifestation of manganism was 8 years, 2 months, with a minimum exposure of 9 months required for symptoms to present. However, the reason for this variable susceptibility is not clear. One likely factor is a difference in work activities and level of exertion. Another is that rates of manganese absorption and/or excretion can vary widely among individuals (Saric et al. 1977a). These toxicokinetic variations may be due to differences in dietary levels of iron and differences in transferrin saturation (Chandra and Tandon 1973; Davis et al. 1992a, 1992b; Mena et al. 1969; Thomson et al. 1971), to differences in dietary levels of other metals (Chowdhury and Chandra 1987; Gruden and Matausic 1989) or of calcium (Cawte et al. 1989), or to different levels of alcohol ingestion (Schafer et al. 1974). Another factor that might be relevant is dietary protein intake: low-level protein intake appears to increase the effect of manganese on brain neurotransmitter levels in exposed animals (Ali et al. 1983a, 1983b, 1985). However, a genetic basis for the wide difference in susceptibility cannot be ruled out.

One group that has received special attention as a potentially susceptible population is the very young. This is mainly because a number of studies indicate that neonates retain a much higher percentage of ingested or injected manganese than adults, both in animals (Keen et al. 1986; Kostial et al. 1978; Rehnberg et al. 1980) and in humans (Zlotkin and Buchanan 1986). The basis for high manganese retention in neonates is not certain, but is presumably a consequence of increased absorption (Mena et al. 1974; Rehnberg et al. 1980) and/or decreased excretion (Kostial et al. 1978; Miller et al. 1975; Rehnberg et al. 1981), possibly because maternal milk is low in manganese (Ballatori et al. 1987). Regardless of the mechanism, the result of the high retention is increased levels of manganese in the tissue of exposed neonatal animals (Miller et al. 1975; Rehnberg et al. 1980, 1981), especially in the brain (Kontur and Fechter 1985, 1988; Kostial et al. 1978; Kristensson et al. 1986; Miller et al. 1975; Rehnberg et al. 1981). This increase has caused several researchers to express concern over possible toxic effects in human infants exposed to manganese in formula (Collipp et al. 1983; Keen et al. 1986; Zlotkin and Buchanan 1986). At least one recent report indicates that an infant's rate of absorption of manganese from infant formulas, cow's milk, and breast milk is similar (Lönnerdal et al. 1994), resulting mainly from recent modifications to formulas to optimize the bioavailability of several essential minerals. There is some limited evidence that prenatal or neonatal exposure of animals to elevated levels of manganese can lead to neurological changes in the newborn (Ali et al. 1983a; Chandra and Shukla 1978; Deskin et al. 1980,

1981; Dorman et al. 2000; Kristensson et al. 1986); other studies have either not observed any neurochemical or neurophysiological effects in young animals exposed to excess manganese or the effects have been transient (Kontur and Fechter 1988; Kostial et al. 1978; Pappas et al. 1997). Currently, there is only one report that indicates that neonatal animals showed adverse neurological effects at a dose of manganese that had no effect on adults (Dorman et al. 2000). Brain concentrations of manganese were elevated in the neonates, but not in the adult animals given comparable doses of manganese for similar durations. The concern is that the young may be more susceptible due to increased absorption and/or retention and the potential toxicity from higher circulating levels of the metal. A few studies have reported increased blood and brain levels of the metal, either because of an inability to clear manganese due to chronic liver disease (Devenyi et al. 1994) or to an excess in parenteral nutrition (Kafritsa et al. 1998; Ono et al. 1995). However, observable neurological signs associated with manganese toxicity were only reported in the case of chronic liver disease (Devenyi et al. 1994). Although data suggest that children, particularly infants, are potentially more susceptible to the toxic effects of manganese, available evidence indicates that individual susceptibility varies greatly. Current information is not sufficient to quantitatively assess how susceptibility in children might differ from adults.

Elderly people might also be somewhat more susceptible to manganese neurotoxicity than the general population. Neurological effects were observed in older persons consuming manganese levels similar to levels found in U.S. surface water and groundwater (Deverel and Millard 1988; EPA 1984; Kondakis et al. 1989). The neurological effects observed in a group of families exposed to manganese in their drinking water were reportedly more severe among the older persons, whereas there was little effect in the youngest (Kawamura et al. 1941). Further, occupational studies indicate that older workers represent the largest numbers of manganese poisoning cases (Rodier 1955; Tanaka and Lieben 1969). More recent occupational (Crump and Rousseau 1999; Gibbs et al. 1999) and environmental (Mergler et al. 1999) manganese exposure studies indicate that increasing age was a factor in poorer performance on certain neurobehavioral tests. For example, Beuter et al. (1999) and Mergler et al. (1999) reported that performance on tests that required regular, rapid, and precise pointing movements was significantly decreased in exposed individuals, especially in those 50 years of age and over with high blood manganese levels. These reports suggest that older persons may have a greater susceptibility to adverse effects from inhaled or ingested manganese. One factor that could contribute to this increased susceptibility is a loss of neuronal cells due to aging or to accumulated neurological damage from other environmental neurotoxicants (Silbergeld 1982). Homeostatic mechanisms might become less effective in aged populations, which leads to higher tissue levels of manganese following exposure (Silbergeld 1982).

Mena et al. (1969) noted that the oral absorption of manganese was increased in individuals with iron-deficiency anemia. Altered nutritional status might be another predisposing factor. The inverse relationship of manganese absorption and iron-status has also been reported in animal models (Davis et al. 1992a, 1992b). It has been suggested that anemic persons may be more susceptible to the toxic effects of manganese because of enhanced absorption of iron and manganese through similar uptake mechanisms (Cotzias et al. 1968). Baldwin et al. (1999) reported an inverse relationship between serum iron and blood manganese levels in individuals environmentally exposed to airborne manganese.

Another group of potential concern is people with liver disease. This is because the main route of manganese excretion is via hepatobiliary transport (see Section 3.4.4), so individuals with impaired biliary secretion capacity would be expected to have a diminished ability to handle manganese excesses. In support of this hypothesis, Hambidge et al. (1989) reported that in a group of infants and children receiving parenteral nutrition, children with liver disease had higher average plasma concentrations of manganese than children without liver disease. Devenyi et al. (1994) also observed increased blood manganese concentrations, abnormal MRI scans indicative of increased manganese in the brain, and dystonia similar to that of patients with manganism, in an 8-year-old girl suffering from cholestatic liver disease. Hauser et al. (1994) reported increased blood and brain manganese in two patients with chronic liver disease and one with cirrhosis of the liver and a portacaval shunt. All three exhibited some form of neuropathy, including postural tremor of the upper extremities and a general lack of alertness, along with failure to concentrate and follow simple commands. In a later study, Hauser et al. (1996) did not observe movement disorders, but did observe the increased blood manganese concentrations and abnormal MRI scans in a group of adults with failing livers. Other studies have shown the link between increased deposition of manganese in the blood and/or the brains of humans with cirrhosis of the liver or chronic liver disease (Pomier-Layrargues et al. 1998; Rose et al. 1999; Spahr et al. 1996).

Patients on parenteral nutrition may be at risk for increased exposure to manganese. Forbes and Forbes (1997) observed that 31 of 32 adults treated with total parenteral nutrition (TPN) due to intestinal failure had increased manganese concentrations in their blood. Nagatomo et al. (1999) observed elevated blood manganese levels and hyperintense signals in the basal ganglia upon T1-weighted MRI in two elderly patients receiving TPN. Both patients exhibited severe symptoms associated with manganese exposure (masked facies, marked rigidity, hypokinesia). When manganese supplementation in the TPN was reduced, the blood and brain levels returned to normal.

Children receiving parenteral nutrition have also been shown to have increased blood manganese concentrations with accompanying hyperintense signals in the globus pallidus as observed by MRI (Fell et al. 1996; Kafritsa et al. 1998; Ono et al. 1995). Fell et al. (1996) studied a group of 57 children receiving parenteral nutrition, 11 of whom had a combination of hypermanganesemia and cholestasis. Four of these 11 patients died; the 7 survivors had whole blood manganese concentrations ranging from 34–101 µg/L. Four months after reduction or removal of manganese from the supplementation, the blood concentration of manganese decreased by a median of 35 µg/L. Two of the seven survivors had movement disorders, one of whom survived to have a MRI scan. The scan revealed bilateral symmetrically increased signal intensity in the globus pallidus and subthalamic nuclei. These signals were also observed in five other children—one from the original group exhibiting cholestasis with hypermanganesemia and five more given parenteral nutrition chronically with no liver disease. These results indicate that the cholestatic condition is not necessary for manganese to accumulate in the brain. A supporting study is provided by Ono et al. (1995) who observed increased blood manganese concentrations and hyperintense signals on MRI in the brain of a 5-year-old child on chronic parenteral nutrition due to a gastrointestinal failure. Five months after the manganese was removed from the parenteral solution, blood manganese levels returned to normal, and the brain MRI scans were almost completely free of abnormal signals. Further, the authors reported no neurological effects from exposure to manganese. Kafritsa et al. (1998) reported results similar to those of Ono et al. (1995). In the latter study, two siblings, one 9 years old and the other 2 years old, had been administered TPN chronically since the ages of 4 and 1 month(s), respectively. While elevated blood and brain manganese levels were reported (via laboratory analyses and MRI), no adverse neurological or developmental effects were observed. Once the manganese supplementation was reduced, the MRI signals abated, and the blood manganese levels returned to a normal range.

Although human interindividual variability is great concerning the ability to tolerate excess amounts of manganese in the body, these data indicate that, in general, children and the elderly may be more susceptible than young and middle-aged adults due to differential toxicokinetics and potential adverse effects superimposed on normal decline in fine motor function with age.

With respect to the respiratory effects of inhaled manganese (e.g., bronchitis, pneumonitis), people with lung disease or people who have exposure to other lung irritants may be especially susceptible. This is supported by the finding that the inhalation of manganese dusts by manganese alloy workers caused an increased incidence of respiratory symptoms (e.g., wheezing, bronchitis) in smokers, but not in nonsmokers (Saric and Lucic-Palaic 1977b).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to manganese. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to manganese. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to manganese.

Leikin JB, Paloucek JB. 2002. Leikin and Paloucek's poisoning and toxicology handbook. Hudson, OH: Lexi-Comp, Inc., 773-774.

Schonwald S. 2004. Manganese. In: Dart RC, eds. Medical toxicology. 3rd ed. Philadelphia, PA: Lippicott Williams & Wilkins, 1433-1434.

WHO. 1999. Concise international chemical assessment document 12. Manganese and its compounds. Geneva: United Nations Environment Programme. International Labour Organisation. World Health Organization. http://whqlibdoc.who.int/publications/1999/924153012X.pdf. August 04, 2008.

3.11.1 Reducing Peak Absorption Following Exposure

There is substantial evidence to indicate that an interaction between iron and manganese occurs during intestinal absorption (Chandra and Tandon 1973; Diez-Ewald et al. 1968; Keen and Zidenberg-Cher 1990; Mena et al. 1969; Rehnberg et al. 1982). Cawte et al. (1989) cite low levels of iron and calcium as "synergistic factors" that impact on the toxic effects associated with manganese exposures. In a dietary study investigating the effects of copper, iron, and ascorbate on manganese absorption in rats, these substances were all found to influence manganese absorption, depending in part on their relative concentrations (Johnson and Korynta 1992).

Evidence from these reports suggests that it may be possible to reduce the uptake of manganese and thereby circumvent the potential for toxic effects caused by current and future exposure to excess manganese through specific dietary supplementation. For example, sufficient iron or calcium stores, as opposed to a deficiency in these or other minerals, may reduce manganese absorption, and thus reduce potential toxicity. It is not known whether ensuring iron and calcium sufficiency will reduce the toxic effects of manganese once it has been absorbed into the body because information on critical levels of manganese at target sites is not available. No consistent clinical data are available documenting benefit from ipecac or dilution after ingestion of metallic, inorganic, or organic manganese (Schonwald 2004).

3.11.2 Reducing Body Burden

Inhaled manganese is readily absorbed by the lungs, although some may be retained there. Larger particles of dust containing manganese may be transported by mucociliary transport from the throat to the gut (Drown et al. 1986). Manganese in the gut may be directly absorbed either by a simple diffusion process (Bell et al. 1989) or by a high-affinity, low-capacity, active-transport mechanism (Garcia-Aranda et al. 1983). Once in the plasma, manganese is reportedly transported by transferrin; however, information on the mechanism of uptake in extrahepatic tissues is limited (Keen and Zidenberg-Cher 1990).

In severe cases of manganese poisoning, chelation therapy may be recommended in order to reduce the body burden of manganese and to help alleviate symptoms. Chelation therapy with agents such as ethylenediaminetetraacetic acid (EDTA) may alleviate some of the neurological signs of manganism, but in cases where it has been used, not all patients have shown improvement, and some of the improvements have not always been permanent (Cook et al. 1974; Schonwald 2004). Nagatomo et al. (1999) recently reported the use of Ca-EDTA treatment to reduce the body burden of two elderly patients with increased blood and brain levels of manganese. These patients exhibited masked faces, hypokinesia, and rigidity that are among the clinical signs of manganese poisoning. The potential use of calcium disodium ethylenediaminetetracetate ($CaNa_2$ EDTA) for the management of heavy metal poisoning was investigated in dogs by Ibim et al. (1992). $CaNa_2$ EDTA-treated dogs (without excess manganese exposure) were found to have decreased manganese levels in their hair. It is possible that the decrease was partially associated with mobilization and redistribution of this element from storage as well as from soft tissues. The authors, however, cautioned that the use of $CaNa_2$ EDTA could adversely affect the metabolism of manganese.

In an attempt to treat seven welders with manganism, a solution of 20% $CaNa_2$ EDTA was administered intravenously at the dose of 1.0 g daily for 3 days followed by a pause for 4 days. The therapy continued for 2–4 courses of this treatment, depending upon the improvement of symptoms. The symptoms, as well as blood manganese concentrations and urinary manganese concentrations, were monitored before and after each course of treatment. EDTA treatment resulted in increased manganese excretion in urine and decreased manganese concentrations in the blood; however, the patients did not show significant improvement in their symptoms (Crossgrove and Zheng 2004). A lack of improvement after EDTA chelation has also been observed in an additional case study of an adult worker (Jiang et al. 2006). It is

postulated that four carboxyl groups in the EDTA structure, which are essential to its chelating property, render the molecule poorly lipophilic, thus preventing it from effectively crossing the blood-brain barrier. Thus, EDTA appears to successfully chelate and remove the extracellular manganese ions in the blood, but with limited access to brain parenchyma, it cannot effectively chelate and remove manganese ions from the brain. Because EDTA cannot significantly remove manganese from damaged neurons, it appears to be of very limited therapeutic value for more advanced cases of manganism.

Cyclohexylene-aminotetraacetic acid (CDTA) and dimercaptol-1-propanesulphonic acid sodium salt (DTPA) were shown to decrease tissue manganese content in rats following inhalation exposure, but it is unknown whether the effects of manganese were alleviated (Wieczorek and Oberdörster 1989a, 1989b).

The use of the anti-tuberculosis drug para-aminosalicylic acid (PAS) to treat manganism has been reported (Jiang et al. 2006). The patient in this case study had palpitations, hand tremor, lower limb myalgia, hypermyotonia, and a distinct festinating gait. She received 6 g PAS per day through an intravenous drip infusion for 4 days and rest for 3 days. Fifteen courses of this treatment were administered to the patient. At the end of PAS treatment, the patient's symptoms were reportedly significantly alleviated, and handwriting recovered to normal. A reexamination at 17 years after PAS therapy found a general normal presentation in clinical, neurologic, brain MRI, and handwriting examinations. Her gait improved, and although it did not improve to an entirely normal status, it could be described as passable. A literature survey of more than 90 cases using PAS (Jiang et al. 2006) indicates a significant therapeutic benefit.

A study in monkeys reported a long half-life of manganese in the brain following inhalation exposure (Newland et al. 1987). Given that neurotoxicity is of concern with manganese exposure, knowledge of the mechanisms behind this longer half-life in the brain may be central to the development of mitigation methods. Newland et al. (1987) reported that this long half-life reflected both redistribution of manganese from other body depots and a slow rate of clearance from the brain. A later study reported that elevated levels in the brain persisted after inhalation exposure (due to redistribution), whereas for subcutaneous exposure, levels declined when administration was stopped (Newland et al. 1989). The authors observed that the accumulation of manganese in the brain was preferential in specific regions, but was unrelated to the route of exposure (Newland et al. 1989). They also reported that there are no known mechanisms or "complexing agents" that have been shown to remove manganese from the brain.

Few data are available regarding the reversibility of the neurological injury produced by prolonged excess manganese exposure. The effects are thought to be largely irreversible, and treatment for manganese intoxication is mainly supportive (Schonwald 2004). However, some evidence indicates that recovery may occur when exposure ceases (Smyth et al. 1973). Anti-Parkinsonian drugs, such as levo-dopa, have been shown to reverse some of the neuromuscular signs of manganism (Ejima et al. 1992; Rosenstock et al. 1971), but these drugs can produce a variety of side effects, and reports have indicated that they are not effective in improving the symptoms of neurotoxicity in manganism patients (Calne et al. 1994; Chu et al. 1995; Cook et al. 1974; Haddad et al. 1998; Huang et al. 1989; Schonwald 2004). Para-aminosalicylic acid was used successfully to treat two patients who exhibited neurological signs of manganese poisoning; one person made an almost complete recovery and the other was significantly improved. The mechanism for this treatment is unknown (Shuqin et al. 1992). Parenti et al. (1988) has proposed the use of antioxidants such as vitamin E, but the effectiveness of this treatment has not been further evaluated.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The oxidation state of manganese may influence both its retention in the body (see Section 3.4.3) and its toxicity (see Section 3.5). Therefore, it is possible that interference with the oxidation of manganese could be a method for preventing manganese cellular uptake and toxicity. Regarding retention, one study suggests that clearance is much more rapid for divalent manganese than for trivalent manganese (Gibbons et al. 1976). Regarding neurotoxicity,Mn(III) appears to be more efficient in enhancing the oxidation of catechols than either Mn(II) or Mn(IV) (Archibald and Tyree 1987). Thus, it is plausible that reducing the formation of Mn(III) could possibly both enhance elimination and prevent neurotoxicity, but no studies were located that evaluate this theory.

Ceruloplasmin is involved in the oxidation of iron and has also been involved in the oxidation of divalent manganese ion to the trivalent state (Gibbons et al. 1976). Selective inhibition of this oxidative function may be a method of mitigating the toxic effects of exposure to manganese. However, inhibition of the oxidation of manganese might also result in adverse effects on transport and cellular uptake of other essential metals, especially iron. Furthermore, it is not completely clear how the oxidation state of manganese is related to its normal function in neural cells or how this role is altered in manganese toxicity. Both Mn(II) and Mn(III) have been reported as components of metalloenzymes (Keen and Zidenberg-Cher 1990; Leach and Lilburn 1978; Utter 1976).

Manganese has been shown to catalyze the oxidation of dopamine *in vitro;* Cawte et al. (1989) reported that the toxicity induced by manganese resulted from the depletion of dopamine and the production of dopamine quinone and hydrogen peroxide through this mechanism. Antioxidants were tested for their ability to inhibit the dopamine oxidation induced by manganese, and it was found that ascorbic acid and thiamine completely inhibited dopamine oxidation both in the presence and absence of manganese. The report did not include data on background oxidation levels nor on the extent of dopamine oxidation in the absence of manganese. Results from treatment with antioxidants were viewed as evidence for their use in mitigating the adverse effects of manganese. However, because dopamine oxidation was inhibited to some degree in the absence of manganese, these data could alternately be interpreted as suggesting a more complex mechanism than the direct action of manganese for inducing dopamine oxidation and subsequent cell toxicity. Further investigation of the inhibition of manganese oxidation as a possible mitigation method should be preceded by additional studies to elucidate the role of manganese in its various oxidation states in normal neuronal cell metabolism and to determine whether oxidative stress is a primary mechanism for neurotoxicity mediated by manganese exposure.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of manganese is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of manganese.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Manganese

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to inorganic manganese are summarized in Figure 3-10. The purpose of this figure is to illustrate the existing information concerning the health effects of manganese. Each dot in the figure indicates that one

or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As the upper part of Figure 3-10 reveals, studies in humans exposed to inorganic manganese have focused mainly on intermediate and chronic inhalation exposure and the resulting neurological effects. There are several reports of humans exposed by ingestion and these too have focused on neurological effects. Reproductive effects have been studied in men exposed to manganese by inhalation, but other effects have generally not been formally investigated.

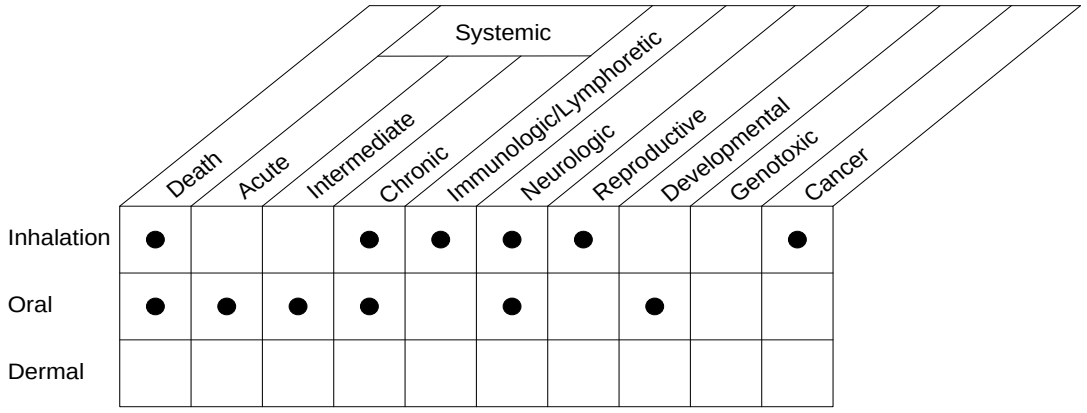
Inorganic manganese toxicity has been investigated in numerous animal studies, both by the oral and the inhalation routes. These studies have included most end points of potential concern. The dermal route for inorganic manganese has not been investigated, but there is no evidence that this exposure pathway is a human health concern. Dermal contact to MMT is expected to occur mainly in occupational settings, and no human dermal contact with mangafodipir is expected to occur. In addition, organic compounds are degraded to some extent in the environment. Thus, dermal effects from organic manganese compounds are not expected to be of great concern for the general population or to persons near hazardous waste sites.

3.12.2 Identification of Data Needs

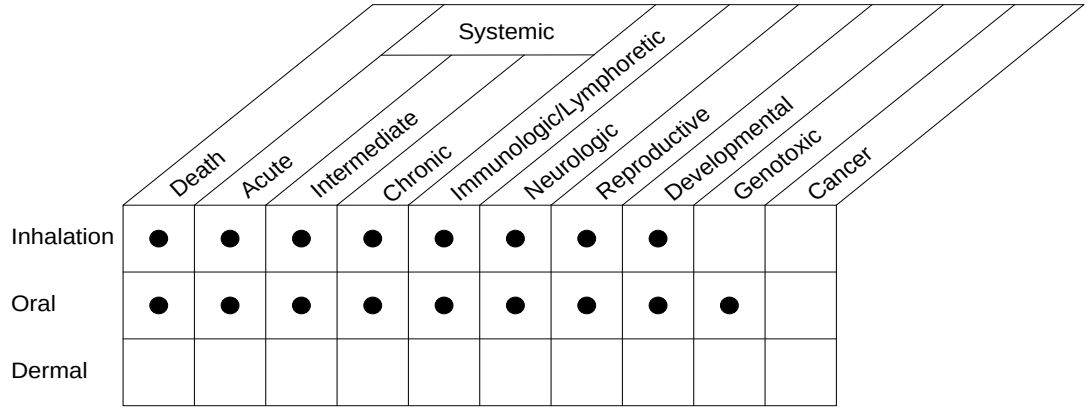
Presented below is a brief review of available information and a discussion of research needs. Although data are lacking, dermal studies to inorganic manganese are not discussed since there is no evidence that this exposure pathway is a human health concern.

Acute-Duration Exposure. Studies in animals and humans indicate that inorganic manganese compounds have very low acute toxicity by any route of exposure. An exception is potassium permanganate, which is an oxidant that can cause severe corrosion of skin or mucosa at the point of contact (Southwood et al. 1987). Acute inhalation exposure to high concentrations of manganese dusts (manganese dioxide, manganese tetroxide) can cause an inflammatory response in the lung, which can

Figure 3-10. Existing Information on Health Effects of Inorganic Manganese



Human



Animal

● Existing Studies

lead to impaired lung function (Maigetter et al. 1976; Shiotsuka 1984). However, this response is characteristic of nearly all inhalable particulate matter (EPA 1985d) and is not dependent on the manganese content of the particle. Large oral doses of highly concentrated solutions of manganese salts given by gavage can cause death in animals (Holbrook et al. 1975; Kostial et al. 1978; Smyth et al. 1969), but oral exposures via food or water have not been found to cause significant acute toxicity (Gianutsos and Murray 1982; NTP 1987a, 1987b). Since the acute database is incomplete and studies demonstrating a dose-response are not available, an acute MRL was not derived. In order to derive acute MRL values, further studies would be helpful to define the threshold for adverse effects following acute exposure to manganese. However, any MRL derived for the oral route would have to take into consideration that manganese is an essential nutrient.

Acute-duration exposure studies in animals exposed to MMT via inhalation or via a dermal pathway are lacking. The dermal pathway is very important, because MMT in gasoline that may be spilled on the skin could penetrate and become absorbed. Although the photolability of the compound is an important obstacle for any animal study, carefully planned and executed analyses of the toxicity of this compound to animal models through these exposure pathways are needed.

The likelihood for exposure to mangafodipir is small and clinical trials in humans have shown a great tolerance for a controlled exposure to the compound. Toxicity studies in several different animal species have been performed, including reproductive and developmental studies (and more specifically, teratogenic analysis). Although behavioral data in the young who have been exposed during gestation are relatively limited, human gestational exposure to this compound is not believed to be very likely. Reports of neurological effects have been limited to complaints of headaches in clinical trials. Further evaluation of these effects relative to the distribution of manganese to the brain during clinical use is warranted. Mangafodipir is administered intravenously, which bypasses homeostatic control of the compound. Although animal studies indicate that a single, clinical dose does not cause accumulation of manganese in the brain for longer than 2 weeks (Gallez et al. 1997), human studies have not monitored central nervous system distribution of manganese following mangafodipir injection for longer than half an hour (Lim et al. 1991). In addition, given the neurotoxic effects of excess manganese, evaluation of patients treated with mangafodipir for neurological sequelae are needed.

Intermediate-Duration Exposure. Intermediate-duration inhalation exposure of humans to manganese compounds can lead to central nervous system effects (Rodier 1955). However, reliable estimates of intermediate-duration NOAELs or LOAELs for neurotoxicity in humans are not available.

Intermediate-duration inhalation studies in animals have yielded NOAEL and LOAEL values for biochemical and neurobehavioral effects (EPA 1977; Morganti et al. 1985; Ulrich et al. 1979a, 1979b), but the range of exposure levels associated with these effects is too wide (an order of magnitude) to define a threshold. Although neurological effects were observed in animals, symptoms characteristic of manganese toxicity (e.g., ataxia, tremor, etc.) are not typically observed in rodent species (with the exception of one study in which ataxia was seen only transiently) (Kristensson et al. 1986). Although other rodent studies indicated decreases in motor activity (Gray and Laskey 1980; Komura and Sakamoto 1991), increased activity and aggression (Chandra 1983; Shukakidze et al. 2003), delayed reflexes (Ali et al. 1983a), or deficits in learning (Shukakidze et al. 2003; Vezér et al. 2005, 2007) the effects are not consistent and are observed over a wide dose range. For these reasons, it is concluded that these data are not sufficient to derive an intermediate-duration inhalation MRL. Epidemiological studies in occupationally exposed human populations that help define the intermediate-duration exposure levels that are associated with neurological effects would be valuable.

Intermediate-duration oral exposure of humans to manganese has been reported to cause neurotoxicity in two cases (Holzgraefe et al. 1986; Kawamura et al. 1941), but the data for quantitating exposure levels are too limited to define the threshold or to judge whether these effects were due entirely to manganese exposure. An epidemiological investigation of people who have ingested high levels of manganese may provide valuable information on the health risk of intermediate-duration oral exposure and may provide sufficient dose-response data from which to derive an MRL. Additional oral studies in animals including rodents may be valuable in revealing cellular and molecular mechanisms of manganese neurotoxicity; studies on nonhuman primates would probably be the most helpful in estimating a MRL because they appear to be the most suitable animal model for manganese-induced neurological effects comparable to effects observed in humans. However, any MRL derived for the oral route would have to take into consideration that manganese is an essential nutrient and account for manganese intake from daily dietary sources.

Intermediate-duration studies of inhalation and oral exposure to MMT in humans and animals are lacking. Animal studies of this duration evaluating systemic toxicity from exposure to MMT and typical environmental concentrations of its combustion products would be helpful to determine body burdens that might be anticipated for the general population in areas that use this compound. Further, these studies would be helpful in determining mechanisms of toxicity and expected adverse effects in exposed populations.

Due to the nature of mangafodipir administration, which typically occurs only once in a subject, no intermediate-duration studies in humans have been identified for this compound. Although there are a few intermediate-duration studies in animals (Grant et al. 1997a; Larsen and Grant 1997; Treinen et al. 1995), they have focused primarily on reproductive and developmental effects. Studies of the potential neurological effects of exposure to this compound are lacking, although the reason for this may be due to the lack of evidence that the compound distributes in the central nervous system. As discussed previously, the exposure to mangafodipir is expected to be very limited due to the compound's clinical use. There are no identified data needs for this compound.

Chronic-Duration Exposure and Cancer. As discussed in Sections 2.3 and 3.2.1.4, and Appendix A, a number of epidemiological studies have reported psychological or neurological effects of exposure to low levels of manganese in the workplace (Bast-Pettersen et al. 2004; Beuter et al. 1999; Blond and Netterstrom 2007; Blond et al. 2007; Bouchard et al. 2003, 2005, 2007a, 2007b; Chia et al. 1993a, 1995; Crump and Rousseau 1999; Deschamps et al. 2001; Gibbs et al. 1999; Iregren 1990; Lucchini et al. 1995, 1999; Mergler et al. 1994; Myers et al. 2003a, 2003b; Roels et al. 1987a, 1992, 1999; Wennberg et al. 1991) or in environmental media close to manganese-emitting industries (Lucchini et al. 2007; Mergler et al. 1999; Rodríguez-Agudelo et al. 2006). Some of these studies have found statistically significant differences between exposed and non-exposed groups or significant associations between exposure indices and neurological effects (Bast-Pettersen et al. 2004; Chia et al. 1993a; Iregren 1990; Lucchini et al. 1995, 1999; Mergler et al. 1994; Roels et al. 1987a, 1992; Wennberg et al. 1991), whereas others have not found significant associations (Deschamps et al. 2001; Gibbs et al. 1999; Myers et al. 2003a, 2003b; Young et al. 2005). Table A-3 in Appendix A summarizes results from these studies.

Additional studies involving follow-up evaluation of previously exposed occupational cohorts may be useful to provide information on threshold levels that are correlated with observed preclinical effects. Additional studies of populations living close to manganese-emitting industries may be useful to better describe neurotoxicological potentials of low-level exposure to air-borne manganese.

In early animal studies, intermediate or chronic inhalation exposure of monkeys and rats to manganese dusts did not produce neurological signs similar to those seen in humans (Bird et al. 1984; EPA 1983c; Ulrich et al. 1979a, 1979b). For example, Ulrich et al. (1979a) reported that monkeys continually exposed for 9 months to aerosols of manganese dioxide at concentrations as high as 1.1 mg manganese/m^3 showed no obvious clinical signs of neurotoxicity, no histopathological changes in brain tissues, and no evidence for limb (leg) tremor or electromyographic effects on flexor and extensor

muscles in the arm. However, in a chronic study with Rhesus monkeys, decreased levels of dopamine were found in several regions of the brain (caudate and globus pallidus) (Bird et al. 1984). Behavioral tests detected signs of neurological effects in mice (increased open-field activity and decreased maternal pup retrieval latency), although these are only seen at relatively high exposure levels (60–70 mg manganese/m^3) (Lown et al. 1984; Morganti et al. 1985).

Other animal intermediate-duration studies provide evidence for associations between decreased neuronal cell counts in the globus pallidus and neurobehavioral changes (increased locomotor activity) in rats exposed by inhalation for 13 weeks to a mixture of manganese phosphate/sulfate (at 1.05 mg manganese/m^3) or manganese sulfate alone (at concentration between 0.009 and 0.9 mg manganese/m^3), but not to manganese phosphate alone at concentrations up to 1.1 mg manganese/m^3 (Normandin et al. 2002; Salehi et al. 2003, 2006; Tapin et al. 2006). Other 13-week rat inhalation exposure studies reported increased brain manganese concentrations and increased locomotor activity after exposure to 3.75 mg manganese/m^3 as metallic manganese (St-Pierre et al. 2001) and increased brain manganese concentrations with no increases in olfactory bulb, cerebellar, or striatal concentrations of glial fibrillary acidic protein (GFAP) after exposure to 0.5 mg manganese/m^3 as manganese sulfate or 0.1 mg manganese/m^3 as manganese phosphate (Dorman et al. 2004b). Other animal studies have examined the influence of inhalation exposure to manganese sulfate on biochemical end points associated with oxidative stress or inflammation in the brain of rats (Erikson et al. 2005, 2006; HaMai et al. 2006; Taylor et al. 2006) and monkeys (Erikson et al. 2007). The results from these studies indicate that acute- or intermediate-duration inhalation exposure to manganese sulfate concentrations ranging from about 0.1 to 1 mg manganese/m^3 can differentially affect brain biochemical markers of neurotoxicity, but understanding of the neurotoxic mechanism of manganese is inadequate to confidently define any one of the observed changes as biologically adverse.

Chronic inhalation studies in animal models (Bird et al. 1984; EPA 1977; Newland et al. 1989; Olanow et al. 1996) indicate that while non-human primates are very sensitive to the neurological effects of manganese at very low doses (depending on exposure route), rodent models do not exhibit the same neurological symptoms as humans and monkeys despite the administration of high doses through inhalation, oral, and intravenous exposure routes. Although there is an apparent difference in susceptibility, neurological effects have been observed in rodents treated with manganese. Additional studies in animals could be valuable to increase our understanding of the mechanism of manganese-induced disease and the basis for the differences between humans and animals.

Some data on neurological or other health effects in humans from repeated or chronic oral intake of manganese exist (Bouchard et al. 2007c; Cawte et al. 1987; He et al. 1994; Holzgraefe et al. 1986; Kawamura et al. 1941; Kilburn 1987; Kondakis et al. 1989; Vieregge et al. 1995; Wasserman et al. 2006; Wright et al. 2006; Zhang et al. 1995). The majority of these studies are limited by uncertainties in the exposure routes, total exposure levels, duration of exposure, or the influence of other confounding factors; none of these studies adequately assessed daily dietary manganese intake. Five studies (Bouchard et al. 2007c; He et al. 1994; Sahni et al. 2007; Wasserman et al. 2006; Zhang et al. 1995) indicate concentrations of manganese in drinking water that may be associated with preclinical neurological effects in children, but the studies have several limitations.

As discussed in Section 2.3, no oral MRLs were derived for acute-, intermediate-, or chronic-duration oral exposure to manganese, even though the limited human data and extensive animal data clearly identify neurobehavioral changes as the most sensitive effect from intermediate- and chronic-duration oral exposure to excess inorganic manganese. However, inconsistencies in the dose-response relationship information across studies evaluating different neurological end points under different experimental conditions in different species, as well as a lack of information concerning all intakes of manganese (e.g., dietary intakes plus administered doses), make it difficult to derive intermediate- or chronic-duration MRLs using standard MRL derivation methodology from the animal studies. An interim guidance value of 0.16 mg manganese/kg/day is recommended for ATSDR public health assessments. The interim guidance value is based on the Tolerable Upper Intake Level for adults of 11 mg manganese/day established by the U.S. Food and Nutrition Board/Institute of Medicine (FNB/IOM 2001) based on a NOAEL for Western diets. The interim guidance value is necessary because of the prevalence of manganese at hazardous waste sites and the fact that manganese is an essential nutrient.

Additional chronic oral studies, especially epidemiological studies in populations exposed to high levels of either inorganic and organic manganese in the environment, particularly the combustion products of MMT in areas of high traffic density, would be valuable for evaluating the potential for adverse effects from oral exposure to excess manganese from the environment in addition to that ingested through dietary intake.

No studies or anecdotal reports were located that described cancer associated with exposure of humans to inorganic manganese. Chronic oral exposure of rats and mice to high doses of manganese sulfate has provided equivocal evidence of carcinogenic potential (NTP 1993); however, the lack of evidence for the

carcinogenic potential of manganese in humans and the equivocal evidence in animals suggest that the potential for cancer may be low. Further animal studies are not needed at this time.

MMT has not been found to induce tumor formation in rodents (Witschi et al. 1981) and additional studies measuring this end point would be useful to corroborate the limited database. Though no studies of carcinogenesis involving mangafodipir exposure were identified, there are no data needs regarding this end point with this compound.

Genotoxicity. One study was located regarding the genotoxic effects of inorganic manganese in humans. An increase in chromosomal aberrations was observed in welders exposed to manganese; however, the welders were also exposed to nickel (known to cause chromosomal aberrations) and iron, so the observed increase could not be attributed solely to manganese (Elias et al. 1989). Some *in vivo* studies in fruit flies and rats have been negative (Dikshith and Chandra 1978; Rasmuson 1985; Valencia et al. 1985), but manganese has been found to be clastogenic in mice (Joardar and Sharma 1990). *In vitro* studies in bacteria, yeast, and cultured mammalian cells have yielded mixed, but mainly positive, results (Casto et al. 1979; De Méo et al. 1991; Joardar and Sharma 1990; Kanematsu et al. 1980; Nishioka 1975; NTP 1993; Oberly et al. 1982; Orgel and Orgel 1965; Singh 1984; Ulitzur and Barak 1988; Wong and Goeddel 1988; Zakour and Glickman 1984). Additional studies, especially in cultured mammalian cells, heritable cell types, or in lymphocytes from exposed humans, would be valuable in clarifying the genotoxic potential of manganese. As for organic manganese, no genotoxicity studies were located regarding MMT and studies measuring this end point are needed. Genotoxicity studies for mangafodipir have shown negative effects (Grant et al. 1997a).

Reproductive Toxicity. Men who are exposed to manganese dust in workplace air report decreased libido and impotency (Emara et al. 1971; Mena et al. 1967; Rodier 1955), and may suffer from sexual dysfunction (Jiang et al. 1996b) and decreased sperm and semen quality (Wu et al. 1996). In addition, studies in animals indicate that manganese can cause direct damage to the testes (Chandra et al. 1973; Seth et al. 1973). While the Jiang et al. (1996b) study suggests testicular damage in occupationally exposed men, additional epidemiological studies involving these subjects or other exposed groups to more fully evaluate reproductive function would be valuable. Results from such studies may provide definitive exposure-response data on reproductive function (e.g., impotence, libido, and number of children).

Additional studies in animals are needed to determine whether the testes are damaged directly from exposure to manganese. Information on adverse reproductive effects in women is not available. Data from studies in female animals indicate that manganese can cause post-implantation loss when administered through both oral and subcutaneous exposure routes in female mice and rats (Colomina et al. 1996; Sánchez et al. 1993; Szakmáry et al. 1995; Treinen et al. 1995). To establish more clearly whether or not this is a human health concern, two types of studies would be valuable. First, single-generation reproductive studies of female animals exposed by the inhalation route could be done. Then, if strong evidence for concern is found in animals from these studies, epidemiological studies that included women and men exposed in the workplace would be valuable to assess the effects of manganese on reproductive function.

Developmental Toxicity. There is a growing body of human data on potential developmental effects of excess manganese, although these studies are generally confined to studies of neurodevelopmental effects as observed in children. The incidences of stillbirths and malformations have been studied in an Australian aboriginal population living on an island where environmental levels of manganese are high (Kilburn 1987), but small population size and lack of data from a suitable control group preclude determining whether reported incidence of developmental abnormalities is higher than average. Hafeman et al. (2007) reported high mortality among infants <1 year of age in a Bangladesh population where the drinking water supplied by certain local wells contained high levels of manganese. Two studies investigated neurobehavioral and school performances (He et al. 1994; Zhang et al. 1995) of children exposed to excess levels of manganese in water and food. However, these studies did not report data on either lengths of exposure to the metal or on excess manganese intake compared to control areas. More recent investigations include epidemiological studies that have detected altered behavioral and cognitive performance among children exposed to excess levels of manganese in their local drinking water (Bouchard et al. 2007c; Wasserman et al. 2006). These results suggest the neurotoxic potential of excessive manganese exposure to children, but these studies have uncertainties that preclude the establishment of causal relationships between the observed effects and manganese exposure. The studies are limited in their ability to address several important concerns, such as whether manganese alone is responsible for the observed effects and the contribution of dietary manganese levels as well as inhalation exposure levels and small sample sizes. Studies evaluating developmental effects with clear analysis of exposure levels and duration are needed to estimate dose-response relationships of manganese toxicity in children.

Several developmental studies have been performed in animals, but they are mainly limited to rodent species and have measured limited developmental end points. One study in pregnant mice that inhaled manganese resulted in decreased pup weight and a transient increase in activity (Lown et al. 1984). Other studies have indicated that oral exposure to manganese adversely affects reproductive development in male mice (Gray and Laskey 1980) and rats (Laskey et al. 1982, 1985). A single study on rats involving oral exposure indicated that manganese caused a transient decrease in pup weight and increased activity (Pappas et al. 1997). Another study involving gavage dosing reported skeletal abnormalities in unborn pups, but these effects were resolved in pups allowed to grow to 100 days of age (Szakmáry et al. 1995). Neurobehavioral effects have been shown in neonates given excess manganese orally from PND 1 to 21 (Dorman et al. 2000; Reichel et al. 2006; Tran et al. 2002a). Several studies have shown neurochemical changes in offspring of dams exposed to increased manganese concentrations (Lai et al. 1991; Garcia et al. 2006, 2007) or in neonatal animals dosed with excess manganese (Chandra and Shukla 1978; Deskin et al. 1980, 1981; Dorman et al. 2000). Also of interest is the possibility that developmental manganese exposure may influence the timing of puberty; such results have been observed in studies of both male and female rats (Lee et al. 2006; Pine et al. 2005). Studies conducted in infant Rhesus monkeys found that soy-based infant formulas (which contain higher manganese levels than cow's milk) and a soy-based infant formula supplemented with manganese produced behavioral changes that may be comparable to those implicated in attention deficit-hyperactivity disorders (Golub et al. 2005).

Other studies indicate that injected manganese is more toxic to a developing fetus than inhaled or ingested manganese. Manganese injected subcutaneously or intravenously during the gestation period causes serious effects on skeletal development and ossification, but studies to date using this exposure pathway have not measured neurological deficits in pups or young rodents. The relevance to humans of results from these injection studies is unclear.

The monkey is increasingly regarded as a more appropriate model for neurological end points; however, monkey studies are extremely expensive and will be limited for this reason. Evaluation of appropriate end points in rodent assays by the oral and inhalation route are needed so that these models can be used to increase the body of knowledge of the developmental toxicity of manganese. Further, the one developmental study involving inhalation exposure (Lown et al. 1984) had many complications; additional studies involving neurobehavioral effects in animals following gestational and postnatal exposure to airborne manganese are necessary. A few developmental studies have involved sectioning fetuses to detect internal malformations (Blazak et al. 1996; Grant et al. 1997a; Szakmáry et al. 1995; Treinen et al. 1995). However, these studies have primarily administered the manganese intravenously,

except for Szakmáry et al. (1995). Additional teratogenesis studies that assess bone malformations following inhalation and oral exposures using a wide range of doses are needed given that manganese overexposure affects the developing skeletal system (Blazak et al. 1996; Grant et al. 1997a; Szakmáry et al. 1995; Treinen et al. 1995). In order to improve the accuracy of the development of an oral MRI for manganese, additional developmental neurotoxicology studies using a functional observational battery design and using a wide range of well-established measures in rodents and primates would be useful (Moser 2000).

Immunotoxicity. Studies in animals indicate that injection or consumption of manganese compounds can cause significant changes in the functioning of several cell types of the immune system (NTP 1993; Rogers et al. 1983; Smialowicz et al. 1985, 1987). However, it is not known whether these changes are associated with significant impairment of immune system function. Further studies are needed to determine whether these effects also occur after inhalation exposure in animals or humans. If so, a battery of immune function tests would be valuable in determining if observed changes result in a significant impairment of immune system function.

Neurotoxicity. Studies in humans exposed to high levels of manganese dust in the workplace provide clear evidence that the chief health effect of concern following manganese exposure is injury to the central nervous system (Emara et al. 1971; Mena et al. 1967; Rodier 1955; Schuler et al. 1957; Smyth et al. 1973). Quantitative data on exposure levels for chronic durations are sufficient to identify a LOAEL for preclinical neurological effects (Iregren 1990; Roels et al. 1987a, 1992), and some of these data have been used to estimate a NOAEL using benchmark dose analysis (Iregren 1990; Roels et al. 1992). These NOAEL estimates are comparable to a NOAEL for early neurological effects recently reported by Gibbs et al. (1999). Thus, no additional epidemiological studies to characterize effects in workers exposed to manganese via inhalation appear necessary at this time. Two recent studies investigated longitudinally whether manganese-induced preclinical effects in workers previously evaluated were reversible (Crump and Rousseau 1999; Roels et al. 1999). Improved performance was observed only in workers exposed to the lowest levels of manganese and effects in others neither improved nor worsened. High variability in the results of neurobehavioral testing from year-to-year was a limitation in the interpretation of results in one of these studies (Crump and Rousseau 1999). Also, the two studies reported conflicting findings on the effect aging the in workers may have had on their performance in certain tests. Additional follow-up studies are needed to further evaluate the reversibility of manganese-induced effects and define threshold exposure levels above which manganese-induced neurological effects are irreversible.

Studies of environmental exposure to airborne manganese report a correlation between high levels of the metal and increased blood manganese levels and subtle neurological effects, particularly in those over 50 years old (Baldwin et al. 1999; Mergler et al. 1999). These studies are also the first to study manganese exposures and potential adverse effects in women. More studies are needed that include analyses of both sexes and assess the relationship between environmental sources of excess manganese, altered manganese body burden, and the potential for adverse effects.

The evidence for neurotoxicity in humans following oral exposure to manganese is inconclusive due to several limitations in the majority of these reports (Bouchard et al. 2007c; Holzgraefe et al. 1986; Kawamura et al. 1941; Kilburn 1987; Kondakis et al. 1989; Wasserman et al. 2006). One report in Japanese adults (Iwami et al. 1994) showed the link between eating food with concentrations of manganese on the high end of the normal range of a typical Western diet (5.79 mg manganese ingested per day) and low intake concentrations of magnesium associated with an increased incidence of motor neuron disease. Four studies in children (Bouchard et al. 2007c; He et al. 1994; Wasserman et al. 2006; Zhang et al. 1995) indicated that those who ingested drinking water and/or who ate food with increased concentrations of manganese (≥0.241 mg/L) for at least 3 years had measurable deficits in performance on certain tests. In addition, the children exposed to manganese performed more poorly in school compared to non-exposed control students (who drank water with manganese concentrations no higher than 0.04 mg/L), as measured in mastery of Chinese, performance in mathematics, and overall grade average (Zhang et al. 1995). These studies show that both adults and children show adverse neurological effects from oral exposure to excess manganese. There are no existing studies showing adverse neurological effects in children as a result of inhalation exposure to the airborne metal, either from locations near work sites or near hazardous waste sites.

There currently exists only one series of studies of potential neurotoxic effects of inhaled environmental manganese (Baldwin et al. 1999; Beuter et al. 1999; Mergler et al. 1999). These exposures most likely resulted from a point source, but the possible contribution of airborne manganese from MMT-gasoline exhaust cannot be excluded. These studies lend support to the possibility that the elderly may be a population susceptible to the neurotoxic effects of excess manganese exposure. Studies are currently needed to further investigate the potential for neurological effects in people, including children, who may have ingested excess amounts of excess manganese from sources in the environment. Clearly defined information on exposure levels and regular dietary intakes should also be captured. Further studies are needed to determine whether manganese from MMT and/or its unique combustion products contribute to

airborne manganese concentrations that can be associated with adverse effects (e.g., respiratory or neurological effects).

Studies in rodents and nonhuman primates indicate that oral intake of high doses of manganese can lead to biochemical and behavioral changes indicative of nervous system effects (Bonilla and Prasad 1984; Chandra 1983; Gupta et al. 1980; Kristensson et al. 1986; Lai et al. 1984; Nachtman et al. 1986), and this is supported by intravenous studies in monkeys (Newland and Weiss 1992). Rodents do not appear to be as susceptible to manganese neurotoxicity as humans; however, a study by Newland and Weiss (1992) indicates that Cebus monkeys would be a reasonable animal model. Further studies in animals may help determine the basis for the apparent differences in route and species susceptibility.

Additional studies in animals concerning the cellular and biochemical basis of manganese neurotoxicity, including a more detailed analysis of precisely which neuronal cell types are damaged and why, are needed. For example, Carl et al. (1993) have performed initial studies investigating the relationship between manganese and the major Mn(II) enzymes (arginase and glutamine synthetase) in epileptic and induced seizures. Further studies may prove helpful in elucidating mechanism(s) of toxic action and could potentially lead to developing methods for mitigating adverse effects induced by manganese.

Epidemiological and Human Dosimetry Studies. As already noted, there are numerous epidemiological studies of workers exposed to manganese dusts in air, and the clinical signs and symptoms of the resulting disease are well established. However, these studies have only involved males and have only involved the inhalation route of exposure. Additional epidemiological studies on populations exposed to manganese dust in the workplace or local environments (e.g., such as near foundries, populations exposed to manganese emissions from MMT-burning automobiles, particularly those living in areas of high-traffic density, and populations exposed to above-average oral intakes [either through water and/or food]) may help to strengthen conclusions on dose-response relationships and no-effect exposure levels. This would be helpful in evaluating potential risks to people who may be exposed to above-average manganese levels near hazardous waste sites.

Biomarkers of Exposure and Effect.

Exposure. Studies in humans have shown that it is difficult to estimate past exposure to manganese by analysis of manganese levels in blood, urine, feces, or tissues (Roels et al. 1987b; Smyth et al. 1973; Valentin and Schiele 1983; Yamada et al. 1986). This is the result of several factors: (1) manganese is a

normal component of the diet and is present in all human tissues and fluids, so above average exposure must be detected as an increase over a variable baseline; (2) manganese is rapidly cleared from the blood and is excreted mainly in the feces, with very little in the urine; and (3) manganese absorption and excretion rates are subject to homeostatic regulation, so above average exposures may result in only small changes in fluid or tissue levels. Probably the most relevant indicator of current exposure is manganese concentrations in tissues, but at present, this can only be measured in autopsy or biopsy samples. Studies on new, noninvasive methods capable of measuring manganese levels *in vivo*, either in the whole body or in specific organs (e.g., brain), would be very helpful in identifying persons with above average exposure. Dorman et al. (2006b) evaluated the use of the pallidal index (PI—ratio of hyperintensities in the globus pallidus and the adjacent subcortical frontal white matter) and the T1 relaxation rate (R1) from MRI to reflect manganese concentrations determined by analytical chemistry in brain regions and concluded that R1 can be used to estimate regional brain manganese concentrations and be used as a reliable biomarker of occupational manganese exposure.

Effect. The principal biological markers of toxic effects from manganese exposure are changes in the levels of various neurotransmitters and related enzymes and receptors in the basal ganglia (Bird et al. 1984; Bonilla and Prasad 1984; Eriksson et al. 1987a, 1987b). Noninvasive methods to detect preclinical changes in these biomarkers or in the functioning of the basal ganglia need to be developed to help identify individuals in whom neurological effects might result. Research to determine the correlation between urinary excretion levels of neurotransmitters, neurotransmitter metabolites, and/or 17-ketosteroids (Bernheimer et al. 1973; Rodier 1955; Siqueira and Moraes 1989) and the probability or severity of neurological injury in exposed people is also needed. Measurements of MnSOD as a biomarker of effect may also be helpful (Greger 1999), but there is a lack of information concerning the relationship of this enzyme to manganese toxicity.

Research in the use of Clara cell protein CC16 may be useful in identifying populations at risk from exposure to MMT; however, the majority of exposure to this compound is expected to arise from inhalation and ingestion of its combustion products. Therefore, increased use of MMT in gasolines necessitates the development of biomarkers of exposure to inorganic manganese compounds, as discussed previously.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of manganese absorption, distribution, and excretion have been studied in both humans and animals. The oral absorption rate is about 3–5% in humans (Davidsson et al. 1988, 1989a; Mena et al. 1969), but the rate

may vary depending on age and dietary iron and manganese intake levels (Chandra and Tandon 1973; Diez-Ewald et al. 1968; Rehnberg et al. 1982; Thomson et al. 1971). Information is needed on the relative proportion of manganese that is absorbed via the gut following mucociliary transport of particles from the lung to the stomach. The oral absorption rate may depend on the chemical form of manganese ingested, but data on this are sparse. Data on the differences in uptake as a function of chemical species (manganese dioxide, manganese tetroxide) and particle size would also be valuable in assessing human health risk from different types of manganese dusts. Absorption of manganese deposited in the lung is expected to be higher for soluble forms of manganese compared with relatively insoluble forms of manganese (Aschner et al. 2005; Roels et al. 1997). Results consistent with nasal uptake of manganese and transport to the brain along neuronal tracts have been obtained in several animal studies (Brenneman et al. 2000; Dorman et al. 2001a, 2002a; Elder et al. 2006; Fechter et al. 2002; Henriksson et al. 1999; Lewis et al. 2005; Normandin et al. 2004; Tjälve and Henriksson 1999; Tjälve et al. 1996; Vitarella et al. 2000). Following nasal instillation of solutions of manganese chloride or sonicated suspensions of ultrafine insoluble manganese oxide particles to rats, similar manganese concentrations were found in the brain olfactory bulb (Elder et al. 2006). These results suggest that ultrafine particles can be distributed from the nasal mucosa to the brain olfactory bulb. Absorption of manganese deposited in the lung or nasal mucosa of rats is expected to be influenced by iron status, with enhanced absorption under iron-deficient conditions and diminished absorption under iron-excess conditions (Thompson et al. 2006, 2007).

Manganese appears to be distributed to all tissues, including the brain (Aschner et al. 2005, 2007; Kristensson et al. 1986; Rehnberg et al. 1980, 1981, 1982). Inhaled manganese appears to be distributed more extensively to the brain than ingested manganese and there are differences in distribution between different forms of manganese (manganese chloride compared with manganese dioxide or manganese phosphate) (Dorman et al. 2001a, 2004b; Roels et al. 1997). Addtional research would be useful in understanding how particle size and solubility of manganese forms influence distribution of manganese to and within the brain. In addition, the metabolism of manganese (specifically, the degree and the rate of oxidation state interconversions) has not been thoroughly investigated. Data on this topic are needed to understand the mechanism of manganese toxicity and would help in evaluating the relative toxicity of different manganese compounds. Excretion of manganese is primarily through the feces (Drown et al. 1986; Klaassen 1974; Mena et al. 1969); because the rate of excretion is an important determinant of manganese levels in the body, further studies would be valuable on the biochemical and physiological mechanisms that regulate manganese excretion.

Additional studies would be useful to more fully elucidate the pharmacokinetic mechanisms responsible for uptake, distribution, and excretion in humans and animals, including studies to determine the following: control rates and processes for uptake of ingested manganese by the intestines and liver, including uptake rates of protein-bound forms by the liver; oxidation rates of manganese in the blood and tissues; relative speciation of Mn(II vs. III) in blood transport mechanisms into the central nervous system, including transfer rates; competition between manganese and iron in terms of transport processes; and distribution following long-term exposures to assess potential storage depots.

Andersen et al. (1999) suggested that an approach to setting acceptable exposure levels for an essential, but neurotoxic, nutrient such as manganese could be based on predicting exposure levels by any route that would increase brain manganese concentrations to a small fraction (e.g., 10–25%) of the variation observed in the general human population. Reliable and validated multiple-route PBTK models for multiple species, including humans, are needed to take this approach to setting acceptable exposure levels. Efforts to develop such models in rats have been recently described (Leavens et al. 2007; Nong et al. 2008; Teeguarden et al. 2007a, 2007b, 2007c). Continued development of these models and extension of them to nonhuman primates and humans would be needed to establish MRLs for manganese by this alternative approach.

Data on the pharmacokinetics of mangafodipir are sufficient for environmental assessment purposes. Additional studies concerning absorption, distribution, metabolism, and excretion of MMT, via inhalation, ingestion, and dermal exposures, would be very helpful.

Comparative Toxicokinetics. Several papers have reviewed the fairly extensive literature showing differences in the expression of manganese neurotoxicity in humans, nonhuman primates, and rodents (Aschner et al. 2005; Gwiazda et al. 2007; Newland et al. 1999). Aschner et al. (2005) concluded that manganese-exposed monkeys show overlapping effects to those observed in patients with manganism (e.g., retention of manganese in the basal ganglia and loss of dopamergic neurons), but similar changes in regional brain manganese concentrations, neurochemical concentrations, and neuropathological effects have been observed less consistently in rodents. Likewise, Gwiazda et al. (2007) concluded from their analysis of estimated internal cumulative doses associated with neurobehavioral, histological, and neurochemical changes in manganese-exposed animals that the range of adverse internal cumulative doses extended more than 2 orders of magnitude above the lowest estimated doses associated with subtle neurological deficits in manganese-exposed workers. The reasons for these differences are poorly understood, but may be due to interspecies differences in toxicokinetics or toxicodynamics (i.e.,

differences in tissue sensitivities). Research to further develop PBTK models in rats that have been recently described (Leavens et al. 2007; Nong et al. 2008; Teeguarden et al. 2007a, 2007b, 2007c) and extend them to nonhuman primates and humans may be useful to increase understanding of interspecies differences in manganese neurotoxicity.

Methods for Reducing Toxic Effects. In general, the methods which provide the greatest likelihood of reducing toxic effects are the same as those aimed at reducing body burden (see section 3.11.2). The recommended methods for the mitigation of manganese toxicity (manganism) are mainly supportive (Schonwald 2004). Administration of anti-Parkinson drugs, such as levo-dopa, is of little use (Calne et al. 1994; Chu et al. 1995; Cook et al. 1974; Schonwald 2004; Huang et al. 1989; Leikin and Paloucek 2002). Chelation therapy with agents such as ethylenediaminetretraacetic acid (EDTA) has reportedly been effective in reducing some of the symptoms (Schonwald 2004; Haddad and Winchester 1990), but was not effective in all cases (Crossgrove and Zheng 2004; Jiang et al. 2006). Studies on the efficacy of newly developed methods to reduce the toxic effects of manganese are needed. The available data indicate that para-aminosalicylate has been successfully used to treat neurological symptoms of manganese poisoning in several patients (Shuqin et al. 1992; Jiang et al. 2006). The use of the antioxidant vitamin E has also been proposed to mitigate manganese-induced effects (Parenti et al. 1988). Additional studies on the efficacy of these treatments are needed. Further evaluation for the mitigation of effects from excess exposure to manganese is also needed.

Methods for reducing toxic effects have not been identified for MMT.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Children have been identified as a potentially susceptible population because of their high absorption and/or retention of manganese as compared to adults. Although some available studies indicate that tissue concentrations of human fetuses are comparable to adults, animal studies indicate that neonates retain higher tissue concentrations than adult animals. Researchers hypothesize that this increased retention of manganese may lead to neurotoxicity. Existing data indicate that the adverse neurological effects of manganese overexposure from intravenous and oral sources are qualitatively similar in children and adults. One study has reported that neonates are more susceptible to the effects of oral exposure to excess manganese than adults (Dorman et al. 2000). Additional quantitative information on the levels of

manganese that result in adverse effects in children as compared to adults for inhalation, oral, and intravenous exposures are needed. Further, analysis of existing data from effects observed in the clinical setting might be helpful.

There are inadequate data on the pharmacokinetics of manganese in children. Although two studies provided typical serum manganese levels in differing ages of healthy children (Alarcón et al. 1996; Rükgauer et al. 1997), no studies have provided any data on the distribution of manganese in infants or adolescents. Studies in animals, particularly nonhuman primates, are needed to clearly elucidate the pharmacokinetic handling of manganese in neonates and the young (absorption, metabolism, distribution, elimination). There are no PBPK models for children, embryos, fetuses and pregnant women, infants and lactating women, or adolescents. Such models would be very informative if they could assist in the identification of depots for manganese storage under conditions of excess exposure, as well as the nutritional needs of these age groups for the compound. One study was available that would provide information on the concentrations of manganese that might be found in the developing fetus of a highly-exposed mother (Jarvinen and Ahlström 1975). Further studies of this nature, especially those that measure neurological end points in live offspring following excess exposure, are needed. Similarly, data are needed to determine whether increased amounts of manganese might be present in the breast milk of a mother with significantly elevated blood or tissue manganese concentrations.

There are likely to be multiple mechanisms of manganese toxicity and most of these have probably been elucidated. However, there is a deficiency in our knowledge of how these mechanisms act singly or in combination to explain the different functional deficits observed in children versus adults. There are inadequate data to determine whether metabolism of manganese is different in children than in adults. Manganese is necessary for normal functioning of certain enzymes. However, there are no definitive data to indicate that children might need more manganese than adults for normal body processes. A few studies suggest that children may have a higher need for manganese than adults, based on the increased retention of manganese in the brains of certain neonatal animals, but this hypothesis has not been proven. Additional studies are necessary to determine the nutritional requirements of children for manganese, especially in infants for which FNB/IOM has not provided any guidelines.

Studies indicate that children exposed to increased concentrations of inorganic manganese, either via the diet, due to inability to clear the compound from the body or through parenteral nutrition, develop neurological dysfunction similar to that of adults (Devenyi et al. 1994; Fell et al. 1996; He et al. 1994; Zhang et al. 1995). Other data exist that indicate that children may not be as susceptible as adults to the

adverse neurological effects of inorganic manganese (Kawamura et al. 1941), but the limitations in this report make predictions about susceptibility inconclusive. Additional animal studies comparing the potential for inorganic manganese to induce neurological effects in different age groups are needed to help understand the susceptibility of the young compared to adults.

The mechanism of action of inorganic manganese toxicity has not been identified. Studies in humans indicate that children and adults with increased manganese deposition in the globus pallidus and other basal regions suffer neuromuscular deficits. It has been suggested that manganese accelerates the autoxidation of catecholamines and contributes to oxidative stress in these affected regions of the brain. Further research is needed to more completely elucidate the mechanism of inorganic manganese toxicity.

There are no dependable biomarkers of exposure or effect that are consistently used in a clinical setting. However, MRI scans have been used in both adults and children to determine whether manganese is accumulating in certain brain regions. More data are needed to determine the sensitivity and specificity of this method.

Available data do not indicate that there are any interactions of manganese with other compounds that occur only in children. Interactions with compounds in adults are expected to also occur in children. Data concerning the significance of any interactions of manganese with other compounds are needed.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies pertaining to manganese have been identified and are shown in Table 3-20.

Table 3-20. Ongoing Studies on Manganese

Investigator	Affiliation	Research description	Sponsor
Aschner, Judy L	Vanderbilt University	Brain manganese deposition in high risk neonates	National Institute of Environmental Health Sciences
Aschner, Michael	Vanderbilt University	Mechanisms of manganese neurotoxicity	National Institute of Environmental Health Sciences
Berkowitz, Bruce A	Wayne State University	Manganese-enhanced MRI studies of retinal neovascularization	National Eye Institute
Brain, Joseph D	Harvard University	Manganese, iron, cadmium, and lead transport from the environment to critical organs	National Institute of Environmental Health Sciences
Culotta, Valeria C	Johns Hopkins University	Intracellular pathways of manganese trafficking	National Institute of Environmental Health Sciences
Dees, WL	Texas A&M University	Actions of manganese on neuroendocrine development	National Institute of Environmental Health Sciences
Dietrich, Kim	University of Cincinnati	Early lead exposure, ADHD, and persistent criminality: Role of genes and environment	National Institute of Environmental Health Sciences
Erikson, Keith M	University of North Carolina Greensboro	Neurotoxicology of dietary iron/manganese interactions	National Institute of Environmental Health Sciences
Glasfeld, Arthur	Reed College	Mechanism and specificity in manganese homeostasis	National Institute of General Medical Sciences
Graziano, Joseph H, Grazi	Columbia University	Research description: Health effects and geochemistry of arsenic and manganese	National Institute of Environmental Health Sciences
Guilarte, Tomas R	Johns Hopkins University	Molecular and behavioral effects of low level Mn exposure	National Institute of Environmental Health Sciences
Gunter, Thomas E	University of Rochester	Mitochondrial role in manganese toxicity	National Institute of Environmental Health Sciences
Hu, Howard, MD	Brigham and Women's Hospital	Gene-metal interactions and Parkinson's disease	National Institute of Environmental Health Sciences
Kanthasamy, Anumantha Gounder, G	Iowa State University	Mechanisms of manganese neurotoxicity	National Institute of Environmental Health Sciences
Klimis-Zacas, D	University of Maine	Manganese, arterial functional properties, and metabolism as related to cardiovascular disease	Department of Agriculture Hatch
Klimis-Zacas, D	University of Maine	Manganese, arterial functional properties, and proteoglycan-lipoprotein interactions	Department of Agriculture Hatch
Klimis-Zacas, D	University Of Maine	Manganese, proteoglycan-lipoprotein interactions, and arterial wall functional properties	Department of Agriculture NRI Competitive

Table 3-20. Ongoing Studies on Manganese

Investigator	Affiliation	Research description	Sponsor
Korrick, Susan A	Brigham and Women's Hospital	Metal and organochlorines exposure: Impact on adolescent behavior and cognition	National Institute of Environmental Health Sciences
Liu, Bin	University of Florida	Combined dopaminergic neurotoxicity of manganese and LPS	National Institute of Environmental Health Sciences
Miller, Gary W	Emory University	Neurotoxicity of nanomaterials: Evaluation of subcellular redox state	National Institute of Environmental Health Sciences
Nass, Richard Michael	Vanderbilt University	Molecular genetics of manganese induced dopamine neuron toxicity	National Institute of Environmental Health Sciences
Oberley, Larry W	University of Iowa	Oxidative stress and metabolism research cluster	National Institute of Environmental Health Sciences
Pecoraro, Vincent L	University of Michigan at Ann Arbor	Structural models for multinuclear manganese enzymes	National Institute of General Medical Sciences
Rao, Rajini	Johns Hopkins University	Secretory pathway calcium and manganese pumps	National Institute of General Medical Sciences
Shine, James P	Harvard University	Exposure assessment of children and metals in mining waste	National Institute of Environmental Health Sciences
Smith, Donald R	University of California Santa Cruz	Role of manganese in neurodegenerative disease	National Institute of Environmental Health Sciences
Srinivasan, Chandra	California State University Fullerton	Superoxide dismutases and ionic manganese in aging	National Institute on Aging
Tjalkens, Ronald B	Colorado State University-Fort Collins	Manganese and basal ganglia dysfunction: Role of NO	National Institute of Environmental Health Sciences
Weisskopf, Marc G	Harvard University	Metal neurotoxicity	National Institute of Environmental Health Sciences
Wessling-Resnick, Marianne	Harvard University	Influence of iron status on the neurotoxicity of inhaled manganese	National Institute of Environmental Health Sciences
Williams, Michael T	Children's Hospital Medical Center, Cincinnati	Effect of lead, manganese, and stress during development	National Institute of Environmental Health Sciences
Wright, Robert O, MD	Brigham and Women's Hospital	Metal mixtures and neurodevelopment	National Institute of Environmental Health Sciences
Zheng, Wei	Purdue University West Lafayette	Choroid plexus as a target in metal-induced neurotoxicity	National Institute of Environmental Health Sciences

Source: FEDRIP 2008

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Table 4-1 lists common synonyms, trade names, and other relevant information regarding the chemical identity of manganese and several of its most important compounds.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of manganese is located in Table 4-2.

Table 4-1. Chemical Identity of Manganese and Compounds[a]

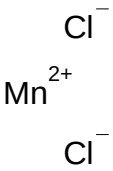
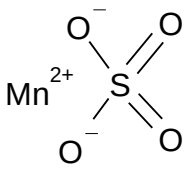
Characteristic	Information		
Chemical name	Manganese	Mn(II) chloride	Manganese sulfate
Synonym(s)	Elemental manganese[b]; collodial manganese[b]; cutaval[b]	Manganese chloride[b]; manganese dichloride	Manganese sulfate
Registered trade name(s)	Cutaval[b]; Mangan[b]	No data	Sorba-spray manganese[b]
Chemical formula	Mn	$MnCl_2$	$MnSO_4$
Chemical structure	Mn		
Identification numbers:			
CAS registry	7439-96-5	7773-01-5	7785-87-7
NIOSH RTECS	009275000[b]	009625000[b]	OP1050000[b]
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	00550[b]	02154[b]	02187[b]
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Manganese and Compounds[a]

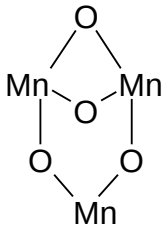
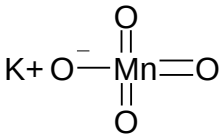
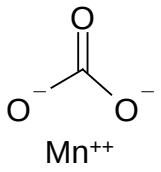
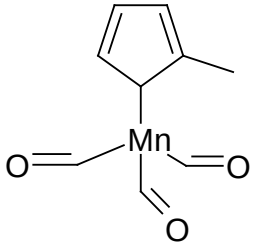
Characteristic	Information		
Chemical name	Manganese (II, III) oxide	Manganese dioxide	Potassium permanganate
Synonym(s)	Manganese tetroxide; mangano-manganic oxide[c]	Manganese peroxide; manganese binoxide; manganese black; battery manganese	Permanganic acid; potassium salt; chameleon mineral[c]
Registered trade name(s)	No data	No data	No data
Chemical formula	Mn_3O_4	MnO_2	$KMnO_4$
Chemical structure			
Identification numbers:			
CAS registry	1317-35-7	1313-13-9	7722-64-7
NIOSH RTECS	OP0900000[b]	No data	SD6475000[b]
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	UN1490[b], IMDG 5.1[b]
HSDB	No data	No data	01218[b]
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Manganese and Compounds[a]

Characteristic	Information		
Chemical name	Mn(II) carbonate	Mangafodipir	Methylcyclopentadienyl manganese tricarbonyl (MMT)
Synonym(s)	Carbonic acid; manganese (2+) salt; manganous carbonate[b]; natural rhodochrosite[b]	Mangafodipir trisodium[d]; MnDPDP[d]	MMT; manganese, tricarbonyl ([1,2,3,4,5-eta]-1-methyl-2,4-cyclopentadien-1yl)-; methylcymantrene; tricarbonyl (2-methylcyclopentadientyl) manganese[b]
Registered trade name(s)	No data	Teslascan[d]; Win 59010[d]	AK-33X; Antiknock-33; CI-2; Combustion Improver-2[b]
Chemical formula	$MnCO_3$	$C_{22}H_{24}MnN_4O_{14}P_2H_3Na_3$	$C_9H_7MnO_3$
Chemical structure		No data	
Identification numbers:			
CAS registry	598-62-9	140678-14-4	12108-13-3
NIOSH RTECS	No data	OO9163250	48184
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	00790[b]	No data	2014
NCI	No data	No data	No data

[a]All information obtained from Sax and Lewis 1987, except where noted.
[b]HSDB 2008
[c]O'Neil et al. 2006
[d]RTECS 2007

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Material Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Manganese and Compounds[a]

Property	Manganese	Mn(II) chloride	Manganese sulfate
Molecular weight	54.94[b]	125.85[b]	151.00[b]
Color	Steel-gray[b]	Pink	Pale rose-red
Physical state	Solid	Solid	Solid
Melting point	1,244 °C[c]	650 °C	700 °C
Boiling point	2,095 °C[b]	1,412 °C[b]	850 °C (decomposes)
Density at 20 °C	7.26 g/cm^3 [b] at 20 °C	2.325 g/cm^3 at 25 °C [b]	3.25 g/cm^3 [d]
Odor	No data	No data	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 20 °C	Decomposes	No data	No data
Acids	Reacts with diluted mineral acids with evolution of hydrogen and formation of divalent manganous salts[b]	No data	No data
Organic solvents	No data	Soluble in alcohol, insoluble in ether	Soluble in alcohol, insoluble in ether
Partition coefficients:			
Log K_{ow}	No data	No data	Not applicable
Log K_{oc}	No data	No data	Not applicable
Vapor pressure at 20 °C	1 Pa at 955 °C[c]	1,000 Pa at 760 °C[c]	No data
Henry's law constant at 25 °C	No data	Not applicable	Not applicable
Autoignition temperature	No data	Noncombustible	No data
Flashpoint	No data	No data	No data
Flammability limits	Flammable and moderately explosive in dust form when exposed to flame[d]	No data	No data
Conversion factors	Not applicable	Not applicable	Not applicable
Explosive limits	Mixture of aluminum and manganese dust may explode in air. Mixtures with ammonium nitrate may explode when heated[d]	No data	No data
Reactivity	Hydrogen[d]; when heated above 200 °C in presence of nitrogen, forms nitrode; violent reaction with NO_2 and oxidants; incandescent reaction with phosphorous, nitryl fluoride, nitric acid[d]	No data	No data

Table 4-2. Physical and Chemical Properties of Manganese and Compounds[a]

Property	Manganese (II, III) oxide	Manganese dioxide	Potassium permanganate
Molecular weight	228.81[b]	86.94[b]	158.03[b]
Color	Brownish-black[b]	Black	Purple
Physical state	Solid	Solid	Solid
Melting point	1,564 °C	Loses oxygen at 535 °C[d]	<240 °C (decomposes)
Boiling point	No data	No data	No data
Density at 20 °C	No data	5.0 g/cm^3 [d]	2.703 g/cm^3
Odor	No data	No data	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 20 °C	Insoluble	Insoluble	No data
Acids	Soluble in hydrochloric acid	Soluble in hydrochloric acid	Soluble in sulfuric acid
Organic solvents	No data	No data	Soluble in acetone
Partition coefficients:			
Log K_{ow}	Not applicable	No data	No data
Log K_{oc}	Not applicable	No data	No data
Vapor pressure at 20 °C	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	Not applicable	Not applicable	Not applicable
Explosive limits	No data	No data	No data
Reactivity	No data	No data	Spontaneously flammable on contact with ethylene glycol

Table 4-2. Physical and Chemical Properties of Manganese and Compounds[a]

Property	Mn(II) carbonate	Mangafodipir trisodium	Methylcyclopentadienyl manganese tricarbonyl (MMT)[f]
Molecular weight	114.95	757.4[e]	218.1
Color	Pink[c]	No data	Yellow to dark orange
Physical state	hexagonal, crystals[c]	Liquid (solution for infusion)	Liquid, solid below 2 °C
Melting point	Decomposes	No data	1.5 °C[d]
Boiling point	No data	No data	232 °C
Density at 20 °C	3.70 g/cm^3 [c]	1.537 g/cm^3 [b]	1.39 g/cm^3
Odor	No data	No data	Faint, pleasant
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 20 °C	Insoluble	459.6 g/L[b]	Insoluble
Acids	Soluble in dilute acid[c]	No data	No data
Organic solvents	No data	23 g/L (methanol); 0.8 g/L (ethanol); 0.6 g/L (acetone); 1.1 g/L (chloroform)[b]	Readily soluble in hydrocarbons and the usual organic solvents including hexane, alcohols, ethers, acetone, ethylene glycol, lubricating oils, gasoline and diesel fuel[b]
Partition coefficients:			
Log K_{ow}	No data	-5.62[b]	No data
Log K_{oc}	No data	No data	No data
Vapor pressure at 20 °C	No data	No data	Ranges from 8 mm Hg at 100 °C to 360.6 mm Hg at 200 °C[b]
Henry's law constant at 25 °C	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	110 °C
Flammability limits	No data	No data	No data
Conversion factors	Not applicable	No data	No data
Explosive limits	No data	No data	No data
Reactivity	No data	No data	Light (decomposes)

[a]All information obtained from Sax and Lewis 1987, except where noted.
[b]O'Neil et al. 2006
[c]Lide 2000
[d]Lewis 2000
[e]RTECS 2007
[f]Data for MMT from NIOSH 2005 unless otherwise noted

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Tables 5-1 and 5-2 list the facilities in each state that manufacture or process manganese, the intended use, and the range of maximum amounts of manganese that are stored on site. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI06 2008). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

Manganese is an abundant element comprising about 0.1% of the earth's crust (Graedel 1978). It does not occur naturally as a base metal, but is a component of over 100 minerals, including various sulfides, oxides, carbonates, silicates, phosphates, and borates (NAS 1973). The most commonly occurring manganese-bearing minerals include pyrolusite (manganese dioxide), rhodocrosite (manganese carbonate), and rhodanate (manganese silicate) (EPA 1984; NAS 1973; Windholz et al. 1983).

Most manganese ore is smelted in electric furnaces to produce ferromanganese, a manganese-iron alloy widely used in the production of steel (EPA 1984; NAS 1973). Approximately 2 tons of manganese ore are required to make 1 ton of ferromanganese (NAS 1973). Production of manganese metal is achieved by aluminum reduction of low iron-content manganese ore, and electrolytically from sulfate or chloride solution (Lewis 2001). Manganese with <0.1% metallic impurities can be produced electrolytically from a manganese sulfate solution (EPA 1984; Lewis 2001).

Manganese compounds are produced either from manganese ores or from manganese metal. For example, manganese chloride is produced by the reaction of hydrochloric acid with manganese oxide (Pisarczyk 2005). Manganese carbonate and manganese sulfate are produced by dissolving manganese carbonate ore (rhodochrosite) or Mn(II) oxide in sulfuric acid (Pisarczyk 2005). Potassium permanganate may be manufactured by the one-step electrolytic conversion of ferromanganese to permanganate, or by a two-step process involving the thermal oxidation of manganese(IV) dioxide of a naturally occurring ore into potassium manganate(VI), followed by electrolytic oxidation to permanganate (Pisarczyk 2005).

Most manganese is mined in open pit or shallow underground mines (EPA 1984; NAS 1973). Manganese ores were previously mined in the United States, but no appreciable quantity has been mined in the United States since 1978 (USGS 2007). The only mine production of manganese in the United States consisted of small amounts of manganiferous material having a natural manganese content of <5%. This type of

Table 5-1. Facilities that Produce, Process, or Use Manganese

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	4	0	99,999	1, 5, 12, 13, 14
AL	93	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	61	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
AZ	36	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	108	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	37	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
CT	25	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
DE	5	100	999,999	1, 3, 4, 5, 8, 10
FL	45	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	62	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14
HI	5	100	99,999	2, 3, 4, 7, 8, 12
IA	94	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	11	1,000	9,999,999	1, 3, 4, 5, 7, 8, 12, 13
IL	169	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	171	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	49	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	96	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	53	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	36	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 14
MD	36	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
ME	21	0	999,999	1, 2, 3, 5, 6, 8, 11, 12, 13
MI	157	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	56	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	76	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	37	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
MT	9	10,000	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12
NC	91	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	16	100	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12
NE	43	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
NH	14	0	49,999,999	1, 5, 7, 8, 11, 12, 13
NJ	65	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
NM	5	1,000	9,999,999	6, 8, 11, 12
NV	32	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	98	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
OH	221	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	72	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OR	57	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PA	212	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	11	100	999,999	2, 3, 4, 7, 8, 11, 12

Table 5-1. Facilities that Produce, Process, or Use Manganese

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
RI	12	0	999,999	2, 3, 4, 8, 9, 11, 12
SC	62	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
SD	29	0	49,999,999	1, 2, 3, 5, 7, 8, 9, 11, 12, 13, 14
TN	99	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	141	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	60	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	58	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VT	4	0	999,999	2, 4, 7, 11, 12
WA	59	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	132	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	44	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WY	11	0	999,999	1, 2, 3, 5, 8, 9, 11, 12, 13, 14

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation component
9. Article component
10. Repackaging
11. Chemical processing aid
12. Manufacturing aid
13. Ancillary/other uses
14. Process impurity

Source: TRI06 2008 (Data are from 2006)

Table 5-2. Facilities that Produce, Process, or Use Manganese Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	12	0	49,999,999	1, 2, 3, 5, 7, 8, 11, 12, 13, 14
AL	141	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	68	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
AZ	55	100	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
CA	100	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	52	100	499,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CT	30	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DC	2	1,000	99,999	12
DE	32	0	9,999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14
FL	88	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	93	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	6	100	999,999	1, 5, 7, 9, 10
IA	90	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	25	0	49,999,999	1, 5, 6, 7, 8, 10, 11, 12, 13
IL	186	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	150	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	68	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	85	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
LA	58	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	28	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
MD	69	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ME	18	0	9,999,999	1, 5, 6, 8, 13, 14
MI	159	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	59	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	79	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	66	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	23	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
NC	116	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	21	1,000	9,999,999	1, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14
NE	49	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
NH	10	0	99,999	1, 2, 3, 5, 7, 8, 9
NJ	86	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	29	100	10,000,000,000	1, 3, 4, 5, 7, 9, 12, 13, 14
NV	33	1,000	499,999,999	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14
NY	113	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	253	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	49	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	48	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Manganese Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PA	243	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	18	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12
RI	5	10,000	999,999	8, 11
SC	91	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	12	100	9,999,999	1, 5, 6, 7, 8, 9, 11, 12, 13, 14
TN	122	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	181	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	71	100	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	64	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VT	3	1,000	99,999	1, 5, 7, 8
WA	72	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	96	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	60	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WY	24	0	999,999	1, 3, 4, 5, 7, 9, 12, 13, 14

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. On-site use/processing
4. Sale/distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation component
9. Article component
10. Repackaging
11. Chemical processing aid
12. Manufacturing aid
13. Ancillary/other uses
14. Process impurity

Source:TRI06 2008 (Data are from 2006)

material was produced in South Carolina for use in coloring brick (USGS 2007). Essentially all manganese ore used in manganese production in the United States is now imported (USGS 2007).

Currently, there are 3,200 facilities in the United States that indicate that they produce, process, or use manganese (TRI06 2008). These facilities are scattered across the United States, with the largest numbers in Ohio (221), Pennsylvania (212), and Indiana (171). Over 3,700 facilities are involved in the distribution or use of manganese or manganese compounds (TRI06 2008). Tables 5-1 and 5-2 list the number of facilities in each state, the ranges of the maximum amounts stored at each facility, and the uses of the material (TRI06 2008).

The organomanganese compound methylcyclopentadienyl manganese tricarbonyl (MMT) is produced in either of the following ways: via the reaction of manganous chloride, cyclopentadiene, and carbon monoxide in the presence of manganese carbonyl and an element of group II or IIIA, or via the reaction of methylcyclopentadiene with manganese carbonyl (EPA 1984; Sax and Lewis 1987). According to data submitted to the EPA by the American Chemistry Council Petroleum Additives Panel, MMT is manufactured by adding methylcyclopentadienyl dimer to a dispersion of sodium metal in diethylene glycol dimethyl ether under a nitrogen environment (EPA 2006b). Keeping the mixture at elevated temperature yields sodium-methylcyclopentadienyl, which is an intermediate in the reaction process. Manganese chloride is added to the stirred mixture containing the sodium methylcyclopentadienyl intermediate. The reaction eventually yields bis(methylcyclopentadienyl)manganese as a second intermediate of the reaction process. The reaction vessel is then pressurized with carbon monoxide, which results in the formation of MMT, which is separated from the reaction mixture via vacuum distillation (EPA 2006b).

No production data from facilities that manufacture or process MMT were found. According to data from the 2007 Directory of Chemical Producers, only one company located in Orangeburg, South Carolina produces MMT in the United States (SRI 2007).

Mn(II) dipyridoxyl diphosphate (MnDPDP), or mangafodipir trisodium, is classified as a drug or therapeutic agent, and no production data were found for it.

5.2 IMPORT/EXPORT

The United States does not produce manganese and is 100% import reliant (USGS 2007). Import and export data for manganese are provided in Table 5-3. Demand for manganese metal comes primarily from the aluminum and steel industry (USGS 2007). Manganese consumption in 2007 was about 13% lower than that of 2006, owing to constant demand by the domestic steel industry and reduction of producer and consumer stocks. From January through August of 2007, domestic steel production was 1.4% lower than that for the same period in 2006 (USGS 2008). The United States imports the bulk of its manganese ore from Gabon, 65%; South Africa, 19%; Australia, 7%; Ghana, 2%; and other nations, 7% (USGS 2007). Ferromanganese is imported from South Africa, 51%; China, 14%; Mexico, 6%; Republic of Korea, 5%; and other nations, 24% (USGS 2007).

There were no data located regarding the import or export of MMT or mangafodipir.

5.3 USE

Metallic manganese (ferromanganese) is used principally in steel production to improve hardness, stiffness, and strength. It is used in carbon steel, stainless steel, high-temperature steel, and tool steel, along with cast iron and superalloys (EPA 1984; NAS 1973). According to data obtained from the U.S. Geological Society (USGS), manganese ore was consumed primarily by eight firms with plants principally in the east and midwest United States (USGS 2008). The majority of ore consumed was associated with steel production, directly in pig iron manufacture and indirectly through upgrading ore to ferroalloys. Additional quantities of ore were used for nonmetallurgical purposes such as production of dry cell batteries, in plant fertilizers and animal feed, and as a brick colorant. Manganese ferroalloys were produced at two smelters, although one operated sporadically throughout the year (USGS 2008). Construction, machinery, and transportation end uses accounted for approximately 24, 10, and 10%, respectively, of manganese demand (USGS 2008). Most of the rest went to a variety of other iron and steel applications. The value of domestic consumption, estimated from foreign trade data, was about $730 million (USGS 2008).

Manganese compounds have a variety of uses. Manganese dioxide is commonly used in production of dry-cell batteries, matches, fireworks, porcelain and glass-bonding materials, amethyst glass, and as the starting material for production of other manganese compounds (EPA 1984; NAS 1973; Venugopal and Luckey 1978). Manganese chloride is used as a precursor for other manganese compounds, as a catalyst in the chlorination of organic compounds, in animal feed to supply essential trace minerals, and in

Table 5-3. Manganese Import/Export Data for 2003–2007

	2003	2004	2005	2006	2007
Imports for consumption[a]					
Manganese ore	347	451	656	572	610
Ferromanganese	238	429	255	358	322
Silicomanganese	267	422	327	400	390
Exports[a]					
Manganese ore	18	123	13	2	2
Ferromanganese	11	9	14	22	33

[a]Data in thousand metric tons gross weight

Source: USGS 2008

dry-cell batteries (EPA 1984). Manganese sulfate is used primarily as a component of fertilizer (60% of total consumption) and as a livestock supplement (30% of total consumption); it is also used in some glazes, varnishes, ceramics, and fungicides (EPA 1984; Windholz et al. 1983). Potassium permanganate's oxidizing power allows it to be used as a disinfectant; an antialgal agent; for metal cleaning, tanning, and bleaching; and as a water purification agent (Lewis 2001). Another common source of manganese is found in the street drug "Bazooka". It is a cocaine-based drug contaminated with manganese-carbonate from free-base preparation methods (Ensing 1985).

MMT is a fuel additive developed in the 1950s to increase the octane level of gasoline and thus improve the antiknock properties of the fuel (Davis 1998; EPA 1984; Lynam et al. 1990; NAS 1973). MMT was introduced into Canada in 1976 and its use increased so substantially that it completely replaced tetraethyl lead in gasoline in that country in 1990 (Zayed et al. 1999a). The major refiners in Canada have voluntarily stopped using MMT, out of concern that its use may harm on-board diagnostic equipment (OBD), which monitors the performance of emissions control devices in the vehicle (ICCT 2004). As a result, as much as 95% of Canadian gasoline is now MMT-free (ICCT 2004). MMT was used as an additive in leaded gasoline in the United States; however, EPA banned its use in unleaded gasoline in 1977 (EPA 1978, 1979a, 1981). In 1995, the ban on MMT use in unleaded gasoline was lifted, and a court decision ordered EPA to register the product for use as a fuel additive (EPA 1995a). Recent data suggest that MMT is currently used only sparsely in the developed world including the United States, although exact quantities are not known (ICCT 2004). Historical data suggest that approximately 70 million pounds of MMT were sold for use in leaded gasoline in the United States between 1976 and 1990 (Veysseyre et al. 1998).

Mangafodipir trisodium (MnDPDP) is used as both a liver- and pancreas-specific contrast agent for magnetic resonance imaging (MRI); it improves lesion detection in MRI of these organs by selectively enhancing the normal parenchyma, but not lesions, so that the contrast between tumorous and normal tissue is increased (Federle et al. 2000).

5.4 DISPOSAL

Manganese is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1998). Disposal of wastes containing manganese is controlled by a number of federal regulations (see Chapter 8).

Disposal of waste manganese into water requires a discharge permit from the EPA (see Chapter 8), but disposal of solid wastes such as manganese metal or manganese compounds is not regulated under current federal law. There are incomplete federal records of this disposal because most, but not all, solid manganese wastes are disposed of by being deposited on land or by being trucked to off-site disposal facilities (TRI06 2008). The total amount of waste manganese disposed of in this way in 2006 was in excess of 200 million pounds (TRI06 2008) (see Tables 6-1 and 6-2).

Manganese and other metals are commonly recycled for future use. In 1998, 218,000 metric tons of manganese were estimated to have been recycled from old scrap, of which 96% was from iron and steel scrap (USGS 2001). In 2007, the USGS reported that manganese was recycled incidentally as a minor constituent of ferrous and nonferrous scrap; however, scrap recovery specifically for manganese was negligible (USGS 2008). No quantitative statistics were provided regarding the amount recovered from steel slag.

No information on disposal of MMT was located.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

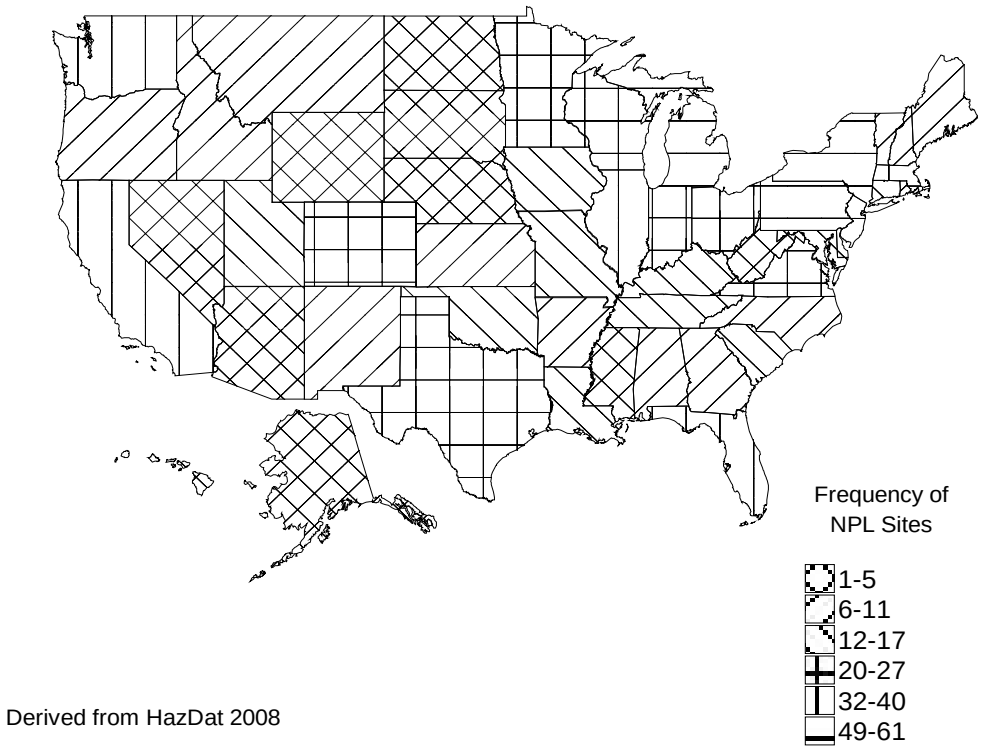
Manganese has been identified in at least 869 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). However, the number of sites evaluated for manganese is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 861 are located within the United States, 5 are located in the Commonwealth of Puerto Rico, 2 are located in the Virgin Islands, and 1 is located in Guam (not shown).

Manganese is ubiquitous in the environment, and human exposure arises from both natural and anthropogenic activities. It occurs naturally in more than 100 minerals with background levels in soil ranging from 40 to 900 mg/kg, with an estimated mean background concentration of 330 mg/kg (Barceloux 1999). Manganese is released to the environment from industrial emissions, fossil fuel combustion, and erosion of manganese-containing soils. Volcanic eruptions can also contribute to levels of manganese in air. Almost 80% of industrial emissions of manganese are attributable to iron and steel production facilities (EPA 2003a). Power plant and coke oven emissions contribute about 20% (EPA 2003a). Manganese may also be released to the environment through the use of MMT as a gasoline additive. Thus, all humans are exposed to manganese, and manganese is a normal component of the human body.

Background levels of manganese in the atmosphere vary widely depending on the proximity of point sources, such as ferroalloy production facilities, coke ovens, and power plants. The estimated average background concentration of manganese in urban areas is approximately 40 ng/m^3, based on measurements obtained in 102 U.S. cities (EPA 2003a; WHO 2004b). Concentrations near source dominated areas were reported to range from 220 to 300 ng/m^3 (WHO 2004b) and rural/remote levels are typically under 10 ng/m^3 (Sweet et al. 1993). Manganese occurs naturally in surface water and groundwater. A median dissolved manganese concentration of 24 µg/L in samples from 286 U.S. rivers and streams was reported (Smith et al. 1987). Natural concentrations of manganese in seawater reportedly range from 0.4 to 10 µg/L (EPA 1984).

The general population is exposed to manganese primarily through food intake. The World Health Organization (WHO) estimates that adults consume between 0.7 and 10.9 mg of manganese per day in the diet, with higher intakes for vegetarians who may consume a larger proportion of manganese-rich nuts, grains, and legumes in their diet as compared to non-vegetarians in the general population (WHO 2004b).

Figure 6-1. Frequency of NPL Sites with Manganese Contamination



Manganese intake from drinking water is substantially lower than intake from food. Using a median drinking-water level of 10 μg/L and an assumption that the average adult drinks 2 L of water/day, an average intake of approximately 0.020 mg/day was estimated (WHO 2004b). Exposure to manganese from air is considered negligible as compared to intake from diet; however, persons in certain occupations may be exposed to much higher levels than the general public (see Section 6.7).

Manganese adsorbed to particulate matter in air can be classified by the size of the particles. Air concentrations can be reported as total suspended particulate matter (TSP), respirable particulates, and fine particulates. In this document, manganese adsorbed to particulate matter <10 microns in aerodynamic diameter is referred to as PM_{10}. The EPA has further divided these tiny particles into "fine" particles of ≤2.5 microns ($PM_{2.5}$) and "coarse" particles of between 2.5 and 10 microns.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

According to the Toxics Release Inventory (TRI), in 2006, a total of 27,094,361 pounds (12,290 metric tons) of manganese was released to the environment from 2,040 large processing facilities (TRI06 2008). An additional 199,804,760 pounds (90,630 metric tons) of manganese compounds were released from 1,748 facilities. Tables 6-1, and 6-2 list the amount of manganese and manganese related compounds, respectively, that were released from all of the facilities that manufacture or process manganese to each medium within each state in 2006 (TRI06 2008). The TRI data should be used with caution because only

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Manganese[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	440	0	0	43,596	0	440	43,596	44,036
AL	46	14,003	2,594	0	311,137	138	39,354	288,519	327,873
AR	28	14,187	202	0	40,397	11,970	14,345	52,410	66,756
AZ	23	1,249	86	0	988,345	5	989,128	557	989,685
CA	52	5,905	446	0	266,849	508	190,728	82,980	273,708
CO	13	673	61	0	14,367	0	686	14,415	15,101
CT	9	6	7	0	550	76	6	633	639
DE	1	0	0	0	14	0	0	14	14
FL	28	1,387	304	0	19,193	10	1,390	19,504	20,894
GA	43	3,256	2,559	0	47,464	10	3,618	49,671	53,289
HI	1	0	0	3	33	0	3	33	36
IA	75	26,407	3,501	0	87,121	387,890	52,459	452,460	504,919
ID	2	206	0	0	1,159,780	0	1,159,986	0	1,159,986
IL	113	16,708	3,288	723	725,350	2,914	17,866	731,117	748,983
IN	142	31,353	5,835	0	487,103	23,334	32,009	515,617	547,626
KS	28	7,838	290	0	1,045,331	159,947	1,013,666	199,740	1,213,406
KY	57	8,743	1,431	0	93,655	16,068	10,660	109,238	119,898
LA	35	11,553	7,316	0	64,028	8,095	17,306	73,686	90,993
MA	16	453	108	0	8,497	737	465	9,329	9,795
MD	12	148	57	0	759	6	148	822	970
ME	5	15	68	0	81	420	20	564	584
MI	101	13,587	3,774	0	418,116	6,311	42,212	399,577	441,789
MN	43	4,752	184	0	86,817	394	4,757	87,390	92,148
MO	59	10,907	1,718	0	20,096	10,164	21,102	21,783	42,885
MS	30	4,955	345	0	67,256	0	8,037	64,518	72,555
MT	3	0	0	0	78,546	0	78,546	0	78,546
NC	58	2,225	140	0	30,064	2,830	2,250	33,009	35,260
ND	7	1,592	7	0	531	0	1,600	530	2,130
NE	17	1,723	307	0	49,079	635	1,770	49,974	51,744
NH	6	87	17,300	0	6,245	0	17,387	6,245	23,632
NJ	10	583	29	0	11,324	0	600	11,336	11,936
NM	1	500	0	0	1,699	0	2,199	0	2,199
NV	11	135	0	0	94,028	0	94,163	0	94,163
NY	43	5,555	8,766	0	320,476	1,182	7,932	328,047	335,979
OH	166	39,047	120,301	2	11,591,066	2,463,430	10,515,399	3,698,447	14,213,846
OK	77	4,384	325	0	62,595	0	10,352	56,952	67,304

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Manganese[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
OR	14	349	0	0	528	0	349	528	877
PA	152	43,170	11,360	0	1,000,943	59,278	375,255	739,495	1,114,751
PR	4	2	0	0	0	16	2	16	18
RI	2	0	0	0	0	0	0	0	0
SC	48	6,328	536	0	85,146	29,788	46,481	75,318	121,799
SD	19	8,727	5	0	26,330	0	16,460	18,602	35,062
TN	62	49,422	1,924	0	348,780	3,943	99,022	305,047	404,069
TX	121	53,231	22,104	5	171,602	624	155,306	92,260	247,566
UT	17	2,559	13	0	747,419	0	738,680	11,311	749,992
VA	29	2,033	608	0	161,608	22,211	2,356	184,105	186,461
WA	26	5,729	42,723	0	139,920	539	51,480	137,431	188,911
WI	171	20,115	8,948	0	2,137,917	12,870	58,935	2,120,915	2,179,850
WV	8	26	1	0	38,324	14	24,026	14,338	38,364
WY	5	193	0	0	71,139	5	71,332	5	71,337
Total	2,040	426,449	269,573	733	23,171,244	3,226,362	15,992,276	11,102,084	27,094,361

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI06 2008 (Data are from 2006)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Manganese Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	5	25,328	750	0	845,025	6,280	871,103	6,280	877,383
AL	68	178,265	875,746	0	5,663,753	2,104,302	5,163,681	3,658,386	8,822,066
AR	50	19,489	441,421	0	1,480,122	989,320	1,844,948	1,085,404	2,930,352
AZ	14	4,047	410,010	0	1,971,519	28,019	2,113,096	300,499	2,413,595
CA	37	7,828	1,059	0	200,104	193	124,029	85,154	209,183
CO	24	5,126	11,022	0	2,246,268	9,100	714,772	1,556,744	2,271,516
CT	10	4,362	1,883	0	60,665	7,840	5,865	68,885	74,750
DC	3	0	4,347	0	6,000	0	10,347	0	10,347
DE	11	4,334	39,657	0	4,092,502	28,305	116,524	4,048,274	4,164,798
FL	37	18,745	202,776	0	3,397,056	33,456	3,360,138	291,895	3,652,032
GA	61	47,377	773,805	0	2,836,912	7,944	3,330,409	335,629	3,666,038
HI	1	38	0	0	26,872	0	38	26,872	26,910
IA	42	41,786	22,496	0	840,340	364,964	227,129	1,042,457	1,269,586
ID	12	841	190,590	0	14,737,870	130	14,679,285	250,146	14,929,431
IL	84	96,010	35,152	0	9,033,549	259,391	5,687,449	3,736,654	9,424,103
IN	79	192,010	93,426	1,900	18,418,915	1,671,366	7,130,422	13,247,195	20,377,618
KS	28	13,257	652	250	244,236	250	220,445	38,200	258,645
KY	47	68,576	147,644	0	1,528,078	119,954	1,660,270	203,982	1,864,252
LA	29	20,544	387,475	0	6,371,936	1,408	6,476,794	304,569	6,781,363
MA	17	1,436	1,331	0	100,634	32,790	61,732	74,459	136,191
MD	26	21,618	90,703	25,571	2,166,200	125,137	2,233,047	196,182	2,429,229
ME	10	2,117	331,758	0	677,049	18,587	792,798	236,713	1,029,511
MI	67	81,060	99,058	2,000	2,612,249	43,241	1,138,887	1,698,721	2,837,608
MN	31	14,598	256,905	0	1,587,019	23,337	1,591,056	290,802	1,881,858
MO	46	13,796	51,704	0	708,194	3,865	418,616	358,943	777,558
MS	33	15,064	288,780	8,506,700	9,204,141	6,158	17,937,765	83,078	18,020,843
MT	9	9,747	29,912	0	1,981,375	46,473	1,849,854	217,652	2,067,506
NC	63	19,836	213,027	0	2,011,149	1,177,640	1,796,233	1,625,420	3,421,652
ND	9	15,474	16,333	0	2,480,954	15,612	1,479,091	1,049,282	2,528,373
NE	22	21,131	500	0	153,009	612,303	161,275	625,668	786,943
NH	1	134	0	0	4,770	0	4,034	870	4,904
NJ	15	3,032	10,005	0	472,763	13,484	31,191	468,093	499,284
NM	6	3,916	1,300	0	828,935	0	834,151	0	834,151
NV	10	12,998	3,611	0	10,169,735	0	9,260,544	925,800	10,186,344
NY	26	4,650	81,183	0	584,743	26,423	261,995	435,004	697,000
OH	138	430,169	642,313	30,514	11,063,512	597,498	6,580,637	6,183,369	12,764,006
OK	32	11,618	48,634	0	750,631	508,644	531,270	788,257	1,319,527

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Manganese Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
OR	23	8,314	144,618	0	2,142,046	323,198	2,004,367	613,809	2,618,176
PA	134	72,526	184,992	0	10,063,261	340,932	5,031,291	5,630,420	10,661,710
PR	6	8,490	401	0	282	0	8,886	287	9,173
RI	1	103	31	0	169	0	134	169	303
SC	44	27,819	378,152	0	6,760,363	6,148	2,292,815	4,879,668	7,172,483
SD	7	38	0	0	27,700	0	22,038	5,700	27,738
TN	53	50,882	293,774	0	16,727,879	38,873	16,041,491	1,069,917	17,111,408
TX	104	66,756	185,907	0	6,283,703	94,244	6,150,141	480,469	6,630,610
UT	20	6,687	761	0	1,271,573	13	1,264,871	14,163	1,279,034
VA	35	19,359	183,002	0	1,522,896	4,563	729,421	1,000,399	1,729,820
VT	1	0	0	0	0	0	0	0	0
WA	25	3,227	187,304	0	814,927	16,167	808,095	213,530	1,021,626
WI	60	23,609	116,184	0	2,533,313	95,152	364,876	2,403,382	2,768,258
WV	26	133,302	13,412	0	1,700,100	24,034	1,325,047	545,801	1,870,848
WY	6	8,493	1,327	0	647,297	0	617,518	39,599	657,117
Total	1,748	1,859,959	7,496,834	8,566,935	172,054,292	9,826,740	137,361,909	62,442,851	199,804,760

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI06 2008 (Data are from 2006)

certain types of facilities are required to report. This is not an exhaustive list. Also, because these data reflect past releases, they may not be representative of current releases at these facilities.

Manganese may also be emitted to the environment through the use of gasoline that contains MMT; however, no data on the amount of MMT that is currently being used in gasoline in the United States were located. No data for releases of mangafodipir to the environment were found. Because mangafodipir is a compound used exclusively in a clinical environmental, it is not expected to be released to the environment and will not be discussed in subsequent sections concerning fate and transport.

6.2.1 Air

Estimated releases of 426,449 pounds (193 metric tons) of manganese to the atmosphere from 2,040 domestic manufacturing and processing facilities in 2006, accounted for about 1.6% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). Estimated releases of 1,859,959 pounds (844 metric tons) of manganese compounds to the atmosphere from 1,748 domestic manufacturing and processing facilities in 2006, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). These releases are summarized in Tables 6-1 and 6-2.

According to data from the National Pollutant Release Inventory (NPRI) maintained by Environment Canada, approximately 273.9 metric tons of manganese were released to air in Canada in 2003 from various industrial sources (Health Canada 2008). The major industrial sources for manganese emissions in Canada were attributed to an iron-ore mine located in Labrador, iron- and steel-related industries, pulp/paper/newsprint mills, fossil fuel electric power generation, and the manufacturing of heating and commercial refrigeration equipment.

Manganese has been identified in air samples collected at 31 of the 869 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

The main sources of manganese release to the air are industrial emissions, combustion of fossil fuels, and reentrainment of manganese-containing soils (EPA 1983c, 1984, 1985c, 1985d, 1987a; Lioy 1983). The principal sources of industrial emissions are ferroalloy production and iron and steel foundries, and the principal sources of combustion emissions are power plants and coke ovens (EPA 1983c, 1985c, 1985d). Atmospheric emissions of manganese and other trace metals from these industrial sources have declined

over the last 2 decades due to the use of advanced pollution control devices and increased government regulations regarding these emissions (EPA 1984, 1985d).

Windblown erosion of dusts and soils is also an important atmospheric source of manganese. Wallace and Slonecker (1997) estimated that the background contribution of windblown soil to fine particulate atmospheric manganese levels was 1–2 ng/m^3 in the United States and Canada. Volcanic eruptions may also release manganese to the atmosphere (Schroeder et al. 1987).

MMT is a manganese-containing compound used to enhance the octane rating in gasoline. MMT was used as an additive in leaded gasoline until the phase-out of leaded gas in the United States in 1995. It was also used in unleaded gasoline for a short period of time in the late 1970's, but was banned as an additive in unleaded gasoline by EPA in 1977 (EPA 1978, 1979a, 1981). In 1995, the ban on MMT use in unleaded gasoline was lifted, and a court decision ordered EPA to register the product for use as a fuel additive, although testing for health effects continues (EPA 1995a). Analysis of manganese levels in the air indicates that vehicular emissions from MMT containing fuels contributed an average of 13 ng manganese/m^3 in southern California, while vehicular emissions were only responsible for about 3 ng/m^3 in central and northern California (Davis et al. 1988). A survey of ambient air concentrations of fine ($PM_{2.5}$) manganese in rural sites in U.S. national parks and in urban sites in California indicated that from 1988 to 1993, ambient concentrations of manganese ranged from 1 ng/m^3 in rural sites to 3 ng/m^3 in urban sites (Wallace and Slonecker 1997). Part of the increase in fine manganese during this period was considered to be the result of the use of MMT in leaded gasoline. It was estimated that automobile emissions from leaded gasoline were responsible for 37% of the fine manganese levels in California in 1992. In 1994, automobile emissions were estimated to contribute 12% of the fine manganese levels in the atmosphere, as the use of leaded gasoline declined. It has been estimated that if MMT were used in all gasoline, urban air manganese levels would be increased by about 50 ng/m^3 (Cooper 1984; Ter Haar et al. 1975). Other authors have estimated that the increase in atmospheric manganese levels would be <20 ng/m^3 (Lynam et al. 1994).

In Canada, where the use of MMT containing gasoline has been extensive, a 10% per year increase in manganese emission rates from MMT in gasoline since 1981 was estimated (Loranger and Zayed 1994). A positive correlation between atmospheric manganese concentration and traffic density has been observed (Loranger and Zayed 1997a; Loranger et al. 1994a). The principal emission product of MMT combustion is a fine particulate matter (0.1–0.4 μm diameter) consisting of manganese oxide (Egyed and Wood 1996; Ter Haar et al. 1975), manganese phosphate, and some manganese sulfate (Lynam et al.

1999). The finding of soluble manganese (<0.4 μm) in snow samples obtained close to a highway in Montreal, Canada suggested a possible contamination from mobile sources (Loranger and Zayed 1997a; Loranger et al. 1995). However, it has been difficult to assess the exact contribution of mobile sources to overall contamination from natural and industrial sources because of the physico-chemical characteristics of manganese particulate, environmental factors affecting its dispersion, and the difficulties in distinguishing between mobile sources of manganese and background manganese levels (Loranger and Zayed 1997a; Veysseyre et al. 1998).

Despite the estimated 10% per year increase in manganese emission rates from the use of MMT in gasoline in Canada, atmospheric manganese concentrations in Montreal have remained fairly constant between 1981 and 1990, and have decreased markedly in 1991 and 1992 (Loranger and Zayed 1994). The decline in manganese concentration after 1990 may have been due to a shutdown in 1991 of a ferromanganese plant located near Montreal. Air concentrations are in general below the EPA reference concentration (RfC) of 0.05 $\mu g/m^3$ for respirable manganese. However, in 1998, it was observed that some atmospheric concentrations in specific microenvironments with important traffic density were higher than the RfC (Zayed et al. 1999a).

6.2.2 Water

Estimated releases of 269,573 pounds (122 metric tons) of manganese to water from 2,040 domestic manufacturing and processing facilities in 2006, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). Estimated releases of 7,496,834 pounds (3,401 metric tons) of manganese compounds to water from 1,748 domestic manufacturing and processing facilities in 2006, accounted for about 4% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). These releases are summarized in Tables 6-1 and 6-2.

Manganese has been identified in surface water and groundwater samples collected at 392 and 692, respectively, of the 869 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

Based on comparison to typical background levels of manganese in surface water or groundwater (see Section 6.4.2), it seems likely that some waste sites where manganese is detected contain only natural levels. Although ambient manganese levels are about 200 μg/L in a number of cases, high levels (in

excess of 1,000 µg/L) have been detected indicating that manganese wastes may lead to significant contamination of water at some sites. For example, at one site in Ohio where "heavy metals" had been disposed, manganese concentrations up to 1,900 µg/L were found in on-site wells (Cooper and Istok 1988). Levels in water at two NPL sites in Missouri ranged from 0.009 to 3.7 µg/L (MDNR 1990). No information is available on the method used to determine these values, so it is not clear whether the data refer to total or dissolved manganese.

6.2.3 Soil

Estimated releases of 23,171,244 pounds (10,510 metric tons) of manganese to soil from 2,040 domestic manufacturing and processing facilities in 2006, accounted for about 86% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). Estimated releases of 172,054,292 pounds (78,043 metric tons) of manganese compounds to the soil from 1,748 domestic manufacturing and processing facilities in 2006, accounted for about 86% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). An additional 8,566,935 pounds (3,886 metric tons) were injected underground. These releases are summarized in Tables 6-1 and 6-2.

Manganese deposition to soils from the use of MMT in gasoline was estimated for two sites in Toronto, Canada (Bhuie et al. 2005). Accounting for variables such as annual average daily traffic (AADT) density, fuel consumption, distance traveled by automobiles, and a manganese content of 10 mg/L of gasoline, the annual average manganese contribution to soils from MMT emissions were calculated as 5.73 and 2.47 mg/kg at two sites (Bhuie et al. 2005). These concentrations were considered insignificant when compared to natural background manganese levels (541 and 557 mg/kg) in soil for these areas.

Manganese has been identified in soil and sediment, samples collected at 355 and 257, respectively, of the 869 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Manganese compounds have negligible vapor pressures (see Table 4-2), but may exist in air as suspended particulate matter derived from industrial emissions or the erosion of soils. Manganese-containing particles are mainly removed from the atmosphere by gravitational settling, with large particles tending to

fall out faster than small particles (EPA 1984). The half-life of airborne particles is usually on the order of days, depending on the size of the particle and atmospheric conditions (Nriagu 1979). Some removal by washout mechanisms such as rain may also occur, although it is of minor significance in comparison to dry deposition (EPA 1984; Turner et al. 1985).

In a study completed by Evans (1989), there were two mechanisms involved in explaining the retention of manganese and other metals in the environment by soil. First, through cation exchange reactions, manganese ions and the charged surface of soil particles form manganese oxides, hydroxides, and oxyhydroxides, which in turn form absorption sites for other metals. Secondly, manganese can be adsorbed to other oxides, hydroxides, and oxyhydroxides through ligand exchange reactions. When the soil solution becomes saturated, these manganese oxides, hydroxides, and oxyhydroxides can precipitate into a new mineral phase and act as a new surface to which other substances can absorb (Evans 1989).

The behavior of heavy metals in the combustion gases of urban waste incinerators was studied by Fernandez et al. (1992). Manganese was detected inside gaseous fly ash particles in the form of oxides and chlorides. When these soluble oxides and chlorides reach environmental media, they can leach out and become mobile (Fernandez et al. 1992).

The transport of manganese in air is largely determined by its particle size. About 80% of the manganese in suspended particulate matter is associated with particles having a mass median aerodynamic diameter (MMAD) of <5 μm (WHO 1981). The compound's small particle size (approximately 80% with a MMAD <5 μm and approximately 50% with an MMAD <2 μm) favors widespread airborne distribution and is within the respirable range (WHO 1981).

The transport and partitioning of manganese in water is controlled by the solubility of the specific chemical form present, which in turn is determined by pH, Eh (oxidation-reduction potential), and the characteristics of the available anions. The metal may exist in water in any of four oxidation states; however, Mn(II) predominates in most waters (pH 4–7), but may become oxidized under alkaline conditions at pH >8 (EPA 1984). The principal anion associated with Mn(II) in water is usually carbonate (CO_3^{-2}), and the concentration of manganese is limited by the relatively low solubility (65 mg/L) of manganese carbonate (Schaanning et al. 1988). Under oxidizing conditions, the solubility of Mn(II) may be controlled by manganese oxide equilibria (Ponnamperuma et al. 1969), with manganese being converted to the Mn(II) or Mn(IV) oxidation states (Rai et al. 1986). In extremely reduced water, the fate of manganese tends to be controlled by formation of a poorly soluble sulfide (EPA 1984).

Manganese is often transported in rivers as suspended sediments. It has been reported that most of the manganese in a South American river came from industrial sources and was bound to suspended particles in the water (Malm et al. 1988).

In an aquifer studied in France, manganese was shown to originate from within the aquifer itself (Jaudon et al. 1989). In the presence of decreased dissolved oxygen in the groundwater, Mn(IV) has been shown to be reduced both chemically and bacterially into the Mn(II) form (Jaudon et al. 1989). This oxidation state is water soluble and easily released into the groundwater.

Manganese in water may be significantly bioconcentrated at lower trophic levels. A bioconcentration factor (BCF) relates the concentration of a chemical in plant and animal tissues to the concentration of the chemical in the water in which they live. Folsom et al. (1963) estimated that the BCFs of manganese were 2,500–6,300 for phytoplankton, 300–5,500 for marine algae, 800–830 for intertidal mussels, and 35–930 for coastal fish. Similarly, Thompson et al. (1972) estimated that the BCFs of manganese were 10,000–20,000 for marine and freshwater plants, 10,000–40,000 for invertebrates, and 100–600 for fish. In general, these data indicate that lower organisms such as algae have larger BCFs than higher organisms. In order to protect consumers from the risk of manganese bioaccumulation in marine mollusks, EPA has set a criterion for manganese at 0.1 mg/L for marine waters (EPA 1993b).

The tendency of soluble manganese compounds to adsorb to soils and is dependent upon the cation exchange capacity and the organic composition of the soil (Curtin et al. 1980; Hemstock and Low 1953; Kabata-Pendias and Pendias 1984; McBride 1979; Schnitzer 1969). Baes and Sharp (1983) noted that soil adsorption constants (the ratio of the concentration in soil to the concentration in water) for Mn(II) span five orders of magnitude, ranging from 0.2 to 10,000 mL/g, increasing as a function of the organic content and the ion exchange capacity of the soil; thus, adsorption may be highly variable. In some cases, adsorption of manganese to soils may not be a readily reversible process. At low concentrations, manganese may be "fixed" by clays and will not be released into solution readily (Reddy and Perkins 1976). At higher concentrations, manganese may be desorbed by ion exchange mechanisms with other ions in solution (Rai et al. 1986). For example, the discharge of waste water effluent into estuarine environments resulted in the mobilization of manganese from the bottom sediments (Helz et al. 1975; Paulson et al. 1984). The metals in the effluent may have been preferentially adsorbed resulting in the release of manganese.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Very little information is available on atmospheric reactions of manganese (EPA 1984). Manganese can react with sulfur dioxide and nitrogen dioxide, but the occurrence of such reactions in the atmosphere has not been demonstrated.

MMT undergoes photolysis rapidly by sunlight in the atmosphere or in aqueous solutions with a very short half-life (i.e., <2 minutes) (Ter Haar et al. 1975; Garrison et al. 1995). The photodegradation products tentatively identified in aqueous photolysis experiments were methylcyclopentadiene, cyclopentadiene, carbon monoxide, manganese carbonyl, and trimanganese tetroxide (Garrison et al. 1995). Undegraded MMT is not likely to be released directly to the atmosphere in significant quantities from it intended use as a gasoline additive. Spectroscopic studies of the tailpipe emissions of MMT-containing gasoline indicated that the manganese in MMT is converted to a mixture of solid manganese oxides, sulfates, and phosphates. The manganese containing particulates were determined to be Mn_3O_4, $MnSO_4 \cdot H_2O$ and a divalent manganese phosphate, $Mn_5(PO_4)[PO_3(OH)]_2 \cdot 4H_2O$ (Mölders et al. 2001; Ressler et al. 2000).

6.3.2.2 Water

Manganese in water may undergo oxidation at high pH or Eh (see Section 6.3.1) and is also subject to microbial activity. For example, Mn(II) in a lake was oxidized during the summer months, but this was inhibited by a microbial poison, indicating that the oxidation was mediated by bacteria (Johnston and Kipphut 1988). The microbial metabolism of manganese is presumed to be a function of pH, temperature, and other factors, but no data were located on this.

The rate of MMT degradation in natural aquifer and sediment systems was determined to be very slow under anaerobic conditions (Garrison et al. 1995). Calculated half-lives ranged from approximately 0.2 to 1.5 years at 25 °C. However, MMT photolyzed rapidly in purified, distilled water exposed to sunlight. The disappearance of MMT followed first-order kinetics, with a calculated half-life of 0.93 minutes. Reaction products included methylcyclopentadiene, cyclopentadiene, carbon monoxide, and a manganese carbonyl that readily oxidized to trimanganese tetroxide.

6.3.2.3 Sediment and Soil

The oxidation state of manganese in soils and sediments may be altered by microbial activity. Geering et al. (1969) observed that Mn(II) in suspensions of silt or clay loams from several areas of the United States was oxidized by microorganisms, leading to the precipitation of manganese minerals. Other studies (Francis 1985) have shown that bacteria and microflora can increase the mobility of manganese in coal-waste solids by increasing dissolution of manganese in subsurface environments.

MMT was found to be stable in a stream bottom sediment under anaerobic conditions. Photodegradation of MMT is not likely to occur in sediments, and it may equilibrate between the sediment, sediment porewater, and water column manganese (Garrison et al. 1995).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to manganese depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of manganese in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on manganese levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring manganese in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Table 6-3 summarizes historic manganese air level data collected over a period of nearly 30 years from numerous urban, nonurban, and source-dominated areas of the United States. Direct comparisons of data from different time periods are complicated because of changes in sample collection and analytical methodology. However, it is clear that manganese levels tend to be higher in source-dominated and urban areas than in nonurban areas. These data also indicate that concentrations in all areas have tended to decrease over the past three decades (EPA 1984; Kleinman et al. 1980). This decrease came as the result of the installation of emission controls in the metals industry (EPA 1984, 1985d). A concurrent decrease in total suspended particulates (TSP) was observed in most areas. Ambient air levels of manganese (PM_{10} and $PM_{2.5}$) in Canadian locations monitored from the late 1980s through the early 2000s were reported to have a 13–77% reduction over that time period (Health Canada 2008). Annual averages of manganese in urban and rural areas without significant manganese pollution are in the range of 10–70 ng/m^3 (0.01–

Table 6-3. Average Levels of Manganese in Ambient Air[a]

	Concentration (ng/m^3)		
Sampling location	1953–1957	1965–1967	1982
Nonurban	60	12	5
Urban	110	73	33
Source dominated	No data	250–8,300	130–140

[a]Adapted from EPA 1984

0.07 μg/m^3) (WHO 1997). The daily intake of manganese in the air by the general population in areas without manganese emitting industries was estimated to be <2 μg/day (WHO 1981). In areas with major foundry facilities, intake may rise to 4–6 μg/day, and in areas associated with ferro- or silicomanganese industries, it may be as high as 10 μg, with 24-hour peak values exceeding 200 μg/day (WHO 1981). Data compiled for 2006 under the EPA Urban Air Toxics Monitoring Program, studied ambient air levels of manganese and several other metals at 20 urban locations across the United States. Manganese (PM_{10}) was detected in 415 samples of urban air at levels ranging from 0.24 to 89.10 ng/m^3 (EPA 2007b). The arithmetic mean, geometric mean, and median concentrations were 10.13, 6.68, and 6.29 ng/m^3, respectively. Manganese levels ranged from 0.85 to 614.00 ng/m^3 in 114 samples of total suspended particulates (TSP) at these 20 urban locations. The arithmetic mean, geometric mean, and median concentrations of manganese in TSP were 47.89, 22.39, and 23.98 ng/m^3, respectively.

During 1988–1993, ambient concentration of fine ($PM_{2.5}$) manganese ranged from 1 ng/m^3 (0.001 μg/m^3) in rural sites in U.S. National Parks to 3 ng/m^3 (0.003 μg/m^3) in urban sites in California (Wallace and Slonecker 1997). There is concern in Canada regarding the combustion of MMT as an important source of manganese contamination in the urban environment, especially in areas of high traffic density. For instance, Loranger and Zayed (1997a) reported significantly higher levels of both respirable and total manganese levels at a high traffic density site (24 and 50 ng/m^3, respectively) in Montreal in contrast to a low traffic density site (15 and 27 ng/m^3, respectively). Temporal variation of respirable and total manganese was similar for both sites, and atmospheric manganese concentrations reflected a positive relationship with the traffic density. However, as discussed in Section 6.2.1, it has been difficult to assess the exact contribution of the combustion of MMT by vehicles to manganese levels in the environment.

In Montreal, Canada, ambient atmospheric concentrations of MMT, and respirable and total manganese, were measured in five microenvironments including a gas station, an underground car park, downtown Montreal, near an expressway, and near an oil refinery (Zayed et al. 1999a). The overall mean concentrations of respirable manganese, total manganese, and MMT measured for all the microenvironments were 36, 103, and 5 ng/m^3, respectively (0.036, 0.103, and 0.005 μg/m^3); however, the mean respirable manganese concentration 53 ng/m^3 (0.053 μg/m^3) near the expressway was greater than the EPA Reference Concentration (RfC) of 0.05 μg/m^3.

The Canadian National Air Pollution Surveillance (NAPS) Program reported that average fine ($PM_{2.5}$) manganese levels from 2003 to 2005 in cities with industrial sources (Windsor and Hamilton) were 9–15 ng/m^3 (Health Canada 2008). In Vancouver, Winnipeg, Montreal, Quebec, Toronto, and Edmonton,

the average levels were 4–14 ng/m^3. In Saskatoon, Ottawa, Victoria, St. John, and background sites, levels were <5 ng/m^3. NAPS also reported manganese PM_{10} levels were: 20–60 ng/m^3 in Hamilton and Windsor; 8–25 ng/m^3 in Montreal, Toronto, Edmonton, Winnipeg, Quebec, Calgary, Vancouver, and Victoria; and generally <10 ng/m^3 in Saskatoon, Ottawa, St. John, Yellowknife, and background sites (Health Canada 2008).

Studies were conducted in Indianapolis, Indiana and Toronto, Canada to assess levels of $PM_{2.5}$ and PM_{10} manganese in indoor, outdoor, and personal air samples (Pellizzari et al. 1999, 2001). The levels observed in Toronto, where MMT had been used in gasoline for over 20 years, were approximately 2 times greater in indoor and outdoor air than in Indianapolis, where MMT was not being used as a gasoline additive. The monitoring data from these studies are summarized in Table 6-4.

6.4.2 Water

Many factors, both environmental (e.g., the presence of high or low levels of other inorganics in drinking water) and biological or host-related (e.g., age, nutritional status, and alcohol consumption) can significantly influence the uptake of manganese by an individual (EPA 1993b). The determination of a single concentration of manganese in drinking water, then, must be recognized as a process that is limited in its ability to reflect the variable nature of manganese toxicity (EPA 1993b).

Concentrations of manganese in surface water are usually reported as dissolved manganese. Although total manganese may be a better indicator, since manganese adsorbed to suspended solids may exceed dissolved manganese in many systems, the bioavailability of manganese in this form has not been established (EPA 1984; NAS 1977). In a 1962–1967 survey of U.S. surface waters, dissolved manganese was detected in 51% of 1,577 samples, at a mean concentration of 59 μg/L. Individual values ranged from 0.3 to 3,230 μg/L. Mean concentrations for 15 different drainage basins in the United States ranged from 2.3 μg/L in the western Great Lakes to 232 μg/L in the Ohio River drainage basin (Kopp and Kroner 1967). A later (1974–1981) survey of U.S. river waters reported a median dissolved manganese concentration of 24 μg/L in samples from 286 locations, with values ranging from <11 μg/L (25th percentile) to >51 μg/L (75th percentile) (Smith et al. 1987). Analyzing data available from the USGS National Water Quality Assessment (NAWQA) database, the EPA reported that the median concentration of manganese was 16 μg/L for surface water and 5 μg/L for groundwater from 20 watersheds and 16 drainage basins in the United States (EPA 2003a). The results of this analysis for all sites are reproduced in Table 6-5. Reported mean groundwater concentrations of manganese were 20 and 90 μg/L

Table 6-4. Levels of $PM_{2.5}$ and PM_{10} in Indoor and Outdoor Air in Toronto, Canada and Indianapolis, Indiana

Location	Number	Median concentration (ng/m^3)	90^{th} concentration (ng/m^3)
PM_{10} Manganese			
Toronto (indoor)	203	6.7	14
Indianapolis (indoor)	59	3.9	8.7
Toronto (outdoor)	203	17	28
Indianapolis (outdoor)	59	8.8	14
$PM_{2.5}$ Manganese			
Toronto (indoor)	187	4.7	9.9
Indianapolis (indoor)	58	2.2	4.6
Toronto (outdoor)	185	8.6	16
Indianapolis (outdoor)	57	3.2	5.8

Sources: Pellizzari et al. 1999, 2001

Table 6-5. Manganese Detections and Concentrations in Surface Water and Groundwater in the United States

	Detection frequency					
	Above the minimal reporting level (1 µg./L)		Above the health reference level[a] (300 µg/L)		Concentration (µg/L)	
	Samples	Sites	Samples	Sites	Median	99th
Surface water						
Urban	99.1%	99.6%	4.6%	13.0%	36	700
Mixed	92.4%	98.5%	1.3%	6.4%	12	400
Agricultural	96.3%	97.2%	3.7%	12.3%	19	700
Forest/rangeland	90.9%	96.4%	5.0%	6.6%	11	800
All sites	94.0%	96.9%	3.0%	10.2%	16	700
Groundwater						
Urban	74.7%	85.3%	17.2%	21.0%	15	5,600
Mixed	56.9%	62.9%	8.9%	9.0%	2	1,300
Agricultural	61.4%	64.0%	11.9%	12.8%	4	1,600
Forest/rangeland	75.3%	81.3%	10.9%	13.8%	12	2,900
All sites	64.1%	70.1%	12.8%	13.8%	5	2,900

[a]The Health Reference Level (HRL) is based on the dietary reference dose (RfD) and application of a modifying factor (MF) of 3 for drinking water, and on an allocation of an assumed 20% relative source contribution from water ingestion as opposed to total manganese exposure.

Source: EPA 2003a

in an analysis of California shallow groundwater from two geologic zones (Deverel and Millard 1988). Values up to 1,300 and 9,600 μg/L have been reported in neutral and acidic groundwater, respectively (EPA 1984). Manganese levels of 9,500–18,600 μg/L have been reported in four private wells in Connecticut (CDHS 1990). Natural concentrations of manganese in seawater reportedly range from 0.4 to 10 μg/L (EPA 1984).

A 1962 survey of public drinking water supplies in 100 large U.S. cities reported that 97% contained <100 μg/L of manganese (USGS 1964). Similarly, a 1969 survey of 969 systems reported that 91% contained <50 μg/L, with a mean concentration of 22 μg/L (U.S. DHEW 1970). Several other studies reported similar manganese concentrations, with mean values ranging from 4 to 32 μg/L (EPA 1984; NAS 1980a; WHO 1981). The EPA analyzed drinking water statistics from Alabama, California, Illinois, New Jersey, and Oregon for occurrence and concentration data for manganese in public water supplies. The data used contained >37,000 analytical results from about 4,000 public water supplies from 1993 to 1997, although some prior monitoring data were also employed in the analysis. The median manganese level for all detections was 10 μg/L and the 99th percentile of the detections was 720 μg/L (EPA 2003a).

6.4.3 Sediment and Soil

Manganese comprises about 0.1% of the earth's crust (Graedel 1978; NAS 1973), and manganese occurs naturally in virtually all soils. Average natural ("background") levels of manganese in soils range from around 40 to 900 mg/kg, with an estimated mean background concentration of 330 mg/kg (Barceloux 1999; Cooper 1984; Eckel and Langley 1988; EPA 1985c; Rope et al. 1988; Schroeder et al. 1987). The maximum value reported was 7,000 mg/kg (Eckel and Langley 1988). Using data from 20 watersheds and 16 drainage basins in the United States, manganese was detected at 100% of the National Water-Quality Assessment Program (NAWQA) stream bed sediment sampling sites. The median and 99th percentile concentrations in bed sediments were reported as 1.1 mg/kg (dry weight) and 9.4 mg/kg (dry weight), respectively (EPA 2003a). Manganese levels as high as 1,900 mg/kg were detected in sediment samples obtained from the Tar Creek Superfund site (a site heavily contaminated with mining wastes) in Ottawa County, Oklahoma (Wright et al. 2006).

Accumulation of manganese in soil usually occurs in the subsoil and not on the soil surface; 60–90% of manganese is found in the sand fraction of the soil (WHO 1981). A preliminary survey was conducted in Utah to provide an initial field measurement of the contamination by manganese oxides from exhaust in roadside soil and plant species due to the addition of MMT to motor vehicle fuels. Soil (0–5 cm)

manganese concentrations were strongly correlated with distance from roadways with moderate and moderately high traffic volumes (Lytle et al. 1994). In addition, exchangeable manganese was found to be significantly higher in an organic soil located at stations with a high traffic density comparing to another one with a low traffic density (Brault et al. 1994). The average soil manganese concentration measured at 1 meter from a moderate to moderately-high traffic volume roadside was 3,046 µg/g dry weight. At 15m, the average soil manganese concentration decreased to 254 µg/g dry weight.

6.4.4 Other Environmental Media

Manganese is a natural component of most foods. A summary of mean manganese concentrations in foods analyzed by the Food and Drug Administration (FDA) Total Diet Study (TDS) 1991–1996 is summarized in Table 6-6. TDS sampling is conducted 4 times annually, once in each of the major geographical regions of the country (west, north central, south, and northeast). Each round of sampling is referred to as an individual market basket survey and for each market basket survey, samples of 260 selected food and beverages were obtained from three cities within the region. The mean and median concentration of manganese in all foods were 2.4 and 1.0 mg/kg, respectively (Capar and Cunningham 2000). The TDS results concluded that detectable levels of manganese were present in roughly 75% of all foods, although approximately 24% of these detections were below the quantification limits used in the study (Capar and Cunningham 2000). The highest manganese level was observed in a sample of shredded wheat cereal (44.4 mg/kg). The five foods with the highest mean manganese levels were oat ring cereal (33.8 mg/kg), raisin bran cereal (28.8 mg/kg), shredded wheat cereal (25.0 mg/kg), mixed nuts (23.2 mg/kg), and granola cereal (20.1 mg/kg). These levels are similar to levels found in previous market basket surveys (Pennington et al. 1986). Tea and leafy green vegetables were the major dietary sources of manganese for young women taking part in a dietary study in Wisconsin (Davis et al. 1992a).

Bioaccumulation of manganese by plants was examined using oats (*Avena nova*) and beans (*Phaseolus vularis*) (Brault et al. 1994). These plants were grown in sandy and organic soil at a control site (greenhouse) and at two outdoor sites near <20,000 and 132,000 vehicles/day respectively. The highest manganese accumulation was found in the fruits and stems of oats grown in the organic and sandy soils at the station with the highest traffic density. Lönnerdal (1997) reported that infant formulas contain 30–75 ppb (0.03–0.075 ppm) manganese, as compared to concentrations of 3–10 ppb (0.003–0.01 ppm) in breast milk and 30 ppb (0.03 ppm) in cow's milk.

Table 6-6. Mean Concentrations of Manganese for FDA's Total Diet Study Market Baskets 1991 through 1997[a]

Food product	Range (mg/kg)
Milk and cheese	Not detected–<2
Eggs	<1
Meat, poultry, and fish	Not detected–3.7
Legumes and nuts	3.4–23.2
Grain products	<1–33.8
Fruit	<1–10.0
Vegetables	<1–5.9
Mixed dishes and meals	<1–3.4
Desserts	Not detected–4.9
Snacks	3.4–9.3
Condiments and sweeteners	Not detected–4.1
Fats and dressings	Not detected–<1
Beverages	Not detected–2.9
Infant and junior foods	Not detected–7.5

[a]A < symbol indicates that manganese was detected, but at a level lower than the limit of quantification.

Source: Capar and Cunningham 2000

During a 1992 survey conducted by Canada's Department of Fisheries and Oceans, concentrations of manganese were detected in the muscle samples of bluefin tuna (*Thunnus thynnus*) (Hellou et al. 1992). Concentrations of manganese in 14 samples of fish muscle ranged from 0.16 to 0.31 µg manganese/g dry weight, with a mean of 0.22 µg/g. Although the analysis was administered with a high accuracy of 94% using inductively coupled plasma-mass spectrometry (ICP-MS), the sample population was small.

In the field survey conducted by Lytle et al. (1994), terrestrial and aquatic plant samples were collected along motorways and local urban roadways throughout Utah during 1992 and 1993. Manganese was detected in the plant samples, with manganese concentrations ranging from 30.2 to 13,680 µg/g dry weight. Manganese was detected in plants found nearest to the motorway. Loranger et al. (1994b) evaluated the use of the pigeon as a monitor for manganese contamination from motor vehicles in urban and rural areas of Canada, a country in which MMT has been used to replace lead in gasoline. Manganese concentrations were similar in the two groups of pigeons for all tissues except the liver and feces; urban pigeons had about 35% more manganese than rural ones. Loranger et al. (1994b) suggested that although pigeon feces and liver may be good biomarkers of manganese contamination, it is premature to associate the excess manganese with the combustion of MMT. Toxicokinetic studies of manganese in both male and female rats suggested that MMT-derived manganese administered in oral doses resulted in higher and more prolonged plasma concentration versus time profiles than inorganic ($MnCl_2$) complexes, leading to the conclusion that MMT-derived manganese was likely to accumulate following repeated exposures (Zheng et al. 2000).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Since manganese is ubiquitous in the environment, the general population is exposed to manganese from both natural and anthropogenic sources. The manganese concentration in blood of healthy adults is reported to range from 4 to 15 µg/L with an average value of about 9 µg/L (Barceloux 1999). Typical daily human exposure levels to manganese from water, air, and food are summarized in Table 6-7 (EPA 1984). As the table illustrates, the most significant exposure for the general population is from food, with an average ingestion rate of 3,800 µg/day (EPA 1984). Other estimates of daily intake for adults range from 2,000 to 8,800 µg (EPA 1984; NAS 1977; Patterson et al. 1984; Pennington et al. 1986; WHO 1984a) and 700–10,900 µg/day (WHO 2004b). Even though gastrointestinal absorption of manganese is low (3–5%), oral exposure is the primary source of absorbed manganese.

Table 6-7. Summary of Typical Human Exposure to Manganese[a]

	Exposure medium		
Parameter	Water	Air	Food
Typical concentration in medium	4 µg/L	0.023 µg/m^3	1.28 µg/calories
Assumed daily intake of medium by 70-kg adult	2 L	20 m^3	3,000 calories
Estimated average daily intake by 70-kg adult	8 µg	0.46 µg[b]	3,800 µg
Assumed absorption fraction	0.03[c]	1[c]	0.03[d]
Approximate absorbed dose	0.24 µg	0.46 µg	114 µg

[a]Adapted from EPA 1984
[b]Assumes 100% deposition in the lungs
[c]No data; assumed value
[d]Vitarella et al. 2000

Manganese intake among individuals varies greatly, depending upon dietary habits. For example, an average cup of tea may contain 0.4–1.3 mg of manganese (Pennington et al. 1986; Schroeder et al. 1966). Thus, an individual consuming three cups of tea per day might receive up to 4 mg/day from this source alone, increasing the average intake from all dietary sources.

As part of the Third National Health and Nutrition Examination Survey (NHANES) conducted by the Centers of Disease Control and Prevention (CDC), manganese was detected at quantifiable levels in urine samples from 73% of 496 participants of the monitoring study (Paschal et al. 1998). The mean urinary manganese concentration in these 496 individuals (aged 6–88 years of age) was 1.19 μg/L (Paschal et al. 1998).

The EPA Reference Dose (RfD)/RfC workgroup in June 1990 set an RfD for manganese in food of 0.14 mg manganese/kg/day, equivalent to about 10 mg/day for a 70-kg man based on chronic manganese uptake (EPA 1993b). The Food and Nutrition Board of the National Research Council (NRC) estimated the adequate and safe intake of manganese for adults at 2–5 mg/day (NAS 1980b). This level was chosen because it includes an "extra margin of safety" of 5 mg/day below the level of 10 mg/day, which the NRC considered to be safe for occasional intake (IRIS 2008).

In the workplace, exposure to manganese is most likely to occur by inhalation of manganese fumes or manganese-containing dusts. This is a concern mainly in the ferromanganese, iron and steel, dry-cell battery, and welding industries (WHO 1986). Exposure may also occur during manganese mining and ore processing; however, the most recent data indicate that only a very small amount of manganese is still mined in the United States (USGS 2007). Excluding insignificant quantities of similar low-grade manganiferous ore, the United States has not mined significant amounts of manganese since 1978 and now relies on imports to fill its needs (USGS 2007). In 1980, it was estimated that in the United States about 300 workers were exposed to pure manganese and about 630,000 workers were exposed to other forms of manganese (NOES 1989). Concentrations as large as 1.5–450 mg manganese/m^3 have been reported in U.S. manganese mines (EPA 1984), 0.30–20 mg manganese/m^3 in ferroalloy production facilities (Saric et al. 1977), and 3–18 mg manganese/m^3 in a dry-cell battery facility (Emara et al. 1971). Steel-manufacturing facilities are significant employers in the United States. There is a potential for manganese exposure to workers in these facilities. Airborne manganese levels in a metal-producing plant in the United States were reported as 0.066 mg/m^3(mean), 0.051 mg/m^3(median) as respirable dust, and 0.18 mg/m^3 in total dust (Gibbs et al. 1999). Exposure levels should not exceed the Occupational Safety and Health Administration (OSHA) time-weighted average Permissible Exposure Limit (PEL) of 1 mg

total manganese/m^3 (see Table 8-1). Average airborne manganese levels during welding operations of two factories located in China were 0.24 and 2.21 mg/m^3 (Wang et al. 2008). Manganese levels in workplace air at a smelting facility in China ranged from 0.30 to 2.9 mg/m^3 in the furnace smelting area and from about 0.2 to 0.8 mg/m^3 in a power control room (Jiang et al. 2007). The workplace air at this facility contained mainly MnO (20%) and SiO_2 (22%), in addition to other trace metals including Fe_2O_3 (4%), CaO (4.5%), MgO (4%), and Al_2O_3 (5%). Thus, for workers in industries using manganese, the major route of exposure may be inhalation from workplace air rather than from ingestion of food.

Occupational exposure to manganese resulting from the combustion of MMT in Montreal, Canada has been studied. Sierra et al. (1995) conducted a study of Montreal automotive workers (garage mechanics) and nonautomotive workers (control group). Exposure to manganese was measured for 5 consecutive working days. In addition, their environmental exposure (at home) was measured on 2 days of the same week. Air sampling was performed by portable pumps; for sampling at homes, workers were asked to wear the pumps as much as possible. At the workplace, the mechanics were exposed to manganese concentrations ranging from 0.010 to 6.673 μg/m^3 (mean of 0.45 μg/m^3), while nonautomotive workers were exposed to manganese concentrations ranging from 0.011 to 1.862 μg/m^3 (mean of 0.04 μg/m^3). The average manganese concentrations in the indoor air of the homes were 0.012 μg/m^3 for the mechanics and were 0.008 μg/m^3 for the nonautomotive workers (Sierra et al. 1995). Based on measurements of manganese particle size distributions, Sierra et al. (1995) estimated that <10% of the manganese exposure of the garage mechanics was due to MMT; however, the exact contribution of MMT could not be determined.

A similar study conducted in Montreal by these investigators, but involving taxi drivers and garage mechanics revealed that garage mechanics at work were exposed to an average of 0.250 μg/m^3 and taxi drivers to 0.024 μg/m^3 (Zayed et al. 1994). In another study, exposure of office workers and taxi drivers to both respirable and total manganese was evaluated (Zayed et al. 1996). Manganese concentrations measured for the office workers ranged from 0.001 to 0.034 μg/m^3 (respirable manganese) and from 0.002 to 0.044 μg/m^3 (total manganese). For the taxi drivers, the manganese concentrations ranged from 0.007 to 0.032 μg/m^3 (respirable manganese) and from 0.008 to 0.073 μg/m^3 (total manganese). Zayed et al. (1996) concluded that the higher exposure to atmospheric manganese in the outdoor urban environment may be at least partly due to the use of MMT in cars. Nevertheless, these investigators indicated that the exposures of taxi drivers to manganese were well below existing exposure and health guidelines.

In order to assess the potential health risks from MMT combustion, Loranger and Zayed (1995) conducted a multi-media assessment (i.e., food, water, and ambient air) of manganese exposure in two groups of workers (garage mechanics and blue-collar workers) potentially exposed to different levels of manganese from MMT. Garage mechanics were exposed to higher air manganese concentrations (0.42 μg/m^3) than blue-collar workers (0.04 μg/m^3). However, for the garage workers, exposure to atmospheric manganese represented only approximately 4% of the total absorbed dose, while ingestion of food represented 95.7% of the total multi-media dose. For the blue collar workers, atmospheric manganese contributed only 0.3% to the total absorbed dose, whereas ingestion of food represented 99.2% of the total multi-media dose. These results were consistent with values of multi-media doses predicted by GADUS, an environmental fate/exposure model (Loranger and Zayed 1997b). Based on governmental standards or criteria for occupational and environmental exposures, Loranger and Zayed (1995) concluded that the manganese levels in food and air may not cause any problems for these workers.

Based on an analysis of data obtained from a large, continuous personal exposure study in Toronto, Canada, a city with widespread use of MMT, it was determined that the general population was exposed to low concentrations (median concentration was 0.008 μg/m^3) of $PM_{2.5}$ manganese in personal air samples (Lynam et al. 1999; Pellizzari et al. 1999). A similar study, which collected 925 personal exposure samples for residents of Toronto, also concluded that MMT was not a significant source of $PM_{2.5}$ manganese inhalation exposure for the general population (Crump 2000). However, personal exposure levels of fine manganese in Toronto were nearly 3 times greater when compared to data obtained from Indianapolis, Indiana where MMT was not being used as a gasoline additive. The median concentration of $PM_{2.5}$ manganese in personal exposure samples from Indianapolis was 0.0028 μg/m^3 (Pellizzari et al. 2001). These data are summarized in Table 6-8. Certain activities such as time spent in subways, metal working, and smoking were associated with higher personal manganese exposure.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults.

Table 6-8. Levels of $PM_{2.5}$ in Personal Air Samples Collected in Toronto, Canada and Indianapolis, Indiana

Location	Number	Median concentration ($\mu g/m^3$)	90^{th} concentration ($\mu g/m^3$)
$PM_{2.5}$ Manganese in personal air			
Toronto	272	0.008	0.016
Indianapolis	240	0.0028	0.006

Source: Pellizzari et al. 1999, 2001

The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children would be exposed to manganese in the same manner as adults. The main source of exposure of children to manganese is through food. Infants and young toddlers who are formula-fed may receive higher daily intakes of manganese than breast-fed infants because of the increased levels of the element in infant formulas as compared to breast milk (Collipp et al. 1983; Cook 1997; Dorner et al. 1989; Keen et al. 1986; Lönnerdal et al. 1983, 1994). For example, a study of 2,339 breast milk samples obtained from nursing mothers in Germany had a mean manganese level of 6.2 μg/L, while two different brands of formula had levels of 77 and 99 μg/L (Dorner et al. 1989). It was concluded that the mean daily manganese intake of formula-fed infants was approximately 13 times greater than that of breast-fed infants.

Manganese concentrations in blood serum of children of different ages are provided in Section 3.4.2. The data indicate that manganese concentrations decrease slightly from the time the infant is 5 days of age until he or she is 12 months of age (Alarcón et al. 1996; Rükgauer et al. 1997). Manganese concentrations increase after this time, and they have been measured as an average of 1.4±1.25 μg/L in children aged 1 month to 18 years (Rükgauer et al. 1997).

Children are exposed *in utero* because manganese in maternal blood crosses the placenta to satisfy the fetus's need for manganese. The compound has been measured in cord blood plasma of premature and full-term infants and their mothers (Wilson et al. 1991). Full-term babies had higher (but not statistically significantly different) blood concentrations of manganese than premature babies, and pregnant women had higher blood concentrations than nonpregnant women. The average manganese concentration in the cord blood of full term babies was 5.5 μg/L, as compared to 5.0 μg/L for preterm babies (Wilson et al. 1991). No correlations were observed between maternal and infant concentrations of manganese. Manganese in breast milk has been found to range from 3.4 to 10 μg/L (Arnaud and Favier 1995; Collipp et al. 1983) depending on the maturity of the milk. The Food and Nutrition Board of the NRC based the recommended manganese intake of infants on the analyses of pooled human milk samples. As discussed above, manganese intakes of infants fed some formulas appear high, but no signs of toxicity have been observed (Dorner et al. 1989; Lönnerdal et al. 1983). Differences in weight-adjusted intake are likely to

be caused by the type of diet that infants and small children receive. It is unknown whether nursing mothers exposed to higher-than-average concentrations of manganese would excrete increased concentrations of the metal in their breast milk.

Young children often eat dirt (exhibiting what is called soil pica, the ingestion of a material unfit for food) and exhibit frequent hand-to-mouth activity; they can be exposed to manganese through this unique pathway if the soils contain the metal. Current estimates indicate that soil pica may be more prevalent in the general population than previously thought and that most children periodically ingest soil to varying degrees; this may be a potential health concern (EPA 1986d; Stanek and Calabrese 1995). The predicted oral average daily intake of manganese for children from soils in the vicinity of a municipal solid waste incinerator was estimated to range from approximately 0.0021 to 0.0032 mg/kg/day (Mari et al. 2007). However, no information was found concerning the bioavailability of manganese from soil and, therefore, determining the actual risk posed to children from this exposure pathway is difficult. This behavior should not pose an increased risk of exposure to manganese in most residential situations where the manganese levels are in the normal or background range. If the soils are from a hazardous waste site that contains high concentrations of manganese, then increased exposure to the compound may occur. Manganese levels in hair samples of 32 children residing near a hazardous waste site (former mining facility) in Northeast Oklahoma ranged from 89.1 to 2,145.3 ppb (471.5 ppb mean) (Wright et al. 2006). The authors found that in school-aged children, higher manganese and arsenic levels in hair samples were associated with significantly lower scores on a standardized test, as well as on tests of verbal learning and memory.

Children who suffer from cholestatic liver disease or who have gastrointestinal disorders that mandate they be given parenteral nutrition may be at increased risk from overexposure to manganese. Increased manganese concentrations in blood and brain, and symptoms of neuromotor dysfunction were observed in an 8-year-old girl with cholestatic liver failure (Devenyi et al. 1994). Children with or without chronic liver disease and a 5-year-old boy who had gastrointestinal disorders, all of whom were administered parenteral nutrition, had abnormal MRI scans indicative of manganese accumulation (Fell et al. 1996; Ono et al. 1995) accompanied by motor disorders (Fell et al. 1996).

Because manganese is a trace element that is essential for normal human health and is predominantly obtained from food, it is unlikely that toxic amounts of manganese will be absorbed from food. However, diets vary and some are higher in manganese than others (diets high in grains and tea, for instance). One case study suggested that a 59-year-old man developed manganism-like symptoms from abusing vitamins

and minerals. This man had very high manganese concentrations in blood, urine, feces, hair, and brain (Banta and Markesbery 1977). Both manganese and iron are bound by transferrin and these elements compete for the binding protein in the body. Therefore, diets that are low in iron allow transferrin to bind more manganese. For this reason, it is important to provide children with a balanced diet to maintain optimal iron and manganese stores in the body. Studies show that adults absorb only 3–5% of manganese ingested from the diet (Davidsson et al. 1988, 1989a; Mena et al. 1969); infants have increased absorption relative to adults (Dorner et al. 1989). Neonatal animals also exhibit increased absorption relative to older animals (Ballatori et al. 1987; Miller et al. 1975; Rehnberg et al. 1981).

Children may be exposed to organic manganese compounds through a variety of routes. They may be exposed to MMT combustion products via inhalation of these products in air, or ingestion of them after deposition on the soil.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

As discussed in Section 6.5, workers in industries using or producing manganese are mostly likely to have higher exposures to manganese, primarily by inhalation of manganese dusts in workplace air as compared to the general population. In a year-long investigation of personal exposure to manganese fine particulate matter ($PM_{2.5}$) for residents of Toronto, Canada, it was determined that workers in the metal industry had the highest personal exposures as compared to other groups. The mean concentration of manganese $PM_{2.5}$ in personal samples for 39 workers engaged in welding, soldering, or other metal working practices was 105 ng/m^3, which was more than 10 times greater than the mean concentration (10 ng/m^3) for 886 non-metal workers (Crump 2000). Smokers and those nearby second-hand smoke were also shown to be exposed to higher levels of fine particulate matter manganese as compared to nonsmokers. The mean concentration of $PM_{2.5}$ manganese in 702 personal air samples of nonsmokers in Toronto, Canada was 10 ng/m^3, while the mean concentration calculated from 223 personal samples obtained from smokers was 27 ng/m^3 (Crump 2000).

Average airborne manganese levels (total dust) in the breathing zone of two factories located in China were 0.24 and 2.21 mg/m^3 (Wang et al. 2008). The greatest levels were observed during welding operations in enclosed spaces. The workers at these two factories had higher measurable manganese levels in their saliva (3.47±1.42 and 5.55±2.31 µg/L), as compared to a control group of non-occupationally exposed individuals (3.04±1.40 µg/L).

Workers in three manganese alloy production plants located in Norway were found to have slightly higher manganese blood and urine levels when compared to a group of non-occupationally exposed individuals. The arithmetic mean manganese level in the blood of workers at these plants was 189 nmol/L (10.3 µg/L) versus 166 nmol/L (9.1 µg/L) for the reference group (Ellingsen et al. 2003c). The urinary arithmetic mean concentrations were 3.9 nmol/mmol creatinine for the occupationally exposed workers and 0.9 nmol/mmol creatinine for the reference group (Ellingsen et al. 2003c). The arithmetic mean inhalable and respirable concentrations of manganese in the air of these production plants were 0.769 and 0.064 mg/m^3, respectively (Ellingsen et al. 2003c). Section 3.2.1.4 summarizes other studies that compared noted health effects with urinary and blood manganese levels of occupationally exposed individuals and reference populations. It has been demonstrated that levels in the blood and urine may not be adequate biomarkers for high level manganese exposure since free manganese usually does not accumulate within the circulatory system (Josephs et al. 2005).

Populations living in the vicinity of ferromanganese or iron and steel manufacturing facilities, coal-fired power plants, or hazardous waste sites may also be exposed to elevated manganese particulate matter in air or water, although this exposure is likely to be much lower than in the workplace. Populations living in regions of natural manganese ore deposits may be exposed to above-average levels in soil, water, or air.

People ingesting large amounts of foods high in manganese also have a potential for higher-than-usual exposure. Included in this group would be vegetarians, who ingest a larger proportion of grains, legumes, and nuts in their diets than the average U.S. population, and heavy tea drinkers. While the intake of manganese from vegetarians may exceed the estimates of daily dietary intake, the bioavailability of manganese from vegetable sources is substantially decreased by dietary components such as fiber and phytates (EPA 1993b). In addition to the population with these dietary habits, individuals with iron deficiency show increased rates of manganese absorption (Mena et al. 1969, 1974); iron deficiency leads to increased brain manganese concentrations in experimental animals (Aschner and Aschner 1990).

Manganese is eliminated from the body primarily through the bile. Interruption of the manufacture or flow of bile can impair the body's ability to clear manganese. Several studies have shown that adults and children (Devenyi et al. 1994; Fell et al. 1996; Hauser et al. 1994, 1996; Pomier-Layrargues et al. 1998; Rose et al. 1999; Spahr et al. 1996), as well as experimental animals (Rose et al. 1999), with cholestatic liver disorders have increased manganese levels in their blood and brain and are at risk from potentially increased exposure to manganese due to their decreased homeostatic control of the compound.

In addition to oral diets, people on partial and total parenteral nutrition may be exposed to increased amounts of manganese. Forbes and Forbes (1997) found that of 32 patients receiving home parenteral nutrition due to digestive problems, 31 had elevated serum manganese levels (0.5–2.4 mg/L). It is unclear whether these levels reflected steady-state conditions due to the time the samples were taken. However, these levels are much higher than other studies involving patients on TPN; thus, it is unlikely that these levels represent steady-state conditions. Further, the normal range reported by these authors (0.275–0.825 mg/L) is elevated compared to other studies, suggesting the possibility that the blood samples were contaminated with exogenous manganese. The authors observed no clinical evidence of toxicity in the patients. Fourteen of the patients suffered iron deficiency anemia; because low iron concentrations are associated with increased manganese uptake, the anemia may have exacerbated the increased blood manganese concentrations. Increased blood manganese levels and MRI scans indicative of increased manganese in brains have been reported in children fed entirely on parenteral nutrition (Fell et al. 1996; Ono et al. 1995). Only in the Fell et al. (1996) study were neurotoxic effects reported. Whole-blood manganese in the children from this study ranged from 9.9 to 110 μg/L. Devenyi et al. (1994) found hyperintense signals in the brain of an 8-year-old child who had cholestatic liver disease and exhibited dystonia and other motor dysfunctions. Nagatomo et al. (1999) reported that two elderly patients who had been administered TPN for 3–4 months exhibited clinical signs of manganism (including masked facies, marked rigidity, hypokinesia) with associated elevated blood manganese levels and hyperintense signals on MRI, localized to the basal ganglia, especially the globus pallidus. Signs of manganism abated upon levodopa treatment and the administration of Ca-EDTA; the high intensity signals on MRI abated when manganese supplementation ceased. In addition to patients on parenteral nutrition, uremic patients on hemodialysis have been found to have increased manganese levels due to increased concentrations of manganese in the dialysis solution (Lin et al. 1996). These studies indicate that while increased levels of manganese in blood and brain are often associated with TPN administration, adverse neurological effects are not always reported. Nagatomo et al. (1999) found increased serum concentrations of manganese and brain abnormalities in two patients who showed Parkinsonism with psychiatric symptoms after 3–4 months of total parenteral nutrition. Discontinuation of manganese supplementation in the parenteral diet, coupled with levodopa treatment, gradually improved both the symptoms and brain abnormalities in the patients.

In comparison to other groups within the general population, persons living close to high density traffic areas, automotive workers, gas station attendants, and taxi drivers may be exposed to higher concentrations of manganese arising from the combustion of MMT. Levels of respirable manganese, in both indoor and outdoor air near an expressway with high traffic density were shown to be greater than

corresponding air samples obtained from a rural location in Montreal, Canada (Bolte et al. 2004). The average concentration of respirable manganese (defined in this study as <5 μm diameter) in outdoor air from the urban location of Montreal was 0.025 μg/m^3, which is 5 times greater than the average of 0.005 μg/m^3 found in the rural location. The average indoor respirable manganese concentration was also greater for the urban area (0.017 μg/m^3) as compared to the rural area (0.007 μg/m^3). However, differences in exposure levels did not lead to significantly greater levels of manganese in blood for residents of these areas. The mean manganese concentration in blood samples obtained from female residents in the urban location (8.4 μg/L) was only slightly greater than the average level observed for females living in the rural location (7.8 μg/L).

It is possible that medical workers may be exposed to higher concentrations of mangafodipir than the general population, although exposure routes other than intravenous are not expected to pose a significant risk.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of manganese is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of manganese.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The fundamental physical and chemical properties of manganese and manganese compounds are known (see Table 4-2), and additional research does not appear necessary.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2006, became available in March of 2008. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Information is available on U.S. import, export and production of manganese ore and related materials (USGS 2007, 2008). It is clear that most manganese is used in steel production. Information regarding the import, export, and use of MMT in U.S. fuels is a data need.

Data from the TRI database provide valuable information on the amounts of manganese released to different environmental media (e.g., air, soil, and water) each year, although details on the chemical form and physical state of the waste materials are not included. These disposal practices are not regulated under current federal law. TRI data may not be complete estimates of total release. Also, because these data reflect past releases, they may not be representative of current releases at these facilities.

Environmental Fate. The partitioning of manganese between water and soil can be fairly well predicted using thermodynamic equilibrium concepts, if soil-specific information is available (Baes and Sharp 1983; Rai et al. 1986). The fate of manganese particles released into the air is determined by the particle size, and the direction and distance of particle transport at a site can be predicted from meteorological data and particle size data (EPA 1984; Nriagu 1979). Transport of manganese in water is determined mainly by the solubility of the manganese compounds present, although suspended particles may also be transported in flowing waters (EPA 1984; Schaanning et al. 1988).

The primary transformations that manganese undergoes in the environment are oxidation/reduction reactions (EPA 1984; Rai et al. 1986). Reactions of manganese with airborne oxidants have not been studied. Information on the rate and extent of such reactions would be helpful in understanding the fate of atmospheric releases. The transformation of manganese in water or soil is dependent mainly on Eh, pH, and available counter ions (EPA 1984). In some soils, manganese may also be oxidized by bacteria (Geering et al. 1969; Johnston and Kipphut 1988). More work is needed on the environmental factors, such as soil composition and pH, which may determine the form in which manganese will appear and thus impact manganese availability and absorption.

Modeling has also provided interesting insight into the contribution of the combustion of MMT to atmospheric manganese (Loranger et al. 1995). According to the model estimations, the contribution of direct emissions from motor vehicles to the atmospheric background manganese (as measured from sampling stations) would be about 50% at <25 m and <8% at 250 m. These results are confirmed with an *in situ* study using snow as the environmental indicator where the average deposition rates of manganese for the top and bottom layers ranged from 0.01 to 0.21 $mg/m^2/day$ (Loranger et al. 1996). The average concentrations of manganese decreased with distance from the road. However, it was impossible to distinguish between directly-emitted manganese from automobiles, manganese enriched road dust, and the naturally-occurring manganese in crustal materials. No study to date has provided the complete answer to this question and this constitutes one of the major remaining data needs regarding the environmental significance of manganese from MMT and the resulting potential for exposure.

Bioavailability from Environmental Media. Manganese is known to be absorbed following inhalation or oral exposure (Mena et al. 1969; Pollack et al. 1965; Zheng et al. 2000), but dermal exposure is not considered to be significant. The uptake of manganese from air, food, milk, and water has been studied (Davidsson et al. 1988, 1989a). However, absorption from soil has not been investigated. In view of the potential for tight binding of manganese to some soil types, studies on this subject would be valuable in evaluating risk to humans, especially children who may ingest contaminated soils near hazardous waste sites. Additional information would also be valuable on the relative bioavailability of different manganese compounds across various environmental media.

Food Chain Bioaccumulation. It has been established that while lower organisms (e.g., plankton, aquatic plants, and some fish) can significantly bioconcentrate manganese, higher organisms (including humans) tend to maintain manganese homeostasis (EPA 1984; Folsom et al. 1963; Thompson et al. 1972). This indicates that the potential for biomagnification of manganese from lower trophic levels to higher ones is low, and it does not appear that additional research in this area is essential at this time.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of manganese in contaminated media at hazardous waste sites are needed so that the information obtained on levels of manganese in the environment can be used in combination with the known body burden of manganese to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Manganese levels have been monitored in all environmental media, including air, water, soil, and food (Capar and Cunningham 2000; EPA 1984; NAS 1980a; Pennington et al. 1986). Estimates are available for the average human intake levels of manganese from water, air, and food (EPA 1984; WHO 2004b).

More specific data on levels in the environment around those particular sites where manganese is believed to have been dumped would be helpful in determining the extent of exposure levels around such waste sites. In particular, data on the concentration of manganese in the air around hazardous waste sites would be valuable in assessing the potential significance of this exposure pathway.

Exposure Levels in Humans. This information is necessary for assessing the need to conduct health studies on these populations. Manganese is a normal component of human tissues and fluids (Sumino et al. 1975; Tipton and Cook 1963). Increased average levels of manganese have been detected in blood and urine of populations exposed to high concentrations of manganese in the workplace (Roels et al. 1987b). Manganese has been measured in hair samples of children residing near a hazardous waste site (Wright et al. 2006); however, the absence of data on levels of manganese in the hair of U.S. children in the general population makes it difficult to draw conclusions about whether the exposures of the children at this site are unusually high. Surveys of manganese levels in the blood or urine of populations living near waste sites could be useful in identifying groups with above-average levels of manganese exposure. More information is also needed to determine whether iron-deficient populations have a higher manganese body burden. Manganese and iron have many physico/chemical similarities and there is a possibility of competition between these elements. Increased manganese concentrations have been shown to inhibit the metabolic function of the iron-dependent enzyme, aconitase (Zheng et al. 1998). Iron deficiency is the single most prevalent nutritional deficiency in the world, and so the potential health risk associated with iron deficiencies exacerbating the brain manganese burden may represent a crucial issue of exposure and susceptibility, and has yet to be evaluated. Air concentrations in areas with high traffic density are sometimes higher than the guide level (Zayed et al. 1999a); therefore, some individuals could be at risk. Research focusing on the environmental level of exposure of certain groups of the population, such as those living near a major highway, is needed.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children are exposed daily to manganese. The compound is an essential trace element vital for the body to function properly and body burden studies are available (Alarcón et al. 1996; Rükgauer et al. 1997). Although the primary pathway for exposure is the diet, studies involving

exposures to airborne manganese (e.g., in dust that may be present at a nearby hazardous waste site or manganese-processing plant) would aid in understanding other pathways that may contribute significantly to children's total body burden of manganese

Soil ingestion is likely the only unique exposure pathway for children. Additional studies concerning bioavailability of manganese from soil would provide important information concerning the proportion of the total daily manganese intake that could originate from ingested soils.

Although infants differ in their weight-adjusted intake of manganese, it is unknown whether older children differ in this parameter. Studies concerning this end point would be very valuable.

Studies involving inhalation or ingestion exposure to MMT in the young are very few (Komura and Sakamoto 1992b, 1994). Although these studies indicate that MMT had very little measurable effect on development, only one dose level was used. Although analytical data indicate that environmental MMT is unlikely to persist (Lynam et al. 1999), it is unknown what typical body burdens of manganese might be in children following long-term exposure to MMT combustion products. Additional studies measuring these end points in the young would be helpful.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for manganese were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2008) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1.

Researchers at the University of Delaware (D.M. Di Toro, principal investigator) are conducting research to develop models for predicting the toxicity and mobilization of individual metals (including manganese) and metal mixtures in sediments. These predictions are critical in evaluating the risk associated with contaminated sediments at Superfund sites.

Thomas R. Guilarte and co-workers at Johns Hopkins University are studying the behavioral and neuropathological changes that occur as a result of chronic exposure to low levels of manganese. The findings from the proposed studies will be used to aid in understanding the mechanism(s) of chronic, low-level manganese neurotoxicity. Moreover, these data will identify sensitive markers for the early detection of manganese neurotoxicity that can be used *in vivo* in humans.

Wei Zheng and co-workers at Purdue University are studying the biomarkers for early diagnosis of manganese toxicity among Chinese smelting workers. They plan to combine exposure indices and biological effects into one parameter for quick clinical assessment of manganese toxicity. They are also conducting clinical trials to investigate the efficacy of para-aminosalicylic acid in treatment of severe manganism. Advanced MRI and MRS techniques along with molecular biotechnology have been used in these studies.

Donald Smith and co-workers at the University of California, Santa Cruz are studying the effect that early manganese exposure in neonatal rats has on neurobehavioral and neurocognitive deficits and comparing these data with epidemiological studies in children.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring manganese, its metabolites, and other biomarkers of exposure and effect to manganese. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

The most common analytical procedures for measuring manganese levels in biological and environmental samples use the methods of atomic absorption spectroscopy (AAS) and atomic emission spectroscopy (AES). In AAS analysis, the sample is aspirated into a flame or in a graphite furnace (GFAAS) until the element atomizes (Tsalev 1983). The ground-state atomic vapor absorbs monochromatic radiation from a source and a photoelectric detector measures the intensity of radiation absorbed at 279.5 nm (Tsalev 1983). Furnace atomic absorption analysis is often used for very low analyte levels and for the analysis of solid samples or slurries (Baruthio et al. 1988). Inductively coupled plasma-atomic emission spectrometry (ICP-AES) analysis is frequently employed for multianalyte analyses that include manganese. Neutron activation analysis is also a very effective method for determining manganese concentrations in different samples (Rose et al. 1999). This technique uses no reagents and a minimum of sample handling; thus, potential contamination with exogenous sources of manganese can be avoided. In addition, the technique has a low detection limit in biological tissues (4 ng/g) and high precision. Further, the technique can be used for environmental samples as well as biological samples. Other methods for measuring manganese include spectrophotometry, mass spectrometry, neutron activation analysis, and x-ray fluorimetry.

It is important to note that none of these methods distinguish between different oxidation states of manganese or between different manganese compounds. Thus, monitoring data on manganese are nearly always available only as total manganese present.

Levels of organometallic species in environmental and toxicological samples are typically in ppb concentrations, ng/mL in solution, or ng/g in solids (Walton et al. 1991). Therefore, methods of determination must be both selective and sensitive, achieved usually by coupling liquid or gas chromatography (GC) with detection via electrochemical, mass spectrometry, and atomic spectrometry detectors. A number of analytical methods for quantifying MMT in gasoline have been described, including simple determination of total elemental manganese by atomic absorption and gas chromatography followed by flame-ionization detection (FID). These methods usually measure MMT by detecting the metallic portion of the compound and reporting detection of MMT as manganese.

X-ray absorption near edge structure (XANES) and x-ray absorption fine structure (XAFS) spectroscopy have been used for the analysis of manganese-containing particulates emitted from automobile exhaust containing MMT (Mölders et al. 2001; Ressler et al. 2000). These methods are particularly useful in determining the chemical speciation and valence state of manganese or other metal complexes attached to particulate matter.

7.1 BIOLOGICAL MATERIALS

Normally, determination of manganese in biological materials requires digestion of the organic matrix prior to analysis. For tissue samples or feces (detection limits ranging from 0.2 to <1 μg/g), this is usually done by treatment with an oxidizing acid mixture such as 3:1:1 (v/v/v) nitric:perchloric:sulfuric acid mixture (Kneip and Crable 1988a). Fluid samples such as blood, saliva, or urine may be digested in the same way (blood, detection limits=1 μg/100 g, 10 μg/L), or manganese can be extracted by an ion exchange resin (urine, detection limit=0.5–2 μg/L) or by chelating agents such as cupferon in methylisobutylketone (urine, detection limit=<1 μg/L). A method for directly measuring concentrations of trace elements in hair that does not require digestion prior to analysis has been developed (Stupar and Dolinsek 1996). While the authors used their technique to determine chromium, lead, and cadmium levels in hair, it is assumed that their slurry sampling or direct solid sampling technique might also work for manganese determination. Table 7-1 summarizes some of the methods used for sample preparation and analysis of manganese in biological materials. It is important to note that special care is needed to avoid contamination of biological materials with exogenous manganese, especially for samples with low levels of manganese (Tsalev 1983; Versieck et al. 1988).

GC-FID may be used to determine levels of MMT in biological tissues and fluids with a detection limit of 1–2 ppm and percent recovery of 93.5–102.7% (Hanzlik et al. 1979).

Table 7-1. Analytical Methods for Determining Manganese in Biological Materials[a]

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Extraction into methylisobutyl-ketone as the cupferon chelate	AAS (furnace technique)	<1 µg/L[b]	No data	Baselt 1988
Urine	Extract with resin, ash resin	ICP-AES	<1 µg/L[b]	100±10	NIOSH 1984d
Blood	Acid digestion	ICP-AES	1 µg/dL	98±2.1	Kneip and Craple 1988a
Blood	Digestion in oxidizing acid	ICP-AES	1 µg/100 g	98±2.1	NIOSH 1984c
Tissue	Digestion in oxidizing acid	ICP-AES	0.2 µg/g	98±2.1	NIOSH 1984c
Tissue	Acid digestion	ICP-AES	0.2 µg/g	104±5.6	Kneip and Craple 1988a
Feces	Dry at 110 °C, ash at 550 °C, dissolve in nitric acid	AAS (furnace technique)	<1 µg/g	102±7	Friedman et al. 1987
Hair	Digestion in concentrated nitric:perchloric acid (3:1) mixture	Flameless AAS	<0.2 µg/g	No data	Collipp et al. 1983
Hair	(a) slurry sample introduction technique (hair powder added to twice distilled water to measure bulk hair trace elements, or (b) direct introduction of hair segments to measure longitudinal gradients	ETAAS (furnace technique)	No data	No data	Stupar and Dolinsek 1996[c]
Methods for determination of MnDPDP					
Human plasma	Mix heparinized blood samples of patients receiving MnDPDP via injection with solid trisodium phosphate dodecahydrate pH 10.0±0.2; ultrafiltrate	Mixed-bed resin HPLC-anion exchange and reverse-phase	0.8–2.3 µM (manganese compounds) 0.1–0.8 µM (zinc compounds) of 50 µL injection volume	85–115	Toft et al. 1997a

[a]Magnetic resonance imaging (MRI) has been useful in determining brain accumulation of manganese, but is not a quantitative method; therefore, it is not listed as an entry in this table.
[b]Estimated from sensitivity and linearity data
[c]Methods were used to determine levels of chromium, lead, and cadmium in hair. Manganese concentrations in hair were evaluated for some, but not all, of the samples and tested one, but not both, new methods. However, it is assumed that both techniques will work for the trace element manganese.

AAS = atomic absorption spectroscopy; HPLC = high performance liquid chromatography; ICP-AES = inductively coupled-plasma atomic emission spectroscopy; MnDPDP = mangafodipir; NIOSH = National Institute for Occupational Safety and Health

Walton et al. (1991) have described high performance liquid chromatography (HPLC) coupled with laser-excited atomic fluorescence spectrometry (LEAFS) to detect various species of MMT. The detection limit for this GC-LEAFS method ranged from 8 to 20 pg of manganese for the various organomanganese species; the detection limit for determining manganese in MMT was 0.4 ng/mL. This limit of detection was several orders of magnitude better than those for HPLC with ultraviolet (UV) detection or HPLC-atomic fluorescence spectrometry (AFC) (Walton et al. 1991), but was worse than detection by GC-FID (DuPuis and Hill 1979). Walton et al. (1991) used their method to determine manganese species present in rat urine after rats had been administered MMT prepared in propylene glycol via subcutaneous injection.

Table 7-1 summarizes some common methods for the determination of manganese in various types of biological materials.

7.2 ENVIRONMENTAL SAMPLES

Manganese in air exists as particulate matter, so sampling is done by drawing air through a filter in order to collect the suspended particles. A variety of filter types (e.g., glass fibers and cellulose acetate) and sampling devices (e.g., low volume, high volume, and dichotomous) are available, depending on the particle sizes of concern and the concentration range of interest. In some cases, material on the filter may be analyzed directly (e.g., by x-ray fluorescence), or the filter may be digested by ashing in acid prior to analysis. In general, sensitivity is dependent on the volume of air drawn through the filter prior to analysis, and typically, detection limits are 1–2 μg/sample.

Several analytical methods from the EPA Office of Solid Waste publication SW-846, entitled *Test Methods for Evaluating Solid Waste, Physical/Chemical Methods* are applicable for analyzing manganese in water, soil, and wastes. In addition, the EPA Emission Measurement Center (EMS) and Office of Water (OW) have standardized methods for the measurement of manganese and other metals in environmental media. Several of these methods, including the analytical instrumentation and detection limits, are summarized in Table 7-2.

Water may either be analyzed directly, or, if the concentration of manganese is low, a concentration step (e.g., evaporation, extraction, and binding to a resin) may be employed (detection limits ranging from 0.005–50 μg/L). In all cases, acid is added to the sample to prevent precipitation of manganese.

Table 7-2. Analytical Methods for Determining Manganese in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect sample on MCE or PVC filter, followed by nitric/perchloric acid ashing	Method 7300 (ICP-AES)	0.2 mg/m^3	94.7–101 (MCE) 99.3–101.9 (PVC)	NIOSH 2003a
Air	Collect sample on MCE filter, followed by hot block/HCl/HNO_3 digestion	Method 7303 (ICP-AES)	1.2 mg/m^3	No data	NIOSH 2003b
Air	Collect sample on MCE or PVC filter, followed by aqua regia ashing	Method 7301 (ICP-AES)	0.2 mg/m^3	91.2–103.5 (MCE) 77.4–93.4 (PVC)	NIOSH 2003c
Water	Acidify with nitric acid	AAS (furnace technique)	0.2 µg/L	No data	EPA 1983b
Water	Acidify with nitric acid	AAS (flame) AAS (furnace) ICP-AES	2 µg/L 0.01 µg/L 1 µg/L	No data No data No data	Taylor 1982
Water	Acidify with nitric acid	Method 311 (AAS)	<10 µg/L	No data	APHA 1998a
Water	Filter and acidify filtrate with HNO_3 and analyze	Method 3113A (AAS furnace technique)	0.2 µg/L	No data	APHA 1998b
Water	Digest sample with HNO_3/HCl and analyze	Method 3120B (ICP-AES)	2 µg/L	No data	APHA 1998c
Water	Acidify with nitric acid	AAS (direct aspiration)	10 µg/L	100±2[a]	EPA 1983a
Water	Acid digest and analyze	Method 3125A (ICP-MS)	0.002 µg/L	91.81–110	APHA 1998d
Water	Preconcentration manganese-containing solution and 3,3'5,5'-tetramethyl-benzidine (TMB) onto filter paper; add oxidant KIO_4 to catalyze oxidation; measure absorbance	Catalytic kinetic method of analysis	0.005 µg/L	No data	Beklemishev et al. 1997
Water, waste water, sludge, and soils	For dissolved constituents: filter, acidify filtrate, and analyze; for samples containing solids: digestion with HNO_3/HCl prior to analysis	Method 200.8 (ICP-MS)	0.01–0.04 µg/L (liquids); 0.05 mg/kg (solids)	95.8–96.9 (water); 95.2–103.6 (wastes)	EPA 1994b

Table 7-2. Analytical Methods for Determining Manganese in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water and wastes	Acid digestion	AAS	10 µg/L	100±2	EPA 1986c
Water, solids, sediment,	For dissolved constituents: filter, acidify filtrate, and analyze; for samples containing solids: digestion with HNO_3/HCl prior to analysis	Method 6010C (ICP-AES)	0.93 µg/L	No data	EPA 2007a
Foods	Digest wet or dry foods with HNO_3–H_2SO_4 mixture (12:2 mL)	AAS (flame) AAS (furnace)	AAS (flame): 0.15 mg/kg AAS (furnace): 1.10 µg/kg	No data	Tinggi et al. 1997
Foods	Digestion with nitric, sulfuric, perchloric acid solution	ICP-AES	0.2 mg/kg	96.2–97	Capar and Cunningham 2000
Methods for MMT determination					
Air	Draw known volume of air through XAD-2 sampling tubes for 10–60 minutes	GC-ECD	0.001 mg/m^3 (in 10-L sample); 0.02 ng from a 2.0 µL injection of a 0.01 µg/mL MMT solution	No data	Gaind et al. 1992
Gasoline	Dilute gasoline in acetone (1:10)	Capillary GC-ACP detector	62 pg/s	No data	Ombaba and Barry 1994
Gasoline	Dilute with hexane (1:99); direct injection	GC-ECD	No data	No data	Gaind et al. 1992
Gasoline	Inject sample	GC-MED	0.25 pg/s	No data	Quimby et al. 1978
Gasoline	Inject sample	GC-FPD	0.6 ppm	No data	Aue et al. 1990

[a]Percent recovery at manganese concentration >80 µg/L; at lower concentrations (10–20 µg/L), percent recoveries were >120%.

AAS = atomic absorption spectrometry; ACP = alternating current plasma; AES = atomic emission spectroscopy; APDC = ammonium pyrrolidine dithiocarbamate; APHA = American Public Health Association; ECD = electron-capture detection; EPA = Environmental Protection Agency; FPD = flame photometric detection; GC = gas chromatography; ICP = inductivity coupled plasma; MCE = mixed cellulose ester; MED = microwave emission detector; MS = mass spectrometry; NIOSH = National Institute for Occupational Safety and Health; PVC = polyvinyl chloride; XRF = x-ray fluorescence

Beklemishev et al. (1997) measured the concentrations of manganese in tap and river water. Their analytical method relies on an indicator reaction that is catalyzed by Mn(II) (the oxidation of 3,3',5,5'-tetramethylbenzidine [TMB] by potassium periodate [KIO_4]) and is carried out on the surface of a paper-based sorbent. The advantages of this novel technique are that it has a much lower detection limit (0.005 μg/L) than do established methods and is transportable, allowing it to be used for rapid tests in the field (i.e., spot tests and similar procedures).

Determination of manganese levels in soils, sludges, or other solid wastes requires an acid extraction/ digestion step prior to analysis. The details vary with the specific characteristics of the sample, but usually treatment will involve heating in nitric acid, oxidation with hydrogen peroxide, and filtration and/or centrifugation to remove insoluble matter.

Manganese levels in foods have been determined in order to define more clearly human dietary requirements or levels of absorption of manganese from the diet (Tinggi et al. 1997). Atomic absorption spectrometry has been the most widely used analytical technique to determine manganese levels in a broad range of foods, as well as other environmental and biological samples (Tinggi et al. 1997). Tinggi et al. (1997) contributed a wet digestion technique using a 12:2 (v/v) nitric:sulfuric acid mixture for their determination, and for food samples with low levels of manganese, they found that the more sensitive graphite furnace atomic absorption analysis was required. Because manganese is often found at very low levels in many foods, its measurement requires methods with similarly low detection limits; these researchers identified detection limits of 0.15 mg/kg (ppm) and 1.10 μg/kg (ppb) for flame and graphite furnace atomic absorption spectrometry, respectively (Tinggi et al. 1997). Neutron activation analysis is an effective technique for measuring manganese in environmental samples; it provides a low detection limit and high precision (Kennedy 1990).

A number of analytical methods for quantifying MMT in gasoline have been described including simple determination of total elemental manganese by atomic absorption (Smith and Palmby 1959) and gas chromatography followed by FID (DuPuis and Hill 1979). The former has measured manganese concentrations from 0.1 to 4 g/gallon of gasoline after dilution of the sample with isooctane to minimize the effects of differences in base stock composition and is accurate to about 3% of the amount of manganese present. The latter has an absolute detection limit of 1.7×10^{-14} g/sample (0.017 pg/s) and could easily measure 6 mg/gallon of manganese in a gasoline sample; it is one of the most sensitive approaches. Aue et al. (1990) described a method in which MMT is detected in gasolines by gas chromatography coupled with flame photometric detection (FPD); the chemiluminescence of manganese

is measured to determine MMT levels in a method that uses simple, inexpensive, and commercially available instrumentation. MMT levels can be determined down to 0.6 ppm (w/w) in gasoline (Aue et al. 1990). In another method showing excellent performance, Quimby et al. (1978) used GC followed by atmospheric pressure helium microwave detection system (or microwave emission detector [MED]); this method has a high degree of selectivity ($1.9x10^6$) and a detection limit of 0.25 pg/s at a wavelength of 257.6 nm.

GC followed by electron-capture detection (ECD) (Gaind et al. 1992) or alternating current plasma (ACP) emission detection (Ombaba and Barry 1994) (detection limit: 62 pg as manganese) has also been described for determination of MMT in gasoline. GC followed by ACP emission detection has been described for detecting MMT in air samples; airborne MMT concentrations as low as 0.001 mg/m^3 can be measured (Ombaba and Barry 1994).

Table 7-2 summarizes some common methods for the determination of manganese in various types of environmental media.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of manganese is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of manganese.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect

Exposure. Sensitive and selective methods are available for the detection and quantitative measurement of manganese in blood, urine, hair, feces, and tissues (Baselt 1988; Collipp et al. 1983; Friedman et al. 1987; Kneip and Crable 1988a; NIOSH 1984c, 1984d). Since levels in biological samples are generally rather low, sample contamination with exogenous manganese can sometimes occur (Tsalev 1983; Versieck et al. 1988). Development of standard methods for limiting this problem would be useful. Measurement of average manganese concentrations in these materials has proved useful in comparing groups of occupationally exposed people to nonexposed people (Roels et al. 1987b), but has not been especially valuable in evaluating human exposure in individuals (Rehnberg et al. 1982). This is due to the inherent variability in intake levels and toxicokinetics of manganese in humans, rather than a limitation in the analytical methods for manganese. Smith et al. (2007) have discussed the limitations of using blood and urine levels of manganese as biomarkers of exposure and have suggested further investigation of using manganese levels in teeth and hair as exposure biomarkers. The use of tooth enamel as a potential biomarker has been explored by Ericson et al. (2007). Josephs et al. (2005) have also discussed the limitations of using manganese levels in serum or urine as a direct measure of exposure since free manganese does not accumulate in the circulatory system. Magnetic resonance imaging (MRI) in conjunction with analysis of manganese in whole blood (MnB), plasma (MnP), or red blood cells has been used in the diagnosis of manganism in humans (Jiang et al. 2007). Development of additional noninvasive methods for measuring whole-body or tissue-specific manganese burdens would be valuable in estimating human exposure levels, but would be limited by the same considerations of individual variability that limit existing methods.

There is a need to evaluate the accuracy and reproducibility of analytical measures of manganese in biological media, so that analytical variability is not inappropriately incorporated into natural biological variability in reported data, as may now be the case.

Effect. No reliable biomarkers of manganese effect are known. Biochemical changes such as altered blood or urinary levels of steroids, neurotransmitters, or their metabolites are plausible biomarkers of exposure, but this possibility has not been thoroughly investigated. Although methods exist for the analysis of these biochemicals, further work to improve the analyses does not seem warranted unless the utility of this approach is established.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. All humans are exposed to manganese, primarily through food (EPA 1984). Near a hazardous waste site that contains manganese or a factory that uses manganese, humans could receive above-average exposure by inhalation of air or ingestion of water, soil, or food. Methods exist for the analysis of manganese in air (NIOSH 2003a, 2003b, 2003c), water (APHA 1998a, 1998b, 1998c, 1998d; EPA 1994b, 2007a), and soils and sediment (EPA 2007a). Methods are also available to analyze manganese in food (Capar and Cunningham 2000; Tinggi et al. 1997).

7.3.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2008) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs pertinent to the analysis of manganese in biological or environmental samples. Donald Smith and co-workers at the University of California, Santa Cruz are studying the role of manganese in neurodegenrative disease using particle induced x-ray emission (PIXE) analyses of *in situ* brain regional manganese levels of rodents(FEDRIP 2008). Carmen Enid Martinez and co-workers at Pennsylvania State University are studying the elemental distribution in soil particles using novel techniques that include synchrotron-based microprobe- x-ray fluorescence (XRF) and x-ray diffraction (XRD) in addition to scanning electron microscopy coupled to energy or wavelength dispersive x-ray analysis (SEM/E-W-DS). Metal solubility measurements are to be studied by inductively coupled plasma emission spectroscopy (ICP), anodic/cathodic stripping voltammetry (A/C-SV), and ion-selective electrodes (ISE).

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

An MRL of $3x10^{-4}$ mg manganese/m^3 (0.3 µg manganese/m^3) in respirable dust has been derived for chronic inhalation exposure to manganese. As discussed in Appendix A, dichotomous models in the EPA Benchmark Dose software were fit to the incidence data for abnormal eye-hand coordination scores in battery workers exposed to respirable manganese (Roels et al. 1992). The model with the lowest AIC was selected as the best fitting model, and the $BMCL_{10}$ from this model, 142 µg respirable manganese/m^3, was selected as the point of departure for the chronic inhalation MRL. The MRL of 0.3 µg respirable manganese/m^3 was derived by adjusting the point of departure to a continuous exposure basis (142 x 5/7 x 8/24) and dividing by an uncertainty factor of 100:

- 10 for uncertainty about human variability including possibly enhanced susceptibility of the elderly, infants, and children; individuals with chronic liver disease or diminished hepatobiliary function; and females and individuals with iron deficiency; and
- 10 for limitations/uncertainties in the database including the lack of epidemiological data for humans chronically exposed to soluble forms of manganese and the concern that the general population may be exposed to more soluble forms of manganese than most of the manganese-exposed workers in the principal and supporting studies and the uncertainty that a factor of 10 for human variability will provide enough protection for manganese effects on brain development in children. In addition, data on developmental toxicity for this route and duration of exposure are lacking. There is limited information on reproductive effects in females (one study in rat dams) and reported effects on male reproductive organs have not been clearly associated with decreased reproductive function. Though it is clear that the neurological system is the target organ for effects from chronic-duration inhalation exposure to manganese, data are lacking to fully characterize the potential risk for all organ systems from chronic inhalation exposure.

No oral MRLs were derived for acute-, intermediate-, or chronic-duration oral exposure to manganese, but an interim guidance value of 0.16 mg manganese/kg/day, based on the Tolerable Upper Intake Level for adults of 11 mg manganese/day (established by the U.S. Food and Nutrition Board/Institute of Medicine [FNB/IOM 2001]) is recommended to be used for ATSDR public health assessments of oral exposure to inorganic forms of manganese. The interim guidance value is necessary because of the prevalence of manganese at hazardous waste sites and the fact that manganese is an essential nutrient. It is recommended to be used until more information on actual intake levels across environmental media can be obtained.

The EPA derived a chronic inhalation RfC of $5x10^{-5}$ mg/m^3 for respirable manganese (IRIS 2008). This value is based on the LOAEL of 0.15 mg/m^3 from a study of battery workers exposed to manganese dioxide (Roels et al. 1992). EPA verified this assessment in 1993. The LOAEL was calculated by dividing the geometric mean concentration of the lifetime-integrated respirable dust concentration for the exposed workers by the average duration of employment in the facility. EPA calculated the RfC by adjusting for continuous exposure and dividing by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 to protect sensitive individuals, and 10 for database limitations reflecting both the less-than-chronic periods of exposure and the lack of developmental data, as well as potential, but unquantified, differences in the toxicity of different forms of manganese). The estimated breathing rate in the exposed workers was assumed to be 10 m^3/workday.

The EPA (IRIS 2008) derived an oral reference dose (RfD) value of 0.14 mg/kg/day manganese from all oral exposures. As of August 2008, this value was last updated in May 1996. The agency suggested using a modifying factor of 1 if the manganese is ingested in food and a modifying factor of 3 if the element is ingested in water or soil. The RfD was developed using a previous determination of the upper range of total dietary intake of 10 mg/day. The modifying factor of 1 was based on composite data on chronic human NOAELs from the World Health Organization (WHO 1973) (0.11–0.13 mg/kg/day), the National Academy of Sciences/National Research Council (1989) "safe and adequate level" (0.04–0.07 mg/kg/day), and a study by Freedland-Graves et al. (1994) concerning nutritional requirements for manganese. The FNB/IOM (2001) re-established an Adequate Intake (AI) value for manganese for men and women at 2.3 and 1.8 mg manganese/day, respectively (for 70-kg individuals, this would result in exposures of 0.033 and 0.026 mg manganese/kg/day, respectively). A Tolerable Upper Intake Level (UL) of 11 mg/day was also set by the FNB/IOM (2001) for adults based on a NOAEL for Western diets (approximately 0.16 mg manganese/kg/day assuming a 70-kg body weight).

The international and national regulations, advisories, and guidelines regarding manganese in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Manganese

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2008
WHO	Air quality guidelines		WHO 2000a
	Manganese[a]	0.15 µg/m^3	
	Drinking water quality guidelines		WHO 2004a
	Manganese[b]	0.4 mg/L	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2007
	Manganese	0.2 mg/m^3	
	MMT[c]	0.2 mg/m^3	
	TLV basis (critical effects)		
	Manganese	Central nervous system impairment	
	MMT	Central nervous system impairment, lung, liver, and kidney damage	
EPA	Second list of AEGL priority chemicals for guideline development		EPA 2008a
	Manganese	Yes	
	MMT	Yes	
NIOSH	Category of pesticides		NIOSH 1992
	Potassium permanganate	Group 1 pesticide	
	REL (10-hour TWA)		NIOSH 2005
	Manganese	1 mg/m^3	
	Manganese (II,III) oxide[d]	Not established	
	MMT[e]	0.2 mg/m^3	
	STEL (15-minute TWA)		
	Manganese	3 mg/m^3	
	IDLH		
	Manganese	500 mg/m^3	
	Target organs		
	Manganese	Respiratory system, central nervous system, blood, and kidneys	
	Manganese (II,III) oxide	Respiratory system, central nervous system, blood, and kidneys	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Manganese

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NIOSH	Target organs *(cont.)*		
	MMT	Eyes, central nervous system, liver, and kidneys	
OSHA	PEL (8-hour TWA) for general industry (ceiling limit)		OSHA 2007c 29 CFR 1910.1000, Table Z-2
	Manganese (compounds and fume)	5 mg/m^3	
	PEL (8-hour TWA) for shipyard industry (ceiling limit)		OSHA 2007a 29 CFR 1915.1000
	Manganese (compounds and fume)	5 mg/m^3	
	PEL (8-hour TWA) for construction industry (ceiling limit)		OSHA 2007b 29 CFR 1926.55, Appendix A
	Manganese (compounds and fume)	5 mg/m^3	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2008b 40 CFR 116.4
	Potassium permanganate	Yes	
	Drinking water contaminant candidate list		EPA 1998
	Manganese	Yes	
	Drinking water standards and health advisories		EPA 2006a
	Manganese		
	1-Day health advisory for a 10-kg child	1 mg/L	
	10-Day health advisory for a 10-kg child	1 mg/L	
	DWEL	1.6 mg/L	
	Lifetime	0.3 mg/L	
	National recommended water quality criteria		EPA 2006c
	Manganese[f]		
	Human health for consumption of water + organism	0.05 mg/L	
	Human health for consumption of organism only	0.1 mg/L	
	National secondary drinking water standards		EPA 2003b
	Manganese[g]	0.05 mg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2008d 40 CFR 117.3
	Potassium permanganate	100 pounds	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Manganese

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
c. Food			
EPA	Inert ingredients permitted for use in nonfood use pesticide products		EPA 2008e
	Mn(II) carbonate	Yes	
	Manganese dioxide	Yes	
	Manganese sulfate	Yes	
	Potassium permanganate	Yes	
FDA	Bottled drinking water		FDA 2007a 21 CFR 165.110
	Manganese	0.05 mg/L	
	EAFUS[h]		FDA 2008
	Potassium permanganate	Yes	
	Indirect food additives: adhesives and components of coatings		FDA 2007b 21 CFR 175.105
	Potassium permanganate	Yes	
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2007
	Manganese	No data	
	MMT	No data	
DEA	Records and reports of listed chemicals		DEA 2007 21 CFR 1310.02
	Potassium permanganate	List II chemical	
EPA	Carcinogenicity classification		IRIS 2008
	Manganese	Group D[I]	
	RfC		
	Manganese	$5x10^{-5}$ mg/m^3	
	RfD		
	Manganese	0.14 mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2008c 40 CFR 302.4
	Manganese[J]	Yes	
	Potassium permanganate[k]	Yes	
	Reportable quantity		
	Manganese	None[l]	
	Potassium permanganate	100 pounds	
	Effective date of toxic chemical release reporting		EPA 2008g 40 CFR 372.65
	Manganese	01/01/1987	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Manganese

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Superfund, emergency planning, and community right-to-know		
	Extremely Hazardous Substances		EPA 2008f 40 CFR 355, Appendix A
	MMT		
	Reportable quantity	100 pounds	
	Threshold planning quantity	100 pounds	
NTP	Carcinogenicity classification	No data	NTP 2005

[a]TWA based on effects other than cancer or odor/annoyance using an averaging time of 1 year.
[b]Concentrations of the substance at or below the health-based guideline value may affect the appearance, taste, or odor of the water, resulting in consumer complaints.
[c]Skin designation refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapors, liquids, and solids.
[d]NIOSH has not established a REL for magnesium oxide fume under the “Proposed Rule on Air Contaminants" (29 CFR 1910, Docket No. H-020) in which NIOSH questioned whether the OSHA PEL for magnesium oxide fume (1 mg/m^3) was adequate enough to protect workers from potential health hazards (NIOSH 2005).
[e]Skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices, gloves, coveralls, goggles, and other appropriate equipment.
[f]The human health criteria are based on carcinogenicity of 10^{-6} risk. This criterion for manganese is not based on toxic effects, but rather is intended to minimize objectionable qualities such as laundry stains and objectionable tastes in beverages.
[g]National Secondary Drinking Water Standards are non-enforceable guidelines regulating contaminants that may cause cosmetic effects (such as skin or tooth discoloration) or aesthetic effects (such as taste, odor, or color) in drinking water.
[h]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[i]Group D: not classifiable as to human carcinogenicity.
[j]Designated CERCLA hazardous substance pursuant to Section 112 of the Clean Air Act.
[k]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.
[l]No reportable quantity is being assigned to the generic or broad class.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DEA = Drug Enforcement Administration; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MMT = methylcyclopentadienyl manganese tricarbonyl; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term expsoure limit; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Manganese
CAS Number: 7439-96-5
Date: August 8, 2008
Profile Status: Draft 3, Pre-Public
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key:
Species: Human

Minimal Risk Level: 0.0003 mg respirable manganese/m^3 (0.3 µg/m^3)

Reference: Roels HA, Ghyselen P, Buchet JP, et al. 1992. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. Br J Ind Med 49:25-34.

Experimental design: Neurological effects of manganese exposure were evaluated in 92 male workers in a dry alkaline battery factory. The control group was 101 age- and area-matched workers not occupationally exposed to manganese but with similar work schedules and workloads. Workers were exposed for an average duration of 5.3 years (range 0.2–17.7 years) to average (geometric mean) concentrations of 0.215 and 0.948 mg manganese/m^3 in respirable and total dust, respectively. The authors noted that the work processes had not changed significantly in the last 15 years, indicating that past exposures should be comparable to those measured in the study. Neurological function was measured using an audioverbal short term memory test, a simple visual reaction time test using a chronoscope, and three manual tests of hand steadiness, coordination, and dexterity. This report provided good documentation of individual exposure data and characterization of the population studied.

Effects noted in study and corresponding doses: Manganese-exposed workers performed significantly worse than the controls on the neurobehavioral tests, with particular differences in simple reaction time, eye-hand coordination, and hand steadiness. Dr. Harry Roels provided the data on the manganese-exposed group evaluated in this study. These data included individual exposure levels and whether the individual had an abnormal performance in the neurobehavioral tests (scores below the 5^{th} percentile score of the control group). Percent precision score in the eye-hand coordination test was the most sensitive end point among the end points showing statistically significantly elevated incidences of abnormal scores and was selected as the basis of the MRL. Average exposure concentration for each worker was calculated by dividing the individual lifetime integrated respirable concentration (LIRD; calculated by Dr. Roels from occupational histories and measurements of workplace air manganese concentrations) by the individual's total number of years working in the factory. Individuals were grouped into eight exposed groups and the control group, and the average of the range in each group was used in benchmark modeling of the incidence data for number of workers with abnormal percent precision eye-hand coordination scores (Table A-1).

Table A-1. Incidence Data for Abnormal Eye-Hand Coordination Scores in Workers Exposed to Respirable Manganese[a]

Group[b]	Range of manganese (respirable) exposure concentrations[c] (µg/m^3)	Average manganese (respirable) exposure concentration (µg/m^3)	Number of workers with abnormal eye-hand coordination score[d]	Total number of workers
1	Control	0	5	101
2	1.0–99	33	1	7
3	100–174	160	3	11
4	175–199	179	3	28
5	200–249	208	3	22
6	250–299	280	1	6
7	300–399	307	2	3
8	400–499	451	4	9
9	>500 (523–650)	564	4	6

[a]Based on individual exposure and dichotomized response data collected by Roels et al. (1992).
[b]Individuals were sorted into 9 groups, based on manganese exposure, for use in benchmark dose modeling
[c]For each individual, the time-weighted average exposure concentration (respirable manganese) was calculated by dividing the individual lifetime integrated respirable concentrations (LIRD) by the individual's respective total number of years exposed.
[d]An abnormal eye-hand coordination score was defined by Roels as a score below the 5th percentile score in the control group for percent precision (52.4) in the eye-hand coordination test.

Available dichotomous models in the EPA Benchmark Dose Software (version 1.4.1c) were fit to the incidence data for abnormal eye-hand coordination scores in workers exposed to respirable manganese (Roels et al. 1992, Table A-1). Results from the modeling are shown in Table A-2, including: (1) the BMC_{10} and the 95% lower confidence limit ($BMCL_{10}$) calculated as an estimate of the concentration associated with a 10% extra risk for an abnormal score; (2) BMC_{05} and $BMCL_{05}$ values; (3) the p-value for the chi-square goodness of fit statistic (adequate fit, $p > 0.1$); and (4) Akaike's Information Criteria (AIC) [lower AIC indicates better fit when comparing models, EPA (2000)]. Based on the chi-square and AIC measures of fit, all of the models provided adequate and comparable fits to the data (the quantal linear and Weibull models had the same parameter values The model with the lowest AIC, the logistic model, was selected as the best fitting model (Table A-2), and the $BMCL_{10}$ from the logistic model, 142 µg/m^3, was selected as the point of departure for the chronic inhalation MRL. Figure A-1 plots predicted risks for abnormal scores from the logistic model and observed incidence values calculated from data in Table A-1.

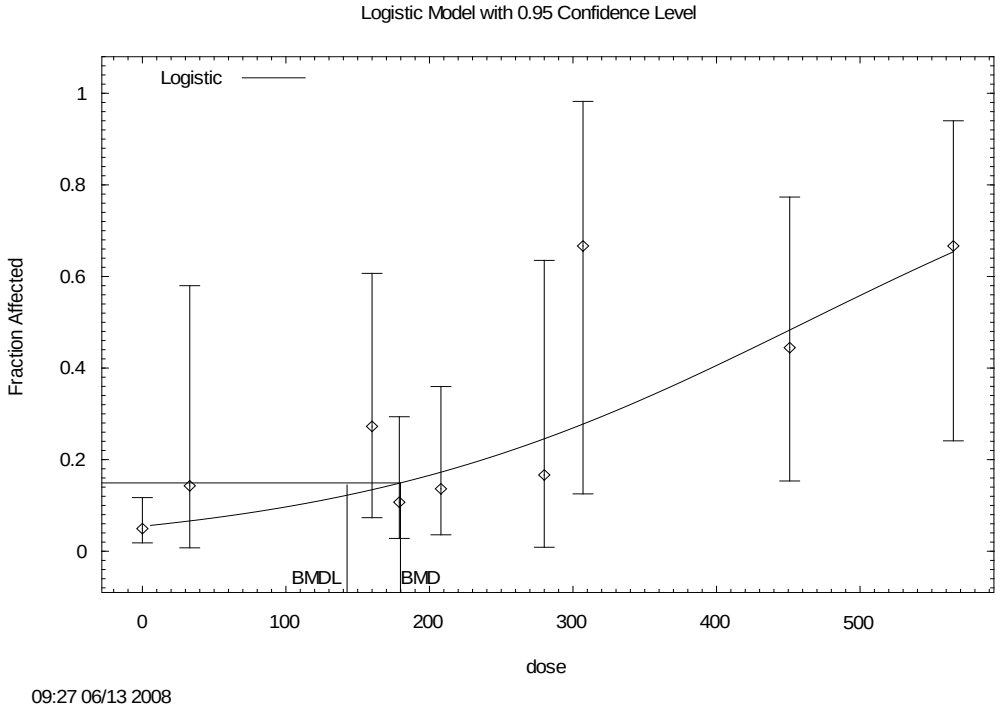
Table A-2. Modeling Results for Incidences of Abnormal Eye-Hand Coordination Scores in Workers Exposed to Respirable Manganese

Model	BMC_{10} ($\mu g/m^3$)	$BMCL_{10}$ ($\mu g/m^3$)	BMC_{05} ($\mu g/m^3$)	$BMCL_{05}$ ($\mu g/m^3$)	x^2 p-value	AIC
Gamma[a]	183.82	87.00	132.27	42.36	0.42	135.47
Logistic	179.80	142.61	109.29	84.14	0.58	133.15
Log-logistic[b]	185.53	91.70	134.25	43.83	0.42	135.48
Multi-stage[c]	110.67	73.28	53.88	35.67	0.42	135.33
Probit	166.66	131.67	98.75	76.14	0.59	133.19
Log-probit[b]	187.21	122.99	143.17	85.52	0.39	135.63
Quantal linear	181.91	88.19	125.38	42.93	0.43	135.37
Weibull[a]	181.91	88.19	125.38	42.93	0.43	135.37

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial with an adequate fit is reported; degree of polynomial=1

Source: Roels et al. 1992

Figure A-1. Predicted (Logistic Model) and Observed Incidence of Abnormal Eye-Hand Coordination Scores in Workers Exposed to Respirable Manganese (Roels et al. 1992)*



*BMD=BMC, BMDL=BMCL; BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of $\mu g/m^3$.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] Other $BMCL_{10}$

Uncertainty and modifying factors used in MRL derivation:

[ ] 10 for the use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability including possibly enhanced susceptibility of the elderly, infants, and children; individuals with chronic liver disease or parenteral nutrition; and females and individuals with iron deficiency.
[X] 10 for limitations/uncertainties in the database including the lack of epidemiological data for humans chronically exposed to soluble forms of manganese and the concern that the general population may be exposed to more soluble forms of manganese than most of the manganese-exposed workers in the principal and supporting studies and the uncertainty that a factor of 10 for human variability will provide enough protection for manganese effects on brain development in children. In addition, data on developmental toxicity for this route and duration of exposure are lacking. There is limited information on reproductive effects in females (one study in rat dams) and reported effects on male reproductive organs have not been clearly associated with decreased reproductive function. Though it is clear that the neurological system is the target organ for effects from chronic-duration inhalation exposure to manganese, data are lacking to fully characterize the potential risk for all organ systems from chronic inhalation exposure.

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure?

[X] 5/7 to account for intermittent exposure (5 days/week)
[X] 8/24 to account for intermittent exposure (8 hours/day)

MRL = 0.1426 mg manganese/m^3 x 5d/7d x 8h/24h x 1/100 = 0.0003 mg manganese/m^3 = 0.3 µg manganese/m^3.

Other additional studies or pertinent information that lend support to this MRL: An alternative approach to selecting a point of departure (averaging $BMCL_{10}$ values across all models in Table A-2) arrived at a similar point of departure of 105 µg respirable manganese/m^3, which would yield an identical MRL value.

Neurological effects from repeated inhalation exposure to manganese are well recognized as effects of high concern based on case reports and epidemiological studies of groups of occupationally exposed people and results from animal inhalation studies. A number of epidemiological studies have used batteries of neurobehavioral tests of neuromotor, cognition, and mood states to study the psychological or neurological effects of exposure to low levels of manganese in the workplace (Bast-Pettersen et al. 2004; Beuter et al. 1999; Blond and Netterstrom 2007; Blond et al. 2007; Bouchard et al. 2003, 2005, 2007a, 2007b; Chia et al. 1993a, 1995; Crump and Rousseau 1999; Deschamps et al. 2001; Gibbs et al. 1999; Iregren 1990; Lucchini et al. 1995, 1999; Mergler et al. 1994; Myers et al. 2003a, 2003b; Roels et al. 1987a, 1992, 1999; Wennberg et al. 1991) or in environmental media close to manganese-emitting industries (Lucchini et al. 2007; Mergler et al. 1999; Rodríguez-Agudelo et al. 2006). Some of these

studies have found statistically significant differences between exposed and non-exposed groups or significant associations between exposure indices and neurological effects (Bast-Pettersen et al. 2004; Chia et al. 1993a; Iregren 1990; Lucchini et al. 1995, 1999; Mergler et al. 1994; Roels et al. 1987a, 1992; Wennberg et al. 1991), whereas others have not found significant associations (Deschamps et al. 2001; Gibbs et al. 1999; Myers et al. 2003a, 2003b; Young et al. 2005). Table A-3 summarizes results from these studies. Comparison of the effect levels in these studies provides support for selection of the Roels et al. (1992) as the basis of the MRL; the advantage of the Roels et al. (1992) study is that individual worker data were available to support a benchmark dose analysis.

Table A-3. Epidemiological Studies of Neurological End Points in Workers Exposed to Low Levels of Manganese in Workplace Air

Reference	Place of work	Estimated exposure (mg manganese/ m^3)[a]	Years worked[b]	Number of exposed	Number of control	Effects
Chia et al. 1993a	Mn ore process	1.59	7.4	17	17	↓ finger tapping, digit symbol, pursuit aiming
Roels et al. 1987a	Mn salt and oxide plant	0.97	7.1	141	104	↓ reaction time, short-term memory, eye-hand coordination, hand steadiness
Roels et al. 1992, 1999	Dry alkaline battery plant	0.948 (0.215)	5.3	92	37	↓ reaction time, short-term memory, eye-hand coordination, hand steadiness
Iregren 1990; Wennberg et al. 1991	Mn foundry	0.14	9.9	30	60	↓ finger tapping, reaction time
Lucchini et al. 1995	Mn alloy plant	0.149	13	58	None	↓ finger tapping, short-term memory with increasing exposure indices
Lucchini et al. 1999	Mn alloy plant	0.097 (0.038)	11.5	61	87	↓ hand movements, finger tapping, short-term memory
Mergler et al. 1994	Mn alloy plant	0.23 (0.04)	16.7	115	115	↓ rapid hand movements, cognitive flexibility; ↑ indices for tension, anger, fatigue, confusion
Gibbs et al. 1999	Mn process plant	0.18 (0.051)	12.7	75	75	No effects on neuromotor tests or self-reported symptoms
Deschamps et al. 2001	Enamels production plant	2.05 (0.035)	19.7	134	137	No effects on self-reported symptoms or several cognitive tests; no neuromotor tests given.
Myers et al. 2003a	Mn mines	0.21	10.8	489	None	No associations between indices of exposure and outcomes from tests of neuromotor and cognitive functions or self-reported symptoms

Table A-3. Epidemiological Studies of Neurological End Points in Workers Exposed to Low Levels of Manganese in Workplace Air

Reference	Place of work	Estimated exposure (mg manganese/m^3)[a]	Years worked[b]	Number of exposed	Number of control	Effects
Myers et al. 2003b; Young et al. 2005	Mn smelter	0.85 (0.58)	18.2	509	67	Neurobehavioral test batteries showed significant effects in only a few of the many end points evaluated
Bast-Pettersen et al. 2004	Mn alloy plant	0.753 (0.049)	20.2	100	100	↑ scores for hand tremor, but no effect on other neuromotor or cognitive tests or symptoms
Blond and Netterstrom 2007; Blond et al. 2007	Steel works	0.07	24	60–92	14–19	↓ fast hand and finger movement, but no effects on slow movements, reaction time, or cognitive end points

[a]Mean, median, or midpoint of reported ranges of manganese concentration in total dust. Values for respirable dust are noted in parentheses when they were available.
[b]Mean, median, or midpoint of reported ranges of years employed at the facility.

The neurological effects associated with prolonged low-level manganese exposure generally have been subtle changes including deficits in tests of neuromotor or cognitive functions and altered mood states; they have been referred to by various authors as preclinical or subclinical neurological effects. Manganese air concentrations associated with these effects in chronically exposed workers range from about 0.07 to 1.59 mg manganese/m^3 (manganese in total or inhalable dust measurements; values for manganese in respirable dust are noted in parentheses in Table A-3). For several of these work environments, values of concentrations of manganese in respirable dust (generally particulate diameters <10 µm) represented <20–80% of the total dust values.

Several benchmark analyses of results from other epidemiological data for neurobehavioral deficits in manganese-exposed workers provide support for the MRL.

Dr. Anders Iregren provided ATSDR with individual worker data on total dust manganese exposure and performance on neurobehavioral tests for the occupational cohort that participated in his study (Iregren 1990; Wennberg et al. 1991). A benchmark analysis was also performed with these data under contract with ATSDR (Clewell and Crump 1999) and the $BMCL_{10}$ value derived from this evaluation was 0.071 mg manganese/m^3 based upon the reported observation that the respirable fraction ranged upwards to 80% of the total dust measured. This $BMCL_{10}$ value is similar to that estimated for the Roels et al. (1992) study (0.105 mg manganese/m^3), thus giving support to the value obtained for the current MRL study.

Clewell et al. (2003) conducted benchmark analyses on data from three neuromotor tests in the Roels et al. (1992) study (visual reaction time, eye-hand coordination, and hand steadiness) and from five neuromotor tests in the Gibbs et al. (1999) study (hole 6 of the hand steadiness test, percent precision of the eye-hand coordination test, reaction time in the complex reaction test, RMS amplitude in the steady test, and tap time). Exposure measures in these analyses were recent measures of manganese concentrations in respirable dust. $BMCL_{10}$ values were 0.257, 0.099, and 0.202 mg manganese/m^3 for the

visual reaction time, eye-hand coordination, and hand steadiness data from the Roels et al. (1992) study. $BMCL_{10}$ values from the analyses of outcomes from the Gibbs et al. (1999) study ranged from 0.09 to 0.27 mg manganese/m^3 (averaging the BMCLs within end points across different benchmark dose models applied to the data). Clewell et al. (2003) did not have individual worker data from the Iregren (1990) or Mergler et al. (1994), but, based on some assumptions about exposures (e.g., all exposed workers were exposed to average concentrations for the facilities and respirable manganese concentrations were calculated for the Iregren workers based on an assumption that 50% of total dust manganese was respirable), they calculated $BMCL_{10}$ values for six end points from the Mergler et al. (1994) study and the simple reaction time end point in the Iregren (1990) study. $BMCL_{10}$ values ranged from 0.1 to 0.3 mg manganese/m^3 from the Mergler et al. (1994) study end points to 0.1 mg manganese/m^3 for the reaction time end point in the Iregren (1990) study.

Health Canada (2008) recently prepared a draft document in which benchmark dose analyses were conducted on data for neurobehavioral end points from the study of Mn alloy workers by Lucchini et al. (1999). Using the average manganese concentrations in respirable dust over the 5-year period before testing as the dose metric, dose-response data for six tests of fine motor control, two aspects of memory tests, and one test of mental arithmetic were fit to linear models, which were used to calculate $BMCL_{05}$ values ranging from about 0.019 to 0.0588 mg manganese/m^3. After adjustment to convert from occupational exposure (5 days/week, 8 hours/24 hours) to continuous exposure, adjusted $BMCL_{05}$ values were divided by a total uncertainty factor of 100 to arrive at prospective reference concentrations. The uncertainty factor was comprised of a factor of 10 to account for interindividual variability in response to manganese to protect possibly enhanced susceptibility of the elderly, infants and children, individuals with asymptomatic pre-parkinsonism, individuals with chronic liver disease or parenteral nutrition, and females and individuals with iron deficiency and a second factor of 10 to account for limitations/ uncertainties in the database including: (1) the general population may be exposed to more soluble forms of manganese than most of the manganese-exposed workers; (2) the lack of extensive studies of the effect of prenatal exposure to manganese; and (3) the potential effects that manganese exposure early in life may have on health outcomes later in life. The prospective reference concentrations ranged from about 0.05 to 0.08 µg manganese/m^3.

The 2000 ATSDR Toxicological Profile for Manganese derived a chronic MRL for inorganic manganese of 0.00004 mg manganese/m^3 (manganese in respirable dust), based on a $BMCL_{10}$ of 0.074 mg manganese/m^3 (manganese in respirable dust) for abnormal performance in tests of hand steadiness, eye-hand coordination, or reaction time in the same study of 92 male workers in a dry alkaline battery plant (Roels et al. 1992) used in the current assessment. The MRL was derived by adjustment of the $BMCL_{10}$ to a continuous exposure basis and division by an uncertainty factor of 500 (10 for human variability, 10 for database deficiencies and limitations, and a modifying factor of 5 for potentially increased susceptibility in children based on differential kinetics in the young).

The current assessment does not use a modifying factor of 5 for potentially increased susceptibility in children based on differential kinetics in the young, because recent studies in lactating rats and their offspring exposed to manganese by the oral or inhalation routes suggest that the human variability factor of 10 provides sufficient protection for the differential kinetics in children and adults. For example, in neonatal rats orally exposed to 25 or 50 mg manganese/kg/day manganese chloride from postnatal day 1 through 21, manganese concentrations in various brain regions were about 2-fold higher than brain manganese concentrations in adult rats exposed to the same oral dose levels for 21 days (Dorman et al. 2000). Similarly, 18-day-old neonatal rats exposed from birth to aerosols of manganese sulfate at 1 mg manganese/m^3, 6 hours/day showed a 2.6-fold increase in striatum manganese concentrations, compared with controls, while lactating adults exposed to the same aerosol concentration showed a 1.7-fold increase compared with controls (Dorman et al. 2005a).

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

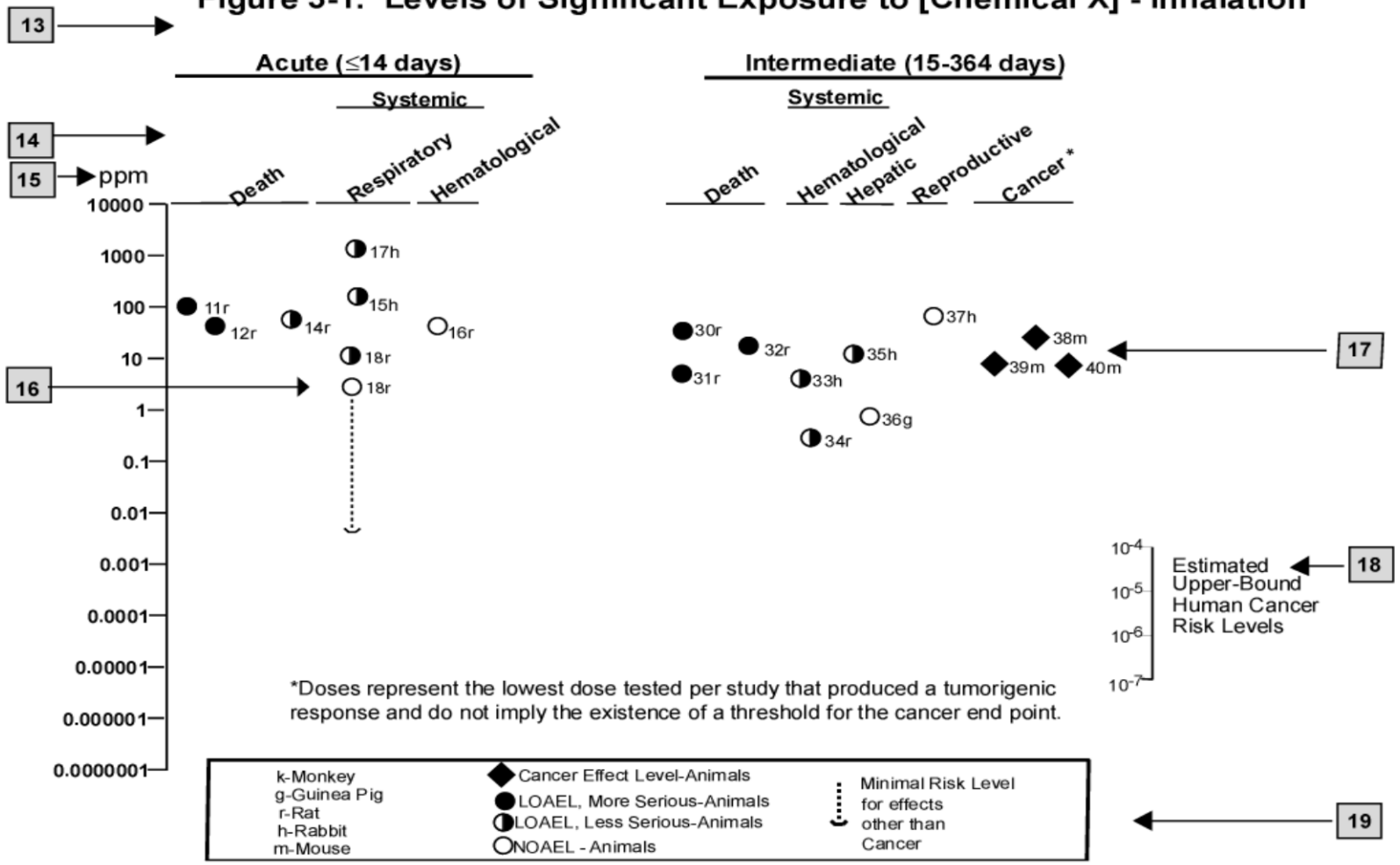
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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TOXICOLOGICAL PROFILE FOR MERCURY

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

March 1999

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Mercury–Draft for Public Comment was released in September 1997. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

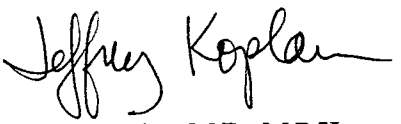
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Jeffrey P. Koplan, M.D., M.P.H.
Administrator
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Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-447-1544 (to be replaced by 1-888-42-ATSDR in 1999)
or 404-639-6357 ***Fax:*** 404-639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://atsdr1.atsdr.cdc.gov:8080

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences (*NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for mercury. The panel consisted of the following members:

1. Mr. Harvey Clewell, K.S. Crump Group, ICF Kaiser International, Inc., Ruston, LA

2. Dr. Ingeborg Harding-Barlow, Private Consultant, Environmental and Occupational Toxicology, 3717 Laguna Ave., Palo Alto, California;

3. Dr. Thomas Hinesly, Professor (Emeritus), Department of Natural Resources and Environmental Sciences, University of Illinois, Champaign-Urbana, Illinois;

4. Dr. Loren D. Koller, Professor, College of Veterinary Medicine, Oregon State University, Corvallis, Oregon; and

5. Dr. Kenneth Reuhl, Professor, Neurotoxicology Laboratory, Rutgers University, Piscataway, New York.

These experts collectively have knowledge of mercury's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewer's comments and determined which comments will be included in the profile. A listing of the profile. A listing of the peer reviewers' comments not incorporated in the profile, with brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about mercury and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Mercury has been found in at least 714 of the 1,467 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which mercury is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to mercury, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals to which you're exposed, as well as your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS MERCURY?

Mercury occurs naturally in the environment and exists in several forms. These forms can be organized under three headings: metallic mercury (also known as elemental mercury), inorganic mercury, and organic mercury. Metallic mercury is a shiny, silver-white metal that is a liquid at room temperature. Metallic mercury is the elemental or pure form of mercury (i.e., it is not combined with other elements). Metallic mercury metal is the familiar liquid metal used in thermometers and some electrical switches. At room temperature, some of the metallic mercury

will evaporate and form mercury vapors. Mercury vapors are colorless and odorless. The higher the temperature, the more vapors will be released from liquid metallic mercury. Some people who have breathed mercury vapors report a metallic taste in their mouths. Metallic mercury has been found at 714 hazardous waste sites nationwide.

Inorganic mercury compounds occur when mercury combines with elements such as chlorine, sulfur, or oxygen. These mercury compounds are also called mercury salts. Most inorganic mercury compounds are white powders or crystals, except for mercuric sulfide (also known as cinnabar) which is red and turns black after exposure to light.

When mercury combines with carbon, the compounds formed are called "organic" mercury compounds or organomercurials. There is a potentially large number of organic mercury compounds; however, by far the most common organic mercury compound in the environment is methylmercury (also known as monomethylmercury). In the past, an organic mercury compound called phenylmercury was used in some commercial products. Another organic mercury compound called dimethylmercury is also used in small amounts as a reference standard for some chemical tests. Dimethylmercury is the only organic mercury compound that has been identified at hazardous waste sites. It was only found in extremely small amounts at two hazardous waste sites nationwide, but it is very harmful to people and animals. Like the inorganic mercury compounds, both methylmercury and phenylmercury exist as "salts" (for example, methylmercuric chloride or phenylmercuric acetate). When pure, most forms of methylmercury and phenylmercury are white crystalline solids. Dimethylmercury, however, is a colorless liquid.

Several forms of mercury occur naturally in the environment. The most common natural forms of mercury found in the environment are metallic mercury, mercuric sulfide (cinnabar ore), mercuric chloride, and methylmercury. Some microorganisms (bacteria and fungi) and natural processes can change the mercury in the environment from one form to another. The most common organic mercury compound that microorganisms and natural processes generate from other forms is methylmercury. Methylmercury is of particular concern because it can build up in certain edible

freshwater and saltwater fish and marine mammals to levels that are many times greater than levels in the surrounding water (see Section 1.2).

Mercury is mined as cinnabar ore, which contains mercuric sulfide. The metallic form is refined from mercuric sulfide ore by heating the ore to temperatures above 1,000 degrees Fahrenheit. This vaporizes the mercury in the ore, and the vapors are then captured and cooled to form the liquid metal mercury. There are many different uses for liquid metallic mercury. It is used in producing of chlorine gas and caustic soda, and in extracting gold from ore or articles that contain gold. It is also used in thermometers, barometers, batteries, and electrical switches. Silver-colored dental fillings typically contain about 50% metallic mercury. Metallic mercury is still used in some herbal or religious remedies in Latin America and Asia, and in rituals or spiritual practices in some Latin American and Caribbean religions such as Voodoo, Santeria, and Espiritismo. These uses may pose a health risk from exposure to mercury both for the user and for others who may be exposed to mercury vapors in contaminated air.

Some inorganic mercury compounds are used as fungicides. Inorganic salts of mercury, including ammoniated mercuric chloride and mercuric iodide, have been used in skin-lightening creams. Mercuric chloride is a topical antiseptic or disinfectant agent. In the past, mercurous chloride was widely used in medicinal products including laxatives, worming medications, and teething powders. It has since been replaced by safer and more effective agents. Other chemicals containing mercury are still used as antibacterials. These products include mercurochrome (contains a small amount of mercury, 2%), and thimerosal and phenylmercuric nitrate, which are used in small amounts as preservatives in some prescription and over-the-counter medicines. Mercuric sulfide and mercuric oxide may be used to color paints, and mercuric sulfide is one of the red coloring agents used in tattoo dyes.

Methylmercury is produced primarily by microorganisms (bacteria and fungi) in the environment, rather than by human activity. Until the 1970s, methylmercury and ethylmercury compounds were used to protect seed grains from fungal infections. Once the adverse health effects of methylmercury were known, the use of methymercury- and ethylmercury as fungicides was

banned. Up until 1991, phenylmercuric compounds were used as antifungal agents in both interior and exterior paints, but this use was also banned because mercury vapors were released from these paints.

Chapter 3 contains more information on the physical and chemical properties of mercury. Chapter 4 contains more information on the production and use of mercury.

1.2 WHAT HAPPENS TO MERCURY WHEN IT ENTERS THE ENVIRONMENT?

Mercury is a naturally occurring metal found throughout the environment. Mercury enters the environment as the result of the normal breakdown of minerals in rocks and soil from exposure to wind and water, and from volcanic activity. Mercury releases from natural sources have remained relatively constant in recent history, resulting in a steady rise in environmental mercury. Human activities since the start of the industrial age (e.g., mining, burning of fossil fuels) have resulted in additional release of mercury to the environment. Estimates of the total annual mercury releases that result from human activities range from one-third to two-thirds of the total mercury releases. A major uncertainty in these estimates is the amount of mercury that is released from water and soils that were previously contaminated by human activities as opposed to new natural releases. The levels of mercury in the atmosphere (i.e., the air you breathe in the general environment) are very, very low and do not pose a health risk; however, the steady release of mercury has resulted in current levels that are three to six times higher than the estimated levels in the preindustrial era atmosphere.

Approximately 80% of the mercury released from human activities is elemental mercury released to the air, primarily from fossil fuel combustion, mining, and smelting, and from solid waste incineration. About 15% of the total is released to the soil from fertilizers, fungicides, and municipal solid waste (for example, from waste that contains discarded batteries, electrical switches, or thermometers). An additional 5% is released from industrial wastewater to water in the environment.

With the exception of mercury ore deposits, the amount of mercury that naturally exists in any one place is usually very low. In contrast, the amount of mercury that may be found in soil at a particular hazardous waste site because of human activity can be high (over 200,000 times natural levels). The mercury in air, water, and soil at hazardous waste sites may come from both natural sources and human activity.

Most of the mercury found in the environment is in the form of metallic mercury and inorganic mercury compounds. Metallic and inorganic mercury enters the air from mining deposits of ores that contain mercury, from the emissions of coal-fired power plants, from burning municipal and medical waste, from the production of cement, and from uncontrolled releases in factories that use mercury. Metallic mercury is a liquid at room temperature, but some of the metal will evaporate into the air and can be carried long distances. In air, the mercury vapor can be changed into other forms of mercury, and can be further transported to water or soil in rain or snow. Inorganic mercury may also enter water or soil from the weathering of rocks that contain mercury, from factories or water treatment facilities that release water contaminated with mercury, and from incineration of municipal garbage that contains mercury (for example, in thermometers, electrical switches, or batteries that have been thrown away). Inorganic or organic compounds of mercury may be released to the water or soil if mercury-containing fungicides are used.

Microorganisms (bacteria, phytoplankton in the ocean, and fungi) convert inorganic mercury to methylmercury. Methylmercury released from microorganisms can enter the water or soil and remain there for a long time, particularly if the methylmercury becomes attached to small particles in the soil or water. Mercury usually stays on the surface of sediments or soil and does not move through the soil to underground water. If mercury enters the water in any form, it is likely to settle to the bottom where it can remain for a long time.

Mercury can enter and accumulate in the food chain. The form of mercury that accumulates in the food chain is methylmercury. Inorganic mercury does not accumulate up the food chain to any extent. When small fish eat the methylmercury in food, it goes into their tissues. When larger fish eat smaller fish or other organisms that contain methylmercury, most of the methylmercury

originally present in the small fish will then be stored in the bodies of the larger fish. As a result, the larger and older fish living in contaminated waters build up the highest amounts of methyl-mercury in their bodies. Saltwater fish (especially sharks and swordfish) that live a long time and can grow to a very large size tend to have the highest levels of mercury in their bodies. Plants (such as corn, wheat, and peas) have very low levels of mercury, even if grown in soils containing mercury at significantly higher than background levels. Mushrooms, however, can accumulate high levels if grown in contaminated soils. For further information on what happens to mercury in the environment, see Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO MERCURY?

Because mercury occurs naturally in the environment, everyone is exposed to very low levels of mercury in air, water, and food. Between 10 and 20 nanograms of mercury per cubic meter (ng/m^3) of air have been measured in urban outdoor air. These levels are hundreds of times lower than levels still considered to be "safe" to breathe. Background levels in nonurban settings are even lower, generally about 6 ng/m^3 or less. Mercury levels in surface water are generally less than 5 parts of mercury per trillion parts of water (5 ppt, or 5 ng per liter of water), about a thousand times lower than "safe" drinking water standards. Normal soil levels range from 20 to 625 parts of mercury per billion parts of soil (20–625 ppb; or 20,000–625,000 ng per kilogram of soil). A part per billion is one thousand times bigger than a part per trillion.

A potential source of exposure to metallic mercury for the general population is mercury released from dental amalgam fillings. An amalgam is a mixture of metals. The amalgam used in silver-colored dental fillings contains approximately 50% metallic mercury, 35% silver, 9% tin, 6% copper, and trace amounts of zinc. When the amalgam is first mixed, it is a soft paste which is inserted into the tooth surface. It hardens within 30 minutes. Once the amalgam is hard, the mercury is bound within the amalgam, but very small amounts are slowly released from the surface of the filling due to corrosion or chewing or grinding motions. Part of the mercury at the surface of the filling may enter the air as mercury vapor or be dissolved in the saliva. The total amount of mercury released from dental amalgam depends upon the total number of fillings and

surface areas of each filling, the chewing and eating habits of the person, and other chemical conditions in the mouth. Estimates of the amount of mercury released from dental amalgams range from 3 to 17 micrograms per day (µg/day). The mercury from dental amalgam may contribute from 0 to more than 75% of your total daily mercury exposure, depending on the number of amalgam fillings you have, the amount of fish consumed, the levels of mercury (mostly as methylmercury) in those fish, and exposure from other less common sources such as mercury spills, religious practices, or herbal remedies that contain mercury. However, it should be kept in mind that exposure to very small amounts of mercury, such as that from dental amalgam fillings, does not necessarily pose a health risk.

Whether the levels of exposure to mercury vapor from dental amalgam are sufficiently high to cause adverse health effects, and exactly what those effects are, continues to be researched and debated by scientists and health officials. U.S. government summaries on the effects of dental amalgam conclude that there is no apparent health hazard to the general population, but that further study is needed to determine the possibility of more subtle behavioral or immune system effects, and to determine the levels of exposure that may lead to adverse effects in sensitive populations. Sensitive populations may include pregnant women, children under the age of 6 (especially up to the age of 3), people with impaired kidney function, and people with hypersensitive immune responses to metals. If you belong to this group, you should discuss your medical condition with your dentist prior to any dental restoration work. Removal of dental amalgams in people who have no indication of adverse effects is not recommended and can put the person at greater risk, if performed improperly. Chelation therapy (used to remove metals from the body tissues) itself presents some health risks, and should be considered only when a licensed occupational or environmental health physician determines it necessary to reduce immediate and significant health risks due to high levels of mercury in the body. For additional information on health risks associated with mercury dental amalgam, see Section 2.5, "More on the Health Effects of Dental Amalgam."

Some religions have practices that may include the use of metallic mercury. Examples of these religions include Santeria (a Cuban-based religion whose followers worship both African deities

and Catholic saints), Voodoo (a Haitian-based set of beliefs and rituals), Palo Mayombe (a secret form of ancestor worship practiced mainly in the Caribbean), and Espiritismo (a spiritual belief system native to Puerto Rico). Not all people who observe these religions use mercury, but when mercury is used in religious, ethnic, or ritualistic practices, exposure to mercury may occur both at the time of the practice and afterwards from contaminated indoor air. Metallic mercury is sold under the name "azogue" (pronounced ah-SEW-gay) in stores called “botanicas.” Botanicas are common in Hispanic and Haitian communities, where azogue may be sold as an herbal remedy or for spiritual practices. The metallic mercury is often sold in capsules or in glass containers. It may be placed in a sealed pouch to be worn on a necklace or in a pocket, or it may be sprinkled in the home or car. Some people may mix azogue in bath water or perfume, or place azogue in devotional candles. Because metallic mercury evaporates into the air, these practices may put anyone breathing the air in the room at risk of exposure to mercury. The longer people breathe the contaminated air, the greater their risk will be. The use of metallic mercury in a home or an apartment not only threatens the health of the people who live there now, but also threatens the health of future residents who may unknowingly be exposed to further release of mercury vapors from contaminated floors or walls.

Metallic mercury is used in a variety of household products and industrial items, including thermostats, fluorescent light bulbs, barometers, glass thermometers, and some blood pressure devices. The mercury in these devices is contained in glass or metal, and generally does not pose a risk unless the item is damaged or broken, and mercury vapors are released. Spills of metallic mercury from broken thermometers or damaged electrical switches in the home may result in exposure to mercury vapors in indoor air. You must be careful when you handle and dispose of all items in the home that contain metallic mercury.

Very small amounts of metallic mercury (for example, a few drops) can raise air concentrations of mercury to levels that may be harmful to health. The longer people breathe the contaminated air, the greater the risk to their health. Metallic mercury and its vapors are extremely difficult to remove from clothes, furniture, carpet, floors, walls, and other such items. If these items are not

properly cleaned, the mercury can remain for months or years, and continue to be a source of exposure.

It is possible for you to be exposed to metallic mercury vapors from breathing contaminated air around hazardous waste sites, waste incinerators, or power plants that burn mercury-containing fuels (such as coal or other fossil fuels), but most outdoor air is not likely to contain levels that would be harmful. Exposure to mercury compounds at hazardous waste sites is much more likely to occur from handling contaminated soil (i.e., children playing in or eating contaminated surface soil), drinking well-water, or eating fish from contaminated waters near those sites. Not all hazardous sites contain mercury, and not all waste sites that do contain mercury have releases of mercury to the air, water, or surface soils.

You can be exposed to mercury vapors from the use of fungicides that contain mercury. Excess use of these products may result in higher-than-average exposures. You may also be exposed to mercury from swallowing or applying to your skin outdated medicinal products (laxatives, worming medications, and teething powders) that contain mercurous chloride. Exposure may also occur from the improper or excessive use of other chemicals containing mercury, such as skin-lightening creams and some topical antiseptic or disinfectant agents (mercurochrome and thimerosal).

Workers are mostly exposed from breathing air that contains mercury vapors, but may also be exposed to other inorganic mercury compounds in the workplace. Occupations that have a greater potential for mercury exposure include manufacturers of electrical equipment or automotive parts that contain mercury, chemical processing plants that use mercury, metal processing, construction where building parts contain mercury (e.g., electrical switches, thermometers), and the medical professions (medical, dental, or other health services) where equipment may contain mercury (e.g., some devices that measure blood pressure contain liquid mercury). Dentists and their assistants may be exposed to metallic mercury from breathing in mercury vapor released from amalgam fillings and to a much lesser extent from skin contact with

amalgam restorations. Family members of workers who have been exposed to mercury may also be exposed to mercury if the worker's clothes are contaminated with mercury particles or liquid.

Some people may be exposed to higher levels of mercury in the form of methylmercury if they have a diet high in fish, shellfish, or marine mammals (whales, seals, dolphins, and walruses) that come from mercury-contaminated waters. Methylmercury accumulates up the food chain, so that fish at the top of the food chain will have the most mercury in their flesh. Of these fish, the largest (i.e., the oldest) fish will have the highest levels. The Food and Drug Administration (FDA) estimates that most people are exposed, on average, to about 50 ng of mercury per kilogram of body weight per day (50 ng/kg/day) in the food they eat. This is about 3.5 micrograms (µg) of mercury per day for an adult of average weight. This level is not thought to result in any harmful effects. A large part of this mercury is in the form of methylmercury and probably comes from eating fish. Commercial fish sold through interstate commerce that are found to have levels of methylmercury above an "action level" of 1 ppm (established by the FDA) cannot be sold to the public. This level itself is below a level associated with adverse effects. However, if you fish in contaminated waters and eat the fish you catch, you may be exposed to higher levels of mercury. Public health advisories are issued by state and federal authorities for local waters that are thought to be contaminated with mercury. These advisories can help noncommercial (sport and subsistence) fishermen and their families to avoid eating fish contaminated with mercury. Foods other than fish that may contain higher than average levels of mercury include wild game, such as wild birds and mammals (bear) that eat large amounts of contaminated fish. People in the most northern climates may be exposed to high levels of mercury from eating meat or fat from marine mammals including whales, dolphins, walruses, and seals. These marine mammals are at or near the top of their marine food chain. Plants contain very little methylmercury or other forms of mercury. Mushrooms grown in mercury-contaminated soil may contain levels of mercury that could pose some risk to health, if large amounts were eaten.

See Chapter 5 for more information on how you might be exposed to mercury.

1.4 HOW CAN MERCURY ENTER AND LEAVE MY BODY?

A person can be exposed to mercury from breathing in contaminated air, from swallowing or eating contaminated water or food, or from having skin contact with mercury. Not all forms of mercury easily enter your body, even if they come in contact with it; so it is important to know which form of mercury you have been exposed to, and by which route (air, food, or skin).

When you swallow small amounts of metallic mercury, for example, from a broken oral thermometer, virtually none (less than 0.01%) of the mercury will enter your body through the stomach or intestines, unless they are diseased. Even when a larger amount of metal mercury (a half of a tablespoon, about 204 grams) was swallowed by one person, very little entered the body. When you breathe in mercury vapors, however, most (about 80%) of the mercury enters your bloodstream directly from your lungs, and then rapidly goes to other parts of your body, including the brain and kidneys. Once in your body, metallic mercury can stay for weeks or months. When metallic mercury enters the brain, it is readily converted to an inorganic form and is "trapped" in the brain for a long time. Metallic mercury in the blood of a pregnant woman can enter her developing child. Most of the metallic mercury will accumulate in your kidneys, but some metallic mercury can also accumulate in the brain. Most of the metallic mercury absorbed into the body eventually leaves in the urine and feces, while smaller amounts leave the body in the exhaled breath.

Inorganic mercury compounds like mercurous chloride and mercuric chloride are white powders and do not generally vaporize at room temperatures like elemental mercury will. If they are inhaled, they are not expected to enter your body as easily as inhaled metallic mercury vapor. When inorganic mercury compounds are swallowed, generally less than 10% is absorbed through the intestinal tract; however, up to 40% may enter the body through the stomach and intestines in some instances. Some inorganic mercury can enter your body through the skin, but only a small amount will pass through your skin compared to the amount that gets into your body from swallowing inorganic mercury.

Once inorganic mercury enters the body and gets into the bloodstream, it moves to many different tissues. Inorganic mercury leaves your body in the urine or feces over a period of several weeks or months. A small amount of the inorganic mercury can be changed in your body to metallic mercury and leave in the breath as a mercury vapor. Inorganic mercury accumulates mostly in the kidneys and does not enter the brain as easily as metallic mercury. Inorganic mercury compounds also do not move as easily from the blood of a pregnant woman to her developing child. In a nursing woman, some of the inorganic mercury in her body will pass into her breast milk.

Methylmercury is the form of mercury most easily absorbed through the gastrointestinal tract (about 95% absorbed). After you eat fish or other foods that are contaminated with methylmercury, the methylmercury enters your bloodstream easily and goes rapidly to other parts of your body. Only small amounts of methylmercury enter the bloodstream directly through the skin, but other forms of organic mercury (in particular dimethylmercury) can rapidly enter the body through the skin. Organic mercury compounds may evaporate slowly at room temperature and may enter your body easily if you breathe in the vapors. Once organic mercury is in the bloodstream, it moves easily to most tissues and readily enters the brain. Methylmercury that is in the blood of a pregnant woman will easily move into the blood of the developing child and then into the child's brain and other tissues. Like metallic mercury, methylmercury can be changed by your body to inorganic mercury. When this happens in the brain, the mercury can remain there for a long time. When methylmercury does leave your body after you have been exposed, it leaves slowly over a period of several months, mostly as inorganic mercury in the feces. As with inorganic mercury, some of the methylmercury in a nursing woman's body will pass into her breast milk.

For more information on how mercury can enter and leave your body, please see Chapter 2.

1.5 HOW CAN MERCURY AFFECT MY HEALTH?

The nervous system is very sensitive to mercury. In poisoning incidents that occurred in other countries, some people who ate fish contaminated with large amounts of methylmercury or seed grains treated with methylmercury or other organic mercury compounds developed permanent

damage to the brain and kidneys. Permanent damage to the brain has also been shown to occur from exposure to sufficiently high levels of metallic mercury. Whether exposure to inorganic mercury results in brain or nerve damage is not as certain, since it does not easily pass from the blood into the brain.

Metallic mercury vapors or organic mercury may affect many different areas of the brain and their associated functions, resulting in a variety of symptoms. These include personality changes (irritability, shyness, nervousness), tremors, changes in vision (constriction (or narrowing) of the visual field), deafness, muscle incoordination, loss of sensation, and difficulties with memory.

Different forms of mercury have different effects on the nervous system, because they do not all move through the body in the same way. When metallic mercury vapors are inhaled, they readily enter the bloodstream and are carried throughout the body and can move into the brain. Breathing in or swallowing large amounts of methylmercury also results in some of the mercury moving into the brain and affecting the nervous system. Inorganic mercury salts, such as mercuric chloride, do not enter the brain as readily as methylmercury or metallic mercury vapor.

The kidneys are also sensitive to the effects of mercury, because mercury accumulates in the kidneys and causes higher exposures to these tissues, and thus more damage. All forms of mercury can cause kidney damage if large enough amounts enter the body. If the damage caused by the mercury is not too great, the kidneys are likely to recover once the body clears itself of the contamination.

Short-term exposure (hours) to high levels of metallic mercury vapor in the air can damage the lining of the mouth and irritate the lungs and airways, causing tightness of the breath, a burning sensation in the lungs, and coughing. Other effects from exposure to mercury vapor include nausea, vomiting, diarrhea, increases in blood pressure or heart rate, skin rashes, and eye irritation. Damage to the lining of the mouth and lungs can also occur from exposure to lower levels of mercury vapor over longer periods (for example, in some occupations where workers were exposed to mercury for many years). Levels of metallic mercury in workplace air are generally much greater than the levels normally encountered by the general population. Current

levels of mercury in workplace air are low, due to increased awareness of mercury's toxic effects. Because of the reduction in the allowable amount of mercury in workplace air, fewer workers are expected to have symptoms of mercury toxicity. Most studies of humans who breathed metallic mercury for a long time indicate that mercury from this type of exposure does not affect the ability to have children. Studies in workers exposed to metallic mercury vapors have also not shown any mercury-related increase in cancer. Skin contact with metallic mercury has been shown to cause an allergic reaction (skin rashes) in some people.

In addition to effects on the kidneys, inorganic mercury can damage the stomach and intestines, producing symptoms of nausea, diarrhea, or severe ulcers if swallowed in large amounts. Effects on the heart have also been observed in children after they accidentally swallowed mercuric chloride. Symptoms included rapid heart rate and increased blood pressure. There is little information on the effects in humans from long-term, low-level exposure to inorganic mercury.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Studies using animals indicate that long-term oral exposure to inorganic mercury salts causes kidney damage, effects on blood pressure and heart rate, and effects on the stomach. Study results also suggest that reactions involving the immune system may occur in sensitive populations after swallowing inorganic mercury salts. Some animal studies report that nervous system damage occurs after long-term exposure to high levels of inorganic mercury. Short-term, high-

level exposure of laboratory animals to inorganic mercury has been shown to affect the developing fetus and may cause termination of the pregnancy.

Animals exposed orally to long-term, high levels of methylmercury or phenylmercury in laboratory studies experienced damage to the kidneys, stomach, and large intestine; changes in blood pressure and heart rate; adverse effects on the developing fetus, sperm, and male reproductive organs; and increases in the number of spontaneous abortions and stillbirths. Adverse effects on the nervous system of animals occur at lower doses than do harmful effects to most other systems of the body. This difference indicates that the nervous system is more sensitive to methylmercury toxicity than are other organs in the body. Animal studies also provide evidence of damage to the nervous system from exposure to methylmercury during development, and evidence suggests that the effects worsen with age, even after the exposure stops.

Some rat and mice strains that are susceptible to autoimmune responses develop kidney damage as a result of an immune response when exposed to relatively low levels of mercury vapor or mercury chloride.

Animals given inorganic mercury salts by mouth for most of their lifetime had increases in some kinds of tumors at the highest dose tested. Rats and mice that received organic mercury (methyl-mercury or phenylmercury) in their drinking water or feed for most of their lives had an increased incidence of cancer of the kidney, but this affected only the males that received the highest amount of mercury given (not the females). Since the high doses caused severe damage to the kidneys prior to the cancer, these animal studies provide only limited information about whether mercury causes cancer in humans. As a result, the Department of Health and Human Services (DHHS) and the International Agency for Research on Cancer (IARC) have not classified mercury as to its human carcinogenicity. The Environmental Protection Agency has determined that mercury chloride and methylmercury are possible human carcinogens. Chapter 2 contains more information on the health effects of mercury in humans and animals.

1.6 HOW CAN MERCURY AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Children are at risk of being exposed to metallic mercury that is not safely contained, to mercury that may be brought home on work clothes or tools, or to methylmercury-contaminated foods. Methylmercury eaten or swallowed by a pregnant woman or metallic mercury that enters her body from breathing contaminated air can also pass into the developing child. Inorganic mercury and methylmercury can also pass from a mother's body into breast milk and into a nursing infant. The amount of mercury in the milk will vary, depending on the degree of exposure and the amount of mercury that enter the nursing woman's body. There are significant benefits to breast feeding, so any concern that a nursing woman may have about mercury levels in her breast milk should be discussed with her doctor. Methylmercury can also accumulate in an unborn baby's blood to a concentration higher than the concentration in the mother.

For similar exposure routes and forms of mercury, the harmful health effects seen in children are similar to the effects seen in adults. High exposure to mercury vapor causes lung, stomach, and intestinal damage and death due to respiratory failure in severe cases. These effects are similar to those seen in adult groups exposed to inhaled metallic mercury vapors at work.

Children who had been exposed to excessive amounts of mercurous chloride tablets for worms or mercurous chloride-containing powders for teething discomfort had increased heart rates and elevated blood pressure. Abnormal heart rhythms were also seen in children who had eaten grains contaminated with very high levels of methylmercury.

Other symptoms of poisonings in children who were treated with mercurous chloride for constipation, worms, or teething discomfort included swollen red gums, excessive salivation, weight loss, diarrhea and/or abdominal pain, and muscle twitching or cramping in the legs and/or arms. Kidney damage is very common after exposure to toxic levels of inorganic mercury.

Metallic mercury or methylmercury that enters the body can also be converted to inorganic mercury and result in kidney damage.

Children who breathe metallic/elemental mercury vapors, eat foods or other substances containing phenylmercury or inorganic mercury salts, or use mercury-containing skin ointments for an extended period may develop a disorder known as acrodynia, or pink disease. Acrodynia can result in severe leg cramps; irritability; and abnormal redness of the skin, followed by peeling of the hands, nose, and soles of the feet. Itching, swelling, fever, fast heart rate, elevated blood pressure, excessive salivation or sweating, rashes, fretfulness, sleeplessness, and/or weakness may also be present. It was once believed that this syndrome occurred only in children, but recent reported cases in teenagers and adults have shown that they can also develop acrodynia.

In critical periods of development before they are born, and in the early months after birth, children and fetuses are particularly sensitive to the harmful effects of metallic mercury and methylmercury on the nervous system. Harmful developmental effects may occur when a pregnant woman is exposed to metallic mercury and some of the mercury is transferred into her developing child. Thus, women who are normally exposed to mercury vapors in the workplace (such as those working in thermometer/barometer or fluorescent light manufacturing or the chlor-alkali industry) should take measures to avoid mercury vapor exposures during pregnancy. Exposures to mercury vapors are relatively rare outside of the workplace, unless metallic mercury is present in the home.

As with mercury vapors, exposure to methylmercury is more dangerous for young children than for adults, because more methylmercury easily passes into the developing brain of young children and may interfere with the development process.

Methylmercury is the form of mercury most commonly associated with a risk for developmental effects. Exposure can come from foods contaminated with mercury on the surface (for example, from seed grain treated with methylmercury to kill fungus) or from foods that contain toxic levels of methylmercury (as in some fish, wild game, and marine mammals). Mothers who are exposed to methylmercury and breast-feed their infant may also expose the child through the milk. The

effects on the infant may be subtle or more pronounced, depending on the amount to which the fetus or young child was exposed. In cases in which the exposure was very small, some effects might not be apparent, such as small decreases in IQ or effects on the brain that may only be determined by the use of very sensitive neuropsychological testing. In instances in which the exposure is great, the effects may be more serious. In some such cases of mercury exposure involving serious exposure to the developing fetus, the effects are delayed. In such cases, the infant may be born apparently normal, but later show effects that may range from the infant being slower to reach developmental milestones, such as the age of first walking and talking, to more severe effects including brain damage with mental retardation, incoordination, and inability to move. Other severe effects observed in children whose mothers were exposed to very toxic levels of mercury during pregnancy include eventual blindness, involuntary muscle contractions and seizures, muscle weakness, and inability to speak. It is important to remember, however, that the severity of these effects depends upon the level of mercury exposure and the time of exposure. The very severe effects just mentioned were reported in large-scale poisoning instances in which pregnant and nursing women were exposed to extremely high levels of methylmercury in contaminated grain used to make bread (in Iraq) or seafood (in Japan) sold to the general population.

Researchers are currently studying the potential for less serious developmental effects, including effects on a child's behavior and ability to learn, think, and solve problems that may result from eating lower levels of methylmercury in foods. A main source of exposure to methylmercury for the pregnant woman and the young child is from eating fish. Most fish purchased in the market in the United States do not have mercury levels that pose a risk to anyone, including pregnant women. Since mercury accumulates in the muscles of fish, larger fish that feed on smaller fish and live for long periods usually have larger concentrations of methylmercury than fish that feed on plants. For example, shark and swordfish normally contain the highest levels of mercury out of all ocean fish. Scientists have an ongoing debate about the value of fish in the diet versus any risk from increased exposure of pregnant women to methylmercury that may be in the fish. The safety of most fish sold commercially in the United States is regulated by the FDA. These fish pose no health risk to those who purchase and eat them. Only fish or wildlife containing relatively high

levels of methylmercury are of concern, and these are discussed in Section 1.7 of this toxicological profile.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO MERCURY?

If your doctor finds that you have been exposed to significant amounts of mercury, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Children may be exposed to metallic mercury if they play with it. Metallic mercury is a heavy, shiny, silver liquid. When metallic mercury is spilled, it forms little balls or beads. Children are sometimes exposed to metallic mercury when they find it in abandoned warehouses or closed factories, and then play with it or pass it around to friends. Children have also taken metallic mercury from school chemistry and physics labs. Broken thermometers and some electrical switches are other sources of metallic mercury. Sometimes children find containers of metallic mercury that were improperly disposed of, or adults may bring home metallic mercury from work, not knowing that it is dangerous.

To protect your children from metallic mercury, teach them not to play with shiny, silver liquids. Schoolteachers (particularly science teachers) and school staff need to know about students' fascination with metallic mercury. Teachers and school staff should teach children about the dangers of getting sick from playing with mercury, and they should keep metallic mercury in a safe and secured area (such as a closed container in a locked storage room) so that children do not have access to it without the supervision of a teacher. Metallic mercury evaporates slowly, and if it is not stored in a closed container, children may breathe toxic mercury vapors.

In the past, mercurous chloride was widely used in medicinal products such as laxatives, worming medications, and teething powders. These older medicines should be properly disposed of and replaced with safer and more effective medicines. Other chemicals containing mercury, such as mercurochrome and thimerosal (sold as Merthiolate and other brands), are still used as antiseptics or as preservatives in eye drops, eye ointments, nasal sprays, and vaccines. Some skin-lightening

creams contain ammoniated mercuric chloride and mercuric iodide. These and all other mercury-containing medicines should be kept safely out of the reach of children to prevent an accidental poisoning. Nonmedicinal products, including some fungicides that contain mercury compounds and paints that contain mercuric sulfide or mercuric oxide, should also be safely stored out of the reach of children.

You should check to see if any medicines or herbal remedies that you or your child use contain mercury. Some traditional Chinese and Indian remedies for stomach disorders (for example, herbal balls) contain mercury, and if you give these remedies to your children, you may harm them. If you are pregnant or nursing a baby and you use mercury-containing ethnic or herbal remedies, you could pass some of the mercury to your unborn child or nursing infant.

If you use metallic mercury or azogue in religious practices, you may expose your children or unborn child to mercury or contaminate your home. Such practices in which mercury containing substances have traditionally been used include Santeria (a Cuban-based religion whose followers worship both African deities and Catholic saints), Voodoo (a Haitian-based set of beliefs and rituals), Palo Mayombe (a secret form of ancestor worship practiced mainly in the Caribbean), or Espiritismo (a spiritual belief system native to Puerto Rico).

Metallic mercury is used in a variety of household products and industrial items, including thermostats, fluorescent light bulbs, barometers, glass thermometers, and some blood pressure measuring devices. You must be careful when you handle and dispose of all items in the home that contain metallic mercury.

If small amounts of mercury are spilled, be very careful cleaning it up. Do not try to vacuum spilled metallic mercury. Using a vacuum cleaner to clean up the mercury causes the mercury to evaporate into the air, creating greater health risks. Trying to vacuum spilled metallic mercury also contaminates the vacuum cleaner. Also, take care not to step on the mercury and track it into other areas of the home. Metallic mercury vapors are very toxic and have no odor. Do not remain unnecessarily in that room, and try not to let metallic mercury contact your eyes, skin, or clothing. If you think you have been exposed directly to metallic mercury, wash yourself

thoroughly and discard contaminated clothing by placing them in a sealed plastic bag. Perhaps the most important thing to remember if you break a household thermometer is do not panic. The amount of mercury contained in an oral thermometer is small and does not present an immediate threat to human health. However, if it is not properly cleaned up and disposed of, it may present a health risk over time, particularly to infants, toddlers, and pregnant women.

If a thermometer breaks on a counter top or uncarpeted floor, remove children from the area. Mercury is not absorbent, so do not try to wipe or blot it up with a cloth or paper towel; that will only spread the mercury and break it up into smaller beads, making it more difficult to find and remove. Instead, clean up the beads of metallic mercury by using one sheet of paper to carefully roll them onto a second sheet of paper, or by sucking very small beads of mercury into an eye dropper. After picking up the metallic mercury in this manner, put it into a plastic bag or airtight container. The paper and eye dropper should also be bagged in a zip-lock plastic container. All plastic bags used in the cleanup should then be taken outside of the house or apartment and disposed of properly, according to instructions provided by your local health department or environmental officials. Try to ventilate the room with outside air, and close the room off from the rest of the home. Use fans (that direct the air to the outside and away from the inside of the house) for a minimum of one hour to speed the ventilation.

If a thermometer breaks and the liquid/metallic mercury spills onto a carpeted floor, try to collect the mercury beads in the manner described in the above paragraph. Depending on the cut or pile of the carpeting, however, it may not be possible to collect all of the spilled mercury. Regardless, do not vacuum. Instead, call your local (county, city, or state) health department and tell them of your situation. (You may also call the Agency for Toxic Substances and Disease Registry [ATSDR] toll-free at 1-888-42-ATSDR [1-888-422-8737] to obtain additional guidance, if local assistance cannot be obtained.)

If larger amounts of metallic mercury are found (for example, a jar of liquid mercury), it should be contained in an airtight container, and you should call your local health department for instructions on how to safely dispose of it. If the mercury is in an open container or the container does not have a lid, place a piece of plastic wrap around the top of the container to prevent

vapors from escaping; then wash your hands thoroughly. If a larger amount is spilled, leave the area and contact your local health department and fire department. Do not simply throw metallic mercury away, but instead seek professional help.

ATSDR and EPA strongly recommend against the use of metallic (liquid) mercury that is not properly enclosed in glass, as it is in thermometers. This form of mercury should not be used or stored in homes, automobiles, day-care centers, schools, offices, or other public buildings. If you notice a child with metallic mercury on his or her clothing, skin, or hair, call the fire department and let them know that the child needs to be decontaminated.

Metallic or inorganic mercury can be carried into the home from a workers' contaminated clothing and shoes. Increased exposure to mercury has been reported in children of workers who are exposed to mercury at work, and increased levels of mercury were measured in places where work clothes were stored and in some washing machines. The children most likely to be exposed to risky levels of mercury are those whose parents work in facilities that use mercury (for example, a scientific glassware manufacturing plant or a chlor-alkali chemical plant), but where no protective uniforms or footgear are used. In some reported cases in which children were exposed in this way, protective clothing was used in the workplace by the parent, but work gloves, clothes, and boots, which were contaminated with mercury, were taken home, thus exposing family members. If you have questions or concerns about exposure to mercury at work, you have a right to obtain information from your employer about your safety and health on the job without fear of punishment. The Occupational Safety and Health Administration (OSHA) requires employers to provide Material Safety Data Sheets (MSDSs) for many of the chemicals used at the workplace. Information on these sheets should include chemical names and hazardous ingredients, important properties (such as fire and explosion data), potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in an emergency. Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools, and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes.

Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your OSHA-approved state occupational safety and health program or OSHA can also answer any further questions you might have, and help your employer identify and correct problems with hazardous substances. If you would like to make a formal complaint about health hazards in your workplace, your OSHA-approved state occupational safety and health program or OSHA office will listen to your complaint and inspect your workplace when necessary.

One way in which people are routinely exposed to extremely small amounts of mercury is through the gradual (but extremely slow) wearing-away process of dental amalgam fillings, which contain approximately 50% mercury. The amount of mercury to which a person might be exposed from dental amalgams would depend on the number of amalgams present and other factors. The Centers for Disease Control and Prevention (CDC) has determined that dental amalgam fillings do not pose a health risk, although they do account for some mercury exposure to those having such fillings. People who frequently grind their teeth or often chew gum can add to the small amount of mercury normally released from those fillings over time. If you are pregnant, the decision of whether to have dental amalgam or a nonmercury material used for fillings, or whether existing amalgam fillings should be repaired or replaced during pregnancy, should be made in consultation with your dentist. The practice of having all your dental amalgam fillings replaced with non-mercury filling materials just to remove the possibility of mercury exposure is not recommended by ATSDR. In fact, the removal of the mercury amalgam fillings would actually expose the patient to a greater amount of mercury for a while. Other sources of mercury may increase your overall exposure, such as the amount of fish consumed per week, especially if caught in local waters contaminated with mercury or of certain species known to be higher in mercury content (shark and swordfish), or an exposure to mercury from a nearby hazardous waste site or incinerator.

You or your children may be exposed to methylmercury when eating certain types of fish caught from contaminated waters, or when eating certain types of wildlife from mercury contaminated areas. Most states, Native American tribes, and U.S. Territories have issued fish and/or wildlife advisories to warn people about methylmercury contaminated fish and/or wildlife. Most of the

methylmercury advisories relate to specific types of freshwater or saltwater fish or shellfish, or freshwater turtles. Each state, Native American tribe, or U.S. Territory sets its own criteria for issuing fish and wildlife advisories. A fish or wildlife advisory will specify which bodies of water or hunting areas have restrictions. The advisory will tell you what types and sizes of fish or game are of concern. The advisory may completely ban eating fish or tell you to limit your meals of a certain type of fish. For example, an advisory may tell you to eat a certain type of fish no more than once a month; or an advisory may tell you only to eat certain parts of fish or game, or how to prepare it to decrease your exposure to methylmercury. The fish or wildlife advisory may be stricter to protect pregnant women, nursing women, and young children. To reduce your children's exposure to methylmercury, you should follow the instructions recommended in the fish or wildlife advisories. Information on Fish and Wildlife Advisories in your state is available from your state public health or natural resources department. Signs may also be posted in certain fishing and hunting areas with information about contaminated fish or wildlife.

FDA currently advises that pregnant women and women of childbearing age who may become pregnant limit their consumption of shark and swordfish to no more that one meal per month. This advice is given because methylmercury levels are relatively high in these fish species. Women of childbearing age are included in this advice because dietary practices immediately before the pregnancy could have a direct bearing on fetal exposure during pregnancy, particularly during the earlier months of pregnancy.

FDA further advises that persons other than pregnant women and women of childbearing age in the general population limit their regular consumption of shark and swordfish (which typically contains methylmercury around 1 ppm) to about 7 ounces per week (about one serving) to stay below the acceptable daily intake for methylmercury. For fish species with methylmercury levels averaging 0.5 ppm, regular consumption should be limited to 14 ounces per week. Recreational and subsistence fishers who eat larger amounts of fish than the general population and routinely fish the same waterbodies may have a higher exposure to methylmercury if these waters are contaminated. People who consume greater than 100 grams of fish (approximately 3.5 ounces) every day are considered high-end consumers. This is over 10 times more than the amount of fish consumed by members of the general population (6.5 g/day). No consumption advice is necessary

for the top ten seafood species that make up about 80% of the seafood sold in the United States: canned tuna, shrimp, pollock, salmon, cod, catfish, clams, flatfish, crabs, and scallops. The methylmercury in these species is generally less than 0.2 ppm, and few people eat more than the suggested weekly limit of fish (i.e., 2.2 pounds).

If you are concerned about a mercury exposure or think that you or your child are experiencing the adverse effects of mercury, you should consult with a doctor or public health official who is familiar with the health effects of mercury.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO MERCURY?

There are reliable and accurate ways to measure mercury levels in the body. These tests all involve taking blood, urine, or hair samples, and must be performed in a doctor's office or in a health clinic. Nursing women may have their breast milk tested for mercury levels, if any of the other samples tested are found to contain significant amounts of mercury. Most of these tests, however, do not determine the form of mercury to which you were exposed. Mercury levels found in blood, urine, breast milk, or hair may be used to determine if adverse health effects are likely to occur (see Section 2.5). Mercury in urine is used to test for exposure to metallic mercury vapor and to inorganic forms of mercury. Measurement of mercury in whole blood or scalp hair is used to monitor exposure to methylmercury. Urine is not useful for determining whether exposure has occurred to methylmercury. Levels found in blood, urine, and hair may be used together to predict possible health effects that may be caused by the different forms of mercury.

Blood and urine levels are used as markers to determine whether someone has been exposed to mercury. They are used to determine whether exposure to mercury has occurred and to give a rough idea of the extent of exposure, but they do not tell exactly how much exposure has occurred. Except for methylmercury exposures, blood is considered useful if samples are taken within a few days of exposure. This is because most forms of mercury in the blood decrease by one-half every three days if exposure has been stopped. Thus, mercury levels in the blood provide

more useful information after recent exposures than after long-term exposures. Several months after an exposure, mercury levels in the blood and urine are much lower. Hair, which is considered useful only for exposures to methylmercury, can be used to show exposures that occurred many months ago, or even more than a year ago if the hair is long enough and careful testing methods are used. After short-term exposures to metallic mercury, mercury vapor can be detected in the breath, but this occurs to a significant extent only within a few days after exposure, and is not a method normally used to determine if mercury exposure has occurred. For more information on testing for mercury levels in the body, see Chapters 2 and 6.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations, on the other hand, provide valuable guidelines to protect public health, but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it for the substance in which you are interested. Some regulations and recommendations for mercury include the following:

EPA and FDA have set a limit of 2 parts inorganic mercury per billion (ppb) parts of water in drinking water. EPA is in the process of revising the Water Quality Criteria for mercury. EPA currently recommends that the level of inorganic mercury in rivers, lakes, and streams be no more than 144 parts mercury per trillion (ppt) parts of water to protect human health (1 ppt is a thousand times less than 1 part per billion, or ppb). EPA has determined that a daily exposure (for an adult of average weight) to inorganic mercury in drinking water at a level up to 2 ppb is not likely to cause any significant adverse health effects. FDA has set a maximum permissible level of 1 part of methylmercury in a million parts (ppm) of seafood products sold through interstate commerce (1 ppm is a thousand times more than 1 ppb). FDA may seize shipments of fish and shellfish containing more than 1 ppm of methylmercury, and may seize treated seed grain containing more than 1 ppm of mercury.

OSHA regulates levels of mercury in the workplace. It has set limits of 0.1 milligrams of mercury per cubic meter of air (mg/m^3)for organic mercury and 0.05 mg/m^3 for metallic mercury vapor in workplace air to protect workers during an 8-hour shift and a 40-hour work week. NIOSH recommends that the amount of metallic mercury vapor in workplace air be limited to an average level of 0.05 mg/m^3 during a 10-hour work shift.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: (404) 639- 6315 or -6324

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of mercury. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Mercury is a metal element that occurs naturally in the environment. Metallic or elemental mercury (Hg^0) is the main form of mercury released into the air by natural processes. Mercury bound to other chemicals may have valence states of either +1 (Hg^{+1}) or +2 (Hg^{+2}). Mercury with a valence state of +1 is referred to as mercurous mercury, and mercury with a valence state of +2 is referred to as mercuric mercury. Many inorganic and organic compounds of mercury can be formed from the mercuric (divalent) cation (Hg^{+2}). For information on the physical and chemical properties of mercury, refer to Chapter 3.

There are many similarities in the toxic effects of the various forms of mercury, but there are also significant differences. In the text, tables, and figures of this profile, the metallic mercury and the inorganic salts, including mercurous chloride, mercuric chloride, mercuric acetate, and mercuric sulfide, are organized under the general heading of inorganic mercury. The organic mercury compounds including methyl-mercuric chloride, dimethylmercury, and phenylmercuric acetate are addressed in this document under the heading of organic mercury. In most discussion in the text, the specific effects are attributable to a particular form, and the form is specified.

The general population is most commonly exposed to mercury primarily from two sources: (1) eating fish and marine mammals (e.g., whales, seals) that may contain some methylmercury in their tissues or (2) from the release of elemental mercury from the dental amalgam used in fillings. It is not known how much of the elemental mercury released from dental amalgam is inhaled as a mercury vapor, how much is breathed out, how much is swallowed in a liquid form, or how much is converted into a mercuric salt that is either swallowed of directly absorbed into the oral mucosa. Exposure to mercury, however, does not necessarily mean that adverse health effects will result. Health effects depend upon the amount of exposure, the form

of mercury, and the route of exposure. Each form and route leads to different effects, and these are discussed in detail in this chapter. The levels of mercury that the general population are exposed to from either fish or dental amalgam are discussed in Chapter 5. Hazard assessments combine the information in Chapter 5 on exposure levels with the dose-response information in this chapter to develop an estimate of the potential for adverse health effects from any given exposure.

In the environment, inorganic mercury can be methylated by microorganisms to methylmercury. Methylmercury will accumulate in the tissues of organisms. The animals at the top of the food chain tend to accumulate the most methylmercury in their bodies. Any source of mercury release to the environment may, therefore, lead to increased levels of methylmercury in tissues of large fish and mammals. Occupational exposures are primarily to metallic mercury vapor. Accidental exposures to mercury are more common than accidental exposures to many hazardous substances, because liquid mercury is shiny and interesting, and because liquid mercury has been used in many electrical and mechanical devices. Accidental exposures, even to small amounts of mercury, may be harmful. Liquid mercury is poorly absorbed by the skin and from the intestines, but vapors that are released from liquid mercury are readily absorbed through the lungs and are very harmful when inhaled. The text in this chapter provides considerable detail on a number of accidental exposures to all forms of mercury. This information is intended to inform the reader and help prevent accidental exposures in the future.

The literature on the health effects of mercury is extensive. However, the human and animal data are generally limited to inhalation exposure to metallic mercury vapors and oral exposure to inorganic and organic mercury compounds. There is limited dermal exposure information on adverse effects from ointments and creams that contain inorganic mercury compounds.

Once absorbed, metallic and inorganic mercury enter an oxidation-reduction cycle. Metallic mercury is oxidized to the divalent inorganic cation in the red blood cells and lungs of humans and animals. Evidence from animal studies suggests that the liver is an additional site of oxidation. Absorbed divalent cation from exposure to mercuric compounds can, in turn, be reduced to the metallic or monovalent form and released as exhaled metallic mercury vapor. In the presence of protein sulfhydryl groups, mercurous mercury (Hg^{+}) disproportionates to one divalent cation (Hg^{+2}) and one molecule at the zero oxidation state (Hg^{0}). The conversion of methylmercury or phenylmercury into divalent inorganic mercury can probably occur soon after absorption, also feeding into the oxidation-reduction pathway.

This profile contains a discussion of acrodynia under Relevance to Public Health (Section 2.5). Acrodynia is an idiosyncratic hypersensitivity response from exposure to mercury and is characterized by certain cardiovascular, dermal, and neurological effects, among others. In the section on health effects by route of exposure, the relevant symptoms are discussed under the appropriate headings without reference to the syndrome. This occurs, in part, because there is some overlap between symptoms characteristic of acrodynia and those seen in persons who are not hypersensitive and, in part, because not every report of a study in which the symptoms were observed states whether the authors considered the affected person to have suffered from acrodynia.

This profile also contains a general discussion of the human exposures to mercury associated with dental amalgam. This discussion is at the end of the Relevance to Public Health Section 2.5, under the heading More on Health Effects and Dental Amalgam.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure — inhalation, oral, and dermal; and then by health effect — death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods — acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure (LSE) for each route and duration are presented in Tables 2-1, 2-2, and 2-3 and illustrated in Figures 2-1, 2-2, and 2-3. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end-points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less

serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Level of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of mercury are indicated in Tables 2-2 and 2-3 and Figures 2-2 and 2-3. Cancer effects could occur at lower exposure levels; however, a range for the upper bound of estimated excess risks (ranging from a risk of 1 in 10,000 to 1 in 10,000,000 [10^{-4} to 10^{-7}]) has not been developed by EPA.

Estimates of human Minimal Risk Levels (or MRLs) have been made for mercury. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. Although the term, MRL, may seem to imply a slight level of risk, MRLs are, in fact, considered to represent safe levels of exposure for all populations, including sensitive subgroups. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic

bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs may be revised.

2.2.1 Inhalation Exposure

Most of the studies on inhalation exposure concern exposure to metallic mercury vapor. For this reason, the term “metallic mercury” will be used in this section instead of “inorganic mercury.” Other forms of inorganic mercury do not pose a risk by the inhalation pathway. Inhalation of sufficient levels of metallic mercury vapor has been associated with systemic toxicity in both humans and animals. The major target organs of metallic mercury-induced toxicity are the kidneys and the central nervous system. At high-exposure levels, respiratory, cardiovascular, and gastrointestinal effects also occur. Some metallic mercury vapor may condense (Milne et al. 1970), or in the case of vapors from dental amalgam, may dissolve in saliva and be ingested (WHO 1991). Condensed droplets are more likely to be ingested than inhaled (resulting in a lower absorbed dose than would be expected for a given concentration in air). Mercury vapor concentrations in the general work environment may also be lower than those in the micro-environment immediately surrounding workers (Bell et al. 1973; Stopford et al. 1978); therefore, estimates of air mercury values in occupational studies should be carefully evaluated for bias towards a level that may be lower than actual exposure levels.

No studies were located concerning effect levels following inhalation exposure to inorganic salts of mercury (e.g., mercuric or mercurous salts, oxides). Also, much of the information located regarding effects of metallic mercury vapors or volatile organic compounds (VOCs) comes from studies with significant limitations. Information on inhalation exposure to organic mercury compounds (e.g., alkyl mercury compounds) in humans is limited to case reports and includes only qualitative data on gastro-intestinal, renal, muscular, and neurological effects. In many cases, it is difficult to determine whether effects observed in exposed persons were directly attributable to mercury exposure. In addition, a great deal of the information on effects associated with inhalation exposure to metallic mercury vapor comes from studies conducted several decades ago, when methods for determining exposure levels were less precise than current methods.

2.2.1.1 Death

Metallic Mercury. Several studies have reported death in humans following accidental acute-duration exposure to high, but unspecified, concentrations of metallic mercury vapor (Campbell 1948; Kanluen and Gottlieb 1991; Matthes et al. 1958; Rowens et al. 1991; Soni et al. 1992; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961). Death in all cases was attributed to respiratory failure. In all of these cases, high levels of mercury vapors were generated by volatilizing metallic mercury by heating.

Available animal data on death from exposure to metallic mercury vapors were also limited to acute-duration exposures (Ashe et al. 1953; Christensen et al. 1937; Livardjani et al. 1991b). Rats, guinea pigs, and mice died from severe pulmonary edema following a 24–48-hour exposure to an unspecified concentration of metallic mercury vapor resulting from spillage of mercury droplets on the floor of a static exposure chamber (Christensen et al. 1937). Exposure of rats to 27 mg/m^3 of elemental mercury vapors for 2 hours, followed by observation for 15 days, resulted in substantial mortality (20 of 32 rats died prior to their scheduled sacrifice) (Livardjani et al. 1991b). Rabbits appeared to be less sensitive, with death occurring in 1 of 2 rabbits exposed to 28.8 mg/m^3 metallic mercury for 30 hours and no deaths in rabbits exposed to the same concentration for 20 hours or less (Ashe et al. 1953).

All reliable LOAEL values for death following exposure to inorganic mercury in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Organic Mercury. Case studies of occupational exposure to alkyl mercury compounds have reported deaths in humans following inhalation exposure to organic mercury vapors. The cause of death was not reported, but most subjects died after developing profound neurotoxicity (Hill 1943; Hook et al. 1954). Exposure to diethylmercury vapor (estimated exposure level = 1–1.1 mg/m^3) for 4–5 months resulted in the death of 2 women (Hill 1943). The cause of death was not reported; however, the symptoms experienced by the women were consistent with mercury toxicity, and autopsies revealed pronounced gastrointestinal disorder. It is unclear whether the gastrointestinal effects were directly attributable to the mercury exposure. A 41-year-old man with 3–4 years of exposure to alkyl mercury compounds used in seed dressing died within approximately 3 months after cleaning up a spill of liquid containing alkyl mercury (Hook et al. 1954). A 57-year-old male employed for 5 years treating lumber with an alkyl mercury preparation (unspecified) died soon after developing neurological toxicity (Lundgren and Swensson 1949).

Table 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
ACUTE EXPOSURE							
Death							
1	Rat (Wistar)	1 or 2 hr				27 M (20/32 died prior to scheduled sacrifice)	Livardjani et al. 1991 ELEM
Systemic							
2	Rat (Wistar)	1 or 2 hr	Resp			27 M (death by asphyxiation; lung edema; hyaline membranes, necrosis of alveolar epithelium; and fibrosis)	Livardjani et al. 1991 ELEM
3	Rabbit	1-30 hr	Resp			28.8 (marked cellular degeneration and some necrosis)	Ashe et al. 1953 ELEM
			Cardio			28.8 (marked cellular degeneration and some necrosis)	
			Gastro			28.8 (marked cellular degeneration and some necrosis)	
			Hepatic			28.8 (widespread necrosis)	
			Renal			28.8 (widespread necrosis)	
Neurological							
4	Rabbit	1-30 hr				28.8 (brain necrosis)	Ashe et al. 1953 ELEM

Table 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Developmental							
5	Rat (Sprague-Dawley)	8 d 1 or 3 hr/d Gd 11-14 + 17-20				1.8 (offspring hypoactive at 3 mo of age, significant retardation in spatial learning, reduced ability to adapt to new environment)	Danielsson et al. 1993 ELEM
6	Rat (Sprague-Dawley)	7d 1,4 hr/d ppd 11-17				0.05 M (offspring hyperactive, significantly impaired spatial learning)	Fredriksson et al. 1992 ELEM
7	Rat (Sprague-Dawley)	6 d 1.5 hr/d Gd 14-19				1.8 (offspring hyperactive, significantly impaired spatial learning, deficits in adaptive behavior)	Fredriksson et al. 1996 ELEM
INTERMEDIATE EXPOSURE							
Systemic							
8	Rat	12-42 wk 5 d/wk 3 hr/d	Resp	3.0 M			Kishi et al. 1978 ELEM
			Hepatic	3.0 M			
			Renal		3.0 M (dense deposits in tubular cells; lysosomal inclusions)		

Table 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
9	Rabbit	1-11 wk 5 d/wk 7 hr/d	Resp		6.0 (unspecified histopathological changes in lungs)		Ashe et al. 1953 ELEM
			Cardio		6.0 (unspecified histopathological changes in heart)		
			Gastro		6.0 (unspecified histopathological changes in colon)		
			Hepatic			6.0 (marked cellular degeneration with mild necrosis in liver)	
			Renal			6.0 (marked cellular degeneration; widespread necrosis in kidneys)	
10	Rabbit	12 wk 5 d/wk	Cardio		0.86 (unspecified histopathological changes)		Ashe et al. 1953 ELEM
			Renal		0.86 (mild to moderate unspecified histopathological changes in the kidneys)		
Immunological/Lymphoreticular							
11	Mouse (SJL/N)	10 wk 5 d/wk 0.5-19 hr/d		0.075 F	0.17 F (serum antinucleolar antibodies)		Warfvinge et al. 1995 ELEM
Neurological							
12	Rat	12-41 wk 5 d/wk 3 hr/d				3.0 M (significant decline in conditioned avoidance response and increase in escape response latency)	Kishi et al. 1978 ELEM

Table 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL			Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)		
13	Rabbit	12 wk 5 d/wk 7 hr/d				0.86	(unspecified histopathological changes in the brain)	Ashe et al. 1953 ELEM
14	Rabbit	1-11 wk 5 d/wk 7 hr/d				6.0	(marked cellular degeneration with brain necrosis)	Ashe et al. 1953 ELEM
15	Rabbit	13 wk 4 d/wk 6 hr/d				4	(tremors)	Fukuda 1971 ELEM
	Developmental							
16	Monkey (Squirrel)	15-17 wk 5 d/wk 4 or 7 hr/d last 2/3 gestation				0.5	(increase in duration and variability in lever-press performance, aberrant transitions)	Newland et al. 1996 ELEM
CHRONIC EXPOSURE								
	Systemic							
17	Rat	72 wk 5 d/wk 7 hr/d	Renal	0.1				Ashe et al. 1953 ELEM
18	Dog	83 wk 5 d/wk 7 hr/d	Renal	0.1				Ashe et al. 1953 ELEM
19	Rabbit	83 wk 5 d/wk 7 hr/d	Renal	0.1				Ashe et al. 1953 ELEM

Table 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Neurological							
20	Human	1-5 yr			0.076 M (difficulty with heel-to-toe gait)		Ehrenberg et al. 1991 ELEM
21	Human	1-41 yr 15.3 yr mean			0.026[b] M (increased frequency of mild intention tremors with weight load)		Fawer et al. 1983 ELEM
22	Human	0.7-24 yr			0.014 (impaired performance on neurobehavioral tests)		Ngim et al. 1992 ELEM

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive a chronic inhalation Minimal Risk Level (MRL) of $2x10^{-4}$ mg/m^3; concentration corrected for intermittent exposure and divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability).

ALT = alanine amino transferase; AST = aspartate aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); ELEM = elemental mercury; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; ppd = postpartum day (s); Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation

Acute (≤14 days)

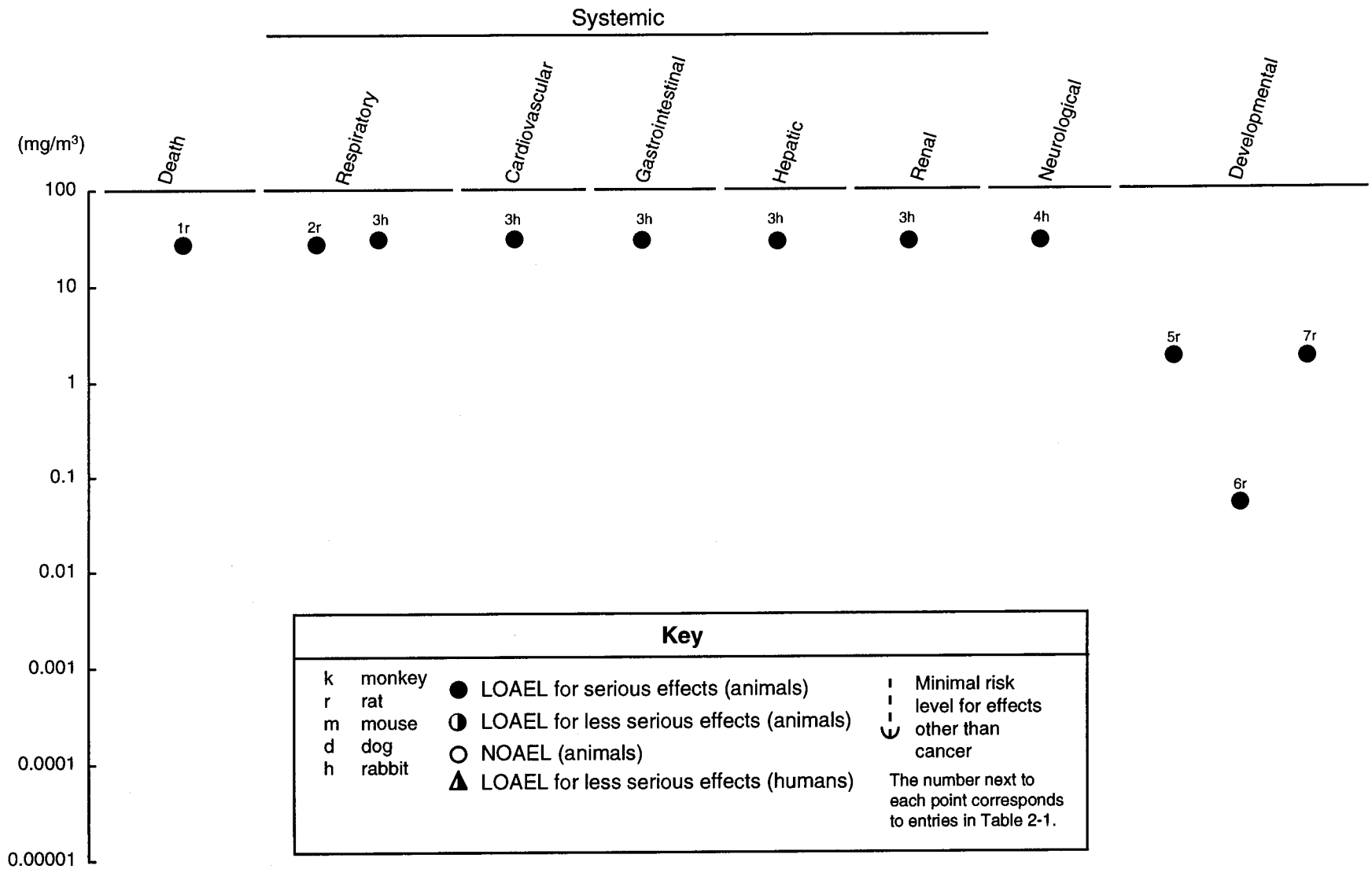


Figure 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (cont.)

Intermediate (15-364 days)

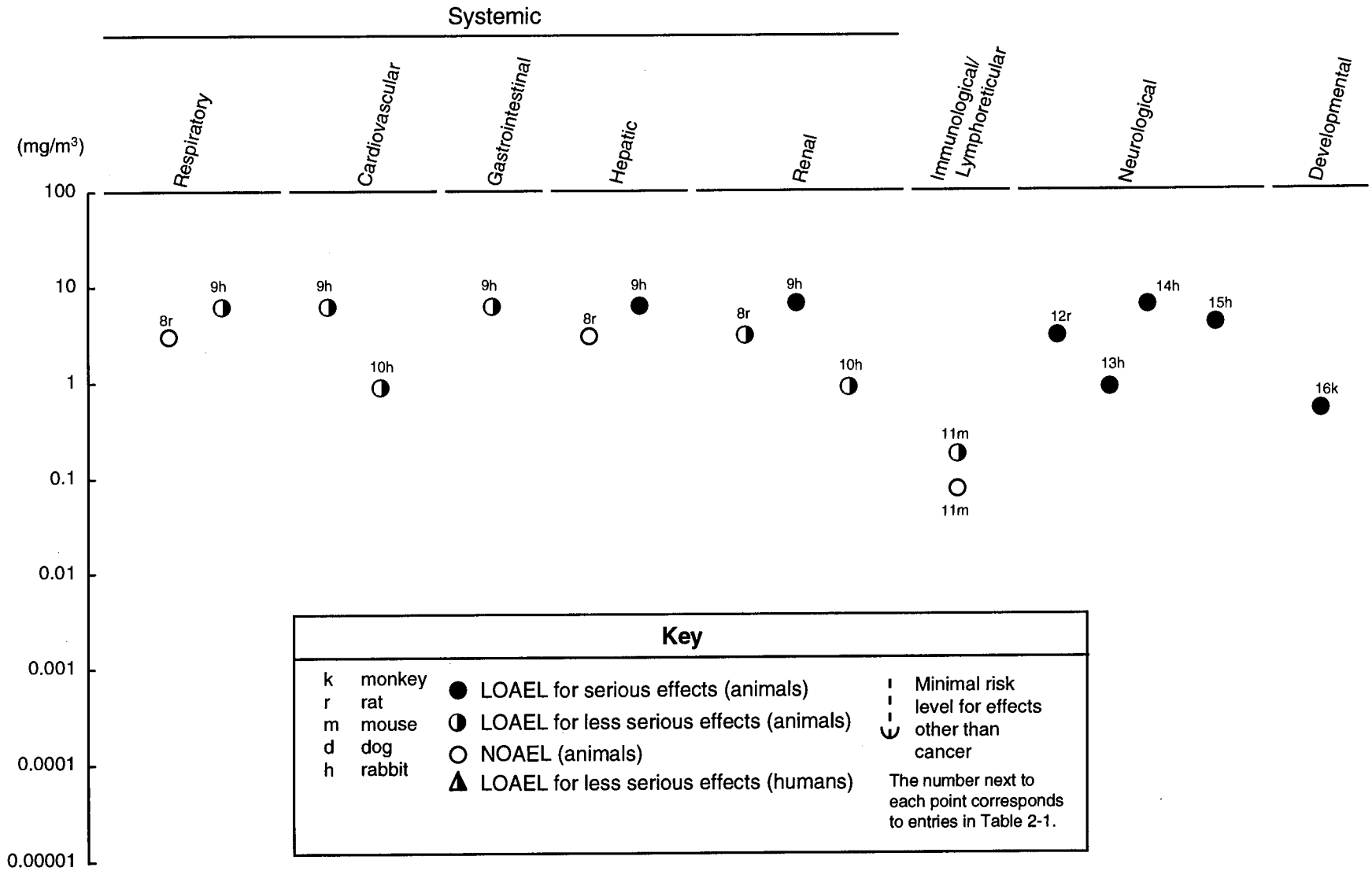
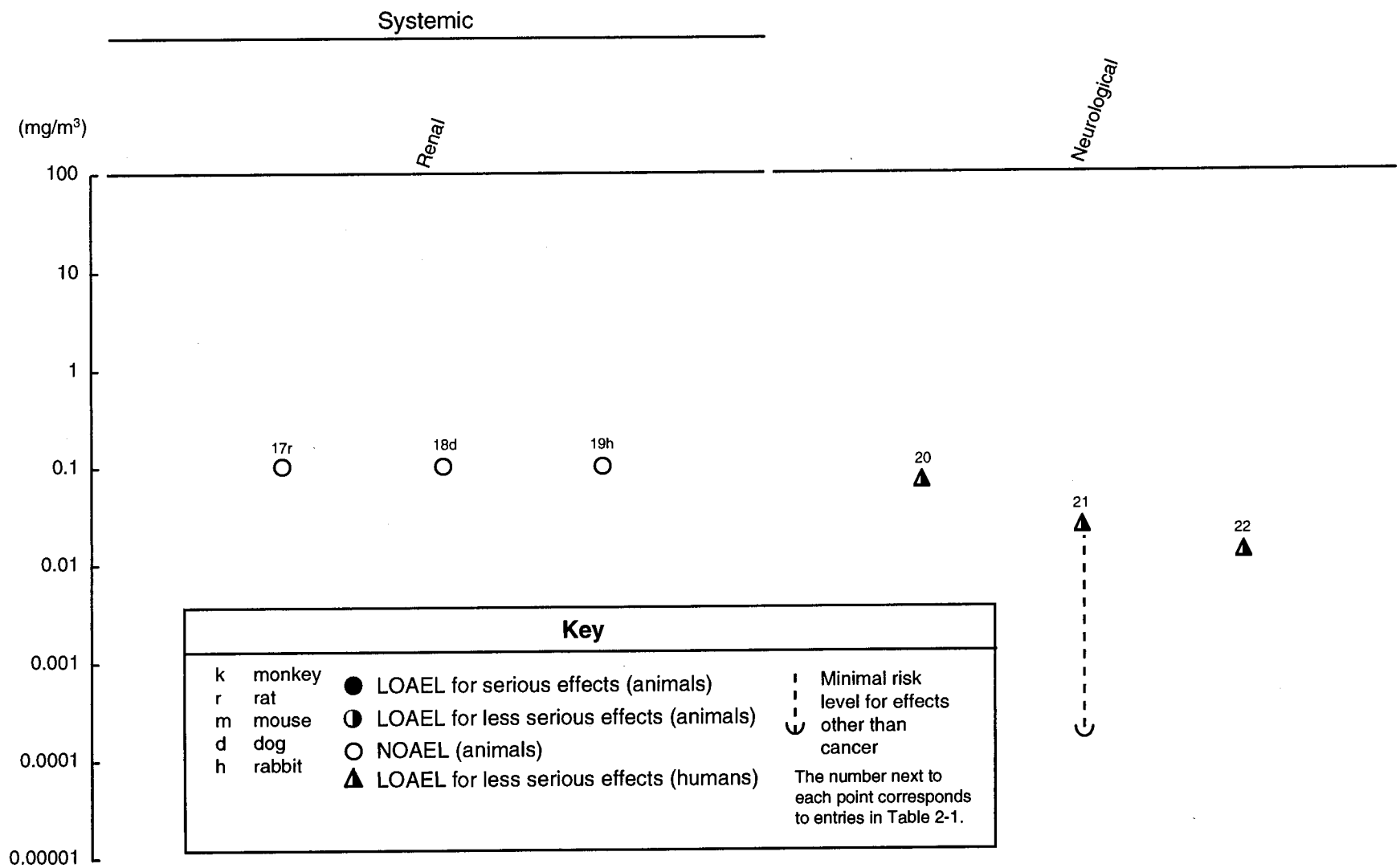


Figure 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (cont.)

Chronic (≥365 days)



A 39-year-old farmer who had treated seeds with phenylmercuric acetate for 6–7 seasons died within several months of developing severe neurological toxicity (Brown 1954).

Four rats died soon after developing severe ataxia following inhalation of unspecified concentrations of methylmercury iodide vapor for 22 days (Hunter et al. 1940).

2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects

Metallic Mercury. In humans, respiratory symptoms are a prominent effect of acute-duration high-level exposure to metallic mercury vapors. The most commonly reported symptoms include cough, dyspnea, and tightness or burning pains in the chest (Bluhm et al. 1992a; Gore and Harding 1987; Haddad and Sternberg 1963; Hallee 1969; Kanluen and Gottlieb 1991; King 1954; Lilis et al. 1985; Matthes et al. 1958; McFarland and Reigel 1978; Milne et al. 1970; Rowens et al. 1991; Snodgrass et al. 1981; Soni et al. 1992; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961). X-ray analyses of the lungs have primarily shown diffuse infiltrates or pneumonitis (Bluhm et al. 1992a; Garnier et al. 1981; Gore and Harding 1987; Hallee 1969; King 1954; Soni et al. 1992; Tennant et al. 1961). Pulmonary function may also be impaired. Airway obstruction, restriction, hyperinflation (Snodgrass et al. 1981), and decreased vital capacity (Lilis et al. 1985; McFarland and Reigel 1978) have been reported. The decreased vital capacity observed by Lilis et al. (1985) persisted for 11 months after exposure. In the more severe cases, respiratory distress, pulmonary edema (alveolar and interstitial), lobar pneumonia, fibrosis, and desquamation of the bronchiolar epithelium have been observed. The ensuing bronchiolar obstruction by mucus and fluid results in alveolar dilation, emphysema, pneumothorax, and possibly death (Campbell 1948; Gore and Harding 1987; Jaffe et al. 1983; Kanluen and Gottlieb 1991; Matthes et al. 1958; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961).

Little information is available regarding exposure levels resulting in the above symptoms. However, workers accidentally exposed to mercury vapors at an estimated concentration of up to 44.3 mg/m^3 for 4–8 hours exhibited chest pains, dyspnea, cough, hemoptysis, impairment of pulmonary function (i.e.,

reduced vital capacity), diffuse pulmonary infiltrates, and evidence of interstitial pneumonitis (McFarland and Reigel 1978).

Very little information was located regarding respiratory effects associated with intermediate-duration exposures. However, two studies noted chronic coughs in subjects exposed to metallic mercury vapor for several weeks (Schwartz et al. 1992; Sexton et al. 1976). No respiratory symptoms and no abnormalities were noted upon examining chest X-rays or the results of pulmonary function tests in a group of chloralkali workers exposed for an average of >6 years to levels of mercury ranging from near 0 to 0.27 mg/m^3 (85% of the group was exposed at or below 0.1 mg/m^3) (Smith et al. 1970).

Respiratory effects in animals have been observed following acute inhalation exposure of metallic mercury vapors. Rats exposed to 27 mg/m^3 of elemental mercury vapors for 2 hours then observed for 15 days displayed dyspnea and death due to asphyxiation (Livardjani et al. 1991b). Respiratory tract lesions included lung edema, necrosis of the alveolar epithelium and hyaline membranes, and occasional lung fibrosis.

Exposure to 28.8 mg/m^3 of mercury vapor lasting from 1 to 20 hours produced effects ranging from mild to moderate pathological changes (unspecified) (Ashe et al. 1953). For exposures lasting 30 hours, marked cellular degeneration and some necrosis were observed in the lungs of 1 rabbit. Less severe respiratory changes (unspecified mild-to-moderate pathological changes) were reported in rabbits following exposure to metallic mercury vapor at 6 mg/m^3 for 7 hours a day, 5 days a week for 1–11 weeks (Ashe et al. 1953). The usefulness of these results is limited because the study did not specify the pathological changes nor distinguish between primary and secondary effects (i.e., pathological changes secondary to induced shock).

Congested lungs were observed in rats exposed to 1 mg/m^3 metallic mercury vapors for 100 hours continuously per week for 6 weeks (Gage 1961). In rats exposed to 3 mg/m^3 mercury vapor for only 3 hours a day, 5 days a week for 12–42 weeks, pathological examination revealed no significant changes in the respiratory system (Kishi et al. 1978). The potential for oral exposure was not quantified in these studies; however, it is likely that most of the exposure was via inhalation.

Organic Mercury. Dyspnea, respiratory depression, and respirations frequently obstructed by mucus were observed in a farmer who had treated grain with phenylmercuric acetate for several seasons (Brown 1954). An autopsy revealed purulent bronchopneumonia. It is unclear whether the respiratory effects were direct

effects of the phenylmercuric acetate or secondary to the severe neurotoxicity also seen in this subject. A case study reported that no respiratory effects were observed in four men inhaling unspecified concentrations of methylmercury for several months (Hunter et al. 1940). Both of these studies are limited because exposure levels were unknown.

No studies were located regarding respiratory effects in animals after inhalation exposure to organic mercury.

Cardiovascular Effects

Metallic Mercury. Increases in heart rate and blood pressure have been reported following inhalation exposure to metallic mercury in humans. Acute inhalation exposure to high concentrations of metallic mercury vapor generated by heating metallic mercury resulted in increased blood pressure (Haddad and Sternberg 1963; Hallee 1969; Snodgrass et al. 1981) and heart rate/palpitations (Bluhm et al. 1992a; Haddad and Sternberg 1963; Hallee 1969; Jaffe et al. 1983; Snodgrass et al. 1981; Soni et al. 1992; Teng and Brennan 1959). In one of these cases, the increase in heart rate was characterized as a sinus tachycardia (Soni et al. 1992). Exposures of longer durations due to spills or occupational exposures have also been reported to result in increased blood pressure (Fagala and Wigg 1992; Foulds et al. 1987; Friberg et al. 1953; Karpathios et al. 1991; Taueg et al. 1992) and increased heart rate (Fagala and Wigg 1992; Foulds et al. 1987). A single case report was located regarding cardiovascular effects resulting from inhalation of mercury vapors released from a paint that contained a high level of phenylmercuric acetate (Aronow et al. 1990). The affected child was diagnosed with acrodynia and exhibited a rapid heart beat and hypertension.

Chronic-duration occupational exposures, however, have given mixed results regarding effects on blood pressure and heart rate. Two studies of workers exposed to relatively low levels of mercury (near 0–0.27 mg/m^3 in one study and an average of 0.075 mg/m^3 in the other) for an average of greater than 6 or 7 years showed no effects on blood pressure or electrocardiography (Schuckmann 1979; Smith et al. 1970). In contrast, workers exposed to an estimated 0.03 mg/m^3 of mercury vapor (estimate based on blood levels) for at least 5 years reported an increased incidence of palpitations, and cardiovascular reflex responses were slightly reduced compared to unexposed matched controls (Piikivi 1989). Also, workers in a thermometer plant had a high incidence of hypertension (5 of 9 workers) (Vroom and Greer 1972). A morbidity and mortality study of chloralkali workers showed an increased likelihood of death due to

ischemic heart and cerebrovascular disease (Barregard et al. 1990). These studies are limited, however, because exposure to other chemicals may have contributed to the effects observed, exposure levels may have been estimated from only a few actual determinations, and other risk factors were not consistently considered.

Significant increases in systolic blood pressure and diastolic blood pressure were found in volunteers with dental amalgam containing mercury when compared to a control group (matched for age and sex) that had no amalgam fillings (Siblerud 1990). However, the length of time that the individuals had the dental amalgams was not reported. Furthermore, the blood pressure levels of the amalgam group were closer than those of the nonamalgam group to "normal" blood pressure levels reported for the general population. The authors suggested that the populations from which such normal values are drawn are likely to include many people with amalgam dental fillings, but without additional data to determine which control group would best represent “normal,” these results have limited use.

In animals, cardiovascular effects were noted following inhalation exposure to mercury vapor. Marked cellular degeneration with some necrosis of heart tissue was observed in rabbits following acute intermittent exposure to 28.8 mg/m^3 metallic mercury vapor for periods ranging from 4 to 30 hours (Ashe et al. 1953). Mild-to-moderate pathological changes (unspecified) were seen for 1–4-hour exposures. Exposures to lower concentrations (0.86–6 mg/m^3) of mercury vapor for periods ranging from 2 to 12 weeks also resulted in mild-to-moderate pathological changes (unspecified) in the hearts of rabbits. The usefulness of these results is limited because the study did not specify the pathological changes nor distinguish between primary and secondary effects (i.e., pathological changes secondary to induced shock).

Organic Mercury. Only two case histories were located regarding cardiovascular effects in persons exposed by inhalation to organic mercury compounds. No cardiovascular effects were reported in four men hospitalized for neurological symptoms after inhaling an unspecified concentration of methylmercury dust for at least several months (Hunter et al. 1940). Elevated blood pressure was reported in two men exposed occupationally to methylmercury compounds (dose not known) (Hook et al. 1954).

No studies were located regarding cardiovascular effects in animals after inhalation exposure to organic mercury.

Gastrointestinal Effects

Metallic Mercury. Many instances of gastrointestinal effects have been reported in humans following acute inhalation exposure to metallic mercury vapor. A classical sign of mercury intoxication is stomatitis (inflammation of the oral mucosa). Accordingly, a number of case studies have reported stomatitis after acute-duration exposure to high concentrations of metallic mercury vapors (Bluhm et al. 1992a; Garnier et al. 1981; Haddad and Sternberg 1963; Snodgrass et al. 1981; Tennant et al. 1961). Occasionally, the stomatitis was accompanied by excessive salivation (Hallee 1969; Karpathios et al. 1991) or difficulty swallowing (Campbell 1948). Other gastrointestinal effects observed after acute-duration exposure to high levels of mercury include abdominal pains (Bluhm et al. 1992a; Campbell 1948; Haddad and Sternberg 1963; Milne et al. 1970; Teng and Brennan 1959), nausea and/or vomiting (Haddad and Sternberg 1963; Hallee 1969; Kanluen and Gottlieb 1991; Lilis et al. 1985; Milne et al. 1970; Rowens et al. 1991; Snodgrass et al. 1981; Soni et al. 1992; Taueg et al. 1992), and diarrhea (Bluhm et al. 1992a; Kanluen and Gottlieb 1991; Rowens et al. 1991; Taueg et al. 1992; Teng and Brennan 1959). The autopsy of a young child who was intoxicated with mercury vapor and died of pulmonary edema revealed a grayish, necrotic mucosa of the stomach and duodenum (Campbell 1948).

Intermediate-duration exposures to mercury spills have also resulted in similar gastrointestinal effects. A case study reported that teenage girls exhibited anorexia, intermittent abdominal cramps, mild diarrhea, painful mouth, and bleeding gingiva 2 weeks after a spill of metallic mercury in their home (on carpet) resulted in the release of metallic mercury vapor (Sexton et al. 1976). Air levels in the home were measured 6 months after the initial spill and ranged from 0.02 to 1 mg Hg/m^3, depending upon the degree of ventilation and proximity to the spill. Fagala and Wigg (1992) reported a case of colicky abdominal pain and diarrhea in a 12-year-old girl exposed to mercury vapors for approximately 6 months after a spill in her home.

Limited information was located regarding gastrointestinal effects in persons who are chronically exposed to elemental mercury vapors. Stomatitis was observed in 22 of 72 workers exposed to mercury vapors in the manufacture of thermometers in the 1940s (Bucknell et al. 1993). Drooling, sore gums, ulcerations of the oral mucosa, and/or diarrhea were observed in 5 of 9 workers in a thermometer-manufacturing plant (Vroom and Greer 1972). A correlation was also observed between mercury exposure levels and unspecified oropharyngeal symptoms in workers from a chloralkali plant (Smith et al. 1970).

Two animal studies assessed the gastrointestinal effects from mercury vapor exposure. In rabbits, effects ranging from mild pathological changes to marked cellular degeneration and some necrosis of the colon were observed following exposure to 28.8 mg/m^3 mercury vapor for 4–30 hours (Ashe et al. 1953). A single exposure to 28.8 mg/m^3 for 1–2 hours or multiple exposures of 6 mg/m^3 for 7 hours a day, 5 days a week for up to 11 weeks resulted in either no changes or mild pathological changes. The usefulness of these results is limited because the study did not specify the pathological changes nor distinguish between primary and secondary effects (i.e., pathological changes secondary to induced shock).

Organic Mercury. Gastrointestinal effects were reported in several case studies of humans exposed to organomercurial compounds. A 39-year-old farmer who had dressed his seeds for several seasons with phenylmercuric acetate exhibited a swollen mouth, reddened and tender gums, carious teeth, a thin blue line at the gums, and an infected and swollen posterior pharyngeal wall (Brown 1954). Similarly, two women who died following 3–5 months of occupational exposure to diethylmercury vapors exhibited inflammation of the mouth and gums, excessive salivation, and unspecified gastrointestinal disorders (Hill 1943). Marked salivation was observed in one man and nausea was observed in another occupationally exposed to alkyl-mercury compounds used for dressing seeds (Hook et al. 1954). Gastrointestinal effects were not, however, observed in four men after inhalation of dust containing methylmercury for several months (Hunter et al. 1940).

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to organic mercury.

Hematological Effects

Metallic Mercury. Initial exposure to high concentrations of elemental mercury vapors produces a syndrome similar to "metal fume fever," which is characterized by fatigue, fever, chills, and elevated leukocyte count. Evidence of moderate-to-high leukocytosis with neutrophilia was reported following acute inhalation exposure to metallic mercury vapor (Campbell 1948; Haddad and Sternberg 1963; Hallee 1969; Jaffe et al. 1983; Lilis et al. 1985; Matthes et al. 1958; Rowens et al. 1991).

Similarly, an elevated white cell count was observed in a 12-year-old girl with a 6-month exposure to mercury vapors from a spill of metallic mercury in her home (Fagala and Wigg 1992). Thrombocytopenia and frequent nosebleeds were reported in two of four family members exposed to mercury vapors in their

home as a result of a spill of metallic mercury (Schwartz et al. 1992). The authors considered this to be a unique reaction to the mercury exposure.

In volunteers with dental amalgam, significantly decreased hemoglobin and hematocrit and increased mean corpuscular hemoglobin concentrations were found compared to controls without dental amalgams (Siblerud 1990). δ-Aminolevulinic acid dehydratase activity in erythrocytes was decreased in workers exposed to elemental mercury in the manufacture of tungsten rods (Wada et al. 1969). The decreases correlated with increases in urinary mercury. The estimated exposure level to mercury in the plant was slightly less than 0.1 mg/m^3. In workers exposed to 0.106–0.783 mg/m^3 mercury vapor, there was a significant increase in α2-macroglobulin and ceruloplasmin (an α-globulin protein active in the storage and transport of copper) compared to unexposed workers (Bencko et al. 1990).

No studies were located regarding hematological effects in animals after inhalation exposure to inorganic mercury.

Organic Mercury. No studies were located regarding hematological effects in humans or animals after inhalation exposure to organic mercury.

Musculoskeletal Effects

Metallic Mercury. A number of studies have reported increases in tremors, muscle fasciculations, myoclonus, or muscle pains after acute (Adams et al. 1983; Bluhm et al. 1992a; Karpathios et al. 1991; McFarland and Reigel 1978), intermediate (Aronow et al. 1990; Barber 1978; Sexton et al. 1976; Taueg et al. 1992), or chronic (Albers et al. 1982, 1988; Bidstrup et al. 1951; Chaffin et al. 1973; Chapman et al. 1990; Fawer et al. 1983; Smith et al. 1970; Verberk et al. 1986; Vroom and Greer 1972; Williamson et al. 1982) exposure to metallic mercury vapor. These effects are probably neurally mediated and are discussed more fully in Section 2.2.1.4.

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to metallic mercury.

Organic Mercury. Exposure to unspecified alkyl mercury compounds has caused muscular effects (e.g., muscle fasciculations, absence of deep reflexes in arms, Babinski reflex) (Brown 1954; Hook et al. 1954;

Hunter et al. 1940). These effects may have been secondary to neurological changes and are discussed more fully in Section 2.2.1.4.

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to organic mercury.

Hepatic Effects

Metallic Mercury. A case study described the acute poisoning of a young child who was exposed to mercury vapors that were produced from heating an unknown quantity of mercury (Jaffe et al. 1983). Hepatocellular effects were characterized by biochemical changes (e.g., elevated serum alanine aminotransferase [ALT]), ornithine carbamyl transferase, and serum bilirubin levels) and evidence of a decrease in the synthesis of hepatic coagulation factors. Similarly, hepatomegaly and central lobular vacuolation were observed in a man who died following acute-duration exposure to high levels of elemental mercury vapors (Kanluen and Gottlieb 1991; Rowens et al. 1991).

Serious liver effects have been noted in animals at high exposure concentrations. Acute inhalation exposure of rabbits to metallic mercury vapor concentrations of 28.8 mg/m^3 for 6–30 hours resulted in effects ranging from moderate pathological changes (unspecified) to severe liver necrosis (Ashe et al. 1953). These effects were less severe (mild effects to degeneration) at shorter exposure durations and following exposure to 6 mg/m^3 mercury vapors for 7 hours a day, 5 days a week for 1–5 weeks (Ashe et al. 1953). Effects ranging from moderate pathological changes to marked cellular degeneration and some necrosis were seen at mercury concentrations of 6 mg/m^3 for 7 hours a day, 5 days a week for 6–11 weeks (Ashe et al. 1953). No hepatic changes were present in a pathological examination of the livers of rats intermittently exposed to 3 mg/m^3 mercury vapor for only 3 hours a day, 5 days a week for 12–42 weeks (Kishi et al. 1978). The studies by Ashe et al. (1953) and Kishi et al. (1978) were deficient in quantitative data, and used a small number of animals. However, available human and animal data suggest that metallic mercury vapors can cause liver effects following acute exposures.

Organic Mercury. Midzonal necrosis in the liver was observed during the autopsy of a farmer who died after treating grain with phenylmercuric acetate for several seasons (Brown 1954). No conclusions can be drawn from this study, however, because other factors may have contributed to the hepatic effects in this subject.

No studies were located regarding hepatic effects in animals after inhalation exposure to organic mercury.

Renal Effects

Metallic Mercury. The kidney is a sensitive target organ of toxicity following inhalation exposure to metallic mercury. This sensitivity may be, in part, because of the relatively high accumulation of mercury in the kidneys. Acute high-concentration inhalation exposure in humans has resulted in effects ranging from mild transient proteinuria or s syndrome has been reported light changes in urinary acid excretion (Bluhm et al. 1992b; Soni et al. 1992); to frank proteinuria, hematuria, and/oliguria (Campbell 1948; Hallee 1969; Snodgrass et al. 1981); to acute renal failure with degeneration or necrosis of the proximal convoluted tubules (Campbell 1948; Jaffe et al. 1983; Kanluen and Gottlieb 1991; Rowens et al. 1991). Actual exposure concentrations are unknown in these cases, but urinary mercury excretion as high as 59–193 µg/hour has been reported (Bluhm et al. 1992b).

A nephrotic in two case studies of intermediate-duration exposure (Agner and Jans 1978; Friberg et al. 1953). In one report, the exposure was to a spill in the home (Agner and Jans 1978); in the other, the exposure was occupational (Friberg et al. 1953). The nephrotic syndrome was characterized by edema and proteinuria with albumin and hyaline casts in the urine. These changes usually abated within a few months following termination of exposure. Among a group of 10 patients who reported adverse effects associated with dental amalgams (the route of exposure in dental amalgams is probably a mixture of inhalation exposure to mercury vapor released from the amalgams, absorption of the vapor through the oral mucosa, and ingestion), a decrease in the ability to concentrate the urine and elevated urinary albumin were observed (Anneroth et al. 1992). Removal of one amalgam resulted in a significant decrease in urinary albumin (it is unknown whether other amalgams remained). In a study of renal function in 10 healthy volunteers having an average of 18 amalgam-filled tooth surfaces both before and after amalgam removal (Sandborgh-Englund and Nygren 1996), no signs of renal toxicity were found in conjunction with mercury released from the amalgam fillings. Although plasma mercury levels increased significantly one day after removal of the fillings (all removals were accomplished in one dental session), glomerular filtration rates were similar both before and after mercury exposure (amalgam removal). Blood, plasma, and urine mercury concentrations were significantly lower 60 days after amalgam removal.

The results from a number of studies show renal toxicity in workers chronically exposed to mercury vapor (Barregard et al. 1988; Bernard et al. 1987; Buchet et al. 1980; Cardenas et al. 1993; Danziger and

Possick 1973; Ehrenberg et al. 1991; Kazantzis et al. 1962; Langworth et al. 1992b; Piikivi and Ruokonen 1989; Roels et al. 1982; Stewart et al. 1977; Stonard et al. 1983; Sunderman 1978; Tubbs et al. 1982). Several of these reports have focused on workers with proteinuria (Danziger and Possick 1973; Kazantzis et al. 1962; Tubbs et al. 1982), while others have examined a variety of urinary parameters in exposed populations. Biopsies in the studies of workers with proteinuria have shown both proximal tubular and glomerular changes. In the report by Kazantzis et al. (1962), heavy albuminuria was reported to be accompanied by both proximal tubular damage and glomerulosclerosis. Examination of tissue samples from two other workers with proteinuria showed changes in the foot processes of cells associated with the glomerular basement membrane and deposition of IgG and C3 (Tubbs et al. 1982).

Comparisons of exposed populations to controls have shown a variety of changes in exposed workers, ranging from no effects (Bernard et al. 1987; Piikivi and Ruokonen 1989) to increases in urinary protein (Stewart et al. 1977), the specific gravity of the urine (Ehrenberg et al. 1991), and urinary *N*-acetyl-β-glucosaminidase (NAG) (Barregard et al. 1988; Boogaard et al. 1996; Langworth et al. 1992b). A detailed examination of markers for urinary dysfunction showed increases in urinary excretion of Tamm-Horsfall glycoprotein and tubular antigens and decreases in urinary pH and excretion of glycoamino-glycans, prostaglandin E2 and F2α, and thromboxane B2 (Cardenas et al. 1993). Several studies have also shown correlations with some of these parameters and urinary mercury content (Buchet et al. 1980; Cardenas et al. 1993; Ehrenberg et al. 1991; Langworth et al. 1992b; Roels et al. 1982; Stonard et al. 1983). Attempts to define threshold levels for effects have produced mixed results. A no-effect level of 72 µg Hg/g creatinine was determined for urinary excretion of albumin, β_2-microglobulin, or retinol binding protein (Bernard et al. 1987). However, other studies have shown increases in urinary albumin at urinary mercury levels >50 µg Hg/g creatinine (Buchet et al. 1980) and increases in urinary *N*-acetyl-β-glucosaminidase at urinary mercury levels of >50 or >100 µg Hg/g creatinine. Boogaard et al. (1996) reported that after exposure to mercury with urinary levels below the biological exposure index of 35 µg/g creatinine, a transient increase in NAG was observed, but there was no correlation with duration of exposure and that this increase was not an early indicator of developing renal dysfunction. More information on correlation between urinary mercury levels and renal toxicity can be found in Section 2.5.

Serious degenerative effects have been observed in the kidneys of animals exposed to moderate-to-high levels of metallic mercury vapors following acute- and intermediate-duration exposures (Ashe et al. 1953). Effects ranging from marked cellular degeneration to tissue destruction and widespread necrosis were observed in rabbits exposed to mercury vapor at a concentration of 28.8 mg/m^3 for 2–30 hours. Moderate

pathological changes (unspecified) were also seen for 1-hour exposures. As the duration of exposure increased to 30 hours, extensive cell necrosis in the kidneys became evident. These results and the following results are limited as to their usefulness because the pathological changes are not described.

In an intermediate-duration study, rabbits exposed to mercury vapor concentrations of 0.86 mg/m^3 for 7 hours a day, 5 days a week for 12 weeks exhibited moderate pathological kidney changes that were reversible with cessation of exposure (Ashe et al. 1953). Larger doses (6 mg/m^3) administered for 7 hours a day, 5 days a week for up to 11 weeks, produced effects that ranged from mild, unspecified, pathological changes to marked cellular degeneration and widespread necrosis (Ashe et al. 1953).

In rats, slight degenerative changes (i.e., dense deposits in tubule cells and lysosomal inclusions) in the renal tubular epithelium were evident following exposure to 3 mg/m^3 mercury vapor for 3 hours a day, 5 days a week for 12–42 weeks (Kishi et al. 1978).

Low-level chronic-duration inhalation exposures to 0.1 mg/m^3 metallic mercury vapor for 7 hours a day, 5 days a week for 72–83 weeks in rats, rabbits, and dogs produced no microscopic evidence of kidney damage (Ashe et al. 1953). Only two dogs were tested in the study.

Organic Mercury. An autopsy of a man who died after acute high-level exposure to alkyl mercury vapor revealed necrosis of the tubule epithelium, swollen granular protoplasm, and nonstainable nuclei in the kidneys (Hook et al. 1954). No studies were available on renal effects following intermediate or chronic-duration exposure to organic mercury vapors in humans.

No studies were located regarding renal effects in animals after inhalation exposure to organic mercury.

Endocrine Effects

Metallic Mercury. A 13-year-old boy exposed to mercury vapors for 2 weeks developed a thyroid enlargement with elevated triiodothyronine, and thyroxine; and low thyroid-stimulating hormone levels (Karpathios et al. 1991). Serum-free thyroxine (T4) and the ratio of free thyroxine to free 3,5,3'-triiodothyronine (T3) were found to be slightly, but significantly, higher in workers with the highest exposure concentrations in a study of chloralkali workers exposed an average of 10 years to metallic mercury vapor (Barregard et al. 1994a, 1994b). Further, serum-free T3 was inversely associated with cumulative mercury exposure, suggesting a possible inhibitory effect of mercury on 5'-deiodinases, which is responsible for the

conversion of T4 to the active hormone T3. In this study, serum total testosterone (but not free testosterone) was positively correlated with cumulative mercury exposure, while prolactin, thyrotrophin, and urinary cortisol concentrations were not associated with exposure. However, two other occupational studies found no relationship between mercury exposure (unspecified concentration) and endocrine function (i.e., testicular, thyroid, and pituitary) (Erfurth et al. 1990; McGregor and Mason 1991). Biochemical indices that were measured in the occupational study by McGregor and Mason (1991) to assess endocrine effects included serum testosterone, sex-hormone binding globulin, thyroid-stimulating hormone, and prolactin. Erfurth et al. (1990) measured both basal serum concentrations of thyrotropin, thyroxine, triiodothyronine, and cortisol, as well as the response to a thyrotropin challenge.

No studies were located regarding endocrine effects in animals after inhalation exposure to metallic mercury.

Organic Mercury. No studies were located regarding endocrine effects in humans or animals after inhalation exposure to organic mercury.

Dermal Effects

Metallic Mercury. Inhalation exposure of individuals to elemental mercury vapors for acute and intermediate durations has resulted in erythematous and pruritic skin rashes (Aronow et al. 1990; Bluhm et al. 1992a; Foulds et al. 1987; Karpathios et al. 1991; Schwartz et al. 1992; Sexton et al. 1976). Other dermal reactions to mercury exposure include heavy perspiration (Aronow et al. 1990; Fagala and Wigg 1992; Karpathios et al. 1991; Sexton et al. 1976) and reddened and/or peeling skin on the palms of the hands and soles of the feet (Aronow et al. 1990; Fagala and Wigg 1992; Karpathios et al. 1991).

No studies were located regarding dermal effects in animals after inhalation exposure to metallic mercury.

Organic Mercury. No studies were located regarding dermal effects in humans or animals after inhalation exposure to organic mercury.

Ocular Effects

Metallic Mercury. Ocular effects observed following acute exposure included red, burning eyes and conjunctivitis (Bluhm et al. 1992a; Sexton et al. 1976). Workers chronically exposed to mercury have also exhibited a peculiar grayish-brown or yellow haze on the outer surface of their lenses (Atkinson 1943; Bidstrup et al. 1951; Locket and Nazroo 1952). These case studies contained insufficient quantitative data for dose-response assessment.

No studies were located regarding ocular effects in animals after inhalation exposure to metallic mercury.

Organic Mercury. No studies were located regarding ocular effects in humans or animals after inhalation exposure to organic mercury.

Other Systemic Effects

Metallic Mercury. Initial exposure to high concentrations of elemental mercury vapors produces a syndrome similar to "metal fume fever," which is characterized by fatigue, fever, chills, and an elevated leukocyte count. Accordingly, several studies have reported fever and/or chills in humans after exposure to high concentrations of elemental mercury vapors (Aronow et al. 1990; Bluhm et al. 1992a; Garnier et al. 1981; Lilis et al. 1985; McFarland and Reigel 1978; Milne et al. 1970; Schwartz et al. 1992; Snodgrass et al. 1981).

Organic Mercury. No studies were located regarding other systemic effects in humans or animals after inhalation exposure to organic mercury.

2.2.1.3 Immunological and Lymphoreticular Effects

Metallic Mercury. The immune reaction in humans to mercury exposure appears to be idiosyncratic, with either increases or decreases in immune activity depending on individual genetic predisposition (see Section 2.4). Therefore, it is not surprising that several studies of workers exposed to elemental mercury vapor have failed to show consistent or marked changes in immune function parameters in large populations. For example, no effect on serum immunoglobulins (IgA, IgG, or IgM) and no increase in autoantibody titres were observed in a group of chloralkali workers exposed for an average of 13.5 years

(Langworth et al. 1992b). Similarly, no increases in antilaminin antibodies were observed in workers exposed for an average of 7.9 years (Bernard et al. 1987), and no increase in antiglomerular basement membrane antibodies or IgE was seen in workers exposed for between 1.5 and 25 years (Cardenas et al. 1993). Slight decreases in IgA and IgG were observed in workers after more than 20 years of exposure to metallic mercury vapors when compared to unexposed controls (Moszczynski et al. 1990b). No significant differences in the concentrations of immunoglobulins or complement components were found in a study of 76 chloralkali workers previously exposed to mercury vapor for an average of 7.9 years (range, 1.1–36.2 years) (Ellingsen et al. 1994). No increase in the prevalence of autoantibodies was observed between the formerly exposed worker group and a control group of 53 age-matched referents. The average time elapsed since the cessation of occupational exposure was 12.3 years (range, 1–35 years).

Evidence of a human autoimmune response has been obtained in a few studies. Examination of the kidneys of two workers with proteinuria revealed granular deposition of IgG and the complement C3 in the glomeruli (Tubbs et al. 1982). Among a group of 10 patients who reported adverse effects associated with dental amalgams (the route of exposure is probably a mixture of inhalation exposure to mercury vapor released from the amalgams and dermal exposure to the amalgams), 3 had increased antiglomerular basement membrane antibodies and 2 had elevated antinuclear antibodies (Anneroth et al. 1992). After removal of one amalgam, there was a significant decrease in IgE (it is unknown whether other amalgams remained). Also, 1 of 89 workers examined by Langworth et al. (1992b) showed a weak reaction to antiglomerular basement membrane, and 8 of 44 workers examined by Cardenas et al. (1993) showed an abnormally high anti-DNA antibody titre. Only two studies have shown increases in immune parameters in exposed populations. Increases in IgA and IgM were observed in workers in a mercury producing plant (Bencko et al. 1990). The study is limited by a lack of information on daily dose levels, duration of employment and potential confounding factors (smoking, alcohol). An increase in anti-DNA antibodies was observed in workers from a chloralkali plant (Cardenas et al. 1993).

Other experimental evidence suggests that mercury can alter a number of parameters of the host's immune system and lead to increased susceptibility to infections, autoimmune diseases, and allergic manifestations. In workers exposed to mercury vapor concentrations of 0.024–0.09 mg/m^3 for less than 10 and up to 31 years (Moszczynski et al. 1995), the stimulation of T-lymphocytes (as manifested by an increased number of T-cells [CD3+], T-helpers [CD4+], and T-suppressors [CD8+]) was observed in peripheral blood; however, no significant effect was seen on NK-cell (CD16+) count. A positive correlation was found between the T-helper cell count and the duration of exposure ($p<0.05$). The combined stimulation of

the T-cell line and an observed decrease in the helper/suppressor ratio were suggestive of an autoimmune response.

In a mercury-producing plant, neutrophil function was found to be significantly reduced in workers with a mean exposure duration of 8 months (range, 0.5–46 months) (Perlingeiro and Queiroz 1995). In this study, both chemotactic and chemical-specific reducing activities of the neutrophils of exposed workers were found to be affected. While improved industrial hygiene practices over a 6-month period resulted in a decrease in urine mercury concentration in the workers, it did not result in the return of neutrophil migration activity to within the normal range. There was, however, no observed increase in the incidence of infections in the mercury-exposed group compared to controls. Based on their observations, Perlingeiro and Queiroz (1995) suggested that even exposures to levels of mercury considered "safe" in some industrial settings may lead to impairment of neutrophil function.

Exposure of genetically susceptible mice to mercury vapor for a period of 10 weeks resulted in an autoimmune response similar to that seen in similar mice after treatment with mercuric chloride by subcutaneous injections and in drinking water (Warfvinge et al. 1995). This response was manifested as a syndrome, which included a general stimulation of the immune system, with hyperimmunoglobulinemia, anti-nucleolar-fibrillarin autoantibodies, and glomerular disease accompanied by vascular immune complex deposits. Actual inhalation exposure times for the 0.3–1 mg Hg/m^3 exposure concentrations varied from 0.5 to 19 hours a day (5 days a week), but doses for individual exposure groups were also expressed in µg/kg/week units. The LOAEL for serum antinucleolar antibodies was determined to be an absorbed dose of 0.170 mg Hg/kg/week (from a 1.5-hour daily exposure to 0.5 mg/m^3) and the corresponding NOAEL was a calculated absorbed dose of 0.075 mg/kg/day (from a 0.5-hour daily exposure to 0.0005 mg/m^3). Higher doses were required for B-cell stimulation and for the development of immune complex deposits.

The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Organic Mercury. No studies were located regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to organic mercury.

2.2.1.4 Neurological Effects

Metallic Mercury. The central nervous system is probably the most sensitive target organ for metallic mercury vapor exposure. Nervous system disorders following exposure to metallic mercury vapors are both consistent and pronounced. Acute-, intermediate-, and chronic-duration exposures elicit similar neurological effects. Symptoms intensify and may become irreversible as exposure duration and/or concentration increases. Most occupational studies discuss chronic-duration exposure to a time-weighted average (TWA) concentration or to a concentration range, thereby preventing the assessment of dose-response relationships within the populations studied. However, the average exposure levels for affected groups are similar in many of these studies.

In humans, several case studies have reported adverse neurological effects following acute inhalation of high concentrations of mercury vapor. A wide variety of cognitive, personality, sensory, and motor disturbances have been reported. The most prominent symptoms include tremors (initially affecting the hands and sometimes spreading to other parts of the body), emotional lability (characterized by irritability, excessive shyness, confidence loss, and nervousness), insomnia, memory loss, neuromuscular changes (weakness, muscle atrophy, muscle twitching), headaches, polyneuropathy (paresthesia, stocking-glove sensory loss, hyperactive tendon reflexes, slowed sensory and motor nerve conduction velocities), and performance deficits in tests of cognitive function (Adams et al. 1983; Bluhm et al. 1992a; Hallee 1969; Jaffe et al. 1983; Karpathios et al. 1991; Lilis et al. 1985; McFarland and Reigel 1978; Snodgrass et al. 1981). A few individuals have also noted hearing loss, visual disturbances (visual field defects), and/or hallucinations (Bluhm et al. 1992a; McFarland and Reigel 1978). In a case study of exposure to a calculated metallic mercury vapor level of 44 mg/m^3 for <8 hours, workers experienced long-lasting feelings of irritability, lack of ambition, and lack of sexual desire (McFarland and Reigel 1978). Three and one-half months after exposure to high levels of mercury vapor during 2 days of an industrial liquid mercury salvaging operation, a 54-year-old man exhibited a syndrome resembling amyotrophic lateral sclerosis, characterized by slowed conduction velocities (suggestive of peripheral nerve damage). Urinary mercury levels were 100 µg/g creatinine at the time of the exam; after an additional 2 months (no treatment administered), levels dropped to less than 30 µg/g creatinine and symptoms disappeared (Adams et al. 1983). In contrast, chelation therapy (2.3 dimercaptosuccinic acid [DMSA] or – acetyl-D,L-penicillamine [NAP]) and lowering of urinary mercury levels did not result in improvement in depression, anxiety, phobias, psychotic-like behavior, interpersonal sensitivity, and hostility observed in another group of workers exposed to high concentrations of mercury vapor for up to 16 hours (Bluhm et al. 1992a).

In case reports of individuals exposed to inorganic mercury vapor for an intermediate duration, similar effects were reported (Barber 1978; Fagala and Wigg 1992; Foulds et al. 1987; Friberg et al. 1953; Sexton et al. 1976; Taueg et al. 1992). After 6 months of exposure to a spill of metallic mercury in the place where she slept, a 12-year-old girl experienced dizziness, joint pains, weakness, insomnia, numbness and tingling in her palms, decreased pinprick and vibration sensations in the lower extremities, intentional tremors, a slowing of the background rhythms on electroencephalograms, irritability, outbursts of temper, shyness, sensitivity, auditory hallucinations, and photophobia (Fagala and Wigg 1992). Similarly, a 4-year-old boy exposed for approximately 1 month to mercury vapors released from paint containing phenylmercuric acetate exhibited irritability, personality change, insomnia, headaches, weakness, and nerve dysfunction in the lower extremities (Aronow et al. 1990). This study is not discussed under organic mercury because the exposure was to metallic mercury vapors released from the paint.

Two adolescents (ages 13 and 15) who were unintentionally exposed to concentrated mercury vapors for 3 months developed a variety of more immediate- and long-term effects (Yeates and Mortensen 1994). In the 15-year-old male, the earliest symptoms included declining school performance, irritability, depression, neurobehavioral complaints, tremor, rash, hypertension, cold intolerance, diaphoresis, headaches, sleep disturbance, paresthesias, and anorexia. He was referred to a pediatric teaching hospital, where he was diagnosed with acrodynia and mercury poisoning. Before undergoing two courses of chelation therapy with 2,3-dimercaptosuccoinic acid (DMSA), his average 24-hour urine mercury and blood mercury levels were 1,314 µg/L and 23 µg/L, respectively. His 13-year-old half-sister, who was also exposed, had pretreatment average 24-hour urine mercury and blood mercury levels of 624 µg/L and 69 µg/L, respectively; her pre-treatment medical symptoms included tremor, rash, anorexia, paresthesias, and neuropsychiatric complaints (e.g., irritability, social withdrawal, and emotional lability). On hospital admission, she was diagnosed with acrodynia and underwent three courses of DMSA treatment, which were complicated by severe peripheral neuropathy, accompanied by a significant weight loss. Although the neuropathy was relatively mild at the time of initial neurological evaluation, it became progressively worse, and eventually the patient required a wheelchair and assistance eating. The neuropathy had resolved by the 1-year follow-up neuropsychological evaluation; however, despite removal from exposure, return of blood and urinary mercury to acceptable levels, and resolution of clinical signs of mercury poisoning and associated neuropsychiatric symptoms, both patients continued to show major deficits in visuoperceptual and constructional skills, nonverbal memory, and abstract reasoning.

A worker (age, mid-40s) exposed to mercury in a thermometer factory for approximately 3.5 years experienced acute, intermediate, chronic, and delayed neurological effects (White et al. 1993). During his employment, he performed a variety of functions, including sweeping mercury off floors with a vacuum cleaner or hose blower, repairing and cleaning machines, disassembling machines containing mercury, and operating a machine that crushed instruments so that he could then separate the mercury from other materials for reuse. From approximately the beginning of his employment at the factory, he experienced a number of symptoms, including blurred vision, ocular pain, rash, a strange taste in the mouth, weakness, memory loss, rage, and irrational behavior. The month following his release by the factory, his urine mercury concentration was measured at 690 µg/L, which confirmed a diagnosis of mercury poisoning. He was treated by chelation with penicillamine over a 2-month period; approximately 2 months after the completion of treatment, his urine mercury level was only 17 µg/L. Approximately 21months after termination of his employment, neurological examination revealed nystagmus on upward gaze, bilateral manual tremor, diminished sensation to pain, peripheral neuropathy, and abnormalities in nerve conduction. An magnetic resonance imaging (MRI) examination revealed mild central and cortical atrophy, with punctiform foci of T2 in both frontal regions, especially underlying the precentral gyri and in the white matter (both subcortical and gyri). The MRI data were interpreted as consistent with diffuse and focal white matter disease. Neuropsychological testing conducted during the same time period revealed problems with cognitive function, fine manual motor coordination, visuospatial analysis and organization, memory for visuospatial information, affect, and personality almost 2 years after cessation of employment at the factory.

In contrast with the long-term (perhaps permanent) effects noted in the previous study, Yang et al. (1994) reported that recovery from chronic elemental mercury intoxication may be complete when patients are removed early from the exposure environment. A 29-year-old worker in a Taiwanese lampsocket-manufacturing facility, with an initial urinary mercury concentration of 610 µg/L (in a 24-hour sample) and a blood mercury concentration of 237 µg/L (reference range, <10 µg/L), exhibited a variety of symptoms, including blurred vision, dysarthria, prominent gingivitis, tremors (usually postural and intentional), unsteady gait, and slow mental response. The TWA concentration of mercury in the air in the room where he spent most of his working time during his 5 years on the job was 0.945 mg/m^3. The worker also had a higher blood lead concentration of 450 µg/L (reference range, <20 µg/L), and lead toxicity or interactions with mercury could have occurred. The man underwent an 8-week course of chelation with D-penicillamine, which resulted in a rapid improvement in gait; a complete recovery from all symptoms occurred over a 4-month period.

A 27-year-old female, who worked primarily in a room with a TWA mercury air concentration of 0.709 g/m^3 and who had been on the job for 1.5 years, showed a variety of symptoms, including gum pain, dizziness, poor attention, bad temper, some numbness, hypersalivation, hyperhidrosis, dizziness, and fatigue. She had initial urine and blood mercury levels of 408 µg/L and 105 µg/L, respectively, but did not require chelation; the symptoms abated fully approximately 2 months following discontinuation of exposure (Yang et al. 1994).

Other chronic-duration exposures to metallic mercury vapor have resulted in tremors (which may be mild or severe depending on the degree of exposure), unsteady walking, irritability, poor concentration, short-term memory deficits, tremulous speech, blurred vision, performance decrements in psychomotor skills (e.g., finger tapping, reduced hand-eye coordination), paresthesias, decreased nerve conduction, and other signs of neurotoxicity (Albers et al. 1988; Bidstrup et al. 1951; Chaffin et al. 1973; Chang et al. 1995; Chapman et al. 1990; Fawer et al. 1983; Langolf et al. 1978; Piikivi et al. 1984; Smith et al. 1970; Sunderman 1978; Uzzell and Oler 1986; Vroom and Greer 1972; Williamson et al. 1982). The majority of studies suggest that motor system disturbances are reversible upon exposure cessation, while cognitive impairments, primarily memory deficits, may be permanent (Chaffin et al. 1973; Hanninen 1982; Miller et al. 1975).

Several studies have noted correlations between exposure level or duration and effects (e.g., memory deficits, psychomotor coordination, motor and sensory nerve conduction velocities, electromyographic abnormalities, evidence of polyneuropathy, tremor, emotional changes, reflex abnormalities, and electroencephalographic changes) (Albers et al. 1982; Iyer et al. 1976; Levine et al. 1982; Smith et al. 1983; Vroom and Greer 1972; Williamson et al. 1982). Early studies suggested that frank neurotoxicity (pronounced tremors, erethism, restriction of visual fields, difficulty seeing) was generally observed at >300 µg mercury in a 24-hour urine (Bidstrup et al. 1951) or at >0.1 mg/m^3 (Smith et al. 1970). More recent studies using sensitive tests for psychomotor skills, tremor, and peripheral nerve function suggest that adverse effects may be associated with very low exposures (see below). However, conflicting information exists regarding thresholds for neurotoxic effects.

Several reports have presented essentially negative findings at low exposure levels (0.025–0.076 mg/m^3). Chloralkali workers exposed to low air levels of mercury vapors for at least 5 years (group average, 14 years) reported an increase in memory disturbances, sleep disorders, anger, fatigue, confusion, and hand tremors compared to the controls (Piikivi and Hanninen 1989). However, tests of psychomotor

coordination and memory showed no significant deficits in the exposed group. The exposed and control groups were matched for age, sex, vocational status, education, and mean number of amalgam fillings. A group-average exposure concentration of 0.025 mg/m^3 mercury vapors was estimated from repeated analyses of blood mercury concentration (mean, 51.3 nmol/L . 10 µg/L) (see the discussion regarding these estimated exposure levels in Section 2.5). Also, no effects on tremors, bimanual coordination, color determination, or reaction time were observed in chloralkali workers with more than 7 years of exposure to low levels of mercury; ambient air levels measured for 2 years prior to testing averaged 0.076 mg/m^3 and the average blood level in the workers was 19.9 µg/L (Schuckmann 1979). Negative findings were also noted when the results of tremor frequency spectra and psychometric tests of a group of chloralkali workers exposed for an average of 13.5 years were compared to unexposed controls (Langworth et al. 1992a). The TWA exposure level was estimated to be 0.025 mg/m^3, based on measurements taken at the time of the study, and blood levels in the workers averaged 55 nmol/L (. 11 µg/L). Despite the negative objective findings, subjective reports of fatigue, memory disturbances, and confusion were significantly higher in the exposed workers.

Boogaard et al. (1996) evaluated the effects of exposure to elemental mercury on the nervous system and the kidneys of workers producing natural gas in the Netherlands. Early signs of alterations in renal and neurological functions were studied in three groups of workers who were exposed to different levels of mercury that were below the current ACGIH biological exposure index of 35 µg/g creatinine. Air concentrations ranged from 10 to 1,500 µg/m^3 (median, 67) at locations where mercury exposure was anticipated; the potential 8-hour TWA exposure ranged from 33 to 781 µg/m^3 (median, 88). Air concentrations ranged from 0 to 6 µg/m^3 at locations where little mercury exposure was expected. Current mercury concentrations in urine were 23.7, 4.1, and 2.4 µg/g in high, low, and control exposure groups, respectively; mercury concentrations in blood were 3.5, 1.5, and 2.2 µg/L, respectively. There were no differences among the three study groups with respect to either motor nerve conduction velocity or tremor frequency spectra of physiological tremors. Also, no significant correlations were found between the results of the neurological tests and any of the present or historical biological monitoring data.

In contrast to the negative findings above, several studies have shown significant effects on tremor or on cognitive skills at comparable or lower group-average exposure levels (0.014–0.076 mg/m^3). Using the same paradigm as Langworth et al. (1992a), a significant difference was seen in the tremor frequency spectra in mercury-exposed workers from three industries who were exposed to low levels of mercury for an average of 15.3 years (range, 1–41 years) when compared to unexposed controls (Fawer et al. 1983).

The TWA mercury concentration measured in the work area at the time of the study was 0.026 mg Hg/m^3 (range not reported). It was assumed that the workers were exposed to the same concentration of mercury for the duration of their employment. However, the group size was small, and the results may have been influenced by a small number of more severely affected individuals. It is also possible that the tremors may have resulted from intermittent exposure to concentrations higher than the TWA. Urinary mercury levels in these workers averaged 11.3 µmol/mol creatinine (. 20 µg/g creatinine). Tremors have also been associated with occupational exposures that produced urinary concentrations of 50–100 µg/g creatinine and blood levels of 10–20 µg/L (Roels et al. 1982). Difficulty with heel-to-toe gait was observed in thermometer-plant workers subjected to mean personal-breathing-zone air concentrations of 0.076 mg/m^3 (range, 0.026–0.27 mg/m^3) (Ehrenberg et al. 1991).

Decreases in performance on tests that measured intelligence (a similarities test) and memory (digit span and visual reproduction tests) were observed in chloralkali workers exposed for an average of 16.9 years to low levels of mercury when compared to an age-matched control group (Piikivi et al. 1984). Significant differences from controls were observed among workers with blood levels >75 nmol/L (. 15 µg/L) and urine levels >280 nmol/L (. 56 µg/L).

Dentists (n=98, mean age 32, range 24–49) with an average of 5.5 years of exposure to low levels of mercury showed impaired performance on several neurobehavioral tests (Ngim et al. 1992). Exposure levels measured at the time of the study ranged from 0.0007 to 0.042 mg/m^3 (average, 0.014 mg/m^3) and blood levels ranged from 0.6 to 57 µg/L (average, 9.8 µg/L). Controls were matched for age, fish consumption, and number of amalgam fillings. Differences in education, sex distribution, and reported use of Chinese traditional medicines that might contain mercury were adjusted for in the statistical analysis. The dentists showed significantly poorer performance on finger tapping (measures motor speed), trail making (measures visual scanning), digit symbol (measures visuomotor coordination and concentration), digit span, logical memory delayed recall (measures visual memory), and Bender-Gestalt time (measures visuomotor coordination). The dentists had a higher aggression score than the controls. Correlations were observed for exposure levels and duration. This study is limited, however, by lack of blinding and failure to report control mercury levels; the statistical procedures used for confounders (use of traditional Chinese medicines) were not reported.

In a study of the relation between cumulative exposure to mercury and chronic health impairment, 298 dentists had their mercury levels measured by an X-ray fluorescence technique. Electrodiagnostic and neuropsychological findings in the dentists with more than 20 µg/g tissue (head and wrist) mercury levels

were compared with those of a control group consisting of dentists with no detectable mercury levels. Twenty-three out of 298 dentists with the highest mercury levels were administered neurological tests and compared to controls. The high mercury group had slowed conduction velocities in motor (median nerve) and sensory (suralnerve) nerves, mild neuropsychological impairment (increased errors in the Bender-Gestalt test), mild visuographic dysfunction, and higher distress levels (self-reported) than the control group. Seven of the high exposure dentists showed manifestations of polyneuropathy. Exposure concentrations were not specified. No polyneuropathies were detected in the control group (Shapiro et al. 1982). Abnormal nerve conduction velocities have also been observed at a mean urine concentration of 450 µg/L in workers from a chloralkali plant (Levine et al. 1982). These workers also experienced weakness, paresthesias, and muscle cramps. Prolongation of brainstem auditory-evoked potentials was observed in workers with urinary mercury levels of 325 µg/g creatinine (Discalzi et al. 1993). Prolonged somatosensory-evoked potentials were found in 28 subjects exposed to 20–96 mg/m^3 of mercury (Langauer-Lewowicka and Kazibutowska 1989).

In animals, as in humans, adverse neurological and behavioral effects are prominent following inhalation exposure to high concentrations of metallic mercury vapor. However, animals appear to be less sensitive than humans. Marked cellular degeneration and widespread necrosis were observed in the brains of rabbits following exposures to metallic mercury vapor at 28.8 mg/m^3 for durations ranging from 2 to 30 hours (Ashe et al. 1953). Exposures of 1 hour produced moderate (unspecified) pathological changes.

Intermediate-duration exposure of rabbits to 6 mg/m^3 mercury vapor for periods of 1–11 weeks produced effects ranging from mild, unspecified, pathological changes to marked cellular degeneration and some necrosis in the brain (Ashe et al. 1953). The more serious degenerative changes were observed at longer exposure durations (i.e., 8 and 11 weeks). Mild-to-moderate pathological changes were revealed in the brains of rabbits exposed to a metallic mercury vapor concentration of 0.86 mg/m^3 for 12 weeks (Ashe et al. 1953). The usefulness of these results is limited because the pathological changes are not specified and no distinction is made between primary and secondary effects (i.e., pathological changes secondary to induced shock).

Two of 6 rabbits exposed to 4 mg/m^3 metallic mercury vapor for 13 weeks exhibited slight tremors and clonus and had mercury concentrations of 0.8–3.7 µg/g wet tissue in the brain (Fukuda 1971). Following intermittent exposure to 3 mg/m^3 for 12–39 weeks, rats exhibited a decline in conditioned avoidance response; however, no histopathological changes were evident (Kishi et al. 1978). The change was

reversible within 12 weeks after exposure cessation and was associated with a decrease in the mercury concentration in brain tissue to below 10 µg/g wet weight (w/w). Mice exposed to an unspecified concentration of metallic mercury vapor intermittently for more than 3 weeks exhibited progressive neurological dysfunction (i.e., wobbling and unresponsiveness to light), beginning 22 days after initial exposure, and subsequently died 4 days later (Ganser and Kirschner 1985).

No studies were located regarding neurological effects in animals following chronic inhalation exposure to inorganic mercury.

Organic Mercury. Exposure to organic mercury via inhalation is extremely rare. The only reports of even its potential occurrence come from a few case histories. Case reports have described neurological effects in humans after inhalation exposure to organic mercury; however, no quantitative data were provided. Following acute inhalation exposure of dust containing methylmercury, four men had initial symptoms including numbness and tingling of limbs, unsteadiness in gait, difficulty in performing fine movements (e.g., buttoning a shirt), irritability, and constricted vision (Hunter et al. 1940). At least 2 years after these occupational exposures, the subjects had not fully recovered from their symptoms. Acute high-level exposure to an unspecified alkyl mercury compound has reportedly caused neurological symptoms (e.g., ataxia, unsteady gait, slurred speech, memory difficulties, tremors) in exposed workers (Hook et al. 1954; Lundgren and Swensson 1949).

A case study reporting neurological effects in a boy after exposure to mercury vapor released from paint containing phenylmercuric acetate (Aronow et al. 1990) was discussed under metallic mercury because the exposure was to metallic mercury vapors released from the paint.

Dimethylmercury is extremely volatile, and extremely toxic (in the 5 mg/kg body weight range). The following case history describes an accidental death due to an occupational spill of only a few drops of dimethylmercury. The primary exposure route is thought to have been dermal, but dimethylmercury is so volatile that inhalation exposure might also have occurred. Blayney et al. (1997) provided the first account of this tragic event. The case history was subsequently detailed by Nierenberg et al. (1998). The exposure occurred to a 48-year-old female chemistry professor who was admitted to the hospital 5 months (154 days) after, as best as can be determined, she inadvertently spilled several drops (estimated at 0.4–0.5 mL, about 1,500 mg) of dimethylmercury from the tip of her pipette onto the back of her disposable latex gloves. The spill was cleaned and the gloves disposed of. Hair analysis on a long strand

of hair revealed that after a brief lag time, mercury content rose rapidly to almost 1,100 ppm (normal level, <0.26 ppm; toxic level, >50 ppm), and then slowly declined with a half-life of 74.6 days. These results support the occurrence of one or several episodes of exposure, and are consistent with laboratory notebook accounts of a single accidental exposure. Testing of family members, laboratory coworkers, and laboratory surfaces failed to reveal any unsuspected mercury spills or other cases of toxic blood or urinary mercury levels. Permeation tests subsequently performed on disposable latex gloves similar to those the patient had worn at the time of the lone exposure revealed that dimethylmercury penetrates such gloves rapidly and completely, with penetration occurring in 15 seconds or less and perhaps instantly. Polyvinyl chloride gloves were equally permeable to dimethylmercury. Five days prior to hospital admission, the patient developed a progressive deterioration in balance, gait, and speech. During the previous 2 months, she had experienced brief episodes (spaced weeks apart) of nausea, diarrhea, and abdominal discomfort, and had lost 6.8 kg (15 lb). Medical examination revealed moderate upper-extremity dysmetria, dystaxic handwriting, a widely based gait, and "mild scanning speech." Routine laboratory test results were normal. Computed tomography (CT) and magnetic resonance imaging (MRI) of the head were normal except for the incidental finding of a probable meningioma, 1 cm in diameter. The cerebrospinal fluid was clear, with a protein concentration of 42 mg/dL and no cells. A preliminary laboratory report indicated that the whole-blood mercury concentration was more than 1,000 µg/L (normal range, 1–8 µg/L; toxic level, >200 µg/L). Chelation therapy with oral succimer (10 mg/kg orally every 8 hours) was begun on day 168 after exposure. Whole blood concentrations rose to 4,000 µg/L after one day of chelation, and urinary mercury levels were 234 µg/L (normal range, 1–5 µg/L; toxic level, >50 µg/L). Despite the initial success of chelation therapy, administration of vitamin E, and a blood exchange transfusion, at 176 days postexposure, the patient became comatose. Further aggressive general support and chelation therapy failed, life support ws removed (following the patient's advance directive), and the patient died 298 days postexposure. Autopsy results revealed diffusely thin cortex of the cerebral hemispheres (to 3 mm), and extensive gliosis of the visual cortex around the calcarine fissure and the superior surface of the superior temporal gyri. The cerebellum showed diffuse atrophy of both vermal and hemispheric folia. Microscope evaluation revealed extensive neuronal loss and gliosis bilaterally within the primary visual and auditory cortices, with milder loss of neurons and gliosis in the motor and sensory cortices. There was widespread loss of cerebellar granular-cell neurons, Purkinje cells, and basket-cell neurons, with evidence of loss of parallel fibers in the molecular layer. Borgmann's gliosis was well developed and widespread.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

Metallic Mercury. No acute-duration exposure data were located regarding reproductive effects in humans after inhalation exposure to metallic mercury. However, several studies found no effect on fertility following intermediate or chronic inhalation exposure to metallic mercury in humans (Alcser et al. 1989; Cordier et al. 1991; Lauwerys et al. 1985). A retrospective cohort study reported that male workers in a U.S. Department of Energy (DOE) plant exposed for at least 4 months had urinary mercury concentrations of 2,144–8,572 µg/L (Alcser et al. 1989). This sample population showed no significant difference in fertility compared to controls (unexposed workers); however, they were never monitored for elemental mercury exposure. In a questionnaire study assessing the fertility of male workers exposed to mercury vapor from various industries (i.e., zinc-mercury amalgam, chloralkali, or electrical equipment product plants), there was no statistically significant difference in the number of children of the exposed group compared to a matched control group (Lauwerys et al. 1985). The concentration of mercury in the urine of these exposed workers ranged from 5.1 to 272.1 µg/g creatinine. No correlation was observed between prolactin, testosterone, luteinizing hormone, and follicle stimulating hormone levels and blood or urine mercury levels in male workers exposed to mercury vapors (Erfurth et al. 1990; McGregor and Mason 1991). Also, no effect on the response of these hormones to challenge with gonadotropin releasing hormone was observed (Erfurth et al. 1990).

Although no effect on fertility was observed in exposed workers, an increase in the rate of spontaneous abortions was reported in association with increased mercury concentrations in the urine of the fathers exposed to metallic mercury in chloralkali plants before the pregnancy (Cordier et al. 1991). There was a significantly increased risk of spontaneous abortion, at a rate of 18.4%, when fathers had more than 50 µg/L mercury in the urine, compared to a rate of 8.6% when fathers were unexposed. Sikorski et al. 1987) reported that women occupationally exposed to metallic mercury vapors (dentists and dental assistants) had more reproductive failures (spontaneous abortions, stillbirths, congenital malformations) and irregular, painful, or hemorrhagic menstrual disorders than a control (unexposed) group of women. The reproductive difficulties and menstrual disorders were correlated with mercury levels identified in scalp and pubic hair collected from the women. It should be noted that this study has been recently severely criticized for what Larsson (1995) calls "erroneous interpretation of results and distortion of conclusions." The Sikorski et al. (1987) paper is nonetheless presented in this toxicological profile as part of the available published data on reported human mercury exposure. Its presence here is based upon its publication in a

credible peer-reviewed international journal and is intended neither as endorsement nor condemnation of the data or conclusions in the 1987 paper.

Rowland et al. (1994) report that 418 women with high exposure to mercury (i.e., female dental assistants) were less fertile than unexposed controls. In this study, the probability of conception with each menstrual cycle (called "fecundability" by the authors) in women who prepared 30 or more amalgams per week and who were evaluated as having 4 or more poor mercury-hygiene practices was 63% of the fecundity of the unexposed controls. Rowland et al. (1994) noted that occupational groups with roughly the same potential for exposure often contain subjects whose actual exposures are quite different, depending on their particular work environment and their work practices within that environment. For example, 20% of the women in the final sample in this study reported preparing more than 30 amalgams per week with 4 or more poor hygiene factors. Among the women preparing the same number of amalgams, this study found differences in "fecundability," based upon each dental assistant's reported number of poor mercury-hygiene factors. One peculiar observation, however, was that women determined to have had low exposure to mercury in their dental occupation were found to be more fertile than unexposed controls. The reason(s) for the observed U-shaped dose-response curve were not known.

In animals, exposure to metallic mercury vapors causes prolongation of the estrous cycle. In a study by Baranski and Szymczyk (1973), female rats exposed via inhalation to metallic mercury (at an average of 2.5 mg/m^3, 6 hours a day, 5 days a week for 21 days) experienced longer estrous cycles than unexposed animals. In addition, estrous cycles during mercury exposure were longer than normal estrous cycles in the same animals prior to exposure. Although the initial phase of the cycle was protracted, complete inhibition of the cycle did not occur. During the second and third weeks of exposure, these rats developed signs of mercury poisoning including restlessness, seizures, and trembling of the entire body. The authors speculated that the effects on the estrous cycle were caused by the action of mercury on the central nervous system (i.e., damage to the hypothalamic regions involved in the control of estrous cycling).

Organic Mercury. No studies were located regarding reproductive effects in humans or animals after inhalation exposure to organic mercury.

The highest NOAELs and all reliable LOAELs for reproductive effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

Metallic Mercury. No association was demonstrated between inhalation exposure of the father and increased rates of major fetal malformations or serious childhood illnesses in a retrospective cohort study of workers at a U.S. DOE plant (Alcser et al. 1989).

A case study of a woman chronically exposed to an undetermined concentration of mercury vapor reported that her first pregnancy resulted in spontaneous abortion, and her second resulted in the death of the newborn soon after birth (Derobert and Tara 1950). It is unclear whether the reproductive toxicity experienced by the woman was due to the mercury exposure. However, after recovery from overt mercury poisoning, she gave birth to a healthy child. A woman occupationally exposed to mercury vapors for 2 years prior to pregnancy and throughout pregnancy was reported to have delivered a viable infant at term (Melkonian and Baker 1988). Urinary mercury in the woman at 15 weeks of pregnancy was 0.875 mg/L (normal levels are approximately 0.004 mg/L). Also, a case report of a woman exposed to mercury vapors in her home during the first 17 weeks of pregnancy reported that the woman delivered a normal child who met all developmental milestones (although the child was not formally tested for psychological development) (Thorpe et al. 1992). Although mercury exposure was not measured, the child was born with hair levels of 3 mg/kg (3 ppm) of mercury. This hair level is comparable to that observed in populations consuming fish once a week (WHO 1990) and suggests that exposure in this case may have been relatively low.

Exposure of neonatal rats to metallic mercury vapor at 0.05 mg/m^3 for 1 or 4 hours a day for 1 week during a period of rapid brain growth (postpartum days 11–17) resulted in subtle behavioral changes when the rats were tested at 4 and 6 months of age (Fredriksson et al. 1992). Offspring of rats exposed for 1 hour/day showed increases in the time necessary to finish a task in the radial arm maze (spatial learning). Offspring of rats exposed for 4 hours a day showed increases in both the time to finish the task and in the number of errors committed. When tested for locomotor activity at 2 months, an increase in rearing was observed in the 4 hour/day group, but repeat testing at 4 months showed lower locomotor, rearing, and total activity than controls. The 1-hour/day exposure group showed no difference from controls at 2 months, and increased activity and decreased rearing at 4 months when compared to controls.

Three groups of 12 pregnant Sprague-Dawley rats were exposed by inhalation to 1.8 mg/m^3 metallic mercury vapor on gestation days (Gd) 11–14 and 17–20 for 1 hour ("low dose") or 3 hours ("high dose").

Hg/kg/day ("high dose"). At postpartum day 3, each litter was reduced to 4 male and 4 female offspring. No significant differences between the mercury-treated offspring and the controls were observed for surface righting, negative geotaxis, pinna unfolding, and tooth eruption. Tests of spontaneous motor activity (locomotion, rearing, rearing time, and total activity) showed that the mercury-treated offspring were hypoactive at 3 months of age; at 14 months, only total activity differed between exposed and control groups. In spatial learning tasks, exposed offspring showed retarded acquisition in the radial-arm maze but no differences in the circular-swim maze. A simple test of learning, habituation to a novel environment (activity chambers), indicated a reduced ability to adapt. The authors conclude that prenatal exposure to mercury vapor results in behavior changes in the offspring similar to those reported for methylmercury. On postpartum days 3–4, the mercury contents in the brain, liver, and kidneys were 0.001, 0.004, and 0.002 mg Hg/kg, respectively, for control offspring; 0.005, 0.053, and 0.033 mg Hg/kg, respectively, for animals exposed for 1 hour a day; and 0.012, 0.112, and 0.068 mg Hg/kg, respectively, for animals exposed for 3 hours a day (Danielsson et al. 1993).

Four groups of 12 pregnant Sprague-Dawley rats were exposed to methylmercury or elemental mercury alone or in combination as follows: (1) administered 2 mg/kg/day methylmercury via gavage during Gd 6–9; (2) exposed by inhalation to 1.8 mg/m^3 metallic mercury (elemental mercury) vapor for 1.5 hours per day during Gd 14–19; (3) exposed to both methylmercury by gavage (2 mg/kg/day, Gd 6–9) and elemental Hg vapor by inhalation (1.8 mg/m^3, Gd 14–19) (methylmercury + elemental mercury); or (4) given combined vehicle administration for each of the 2 treatments (control). The inhalation regimen corresponded to an approximate dose of 0.1 mg Hg/kg/day. At postpartum day 3, each litter was reduced to 4 male offspring. There were no differences between any of the groups in maternal body weight gain before parturition. No differences in body weight, pinna unfolding, tooth eruption, surface righting reflex, and negative geotaxis were observed in the offspring. Offspring of dams exposed to elemental Hg showed hyperactivity in the spontaneous motor activity test chambers over all three parameters: locomotion, rearing, and total activity; this effect was potentiated in the animals of the methylmercury + elemental Hg group. In the swim maze test, the methylmercury + elemental mercury and elemental mercury groups evidenced longer latencies to reach a submerged platform, which they had learned to mount the day before, compared to either the control group or the methylmercury group. In the modified enclosed radial-arm maze, both the methylmercury + elemental Hg and elemental Hg groups showed more ambulations and rearings in the activity test prior to the learning test. During the learning trial, the same groups (i.e., methylmercury + elemental Hg and elemental Hg) showed longer latencies and made more errors in

acquiring all eight pellets. Generally, the results indicate that prenatal exposure to elemental mercury causes alterations to both spontaneous and learned behaviors, suggesting some deficit in the adaptive functions of the rats. Co-exposure to methylmercury, which by itself did not alter these functions at the dose given in this study, served to aggravate the changes significantly. Brain mercury concentrations in offspring were 1 ng/g w/w in the controls, 4 ng/g in the methylmercury group, 5 ng/g in the elemental Hg group, and 12 ng/g in the methylmercury + elemental Hg group (Fredriksson et al. 1996).

Adult female rats were exposed to metallic mercury vapor at 2.5 mg/m^3 for 3 weeks prior to fertilization and during Gd 7–20 (Baranski and Szymczyk 1973). A decrease in the number of living fetuses was observed in these dams compared to unexposed controls, and all pups born to the exposed dams died by the sixth day after birth. However, no difference in the occurrence of developmental abnormalities was observed between exposed and control groups. The cause of death of the pups in the mercury-exposed group was unknown, although an unspecified percentage of the deaths was attributed by the authors to a failure of lactation in the dams. Death of pups was also observed in another experiment in which dams were only exposed to the same dose level prior to fertilization, supporting the conclusion that high mortality in the first experiment was due, at least in part, to the poor health of the mothers. Without further information, this study must be considered inconclusive regarding developmental effects.

Newland et al. (1996) studied the offspring of pregnant squirrel monkeys exposed to 0.5 or 1 mg/m^3 of mercury vapor for 4 or 7 hours per day, 5 days per week during the last two-thirds or more of the gestation period. One female and 2 male offspring came from mothers exposed to 0.5 mg/m^3 mercury vapor during gestation weeks 5–19, 5–21, or 6–22 for a total of 247–510 hours, resulting in total doses of 1,304–2,900 µg (20–38 µg/day); and 3 male offspring came from mothers exposed to 1 mg/m^3 mercury vapor during gestation weeks 7–21, 3–18, or 8–21 for a total of 283–402 hours, resulting in total doses of 2,901–4,305 µg (42–62 µg/day). Five male offspring born about the same time as the exposed monkeys served as controls. Lever pressing was maintained under a Concurrent Random-Interval 30 schedule of reinforcement. Time allocation on each lever was examined during behavioral transitions and in a steady state. Median maternal blood levels ranged from 0.025 to 0.09 µg/g in animals exposed to 0.5 mg/m^3 and from 0.12 to 0.18 µg/g in animals exposed to 1 mg/m^3. No differences in birth weight, weight gain, or body weight at time of behavioral testing were observed between exposed and control offspring. No difference in sensitivity to reinforcer ratios was identified in the steady state, but there was much more variability in the steady-state performance of exposed monkeys, as indicated by the standard deviation of the regression, than in controls. Logistic regression was used to examine the transition to new schedule

parameters. Exposed monkeys were found to produce smaller or slower transitions than controls. The magnitude and stability of lever-press durations for controls and exposed monkeys were indistinguishable early in the experiment, but at the end, the exposed monkeys had longer lever-press durations and the session-to-session variability was much greater. One monkey's exposure began during the third week of gestation (earlier than any of the others) and its behavior was so erratic that some of the analyses could not be accomplished. Long-term effects of prenatal mercury vapor exposure included instability in lever-press durations and steady-state performance under concurrent schedules of reinforcement as well as aberrant transitions (Newland et al. 1996).

Organic Mercury. No studies were located regarding developmental effects in humans or animals after inhalation exposure to organic mercury.

The highest NOAELs and all reliable LOAELs for developmental effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

There is inconclusive evidence that occupational exposure to metallic mercury and to organic and inorganic mercury compounds, primarily through inhalation, causes structural and numerical chromosome aberrations in human lymphocytes. In one study, significant increases in the frequency of acentric fragments (chromosome breaks) occurred in 4 workers exposed to high concentrations of metallic mercury and in 18 workers exposed to a mixture of mercuric chloride, methylmercuric chloride, and ethylmercuric chloride (Popescu et al. 1979). Mercury concentrations in the workplace ranged from 0.15 to 0.44 mg/m^3; the urinary excretion level of mercury for both exposed groups was . 890 µg/L. The findings of this study are suspect because the control group was not matched for sex, smoking habits, or sample size. Additionally, one of the four individuals in the metallic mercury group had a history of benzene poisoning, which was reflected in the unusually high frequency of abnormal chromosome morphology seen in this individual. No difference in the incidence of aneuploidy was found between the exposed workers and the controls. In an earlier study, an apparent association between increased chromosome aberrations and workplace exposure to mercury (as measured by urinary mercury levels) was reported (Verschaeve et al. 1976). However, the study was not well controlled (i.e., not matched for sex, smoking habits, or sample size), and the only significant increase in structural aberrations occurred in the three workers exposed to ethylmercury. Significant increases in aneuploid were also noted for the exposure groups compared to the

control subjects. However, these data should also be interpreted with caution since age has an influence on aneuploidy, and in this study, there was a general trend toward a higher incidence of aneuploidy in the older exposed workers (ages 36–63 years). It is noteworthy that in a subsequent study performed by these investigators (Verschaeve et al. 1979), no adverse effects on the structure or number of chromosomes were demonstrated in 28 subjects exposed to moderate levels of metallic mercury (urinary levels of 50 µg/L). The authors concluded that the results from their 1976 study, showing an association between increased chromosomal aberrations and occupational exposure to mercury, may have been affected by factors other than exposure to mercury compounds.

No increased frequency of structural aberrations was found in 22 workers exposed to mercury vapors; no information was provided on numerical aberrations (Mabille et al. 1984). The mean duration of exposure was 4 years, and the mean urinary and blood mercury levels in the exposed group were 117 µg/g creatinine and 0.031 µg/mL, respectively. More recently, peripheral lymphocytes from 26 male chloralkali workers exposed to mercury vapors (25–50 µg/m^3), for a mean exposure time of 10 years, were analyzed for micronucleus induction. The results were compared to results obtained from 26 unexposed subjects (Barregard et al. 1991). Groups were matched for age (±7 years) and smoking habits; plasma, erythrocyte, and urine mercury levels were determined. Parallel lymphocyte cultures from each donor group were incubated in the presence of pokeweed mitogen, which stimulates both B- and T-lymphocytes, and phytohemagglutinin, which primarily activates T-cells. The analysis showed no significant increase in the frequency or the size of micronuclei in the exposed versus the control group. Nor was there a correlation between micronuclei induction and plasma, erythrocyte, or urinary levels of mercury. Within the exposed group, however, there was a significant correlation between micronuclei induction in phytohemagglutinin-stimulated lymphocytes and cumulative exposure (whole-blood mercury level over employment time); the response was independent of age or smoking habits. These results, suggesting a genotoxic effect on T-lymphocytes, are unusual since there is evidence that B-lymphocytes may be more sensitive indicators of chemically induced clastogenesis than T-lymphocytes (Högstedt et al. 1988). The authors stated that the evidence of a genotoxic response confined to T-lymphocytes could have been a random finding but hypothesized that long-term exposure to mercury may cause an accumulation of cytogenetic effects.

Similarly, there was no correlation between urinary mercury levels (60–245 µg/L) or the duration of exposure (11–34 years) and increased frequency of structural aberrations and micronuclei in the lymphocytes of 29 male workers exposed to mercury fulminate (Anwar and Gabal 1991). From the overall

results, the authors concluded that mercury in the manufacturing process may not have been the clastogen. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

Metallic Mercury. There is no evidence from epidemiological studies that indicates inhalation of metallic mercury produces cancer in humans (Cragle et al. 1984; Kazantzis 1981). No evidence of an association between metallic mercury exposure and cancer mortality was found in a group of workers employed in a facility utilizing the metal in a lithium isotope separation process (Cragle et al. 1984). Overall mortality in the mercury-exposed group was less than that of the standard white male population and that of a control group of men who were not exposed to mercury. Similarly, no excess of cancer of the kidneys or nervous system was found among a cohort of 674 Norwegian men exposed to mercury vapors for more than 1 year at 2 chloralkali plants (Ellingsen et al. 1993). An excess in lung cancer (type not specified) was found in Swedish chloralkali workers 10 years after the end of long-term, high-level exposure to metallic mercury (Barregard et al. 1990). However, these workers had also been exposed to asbestos. Furthermore, no data on smoking status was provided, although the study implied that the workers did not smoke much.

No studies were located regarding cancer in animals after inhalation exposure to metallic mercury.

Organic Mercury. Associations were reported between the use of mercury-containing fungicides (i.e., mercury levels in hair) and leukemia in farmers and between the use of mercury-containing seed dressings and leukemia in cattle (Janicki et al. 1987). However, the study was limited in reporting methodology used to conduct this study. Furthermore, the study did not adequately address exposure to other chemicals, or adjust for other leukemia risk factors.

No studies were located regarding cancer in animals after inhalation exposure to organic mercury.

2.2.2 Oral Exposure

The bulk of the information regarding toxicity resulting from oral exposure to inorganic mercury comes from studies of mercuric chloride. However, a few studies are also available on the effects of oral exposure to mercuric acetate, mercurous chloride (calomel), and mercuric sulfide (cinnabar). Discussion of these

compounds has not been separated in this section, but the specific inorganic compound responsible for any effect is noted both in the text and in Table 2-2 and Figure 2-2.

Health effects following oral exposure to organic mercury were observed in humans and animals. The majority of the studies used to derive the NOAELs and LOAELs shown in Table 2-3 and Figure 2-3 concern exposure to methylmercuric chloride; however, in several studies, exposure was to methylmercuric acetate, methylmercuric hydroxide, methylmercuric dicyanidiamide, or phenylmercuric acetate. These chemicals are discussed together in Table 2-3 and Figure 2-3. In order to facilitate a comparison of studies using different compounds of mercury (either organic or inorganic), all doses are expressed in terms of the mercury exposure (mg Hg/kg/day) rather than to the mercury compound (HgX or RHgX/kg/day) to which one is exposed. For example, a dose of 1 mg/kg (when the compound is methylmercuric chloride) refers to 1 mg/kg mercury rather than 1 mg/kg methylmercuric chloride.

2.2.2.1 Death

Inorganic Mercury. A lethal dose of mercuric chloride was estimated to be 10–42 mg Hg/kg for a 70-kg adult (Gleason et al. 1957). Death from oral exposure to inorganic mercury is usually caused by shock, cardiovascular collapse, acute renal failure, and severe gastrointestinal damage (Gleason et al. 1957; Murphy et al. 1979; Troen et al. 1951). Eighteen cases of human poisoning (suicide attempts in some cases) were reported by Troen et al. (1951); 9 patients died following oral ingestion of single doses of mercuric chloride (range, 29–>50 mg Hg/kg). The most common findings in these cases were gastro-intestinal lesions (e.g., mild gastritis to severe necrotizing ulceration of the mucosa) and renal involvement (e.g., albuminuria, anuria, and uremia). Death of a 50-year-old woman due to ingestion of an unspecified amount of mercurous chloride in Chinese medicine has also been reported (Kang-Yum and Oransky 1992). The death was attributed to renal failure.

In rats, the oral LD_{50} values (lethal dose, 50% kill) ranged from 25.9 to 77.7 mg Hg/kg as mercuric chloride (Kostial et al. 1978). The signs of acute mercury toxicity in animals were similar to those described above for humans. Male rats appeared to be slightly more sensitive to the lethal effects of mercuric chloride; 2 of 5 male rats and no female rats died when given gavage doses of 14.8 mg Hg/kg, 5 days a week for 2 weeks (Dieter et al. 1992; NTP 1993). Mice showed slightly less toxicity, with no deaths at 14.8 mg Hg/kg, death in 1 male at 29 mg Hg/kg, and deaths in 5 of 5 males and 4 of 5 females at 59 mg Hg/kg when administered by gavage over the same period (NTP 1993).

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Fischer- 344)	14 d 5 d/wk 1 x/d (GW)				14.8 M (2/5 males died)	Dieter et al. 1992; NTP 1993 MC
2	Rat	once (G)				25.9 (LD_{50})	Kostial et al. 1978 MC
3	Mouse (B6C3F1)	14 d 5 d/wk 1 x/d (GW)				59 (5/5 males; 4/5 females died)	NTP 1993 MC
	Systemic						
4	Human	once (C)	Gastro		30 F (nausea, vomiting, abdominal cramps, diarrhea)		Afonso and deAlvarez 1960 MC
			Renal			30 F (acute renal failure, oliguria, proteinuria, hematuria)	
5	Rat (Long- Evans)	6 d 1 x/d (GW)	Endocr		7.4 F (increased release of iodine from thyroid)		Goldman and Blackburn 1979 MC

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
6	Rat (Sprague-Dawley)	once (G)	Hemato		7.4 F (9-10% decrease in hemoglobin, erythrocytes, hematocrit)		Lecavalier et al. 1994 MC
			Hepatic		7.4 F (decreased lactate dehydrogenase)		
			Renal		7.4 F (mild histopthological changes - protein casts, cellular casts, and interstitial sclerosis)		
			Bd Wt	9.2 F			
7	Rat (Fischer- 344)	14 d 5 d/wk 1 x/d (GW)	Renal	0.93[b]	1.9 M (increased absolute and 3.7 F relative kidney weight)	7.4 (minimal to mild acute renal necrosis)	NTP 1993; Dieter et al. 1992 MC
			Bd Wt	7.4 M	14.8 M (10% decreased body weight in males)		
8	Mouse (Bom:NMRI)	once (GW)	Renal	5 F	10 F (decreased renal selenium-dependent glutathione peroxidase activity; minor renal tubular damage)	20 (proximal tubule necrosis)	Nielson et al. 1991 MC
9	Mouse (B6C3F1)	14 d 5 d/wk 1 x/d (GW)	Renal		3.7 (increased absolute and relative kidney weight)	59 (acute renal necrosis)	NTP 1993 MC
			Gastro	29	59 (stomach inflammation and necrosis)		
			Bd Wt	59			
10	Mouse (Swiss)	10 d 1 x/d (GW)	Endocr		6 F (decreased serum triiodothryonine)		Sin et al. 1990 MS

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
11	Mouse (Swiss)	10 d 1 x/d (GW)	Endocr		6 F (decreased serum thyroxine and triiodothyronine)		Sin et al. 1990 MC
	Immunological/Lymphoreticular						
12	Mouse (B6C3F1)	14 d 5 x/wk 1 x/d (GW)		7.4 F	14.8 F (decreased thymus weight)		NTP 1993 MC
	INTERMEDIATE EXPOSURE						
	Systemic						
13	Rat (Charles Foster)	60-180 d ad lib (W)	Endocr		2.6 M (increased corticosterone levels in adrenal and plasma)		Agrawal and Chansouria 1989 MC
14	Rat (Wistar)	350 d ad lib (W)	Cardio		7M (increased blood pressure and cardiac inotropy)		Boscolo et al. 1989 MC
			Renal		7M (tubular degeneration and membraneous glomerulonephritis)		
15	Rat (Sprague-Dawley)	350 d ad lib (W)	Cardio		7M (increased blood pressure and cardiac inotrophy)		Boscolo et al. 1989; Carmignani et al. 1989 MC
			Renal		7M (hydropic degeneration and desquamation of the tubular cells)		

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
16	Rat (Wistar)	180 d ad lib (W)	Cardio		28 M (increased blood pressure; decreased cardiac contractility)		Carmignani et al. 1992 MC
			Renal			28 M (mesangial proliferative glomerulonephritis; decreased acid phosphatase in lysosomes of tubular cells)	
17	Rat (Fischer- 344)	26 wk 5 d/wk 1 x/d (GW)	Renal	0.23 [c]	0.46 (increased absolute and relative kidney weight)	0.93 M (tubular necrosis)	Dieter et al. 1992; NTP 1993 MC
			Bd Wt	1.9 M 0.46 F	3.7 M 0.93 F (10% decrease in body weight gain)		
18	Rat (Long- Evans)	40 d 1 x/d (G)	Endocr		5.3 F (increased thyroid activity; decreased triiodothyronine synthesis)		Goldman and Blackburn 1979 MC
19	Rat (Sprague-Dawley)	3 mo ad lib (F)	Resp			2.2 F (respiratory difficulties; forceful and labored breathing)	Goldman and Blackburn 1979 MC
			Endocr		2.2 F (decreased thyroidal iodine uptake, iodine release, and iodine turnover)		

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
20	Rat (Wistar)	4 wk ad lib (F)	Hepatic	5 M 11.1 F	10 M (decreased absolute liver 22.2 F weight)		Jonker et al. 1993b MC
			Renal			5 M (nephrosis and 5.5 F proteinaceous casts, increased relative kidney weight)	
			Endocr	10 M	20 M (increased relative adrenal weight)		
				11.1 F	22.2 F (decreased absolute adrenal weight)		
			Bd Wt	5 M		10 M (21% decreased body weight)	
				11.1 F		22.2 F (27% decreased body weight)	
			Other		5 M (decreased food and 5.5 F water intake)		
21	Rat (Wistar)	4 wk ad lib (F)	Renal	1 M	8 M (ketones in urine, increased relative weight of kidneys, slight histopathological changes to outer cortex basophilic tubules)		Jonker et al. 1993b MC
					1.1 F (increased absolute and relative kidney weight)		
			Bd Wt	8 M 8.9 F			
22	Mouse (B6C3F1)	7 wk ad lib (W)	Renal	0.6 M	2.9 M (nuclear swelling in epithelial cells)		Dieter et al. 1983 MC
			Hepatic		2.9 M (increased liver weight)		
			Endocr	14.3 M			

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
23	Mouse (SJL/N)	10 wk ad lib (W)	Renal	0.28 F	0.56 F (increased granular IgG deposits; slight glomerular endocapillary cell hyperplasia; slight tubular atrophy, inflammation, and fibrosis)		Hultman and Enestrom 1992 MC
24	Mouse (B6C3F1)	26 wk 5 d/wk 1 x/d (GW)	Renal	1.9 M 14.8 F	3.7 M (cytoplasmic vacuolation of tubule epithelium, increased absolute weight)		NTP 1993 MC
			Bd Wt	7.4 M 14.8 F		14.8 M (26% decrease in body weight gain in males)	
25	Mouse (Swiss)	4 wk 1 x/d (GW)	Endocr		6 F (decreased serum thyroxine)		Sin and Teh 1992 MS
	Immunological/Lymphoreticular						
26	Mouse (B6C3F1)	7 wk ad lib (W)		0.6 M	2.9 M (suppression of lymphoproliferative response to T-cell, concanavalin A and phytohemagglutinin)		Deiter et al. 1983 MC
	Neurological						
27	Rat (Sprague-Dawley)	3 mo ad lib (F)				2.2 F (inactivity; abnormal gait)	Goldman and Blackburn 1979 MC

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Death						
28	Rat (Fischer- 344)	2 yr 5 d/wk 1 x/d (GW)				1.9 M (40/50 males died versus 24/50 control male deaths)	Dieter et al. 1992; NTP 1993 MC
	Systemic						
29	Rat (Fischer- 344)	2 yr 5 d/wk 1 x/d (GW)	Resp	1.9	3.7 (increase in nasal inflammmation)		NTP 1993 MC
			Gastro		1.9 M (forestomach epithelial hyperplasia; inflammation of the cecum)		
			Renal			1.9 M (marked thickening of glomerular and tubular basement membranes; degeneration and atrophy of tubule epithelium)	
			Bd Wt			1.9 (24% decrease in male body weight gain and 16% decrease in female body weight gain)	
30	Mouse (B6C3F1)	2 yr 5 d/wk 1 x/d (GW)	Renal		3.7 F (foci of proximal tubule with thickened basement membrane; basophilic cells with scant cytoplasm)		NTP 1993 MC

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)		
	Cancer							
31	Rat (Fischer- 344)	2 yr 5 d/wk 1x/d (GW)				3.7	(CEL: forestomach squamous cell papillomas in males and females; thyroid follicular cell carcinomas in males)	NTP 1993 MC

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an acute oral Minimal Risk Level (MRL) of $7x10^{-3}$ mg mercury/kg/day; dose corrected for 5 day/week exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive an intermediate oral MRL of $2x10^{-3}$ mg mercury/kg/day; dose corrected for 5 day/week exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) gavage with oil; (GW) gavage with water; Hemato = hematological; Hg = mercury; hr = hour(s); IgG = immunoglobulin G; LD_{50} = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; MA = mercuric acetate; MC = mercuric chloride; MN = mercuric nitrate; MS = mercuric sulfide; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; ppd = postpartum day (s); Resp = respiratory; (W) = drinking water; wk = week(s); x = times; yr = year(s)

Figure 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral

Acute (≤14 days)

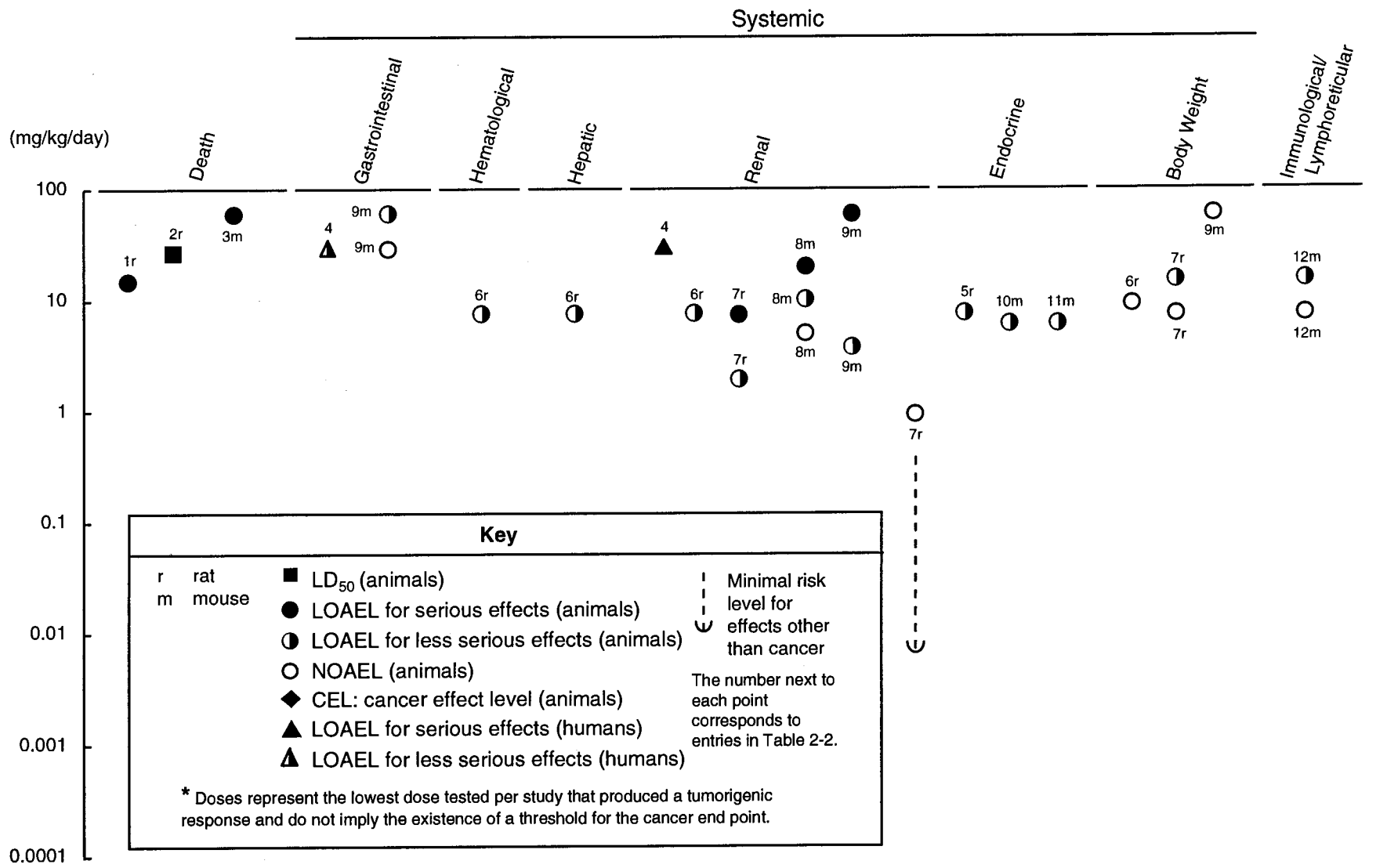


Figure 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (cont.)

Intermediate (15-364 days)

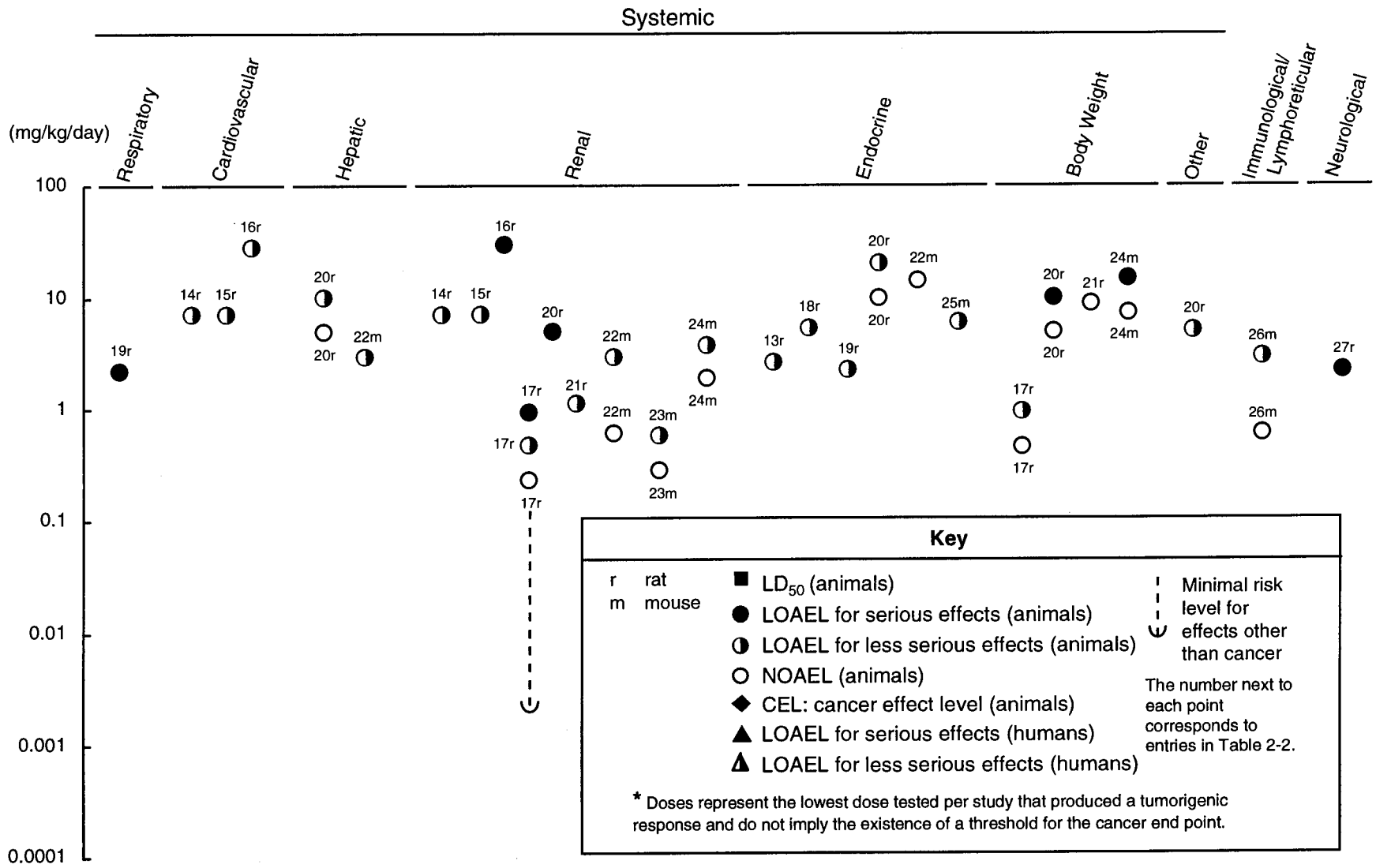


Figure 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (cont.)

Chronic (≥365 days)

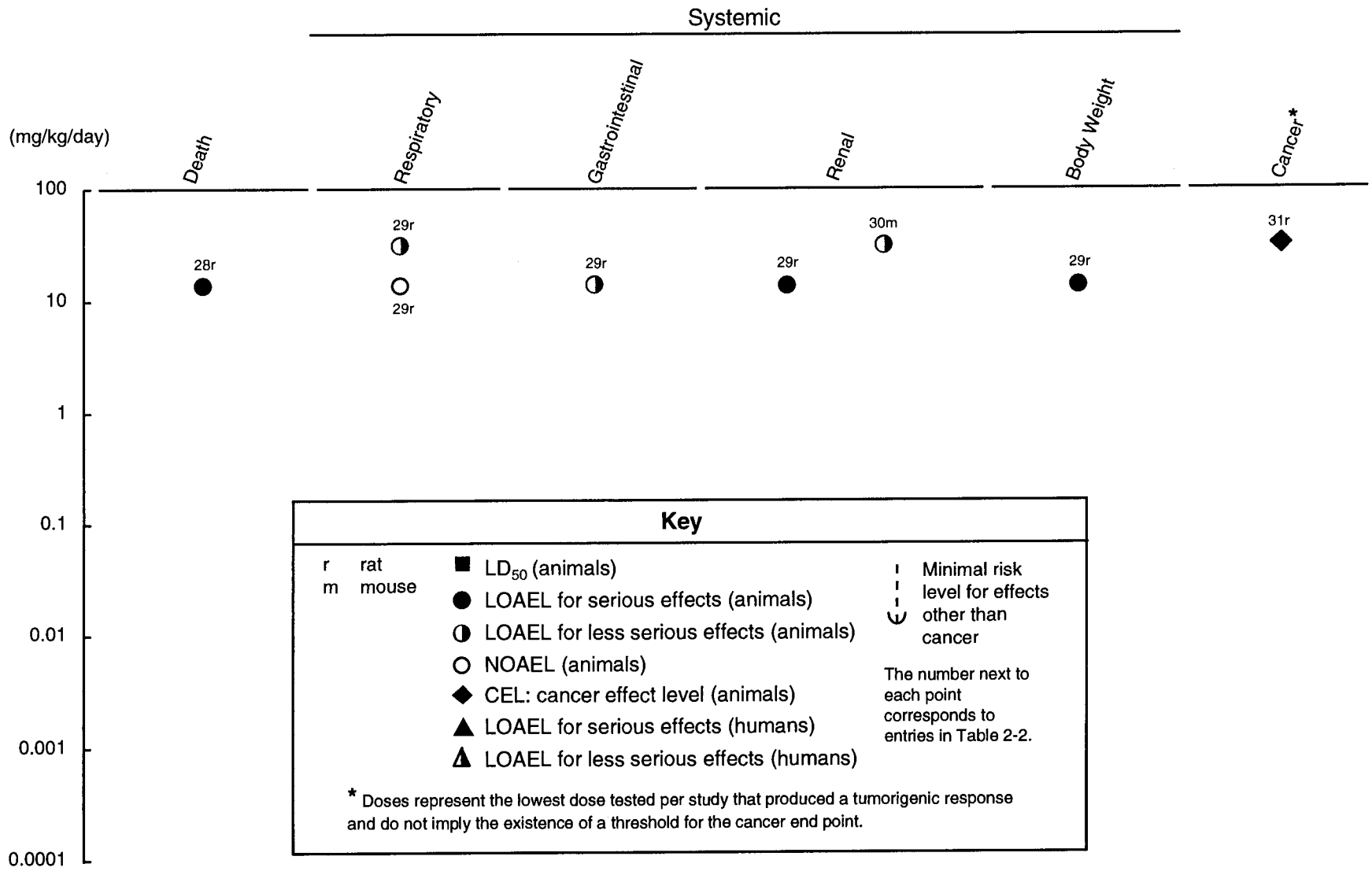


Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Mouse (C57BL/6N)	once (G)				16 M (4/6 died) 40 F (4/6 died)	Yasutake et al. 1991b MMC
	Systemic						
2	Rat (Sprague-Dawley)	2 d 1 x/d (GW)	Cardio		12M (18% decreased heart rate)		Arito and Takahashi 1991 MMC
			Other		12M (hypothermia)		
3	Mouse (C57BL/6N)	once (G)	Renal	8 M 24 F	16 M 32 F (decreased phenolsulfonphthalein excretion, increased serum creatinine, swollen tubular epithelial cells)		Yasutake et al. 1991b MMC
	Neurological						
4	Rat (Sprague-Dawley)	2 d 1 x/d (GW)		1.32 M	4M (decreased paradoxical sleep and increased slow-wave sleep)		Arito and Takahashi 1991 MMC
5	Rat (Sprague-Dawley)	once (G)			0.80 M (dye transport across blood-brain barrier)		Chang and Hartmann 1972b MMC
6	Rat (Wistar)	2 d 1 x/d (G)			10M (impaired performance in tilting plane test)	20 M (decreased nerve conduction velocity; edema and Wallerian degeneration of peripheral nerves)	Fehling et al. 1975 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
7	Rat (Wistar)	8 d 1 x/d Gd 7-14 (GW)		4 F		6 F (spasms; gait disturbance; hind limb crossing in dams)	Fuyuta et al. 1978 MMC
8	Rat (Wistar)	9, 13, or 21 d 1 x/d Gd 12-20, 0-12, or 0-20 (GW)		2 F		4 F (hindlimb crossing in dams)	Inouye and Murakami 1975 MMC
9	Rat (Wistar)	10 d 1 x/d (F)				6.9 M (ataxia; instability walking; peripheral nerve degeneration)	Miyakawa et al. 1974 MMS
10	Rat (Sprague-Dawley)	Once (G)		16 M		20 M (decreased activity in t-maze test)	Post et al. 1973 MMC
11	Rabbit (New Zealand)	1-4 d 1 x/d (G)				5.5 (degeneration of ganglion cells, cerebellum, and cerebral cortex)	Jacobs et al. 1977 MMA
	Reproductive						
12	Rat (Wistar)	7 d 1 x/d (G)				5 M (reduced mean litter size in untreated females)	Khera 1973b MMC
13	Rat (Fischer- 344)	once Gd 7 (G)				8 F (16.7% postimplantation loss, 32.3% decreased litter weight, 14.0% decrease in maternal weight gain)	Lee and Han 1995 MMC
14	Mouse (ICR)	once Gd 10 (GW)		16 F		20 F (increased resorptions; decreased fetuses per litter)	Fuyuta et al. 1979 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
15	Mouse (CFW)	once Gd 8 (G)		2 F		3 F (decreased number of pups per litter)	Hughes and Annau 1976 MMH
16	Mouse (Swiss-Webster)	5-7 d 1 x/d (G)		5 M			Khera 1973b MMC
17	Gn Pig (Hartley)	once Gd 21, 28, 35, 42 (GW)				11.5 F (increased abortions)	Inouye and Kajiwara 1988b MMC
18	Hamster	once Gd 8 (GW)		15.8 F		22 F (increased resorption)	Gale 1974 MA
	Developmental						
19	Human	NS (F)			0.0012 (delayed walking; abnormal motor scores)		Cox et al. 1989 MMC
20	Rat (Wistar)	4 d 1 x/d Gd 6-9 (G)		0.004	0.008 (reduction in behavioral performance of offspring)		Bornhausen et al. 1980 MMC
21	Rat (Sprague-Dawley)	Once Gd 15 (GW)			6.4 (decreased glutamate receptor binding affinity and decreased avoidance latency in offspring)		Cagiano et al. 1990 MMC
22	Rat (Sprague-Dawley)	4 d 1 x/d Gd 6-9 (G)		1.6			Fredriksson et al. 1996 (MM)

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
23	Rat (Wistar)	8 d 1 x/d Gd 7-14 (GW)		2			4	(decreased fetal weight; increased malformations [total]; hydrocephaly; wavy ribs)	Fuyuta et al. 1978 MMC
24	Rat (ddN)	once Gd 6, 7, 8, 9, 10 (GW)					24	(fetal deaths; edema; brain lesions; cleft palate)	Inouye and Murakami 1975 MMC
25	Rat (Wistar)	9, 13, or 21 d 1 x/d Gd 12-20, 0-12, or 0-20 (GW)					2	(fetal edema and brain lesions)	Inouye and Murakami 1975 MMC
26	Rat (Fischer- 344)	once Gd 7 (G)					8	(curved backbones, 9.6% reduced fetal body length)	Lee and Han 1995 MMC
27	Rat	9 d Gd 6-14 ad lib (W)		0.2	4	(increased number of fetuses with delayed ossification or calcification)			Nolen et al. 1972 MMC
28	Rat (Wistar)	4 d Gd 6-9 (G)		0.04	0.4	(increased startle response in offspring)	4	(dendritic spine abnormalities)	Stoltenburg-Didinger and Markwort 1990 MMC
29	Rat (Sprague-Dawley)	once Gd 15 (G)					6.4	(21.3-53% decr maximum number of muscarinic receptors in brain, signif. decr avoidance latency in offspring)	Zanoli et al. 1994 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
30	Mouse (C57BL/6N)	8 d 1 x/d Gd 6-13 (GW)					2	(increased malformations [total]; decreased ossification; absence of 1 or more sterebrae)	Fuyuta et al. 1978 MMC
31	Mouse (ICR)	once Gd 10 (GW)			8	(incomplete fusion of sternebrae)	12	(cleft palate; decreased fetal weight)	Fuyuta et al. 1979 MMC
32	Mouse (CFW)	once Gd 8 (G)		2	3	(decreased number of avoidances and increased escapes in offspring)			Hughes and Annau 1976 MMH
33	Mouse (C3H/HeN)	once Gd 13, 14, 15, 16 (GW)					16	(decreased survival of offspring; impaired righting response; gait and hindlimb crossing; decreased brain weight; dilated lateral ventricles; smaller caudate putamen)	Inouye et al. 1985 MMC
34	Mouse (Swiss-Webster)	12 d Gd 6-17 (GO)		1.0			5.0	(100% stillbirths; failure to litter)	Khera and Tabacova 1973 MMC
35	Mouse (ICR)	once Gd 10 or 12 (GW)		12			16	(cleft palate; dilation of renal pelvis; decreased fetal weight)	Yasuda et al. 1985 MMC
36	Gn Pig (Hartley)	once Gd 21, 28, 35, 42 (GW)					11.5	(retarded fetal brain development)	Inouye and Kajiwara 1988b MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
37	Hamster	once Gd 8 (GW)		2.5	5	(decreased crown-rump length)	22	(increased resorption)	Gale 1974 MA
38	Hamster (Golden Syrian)	once Gd 10 ; or 6d 1 x/d Gd 10-15 (GW)					1.6	(degeneration of cerebellar neurons in neonates)	Reuhl et al. 1981a MMC
39	Hamster (Golden Syrian)	Once Gd 10; or 56d 1 x/d Gd 10-15 (GW)					1.6	(degeneration of cerebellar neurons in offspring 10 months postexposure)	Reuhl et al. 1981b MMC
	INTERMEDIATE EXPOSURE								
	Death								
40	Mouse (ICR)	26 wk ad lib (F)					3.1	(51/60 males and 59/60 females died versus 1/60 male and 1/60 female controls)	Mitsumori et al. 1981 MMC
	Systemic								
41	Rat	12 wk ad lib (F)	Renal		0.08	(cytoplasmic mass in proximal tubule cells)			Fowler 1972 MMC
42	Rat (albino)	3-12 wk 5 d/wk (G)	Renal		0.84 F	(fibrosis, inflammation, and large foci in renal cortex)			Magos and Butler 1972 MMD

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
43	Rat (Wistar)	23-28 d 7 d/wk or 1 x every 3 d for 13 d (G)	Cardio		0.4 M (increased systolic pressure)		Wakita 1987 MMC
44	Mouse (ICR)	26 wk ad lib (F)	Renal	0.15	0.6 (toxic epithelial degeneration of renal proximal tubules)		Hirano et al. 1986 MMC
45	Mouse (BALB/c)	12 wk ad lib (F)	Hepatic	0.5 F			Ilback 1991 MM
			Renal	0.5 F			
			Endocr		0.5 F (22% decrease in thymus weight)		
	Immunological/Lymphoreticular						
46	Mouse (BALB/c)	12 wk ad lib (F)			0.5 F (reduced natural killer T-cell activity; decreased thymus weight and cell number)		Ilback 1991 MM
	Neurological						
47	Monkey (Macaca fascicularis)	NS 1 x/d (G)		0.043 F		0.077 F (intention tremor)	Burbacher et al. 1984 MMH
48	Monkey (Macaca fascicularis)	4 mo 1 x/d (G)		0.06 F		0.08 F (slight tremor; gross motor incoordination; blindness)	Burbacher et al. 1988 MMH
49	Monkey (Macaca fascicularis)	6 mo (in apple juice)			0.05 F (72% increased number of reactive glia)		Charleston et al. 1994 MM

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
50	Monkey (macaca fascicularis)	150 d 1 x/d (W)		0.04 F			Petruccioli and Turillazzi 1991 MMC
51	Rat (Holtzman)	1-6 wk 7 d/wk (G)				0.8 M (focal cytoplasmic degeneration of dorsal root ganglia and cerebellum, severe ataxia)	Chang and Hartmann 1972a MMC
52	Rat	3-12 wk 5 d/wk (G)		0.84 F		1.68 F (ataxia; edema and necrosis of cerebellum)	Magos and Butler 1972 MMD
53	Rat (Sprague-Dawley)	15 d 1 x/3d (GO)			0.8 M (decreased synthesis of dopamine neurotransmitter)		Sharma et al. 1982 MMC
54	Rat (Wistar)	50 d 7 d/wk (G)			3.20 M (decreased neurotransmitter activities in cerebellum)		Tsuzuki 1981 MMC
55	Rat	8 wk 7 d/wk (G)				1.6 M (extensive degeneration of dorsal root fiber)	Yip and Chang 1981 MMC
56	Mouse (CD-1)	60 d 7 d/wk (G)		0.25 M		1.0 M (hindleg weakness; microgliocytosis and degeneration)	Berthoud et al. 1976 MMC
57	Mouse	28 wk ad lib (W)				1.9 M (degenerative changes of Purkinje cells and granule cell loss in cerebellum)	MacDonald and Harbison 1977 MMC
58	Cat	11 mo ad lib (F)				0.015 (degeneration of cerebellum and necrosis of dorsal root ganglia)	Chang et al. 1974 MM

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
59	Cat	44-243 d 1 x/d (GW)				0.25 (neuronal degeneration; distorted myelination)	Khera et al. 1974 MMC
	Reproductive						
60	Monkey (Macaca fascicularis)	4 mo 1 x/d (G)		0.04 F		0.06 F (abortion, stillbirth, decreased conception)	Burbacher et al. 1988 MMH
	Developmental						
61	Human	NS (F)			0.0012 (delayed walking; abnormal motor scores)		Cox et al. 1989 MMC
62	Monkey	28-29 d 1 x/d ppd 1-28 or 29 (W)				0.5 (loss of dexterity, locomotor activity; ataxia; blindness; comatose; neuronal degeneration)	Willes et al. 1978 MMC
63	Rat (Wistar)	2 wk prior to mating through weaning (W)			0.08 (impaired tactile-kinesthetic function in offspring)		Elsner 1991 MMC
64	Rat	47 d prior to and during gestation (W)		0.7	1.4 (depression of membrane synthesis, monoamine oxidase, and cytochrome oxidase in fetal hepatocyte mitochodrial membranes)		Fowler and Woods 1977 MMH

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
65	Rat (Sprague-Dawley)	15-17 wk 11 wk, Gd 1-21, pp (F)			0.5	(decreased cell-mediated cytotoxicity, increased thymus lymphocyte activity in fetus)			Ilback et al. 1991 MM
66	Rat	approx 52 d ad lib (F)		0.05			0.25	(increased incidence of eye defects in fetuses)	Khera and Tabacova 1973 MMC
67	Rat (Sprague-Dawley)	approx 25 wks; 14 wks prior to mating through ppd 50 (F)			0.195	(increased norepinephrine levels in cerebellum of offspring, increased brain weight)			Lindstrom et al. 1991 MMC
68	Rat	68 d Gd 1 to ppd 42 (G)					0.10	(decreased swimming ability and righting reflex; retarded maze learning in offspring)	Olson and Boush 1975 MMH
69	Mouse (BALB/c)	15 wk ad lib (F)			5.0	(increased proliferatiuve response of pup splenocytes)			Thuvander et al 1996 MMC
	CHRONIC EXPOSURE								
	Death								
70	Mouse (B6C3F1)	104 wk ad lib (F)					0.69 M	(50/60 males died versus 31/60 controls)	Mitsumori et al. 1990 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
71	Rat (Wistar)	2 yr ad lib (W)	Gastro	0.4 M		4.2 M (ulcerative cecitis)	Solecki et al. 1991 PMA
			Hemato	0.4 M		4.2 M (decreased hemoglobin, erythrocyte and hematocrit)	
			Renal			0.4 M (increased severity of renal nephrosis)	
			Endocr		4.2 M (significant increased adrenal absolute weight [5%])		
			Bd Wt		0.4 M (approximately 10% decrease in body weight gain)		
72	Rat (NS)	2 yr ad lib (F)	Resp	0.1			Verschuuren et al. 1976 MMC
			Cardio	0.1			
			Gastro	0.1			
			Hemato	0.1			
			Musc/skel	0.1			
			Hepatic	0.1			
			Renal	0.02	0.1 (increased kidney weight; decreased kidney enzymes)		
			Dermal	0.1			
			Ocular	0.1			
73	Mouse (ICR)	104 wk ad lib (F)	Renal	0.03 M 0.11 F		0.15 M (incr chronic nephropathy) 0.6 F	Hirano et al. 1986 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
74	Mouse (B6C3F1)	104 wk ad lib (F)	Gastro	0.14 M 0.6 F	0.69 M (stomach ulceration)		Mitsumori et al. 1990 MMC
			Renal	0.03 M 0.13 F		0.14 M 0.6 F (increased chronic nephropathy with epithelial cell degeneration; regeneration of the proximal tubules; interstitial fibrosis)	
	Neurological						
75	Monkey (Macaca fascicularis)	NS 1 x/d (G)		0.043 F		0.077 F (intention tremor)	Burbacher et al. 1984 MMH
76	Monkey (Macaca fascicularis)	12 or 18 mo			0.05 F (89-152% increased number of reactive glia)		Charleston et al. 1994 MM
77	Monkey (Cynomolgus)	6.5-7 yr 7 d/wk 1 x/d (G)				0.05 (decreased fine motor performance; diminished touch and pinprick sensitivity)	Rice 1989c MMC
78	Monkey (Cynomolgus)	3-4 yr 7 d/wk 1 x/d				0.05 (spatial visual impairment)	Rice and Gilbert 1982 MMC
79	Monkey (Cynomolgus)	7 yr 1 x/d (C)			0.05 (impaired high-frequency hearing)		Rice and Gilbert 1992 MMC
80	Rat (NS)	2 yr ad lib (F)		0.1			Verschuuren et al. 1976 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
81	Mouse (ICR)	104 wk ad lib (F)		0.11 F		0.6 F (degeneration or fibrosis of sciatic nerve)	Hirano et al. 1986 MMC
82	Mouse (B6C3F1)	104 wk ad lib (F)		0.14 M		0.69 M (sensory neuropathy; cerebral and cerebellar neuronal necrosis; posterior paralysis)	Mitsumori et al. 1990 MMC
83	Cat	2 yr 7 d/wk (F)		0.020	0.046 (impaired hopping reaction; hypalgesia)	0.074 (degeneration of dorsal root ganglia, cerebellar granular cell degeneration)	Charbonneau et al. 1976 MMC
	Reproductive						
84	Rat (NS)	2 yr ad lib (F)		0.1			Verschuuren et al. 1976 MMC
85	Mouse (ICR)	104 wk ad lib (F)		0.15 M		0.73 M (decreased spermatogenesis)	Hirano et al. 1986 MMC
86	Mouse (B6C3F1)	104 wk ad lib (F)		0.14 M		0.69 M (tubular atrophy of the testes)	Mitsumori et al. 1990 MMC
	Developmental						
87	Human	NS (F)		0.00062 BMDL			Crump et al. 1998 MM
88	Human	NS (F)		0.0013[b]			Davidson et al. 1998 MM
89	Human	NS (F)		0.0005			Myers et al. 1997 MM

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
90	Monkey (Macaque)	328-907 d 1 x/d (W)				0.04-0.06	(impaired visual recognition memory in offspring)	Gunderson et al. 1988 MMH
	Cancer							
91	Rat (Wistar)	2 yr ad lib (W)				4.2 M	(CEL: renal cell adenoma)	Solecki et al. 1991 PMA
92	Mouse (ICR)	104 wk ad lib (F)				0.73 M	(CEL: renal epithelial adenocarcinoma in males)	Hirano et al. 1986 MMC
93	Mouse (ICR)	78 wk ad lib (F)				1.6 M	(CEL: renal adenomas and adenocarcinomas)	Mitsumori et al. 1981 MMC
94	Mouse (B6C3F1)	104 wk ad lib (F)				0.69 M	(CEL: renal epithelial cell adenomas and carcinomas)	Mitsumori et al. 1990 MMC

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive a chronic oral Minimal Risk Level (MRL) of $3x10^{-4}$ mg mercury/kg/day; the NOAEL dose was derived from hair levels, uncertainty factors of 1.5 for pharmacokinetic and 1.5 for pharmacodynamic variability in the relationship between mercury hair levels and mercury ingestion rates, and a modifying factor of 1.5 for domain-specific differences between the Faroe and Seychelles studies ((1.5 + 1.5) x 1.5 = 4.5). No other uncertainty factor was used since the children exposed in utero represent the most sensitive population.

ad lib = ad libitum; ALT = alanine amino transferase; AMC = ammoniated mercuric chloride; approx = approximately; AST = aspartate aminotransferase; Bd Wt = body weight; BMDL = benchmark dose, lower limit (95%); Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; (GO) gavage with oil; (GW) gavage with water; Hemato = hematological; Hg = mercury; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; MM = methylmercury; MMA = methylmercuric acetate; MMC = methylmercuric chloride; MMD = methylmercuric dicyandiamide; MMH = methylmercuric hydoxide; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; ppd = postpartum day(s); Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 2-3. Levels of Significant Exposure to Organic Mercury - Oral

Acute (≤14 days)

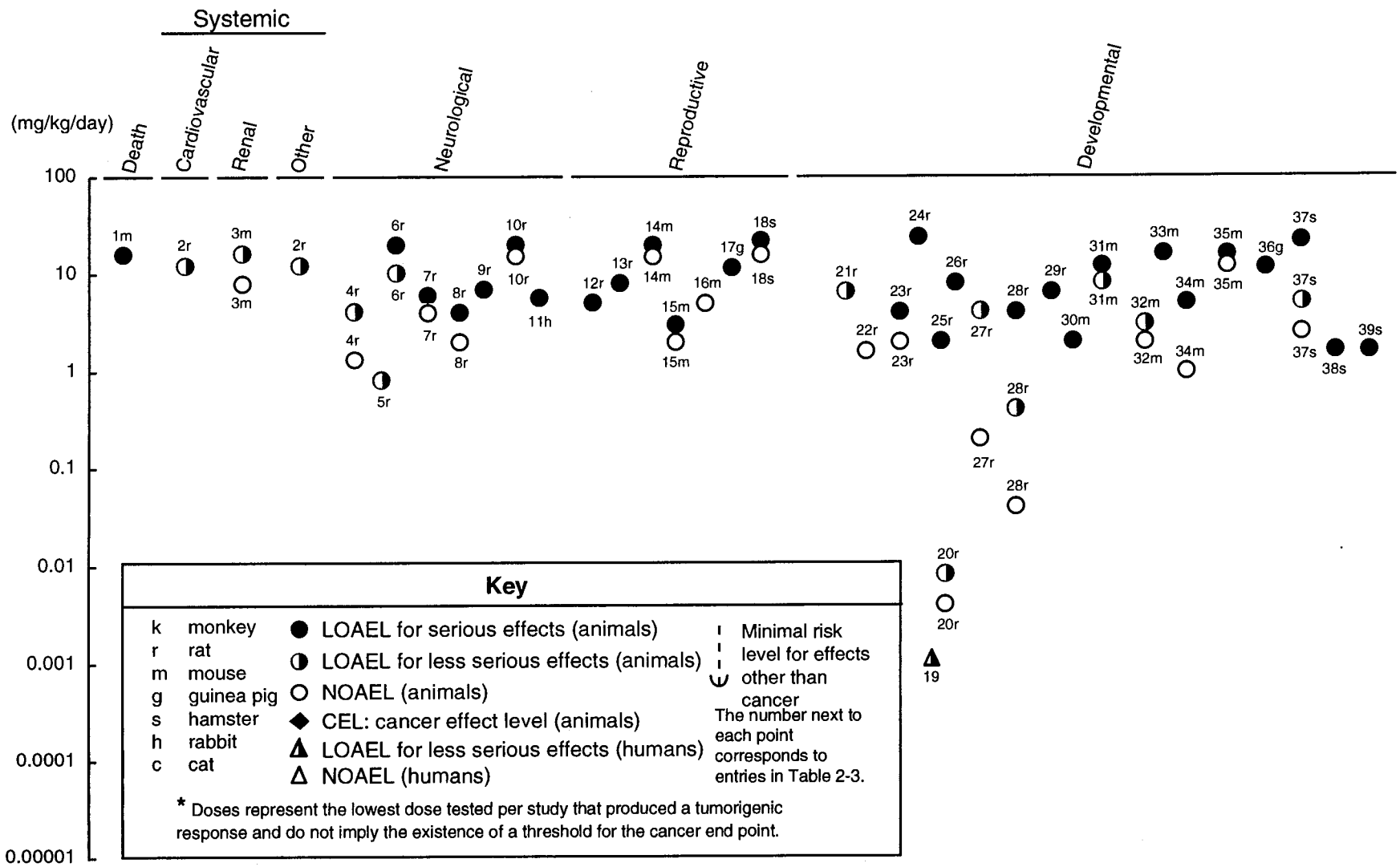


Figure 2-3. Levels of Significant Exposure to Organic Mercury - Oral (cont.)

Intermediate (15-364 days)

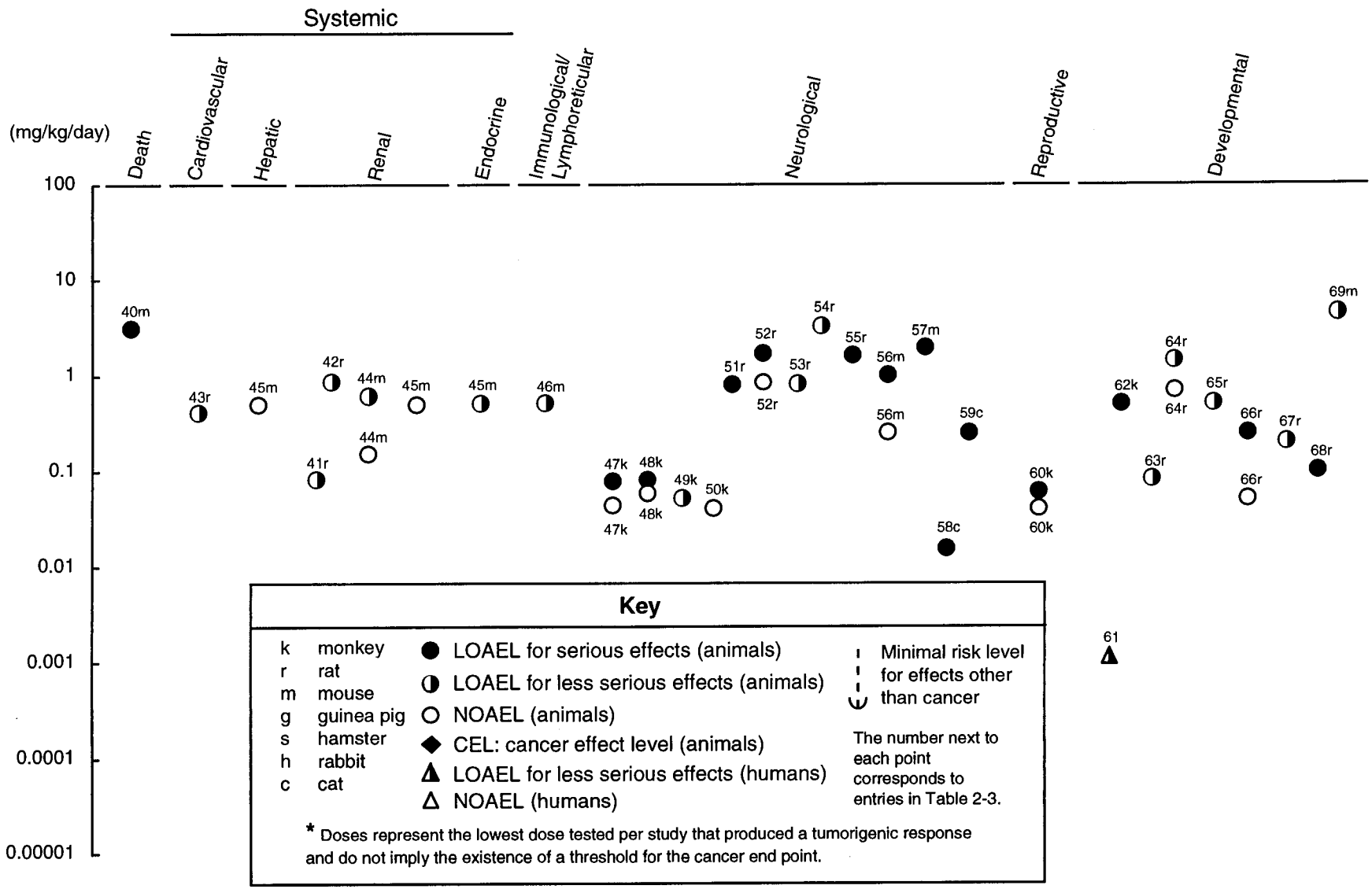
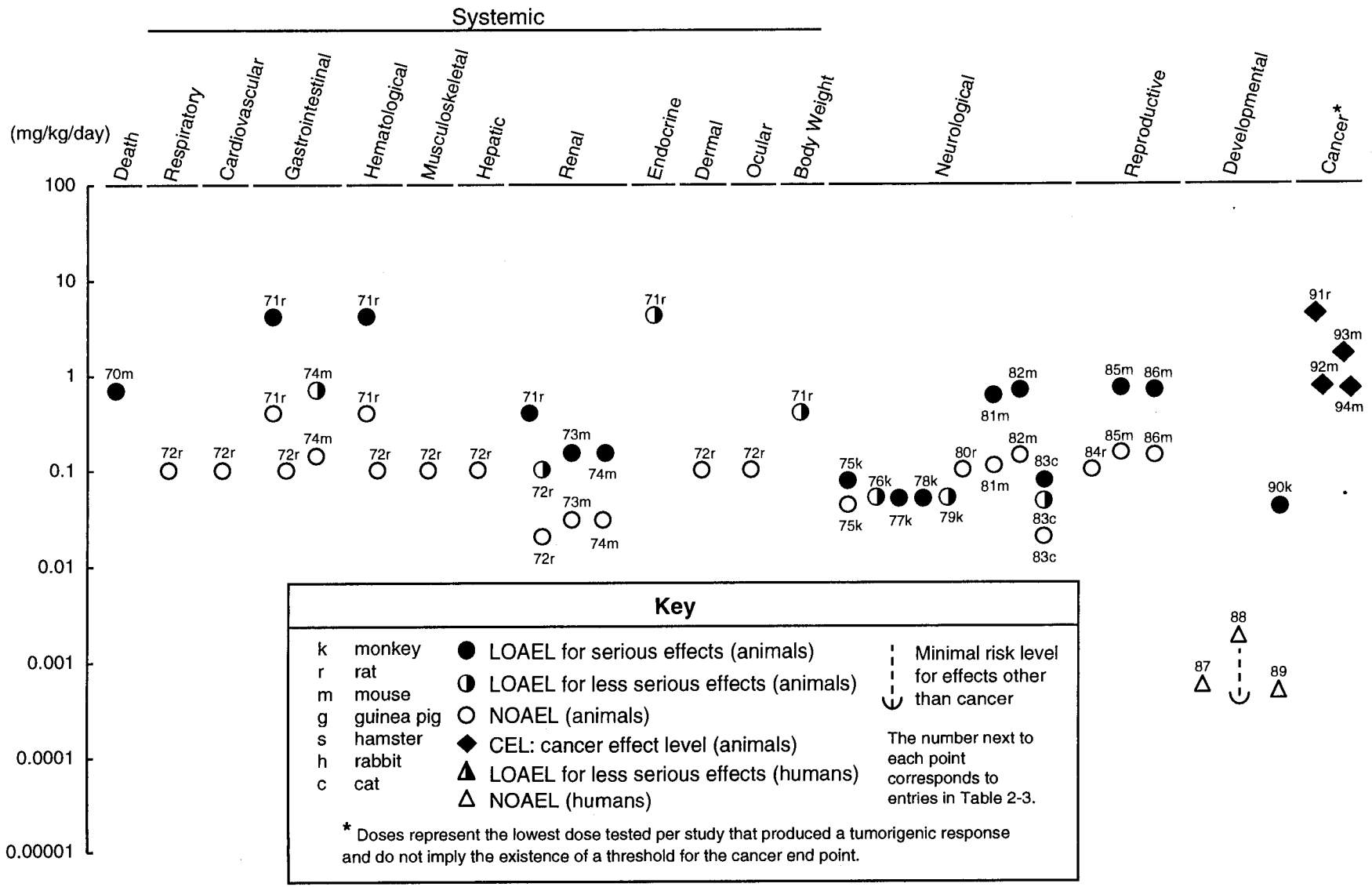


Figure 2-3. Levels of Significant Exposure to Organic Mercury - Oral (cont.)

Chronic (≥365 days)



Chronic exposure to mercuric chloride resulted in increased mortality in male rats at 1.9 mg Hg/kg/day but no increase in mortality in female rats at up to 3.7 mg Hg/kg/day or in either male or female mice at up to 7.4 mg Hg/kg/day (NTP 1993). Renal lesions in the male rats were thought to contribute to the early deaths in these animals.

The highest NOAEL values and all reliable LOAEL values for death for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2 for inorganic mercury.

Organic Mercury. The acute lethal dose of organic mercury compounds for humans is difficult to assess from the available literature. Death resulting from organic mercury ingestion has been amply documented following outbreaks of poisoning (Minamata disease) after consumption of methylmercury-contaminated fish in Minamata, Japan (Tsubaki and Takahashi 1986) and after consumption of grains contaminated with methyl- and ethylmercury in Iraq (Al-Saleem and the Clinical Committee on Mercury Poisoning 1976; Bakir et al. 1973). Death occurred in two boys who ate meat from a butchered hog that had been fed seed treated with ethylmercuric chloride (Cinca et al. 1979). However, primarily because of the delay between mercury consumption and the onset of symptoms, the amount of organic mercury ingested in these cases is difficult to determine. Fatal doses estimated from tissue concentrations range from 10 to 60 mg/kg (EPA 1985b). A case-control study examining the cause of death for patients with Minamata disease compared to the cause of death in unexposed persons showed that those patients who died prior to 1970 had significantly increased noninflammatory diseases of the nervous system; Minamata disease was reported as the underlying cause of death (Tamashiro et al. 1984). For this group, pneumonia and nonischemic heart disease were reported as prominent secondary cause of death. For those patients who died between 1970 and 1980, significant increases in Minamata disease were reported as the primary cause of death. Nonischemic heart disease correlated with the incidence of Minamata disease, and noninflammatory central nervous system disease was a prominent secondary cause of death in this group.

Methylmercury toxicity is very strain- and sex-specific in mice. A single oral dose of methylmercuric chloride at 16 mg Hg/kg resulted in the death of 4 of 6 male mice (C57BL/6N Jcl strain) but no deaths in females (Yasutake et al. 1991b). No increase in mortality was observed in female mice until 40 mg Hg/kg was administered, at which dosage 4 of 6 females died. Twenty-six weeks of dietary exposure to methyl-mercuric chloride resulted in increased mortality in both male and female mice (ICR strain) at 3.1 mg Hg/kg/day (Mitsumori et al. 1981). Chronic (104 weeks) dietary exposure to methylmercuric

chloride resulted in increased deaths in male mice ($B6C3F_1$ strain) at 0.69 mg Hg/kg/day but no increased mortality in females at up to 0.60 mg Hg/kg/day (Mitsumori et al. 1990).

The highest NOAEL values and all reliable LOAEL values for death for each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3 for organic mercury.

2.2.2.2 Systemic Effects

Ingestion of mercury compounds has been associated with systemic toxicity in both humans and animals. As with inhalation exposure to metallic mercury vapor, the major target organs of toxicity following oral exposure to inorganic and organic mercury are the kidneys and the central nervous system, respectively. Available information is limited mainly to that concerning exposure to mercuric chloride and methyl-mercuric chloride. Oral exposure to mercury, especially the organic mercury form, has also been observed to result in adverse developmental effects in humans and experimental animals. A discussion of the differences in the toxicities of metallic mercury, inorganic compounds, and organic compounds of mercury is presented in Section 2.5. The systemic effects observed after oral exposure are discussed below.

The highest NOAEL values and all reliable LOAEL values for systemic effects for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2 for inorganic mercury, and recorded in Table 2-3 and plotted in Figure 2-3 for organic mercury.

Respiratory Effects

Inorganic Mercury. Extremely limited information was located regarding respiratory effects in humans after oral exposure to inorganic forms of mercury. A 35-year-old man who swallowed an unknown amount of mercuric chloride had severe pulmonary edema and required artificial ventilation (Murphy et al. 1979). Fine rales were detected in a 19-month-old boy who swallowed powdered mercuric chloride (Samuels et al. 1982). A 50-year-old female who ingested 5 tablets of a Chinese medicine that contained an unspecified amount of mercurous chloride (Kang-Yum and Oransky 1992) experienced shortness of breath.

The only study located regarding respiratory effects in animals after oral exposure to inorganic mercury described forceful and labored breathing, bleeding from the nose, and other unspecified respiratory

difficulties in Long-Evans rats after dietary exposure to 2.2 mg Hg/kg/day as mercuric chloride for 3 months (Goldman and Blackburn 1979).

Organic Mercury. Limited information was located regarding respiratory effects in humans after oral exposure to organic mercury. Two boys who died after eating meat from a hog that had eaten seed treated with ethylmercuric chloride developed bronchopneumonia and edematous alveolitis, and required artificial ventilation (Cinca et al. 1979). Bronchopneumonia was also identified as the cause of death in four adults and one infant who died as the result of methylmercury poisoning in Iraq during 1972 (Al-Saleem and the Clinical Committee on Mercury Poisoning 1976). It is unclear whether these respiratory effects were the result of direct effects on the respiratory system or were secondary to other effects.

The only information located regarding respiratory effects in animals after oral exposure to organic mercury comes from a study in which rats were exposed to methylmercuric chloride in the diet for 2 years (Verschuuren et al. 1976). This study showed no treatment-related histopathological lesions in the lungs of exposed rats at 0.1 mg Hg/kg/day.

Cardiovascular Effects

Inorganic Mercury. Cardiovascular toxicity has been observed following ingestion of mercuric chloride and mercurous chloride in humans. The majority of the information regarding cardiovascular effects comes from reports of children who were treated with mercurous chloride tablets for worms or mercurous chloride-containing powders for teething discomfort (Warkany and Hubbard 1953). These authors described multiple cases in which tachycardia and elevated blood pressure were observed in the affected children. The only information located regarding cardiovascular effects in humans after ingestion of mercuric chloride comes from a case study of a 22-year-old who attempted suicide by ingesting approximately 20 mg Hg/kg as mercuric chloride (Chugh et al. 1978). An electrocardiogram showed no P wave, prolongation of the QRS segment, and a high T wave. The authors suggested that these cardiovascular effects were secondary to severe hyperkalemia.

Exposure of rats to 28 mg Hg/kg/day as mercuric chloride for 180 days in drinking water resulted in an increase in blood pressure, a decrease in cardiac contractility, and no effect on heart rate (Carmignani et al. 1992). The increase in blood pressure was attributed to a vasoconstrictor effect, and the decrease in contractility was attributed to the direct toxic effect of the mercury on the cardiac muscle. Slightly

different results were obtained following 350-day exposure of a different strain of rats to 7 mg Hg/kg/day as mercuric chloride in drinking water (Boscolo et al. 1989; Carmignani et al. 1989). In the chronic study, positive inotropic response, increased blood pressure and cardiac contractility, and decreased baroreceptor reflex sensitivity were observed. The investigators suggested that the mechanism for the cardiac effects in the chronic study involved the release of norepinephrine from presynaptic nerve terminals. Evidence of this release was provided by the fact that mercury administration reduced the cardiovascular response to bretylium (which blocks presynaptic release of the neurotransmitter norepinephrine) but not tyramine (which releases neurotransmitter from nerve terminals).

Organic Mercury. Electrocardiography in four family members who ate meat from a hog that had consumed seed treated with ethylmercuric chloride had abnormal heart rhythms (ST segment depression and T wave inversion) (Cinca et al. 1979). Death of the two children in the family was attributed to cardiac arrest, and autopsy of these boys showed myocarditis. Cardiovascular abnormalities were also observed in severe cases of poisoning in the Iraqi epidemic of 1956, when widespread poisoning resulted from eating flour made from seed grains treated with ethylmercury *p*-toluene sulfonanilide (Jalili and Abbasi 1961). These abnormalities included irregular pulse, occasionally with bradycardia, and electrocardiograms showing ventricular ectopic beats, prolongation of the Q-T interval, depression of the S-T segment, and T inversion.

A decrease in heart rate was observed in male rats given 2 gavage doses of 12 mg Hg/kg as methylmercuric chloride (Arito and Takahashi 1991). An increase in systolic blood pressure was observed in male rats after daily oral gavage doses of 0.4 mg Hg/kg/day as methylmercuric chloride for 3–4 weeks (Wakita 1987). This effect began approximately 60 days after initiation of exposure and persisted for at least 9 months. No treatment-related histopathological changes were observed in the hearts of rats exposed to 0.1 mg Hg/kg/day as methylmercuric chloride in the diet for up to 2 years (Verschuuren et al. 1976).

Gastrointestinal Effects

Inorganic Mercury. Ingestion of metallic mercury results in negligible absorption and little effect on the gastrointestinal tract. The two case histories identified are unusual in that the dose levels could be reasonably well quantified. The first case history reported ingestion of 15 mL (204 g) of metallic mercury by a 17-year-old male storekeeper who swallowed mercury from the pendulum of a clock (apparently out of curiosity rather than as a suicide attempt). On admission, and 24 hours later, he was symptom free, and

physical examination was normal. The patient complained of no gastrointestinal symptoms, and was treated with a mild laxative and bedrest (Wright et al. 1980).

In a second and massive incidence of ingestion, a 42-year-old man who had spent much of his life (since the age of 13) repairing instruments that contained mercury, intentionally ingested an estimated 220 mL (about 3,000 g) while repairing a sphygmomanometer (Lin and Lim 1993). Upon admission, the patient presented with significantly elevated mercury blood levels (103 µg/L, normal <10 µg/L) and urine levels (73µg/L, normal <20µg/L). In the previous 2 years he had developed mild hand tremors, forgetfulness, irritability, and fatigue. Only a mild abdominal discomfort and no hepatic complications were observed at admission. The neurological symptoms were attributed to the long occupational exposure to mercury and not to the recent acute exposure. The initial radiological examination showed a conglomeration of mercury globules in the fundus of the stomach and ascending colon, with fine metallic spots dispersed throughout the small intestine. Abdominal ultrasonography was normal. He was treated with immediate gastric lavage and cathartics. He also received D-penicillamine 1 g/day orally for 7 days. Seven days later, there were only spots of metallic mercury in the ascending colon. By 2 weeks, most of the mercury had been excreted in the feces and was measured at a total volume of 220 mL (this number was used to estimate the amount initially ingested). The authors reported that systemic absorption appeared low, based on the return to low levels of mercury in the urine and blood over the 10 days of monitoring following the exposure. A subsequent evaluation 6 months later revealed no further gastrointestinal involvement.

Ingestion of mercuric chloride is highly irritating to the tissues of the gastrointestinal tract. Blisters and ulcers on the lips and tongue and vomiting were observed in a 19-month-old boy who ingested an unknown amount of mercuric chloride powder (Samuels et al. 1982). Similarly ingestion of a lethal dose of mercuric chloride by a 35-year-old man resulted in vomiting, diarrhea, colicky abdominal pain, oropharyngeal pain, and ulceration and hemorrhages throughout the length of the gastrointestinal tract (Murphy et al. 1979). Ingestion by a woman of 30 mg Hg/kg as mercuric chloride resulted in severe abdominal pain, diarrhea, nausea, and vomiting (Afonso and deAlvarez 1960). Another report of an attempted suicide by a 22-year-old reported ulceration of the mouth and throat and bloody vomit after ingestion of approximately 20 mg Hg/kg (Chugh et al. 1978). Because of vomiting, the actual effective dose was unknown.

Reports of ingestion of mercurous chloride have not found similar caustic effects; however, a 50-year-old woman who ingested an unspecified amount of mercurous chloride in a Chinese medicine experienced nausea and vomiting (Kang-Yum and Oransky 1992). Several children who were treated with mercurous

chloride for constipation, worms, or teething discomfort had swollen red gums, excessive salivation, anorexia, diarrhea, and/or abdominal pain (Warkany and Hubbard 1953).

Inflammation and necrosis of the glandular stomach were observed in mice that were given oral doses of 59 mg Hg/kg as mercuric chloride 5 days a week for 2 weeks (NTP 1993). In a 2-year gavage study, an increased incidence of forestomach hyperplasia was observed in male rats exposed to 1.9 or 3.7 mg Hg/kg/day as mercuric chloride compared to the control group.

Organic Mercury. Case studies of individuals who were orally exposed to alkyl mercury compounds (unspecified form) reported diarrhea, tenesmus, irritation, and blisters in the upper gastrointestinal tract (Lundgren and Swensson 1949). Ingestion of meat from a hog that was fed seed treated with ethylmercuric chloride resulted in vomiting in two of the family members (Cinca et al. 1979). No quantitative data were available. Ingestion of flour made from seed grains that had been treated with ethylmercury *p*-toluene sulfonanilide also commonly resulted in abdominal pain and vomiting, diarrhea, or constipation (Jalili and Abbasi 1961).

Pfab et al. (1996) reported a case of a 44-year-old man who ingested 83 mg/kg Thiomersal in a suicide attempt (5 g/60 kg). Thiomersal is a widely used alkyl-aryl-organomercurial bactericide. The man developed gastritis, renal tubular failure, dermatitis, gingivitis, delirium, coma, polyneuropathy, and respiratory failure. Treatment was symptomatic plus gastric lavage and the oral chelation with dimercaptopropane sulfonate and dimercaptosuccinic acid. The patient's condition was at its worst on day 17; however, the patient recovered completely (after several months). Maximum mercury concentrations were: blood, 14 mg/L; serum, 1.7 mg/L; urine, 10.7 mg/L; and cerebrospinal fluid, 0.025 mg/L. Mercury concentration in blood declined with two velocities: first with a half-time of 2.2 days, then with a half-time of 40.5 days. The decline of mercury concentration in blood, urinary mercury excretion, and renal mercury clearance were not substantially influenced by chelation therapy.

Exposure of rats to phenylmercuric acetate for 2 years resulted in necrosis and ulceration of the cecum at doses as low as 4.2 mg Hg/kg/day in drinking water; no effect was observed at 1.7 mg Hg/kg/day in the feed (Fitzhugh et al. 1950; Solecki et al. 1991). Mice showed ulceration of the glandular stomach after 2 years of dietary exposure to methylmercuric chloride at 0.69 mg Hg/kg/day (Mitsumori et al. 1990). In contrast, no treatment-related histopathological lesions in the stomach or jejunum were observed in rats exposed via the diet to 0.1 mg Hg/kg/day as methylmercuric chloride (Verschuuren et al. 1976).

Hematological Effects

Inorganic Mercury. Information is limited regarding hematological effects in humans after ingestion of inorganic mercury. The only information located regarding hematological effects in humans was the report of anemia that developed (probably secondary to massive gastrointestinal hemorrhaging) in a 35-year-old man who ingested a lethal amount of mercuric chloride (Murphy et al. 1979). Bone marrow activity in the afflicted man was normal, but thrombocytopenia was also observed.

Groups of 10 female Sprague-Dawley rats were administered a single gavage dose of mercuric chloride at 7.4 or 9.2 mg Hg/kg in water and necropsied at 14 days postexposure. Blood samples were analyzed for hemoglobin concentration, hematocrit value, erythrocyte counts, total and differential leukocyte counts, and platelet counts. Serum was analyzed for sodium, potassium, inorganic phosphorus, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), total protein, calcium, cholesterol, glucose, uric acid, and lactate dehydrogenase (LDH). There were no effects on body weight, and weights of other organs were not affected. Significant decreases in hemoglobin, erythrocytes, and hematocrit were also reported. There was a significant decrease in serum protein and calcium in the low-dose mercury group only. Mercury was found mainly in the kidneys (12.6 and 18.9 ppm at the low and high dose, respectively), but trace amounts were also detected in the liver, brain, and serum (Lecavalier et al. 1994).

No other studies were located regarding hematological effects in animals after oral exposure to inorganic mercury.

Organic Mercury. No studies were located regarding hematological effects in humans after oral exposure to organic mercury.

Rats that received phenylmercuric acetate in their drinking water for 2 years showed decreases in hemoglobin, hematocrit, and red blood cell counts at a dose of 4.2 mg Hg/kg/day (Solecki et al. 1991). The anemia observed in this study may have been secondary to blood loss associated with the ulcerative lesions in the large intestine seen at this dose (see Gastrointestinal Effects above). No treatment-related changes were observed in hematological parameters measured in rats (strain not specified) exposed via the diet for 2 years to 0.1 mg Hg/kg/day as methylmercuric chloride (Verschuuren et al. 1976).

Musculoskeletal Effects

Inorganic Mercury. A single case report was identified that found evidence of skeletal muscle degeneration (markedly elevated serum aldolase, LDH, and creatinine phosphokinase; and the presence of pigment granular casts and myoglobin in the urine) in a 22-year-old man who ingested 2 g of mercuric chloride in an attempt to commit suicide (Chugh et al. 1978). Several children who were treated with mercurous chloride for constipation, worms, or teething discomfort experienced muscle twitching or cramping in the legs and/or arms (Warkany and Hubbard 1953). The muscular effects were probably secondary to changes in electrolyte balance (i.e., potassium imbalance due to fluid loss or renal wasting).

No studies were located regarding musculoskeletal effects in animals after oral exposure to inorganic mercury.

Organic Mercury. Autopsy of one of two boys who died after eating meat from a hog that had consumed seed treated with ethylmercuric chloride showed muscle wasting (Cinca et al. 1979). This effect was probably secondary to neurotoxicity. Electromyography in the two surviving members of the family showed no abnormalities. Musculoskeletal effects observed in Iraqis poisoned by consuming flour made from grains treated with ethylmercury *p*-toluene sulfonanilide included deep skeletal pain and muscle twitching or fasciculations (Jalili and Abbasi 1961). It is likely that these effects were secondary to effects on the nervous system.

No treatment-related histopathological changes in skeletal muscle were observed in rats exposed via the diet for 2 years to 0.1 mg Hg/kg/day as methylmercuric chloride (Verschuuren et al. 1976).

Hepatic Effects

Inorganic Mercury. Limited information was located regarding hepatic effects in humans who ingested inorganic mercury. A 35-year-old man who ingested a lethal dose of mercuric chloride became jaundiced and exhibited elevated AST, alkaline phosphatase, LDH, and bilirubin (Murphy et al. 1979). An autopsy revealed an enlarged and softened liver. Hepatic enlargement was also observed in a 19-month-old boy who ingested an unknown amount of powdered mercuric chloride (Samuels et al. 1982).

Limited information was located regarding the hepatic effects of inorganic mercury in animals.

Groups of 10 female Sprague-Dawley rats were administered a single gavage dose of mercuric chloride at 7.4 or 9.2 mg Hg/kg in water and necropsied at 14 days postexposure. There were no effects on body or relative liver weights from mercuric chloride exposure. LDH activity was significantly decreased in animals exposed to $HgCl_2$ at both dose levels. Mercury was found mainly in the kidneys (12.6 and 18.9 ppm at the low and high dose, respectively), but trace amounts were also detected in the liver, brain, and serum (Lecavalier et al. 1994).

Two intermediate-duration studies in rats showed biochemical changes following ingestion of mercuric chloride (Jonker et al. 1993b; Rana and Boora 1992). Increases in hepatic lipid peroxidation and decreases in glutathione peroxidase were observed in rats orally exposed to an unspecified dose of mercuric chloride for 30 days (Rana and Boora 1992). In a 4-week range-finding study, groups of 5 rats per sex (10 per sex for controls) received diets containing mercuric chloride at 5, 10, or 20 mg Hg/kg/day in males and 5.5, 11.1, and 22.2 mg Hg/kg/day in females. Absolute liver weight decreased starting at the mid-dose group in males and in the high-dose group in females (Jonker et al. 1993b). The liver weight significantly increased in mice given 2.9 mg Hg/kg/day as mercuric chloride in the drinking water for 7 weeks; however, no histopathological changes were observed (Dieter et al. 1983). Male rats administered mercuric chloride by gavage for 2 years showed a slight increase in acute hepatic necrosis (11 of 50 versus 4 of 50 in controls); however, it is unclear whether this increase was statistically significant (NTP 1993).

Organic Mercury. Extremely limited information was also obtained regarding the hepatic effects of organic mercury exposure. An autopsy of four adults and four infants who died as the result of methyl-mercury poisoning in Iraq in 1972 reported fatty changes in the liver occurred in most cases (Al-Saleem and the Clinical Committee on Mercury Poisoning 1976). It is unclear whether these changes were the direct result of methylmercury on the liver or whether they were due to other causes. The prevalence of liver disease in a population from the Minamata area was not significantly increased when compared to unexposed controls (Futatsuka et al. 1992).

No treatment-related changes were observed in hepatic parameters measured in rats exposed via the diet to 0.1 mg Hg/kg/day as methylmercuric chloride (Verschuuren et al. 1976).

Renal Effects

Inorganic Mercury. The kidney appears to be the critical organ of toxicity for the ingestion of mercuric salts. Renal effects in humans have been observed following acute oral exposure to inorganic mercury. Acute renal failure has been observed in a number of case studies of mercuric chloride ingestion (Afonso and deAlvarez 1960; Murphy et al. 1979; Samuels et al. 1982). An autopsy of a 35-year-old man who ingested a lethal dose of mercuric chloride and exhibited acute renal failure showed pale and swollen kidneys (Murphy et al. 1979). A case study reported acute renal failure characterized by oliguria, proteinuria, hematuria, and granular casts in a woman who ingested 30 mg Hg/kg as mercuric chloride (Afonso and deAlvarez 1960). Another case study reported a dramatic increase in urinary protein secretion by a patient who ingested a single dose of 15.8 mg Hg/kg as mercuric chloride (assuming a body weight of 70 kg) (Pesce et al. 1977). The authors of the report surmised that the increased excretion of both albumin and β_2-microglobulin was indicative of mercury-induced tubular and glomerular pathology. Acute renal failure that persisted for 10 days was also observed in a 19-month-old child who ingested an unknown amount of powdered mercuric chloride (Samuels et al. 1982). Decreased urine was observed in a 22-year-old who attempted suicide by ingesting approximately 20 mg Hg/kg (Chugh et al. 1978). Myoglobin and pigmented casts were observed in the urine, and the authors suggested that these observations, in combination with a highly elevated level of serum creatine phosphokinase, indicated that rhabdomyolysis may have contributed to the renal failure.

Ingestion of mercurous chloride has also resulted in renal toxicity in humans. Decreased urinary output and edema were observed in a 60-year-old woman who ingested an unspecified amount of mercurous chloride in a Chinese medicine (Kang-Yum and Oransky 1992). Renal failure was a contributing factor in the death of this woman. Renal failure also developed in two female patients who chronically ingested a mercurous chloride-containing laxative (Davis et al. 1974).

Renal toxicity has been observed in Fischer 344 rats and B6C3F$_1$ mice following acute-, intermediate-, and chronic-duration exposures to mercuric chloride (Dieter et al. 1992; NTP 1993). In the 14-day study, male and female rats were exposed by gavage to 0.93–14.8 mg Hg/kg/day as mercuric chloride for 5 days a week. There was a significant increase in the absolute and relative kidney weights of males beginning at the 1.9-mg/kg/day dose level. An increased incidence of tubular necrosis was observed in rats exposed to at least 3.7 mg/kg/day; severity progressed with increasing dose levels. Increases in urinary levels of alkaline phosphatase, AST, and LDH were also observed at 3.7 mg Hg/kg/day; at 7.4 mg Hg/kg/day,

increased urinary γ-glutamyltransferase activity was also observed. Mice given a single gavage dose of 10 mg/Hg/kg as mercuric chloride showed minor renal tubular damage and rapid regeneration of the tubular epithelium (Nielsen et al. 1991). At 20 mg Hg/kg/day, the mice showed necrosis of the proximal tubules. Mice given gavage doses of mercuric chloride 5 days a week for 2 weeks showed an increase in absolute and relative kidney weights at 3.7 mg Hg/kg/day and acute renal necrosis at 59 mg Hg/kg/day (NTP 1993).

Groups of 10 female Sprague-Dawley rats were administered a single gavage dose of mercuric chloride at 7.4 or 9.2 mg Hg/kg in water and necropsied at 14 days postexposure. No effects on body weight or weights of other organs were found. Mercury was found mainly in the kidneys (12.6 and 18.9 ppm at the low and high doses, respectively), but trace amounts were also detected in the liver, brain, and serum. Mild-to-moderate morphological changes, consisting of protein casts, cellular casts, and interstitial sclerosis, were noted in the kidneys of $HgCl_2$-treated animals in both groups (Lecavalier et al. 1994).

In a 4-week range-finding study, groups of 5 rats per sex (10 per sex for controls) received diets containing mercuric chloride at 5, 10, or 20 mg Hg/kg/day for males and 5.5, 11.1, and 22.2 mg Hg/kg/day for females. Nephrosis and proteinaceous casts in the kidneys were observed in all groups (males and females) fed mercuric chloride. An increased number of epithelial cells in the urine was observed in males exposed at the low dose; however, this effect was not observed at higher dose levels and the authors noted that the effect could not be ascribed to treatment. The minimum-nephrotoxic-effect level (MNEL) and the no-nephrotoxic-effect level (NNEL) for mercuric chloride in feed were determined to be 8 mg Hg/kg/day in males and 8.9 mg Hg/kg/day in females and 1 mg Hg/kg/day in males and 1.1 mg Hg/kg/day in females, respectively (Jonker et al. 1993b). In a follow-up 4-week study, 10-week-old Wistar rats were fed mercuric chloride at the MNEL and NNEL. In males, the MNEL resulted in the presence of ketones in urine and an increase in the relative weight of kidneys. Effects observed in females in the MNEL group included decreased density of urine and increased absolute and relative kidney weights. Increased absolute and relative kidney weights were also seen in females at the NNEL. A few histopathological changes were found in the basophilic tubules in the outer cortex of the kidneys in 5 of 5 males and 1 of 5 females exposed to the MNEL (Jonker et al. 1993b).

Similarly, male mice receiving mercuric chloride in drinking water for 7 weeks showed slight degeneration of the tubular epithelial cells (nuclear swelling) at 2.9 mg Hg/kg/day and minimal renal nephropathy

(dilated tubules with either flattened eosinophilic epithelial cells or large cytomegalic cells with foamy cytoplasm) at 14.3 mg Hg/kg/day (Dieter et al. 1983).

In a 6-month exposure to 0.23–3.7 mg Hg/kg/day, a significant increase in severity of nephropathy (i.e., dilated tubules with hyaline casts, foci of tubular regeneration, and thickened tubular basement membrane) was observed in Fischer 344 rats exposed to 0.93 mg/kg/day of mercuric chloride compared to the controls (NTP 1993). The absolute and relative kidney weights were increased in males at 0.46 mg/kg/day. In $B6C3F_1$ mice, the incidence and severity of cytoplasmic vacuolation of renal tubule epithelium increased in males exposed to at least 3.7 mg Hg/kg/day as mercuric chloride for 6 months (NTP 1993). Administration of large doses of mercuric chloride (28 mg Hg/kg/day) in the drinking water for 6 months also resulted in focal degeneration of the tubular cells with decreased acid phosphatase in the lysosomes (indicative of the release of the lysosomal contents) (Carmignani et al. 1992). Notably, at this dose, renal glomerular changes were also evident. The glomeruli showed hypercellularity, and there was deposition of amorphous material in the mesangium; thickening of the basement membrane with IgM present was also observed.

When a strain of mice (SJL/N) sensitive to the immunotoxic effects of mercury was given mercuric chloride in the drinking water at 0.56 mg Hg/kg/day for 10 weeks, slight glomerular cell hyperplasia with granular IgG deposits in the renal mesangium and glomerular blood vessels were observed (Hultman and Enestrom 1992). No tubular necrosis was observed.

In a 2-year study, male rats gavaged with 1.9 or 3.7 mg Hg/kg/day as mercuric chloride 5 days a week exhibited an incidence of marked nephropathy (described as thickening of glomerular and tubular basement membranes and degeneration and atrophy of tubular epithelium) that was significantly greater in severity than in the control group (NTP 1993). In addition, the incidence of renal tubule hyperplasia was increased in the high-dose male rats. In the same study, the incidence and severity of nephropathy were significantly greater in male and female mice gavaged with 3.7 and 7.4 mg Hg/kg/day as mercuric chloride 5 days a week than in the controls. Administration of 7 mg Hg/kg/day as mercuric chloride to rats in the drinking water resulted in hydropic degeneration and desquamation of tubule cells (Carmignani et al. 1989). Electron microscopy showed lysosomal alterations in the proximal tubules and thickening of the basal membrane of the glomeruli.

Organic Mercury. Data on renal toxicity associated with ingestion of methylmercury in humans come from several case studies. An outbreak of ethylmercury fungicide-induced poisoning was reported by Jalili and Abbasi (1961). Affected individuals exhibited polyuria, polydypsia, and albuminuria. Two boys who ingested meat from a hog that had consumed seed treated with ethylmercuric chloride also had increased blood urea, urinary protein, and urinary sediment (Cinca et al. 1979); an autopsy revealed nephritis. A 13-month-old boy who ate porridge made from flour treated with an alkyl mercury compound (specific mercury compound not reported) experienced albuminuria, red and white cells, and casts in the urine (Engleson and Herner 1952). In autopsies carried out to evaluate the cause of death in 4 adults and 4 infants from the Iraqi epidemic of 1972, one case exhibited tubular degeneration in the kidneys (whether an adult or child was not specified) (Al-Saleem and the Clinical Committee on Mercury Poisoning 1976).

Organic mercury-induced nephrotoxicity has been demonstrated in rodents following acute-, intermediate-, and chronic-duration exposure. The usefulness of results from subchronic studies may be limited because the pathological changes observed were often not distinguished as primary or secondary effects (i.e., pathological changes secondary to induced shock). Nonetheless, they provide some useful indication of potential effects.

Administration of methylmercuric chloride to mice in a single gavage dose of 16 mg Hg/kg resulted in decreased renal function (decreased phenolsulfonphthalein excretion), increased plasma creatinine, and swelling of tubular epithelial cells, with exfoliation of the cells into the tubular lumen (Yasutake et al. 1991b). Although no effects were observed after a single gavage dose of 8 mg Hg/kg (Yasutake et al. 1991b), 5 daily gavage doses of 8 mg Hg/kg/day as methylmercuric chloride in rats resulted in vacuolization and tubular dilation in the proximal tubules with ongoing regeneration (Magos et al. 1985). Similar effects were observed after 5 doses of 8 mg Hg/kg/day as ethylmercuric chloride (Magos et al. 1985).

In an intermediate-duration study, histopathological changes were observed in the kidneys of female rats exposed to 0.86, 1.68, or 3.36 mg Hg/kg/day as methylmercury dicyanidiamide by gavage 5 days a week for 3–12 weeks (Magos and Butler 1972). The low-dose group exhibited large foci of basophilic tubular epithelial cells, desquamation, fibrosis, and inflammation in the renal cortex; however, no control group was used in the study (Magos and Butler 1972). A 12-week diet containing 0.08 mg Hg/kg/day as methyl-mercury caused ultrastructural changes (cytoplasmic masses containing ribosomes and bundles of smooth endoplasmic reticulum) in kidney proximal tubule cells of female rats, despite the normal appearance of the

glomeruli at the light microscopic level (Fowler 1972). The author concluded that these changes could be a result of metabolism to inorganic mercury and may account for proteinuria observed in exposed humans. Administration of methylmercuric chloride in the diet of mice for 26 weeks at a dose of 0.6 mg Hg/kg/day resulted in degeneration of the proximal tubules characterized by nuclear swelling and vacuolation of the cytoplasm (Hirano et al. 1986).

Rats fed daily doses of phenylmercuric acetate for up to 2 years exhibited slight-to-moderate renal damage (e.g., tubular dilatation, atrophy, granularity, fibrosis) (Fitzhugh et al. 1950). These effects were evident at doses (beginning at 0.02 mg Hg/kg/day) that were two orders of magnitude lower than those required to induce detectable effects in the mercuric acetate-treated rats (Fitzhugh et al. 1950). A NOAEL of 0.005 mg Hg/kg/day was determined. The authors concluded that some of the histological changes were present to some degree in the control animals, suggesting that low levels of mercury apparently hasten the normal degenerative processes of the kidneys (see Inorganic Mercury above). Problems in this study limit its usefulness in determining effect levels. Increased severity of renal nephrosis was also observed in another study in which rats were given 0.4 mg Hg/kg/day as phenylmercuric acetate in the drinking water for 2 years (Solecki et al. 1991). Lower doses in this study were not tested. Mice given methylmercuric chloride in the diet at a dose of 0.13 mg Hg/kg/day showed epithelial cell degeneration and interstitial fibrosis, with ongoing regeneration of the tubules present (Mitsumori et al. 1990); no effect was observed at 0.03 mg Hg/kg/day. Similar effects were seen in mice given methylmercuric chloride in the diet for 2 years at a dose of 0.11 mg Hg/kg/day (Hirano et al. 1986). Rats given methylmercuric chloride in the diet for 2 years at a dose of 0.1 mg Hg/kg/day had increased kidney weights and decreased enzymes (alkaline phosphatase, ATPase, NADH- and NADPH-oxidoreductase, and AMPase) in the proximal convoluted tubules (Verschuuren et al. 1976). However, histopathological examination revealed no treatment-related lesions.

A 2-year study conducted with mercuric acetate in the feed of rats showed an increased severity of renal damage at doses of mercury as low as 2 mg Hg/kg/day (Fitzhugh et al. 1950). Rats initially showed hypertrophy and dilation of the proximal convoluted tubules. At this stage, eosinophilia, rounding, and granular degeneration of the epithelial cells were observed. Occasionally basophilic cytoplasm and sloughing of the cells were observed. As the lesion progressed, tubular dilation increased, and hyaline casts appeared within the tubules; fibrosis and inflammation were observed. Finally, tubules appeared as cysts, and extensive fibrosis and glomerular changes were observed. However, this study was limited because

group sizes were small, survival data were not reported, and a considerable number of early deaths from pneumonia were noted.

Endocrine Effects

Inorganic Mercury. No studies were located regarding endocrine effects in humans after oral exposure to inorganic mercury.

Several studies have reported effects on the thyroid after acute- or intermediate-duration exposure to mercuric chloride. An increase in iodine release from the thyroid was observed following gavage administration of 7.4 mg Hg/kg/day as mercuric chloride to rats for 6 days (Goldman and Blackburn 1979). Serum levels of thyroid hormones (triiodothyronine and/or thyroxine) in mice decreased after administration of 6 mg Hg/kg/day as mercuric chloride or mercuric sulfide for 10 days by gavage (Sin et al. 1990). Similar effects were observed after 4 weeks of dosing with mercuric sulfide (Sin and The 1992). Administration by gavage of 5.3 mg Hg/kg/day as mercuric chloride to rats for 40 days resulted in increased thyroid weight, thyroidal iodine uptake, and protein-bound iodine in the serum (Goldman and Blackburn 1979). Decreased triiodothyronine and monoiodotyrosine were also observed. Dietary exposure of rats to 2.2 mg Hg/kg/day as mercuric chloride for 3 months resulted in decreased thyroidal iodine uptake, release, and turnover (Goldman and Blackburn 1979). Adrenocortical function was evaluated in male rats exposed to 0, 9, 18, or 36 mg Hg/kg/day as mercuric chloride in drinking water for 60–180 days (Agrawal and Chansouria 1989). A significant increase in adrenal and plasma corticosterone levels in all dose groups was observed after 120 days of exposure. After 180 days of exposure, corticosterone levels had returned to control values. The relative adrenal gland weight was significantly increased for all exposed groups compared to control values.

In a 4-week range-finding study, groups of 5 rats per sex (10 per sex for controls) received diets containing mercuric chloride at 5, 10, or 20 mg Hg/kg/day in males and 5.5, 11.1, and 22.2 mg Hg/kg/day in females. The high dose resulted in an increased relative adrenal weight in males and a decreased absolute adrenal weight in females (Jonker et al. 1993b)

Organic Mercury. No studies were located regarding endocrine effects in humans or animals after oral exposure to organic mercury.

Dermal Effects

Inorganic Mercury. Limited information was located regarding dermal effects of inorganic mercury in humans. Several children who were treated with medications containing mercurous chloride for constipation, worms, or teething discomfort exhibited flushing of the palms of the hands and soles of the feet (Warkany and Hubbard 1953). The flushing was frequently accompanied by itching, swelling, and desquamation of these areas. Morbilliform rashes, conjunctivitis, and excessive perspiration were also frequently observed in the affected children. Patch tests conducted in several children revealed that the rashes were not allergic reactions to the mercury. Kang-Yum and Oransky (1992) reported hives in a woman who ingested a Chinese medicine containing an unspecified amount of mercurous chloride, which suggests an allergic response to the medicine.

No studies were located regarding dermal effects in animals after oral exposure to inorganic mercury.

Organic Mercury. Only a few studies were identified regarding dermal effects of organic mercury, however, the case history concerning dimethylmercury exposure is a very important alert to the hazards of this organomercurial.

Blayney et al. (1997) originally reported the fatal case of a dimethylmercury exposure after a dermal exposure to an extremely small amount of material. The case history was subsequently detailed by Nierenberg et al. (1998). The exposure occurred to a 48-year-old female chemistry professor who was admitted to the hospital 5 months (154 days) after, as best as can be determined, she inadvertently spilled several drops (estimated at 0.4–0.5 mL; about 1,500 mg) of dimethylmercury from the tip of her pipette onto the back of her disposable latex gloves. The spill was cleaned and the gloves disposed of. Hair analysis on a long strand of hair revealed that after a brief lag time, mercury content rose rapidly to almost 1,100 ppm (normal level, <0.26 ppm; toxic level, >50 ppm), and then slowly declined with a half-life of 74.6 days. These results support the occurrence of one or several episodes of exposure, and are consistent with laboratory notebook accounts of a single accidental exposure. Testing of family members, laboratory coworkers, and laboratory surfaces failed to reveal any unsuspected mercury spills or other cases of toxic blood or urinary mercury levels. Permeation tests subsequently performed on disposable latex gloves similar to those the patient had worn at the time of the lone exposure revealed that dimethylmercury penetrates such gloves rapidly and completely, with penetration occurring in 15 seconds or less and perhaps instantly. Polyvinyl chloride gloves were equally permeable to dimethylmercury. Five days prior to

admission, the patient developed a progressive deterioration in balance, gait, and speech. During the previous 2 months, she had experienced brief episodes (spaced weeks apart) of nausea, diarrhea, and abdominal discomfort; and had lost 6.8 kg (15 lb). Medical examination revealed moderate upper-extremity dysmetria, dystaxic handwriting, a widely based gait, and "mild scanning speech." Routine laboratory test results were normal. Computed tomography (CT) and magnetic resonance imaging (MRI) of the head were normal except for the incidental finding of a probable meningioma, 1 cm in diameter. The cerebrospinal fluid was clear, with a protein concentration of 42 mg/dL and no cells. A preliminary laboratory report indicated that the whole-blood mercury concentration was more than 1,000 µg/L (normal range, 1–8 µg/L; toxic level, >200 µg/L). Chelation therapy with oral succimer (10 mg/kg orally every 8 hours) was begun on day 168 after exposure. Whole blood concentrations rose to 4,000 µg/L after one day of chelation, and urinary mercury levels were 234 µg/L (normal range, 1–5 µg/L; toxic level, >50 µg/L). Despite the initial success of chelation therapy, administration of vitamin E, and a blood exchange transfusion, at 176 days postexposure, the patient became comatose. Further aggressive general support and chelation therapy failed, life support ws removed (following the patient's advance directive), and the patient died 298 days post exposure. Autopsy results revealed diffusely thin cortex of the cerebral hemispheres (to 3 mm), and extensive gliosis of the visual cortex around the calcarine fissure and the superior surface of the superior temporal gyri. The cerebellum showed diffuse atrophy of both vermal and hemispheric folia. Microscope evaluation revealed extensive neuronal loss and gliosis bilaterally within the primary visual and auditory cortices, with milder loss of neurons and gliosis in the motor and sensory cortices. There was widespread loss of cerebellar granular-cell neurons, Purkinje cells, and basket-cell neurons, with evidence of loss of parallel fibers in the molecular layer. Bergmann's gliosis was well developed and widespread.

In the only other organic mercury studies identified for dermal exposures, a study of a large group of people who consumed methylmercury-contaminated bread over a 1- to 3-month period showed a dose-related history of rashes (Al-Mufti et al. 1976). These may also have been allergic responses. A 13-month-old child who ingested porridge made from flour that had been treated with an alkyl mercury compound (specific mercury compound not reported) developed a measles-like rash, fever, and facial flushing (Engleson and Herner 1952). Also, Iraqis who consumed flour made from grain treated with ethylmercury *p*-toluene sulfonanilide exhibited skin lesions consisting of pruritus on the palms, soles, and genitalia (Jalili and Abbasi 1961). In severe cases, exfoliative dermatitis of the hands and feet was also observed.

The only information located regarding dermal effects in animals after oral exposure to organic mercury comes from a study in which rats were exposed to methylmercuric chloride in the diet for 2 years (Verschuuren et al. 1976). No treatment-related lesions were observed upon histopathological examination of the skin of rats exposed to 0.1 mg Hg/kg/day.

Ocular Effects

Inorganic Mercury. No information was located regarding ocular effects in humans from ingestion of inorganic mercury.

No studies were located regarding ocular effects in animals after oral exposure to inorganic mercury.

Organic Mercury. No information was located regarding ocular effects in humans from ingestion of organic mercury. While visual effects result from methylmercury exposure, they are cortical in origin (see neurotoxicity below).

The only report of ocular effects in animals after oral exposure to organic mercury comes from a study in which rats were exposed to methylmercuric chloride via the diet for 2 years (Verschuuren et al. 1976). No treatment-related lesions were observed upon histopathological examination of the eyes of rats exposed to 0.1 mg Hg/kg/day. As in humans, the visual effects resulting from methylmercury exposure in primates are considered to be centrally mediated (Rice and Gilbert 1982, 1990).

Body Weight Effects

Inorganic Mercury. No information was located regarding body weight effects in humans from ingestion of inorganic mercury.

A single dose of mercuric chloride administered to female Sprague-Dawley rats (10/group) at 7.4 or 9.2 mg Hg/kg in water resulted in no effects on body weight at 14 days postexposure (Lecavalier et al. 1994). However, a number of animal studies have reported decreases in body weight or body weight gain after ingestion of mercuric chloride (Chang and Hartmann 1972a; Dieter et al. 1992; NTP 1993). After a 4-week exposure to mercuric chloride in the food, male Wistar rats had a 21% body weight decrease at 10 mg Hg/kg/day, and female Wistar rats had a 27% decrease in body weight at 22.2 mg Hg/kg/day. No

significant loss was observed at the next-lower-dose groups of 5 and 11.1 mg Hg/kg/day in males and females, respectively (Jonker et al. 1993b).

Doses of 14.8 mg Hg/kg/day administered to rats 5 days a week for 2 weeks resulted in a 10% decrease in male body weight gain (NTP 1993). Much lower doses produced decreases in body weight gain when administered over longer periods. In rats, decreases in body weight gain of approximately 10% were observed with doses of 0.93 mg Hg/kg as mercuric chloride when administered by gavage 5 days a week for 6 months (NTP 1993). Mice were less sensitive, showing no effect at 7.4 mg Hg/kg/day and a 26% decrease in body weight gain at 14.8 mg Hg/kg/day in the same study (NTP 1993).

Organic Mercury. No information was located regarding body weight effects in humans from ingestion of organic mercury.

A number of animal studies have reported decreases in body weight or body weight gain after ingestion of methyl or phenyl mercury. A 20–25% decrease in body weight gain in male and female rats was observed after 5 gavage doses of 8 mg Hg/kg/day as methylmercuric chloride or ethylmercuric chloride (Magos et al. 1985). In intermediate-duration studies with methylmercury, biologically significant decreases in body weight gain have been observed in rats after exposure to doses as low as 0.8 mg Hg/kg/day for 6 weeks (Chang and Hartmann 1972a) and in mice after exposure to 1 mg Hg/kg/day for 60 days (Berthoud et al. 1976). No effect on female body weight gain was observed after dietary exposure to 0.195 mg Hg/kg/day as methylmercuric chloride for 14 weeks (Lindstrom et al. 1991). A 2-year exposure to 0.4 mg Hg/kg/day as phenylmercuric acetate in the feed resulted in a 10% decrease in body weight gain in rats (Solecki et al. 1991). Gavage administration of methylmercuric chloride to rats for 2 days at 12 mg Hg/kg/day resulted in a persistent decrease in the body temperature of the rats (Arito and Takahashi 1991).

Other Systemic Effects

Inorganic Mercury. Several children who were treated with mercurous chloride contained in powders or tablets for constipation, worms, or teething discomfort exhibited low-grade or intermittent fevers (Warkany and Hubbard 1953).

No studies were located on other systemic effects in animals after oral exposure to inorganic mercury.

Organic Mercury. No studies were located regarding other systemic effects in humans or animals after oral exposure to organic mercury.

2.2.2.3 Immunological and Lymphoreticular Effects

Inorganic Mercury. No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to inorganic mercury.

The immune response to mercury exposure is complex, depending in part on the dose of mercury and the genetic characteristics of the exposed population (see Section 2.4). Administration of 14.8 mg Hg/kg/day as mercuric chloride to $B6C3F_1$ mice 5 days a week for 2 weeks resulted in a decrease in thymus weight (NTP 1993), suggesting immune suppression. However, a 2-week exposure to 0.7 mg Hg/kg/day as mercuric chloride in the drinking water resulted in an increase in the lymphoproliferative response after stimulation with T-cell mitogens in a strain of mice particularly sensitive to the autoimmune effects of mercury (SJL/N) (Hultman and Johansson 1991). In contrast, a similar exposure of a strain of mice (DBA/2) not predisposed to the autoimmune effects of mercury showed no increase in lymphocyte proliferation.

A significant suppression of the lymphoproliferative response to T-cell mitogens, concanavalin A, and phytohemagglutinin was observed in male $B6C3F_1$ mice administered 2.9 or 14.3 mg Hg/kg/day as mercuric chloride in drinking water for 7 weeks (Dieter et al. 1983). A significant decrease in the weight of the thymus and spleen and a decrease in antibody response were also exhibited at 14.3 mg Hg/kg/day. An increase in B-cell-mediated lymphoproliferation was, however, observed at both 2.9 and 14.3 mg Hg/kg/day. No immunological effects were observed at the lowest dose of 0.57 mg Hg/kg/day. When SJL/N mice were administered mercuric chloride in the drinking water for 10 weeks, an increase in circulating antinucleolar antibodies was observed at 0.28 mg Hg/kg/day, and deposition of granular IgG deposits was observed in the renal mesangium and glomerular blood vessels at 0.56 mg Hg/kg/day (Hultman and Enestrom 1992).

In rats, immune deposits have been observed in the basement membrane of the intestines and kidneys following gavage exposure to 2.2 mg Hg/kg/day as mercuric chloride twice weekly for 2 months, although no functional changes were evident in these tissues (Andres 1984). The observation of these deposits suggests that autoimmunity to specific components of these tissues has developed.

The highest NOAEL values and all reliable LOAEL values for immunological and lymphoreticular effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2 for inorganic mercury.

Organic Mercury. No studies were located regarding immunological effects in humans after oral exposure to organic mercury.

In BALB/c mice administered a diet containing 0.5 mg Hg/kg/day as methylmercury for 12 weeks, the thymus weight and cell number decreased by 22 and 50%, respectively, compared to the control group (Ilback 1991). The natural killer cell activity was reduced by 44 and 75% in the spleen and blood, respectively. However, the lymphoproliferative response in the spleen increased at this dose of mercury.

The LOAEL value for immunological and lymphoreticular effects in mice for intermediate-duration oral exposure to organic mercury is recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.4 Neurological Effects

Inorganic Mercury. The oral absorption of metallic mercury is negligible, and even massive doses have not resulted in neurological effects. The wo case histories identified are unusual in that the dose levels could be reasonably well quantified. The first case history reported ingestion of 15 mL (204 g) of metallic mercury by a 17-year-old male storekeeper who swallowed mercury from the pendulum of a clock (apparently out of curiosity rather than as a suicide attempt). On admission, and 24 hours later, he was symptom free, and physical examination was normal. The patient complained of no gastrointestinal symptoms, and was treated with a mild laxative and bed rest. The results of serial daily urine mercury estimates were normal (all less than 15 µg) and did not suggest significant absorption. The radiological investigation illustrated a characteristic pattern of finely divided globules of mercury in the gastrointestinal tract (Wright et al. 1980).

The second and massive incidence of ingestion involved a 42-year-old man who had spent much of his life (since the age of 13) repairing instruments that contained mercury. He intentionally ingested an estimated 220 mL (or about 3,000 g) while repairing a sphygmomanometer (Lin and Lim 1993). Upon admission, the patient presented with significantly elevated mercury blood levels (103 µg/L, normal <10 µg/L) and urine levels (73 µg/L, <20 µg/L). In the previous 2 years he had developed mild hand tremors,

forgetfulness, irritability, and fatigue. The occupational exposures made it difficult to determine any additional neurological effects from the acute exposure. There was no history of peripheral neuropathy, vertigo, insomnia, or muscular weakness. Neuropsychiatric and psychology evaluations indicated poor concentration and a defect in recent memory. EEG results indicated diffuse cortical dysfunction predominantly on the left hemisphere. He was treated with immediate gastric lavage and cathartics. He also received D-penicillamine 1 g/day orally for 7 days. Blood and urine mercury levels obtained 3 days after chelating therapy were 116.9 and 22.9µg/L, respectively. By 2 weeks postexposure, most of the mercury had been excreted in the feces and was measured at a total volume of 220 mL (this number was used to estimate the amount initially ingested). The patient was lost to follow-up, but returned to the hospital 6 months later (for glycemic control), at which time examination revealed a lessening of his hand tremors.

Most case studies of neurotoxicity in humans induced by oral exposure to inorganic mercury salts have reported neurotoxic effects as the result of ingestion of therapeutic agents that contain mercurous chloride (e.g., teething powders, ointments, and laxatives). Several children treated with tablets or powders containing mercurous chloride exhibited irritability, fretfulness, sleeplessness, weakness, photophobia, muscle twitching, hyperactive or hypoactive tendon reflexes, and/or confusion (Warkany and Hubbard 1953). A 4-year-old boy who had been given a Chinese medicine containing mercurous chloride for 3 months developed drooling, dysphagia, irregular arm movements, and impaired gait (Kang-Yum and Oransky 1992). Davis et al. (1974) reported that two women developed dementia and irritability due to chronic ingestion of a tablet laxative that contained 120 mg of USP-grade mercurous chloride (0.72 mg Hg/kg/day, assuming an average body weight of 70 kg). One woman had taken 2 tablets daily for 25 years, and the other woman took 2 tablets daily for 6 years. Both patients died from inorganic mercury poisoning, and at autopsy, low brain weight and volume and a reduced number of nerve cells in the cerebellum were seen. Light microscopic analysis revealed granules of mercury within neuronal cytoplasm. Electron microscopy revealed mercury deposits in some neurons.

In addition, neurotoxicity has been observed after ingestion of lethal doses of mercuric chloride. Blurred vision and diplopia were reported by a 35-year-old man who ingested a lethal dose of mercuric chloride (Murphy et al. 1979). Prior to death, the man experienced repeated seizures. An autopsy revealed abscesses on the occipital lobe and cerebellum.

Acute- and intermediate-duration studies describing neurotoxic effects in animals following exposure to inorganic mercury salts are limited. A study was conducted by Chang and Hartmann (1972b) in which mercuric chloride was administered both by gavage and subcutaneously. Evidence of disruption of the blood-brain barrier (i.e., leakage of dye into the brain tissue) was observed 12 hours after a single dose of 0.74 mg Hg/kg as mercuric chloride in rats (Chang and Hartmann 1972b). These investigators also administered 0.74 mg Hg/kg/day as mercuric chloride to rats for up to 11 weeks. Within 2 weeks, there were coagulative or lucid changes in cerebellar granule cells and fragmentation, vacuolation, and cytoplasmic lesions in the neurons of dorsal root ganglia. Neurological disturbances consisted of severe ataxia and sensory loss, with an accompanying loss in body weight. No conclusions regarding the oral neurotoxicity of mercuric chloride can be drawn from the results of this study because the discussion of the results observed in the study did not clearly differentiate whether the effects were observed as the result of oral or subcutaneous exposure. It is expected that mercuric chloride administered subcutaneously would be much more toxic than that administered orally because of the very poor absorption of inorganic forms of mercury from the gastrointestinal tract.

Dietary exposure of rats to 2.2 mg Hg/kg/day as mercuric chloride for 3 months resulted in inactivity and abnormal gait (Goldman and Blackburn 1979). However, it is unclear whether the effects observed in this study were the direct result of effects on the nervous system, or whether they may have been secondary to other toxic effects. No evidence of neurotoxicity (clinical signs of neurotoxicity and optic and peripheral nerve structure) was seen in mice administered 0.74 or 2.2 mg Hg/kg/day as mercuric chloride in the drinking water for 110 days (Ganser and Kirschner 1985). The investigators increased the dose administered to the low-dosed animals to 7.4–14.8 mg Hg/kg/day for an additional 400 days; however, still no neurotoxic effects were observed. Similarly, no histopathological evidence of brain lesions was observed in rats receiving gavage doses of mercuric chloride as high as 3.7 mg Hg/kg/day 5 days a week for up to 2 years or in mice receiving gavage doses as high as 7.4 mg Hg/kg/day 5 days a week for up to 2 years (NTP 1993).

The highest NOAEL values and all reliable LOAEL values for neurotoxic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2 for inorganic mercury.

Organic Mercury. Most of the information concerning neurotoxicity in humans following oral exposure to organic mercury comes from reports describing the effects of ingesting contaminated fish or fungicide-treated grains (or meat from animals fed such grains). Information about doses at which the effects

occurred is frequently limited because of difficulties in retracing prior exposure and uncertainties in estimating dose levels based on assumed food intake and contamination levels.

Although isolated instances of alkyl mercury poisoning have been reported (Cinca et al. 1979; Engleson and Herner 1952), the epidemic poisonings in Japan and Iraq focused attention on the neurotoxicity of these compounds. The first reported widespread outbreak of neurological disorders associated with the ingestion of methylmercury-contaminated fish occurred in the Minamata area of Japan (Kutsuna 1968). The neurological syndrome was characterized by a long list of symptoms including prickling, tingling sensation in the extremities (paresthesia); impaired peripheral vision, hearing, taste, and smell; slurred speech; unsteadiness of gait and limbs; muscle weakness; irritability; memory loss; depression; and sleeping difficulties (Kutsuna 1968; Tsubaki and Takahashi 1986). Elevated concentrations of methylmercury were observed in the hair and brains of victims (see Section 2.5). Epidemics of similar neurological disorders were reported in Iraq in 1956 and 1960 (Bakir et al. 1973; Jalili and Abbasi 1961) as the result of eating flour made from seed grain treated with ethylmercury *p*-toluene sulfonanilide. Affected individuals had an inability to walk, cerebellar ataxia, speech difficulties, paraplegia, spasticity, abnormal reflexes, restriction of visual fields or blindness, tremors, paresthesia, insomnia, confusion, hallucinations, excitement, and loss of consciousness. In the winter of 1971–1972 in Iraq, more than 6,530 patients required hospitalization and 459 deaths occurred, usually due to central nervous system damage, after the ingestion of contaminated bread prepared from wheat and other cereals treated with a methylmercury fungicide (Bakir et al. 1973).

Al-Mufti et al. (1976) attempted to correlate symptoms of the poisoning incident with an estimate of methylmercury intake based on average levels found in grain and self-reported estimates of the number of loaves ingested. A number of assumptions were made in the estimates, and there were logistical constraints in surveying the widely spread rural population in Iraq. Moreover, only a total mercury intake was derived and compared with the results of a clinical evaluation and a survey for symptoms. Nonetheless, interesting and useful results were reported based on the 2,147 people surveyed. The mean period of exposure for the Iraqi population exposed to contaminated bread was 32 days, with some people consuming the bread for as long as 3 months. A mean of 121 loaves per person was eaten; the maximum was 480 loaves. Based on the mean number of loaves, the total intake of methylmercury was estimated at between 80 mg and 250 mg. However, those who had consumed the most loaves may have ingested up to 1,000 mg of methylmercury over a 3-month period. Of those with symptoms of alkylmercury poisoning at the time of the survey (October 1972–May 1973), 80% had eaten more than 100 loaves. Of the 75 people who had reported eating more than 200 loaves, 53 (71%) presented with some evidence of poisoning. The incidence rate for

poisoning was estimated at 271 per 1,000; this includes a mortality of 59 per 1,000, a severe disability rate of 32 per 1,000, a rate of mild or moderate disability of 41 per 1,000; and a rate for those with only a subjective evidence of poisoning of 138 per 1,000. Based on estimates of total intake, dose-related increases were observed in the incidence and severity of paresthesia, astereognosis (loss of the ability to judge the form of an object by touch), persistent pain in the limbs, persistent headaches, difficulty walking, difficulty using the arms, and changes in speech, sight, and hearing. The most commonly observed symptom was paresthesia, most frequently involving the extremities but also on the trunk and the circumoral region. Difficulty walking and a feeling of weakness were the next most common symptoms. The total estimated intake in total milligrams associated with the four categories (no evidence of poisoning, subjective evidence, mild to moderate evidence, and severe symptoms) is as follows for all ages combined (number of persons in parentheses): 95 mg (n=59), 141 mg (n=131), 160 mg (n=35), 173 mg (n=22). This dose range is small for such dramatically different health states, and does not widen when the data are evaluated by age group. Interestingly, the total intake associated with severity of symptoms decreases on a mg/kg body weight basis with increasing age in contrast with what would be expected if children were more susceptible. For example, intakes (mg/kg over the total exposure period) associated with severe symptoms are as follows for the age groups 5–9 years, 10–14 years, and 15 years and older, respectively: 7.8 mg/kg (n=9), 4 mg/kg (n=7), and 3.6 mg/kg (n=6). Comparable numbers are for the mild/moderate symptoms and the subjective symptoms (shown): 6 mg/kg (n=19), 3.4 mg/kg (n=20), and 2.4 mg/kg (n=92). It is possible that child sensitivity may not be as large a factor when exposures reach the levels experienced in Iraq.

Neurotoxic effects seen in the Minamata (Japan) and Iraqi poisonings have been associated with neuronal degeneration and glial proliferation in the cortical and cerebellar gray matter and basal ganglia (Al-Saleem and the Clinical Committee on Mercury Poisoning 1976), and derangement of basic developmental processes such as neuronal migration (Choi et al. 1978; Matsumoto et al. 1965) and neuronal cell division (Sager et al. 1983). In the brain, Purkinje, basket, and stellate cells were severely affected. Granule cells were variably affected. Sural nerves removed from two women with neurotoxicity associated with the Minamata incident also showed evidence of peripheral nerve degeneration and regeneration (Miyakawa et al. 1976).

Similar effects have been observed in persons ingesting meat contaminated with ethylmercuric chloride (Cinca et al. 1979). Neurotoxic signs observed in two boys who ultimately died as the result of the exposure included gait disturbance, ataxia, dysarthria, dysphagia, aphonia, hyperreactive tendon reflexes,

hypotonia, spasticity, mydriasis, horizontal nystagmus, agitation, and coma. Electroencephalography showed decreased alpha activity and increased slow-wave activity. Autopsy showed nerve cell loss and glial proliferation in the cerebral cortex (calcarine cortex, midbrain, bulbar reticular formation), demyelination, granule cell loss in the cerebellum, and motor neuron loss in the ventral horns of the spinal cord. Neurotoxic signs in the surviving family members were generally similar (ataxia, gait impairment, spasticity, drowsiness, intentional tremor, agitation, hypoesthesia in the limbs, speech difficulties, and visual disturbances); all but the narrowing of the visual fields resolved after termination of exposure.

A New Mexico family, including a pregnant woman, a 20-year-old female, and 2 children (a 13-year-old male and an 8-year-old female) ate meat from a hog inadvertently fed seed grain treated with a fungicide containing methylmercury and experienced severe, delayed neurological effects (Davis et al. 1994). Several months after the exposures, the children developed symptoms of neurological dysfunction. The newborn child of the exposed mother showed signs of central nervous system disorder from birth. Twenty-two years after the 3-month exposure period, the people who were 20 and 13 years old at time of exposure had developed cortical blindness or constricted visual fields, diminished hand proprioception, choreoathetosis, and attention deficits. MRI examination of these two revealed residual brain damage in the calcarine cortices, parietal cortices, and cerebellum. The brain of the person who was exposed at age 8 (who died of aspiration pneumonia with a superimposed *Klebsiella* bronchopneumonia and sepsis at age 29) showed cortical atrophy, neuronal loss, and gliosis, most pronounced in the paracentral and parieto-occipital regions. Regional brain mercury levels correlated with the extent of brain damage. The youngest (*in utero* at the time of exposure) developed quadriplegia, blindness, severe mental retardation, choreoathetosis, and seizures, and died at age 21. The inorganic mercury levels in different regions of the brain of the 29-year-old patient ranged from 82 to 100% of the total mercury present. Since inorganic mercury crosses the blood-brain barrier poorly, biotransformation of the methylmercury to inorganic mercury may have occurred after the methylmercury crossed the blood-brain barrier, accounting for its observed persistence in the brain and its possible contribution to the brain damage.

LeBel et al. (1996) studied early nervous system dysfunction in Amazonian populations exposed to low levels of methylmercury. A preliminary study was undertaken in two villages on the Tapajos River, an effluent of the Amazon, situated over 200 km downstream from the methylmercury extraction areas. The study population included 29 young adults $35 years (14 women and 15 men) randomly chosen from a previous survey. Hair analyses were conducted with cold vapor atomic fluorescence spectrophotometry. Total hair Hg (THg) varied between 5.6 µg/g and 38.4 µg/g, with MeHg levels from 72.2% to 93.3% of

the THg. A quantitative behavioral neurophysiological test battery, designed for use under standard conditions in an area without electricity and for persons with minimal formal education was administered to all participants. The results of visual testing showed that although all participants had good near and far visual acuity, color discrimination capacity (Lanthony D-15 desaturated panel) decreased with increasing THg ($F=4.1$; $p=0.05$); near visual contrast sensitivity profiles (Vistech 6000) and peripheral visual field profiles (Goldman Perimetry with Targets I and V) were reduced for those with the highest levels of THg. For the women, manual dexterity (Santa Ana, Helsinki version) decreased with increasing THg ($F=16.7$; $p<0.01$); this was not the case for the men. Although the women showed a tendency towards reduced grip strength, muscular fatigue did not vary with THg for either sex. The authors claim that this study demonstrates that it is possible, using a sensitive test battery, to detect alterations in nervous system functions, consistent with knowledge of Hg toxicity, at levels below the currently recognized threshold of 50 µg/g THg.

Mental retardation has not generally been reported as a neurotoxic effect of alkyl mercurial exposure in adults. However, a 9-month-old infant who received porridge made from alkyl mercury-contaminated grains for approximately 4 months lost the ability to crawl or walk and exhibited persistent mental retardation (Engleson and Herner 1952). These effects are similar to those seen in infants born to mothers who consumed methylmercury-contaminated food during pregnancy (see Section 2.2.2.6), suggesting that in addition to the prenatal period, infancy may also be a susceptible period for the development of these types of effects.

Studies in experimental animals also indicate that organic mercury is a potent neurotoxicant. Adult female monkeys *(Macaca fascicularis)* were exposed to methylmercury (0.050 mg Hg/kg/day) in apple juice by mouth for 6, 12, or 18 months, or 12 months followed by 6 months without exposure (clearance group). A fifth group of monkeys was administered mercuric chloride (0.200 mg Hg/kg/day) by constant-rate intravenous infusion through an in-dwelling catheter for 3 months. Controls were housed and handled with the exposed monkeys, but were not administered mercury. The number of neurons, astrocytes, reactive glia, oligodendrocytes, endothelia, and pericytes in the cortex of the calcarine sulcus was estimated by use of the optical volume fractionator stereology technique. Reactive glia showed a significant increase in number for every treatment group, increasing 72% in the 6-month, 152% in the 12-month, and 120% in the 18-month methylmercury-exposed groups, and the number of reactive glia in the clearance group remained elevated (89%). In the mercuric chloride group, there was a 165% increase in the number of reactive glia. Neurons, astrocytes, oligodendrocytes, endothelia, and pericytes showed no significant change in number in

any exposure group. The methylmercury-treated monkeys (all groups) appeared normal in terms of cage behavior throughout the entire exposure period, supporting the conclusion that there was no significant loss in the neuron population. Examination of tissue samples did not reveal any apparent degradation in the structure of neurons or chronic changes in the glial cells (e.g., the appearance of hypertrophic astrocytes), which are commonly observed following exposure to high levels of mercury. No apparent dilation of the perivascular spaces was observed. The average volume of the cortex of the calcarine sulcus did not differ significantly from controls for any methylmercury-treated group. The methylmercury-clearance group had low levels of methylmercury present in tissues; however, the level of inorganic mercury was also elevated. The astrocytes and microglia in the methylmercury group contained the largest deposits of inorganic mercury. Comparing the results of the methylmercury and inorganic mercury groups suggests that inorganic mercury may be responsible for the increase in reactive glia (Charleston et al. 1994).

Charleston et al. (1996) studied the effects of long-term subclinical exposure to methylmercury on the number of neurons, oligodendrocytes, astrocytes, microglia, endothelial cells and pericytes within the thalamus from the left side of the brain of the monkey *Macaca fascicularis.* These parameters were determined by use of the Optical Volume Fractionator stereological method. The accumulated burden of inorganic mercury (IHg) within these same cell types has been determined by autometallographic methods. Four groups of female monkeys (n=4-5) were exposed to 50 µg Hg/kg/day methylmercury in apple juice for 6, 12, or 18 months, or 12 months followed by 6 months without exposure (clearance group). One control animal each was sacrificed with the 6- and 12-month exposure groups, and two additional animals were sacrificed at the end of the experiment. All monkeys appeared normal—no changes in behavior or motor skills were observed. Hematological function (white blood cell count and differentiation, erythrocyte count, hemoglobin, hematocrit, and red cell indices) and blood chemistry (urea nitrogen, creatine, bilirubin, albumin, total protein, alkaline phosphatase, and electrolytes) were normal. No weight loss was observed. Neurons, oligodendrocytes, endothelia, and pericytes did not show a significant change in cell number for any exposure group. Astrocyte cell number exhibited a significant decline for both the 6-month (44.6%) and clearance exposure groups (37.2%); decreased astrocyte counts were also observed in the other exposure groups, but these were not significant. The microglia, in contrast, showed a significant increase in the 18-month (228%) and clearance exposure groups (162%). Results from mercury speciation and quantification analysis of contralateral matched samples from the thalamus of the right side of the brain from these same monkeys indicated that methylmercury concentrations plateaued at around 12 months exposure, whereas the inorganic levels, presumably derived from demethylation of methylmercury, continued to increase throughout all exposure durations. Autometallographic determination of the

distribution of IHg by cell type indicates that both the astrocytes and microglia contain substantially elevated IHg deposits relative to all other cell types. The data suggest that the inorganic mercury present in the brain, accumulating after long-term subclinical methylmercury exposure, may be a proximate toxic form of mercury responsible for the changes within the astrocyte and microglial populations.

Rice (1996a) evaluated delayed neurotoxicity produced by methylmercury in monkeys treated with methylmercury from birth to 7 years of age. When these monkeys reached 13 years of age, individuals began exhibiting clumsiness not present previously. Further exploration revealed that treated monkeys required more time to retrieve treats than did nonexposed monkeys and displayed abnormalities on a clinical assessment of sense of touch in hands and feet, despite the fact that clinical examinations performed routinely during the period of dosing had not yielded abnormal results. Another group of monkeys, dosed from *in utero* to 4 years of age, also took longer to retrieve treats when assessed years after cessation of exposure. These observations were pursued in both groups of monkeys by objective assessment of somatosensory function in the hands: both groups of monkeys exhibited impaired vibration sensitivity. The results suggest that a delayed neurotoxicity occurred when these monkeys reached middle age. The author notes persons with Minamata disease also have symptoms of delayed neurotoxicity. The results from a study of more than 1,100 Minamata patients over the age of 40 indicated a difficulty in performing daily activities that increased as a function of age compared to matched controls. Methylmercury may represent the only environmental toxicant for which there is good evidence for delayed neurotoxicity observable many years after cessation of exposure.

Rice (1996b) further compares the sensory and cognitive effects of developmental methylmercury exposure in monkeys to the effects in rodents. Developmental exposure to methylmercury in the Macaque monkey produced impairment of function in the visual, auditory, and somatosensory systems. In addition, delayed neurotoxicity was observed in monkeys years after cessation of dosing, manifested as overall clumsiness and slowness in reaching for objects. The effects of developmental methylmercury exposure on cognitive function in monkeys are more equivocal; both positive and negative results have been obtained, with no obvious pattern with regard to possible domains of impairment. Prenatal methylmercury exposure in rodents produced retarded development and impairment of motor function, while the evidence for cognitive impairment is less consistent. Derivation of reference doses based on these data from monkeys and rodents is remarkably congruent, and is virtually identical to values derived from evidence for developmental impairment in humans. Research needs include determination of neurotoxic effects at lower body burdens

in the monkey, including dose-effect data, and a more systematic exploration of the pattern of behavioral deficits in both primates and rodents.

Gilbert et al. (1996) used fixed interval/fixed ratio performance in adult monkeys to evaluate effects from exposure *in utero* to methylmercury. The fixed interval/fixed ratio (FI/FR) schedule is considered to be a sensitive indicator of neurotoxicity. In the present study, monkeys (*Macaca fascicularis*) were exposed *in utero* to methylmercury. Maternal doses of methylmercury of 0, 50, 70, or 90 µg/kg/day (in apple juice) (n=11, 9, 2, and 2, respectively) resulted in infant blood mercury levels at birth ranging from 1.04 to 2.45 ppm. Monkeys were tested on a multiple FI/FR schedule of reinforcement at 8–10 years of age. Four FI/FR cycles were run per session. Pause time and run rate were calculated for FI and FR components, as well as FI quarter-life and local FI response rates. Methylmercury treatment and sex effects were investigated by fitting a linear orthogonal polynomial regression to each monkey's profile across sessions and performing two-way ANOVAs on the resulting linear and intercept terms. Results from all treated monkeys were combined and compared to the control group. There were no treatment-related effects on either the fixed interval (FI) or fixed ratio (FR) component for pause time or run rate. Analysis of the quarter-life revealed a significant treatment by sex effect as well as a main effect for sex. Post hoc t-tests revealed a significant difference in quarter-life of treated male and female monkeys and a marginal difference between treated and control males. The FI run rate of the male monkeys was significantly greater than that of the female monkeys whereas the FR run rate of the males was marginally greater. These results indicate that there may be a differential effect of methylmercury on male and female monkeys, which could be interpreted as an effect on temporal discrimination. The authors concluded that adult monkeys exposed to *in utero* methylmercury exhibited very limited sex-related effects on the FI/FR intermittent schedule of reinforcement.

Typical neurotoxic signs observed in rats exposed to methylmercury include muscle spasms, gait disturbances, flailing, and hindlimb crossing (Fuyuta et al. 1978; Inouye and Murakami 1975; Magos et al. 1980, 1985). These effects have been observed after acute-duration gavage dosing with methylmercury concentrations at doses as low as 4 mg Hg/kg/day for 8 days (Inouye and Murakami 1975) and may not be observed until several days after cessation of dosing (Inouye and Murakami 1975; Magos et al. 1985). Histopathological examination of the nervous systems of affected rats has shown degeneration of cerebellar granule cells and dorsal root ganglia (Magos et al. 1980, 1985) and degenerative changes in peripheral nerves (Fehling et al. 1975; Miyakawa et al. 1974, 1976). Comparison of the effects of 5 doses of 8 mg Hg/kg/day as ethyl- or methylmercury showed dorsal root damage as well as flailing and hindlimb

crossing after exposure to both chemicals, but only methylmercury caused substantial cerebellar damage (Magos et al. 1985). Additional changes in rats exposed to methylmercury have also been observed. Rats exposed to a single gavage dose of 19.9 mg Hg/kg as methylmercuric chloride were found to have statistically significant differences in open-field tests, such as decreases in standing upright, area traversed, and activity, compared to controls. However, no accompanying histopathological changes were observed (Post et al. 1973). The exposed animals were also lethargic and ataxic initially, but symptoms disappeared within 2–3 hours. Changes in the phases of sleep were also observed in rats given 2 doses of 4 mg Hg/kg/day as methylmercuric chloride (Arito and Takahashi 1991). Paradoxical sleep was decreased and slow-wave sleep was increased. At a higher dose (12 mg Hg/kg/day for 2 days), circadian sleep patterns were also disrupted. Administration of a single dose of methylmercuric chloride (0.8 mg Hg/kg) produced blood-brain barrier dysfunction in rats (Chang and Hartmann 1972b) similar to that reported for inorganic mercury as discussed previously. In rabbits given 5.5 mg Hg/kg as methylmercuric acetate for 1–4 days, widespread neuronal degenerative changes (in cervical ganglion cells, cerebellum, and cerebral cortex) have been observed without accompanying behavioral changes (Jacobs et al. 1977).

Longer-duration studies in animals have shown qualitatively similar effects, but generally at lower daily doses with increasing durations of exposure. Rats given a dose of 10 mg Hg/kg as methylmercuric chloride once every 3 days for 15 days showed degeneration in the cerebellum with flailing and hind leg crossing (Leyshon and Morgan 1991). Rats given a TWA dose of 2.1 mg Hg/kg/day as methylmercury iodide or 2.4 mg Hg/kg/day as methylmercury nitrate by oral gavage for 29 days became weak and severely ataxic and developed paralysis of the hind legs (Hunter et al. 1940). Severe degeneration of peripheral nerves, posterior spinal roots, and trigeminal nerves were reported. Severe degenerative changes were also observed in the dorsal root fibers of rats given 1.6 mg Hg/kg/day as methylmercuric chloride for 8 weeks (Yip and Chang 1981). Similarly, ataxia (beginning the second week of exposure) and cerebellar edema and necrosis occurred in rats after 7 weeks of exposure by gavage to 1.68 mg Hg/kg as methylmercury dicyanidiamide for 5 days a week (Magos and Butler 1972). When rats were administered 0.8 mg Hg/kg/day as methylmercuric chloride by gavage for up to 11 weeks, effects similar to those reported for mercuric chloride (e.g., neuronal degeneration of the cerebellum and dorsal root ganglia and neurotoxic clinical signs) were seen but with increased severity (Chang and Hartmann 1972a).

Mice have shown comparable effects at similar doses. Mice exposed to 1.9 or 9.5 mg Hg/kg/day as methylmercury in the drinking water for 28 weeks exhibited degeneration of Purkinje cells and loss of granular cells in the cerebellum (MacDonald and Harbison 1977). At the higher of these doses, hind limb

paralysis was observed as early as 8 days, whereas at 1.9 mg Hg/kg/day, decreases in motor activity and hind limb paralysis did not develop until 24 weeks of exposure. Interestingly, cerebellar lesions were observed at 1.9 mg Hg/kg/day as early as 8 days after the start of dosing. Neuronal degeneration and microgliosis were observed in the corpus striatum, cerebral cortex, thalamus, and hypothalamus, accompanied by hind leg weakness, in mice administered 1 or 4 mg Hg/kg/day as methylmercuric chloride by gavage for 60 days (Berthoud et al. 1976). Similarly, a marked neurotoxic disturbance (not further identified) was reported in mice that received 3.1 mg Hg/kg/day as methylmercuric chloride in the diet for 26 weeks (Mitsumori et al. 1981). No effects of this type were observed in this study at 1.6 mg Hg/kg/day, but it is unknown whether more subtle neurological effects may have been missed, as the intent of this study was not to identify neurotoxic effects of methylmercury.

Some studies suggest that cats and monkeys are more sensitive to the neurotoxic effects of organic mercury than rodents. Cats fed tuna contaminated with methylmercury at doses equivalent to 0.015 mg Hg/kg/day for 11 months, starting when the cats were kittens, displayed degenerative changes in the cerebellum and the cerebral cortex (Chang et al. 1974). However, only 3 of 16 animals exhibited incoordination and weakness. Similarly, cats given gavage doses of methylmercuric chloride as low as 0.25 mg Hg/kg/day for 44–243 days displayed degenerative lesions in the granule and Purkinje cells of the cerebral cortex and/or cerebellum and degenerative changes in the white matter, but no manifestations of neurotoxicity (ataxia, loss of righting reflex, visual and sensory impairments) were observed until 0.5 mg Hg/kg/day was given (Khera et al. 1974). Neonatal monkeys given 0.5 mg Hg/kg/day as methylmercuric chloride in infant formula for 28–29 days exhibited stumbling and falling prior to termination of exposure (Willes et al. 1978). Despite the termination of exposure, abnormalities in the several reflexes; blindness; abnormal behavior consisting of shrieking, crying, and temper tantrums; and coma developed. Histopathological analyses showed diffuse degeneration in the cerebral cortex (especially the calcarine, insular, pre-, and postcentral gyri, and occipital lobe), cerebellum, basal ganglia, thalamus, amygdala, and lateral geniculate nuclei. Macaque monkeys exposed to methylmercuric chloride in biscuits exhibited tremors and visual field impairment (Evans et al. 1977). These effects were observed in animals that were first administered 4–5 priming doses of 1 mg Hg/kg at 5-day intervals (no toxicity observed), followed by "maintenance" doses of 0.5–0.6 mg Hg/kg once a week for 87–256 days. Squirrel monkeys developed similar symptoms after receiving a single priming dose of 1 or 2 mg Hg/kg as methylmercuric chloride by gavage, followed 77 days later by maintenance doses of 0.2 mg Hg/kg once a week for 90–270 days (Evans et al. 1977). The doses were adjusted to maintain steady-state blood mercury levels in the range of 1–4 ppm. No tremors or convulsions were observed in female monkeys (*Macaca fascicularis*) during a 150-day exposure

to methylmercury chloride at 0.04 mg Hg/kg/day (Petruccioli and Turillazzi 1991). However, beginning at 177–395 days after exposure to methylmercuric hydroxide at 0.08 mg Hg/kg/day, 6 of 7 female monkeys (*Macaca fascicularis*) exhibited slight tremors and decreased sucking responses, followed by claw-like grasp, gross motor incoordination, and apparent blindness (Burbacher et al. 1984, 1988). These effects were also observed in one animal from each of the lower-dose groups (0.04 and 0.06 mg Hg/kg/day) (Burbacher et al. 1988).

Miyama et al. (1983) attempted to correlate electrophysiological changes with "early" neurological signs in rats during dietary exposure to methylmercuric chloride for an unspecified period of time. They observed the following sequence in the onset of electrophysiological-somatic signs: fall in compound action potential > decrease in sensory nerve conduction velocity > tail rotation > weight loss. However, varying doses of selenium were co-administered with the methylmercury, complicating the interpretation of these results.

Evidence for a neurochemical component of methylmercury-induced toxicity following intermediate-duration exposures has been reported (Concas et al. 1983; Sharma et al. 1982; Tsuzuki 1981). A depression in the synthesis of the neurotransmitter, dopamine (whole-brain levels), was observed in the absence of clinical signs of neurotoxicity in rats fed doses as low as 0.8 mg Hg/kg/day as methylmercuric chloride once every 3 days for 15 days (Sharma et al. 1982). An increased number (but not an affinity) of benzodiazepine receptor binding sites and a decreased content of cyclic guanosine monophosphate (cGMP) were observed in the cerebellar cortex of rats administered 3.92 mg Hg/kg/day as methylmercuric chloride in the drinking water for 20 days (Concas et al. 1983). Activities of several enzymes associated with central neurotransmitter metabolism in the cerebellum (e.g., acetylcholinesterase, tryptophan hydroxylase, monoamine oxidase, catechol-*o*-methyltransferase) were depressed in rats administered 3.2 mg Hg/kg/day as methylmercury by gavage for 50 days (Tsuzuki 1981). These findings suggest that an alteration in neurotransmission may be one mechanism of action for mercury-induced neurotoxicity. However, the observed effects on the neurotransmitters may be secondary to other effects on the nervous system.

The chronic neurotoxic effects of methylmercury in animals are similar to those seen after intermediate exposure. Mice administered methylmercuric chloride in the diet for 2 years at approximately 0.6 mg Hg/kg/day showed posterior paralysis and sensory neuropathy, characterized by cerebral and cerebellar necrosis, as well as degeneration of spinal dorsal nerve roots and the sciatic nerve (Hirano et al. 1986; Mitsumori et al. 1990). Cats fed contaminated fish or contaminated fish and methylmercury at doses

as low as 0.046 mg Hg/kg/day for 2 years exhibited neurobehavioral toxic signs, including mild impairment of motor activity and diminished sensitivity to pain (Charbonneau et al. 1976). These effects began after 60 weeks of exposure but did not progress during the remainder of the 2 years of exposure. At higher doses of 0.074 and 0.18 mg Hg/kg/day, ataxia, alterations in gait, motor incoordination, muscle weakness, changes in temperament, and convulsions were also observed. Histopathological analyses showed neuronal degeneration in the motor, sensory, auditory, and occipital cortices and cerebellar granule cell degeneration. Five monkeys fed 0.05 mg Hg/kg/day as methylmercuric chloride from birth until the age of 3–4 years displayed impaired spatial vision at that time (Rice and Gilbert 1982). Continued dosing until 6.5–7 years of age resulted in clumsiness, decreased fine motor performance, and insensitivity to touch when tested at 13 years of age (Rice 1989c). Impaired high-frequency hearing was also displayed by these monkeys when tested at 14 years of age (Rice and Gilbert 1992). It is noteworthy that a wide range of neurotoxic symptoms (motor, visual, and auditory) were observed in a species similar to humans several years after dosing had ceased. No clinical signs or histopathological evidence of neurotoxicity was observed in rats that received 0.1 mg Hg/kg/day as methylmercuric chloride in the diet for 2 years (Verschuuren et al. 1976).

Deficiencies in many of the studies make it difficult to fully evaluate the quality of the data reported. General problems include the following: (1) many details of experimental protocols were omitted, thereby prohibiting an evaluation of the study's adequacy; (2) very often, only one dose was used, so an analysis of any possible dose-response relationships was not possible, and the possibility that certain observed effects were not compound-related cannot be excluded; (3) control data often were not presented; and (4) the results were frequently described in subjective terms, and no attempt was made to quantitate the data. Despite these limitations, animal studies do provide irrefutable evidence that the central and peripheral nervous systems are target organs for organic mercury-induced toxicity.

In summary, methylmercury is neurotoxic to humans and to several species of experimental animals following acute, intermediate, and chronic oral exposure. The major effects that are seen across the studies include motor disturbances, such as ataxia and tremors, as well as signs of sensory dysfunction, such as impaired vision. The predominant neuropathological feature is degenerative changes in the cerebellum, which is likely to be the mechanism involved in many of the motor dysfunctions. In humans, disruptions of higher functions have also been noted, as evidenced by depression and irritability.

The highest NOAEL values and all reliable LOAEL values for neurotoxic effects in each species and duration category are listed in Table 2-3 and plotted in Figure 2-3 for organic mercury.

2.2.2.5 Reproductive Effects

Inorganic Mercury. In an attempt to terminate her pregnancy, a 31-year-old woman ingested 30 mg Hg/kg as mercuric chloride in week 10 of her pregnancy (Afonso and deAlvarez 1960). Despite gastric lavage and treatment with dicapmerol, 13 days after exposure vaginal bleeding and uterine cramps occurred, followed by spontaneous abortion of the fetus and placenta. It was inconclusive whether the abortion was directly due to the mercury exposure.

Organic Mercury. No studies were located regarding reproductive effects in humans following oral exposure to organic mercury.

Abortions and decreased mean litter size are the predominant reproductive effects in different species of animals following oral exposure to organic mercury. Groups of 30 pregnant Fischer 344 rats were orally administered 10, 20, or 30 mg/kg as methylmercuric chloride dissolved in saline on Gd 7. Controls were given saline only (n=30). Maternal body weight gain and deaths were monitored. On Gd 20, the dams were laparotomized under ether anesthesia, and the fetuses were removed. Surviving fetuses were examined for gross toxic effects, sex, and weight; half were stained for skeletal examination. Mercury levels in maternal and fetal organs were measured. The LD_{50} of methylmercuric chloride for fetuses was calculated. Maternal body weights were decreased for 2 days in rats given 10 mg/kg, for 6 days in rats given 20 mg/kg, and were continuously decreased for rats given 30 mg/kg methylmercuric chloride. Survival rates of fetuses were 19.2, 41.4, and 91.1% less than controls for the 10, 20, and 30 mg/kg methylmercuric chloride groups, respectively. Implantation sites in the 3 groups decreased by 5.9, 13.7, and 22.5%, respectively, compared with controls. Preimplantation losses in the 3 groups were 17.2, 24.8, and 30.1%, respectively; postimplantation losses were 16.7, 34.1, and 88.9%, respectively. The reduction of litter weight was greatly enhanced with increasing methylmercuric chloride doses (32.3, 67.0, and 89.2%, respectively), presumably due to postimplantation loss, which already increased at high treatment levels. The LD_{50} of methylmercuric chloride for fetuses was determined to be 16.5 mg/kg. Mercury content in maternal organs was highest in the kidneys, followed by blood, spleen, liver, and brain, while in fetal organs it was highest in the liver (Lee and Han 1995).

Pregnant hamsters that received a single oral gavage dose of mercuric acetate on Gd 8 showed an increase in the incidence of resorptions at doses as low as 22 mg Hg/kg (Gale 1974). The incidence of resorptions was 35% at 22 mg Hg/kg, and increases were observed in a dose-related manner (53% at 32 mg Hg/kg, 68% at 47 mg Hg/kg, and 99% at 63 mg Hg/kg).

In a study by Khera (1973), after 5–7 days of oral gavage doses of 1, 2.5, or 5 mg Hg/kg/day as methylmercuric chloride, male rats were mated to unexposed female rats. A dose-related reduction of mean litter size was attributed to preimplantation losses from incompatibility of sperm-to-implantation events after mercury treatment of the parent male rat. At doses of 2 mg Hg/kg/day as methylmercury by gavage during Gd 6–9, pregnant Sprague-Dawley rats showed no differences in maternal body weight gain before parturition or in the body weights of the offspring (Fredriksson et al. 1996).

In male mice, no reduction in the incidence of fertile matings was observed after administration of 5–7 oral doses of up to 5 mg Hg/kg/day as methylmercuric chloride (Khera 1973). There was a significant dose-related decrease in the number of pups born per litter in mice receiving oral doses of 3, 5, or 10 mg Hg/kg administered on Gd 8 as methylmercuric hydroxide (Hughes and Annau 1976). Effects were not observed at 2 mg Hg/kg/day. Similarly, female mice administered 20 mg Hg/kg/day as methylmercuric chloride by gavage on Gd 10 had increased resorptions, decreased live fetuses per litter, and decreased numbers of fetuses per litter (Fuyuta et al. 1978). After guinea pigs were exposed to 11.5 mg Hg/kg as methylmercuric chloride by gavage on Gd 21, 28, 35, 42, or 49, half of the litters were aborted 4–6 days after treatment (Inouye and Kajiwara 1988). An increased rate of reproductive failure due to decreased conceptions and increased early abortions and stillbirths occurred in female monkeys exposed to 0.06 or 0.08 mg Hg/kg/day as methylmercury for 4 months (Burbacher et al. 1988). The menstrual cycle length was not affected at these dose levels. Reproductive effects were not observed in monkeys exposed to 0.04 mg/kg/day for the same duration.

Testicular functions were studied in monkeys *(M. fascicularis)* exposed to 0.025 or 0.035 mg Hg/kg/day as methylmercury by gavage for 20 weeks (Mohamed et al. 1987). The mean percentage of motile spermatozoa and the mean sperm speed were significantly decreased for both treatment groups compared to controls. Morphological examination of semen smears indicated an increased incidence of tail defects (primarily bent and kinked tails) in both exposed groups. No histopathological effects were evident on the testes. The study was limited because there were only three animals in each exposure group.

Testicular effects were also observed after chronic-duration exposure to methylmercuric chloride. Tubular atrophy of the testes was observed in mice ingesting 0.69 mg Hg/kg/day in their feed for up to 2 years (Mitsumori et al. 1990). Decreased spermatogenesis was observed in mice receiving 0.73 mg Hg/kg/day in the diet (Hirano et al. 1986). No adverse effects on the testes were observed in these studies at 0.14–0.15 mg Hg/kg/day. Similarly, no adverse effects were observed in the testes, prostate, ovaries, or uterus of rats exposed through the diet to 0.1 mg Hg/kg/day as methylmercuric chloride for 2 years (Verschuuren et al. 1976).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3 for organic mercury.

2.2.2.6 Developmental Effects

Inorganic Mercury. No studies were located regarding developmental effects in humans or animals following oral exposure to inorganic mercury.

Organic Mercury. When grains treated with fungicides containing mercury have been accidentally consumed or when fish with high levels of methylmercury have been eaten, epidemics of human mercury poisonings have occurred with high incidences of developmental toxicity. These episodes, as well as case reports from isolated incidences of maternal consumption of organic forms of mercury during pregnancy, have provided evidence that the developing nervous system of the fetus is highly sensitive to mercury toxicity. The first such incident was reported in Sweden in 1952 when flour from grain treated with an unspecified alkyl mercury compound ingested by a pregnant woman was associated with developmental toxicity. An apparently normal infant was born, but the infant later displayed brain damage manifested by mental retardation, incoordination, and inability to move (Engleson and Herner 1952). A 40-year-old woman, 3 months pregnant, consumed methylmercury-contaminated meat for an unspecified duration and subsequently delivered a male infant with elevated urinary mercury levels (Snyder and Seelinger 1976). At 3 months, the infant was hypotonic, irritable, and exhibited myoclonic seizures. At 6 years of age, the child displayed severe neurological impairment (e.g., blindness, myoclonic seizures, neuromuscular weakness, inability to speak) (Snyder and Seelinger 1976). In the 1955 mercury poisoning outbreak in Minamata, Japan, severe brain damage was described in 22 infants whose mothers had ingested fish contaminated with methylmercury during pregnancy (Harada 1978). The types of nervous system effects described in the Minamata outbreak included mental retardation; retention of primitive reflexes; cerebellar symptoms;

dysarthria; hyperkinesia; hypersalivation; atrophy and hypoplasia of the cerebral cortex, corpus callosum, and granule cell layer of the cerebellum; dysmyelination of the pyramidal tracts; and an abnormal neuronal cytoarchitecture. It has been suggested that the widespread damage involved derangement of basic developmental processes, such as neuronal migration (Choi et al. 1978; Matsumoto et al. 1965) and neuronal cell division (Sager et al. 1983).

Large-scale poisonings also occurred in Iraq in 1956 and 1960 (Bakir et al. 1973). Thirty-one pregnant women were victims of poisoning; 14 women died from ingesting wheat flour from seeds treated with ethylmercury *p*-toluene sulfonanilide (Bakir et al. 1973). Infants were born with blood mercury concentrations of 250 µg/100 mL and suffered severe brain damage. Similar cases of severe brain damage resulting from prenatal exposure to methylmercury were reported in an outbreak of methylmercury poisoning in Iraq occurring in 1971–1972 (Amin-Zaki et al. 1974). Attempts to correlate symptoms with exposure levels have shown that a dose-response relationship exists between the severity of the neurological symptoms in offspring and the maternal intake of methylmercury (as determined using analysis of hair for mercury content) (Cox et al. 1989; Marsh et al. 1980, 1981, 1987). Delays in walking and talking were more often associated with lower peak hair levels during pregnancy than were mental retardation and seizures (Marsh et al. 1981, 1987). These studies showed that the most severely affected children had been exposed to methylmercury during the second trimester of pregnancy. Male offspring were more severely affected than female offspring. Neurological abnormalities have also been observed among offspring of Cree Indians in Quebec, Canada, exposed to methylmercury in fish (McKeown-Eyssen et al. 1983).

A significant correlation was observed between male offspring with abnormal muscle tone or reflexes and maternal prenatal exposure (as determined using hair levels). An analysis of peak hair mercury levels during pregnancy in mothers exposed during the 1971–1972 outbreak in Iraq has led to an estimated population threshold of 10 ppm (highest value during pregnancy, for total mercury in hair) associated with delays in the onset of walking in infants (Cox et al. 1989). However, this estimated threshold for the Iraqi population depends heavily on the assumed background frequency for abnormal onset of walking time, as well as the threshold chosen to define onset of walking as abnormal. Furthermore, most of the positive responses (i.e., reported delays in onset of walking or talking) were observed for maternal hair levels above about 60 ppm. Only 3 of 24 children with positive responses were born to mothers with hair levels below 59 ppm. The peak total mercury hair levels during pregnancy for the mothers of those 3 children were 14, 18, and 38 ppm (WHO 1990). A maternal exposure level of 0.0012 mg/kg/day, corresponding to a hair

level of 14 ppm, was estimated for the Iraqi women using a simple, one-compartment pharmacokinetic model (see Section 2.4).

Davidson et al. (1995b) studied the effects of prenatal methylmercury exposure from a diet high in fish on developmental milestones in children living in the Republic of Seychelles (i.e., the Seychelles Child Development Study (SCDS). In this double blind study, children were evaluated with the Bayley Scales of Infant Development (BSID) at 19 months of age (n=738). The 19-month cohort represented 94% of the initially enrolled pairs. The cohort was evaluated again at 29 months (n=736) with the BSID and the Bayley Infant Behavior Record. Mercury exposure was determined by cold vapor atomic absorption analysis of maternal hair segments during pregnancy. The 29-month cohort represented approximately 50% of all live births in the year 1989. This particular study population was carefully selected based on the following reasons: (1) they regularly consume a high quantity and variety of ocean fish; (2) pre-study mercury concentration in maternal hair was in the appropriate range (<5 to >45 ppm) to study low-level exposure; (3) there is no local industry for pollution, and the Seychelles location is 1,000 miles from any continent or large population center; (4) the Seychellois population is highly literate, cooperative, and has minimal immigration; and (5) the Seychellois constitute a generally healthy population, with low maternal alcohol and tobacco use. The association between maternal hair mercury concentrations and neurodevelopmental outcomes at 19 and 29 months of age was examined by multiple regression analysis with adjustment for confounding variables. Testing was performed by a team of Seychellois nurses extensively trained in administration of the BSID.

Maternal hair concentrations measured in hair segments that corresponded to pregnancy ranged from 0.5 to 26.7 ppm, with a median exposure of 5.9 ppm for the entire study group. The mean BSID Mental Scale Indexes at both 19 and 29 months were comparable to the mean performance of U.S. children. The mean BSID Psychomotor Scale Indexes at 19 and 29 months were 2 standard deviation units above U.S. norms, but consistent with previous findings of motoric precocity in children reared in African countries. No effect of mercury was detected on BSID scores at either age. On the Bayley Infant Behavior Record, activity level in boys, but not girls, decreased with increasing mercury exposure. The only subjective observation correlated with prenatal mercury exposure was a slight decrease in activity level in boys (but not girls) as determined by the Bayley Infant Behavior Record.

The overall study cohort was broken down into sub-groups based upon maternal hair mercury concentration as follows: $3 ppm (n=164), 4–6 ppm (n=215), 7–9 ppm (n=161), 10–12 ppm (n=97), and

>12 ppm (n=99). No significant or remarkable effect on the activity of the respective groups of children was observed outside the highest concentration group (i.e., maternal hair concentrations >12 ppm). When boys were examined separately, there appeared to be a trend toward decreased activity with increasing mercury concentrations, most visible above the group median value of 5.9 ppm. The mercury effect was highly significant in males (p=0.0004), but it was not statistically significant (p=0.87) in females. The activity level scores for males decreases 1/10 point (on a 9-point scale) for every ppm of mercury in maternal hair. While the activity score for the overall cohort was comparable to the mode of 5 for U.S. children, those children born to mothers with hair mercury levels of 20 ppm, males scored >1 point below the U.S. mode value. Scores of females remained at the comparable value for U.S. children, regardless of the magnitude of maternal hair mercury level. When the subjective activity scores for male and female children are evaluated collectively, no significant/remarkable decrease in activity is apparent outside the >12 ppm maternal hair concentration group. The affect on activity level in boys is not considered an adverse effect, and the 5.9 ppm level is categorized as a NOAEL. Since the children had been exposed *in utero*, they represent the most sensitive subpopulation.

Myers et al. (1997) evaluated the population of the SCDS for developmental milestones similar to those determined in Iraq. As part of this ongoing study, cohort children were evaluated at 6.5, 19, 29, and 66 months of age. At 19 months care-givers were asked at what age the child walked (n=720 out of 738) and talked (n=680). Prenatal mercury exposure was determined by atomic absorption analysis of maternal hair segments corresponding to hair growth during the pregnancy.

The median mercury level in maternal hair for the cohort in this analysis was 5.8 ppm with a range of 0.5–26.7 ppm. The mean age (in months) at walking was 10.7 (SD=1.9) for females and 10.6 (SD=2.0) for males. The mean age for talking (in months) was 10.5 (SD=2.6) for females, and 11.0 (SD=2.9) for males. After adjusting for covariates and statistical outliers, no association was found between the age at which Seychellois children walked or talked and prenatal exposure to mercury. The ages for achievement of the developmental milestones were normal for walking and talking in the Seychellois toddlers following prenatal exposure to methylmercury from a maternal fish diet. The 5.8 ppm NOAEL of this study is thus considerably below the one derived from the dose-response analysis of the data for the Iraqi methymercury poisonings (10 ppm).

The SCDS cohort continues to be monitored and evaluated for developmental effects. In an analysis of the latest round of outcome measures for children at age 66 months (n=708), Davidson et al. (1998) report no

adverse developmental effects associated with prenatal and postnatal exposure to methylmercury in fish at the levels experienced in this cohort. The actual exposure is reflected in a mean maternal hair level of 6.8 ppm for the prenatal exposure (SD=4.5, n=711, range, 0.5-26.7) and in a mean children's hair level of 6.5 ppm (SD=3.3, n=708, range, 0.9-25.8) for both the prenatal and subsequent postnatal exposure. The age-appropriate main outcome measures included: (1) the McCarthy Scales of Children's Abilities, (2) the Preschool Language Scale, (3) the Woodcock-Johnson Tests of Achievement—Letter and Word Recognition, (4) Woodcock-Johnson Tests of Achievement—Applied Problems and, (5) the Bender Gestalt test, and (6) the Child Behavior Checklist. The test results were similar to what would be expected from a healthy, well-developing U.S. population. No test indicated a deleterious effect of methylmercury from the exposure levels received in this population. Four of the six measures showed better scores in the highest MeHg groups compared with lower groups for both prenatal and postnatal exposure. The authors conclude that this result is likely due to the benefits of increased levels of fish in the diet, possibly because of increased consumption of omega-3-fatty acids. Serum from a subset of 49 of the children was sampled for polychlorinated biphenyl (PCB) levels. None of the samples had detectable levels (detection limit 0.2 ng/mL) for any of the 28 congeners assayed (from congener 28 to 206), indicating that was no concurrent (i.e, potentially confounding) exposure to PCBs in this population. The median level of total mercury for each of 25 species sampled was 0.004–0.75 ppm, with most medians in the range of 0.05–0.25 ppm, levels that are comparable to fish in the U.S. market. The authors conclude, that this most recent NOAEL of 6.8 ppm for the SCDS cohort at 66 months of age strongly supports the findings at earlier ages, and that the benefits of eating fish outweigh the small risk of adverse effects from an increased exposure to methylmercury for this exposure pathway.

Weihe et al. (1996) began a long-term evaluation of the health implications for people living in the Faroe Islands who are exposed to heavy metals and polychlorinated biphenyls (PCBs) from the consumption of fish and pilot whales. A birth cohort of 1,000 children was examined at approximately 7 years of age for neurobehavioral dysfunctions associated with prenatal exposure to mercury and PCB. Preliminary analyses of the data show that several neurobehavioral tests are associated with mercury exposure parameters. With emphasis on prenatal exposures to PCB, another cohort was generated during 1994–1995, and this cohort will be followed closely during the next years. In the Faroe Islands, marine food constitutes a considerable part of the diet. In addition to fish, both meat and blubber from pilot whales are included in the diet. Muscle tissue of pilot whales caught in the Faroe Islands contains an average mercury concentration of 3.3 µg/g (16 nmol/g), about half of which is methylmercury. In some years an evenly distributed annual catch of pilot whales would make the average dietary intake of mercury close to more than the Provisional

Temporary Weekly Intake of 0.3 mg recommended by WHO. In 1 of 8 consecutive births, the mercury concentration in maternal hair exceeded a limit of 10 µg/g, a level where neurobehavioral dysfunction in the child may occur. The maximum level was 39.1 µg/g. Mercury concentrations in umbilical cord blood showed a similar distribution with a maximum of 351 µg/L. The large variation in mercury exposure is associated with differences in the frequency of whale dinners. The average PCB concentration in pilot whale blubber is very high (about 30 µg/g). With an estimated daily consumption of 7 g of blubber, the average daily PCB intake could therefore exceed 200 µg (i.e., close to the Acceptable Daily Intake). In Scandinavia, the average daily PCB intake is about 15–20 µg.

In the continuation of this work, Grandjean et al. (1997b, 1998) studied a cohort of 1,022 consecutive singleton births generated during 1986–1987 in the Faroe Islands. Increased methylmercury exposure from maternal consumption of pilot whale meat was estimated from mercury concentrations in cord blood and maternal hair. At approximately 7 years of age, 917 of the children underwent detailed neurobehavioral examination. Neuropsychological tests included Finger Tapping; Hand-Eye Coordination; reaction time on a Continuous Performance Test; Wechsler Intelligence Scale for Children-Revised Digit Spans, Similarities, and Block Designs; Bender Visual Motor Gestalt Test; Boston Naming Test; and California Verbal Learning Test (Children). Neurophysiological tests emphasized motor coordination, perceptual-motor performance, and visual acuity; pattern reversal visual evoked potentials (VEP) with binocular full-field stimulation, brain stem auditory evoked potentials (BAEP), postural sway, and the coefficient of variation for R-R interpeak intervals (CVRR) on the electrocardiogram were measured. Mercury in cord blood, maternal hair (at parturition), child hair at 12 months, and child hair at 7 years of age were measured. The geometric average mercury concentrations were 22.9, 4.27, 1.12, and 2.99 µg/g, respectively. Mercury concentrations in cord blood were most closely associated with the concentrations in maternal hair at parturition and less so with children's hair at 12 months and 7 years. Clinical examination and neurophysiological testing did not reveal any clear-cut mercury-related abnormalities. However, mercury-related neuropsychological dysfunctions were most pronounced in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions. The authors state that these associations remain after adjustment for covariates and after exclusion of children with maternal hair mercury concentrations above 10 µg/g (50 nmol/g). They further conclude that the effects on brain function associated with prenatal methylmercury exposure appear diverse, with early dysfunction in the Faroe Island population detectable at exposure levels currently considered to be safe.

In animals, there is evidence of developmental effects following oral exposure to organic mercury during gestation, lactation, and/or postweaning. Increases in several parameters indicative of developmental toxicity have been observed. Not all studies have examined neurological end points, but developmental neurotoxicity has been observed at very low exposure levels.

Methylmercuric chloride administered via gavage to pregnant rats at 8 mg Hg/kg on Gd 10 resulted in increased skeletal variations (incomplete fusion of the sternebrae) (Fuyuta et al. 1979). At higher doses, decreased fetal weight and increased malformations (cleft palate) were observed. Administration of lower doses of methylmercury (4 mg Hg/kg/day) for a longer duration of gestation (Gd 7–9 or 6–14) resulted in an increased incidence of rat fetuses with incomplete ossification or calcification (Nolen et al. 1972). The incidence of skeletal variations at 0.2 mg/kg/day was not significantly different from controls. Methylmercuric chloride administered to pregnant rats (n=10) via gavage at 2 mg Hg/kg/day throughout gestation (Gd 0–20) resulted in increased numbers of malformed fetuses (Inouye and Murakami 1975). The most common malformations were generalized edema and brain lesions. When methylmercuric chloride was administration to pregnant rats at 4 mg Hg/kg/day during Gd 7–14, there was a decreased fetal weight and an increased number of total malformations, hydrocephalus, and wavy ribs (Fuyuta et al. 1978). At 6 mg Hg/kg/day, increased resorptions, fetal deaths, cleft palate, generalized edema, brain lesions, absence of vertebral centra, and defects of the sternum were observed. Skeletal variations seen at 6 mg Hg/kg/day included absence of one or more sternebrae, bipartite sternebrae, and bilobed vertebral centra. Administration of a single dose of 24 mg Hg/kg as methylmercuric chloride to pregnant rats during Gd 6–12 resulted in decreased fetal weights and increased malformations (Inouye and Murakami 1975). The incidence of malformations (hydrocephalus, cleft palate, micrognathia, microglossia, generalized edema, subcutaneous bleeding, and hydronephrosis and hypoplasia of the kidneys) increased with later treatments (after Gd 7). Hydrocephalic brains had lesions in the brain mantle, corpus callosum, caudate putamen, and primordial cerebellum. Brains without hydrocephalus had lesions in similar brain areas, as well as dilation of the third ventricle and partial ablation of the ependymal lining.

Groups of 30 pregnant Fischer 344 rats were orally administered 10, 20, or 30 mg/kg methylmercuric chloride dissolved in saline on Gd 7. Controls were given saline only (n=30). Maternal body weight gain and deaths were monitored. Maternal body weights were decreased for 2 days in rats given 10 mg/kg as methylmercuric chloride and for 6 days in rats given 20 mg/kg and were continuously decreased for those given 30 mg/kg. Maternal death rates were 6.7, 16.7, and 30% in the 10, 20, and 30 mg/kg methylmercuric chloride dose groups; no control dams died. Survival rates of fetuses were 19.2, 41.4, and 91.1%

less than controls for the 10, 20, and 30 mg/kg methylmercuric chloride groups, respectively. The LD_{50} of methylmercuric chloride for fetuses was determined to be 16.5 mg/kg. The backbones of fetuses were severely curved at the high-dose level; mean fetal body lengths were reduced by 9.6, 21.7, and 48.8% in the 10, 20, and 30 mg/kg methylmercuric chloride groups, respectively, as compared to controls. Mercury content in maternal organs was highest in kidneys, followed by blood, spleen, liver, and brain, while in fetal organs it was highest in liver. Fetal liver and brain contained more mercury than maternal liver and brain; however, fetal kidneys retained less mercury than maternal kidneys. The fetal ossification center was not completely formed in sternebrae, particularly in the fifth and second bones, pelvic bones, and pectoral phalanges of fetuses in rats treated with 30 mg/kg methylmercuric chloride. The ossified lengths of skeletal bone stained with alizarin red S were developed least in the fifth sternebrae, metacarpals in the pectoral girdle, and ischium in the pelvic girdle, and were severely retarded in development as position of the ribs goes from the sixth bone (center) to the first and 13th bone (each edge) (Lee and Han 1995).

Four groups of 12 pregnant Sprague-Dawley rats were exposed to methylmercury or elemental mercury alone or in combination as follows: one group was administered 2 mg/kg/day methylmercury via gavage during Gd 6–9; another was exposed by inhalation to 1.8 mg/m^3 metallic mercury (elemental Hg) vapor for 1.5 hours per day during Gd 14–19; a third was exposed to both methylmercury by gavage (2 mg/kg/day, Gd 6–9) and elemental Hg vapor by inhalation (1.8 mg/m^3, Gd 14–19) (methylmercury + elemental Hg); a fourth group was given combined vehicle administration for each of the 2 treatments (control). The inhalation regimen corresponded to an approximate dose of 0.1 mg Hg/kg/day. Maternal body weights were monitored. At postpartum day 3, each litter was reduced to 4 male offspring. Body weight, pinna unfolding, tooth eruption, and eye opening were monitored. Testing of behavioral function was performed between 4 and 5 months of age and included spontaneous motor activity, spatial learning in a circular bath, and instrumental maze learning for food reward. Surface righting reflex and negative geotaxis were measured before weaning. There were no differences between any of the groups in maternal body weight gain or in body weight, pinna unfolding, tooth eruption, surface righting reflex, and negative geotaxis in offspring. Offspring of dams exposed to elemental mercury showed hyperactivity in the spontaneous motor activity test chambers over all three of the following parameters: locomotion, rearing, and total activity. This effect was potentiated in the animals of the methylmercury + elemental mercury group. In the swim maze test, the methylmercury + elemental mercury and elemental mercury groups evidenced longer latencies to reach a submerged platform, which they had learned to mount the day before, compared to either the control or methylmercury groups. In the modified, enclosed radial-arm maze, both the methyl-mercury + elemental Hg and elemental Hg groups showed more ambulations and rearings in the activity

test prior to the learning test. During the learning trial, the same groups (i.e., methylmercury + elemental mercury and elemental mercury) showed longer latencies and made more errors in acquiring all eight pellets. Generally, the results indicate that co-exposure to methylmercury, which by itself did not alter these functions at the dose given in this study, served to significantly enhance the effects of prenatal exposure to elemental mercury (i.e., alterations to both spontaneous and learned behaviors). Brain mercury concentrations in offspring were 1 ng/g w/w in the controls, 4 ng/g in the methylmercury group, 5 ng/g in the elemental mercury group, and 12 ng/g in the methylmercury + elemental mercury group (Fredriksson et al. 1996).

Pregnant Sprague-Dawley rats were treated by gavage with a single oral dose of 8 mg/kg of methylmercury chloride or saline on Gd 15. Within 24 hours after birth, litters were reduced to 6 pups per litter. Pups were weighed weekly and weaned 21 days after birth. Offspring of control and treated rats were killed at 14, 21, and 60 days of age. The binding characteristics of muscarinic receptors labeled in cortical membrane preparation by [3H]-L-quinuclidinyl benzilate were studied, and the mercury level in the same brain area was assessed. Total mercury content in cortical tissues was determined at 21 and 60 days of age. Furthermore, the performance in passive avoidance tasks was evaluated in 10 rats from each group at 8 weeks of age. No differences in mortality or weight gain were observed in methylmercury-exposed pups compared to controls. At 21 days of age, the level of mercury in the cortex was about 30 times higher in exposed rats than in controls (190.2 ng/g w/w versus 6.4 ng/g); at 60 days, mercury levels did not differ significantly (7.4 versus 5 ng/g, respectively). Perinatal exposure to methylmercury significantly reduced the maximum number of muscarinic receptors (Bmax) in the brain of 14-day-old (53%) and 21-day-old (21.3%) rats, while there was no notable difference in 60-day-old rats. This phenomenon seems to be strictly related to the presence of mercury in the cortex since it disappeared with the normalization of mercury levels in the brain. Despite the recovery of muscarinic receptor densities in methylmercury-exposed rats at 8 weeks of age, the avoidance latency was reduced in passive avoidance tests, indicating learning and memory deficits in these animals (Zanoli et al. 1994).

Similar effects were observed in mice exposed to organic mercury. Methylmercuric chloride administered orally by gavage to mice at 5 mg Hg/kg/day during Gd 6–17 resulted in 100% stillbirths or neonatal deaths and the failure of 6 of 9 dams to deliver, with no apparent maternal toxicity (Khera and Tabacova 1973). At lower doses (2 and 4 mg Hg/kg/day) for a shorter duration during gestation (days 6–13), no increase in deaths or resorptions was observed, but increases in malformations, skeletal variations, and delays in ossification were observed (Fuyuta et al. 1978). A higher dose of methylmercuric chloride (16 mg Hg/kg)

administered to mice by gavage on either Gd 10 or 12 resulted in decreased fetal weight, cleft palate, and dilation of the renal pelvis (Yasuda et al. 1985).

Thuvander et al. (1996) evaluated the immunomodulation of methylmercury from perinatal exposure in mice. Offspring from Balb/c mice were exposed to methylmercuric chloride in the diet. Dams (16.0±0.5g) were exposed to 0 (n=72), 0.5 (n=27), or 5 (n=37) mg Hg/kg for 10 weeks prior to mating, and during gestation and lactation. Pups were exposed to mercury until day 15 of lactation; thereafter, the pups were given control milk and control diet. Samples for mercury analysis were collected from the pups on days 22 and 50, and for immunological studies on days 10, 22, and 50. Immunological parameters included numbers of splenocytes and thymocytes, proportions of lymphocyte subpopulations within the thymus, the proliferative response of splenocytes to the B-cell mitogen LPS, NK-cell activity of splenocytes, and the primary antibody response to a viral antigen. Eight pups (n=8NS) were taken from at least three different litters for the immune function analysis.

No disturbances in the behavior of dams or pups were observed for any of the dose groups. All dams gave birth to normal sized litters (8–10 animals/litter). The high dose dams did have a small (4%) but significant increase in body weight (weeks 4, 5, 9 $p<0.05$, week 8 $p<0.01$). The exposure resulted in significantly increased total Hg concentrations in whole blood of offspring on day 22 and 50 from the 5 mg Hg/kg group (170 and 22 ng Hg/g blood in 5 mg/kg dose group compared to 7 and 5 ng Hg/g in control, respectively), and of offspring from the 0.5 mg Hg/kg group on day 22 (24 ng Hg/g compared to 7 ng Hg/g in control). On day 50, blood mercury levels in the 0.5 mg Hg/kg group had decreased to 11 ng Hg/g compared to 5 ng Hg/g in controls. Pups showed a decreased body weight (8%) in the 5 mg/kg group at 10 days of age. Significantly increased numbers of splenocytes were found only in offspring from the 0.5 mg Hg/kg group at 10 and 22 days, and increased number of thymocytes in the 0.5 mg/kg group at 22 days. Flow cytometry analysis of thymocytes revealed increased numbers and altered proportions of lymphocyte subpopulations within the thymus in offspring from both of the exposed groups at 22 days. The only sign of immunosuppression was a decrease in the proportion of CD4+ thymocytes at 10 days, but this was seen in both mercury groups so was probably not related to a decrease in body weight. The proliferative response of splenocytes to the B-cell mitogen LPS was increased in offspring from dams exposed to 5 mg Hg/kg, and the primary antibody response to a viral antigen was stimulated in pups from dams exposed to 0.5 mg Hg/kg. No significant differences were observed in the NK-cell activity of splenocytes except for a transient increase in activity at 22 days in the 5 mg/kg group at one of the two effector-to-target-cell ratios tested. The present results indicate that placental and lactational transfer of

low dose mercury affects thymocyte development and stimulates certain mitogen- or antigen-induced lymphocyte activities in mice. The authors note that these results, in the context of other studies where methylmercury was observed to have suppressive effects, suggests that methylmercury enhances immune function within a narrow dose range. The blood levels of mercury in the present study are close to the levels found in fish-eating populations. The authors note that the clinical relevance of slight stimulation of some immune functions is unknown, but the induction of autoimmunity by methylmercury can not be excluded.

Groups of guinea pigs exposed to a single dose of 11.5 mg Hg/kg as methylmercuric chloride at various times during gestation (66–69 days) showed differences in the manifestation of developmental neurotoxicity, depending on the period of development when exposure occurred (Inouye and Kajiwara 1988). Primarily developmental disturbances of the brain (e.g., smaller brains, dilated lateral ventricles, reduced size of hippocampus and nucleus caudate-putamen) occurred with exposures at 3, 4, or 5 weeks of pregnancy. Exposure during a later pregnancy stage (6 or 7 weeks) produced widespread focal degeneration of neurons in the neocortical region of fetal brains. In hamsters, methylmercuric chloride administered as a single dose of 8 mg on Gd 10 or of 1.6 mg Hg/kg/day on Gd 10–15 resulted in degeneration of cerebellar neurons in neonates (Reuhl et al. 1981a). Examination of offspring 275–300 days after birth showed similar degeneration (Reuhl et al. 1981b). It was not reported whether these histopathological changes correlated with behavioral changes.

Functional disturbances have also been observed following exposure to methylmercuric chloride during gestation. A single dose of 16 mg Hg/kg as methylmercuric chloride administered on Gd 13, 14, 15, 16, or 17 resulted in decreased spontaneous locomotor activity at 5 weeks of age, decreased righting response, abnormal tail position during walking, flexion, and crossing of the hindlimbs (Inouye et al. 1985). Histopathological examination of these animals showed dilated lateral ventricles, decreased caudate putamen, and a slightly simplified cerebellar pattern. Neonates in this study were cross-fostered within 24 hours after birth to prevent intake of mercury through the milk. The offspring of mice receiving 3, 5, or 10 mg Hg/kg/day as methylmercuric hydroxide on day 8 of gestation exhibited a decreased number of avoidances, an increased number of escapes, and an increased trials to reach the criterion on a 2-way avoidance task (Hughes and Annau 1976). No effects were present in the 2 mg Hg/kg dose group. Offspring of rats exposed to 4 mg Hg/kg/day as methylmercuric chloride on Gd 6–9 showed impaired swimming behavior, increased passiveness, and an increased startle response (Stoltenburg-Didinger and Markwort 1990). At 0.4 mg Hg/kg/day, the offspring showed an increased startle response, but at 0.04 mg

Hg/kg/day, no effects were observed. Exposure to 6.4 mg Hg/kg as methylmercuric chloride on Gd 15 resulted in decreases in spontaneous locomotor activity, increased sensitivity to pentylenetetrazol-induced convulsions, and a transient increase in γ-aminobutyric acid (GABA) and benzodiazepine receptors (Guidetti et al. 1992). Using the same exposure paradigm, shorter avoidance latency was observed in 14-, 21-, and 61-day-old rats (Cagiano et al. 1990). Glutamate receptor binding affinity and dopamine receptor number were also significantly affected in the brains of these offspring. Thus, multiple neurotransmitter systems may participate in the neurological effects observed.

A sensitive test for neurological effects of gestational exposure to methylmercury is operant behavioral performance (i.e., rewarded responses to total lever presses). Bornhausen et al. (1980) reported a significant reduction in operant behavioral performance in 4-month-old rat offspring exposed to methylmercuric chloride at 0.008 mg Hg/kg/day on Gd 6–9. A dose of 0.004 mg Hg/kg/day did not alter the behavioral performance of the offspring. No other studies have confirmed this result to date.

Pregnant hamsters received single oral gavage doses of 2.5–63 mg Hg/kg as mercuric acetate on Gd 8 (Gale 1974). Decreased crown-rump length was observed at 5 mg Hg/kg, although this effect did not increase linearly with the dose level. The incidence of resorptions increased at 22 mg Hg/kg and occurred in a dose-related manner. Other effects that occurred at higher dose levels included growth-retarded or edematous embryos. No significant developmental effects were evident at 2.5 mg Hg/kg.

Developmental neurotoxicity and changes in tissues, including the liver and immune system, have been observed in studies in which exposure occurred prior to gestation and/or was continued after gestation for intermediate durations. Retarded behavioral maturation (swimming behavior, righting reflexes) and learning disability (maze learning) were demonstrated in rat offspring receiving a diet of 0.1 mg Hg/kg/day (unspecified forms of mercury) in a contaminated fish diet from Gd 1 to postnatal day 42 (Olson and Boush 1975). Decreased performance in a paradigm intended to assess tactile-kinesthetic function (use of too much force) was observed in offspring of rats exposed to 0.08 mg Hg/kg/day as methylmercuric chloride for 2 weeks prior to mating through weaning (Elsner 1991). No morphological changes were observed in the brains of the offspring of maternal rats given 0.195 mg Hg/kg/day as methylmercuric chloride for 14 weeks prior to mating through postpartum day 50 (Lindstrom et al. 1991). However, norepinephrine levels in the cerebellum of offspring were significantly increased. Methylmercuric chloride at doses of 0.25 mg Hg/kg/day administered beginning several weeks prior to gestation resulted in an increase in the incidence of unilateral or bilateral ocular lesions in the neonates, associated with histological changes in the

Harderian, exorbital lachrymal, and parotid salivary glands (Khera and Tabacova 1973). No effects occurred at the lower dose of 0.05 mg Hg/kg/day. Fetal liver injury at the ultrastructural level (e.g., decreased mitochondrial volume density, enzyme activity, and protein synthesis in fetal hepatocytes) was reported after chronic exposure to low doses of 0.7–1.4 mg Hg/kg/day as methylmercury in the drinking water of rats for 1 month before mating and up to the end of pregnancy (Fowler and Woods 1977). The developing immune system was affected in newborn Sprague-Dawley rats exposed to 0.5 mg Hg/kg/day as methylmercury through the placenta and/or milk (Ilback et al. 1991). Results showed that exposure caused increased thymus lymphocyte activity in offspring exposed during gestation and lactation, while decreased spleen lymphocyte activities were observed in offspring exposed during lactation only. Cell-mediated cytotoxicity was decreased by 41% ($p<0.01$) in offspring exposed during gestation and lactation.

In chronic-duration studies, impaired visual function has been reported. Impaired visual recognition memory was reported for 50-to-60-day-old monkeys born to mothers that received 0.04 or 0.06 mg Hg/kg/day as methylmercury in apple juice for an average of 168 or 747 days prior to mating (Gunderson et al. 1988). In this study, neonates were separated from their mothers at birth to prevent intake of mercury while nursing. Impaired spatial visual function was observed in another study in which infant monkeys were exposed to 0.01, 0.025, or 0.05 mg Hg/kg/day as methylmercuric chloride throughout gestation, followed by gavage doses 5 days a week until 4–4.5 years of age (Rice and Gilbert 1990). The study was limited, however, because only 1–5 animals were tested at each dose level. Furthermore, two of the high-dose animals were unavailable for testing as a result of overt mercury intoxication, and thus the two most affected animals were eliminated. Slight changes in temporal discrimination were also observed in these monkeys at 2–3 years of age (Rice 1992). However, no LOAEL can be determined for this effect because results from monkeys at the mid- and high doses were pooled.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3 for organic mercury.

2.2.2.7 Genotoxic Effects

Several studies were located regarding genotoxic effects in humans after oral exposure to organic mercury. A positive correlation between blood mercury levels and structural and numerical chromosome aberrations was found in the lymphocytes of 23 people who consumed mercury-contaminated fish (Skerfving et al. 1974). However, several factors preclude acceptance of these findings as valid. With respect to the

increased incidence of structural aberrations, smokers were not identified, it was unclear whether chromatid and chromosome gaps were excluded from the evaluation, and significant effects were obtained only from lymphocyte cultures initiated several days after collection. The more reliable approach of initiating cultures on the day of collection did not yield significant results. Similarly, the evidence of aneuploidy is suspect. Considering the age of the subjects (54–89 years in the control group and 47–84 years in the exposure group), the average incidence of aneuploidy in the control (1.8%) and exposed (2.8%) groups was lower than would be expected, according to results indicating that aneuploidy in humans increases with age (Cimino et al. 1986). Skerfving et al. (1970) also reported that a significant ($p<0.05$) correlation was found between mercury concentrations and chromosome breaks in the lymphocytes of 9 subjects who had consumed fish contaminated with methylmercury. For reasons similar to those listed for the evaluation of the report by Skerfving et al. (1974), there is not yet a scientific basis to support an association between consumption of fish containing high methylmercury and clastogenesis in human lymphocytes. In addition, one of the test subjects was regularly medicated with isoproterenol, a known clastogen for mammalian cells. Although an increased incidence of sister chromatid exchange was reported in humans who ate mercury-contaminated seal meat (Wulf et al. 1986), data on smoking and consumption of other heavy metals (lead and cadmium) were not provided. Therefore, the possible relevance of the increase in sister chromatid exchanges (SCEs) cannot be determined. A statistical correlation between micronucleus frequency in peripheral blood lymphocytes and total mercury concentration in blood ($p=0.00041$), as well as between micronucleus frequency and age ($p=0.017$), was found in a population of fishers who had eaten mercury contaminated seafood (Franchi et al. 1994).

A single oral gavage administration of mercuric chloride to male Swiss albino mice (5 per group) at doses of 2.2, 4.4, or 8.9 mg Hg/kg induced a dose-related increase in the frequency of chromosome aberrations and the percentage of aberrant cells in the bone marrow (Ghosh et al. 1991). Chromatid breaks were the most common aberration. There was no clear evidence of unscheduled DNA synthesis (UDS) in lymphocytes harvested from male and female cats (3 per group) chronically exposed (39 months) to dietary concentrations of 0.0084, 0.020, or 0.046 mg Hg/kg/day as methylmercury (Miller et al. 1979). In a parallel study, significant increases in nuclear abnormalities were scored in bone marrow cells collected from the three treatment groups (5–8 cats per group); the response, however, was not dose-related. Signs of compound toxicity (slight neurological impairment and minimal central nervous system pathology) were seen in the high-dose group, but these animals yielded the lowest number of abnormal chromosome figures.

Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

Inorganic Mercury. No studies were located regarding cancer in humans after oral exposure to inorganic mercury.

Results of a 2-year National Toxicology Project (NTP 1993) study indicated that mercuric chloride may induce tumors in rats. Fischer 344 rats (60 per sex per group) received 0, 1.9, or 3.7 mg Hg/kg/day as mercuric chloride by gavage for 2 years. There were increases in the incidence of forestomach squamous cell papillomas and an increase in the incidence of thyroid follicular cell carcinomas in males in the 3.7 mg/kg group (NTP 1993). In $B6C3F_1$ mice exposed to 0, 3.7, or 7.4 mg Hg/kg/day as mercuric chloride, renal tubule tumors were evident in 3 of the 49 high-dose males (NTP 1993), but the incidence of these tumors was not significantly increased. There was no evidence of carcinogenicity in the exposed female mice. The cancer effect level (CEL) from this study is recorded in Table 2-2 and is plotted in Figure 2-2.

Organic Mercury. No studies were located regarding cancer in humans following oral exposure to organic mercury.

Significant increases in renal tumors have been observed in rodents exposed either to methylmercuric chloride or phenylmercuric acetate. Dietary exposure of both ICR and $B6C3F_1$ mice for 2 years has resulted in significant increases in renal epithelial cell tumors (Hirano et al. 1986; Mitsumori et al. 1981, 1990). At the highest dose of 0.69 mg Hg/kg/day (dose levels 0, 0.03, 0.14, 0.69), only male $B6C3F_1$ mice (n=60M,60F) showed significant increases in the incidence of renal epithelial cell adenomas and carcinomas (Mitsumori et al. 1990). No tumors were observed in the females $B6C3F_1$ mice exposed to up to 0.6 mg Hg/kg/day. The high dose in males and females also resulted in chronic nephropathy and regeneration of the proximal tubules (more severe in males). At 0.73 mg Hg/kg/day, male ICR mice showed significant increases in the incidence of epithelial cell adenocarcinomas (Hirano et al. 1986). Similar effects were observed in the ICR male mice at the highest dose of 1.6 mg Hg/kg/day (Mitsumori et al. 1981). No increase in tumor incidence was observed in rats exposed via the diet for 2 years to methyl-mercuric chloride at doses as high as 0.1 mg Hg/kg/day (Verschuuren et al. 1976).

Exposure of male Wistar rats to phenylmercuric acetate in the drinking water at 4.2 mg Hg/kg/day for 2 years resulted in a significant increase in renal cell adenomas (Solecki et al. 1991). However, this report

is limited because the assay was not intended as a carcinogenicity assay, and too few animals were used (20 per dose) to adequately assess the carcinogenicity of the phenylmercuric acetate.

No tumors or precancerous lesions were reported in rats administered 0.04–66.0 mg Hg/kg/day as phenylmercuric acetate in the diet for 2 years (Fitzhugh et al. 1950). As discussed above for mercuric acetate, no conclusions can be drawn from this study because of its limitations.

In a 2-year oral chronic-duration feeding study, no tumors or precancerous lesions were noted in rats administered mercuric acetate in the diet at doses of 0.2–66 mg Hg/kg/day (Fitzhugh et al. 1950); no conclusions could be derived on the carcinogenicity of mercuric acetate. The study was limited because the group sizes were small (10–12 rats per group); survival data were not reported; a considerable but unspecified number of rats reportedly died from pneumonia, which reduced the sensitivity of the study to detect a carcinogenic response; and only limited histopathological analyses were performed.

The CELs from these studies are recorded in Table 2-3 and plotted in Figure 2-3.

2.2.3 Dermal Exposure

Occupational exposure to both inorganic and organic mercury compounds may result in dermal as well as inhalation exposure to these chemicals. The results reported in Section 2.2.1 regarding the effects associated with occupational exposure to mercury-containing chemicals will not be repeated here. The studies discussed below concern reports in which dermal exposure was expected to be the primary route of exposure.

2.2.3.1 Death

Inorganic Mercury. A case study reported that a 27-year-old woman died 4 days after inserting an 8.75-g tablet of mercuric chloride (93 mg Hg/kg assuming 70-kg weight) into her vagina (Millar 1916). Another case study described the death of a man who had been receiving treatment for a wound with daily applications for approximately 2 months of a Chinese medicine containing mercurous chloride (Kang-Yum and Oransky 1992). The patient was reported to have died from renal failure.

An early study conducted by Schamberg et al. (1918) reported death in rabbits after an ointment containing 50% mercury was “rubbed” into the skin for 5 minutes; however, inadequate experimental methodology and an absence of study details prevent a determination of the amount of mercury involved.

Organic Mercury. No studies were located regarding death in humans or animals after dermal exposure to organic mercury.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, hematological, musculoskeletal, or hepatic effects in humans or animals after dermal exposure to inorganic or organic mercury.

Cardiovascular Effects

Inorganic Mercury. A number of children who were treated with an ammoniated mercury ointment or whose diapers had been rinsed in a mercuric chloride solution experienced tachycardia and elevated blood pressure (Warkany and Hubbard 1953).

No studies were located regarding cardiovascular effects in animals after dermal exposure to inorganic mercury.

Organic Mercury. No studies were located regarding cardiovascular effects in humans or animals after dermal exposure to organic mercury.

Gastrointestinal Effects

Inorganic Mercury. Patients who were hypersensitive to mercury (indicated by positive patch tests) developed stomatitis at the sites of contact with amalgam fillings (Veien 1990). The contact stomatitis faded when amalgam fillings were removed but persisted in a patient who chose to leave them in place. Abdominal pain, nausea, vomiting, and black stools were seen in a man who had been receiving treatment for a wound with daily applications for about 2 months of a Chinese medicine containing mercurous chloride (Kang-Yum and Oransky 1992). Anorexia was reported in a child who had been treated with an ammoniated mercury-containing ointment (Warkany and Hubbard 1953). Extensive necrosis, swelling, and

ulceration in the intestinal mucosa, vomiting, and diarrhea occurred in a woman who inserted a mercuric chloride tablet into her vagina (Millar 1916).

No studies were located regarding gastrointestinal effects in animals following dermal exposure to inorganic mercury.

Organic Mercury. No studies were located regarding gastrointestinal effects in humans or animals after dermal exposure to organic mercury.

Renal Effects

Inorganic Mercury. Congested medulla; pale and swollen cortex; and extensive necrosis, degeneration, and calcification of tubular epithelium were reported in the kidneys of a 27-year-old woman after inserting an 8.75-g tablet of mercuric chloride (93 mg Hg/kg assuming 70-kg weight) into her vagina (Millar 1916). Decreased renal output and renal failure were reported in a man who had been receiving daily applications for 2 months of a Chinese medicine containing mercurous chloride (Kang-Yum and Oransky 1992). A woman who used a depigmenting cream containing mercuric ammonium chloride for approximately 18 years developed an impaired renal function (Dyall-Smith and Scurry 1990). Similarly, a man who used an ointment containing ammoniated mercury for psoriasis for more than 10 years developed a nephrotic syndrome with severe edema (Williams and Bridge 1958). A study of young African women who used skin lightening creams containing ammoniated mercuric chloride for 1–36 months (average, 13 months) showed a nephrotic syndrome among a large portion of the women (Barr et al. 1972). The syndrome was characterized by elevated urinary protein, edema, decreased serum albumin, alpha-1-globulin, beta-globulin, and gamma globulin and increased alpha-2-globulin. Remission was observed in 77% of those who discontinued use of the creams.

No studies were located regarding renal effects in animals after dermal exposure to inorganic mercury.

Organic Mercury. No studies were located regarding renal effects in humans or animals after dermal exposure to organic mercury.

Endocrine Effects

No studies were located regarding endocrine effects in humans or animals after dermal exposure to inorganic or organic mercury.

Organic Mercury. No studies were located regarding endocrine effects in humans or animals after dermal exposure to organic mercury.

Dermal Effects

Inorganic Mercury. Contact dermatitis caused by acute, longer-term, or occupational inorganic mercury exposure has been described in a number of case reports (Bagley et al. 1987; Biro and Klein 1967; Faria and Freitas 1992; Goh and Ng 1988; Handley et al. 1993; Kanerva et al. 1993; Nordlind and Liden 1992; Pambor and Timmel 1989; Skoglund and Egelrud 1991; Veien 1990). Patch tests conducted in many of the cases show some cross-reactivity between various inorganic and organic forms of mercury (Faria and Freitas 1992; Handley et al. 1993; Kanerva et al. 1993; Pambor and Timmel 1989; Veien 1990). In these studies, dermal exposure occurred as a result of the breakage of mercury-containing thermometers or sphygmomanometers, dental amalgams containing elemental mercury, inoculation with vaccines containing merthiolate preservatives, or mercuric sulfide in tattoos. One report of contact dermatitis caused by a mercuric sulfide-containing tattoo suggested that the reaction was not to mercuric sulfide itself but to a mercury derivative that was formed in the skin (Biro and Klein 1967).

Excluding reports of contact dermatitis, limited information was obtained regarding the dermal effects of inorganic mercury. Application of an ammoniated mercury ointment to the skin of children or exposure to diapers that had been rinsed in a mercuric chloride-containing solution resulted in itching, flushing, swelling, and/or desquamation of the palms of the hands and soles of the feet (Warkany and Hubbard 1953). In addition, rashes, conjunctivitis, and/or excessive perspiration were observed. These dermal reactions were not attributed to allergic-type reactions to the mercury. A 23-month-old boy who was exposed to an unspecified form of mercury also developed a "diffuse, pinpoint, erythematous, papular rash" and bright red finger tips "with large sheets of peeling skin" (Tunnessen et al. 1987).

Application of a 1% solution of ammoniated mercuric chloride to the skin resulted in only minor irritation in 2 of 11 exposed subjects (Kawahara et al. 1993). After 18 years of using a mercury-containing cream, a

patient exhibited blue-black pigmentation in a perifollicular distribution on the chin and glabella (Dyall-Smith and Scurry 1990). A skin biopsy revealed black nonrefractile granules in the cytoplasm of macrophages in the papillary dermis and around the upper part of hair follicles. A boy who broke a thermometer in his mouth developed a mass consisting of hyperplasia of the epidermis, necrosis, and ulceration (Sau et al. 1991). This effect may have resulted from a combined effect of the physical injury and the mercury metal.

No studies were located regarding dermal effects in animals after dermal exposure to inorganic mercury.

Organic Mercury. Case report studies suggest that dermal exposure to methylmercury or phenylmercury in humans can cause rashes and blisters on the skin (Hunter et al. 1940; Morris 1960). A 33-year-old male worker exposed to methylmercury nitrate dust for 2 years developed burns and blisters on his forearm (Hunter et al. 1940). These effects healed within 9 days. Sensitivity to phenylmercuric salts is shown by individuals who developed itchy, pruritic, papular eruptions or rashes on their skin following acute dermal exposure (Morris 1960). A 54-year-old woman with a family history of atopy was found to display erythema (at 30 minutes postexposure) and urticaria (at 60 minutes) when treated topically with a 0.01% solution of phenylmercuric acetate (Torresani et al. 1993). This positive reaction was associated with aggravation of facial edema and an attack of bronchospasm. The woman, who was a farmer, was believed to have been previously exposed to phenylmercuric acetate during contact with pesticides and herbicides used on farm crops.

No studies were located regarding dermal effects in animals following dermal exposure to organic mercury.

Ocular Effects. No studies were located regarding ocular effects in humans or animals after dermal exposure to inorganic or organic mercury.

Body Weight Effects. No studies were located regarding body weight effects in humans or animals after dermal exposure to inorganic or organic mercury.

2.2.3.3 Immunological and Lymphoreticular Effects

Inorganic Mercury. As indicated above, contact dermatitis may develop as a result of acute or occupational exposure to inorganic mercury (Anneroth et al. 1992; Bagley et al. 1987; Biro and Klein

1967; Faria and Freitas 1992; Goh and Ng 1988; Nordlind and Liden 1992; Pambor and Timmel 1989; Skoglund and Egelrud 1991; Veien 1990). Patch tests conducted in many of the cases show some cross-reactivity between various inorganic and organic forms of mercury (Faria and Freitas 1992; Pambor and Timmel 1989; Veien 1990). In these studies, dermal exposure occurred as a result of the breakage of mercury-containing thermometers or sphygmomanometers, dental amalgams containing elemental mercury, or mercuric sulfide in tattoos. One report of contact dermatitis caused by mercuric sulfide in a tattoo suggested that the reaction was not to mercuric sulfide itself but to a mercury derivative that was formed in the skin (Biro and Klein 1967).

No studies were located regarding immunological or lymphoreticular effects in animals following dermal exposure to inorganic mercury.

Organic Mercury. No studies were located regarding immunological or lymphoreticular effects in humans or animals after dermal exposure to organic mercury.

2.2.3.4 Neurological Effects

Inorganic Mercury. DeBont et al. (1986) described a 4-month-old boy who had signs of acrodynia accompanied by coma, paralysis of one side of the body, generalized muscle stiffness, and muscular tremors 12 days after he was treated with yellow mercuric oxide ointment for eczema. Topical application of a depigmenting cream containing 17.5% mercuric ammonium chloride for 18 years resulted in mild tremors, anxiety, depression, and paranoid delusions in a 42-year-old woman (Dyall-Smith and Scurry 1990). Children who were treated with an ointment containing ammoniated mercury or who were exposed to diapers that had been rinsed in a mercuric chloride-containing solution experienced irritability, fretfulness, and sleeplessness (Warkany and Hubbard 1953).

No studies were located regarding neurological effects in animals after dermal exposure to inorganic mercury.

Organic Mercury. No studies were located regarding neurological effects in humans or animals after dermal exposure to organic mercury.

No studies were located regarding the following effects in humans or animals after dermal exposure to inorganic or organic mercury:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to inorganic or organic mercury.

2.3 TOXICOKINETICS

Absorption is high (approximately 70–80%) for inhaled metallic mercury vapor, and negligible for oral exposure to liquid metallic mercury. Absorption of inorganic mercuric salts may range from 2 to 38% depending upon the form and test conditions. Oral absorption of organic mercury is nearly complete, but respiratory absorption data are lacking, particularly for the alkyl mercurials.

The distribution data for metallic, inorganic, and organic mercury are consistent in identifying the kidney as the organ with the highest mercury bioaccumulation. Because of its high lipophilicity, metallic mercury can also be transferred readily through the placenta and blood-brain barrier. The oxidation of metallic mercury to inorganic divalent cation in the brain can result in retention in the brain. Inorganic mercury compounds can reach most organs; however, their low lipophilicity reduces their ability to penetrate barriers to and accumulate in the brain and fetus. The distribution of methylmercury is similar to that of metallic mercury; a relatively large amount of mercury can accumulate in the brain and fetus (compared to inorganic mercury) because of its ability to penetrate the blood-brain and placental barriers and its conversion in the brain and fetus to the inorganic divalent cation.

Metallic mercury can be oxidized to inorganic divalent mercury by the hydrogen peroxidase-catalase pathway, which is present in most tissues. The inorganic divalent cation can, in turn, be reduced to

metallic mercury. The mercurous ion is unstable in the presence of sulfhydryl groups, and undergoes disproportionation into one atom of metallic mercury and one ion of mercuric mercury. As with metallic mercury, organic mercury can also be converted to inorganic divalent mercury; however, the extent of conversion is less than with metallic mercury.

Following exposure to metallic mercury, the elimination of mercury can occur via the urine, feces, and expired air. Following exposure to inorganic mercury (mercuric), mercury is eliminated in the urine and feces. Organic mercury compounds are excreted predominantly via the feces in humans. In animals, methylmercury is excreted in the feces, and phenylmercury compounds are initially excreted in the feces and then in the urine. Organic mercury compounds are excreted predominantly in the inorganic form. Both inorganic mercury and methylmercury are excreted in breast milk.

Absorption of metallic mercury vapor is believed to occur by rapid diffusion through the lungs. Oral absorption of inorganic mercuric mercury compounds may also involve rapid diffusion through the gastro-intestinal tract. The mechanism for oral absorption of mercurous mercury compounds is not known. Oral absorption of organic mercury is believed to depend on the ability of the organic mercury molecule to bind to molecules such as cysteine. The mechanism of action of inorganic and organic mercury compounds may involve the affinity of these chemicals for sulfhydryl or thiol groups of proteins and other biological compounds.

2.3.1 Absorption

Absorption following inhalation of metallic mercury vapors is relatively high. Absorption following acute oral exposure to metallic mercury is negligible in both humans and animals. Methyl- and phenylmercury compounds are absorbed much more readily than inorganic mercury. Animal studies suggest oral absorption of both organic and inorganic mercury may be influenced by age and diet. Limited information was located regarding dermal absorption of inorganic or organic mercury compounds in humans or animals.

2.3.1.1 Inhalation Exposure

Metallic and Inorganic Mercury. There are limited quantitative data on the absorption of metallic mercury vapor by humans after inhalation exposure, although it is the most common route of inorganic mercury uptake. Metallic mercury is highly lipophilic, and absorption of the inhaled vapor, followed by rapid diffusion across the alveolar membranes of the lungs into the blood, has been reported to be substantial. Exposure to 0.1–0.2 mg/m^3 elemental mercury vapor resulted in approximately 74–80% of inhaled elemental mercury vapor being retained in human tissues (Hursh et al. 1976; Teisinger and Fiserova-Bergerova 1965). Indirect evidence of rapid absorption was provided by elevated mercury levels found in red blood cells, plasma, and excreta of 5 volunteers who inhaled radiolabeled mercury for 14–24 minutes (Cherian et al. 1978). Elevated blood levels of mercury were also observed in humans following a brief occupational exposure (3 days) to less than 0.1 mg/m^3 metallic mercury vapor (Barregard et al. 1992).

Recently, Sandborgh-Englund et al. (1998) evaluated the absorption, blood levels, and excretion of mercury in humans after a single dose of mercury vapor. Nine healthy volunteers (2M, 7F) were exposed to 400 µg Hg/m^3 mercury vapor in air (median 399 µg Hg/m^3; range, 365–430 µg Hg/m^3) for 15 minutes. This dose corresponded to 5.5 nmol Hg/kg body weight. Samples of exhaled air, blood, and urine were collected for 30 days after exposure. The median retention of elemental Hg was 69% of the inhaled dose. During the first 3 days after exposure 7.5–12% of the absorbed dose was lost by exhalation, with the median half-time of Hg in expired breath being 2 days. In blood and plasma, a rapid absorption phase of Hg was seen, followed by a biexponential decline of the curves in both media. A substantial interindividual variation was observed in the area under the concentration-time curves of Hg in blood and plasma. In plasma, the median half-time of the second phase was 10 days. About 1.0% of the absorbed Hg was excreted via the urine during the first 3 days after exposure whereas the estimated amount excreted during the 30 days ranged from 8 to 40%. In order to evaluate the chronic exposure to mercury from dental amalgam in the general population, the daily Hg dose from the fillings was estimated based on the plasma Hg levels of subjects with amalgam fillings and the plasma clearance obtained in this study. The daily dose was estimated to be from 5 to 9 µg/day in subjects with an average number of amalgam fillings.

There are few reports regarding the respiratory absorption of elemental and inorganic mercury compounds in animals. Elevated levels of mercury were detected in blood and tissues of pregnant or nursing guinea pigs after short-term exposure (2–2.5 hours) to metallic mercury vapors (6–10 mg/m^3) (Yoshida et al.

1990, 1992). Following repeated exposure (5 weeks) of rats to mercury vapor (1 mg/m^3), high levels were detected in the blood and brain (Warfvinge et al. 1992). The absorption of inorganic divalent mercury has not been measured, but it is estimated to be approximately 40% in dogs (Morrow et al. 1964).

Organic Mercury. No studies were located regarding absorption in humans or animals after inhalation exposure to compounds of phenyl- or methylmercury. However, indirect evidence indicates organic mercury can be absorbed readily through the lungs. Following inhalation of ^{203}Hg-labeled dimethyl-mercury, radioactivity was excreted within 6 hours, followed by a slower excretion phase (Ostlund 1969).

2.3.1.2 Oral Exposure

Metallic and Inorganic Mercury. Few studies in humans were located regarding absorption of ingested metallic or inorganic mercury. For metallic mercury, ingesting small amounts such as contained in a standard thermometer (about 0.1 mL or about 1 g) does not produce symptoms of intoxication (Wright et al. 1980). Reports of ingestion of substantial amounts of elemental mercury indicate that absorption is negligible (Sue 1994; Wright et al. 1980). Two case histories were identified on acute effects of relatively large ingestions of metallic mercury. The first case history was described an ingestion of 15 mL (204 g) of metallic mercury by a 17-year-old male storekeeper who swallowed mercury from the pendulum of a clock (apparently out of curiosity rather than as a suicide attempt). On admission, and 24 hours later, he was symptom free, and physical examination was normal. The patient had no gastrointestinal symptoms, and was treated with a mild laxative and bed rest. The results of serial daily urine mercury estimates were normal (all less than 15 µg), and did not suggest significant absorption. The radiological investigation illustrated a characteristic pattern of finely divided globules of mercury in the gastrointestinal tract (Wright et al. 1980).

A second and massive incidence of ingestion involved a 42-year-old man who had spent much of his life (since the age of 13) repairing instruments that contained mercury. He intentionally ingested an estimated 220 mL (about 3,000 g) of mercury (Lin and Lim 1993). Upon admission, the patient presented with significantly elevated mercury blood levels (103 µg/L, normal <10 µg/L) and urine levels (73 µg/L, normal <20 µg/L). It is not known how much the occupational exposure had contributed to these levels. The patient was treated with immediate gastric lavage and cathartics. He also received D-penicillamine 1 g/day orally for 7 days. Blood and urine mercury levels obtained 3 days after chelation therapy were 116.9 and 22.9 µg/L, respectively. By 2 weeks postexposure, most of the mercury had been excreted in the feces and

was measured at a total volume of 220 mL (this number was used to estimate the amount initially ingested). The patient was lost to follow-up for 6 months, but at 10 months following the incident, blood mercury had decreased to 1 µg/L and urine mercury to µg/L.

Approximately 15% of a trace dose of mercuric nitrate in an aqueous solution or bound to calf liver protein was absorbed by the gastrointestinal tract of humans (Rahola et al. 1973). The mercurous ion demonstrated limited absorption. No information was located regarding the percentage of absorption of mercuric chloride by the gastrointestinal tract of humans. However, an extremely high serum inorganic mercury concentration (116.5 nmol/mL) was found in a woman who ingested a potentially lethal dose of powdered mercuric chloride (13.8 mg Hg/kg) (Suzuki et al. 1992). Similarly, no information was located regarding the percentage of absorption of mercuric sulfide by the gastrointestinal tract in humans. However, elevated mercury was detected in the urine of two subjects who ingested an unspecified amount of mercuric sulfide (Yeoh et al. 1989).

A number of animal studies indicate absorption of inorganic mercury in the 10–30% range. In earlier studies, absorption rate was reported as low. Only 1–2% of an orally administered dose of mercuric chloride was absorbed in mice (Clarkson 1971). In rats, using whole-body retention data, estimated mercuric chloride absorptions of 3–4, 8.5, and 6.5% were calculated for single oral doses of 0.2–12.5, 17.5, and 20 mg/kg, respectively (Piotrowski et al. 1992). More recent studies using whole-body retention data, however, indicate absorption of 20–25% calculated from single oral doses of 0.2–20 mg Hg/kg as mercuric chloride in mice. Comparison was made of retention data after oral and intraperitoneal dosing, taking excretion and intestinal reabsorption into account (Nielsen and Andersen 1990). In a subsequent study, the whole-body retention of mercury after mercuric chloride administration was observed to initially decline rapidly, indicating incomplete intestinal absorption (Nielsen and Andersen 1992). Mercury was rapidly cleared from the gastrointestinal tract (to <30% of the initial dose within 2 days), and relative carcass retention increased throughout the experimental period, reaching levels around 40% of initial whole-body retention. Blood levels of mercury were closely correlated to whole-body retention of mercury during the first 3 days after administration of mercuric chloride (1 mg Hg/kg). After the initial 3 days, the amount of mercury in the blood declined more rapidly than the whole-body burden.

Morcillo and Santamaria (1995) report absorption of 30–40% for radiolabeled mercuric chloride when administered in drinking water at 5, 50, and 500 µM Hg for 8 weeks to male rats. The percentage of total

mercury excreted by the fecal route was significantly lower in the 500 compared to the 5 and 50 µM Hg group.

The rate of oral absorption of mercuric mercury compounds in rats is dependent on several factors (e.g., intestinal pH, compound dissociation) (Endo et al. 1990). Age and diet also can influence the extent of absorption in mice (Kostial et al. 1978). One-week-old suckling mice absorbed 38% of the orally administered mercuric chloride, whereas adult mice absorbed only 1% of the dose in standard diets. When the adult mice received a milk diet instead of the standard diet, absorption increased to 7% of the administered dose (Kostial et al. 1978).

Several studies suggest that the bioavailability of mercuric sulfide in animals is less than that of mercuric chloride (Sin et al. 1983, 1990; Yeoh et al. 1986, 1989). For example, Sin et al. (1983) found an increase in tissue levels of mercury in mice orally exposed to low doses of mercuric chloride, but elevated levels of mercury were not found in the tissues of mice fed an equivalent weight of mercury as mercuric sulfide. This finding indicates a difference in bioavailability between $HgCl_2$ and HgS in mice. However, a quantitative determination of the relative bioavailabilities of mercuric sulfide versus mercuric chloride has not been derived in the available studies. Furthermore, the relative bioavailability of mercuric sulfide in humans has not been examined.

Organic Mercury. Organic mercury compounds are more readily absorbed by the oral route than inorganic mercury compounds. Based on retention and excretion studies in humans, approximately 95% of an oral tracer dose of aqueous methylmercuric nitrate was absorbed (Aberg et al. 1969). Absorption of mercury was also reported in studies in which volunteers received doses of methylmercury bound to protein (Miettinen 1973) or ate bread contaminated with a fungicide that contained methylmercury (Al-Shahristani et al. 1976); however, no quantitative data regarding the percentage of absorption were available.

In vitro evidence suggests that organic mercury is also readily absorbed in the gastrointestinal tract and that methylmercuric chloride is absorbed to a greater extent than phenylmercuric chloride (Endo et al. 1989). Complexing of methylmercury with nonprotein sulfhydryls also may play a role in intestinal absorption and reabsorption (Urano et al. 1990). Phenylmercuric salt in the diet was completely absorbed in mice (Clarkson 1972a) and readily absorbed in rats following long-term oral administration (Fitzhugh et al. 1950). Absorption was nearly complete within 6 hours after female cynomolgus monkeys were given 0.5 mg Hg/kg as methylmercuric chloride by gavage (Rice 1989b). Following a single oral exposure

(1 mg/kg) of methylmercuric chloride, the level of mercury in the blood of mice declined slowly. At day 14 post-dosing, the blood level was still around 25% of the value at day 1 (Nielsen 1992). Blood levels of mercury were closely correlated to whole-body retention of mercury during the first 3 days after administration of methylmercuric chloride (1 mg Hg/kg) (Nielsen and Andersen 1992). However, at later times after administration, the amount of mercury in the blood declined more rapidly than the whole-body burden. The gastrointestinal retention of mercury slowly decreased in mice given organic mercury. This phenomenon is probably the result of biliary excretion and reabsorption of mercury (Nielsen and Andersen 1992).

Bioavailability of methylmercury in food. Measurements of absorption and toxicity have generally been made using aqueous solutions of methylmercury. The absorption and bioavailability of methylmercury in food, specifically fish and bread, may be affected by dietary components. Potential confounders that may affect bioavailability of methylmercury are dietary phytate and other dietary fibrous materials found in bread and the complexation of methylmercury with selenium in fish.

Dietary fiber and phytate. Dietary fiber and phytate are known as potential inhibitors of the absorption of divalent cations; however, the literature regarding the effect of dietary fiber and phytate on the bioavailability of minerals is contradictory. Data by Yannai and Sachs (1993) indicate that phytate does not affect methylmercury absorption. Yannai and Sachs (1993) compared the absorption by rats of mercury found intrinsically in experimental fish meal with and without added phytate and found no significant differences in the absorption of Hg (93±5%) between 2 experimental fish meal diets (containing 1.4 µmol Hg/kg diet), with or without added sodium phytate. The authors speculated that phytate might be preferentially bound to zinc, iron, and copper, which were present at much higher concentrations in the diet.

In another experiment by Yannai and Sachs (1993), the absorption of mercury was reduced when rats were fed a mercury-contaminated corn diet and corn silage meal. Mercury was incorporated intrinsically into the corn diet using radioactive isotopes (^{203}Hg) infused by capillary action into the stalks of developing corn plants, which then incorporated trace amounts of isotopes into developing kernels. The corn silage meal was from a crop grown in the vicinity of an industrial zone and contained elevated amounts of mercury. Reduced absorptions of 48 and 51% were found for the corn silage and corn diet experiments, respectively.

The reduced bioavailability of the plant food diet compared with the animal-based diet (fish meal) may be due to the presence of indigestible fibrous materials present in plants. Another factor that might affect absorption is the form of mercury (^{203}Hg and methylmercury in the corn and fish meal diets, respectively). The experiments by Yannai and Sachs (1993) are different from other absorption experiments because mercury was intrinsic to the fish, grain, or silage, while in other studies mercury is simply mixed with the experimental diet, usually as mercury salts. In the Iraqi epidemic, methylmercury fungicide was applied extrinsically to wheat that was made into bread. However, no studies were located that measured the absorption of methylmercury when mixed with grain. It is also not known whether the putative component(s) of grain affecting bioavailability are the same in corn and wheat.

Interaction with selenium in diet. The co-administration of methylmercury and selenium is known to depress methylmercury toxicity (Cuvin-Aralar and Furness 1991; Imura and Naganuma 1991). Furthermore, the level of selenium in human hair has been found to negatively correlate with the level of mercury in brain tissue (Suzuki et al. 1993). Methylmercury forms a bismethylmercury selenide complex. Selenium in foods (especially fish) may also complex with methylmercury and, therefore, may potentially reduce the bioavailability of methylmercury. The available data indicate that neither methylmercury uptake nor bioavailability is affected by its presence in fish. Experimental studies on the metabolism of methyl-mercury in humans following oral ingestion using methylmercury bound to fish muscle protein have shown that absorption is almost complete (95% absorbed) (Miettinen 1973). Animal studies also support this absorption value. Data on cats given fish homogenates indicate absorptions of $90% of methylmercury added to the homogenate, of methylmercury accumulated by fish *in vivo*, or from methylmercury proteinate (Berglund et al. 1971). Using blood and tissue levels as evidence of absorption, Charbonneau et al. (1976) concluded that there was no difference in the biological availability of methylmercury administered to adult cats (0.003, 0.0084, 0.020, 0.046, 0.074, or 0.176 mg Hg/kg/day 7 days a week for 2 years) either as pure methylmercuric chloride in corn oil added to a diet containing uncontaminated fish or as methylmercury-contaminated fish. In the 2 highest dose groups (0.074 and 0.176 mg Hg), at 100 weeks of exposure no significant differences were seen in total mercury concentrations in blood between groups receiving the dose as methylmercuric chloride or as contaminated fish at the same dose level. In addition, monthly blood levels were comparable for all dose groups. No significant differences were seen at 100 weeks in total mercury concentrations in the nervous system tissue or other tissues (renal cortex, renal medulla, liver, spleen, adrenal, bladder, atria, ventricle, ovaries, testes, muscle) between the 2 highest dose groups receiving the dose as methylmercuric chloride or as contaminated fish at the same dose level.

2.3.1.3 Dermal Exposure

Metallic and Inorganic Mercury. Hursh et al. (1989) conclude that dermal absorption of mercury vapor poses a very minor occupational hazard compared to inhalation exposure. They measured dermal absorption of radiolabeled metallic mercury vapor in five human volunteers, using arm skin as representing the whole body skin. About half of the mercury taken up was shed by desquamation of epidermal cells during the following several weeks. The remainder was slowly and diffusely released into the general circulation in contrast to the rapid release and more focal release from the lungs. When absorption for the total skin area (as represented by the forearm skin) was compared with the inhalation route for the same ambient concentration, the dermal route absorbed was estimated at 2.6% of the amount absorbed by the lung.

There was no information found on the dermal absorption of liquid metallic mercury, but unless the skin surface was damaged or the contaminated surface was occluded, it would not be expected to be high (i.e., in light of the very low absorption rate from the gastrointestinal tract). On the other hand, sloughing from the gastrointestinal tract may account for the low rate of absorption.

Indirect evidence of dermal absorption is provided by clinical case studies in which mercury intoxication was reported in individuals following dermal application of ointments that contained inorganic mercury salts (Bourgeois et al. 1986; DeBont et al. 1986).

Absorption of mercurous salts in animals can occur through the skin (Schamberg et al. 1918); however, no quantitative data are available. The rate of absorption for mercuric chloride was not evaluated in any study. However, skin biopsies taken from 2 to 96 hours after application of a 0.1% solution of mercuric chloride showed electron-dense deposits, tentatively identified as mercury, in the cells in the dermis, indicating that mercuric chloride could penetrate the outer layer of the skin (Silberberg et al. 1969).

Organic Mercury. No information was identified for absorption of methylmercury via dermal absorption. There is extremely important hazard assessment information on the dermal absorption of dialkylmercurials. A case history indicates nearly complete absorption of dimethylmercury through the skin resulting in a highly toxic exposure pathway. The exposure occurred to a 48-year-old female chemistry professor who was admitted to the hospital 5 months (154 days) after she inadvertently spilled several drops (estimated at 0.4–0.5 mL) of dimethylmercury from the tip of her pipette onto the back of her disposable latex gloves

(Blayney et al. 1997; Nierenberg et al. 1998). The spill was cleaned and the gloves disposed of. Hair analysis on a long strand of hair revealed that, after a brief lag time, mercury content rose rapidly to almost 1,100 ppm (normal level <0.26 ppm, toxic level >50 ppm), and then slowly declined, with a half-life of 74.6 days. These results support the occurrence of one or several episodes of exposure, and are consistent with laboratory notebook accounts of a single accidental exposure. Testing of family members, laboratory coworkers, and laboratory surfaces also failed to reveal any unsuspected mercury spills or other cases of toxic blood or urinary mercury levels. Permeation tests subsequently performed on disposable latex gloves similar to those the patient had worn at the time of the lone exposure revealed that dimethylmercury penetrates such gloves rapidly and completely, with penetration occurring in 15 seconds or less and perhaps instantly. Severe neurotoxicity developed 5 months postexposure and the patient died 9 months postexposure. The mercury content of hair, blood, and urine were monitored from 5 months postexposure (i.e., following admission of the patient to the hospital) until the patient died. Based on the half-lives and kinetics of mercury in the body, the hair and blood levels were used to estimate the total body burden and the amount of the initial acute dermal dose. They determined that a dose of 0.44 mL of liquid Dimethylmercury (about 1,344 mg), if completely absorbed, would have been sufficient to have produced the levels observed in the patient. This amount is in good agreement with the patient's account and the laboratory records on the amount spilled. Some inhalation exposure, however, could also have occurred during the cleanup of the spill, so this finding needs additional confirmation.

Infants exposed to diapers that had been treated with a phenylmercury fungicide exhibited higher urinary levels of mercury than unexposed infants (Gotelli et al. 1985). In rats, dermal absorption of phenylmercuric acetate from the vaginal tract was 75% of the dose within 8 hours after administration (Laug and Kunze 1949).

2.3.1.4 Other Routes of Exposure

There is some information on the subcutaneous injection of metallic mercury. Schwarz et al. (1996) describe a case history of a female nurse who accidentally plunged a mercury thermometer into her left hand while shaking it. Radiographic imaging revealed that some liquid metallic mercury had infiltrated into the soft tissues of her palm (amount unspecified). The diffusely distributed mercury could not be removed surgically. No immediate follow-up mercury levels in blood or urine were reported. A slightly elevated blood mercury concentration (15 µg/L, toxic level >50) was reported 2 years after this event, which then

declined (no reason provided). Other sources of mercury could have caused the increase, so little can be concluded about how much of the subcutaneous liquid mercury entered the systemic circulation.

In a much more informative case history, a 19-year-old man had injected mercury subcutaneously (Bradberry et al. 1996). Blood and urine mercury concentrations were followed for 6 years after presentation. Hematological and biochemical profiles were normal. Histological results indicated a chronic inflammatory reaction with granuloma formation, secondary to the globular mercury. A postoperative X-ray of the elbow indicated persistent subcutaneous mercury particles. Apart from the initial local discomfort, the patient remained asymptomatic and clinical examination revealed no abnormality up to 6 years postsurgery. No systemic features of mercury poisoning were evident. Blood mercury levels declined from 60 to 70 µg/L at 1 year postoperation to 10 µg/L at 6 years. Serial sampling results of total mercury in 24 urine collections indicated peaks up to 1.2 mg during the first year postoperation, which declined to 59 µg/L at 6 years. The elevated blood and urine levels indicate some systemic absorption. The effects of the surgery on migration of mercury from the subcutaneous tissue to the systemic circulation are not known.

2.3.2 Distribution

In humans, metallic mercury is distributed throughout the body following inhalation exposure. It can readily cross the blood-brain and placental barriers because of its high lipophilicity. After oxidation to mercuric mercury, it accumulates primarily in the kidneys. Inorganic divalent mercury compounds similarly reach all organs; however, the extent of accumulation in the brain and fetus is lower than metallic mercury because of the lower lipophilicity of inorganic mercury compounds. Organic mercury compounds distribute throughout the body following oral exposure and have the highest accumulation in the kidneys. As with metallic mercury, the ability of methyl- and phenyl mercury compounds to cross the blood-brain and placental barriers allows distribution, and subsequent accumulation, in the brain and fetus.

2.3.2.1 Inhalation Exposure

Metallic Mercury. The lipophilic nature of metallic mercury results in its distribution throughout the body. Metallic mercury in solution in the body is highly lipophilic, thereby allowing it to cross blood-brain and placental barriers with ease (Clarkson 1989). Mercury distributes to all tissues and reaches peak levels within 24 hours, except in the brain where peak levels are achieved within 2–3 days (Hursh et al. 1976).

The longest retention of mercury after inhalation of mercury vapor occurs in the brain (Takahata et al. 1970). Japanese workers who died 10 years after their last exposure to metallic mercury vapors still had high residual levels of mercury in their brains (Takahata et al. 1970). Autopsies of 3 dentists revealed 0.945–2.110 mg Hg/kg in the renal cortex, compared to 0.021–0.810 mg Hg/kg for unexposed controls (Nylander et al. 1989).

In volunteers who inhaled a tracer dose of metallic mercury vapor for 20 minutes, approximately 2% of the absorbed dose was deposited per liter of whole blood after the initial distribution was complete (Cherian et al. 1978). Uptake into the red blood cells was complete after 2 hours, but plasma uptake was not complete until after 24 hours. Mercury concentration in red blood cells was twice that measured in the plasma. This ratio persisted for at least 6 days after exposure. However, the ratios of 1–2 have been reported for metallic mercury vapor (Miettinen 1973).

Exposure of rats to mercury vapor (10–100 µg/m^3) for 6 hours a day, 5 days a week from the 4th through 11th weeks of life resulted in measurable amounts of mercury in the blood, hair, teeth, kidneys, brain, lungs, liver, spleen, and tongue, with the kidney cortex having the highest mercury concentration (Eide and Wesenberg 1993). Further, tissue concentrations were positively and significantly correlated with exposure concentrations. In this study, the rat molars were found to have the highest correlation coefficient with measured kidney mercury values, leading to a suggestion by the authors that human deciduous teeth may be useful indicators of chronic mercury exposure and of the mercury uptake by the kidneys and cerebrum (Eide and Wesenberg 1993). In another study, a 4-hour exposure of mice to metallic mercury vapor produced the highest mercury retention in the brain compared to other organs (Berlin et al. 1966). Exposure of mice to metallic mercury vapor (8 mg/m^3, for 6 hours a day for 10 days) resulted in higher mercury levels in the gray than in the white brain matter (Cassano et al. 1966, 1969). Exposure of rats to 1 mg/m^3 metallic mercury vapor for 24 hours a day every day for 5 weeks or 6 hours a day, 3 days a week for 5 weeks resulted in mean mercury brain concentrations of 5.03 and 0.71 µg/g, respectively (Warfvinge et al. 1992). Mercury was found primarily in the neocortex, basal nuclei, and the cerebellar Purkinje cells.

Mercury also accumulates in several cell types populating the dorsal root ganglia (Schionning et al. 1991). After 12–14 hours of exposure of rats to a relatively small amount of metallic mercury vapor (0.55 mg/m^3), accumulation of mercury was observed within all cell types examined (ganglion cells, satellite cells, fibroblasts, and macrophages). Mercury has also been detected in dorsal root neurons and satellite cells of

primates exposed for one year to mercury through amalgams in dental fillings or the maxillary bone (Danscher et al. 1990).

The kidney is the major organ of mercury deposition after inhalation exposure to metallic mercury vapor. Mercury concentrations in the kidneys are orders of magnitude higher than in other tissues (Rothstein and Hayes 1964). Monkeys exposed for one year to metallic mercury vapor from amalgam in dental fillings accumulated mercury in the spinal ganglia, anterior pituitary, adrenal, medulla, liver, kidneys, lungs, and intestinal lymph glands (Danscher et al. 1990). The largest deposits of mercury were found in the kidneys (2.5–5.2 ppm), specifically in the proximal tubule cells.

The kidney contains metallothionein, a metal-binding protein that is also found in fetal and maternal livers and other organs. In the kidneys, the production of metallothionein is stimulated by exposure to mercury. The increased levels of metallothionein increase the amount of mercuric ion binding in the kidneys (Cherian and Clarkson 1976; Piotrowski et al. 1973). Three classes of sulfhydryl groups have been identified in the kidneys, with metallothionein having the greatest affinity for mercury (Clarkson and Magos 1966). Low molecular-weight complexes of mercury have been identified in the urine, suggesting that they may exist in the kidneys and contribute to the kidneys' accumulation of mercury (Piotrowski et al. 1973).

Metallothionein exists in higher concentration in the fetal liver than in the maternal liver of rats. Exposure to mercury in the pregnant dam results in the binding of mercury to metallothionein in fetal liver initially, followed by a redistribution to other organs (Yoshida et al. 1990). Metallothionein and mercury levels were elevated in the kidneys of guinea pig neonates exposed to 6–10 mg/m^3 mercury vapor (Piotrowski et al. 1973).

After exposure to mercury vapor, mercury is distributed throughout the body in different chemical and physical states. Metallic mercury dissolves in the blood upon inhalation, and some remains unchanged (Magos 1967). Metallic mercury in the blood is oxidized to its divalent form in the red blood cells (Halbach and Clarkson 1978). The divalent cation exists as a diffusible or nondiffusible form. The nondiffusible form is mercuric ions that bind to protein and are held in high-molecular weight complexes, existing in equilibrium with the diffusible form.

In the plasma, the mercuric ion is predominantly nondiffusible and binds to albumin and globulins (Berlin and Gibson 1963; Cember et al. 1968; Clarkson et al. 1961). Following mercuric salt administration,

levels of mercuric ions in the plasma are similar to levels of mercuric ions in the red blood cells. Binding of mercury also occurs in tissues, and retention varies, with the brain retaining mercury the longest.

The influence of age on mercury distribution following exposure to metallic mercury was evaluated in neonatal (12 hours old) and adult guinea pigs exposed to 8 or 10 mg Hg/m^3 vapor for 120 minutes (Yoshida et al. 1989). The mercury concentrations were 28, 58, and 64% higher in the brain, lungs, and heart, respectively, of the neonates compared to the mothers. However, the mercury level in the kidneys was approximately 50% lower in the neonates. The lower uptake of mercury in the kidneys of neonates may be due to the functional immaturity of the kidneys at parturition. The higher levels in other highly perfused tissues suggest that mercury accumulation in organs is dependent on how easily metallic mercury can reach the tissues from blood. Similar findings were reported by Jugo (1976) who found higher mercury concentrations in the liver, blood, and brain, but lower concentrations in the kidneys of 2-week-old rats compared to similar tissues in 21-week-old rats. These results also suggest that infants may accumulate mercury more readily after acute exposure and, therefore, may be more likely to exhibit neurotoxicity from mercury vapors.

The extent of mercury accumulation with aging was studied in mice maintained under normal care conditions in a conventional rodent colony without exposure to known mercury sources other than background concentrations normally found in food, water, and air (Massie et al. 1993). There was no significant change in the total amount of mercury in the organs (lungs, heart, brain, and liver) from male C57BL/6J mice ranging in age from 133 to 904 days. However, the ratios of mercury levels in the brain to mercury levels in the liver and kidneys were found to increase significantly and dramatically with age. The increase with aging in the brain-to-liver and brain-to-kidneys ratios suggests that mercury removal from the brain may be less efficient in some older organisms.

Metallic mercury vapor easily penetrates the placental barrier and accumulates in fetal tissues. The high lipophilicity of metallic mercury favors its penetration across the barrier. The uptake of mercury appears to increase during the later gestation period in mice, as indicated by increased mercury accumulation in the fetus after exposure to metallic mercury (Dencker et al. 1983). Guinea pig fetuses that were exposed to 6–13 mg/m^3 mercury vapor during late gestation had elevated mercury concentrations in the liver, while the levels in other tissues were only slightly increased relative to controls (Yoshida et al. 1990). Newborn guinea pigs that were nursed by their mothers, who had been and exposed to mercury vapor (6–9 mg/m^3) for 120 minutes immediately after parturition, had the highest mercury concentrations in the kidneys,

followed by the liver and lungs (Yoshida et al. 1992). In the brain and whole blood, mercury concentrations were slightly elevated compared to nonexposed controls. Levels of mercury in the fetus were approximately 4 times higher after exposure to metallic mercury vapor than after mercuric chloride administration for mice and 10–40 times higher for rats (Clarkson et al. 1972). The transport of the mercuric ions is limited at the placental barrier by the presence of high-affinity binding sites (Dencker et al. 1983).

Inorganic Mercury. No studies were located regarding the distribution of inorganic mercury in humans or animals following inhalation exposure to inorganic mercury compounds.

Organic Mercury. No studies were located regarding the distribution of organic mercury in humans or animals following inhalation exposure to organic mercury compounds.

2.3.2.2 Oral Exposure

Metallic and Inorganic Mercury. Data on the distribution of ingested elemental mercury were not located, and data on the ingestion of inorganic mercury are limited. The metallic mercury that is absorbed from an oral exposure is expected to resemble many aspects of the distribution of mercuric salts because metallic mercury is oxidized to mercuric ion in biological fluids, and the resulting distribution reflects that of the mercuric ion. Unlike elemental mercury, however, the amount of divalent mercury that crosses the blood-brain and placental barriers is much lower because of its lower lipid solubility (Clarkson 1989).

In some studies there is a combined exposure to both organic and inorganic mercury. Oskarsson et al. (1996) assessed the total and inorganic mercury content in breast milk and blood in relation to fish consumption and amalgam fillings. Total mercury concentrations were evaluated in breast milk, blood, and hair samples collected 6 weeks after delivery from 30 lactating Swedish women. In breast milk, about half of the total mercury was inorganic and half was methylmercury, whereas in blood only 26% was inorganic and 74% was methylmercury. The results of a regression analysis for mercury in hair, blood, and milk indicated that there was an efficient transfer of inorganic mercury from blood to breast milk and that mercury from amalgam fillings was probably the main source of mercury in breast milk, while methylmercury levels in blood did not appear to be efficiently transferred to breast milk. Exposure of the infant to mercury in breast milk was calculated to range up to 0.3 µg/kg/day, of which approximately one-half was inorganic mercury. This exposure corresponds to approximately one-half the tolerable daily

intake of total mercury for adults recommended by the World Health organization. The authors concluded that efforts should be made to decrease total mercury burden in women of reproductive age Oskarsson et al. (1996).

Inorganic Mercury. The liver and kidneys of mice had the highest mercury levels 14 days after exposure to a single oral dose of 0.2–20 mg ^{203}Hg/kg as mercuric chloride (Nielsen and Andersen 1990). The brain has substantially lower mercury levels; however, retention was longest in this tissue. Sin et al. (1983) report that the kidneys also had the highest mercury levels following repeated oral exposure of mice to mercuric chloride (4–5 mg Hg/kg) for 2–8 weeks. Mercuric sulfide did not accumulate in the tissues of mice to any significant extent following exposure to low levels of mercuric sulfide (4–5 mg Hg/kg) for 2–8 weeks (Sin et al. 1983). However, the mercury content in the liver and kidneys of mice treated with higher doses of mercuric sulfide (. 8–200 mg Hg/kg/day) for 7 days was significantly increased compared to the controls (Yeoh et al. 1986, 1989). Mice fed mercuric sulfide (86 mg Hg/kg/day) for 1 week exhibited a 21-fold increase in the kidneys' mercury content ($p<0.001$) and an 8.6-fold increase in the liver content compared to controls (Yeoh et al. 1989). Moderate renal effects, with a corresponding mercury concentration of 50 µg/g in the kidneys, were seen in rats exposed to mercuric nitrate (Fitzhugh et al. 1950).

Mercury can accumulate in human hair following oral exposure to mercuric chloride (Suzuki et al. 1992). Hair mercury levels, determined using segmental hair analysis, can be used to monitor exposure to mercury and may leave a historical record of exposure or uptake. In hair cut 41 days after mercuric mercury ingestion (13.8 mg/kg), a sharp peak (40 nmol/g [8 µg/g]) was found in the 1 cm segment closest to the scalp, while the levels were #5 nmol/g in all other segments. Ninety-five days after ingestion, the peak of inorganic mercury shifted to the 2–3 cm segment, while 160 days after ingestion the peak shifted to the 3–4 cm segment. During this time, the height of the peak decreased. An estimated biological half-life of inorganic mercury in hair was 57.8 days. Inorganic mercury in hair had different patterns of longitudinal variation from that of organic mercury.

Organic Mercury. Distribution of organic mercury compounds in humans and animals is similar to that of metallic mercury. Methylmercury distributes readily to all tissues, including the brain and fetus, after absorption from the gastrointestinal tract. The uniform tissue distribution is due to methylmercury's ability to cross diffusion barriers and penetrate all membranes without difficulty (Aberg et al. 1969; Miettinen 1973). Thus, tissue concentrations tend to remain constant relative to blood levels. About 90% of the

methylmercury in blood is found in the red blood cells (Kershaw et al. 1980). The mean mercury concentrations in red blood cells were 27.5 ng/g and 20.4 ng/g in males and females, respectively, exposed to mercury, primarily from mercury-contaminated fish (Sakamoto et al. 1991). Because of this uniform distribution in tissues, blood levels are a good indicator of tissue concentrations independent of dose (Nordberg 1976).

Although distribution is generally uniform, the highest levels of organic mercury are found in the kidneys (Nielsen and Andersen 1991b; Rice 1989b; Ryan et al. 1991). After a single oral dose of 0.04, 0.2, 1, or 5 mg Hg/kg as methylmercuric chloride administered to mice, mercury was retained mostly in the kidneys and liver at 14 days postexposure (Nielsen and Andersen 1991a). The deposition of mercury in the carcass was about 70%, with retention primarily in the skin, hair, and muscles and to a lower degree in the fat and bones (Nielsen and Andersen 1991b). More than 200 days after cynomolgus monkeys were given 0.025 and 0.05 mg Hg/kg/day as methylmercuric chloride in apple juice for about 2 years, the kidneys contained 10.18–27.89 ppm mercury in the cortex and 1.12–10.11 ppm in the medulla, compared to <2 ppm in the other tissues measured (Rice 1989b).

Demethylation of methylmercury to inorganic mercury is species-, tissue-, dose-, and time-dependent. The demethylated inorganic mercury accumulates in the kidney and liver. Suda et al. (1991) evaluated the transformation of methylmercury to inorganic mercury by phagocytic cells. The liver and kidneys are also potential sites of biotransformation (Lind et al. 1988; Magos et al. 1976; Norseth and Clarkson 1970).

The distribution of mercury in the brain has been studied in humans following oral absorption of organic mercury. It is suggested by Aschner and Aschner (1990) that, following acute exposure to methylmercury, most of the total mercury in the brain is represented by organic mercury; however, after chronic exposure, most of the mercury in the brain is inorganic mercury. An explanation for these findings is that organic mercury is converted into inorganic mercury in the brain. After chronic methylmercury exposure in monkeys, estimated half-lives were considerably longer in brain than in blood, also possibly due to conversion of methylmercury to a form that is highly bound to brain tissue (Rice 1989b).

The autopsy of a man whose first symptoms of methylmercury poisoning occurred 26 years earlier revealed that the highest mercury levels (0.62–1.19 µg Hg/g) were in the gyrus of the cerebral cortex, cerebellum, pallidum, and occipital pole of the brain (Takeuchi et al. 1989). Furthermore, total mercury levels (0.02–1.19 µg/g) were much higher than methylmercury levels (approximately <0.01 µg/g) in the brain.

This finding supports the assumption by Suda et al. (1989) that ingested methylmercury is dealkylated to inorganic mercury in the brain.

Monkeys were fed 0.05 or 0.09 mg Hg/kg/day as methylmercury, containing 5% impurity of inorganic mercury, for 0.5–1.5 years (Lind et al. 1988). The low-dosed monkeys were found to have 10–33% of the total mercury present in the inorganic form in brain cortices, while the high-dosed monkeys had 90% in the inorganic form. Demethylation of methylmercury in the brain, as well as in other organs, including the kidneys and liver, is believed to contribute substantially to the high concentration of inorganic mercury in the brain. Following oral exposure to methylmercuric chloride, regional distribution of total mercury in the brain of monkeys was observed; the highest levels were in the thalamus and hypothalamus (Rice 1989b).

In contrast, in the brain of 21-day-old neonatal rats that had been previously exposed to a gavage dose of 6.4 mg Hg/kg as methylmercury chloride *in utero*, the cerebellum had the highest mercury concentrations and the brainstem had the lowest (Braghiroli et al. 1990). By 60 days of age, concentrations in the brain reached normal values, with an estimated half-life of approximately 37 days (Braghiroli et al. 1990). Therefore, age can affect regional distribution in the brain of animals.

Massie et al. (1993) reported no significant change in the total amount of mercury in the organs (lung, heart, kidney, brain, and liver) of male C57BL/6J mice ranging in age from 133 to 904 days of age maintained under conventional conditions with no known source of mercury exposure other than background concentrations. The ratio of mercury in the brain to that in the liver or to that in the kidney was significantly increased with age, indicating that older mice are less able to maintain a low brain-to-liver ratio of mercury regardless of the total body content of mercury.

In a study of organs from sledge dogs fed methylmercury-laden meat and organs from predatory marine animals (Hansen and Danscher 1995), the highest concentration of total mercury was found in the mesenterial lymph nodes, followed by liver and kidneys, indicating that the lymphatic system may play an important role in the transport of mercury to target organs. The tissue concentrations of mercury observed in this study were found to be age-related, and the results suggest that demethylation takes place in all organs, except the skeletal muscle. Demethylation of methylmercury was found to be lower in the brain than in other organs (Hansen and Danscher 1995).

Mercury accumulates in hair following exposure to methylmercury in humans and mice (Grandjean et al.

1992; Nielsen and Andersen 1991a, 1991b; Soria et al. 1992; Suzuki et al. 1992). Hair mercury levels, determined using segmental hair analysis, can be used to monitor exposure to mercury and may leave a historical record of exposure or uptake (Phelps et al. 1980; Suzuki et al. 1992). The concentration of mercury in the hair is considered proportional to the concentration of mercury in the blood. Correlations can be drawn to determine blood concentrations of mercury relative to its concentration in the hair (see the discussion of the methylmercury MRL in Section 2.5). Mercury concentrations in maternal hair were significantly correlated with cord blood levels of mercury in pregnant women who had frequently ingested whale meat throughout pregnancy (Grandjean et al. 1992). The frequent ingestion of whale meat dinners during pregnancy and, to a lesser degree, the frequent consumption of fish, as well as increased parity or age, were associated with high mercury concentrations in cord blood and hair. The incorporation of mercury into hair is irreversible; the loss of hair mercury occurs as the result of hair loss (Nielsen and Andersen 1991b).

As with metallic mercury, methylmercury can readily traverse the placental barrier. In humans with no known exposure to mercury, blood mercury levels increased with advancing gestation such that the mean blood mercury level on admission for delivery (1.15 ppb) was significantly higher than that of the first prenatal visit (0.79 ppb) (Kuntz et al. 1982). Cord blood levels were similar to maternal blood values in labor and postpartum. Concentrations of methylmercury in the fetal blood are slightly higher than in the maternal blood (Inouye and Kajiwara 1988; Kuhnert et al. 1981). Following an oral dose of methylmercuric chloride during gestation, accumulation of mercury was much greater in the fetal kidneys than in the maternal kidneys of guinea pigs (Inouye and Kajiwara 1988). Mercury levels in the liver were slightly higher in the fetus compared to the dam when exposed to organic mercury at late gestation but were similar at early gestation. Distribution of mercury in the maternal and fetal brains was uneven, with the highest concentrations in the neopallium, diencephalon, and mesencephalon and the lowest in the rhombencephalon. Exposure at later gestational weeks resulted in higher concentrations for both maternal and fetal brains (Inouye and Kajiwara 1988).

Methylmercury may also be secreted in mother's milk (Bakir et al. 1973). Following intravenous dosing of methylmercuric chloride (1.6 mg Hg/kg) to pregnant mice on one of days 9–17 of pregnancy, methylmercury was readily transferred to the fetuses from the mothers more predominantly at the later gestational stage (Inouye and Kajiwara 1990). The placental transfer of methylmercury was more efficient compared to the lactational transfer in rats exposed to methylmercury in the diet during 11 weeks prior to mating, during gestation, and during lactation (Sundberg and Oskarsson 1992). A higher concentration of mercury

in the brain in relation to the blood mercury concentration was found after exposure *in utero* compared to exposure in milk. Mercury was present as methylmercury in the blood of the offspring exposed only during gestation, indicating little or no demethylation during the first 15 days after birth. However, inorganic mercury was present in the blood of offspring exposed only through milk, probably resulting from demethylation of methylmercury in the dam and transport of inorganic mercury to the sucklings through milk.

In animal studies, mercury transfer to and distribution in offspring depends on the form administered to the dam. Yoshida et al. (1994) administered either mercury chloride or methylmercury at 1 mg Hg/kg body weight to maternal guinea pigs (Hartley strain) via intraperitoneal injection 12 hours after parturition. Exposure of the offspring was studied on days 3, 5, and 10 postpartum. Concentrations of mercury were lower in the milk than in maternal plasma regardless of the form of administered mercury, but total milk mercury was higher in the dams given mercury chloride. While the ratio of methylmercury to total mercury decreased in plasma from dams, it did not decrease in the milk. Regardless of the form of mercury given to the dams, the highest concentration of mercury in the offspring was found in the kidney, followed by the liver and the brain. Brain mercury, however, was significantly higher in the offspring of methylmercury-treated dams. Mercury levels in major organs of the offspring peaked at 5 days from mercury-chloride-treated dams and at 10 days from methylmercury-treated dams.

Tissue distribution of phenylmercury is initially similar to methylmercury. One week after administration, the distribution pattern resembles that seen after administration of inorganic compounds (Nordberg 1976). Once in the blood, phenylmercury distributes to a greater extent into the red blood cells than the plasma. Phenylmercury also predominantly distributes to the liver (Berlin 1963). It is less permeable to the placental and blood-brain barriers than methylmercury (Yamaguchi and Nunotani 1974). Phenylmercury also accumulates in the fur of rats but to a lesser extent than detected with methylmercury exposure (Gage 1964).

2.3.2.3 Dermal Exposure

No information was identified for distribution of metallic, inorganic, or methylmercury via dermal absorption. A case history for a dermal absorption of dimethylmercury (see Section 2.3.1.3) does provide some information on distribution (Blayney et al. 1997; Nierenberg et al. 1998). A 48-year-old female absorbed approximately 0.4–0.5 mL of dimethylmercury (about 1,500 mg) through the skin on the dorsal

side of her hand. A preliminary laboratory report at 5 months after exposure indicated that the whole-blood mercury concentration was more than 1,000 µg/L (normal range, 1–8 µg/L; toxic level, >200 µg/L). Chelation therapy with oral succimer (10 mg/kg orally every 8 hours) was begun on day 168 after exposure. Whole blood concentrations rose to 4,000 µg/L after one day of chelation, and urinary mercury levels were 234 µg/L (normal range, 1–5 µg/L; toxic level, >50 µg/L). Chelation therapy continued up to the time of the patients death 298 days postexposure, with blood mercury level falling to around 200 µg/L. Metal analysis of the patient's tissues revealed extremely high levels of mercury in the frontal lobe and visual cortex (average value, 3.1 µg/g [3,100 ppb]), liver (20.1 µg/g), and kidney cortex (34.8 µg/g). The mercury content in the brain was approximately 6 times that of the whole blood at the time of death, and was much higher than levels in the brains of nonmercury exposed patients (2–50 ppb).

2.3.2.4 Other Routes of Exposure

Strain and sex differences were observed in renal mercury accumulation 4 hours after a subcutaneous methylmercuric chloride injection (1 µmol/kg) to 5 strains (BALB/cA, C57BL/6N, CBA/JN, C3H/HeN, and ICR) of male mice and 3 strains (BALB/cA, C57BL/6N, and ICR) of female mice (Tanaka et al. 1991). Mercury was distributed to the kidneys, brain, heart, lungs, liver, spleen, carcass, plasma, and red blood cells of all mice tested. Strain and sex differences were found in renal mercury content. In three strains (ICR, BALB/cA, and C57BL/6N), males showed higher renal mercury levels than females.

Differences in tissue concentrations in different inbred mice strains were evaluated by Griem et al. (1997). Female mice from five different strains (C57BL/6, B10.D2, B10.S, A.SW, and DBA/2) received 3 weekly subcutaneous injections of 0.5 mg Hg/kg body weight for up to 12 weeks. Except for the thymus, in which mercury concentrations continued to increase, steady state levels were obtained in blood and liver after 4 weeks and in spleen and kidney after 8 weeks. In the closely related strains C57BL/6, B10.D2, and B10.S, which differ only or primarily at the major histocompatibility complex, mercury concentrations in blood and liver were about 2-fold lower and renal concentrations were from 3- to 5-fold lower than measured in A.SW, and DBA/2 strains. Mercury concentrations in the spleen of C57BL/6, B10.D2, B10.S mice were significantly higher than in the spleen of A.SW, and DBA/2 mice. The higher concentration of Hg in this immune system organ concentration of C57BL/6, B10.D2, B10.S correlates with the increased susceptibility of these strains to a mercury chloride-induced systemic autoimmune syndrome. The strains with lower splenic mercury are more resistant.

Treatment of mice with ethanol results in increased accumulation of mercury in the fetus (Khayat and Dencker 1982). The concurrent generation of NADPH during the oxidation of alcohol enhances the reduction of mercuric ion to metallic mercury, making it more favorable for permeating the placenta. Mercuric chloride's limited ability to cross the placental barrier was also demonstrated in an intravenous study using mice (Inouye and Kajiwara 1990). Following intravenous dosing of mercuric chloride (1.4 mg/kg) to pregnant mice on 1 day between days 9 and 17 of pregnancy, mercuric chloride was transferred inefficiently to the fetus, being blocked almost completely by the fetal membrane. The mercury accumulated in the placenta and yolk sac but not in the amnion or fetal body (Inouye and Kajiwara 1990). A histochemical study demonstrated that mercuric mercury (Hg^{+2}) was blocked in the proximal wall of the yolk sac.

2.3.3 Metabolism

The available evidence indicates that the metabolism of all forms of mercury is similar for humans and animals. Once absorbed, metallic and inorganic mercury enter an oxidation-reduction cycle. Metallic mercury is oxidized to the divalent inorganic cation in the red blood cells and lungs of humans and animals. Evidence from animal studies suggests the liver as an additional site of oxidation. Absorbed divalent cation from exposure to mercuric mercury compounds can, in turn, be reduced to the metallic or monovalent form and released as exhaled metallic mercury vapor. In the presence of protein sulfhydryl groups, mercurous mercury (Hg^{+}) disproportionates to one divalent cation (Hg^{+2}) and one molecule at the zero oxidation state (Hg^{0}). The conversion of methylmercury or phenylmercury into divalent inorganic mercury can probably occur soon after absorption, also feeding into the oxidation-reduction pathway.

Metallic and Inorganic Mercury. Metallic mercury vapor is inhaled through the lungs and rapidly enters the bloodstream. The dissolved vapor can undergo rapid oxidation, primarily in the red blood cells, to its inorganic divalent form by the hydrogen peroxide-catalase pathway (Clarkson 1989; Halbach and Clarkson 1978). It is believed that the rate of oxidation is dependent on: (1) concentration of catalase in the tissue; (2) endogenous production of hydrogen peroxide; and (3) availability of mercury vapor at the oxidation site (Magos et al. 1978). In red blood cells *in vivo*, hydrogen peroxide production is probably a rate-determining step because Nielsen-Kudsk (1973) found that stimulation of hydrogen peroxide production in red cells increased the uptake of mercury vapors in red blood cells. After a low dose, the total mercury content in the blood is proportionately higher than (to the administered dose) after a high dose, indicating that a higher proportion of the lower dose is oxidized (Magos et al. 1989). The hydrogen peroxide-catalase

pathway in red cells may become saturated at higher dose levels (Magos et al. 1989). This oxidation pathway of metallic mercury can be inhibited by ethanol since ethanol is a competitive substrate for the hydrogen peroxide catalase and, consequently, can block mercury uptake by red blood cells (Nielsen-Kudsk 1973).

The oxidation of metallic mercury may also occur in the brain, liver (adult and fetal) (Magos et al. 1978), lungs (Hursh et al. 1980), and probably all other tissues to some degree (Clarkson 1989). In rat liver homogenates, hydrogen peroxide catalase is the predominant oxidative pathway in tissues. Its capacity is very high. Unlike oxidation in red cells, the rate-limiting step in *in vitro* oxidation in the liver is dependent on the rate of mercury delivery to the enzyme (Magos et al. 1978). Unoxidized metallic mercury can still reach the brain because the oxidation of metallic mercury is a slow process compared with the circulation time from the lungs to the brain (Magos 1967). In the brain, unoxidized metallic mercury can be oxidized and become trapped in the brain because it is more difficult for the divalent form to cross the barrier. Autoradiographic studies suggest that mercury oxidation also occurs in the placenta and fetus (Dencker et al. 1983), although the extent of oxidation is not known. The rate of distribution of metallic mercury to the brain and fetus is probably nonlinear because the rate of oxidation in red cells is nonlinear (i.e., can become saturated at higher doses) (Magos et al. 1989).

There is evidence to suggest that the divalent inorganic mercury cation is reduced by mammalian tissue to metallic mercury after its oxidation. Rats and mice pretreated parenterally with mercuric chloride exhale metallic mercury vapor (Clarkson and Rothstein 1964; Dunn et al. 1981a). Liver and kidney homogenates in animals also release mercury vapor after exposure to mercuric chloride. The amount of mercury released increases upon treatment with ethanol (Dunn et al. 1981b). This increase suggests that glutathione reductase is responsible for mercuric ion reduction (Williams et al. 1982). Oxidation of alcohol to acetaldehyde stimulates NADPH production, which is required for mercuric ion reduction. However, alcohol is primarily oxidized in the liver, and this location is not consistent with the increases in metallic mercury vapor released from the kidney homogenates (Dunn et al. 1981b).

Organic Mercury. Once absorbed, methylmercury can apparently be converted into inorganic mercury in tissues, specifically the divalent cation (Hg^{+2}) (Dunn and Clarkson 1980). Several investigators have reported high levels of inorganic mercury in tissues (Magos and Butler 1972; WHO 1990) and feces after methylmercury exposure (Turner et al. 1975). Rat liver microsomes can degrade methylmercury into inorganic mercury. Inorganic mercury production from methylmercury paralleled the hydroxyl radical

production (Suda and Hirayama 1992). The promotion and inhibition of the hydroxyl radical formation and the hydroxyl radical scavenger, affected inorganic mercury production. These results suggest that hydroxyl radicals produced from microsomes may play a predominant role in alkyl mercury degradation. NADPH-cytochrome P-450 reductase is known to be responsible for hydroxyl radical production in liver microsomes. Alkyl mercury degradation varied in proportion to the enzyme activities and hydroxyl radical production. These results suggest that hydroxyl radicals produced by cytochrome P-450 reductase might be the primary reactive species that induces alkyl mercury degradation. *In vitro* studies using a peroxidase-hydrogen peroxide-halide system indicated that besides the hydroxyl radical, hypochlorous acid (HOCl) scavengers are also capable of degrading methylmercury (Suda and Takahashi 1992). Also, metallic mercury exhaled in mice dosed with methylmercury was dependent on the level of inorganic mercury present in the tissue (Dunn and Clarkson 1980). The cation then enters the oxidation-reduction cycle, and metabolism occurs as discussed previously under Inorganic Mercury.

A small amount of an oral dose of methylmercuric chloride can also be converted into inorganic mercury in the intestinal flora (Nakamura et al. 1977; Rowland et al. 1980). However, inorganic mercury is poorly absorbed across the intestinal wall and, therefore, most of it is excreted.

Phenylmercury also rapidly metabolizes to inorganic mercury (Nordberg 1976). The metabolism of phenyl-mercury involves hydroxylation of the benzene ring to an unstable metabolite that spontaneously releases inorganic mercury. Consequently, its tissue disposition following initial metabolism resembles that seen after the administration of inorganic salts (Gage 1973).

Studies in mice indicate that toxicity from exposure to dimethylmercury is the result of metabolic conversion of dimethylmercury to methylmercury, and that dimethylmercury does not enter the brain until it has been metabolized to methylmercury, which occurs over the first several days following absorption (Ostland 1969). Nierenberg et al. (1998) report the results of an analyses of mercury content in the hair of a 48-year-old female who died subsequent to an acute exposure to dimethylmercury. The results are consistent with the kinetic profiles for methylmercury, and support the hypothesis of a rapid conversion of dimethylmercury to a methylmercury metabolite.

2.3.4 Elimination and Excretion

Elimination of metallic mercury occurs through the urine, feces, and expired air, while inorganic mercury is excreted in the urine and feces in humans. Animal data on excretion are limited but indicate that excretion is species and dose dependent. The feces are a major elimination route for inorganic mercury compounds, but high acute doses increase the percentage of excretion via the urine. Excretion of organic mercury is predominantly thought to occur through the fecal (biliary) route in humans. In animals, phenylmercury is excreted initially though the bile and then shifts to urine, whereas methylmercury is primarily excreted in the bile and then the feces. Age is a factor in the elimination of mercury in rats following inorganic and organic mercury exposure, with younger rats demonstrating significantly higher retention than older rats. Both inorganic and organic mercury compounds can be excreted in breast milk. There are no data suggesting that the route of exposure affects the ultimate elimination of inorganic and organic mercury that is absorbed into the body.

Metallic and Inorganic Mercury. The urine and feces are the main excretory pathways of metallic and inorganic mercury in humans, with a body burden half-life of approximately 1–2 months (Clarkson 1989). In a study of former chloralkali workers exposed to metallic mercury vapor for 2–18 years (median, 5 years), Sallsten et al. (1995) found that the elimination of mercury in urine was well characterized by a one-compartment model, which estimated a half-life of 55 days. There was a tendency toward longer half-lives with shorter duration exposures than with long-term exposure, when uptake and elimination have reached a steady state. This might be due to the induction of a higher metabolic rate after a longer exposure time, but there is no experimental evidence to support such an effect (Sallsten et al. 1995). For high-level exposure to inorganic divalent mercury, the urine is probably the major elimination route, with a half-life similar to that of metallic mercury (Clarkson 1989). An elimination half-life from urine was estimated to be 25.9 days following an acute exposure to a high level of mercuric chloride (13.8 mg/kg) (Suzuki et al. 1992). Exhalation in the lungs and secretion in saliva, bile, and sweat may also contribute a small portion to the excretion process (Joselow et al. 1968b; Lovejoy et al. 1974). After an acute mercury exposure in humans, urinary excretion accounts for 13% of the total body burden. After long-term exposure, urinary excretion increases to 58%. Humans inhaling mercury vapor for less than an hour expired approximately 7% of the retained dose of mercury (Cherian et al. 1978; Hursh et al. 1976). The half-life for this elimination pathway was 14–25 hours; therefore, excretion through expired air is negligible 5–7 days after exposure (Cherian et al. 1978). Using a two-compartment model, elimination half-lives in the urine of workers exposed for 20–45 hours to >0.1 mg/m^3 metallic mercury vapor were

estimated to be 28 and 41 days for a fast and slow phase, respectively (Barregard et al. 1992). Mercury is excreted in the urine following oral exposure to mercuric sulfide (0.5 mg Hg/kg) (Yeoh et al. 1989).

The overall elimination rate of inorganic mercury from the body is the same as the rate of elimination from the kidneys, where most of the body burden is localized (see Table 2-4). Inorganic mercury is also readily cleared from the lung. Elimination from the blood and the brain is thought to be a biphasic process with an initial rapid phase in which the decline in the body burden is associated with high levels of mercury being cleared from tissues, followed by a slower phase of mercury clearance from the same tissues (Takahata et al. 1970). An even longer terminal-elimination phase is also possible because of persistent accumulation of mercury, primarily in the brain (Takahata et al. 1970). Following a single oral dose of divalent mercury in 10 volunteers, 85% of the ^{203}Hg activity was excreted within 4–5 days, predominantly in the feces (Rahola et al. 1973).

Following acute mercury vapor intoxication of two humans, it was found that, despite chelation therapy with multiple chelators (2,3-dimercaptopropanol [BAL] followed by 2,3-dimercaptosuccoinic acid [DMSA]), relatively high concentrations of mercury remained in the plasma for a very long time (Houeto et al. 1994). The authors suggested that this could be explained by the progressive release of mercury from red blood cells and tissues after oxidation. In a group of chloralkali workers exposed to metallic mercury vapor for 1–24 years (median, 10 years), a decrease in the mercury concentration (following temporary discontinuation of exposure) in whole blood, plasma, and erythrocytes was found to be best characterized by a two-compartment model (Sallsten et al. 1993). Using a two-compartment model, half-lives were estimated, respectively, to be 3.8 and 45 days for the fast and slow phase in whole blood; plasma, 2 and 36 days in plasma, and 3.6 and 16 days in erythrocytes. The half-lives for the slow phases in whole blood and plasma were longer, and the relative fractions of the slow phases were higher (about 50%) after long-term exposures than after brief exposures (Sallsten et al. 1993).

Workers exposed to vapors of 0.016–0.68 mg Hg/m^3 had detectable levels of mercury in the urine (>2 µg Hg/L) (Stopford et al. 1978). Metallic mercury accounted for <1% of the total mercury in the urine. The rapid appearance of metallic mercury in the urine is probably due to mercury filtered directly from the blood through the glomerulus, whereas mercuric ions found in the urine are attributable to the mercury taken up by the kidneys prior to excretion. Therefore, urinary metallic mercury provides a relative index for blood levels of metallic mercury, and urinary mercuric ions provide a relative index for kidney levels of inorganic mercury. Three different forms of mercury have been identified in the urine from

Table 2-4. Half-lives of Inorganic Mercury in Humans

Tissue	Half-life	Phase	Reference
Lung	2 days	Early phase	Berlin et al. 1969a
Brain	20 days	Biphasic	Hursh et al. 1976
Blood	3.3 days	Early phase	Cherian et al. 1978
Plasma	3.3 days	Early phase	Cherian et al. 1978
Blood	2.4 days	Early phase	Clarkson 1978
Blood	15 days	Late phase	Clarkson 1978
Blood	28 days	Late phase	Rahola et al. 1973
Whole body	60 days		Rahola et al. 1973
Whole body	60 days		Hursh et al. 1976
Kidney	60 days		Hursh et al. 1976

Compiled from: Bakir et al. 1973; Cox et al. 1989; Kershaw et al. 1980; Miettenen et al. 1971; Sherlock et al. 1984

workers occupationally exposed to mercury: a metallic form, a mercuric-cysteine complex that is reducible, and a large complex in which the mercury can only be released by organic destruction (Henderson et al. 1974).

Data are limited on elimination of metallic and inorganic mercury in animals. Initial excretion of mercury is predominantly in the fecal matter following inhalation of metallic mercury vapor, but as mercury concentrations increase in the kidneys, urinary excretion increases (Rothstein and Hayes 1964). After inhalation, approximately 10–20% of the total excreted metallic mercury is by exhalation (Rothstein and Hayes 1964). Mercury is excreted in the urine of mice exposed orally to mercuric sulfide (. 8–200 mg Hg/kg) (Yeoh et al. 1986, 1989). The amount of mercury in the urine of the treated group was 4.5–15-fold greater than the control levels. Urinary rates of mercury excretion were 1.6–2.2 ng/hour. Neonatal rats (1, 8, and 15 days old) eliminated mercury slower than older rats (22 and 29 days old) given mercuric chloride subcutaneously (Daston et al. 1986).

Inorganic mercury is also excreted in breast milk (Yoshida et al. 1992). Newborn guinea pigs were exposed to inorganic mercury in breast milk from mothers exposed to mercury vapor (6–9 mg/m^3) for 120 minutes after parturition (Yoshida et al. 1992). Mercury concentrations in breast milk were slightly lower than plasma mercury concentrations of the maternal guinea pigs over the observation period. Ratios of milk to plasma were 0.24–0.44 on day 3, 0.45–0.46 on day 5, and 0.46–0.66 on day 10. The decrease in the mercury concentration in breast milk with time was slower than that in maternal plasma. The distribution of mercury to organs in the suckling neonates indicated that they were exposed to the inorganic rather than to elemental mercury.

Sundberg et al. (1998) studied the elimination of radiolabeled inorganic mercury in lactating and nonlactating mice exposed to mercuric chloride via a single intravenous injection at 0.5 mg Hg/kg body weight. A three-compartment pharmacokinetic model was used to fit the data. The study was designed to provide additional information on the speciation of mercury in breast milk and the differences between methylmercury and inorganic mercury migration into milk. Unlike placenta, where methylmercury moves more easily across the placental border than inorganic mercury, inorganic mercury is more readily eliminated in milk than methylmercury. For inorganic mercury, no significant differences were observed between lactating and nonlactating mice for plasma clearance (43.3 and 44.4 mL/hour/kg, respectively) and volume of
distribution (4,950 and 3,780 mL/kg). The terminal half-lives of inorganic mercury in plasma were 297 hours for lactating, and 162 hours for nonlactating mice. The milk-to-plasma concentration ratio

for inorganic mercury varied between 0.1 and 3.6, with a mean of 0.64 at plasma levels below 300 ng Hg/g (in the linear region of the relationship) and a mean of 0.17 at higher plasma mercury levels. In contrast, the values for the methylmercury kinetic parameters were significantly higher in lactating than nonlactating mice: plasma clearance (93.5 and 47.1 mL/hour/kg, respectively) and volume of distribution (18,500 and 9,400 mL/kg, respectively). The terminal half-life of methylmercury in plasma was 170 hours for lactating and 158 hours for nonlactating mice. The milk-to- plasma concentration ratios for total mercury after methylmercury administration were lower than those seen with inorganic mercury, and varied between 0.1 and 0.7 with a mean of 0.20. The nearly five-fold higher peak value for plasma to blood mercury levels observed for inorganic mercury reflects the more efficient migration of inorganic mercury from blood to milk compared with that for methylmercury. Mercury concentrations in milk also decreased more quickly for inorganic (terminal half-life of 107 hours) than for methylmercury (constant levels throughout the 9-day follow-up period postexposure). The authors hypothesize that the nonlinear relationship between mercury in milk and plasma following inorganic mercury administration suggests that inorganic mercury enters the mammary gland via a carrier-mediated transport system that is saturated at high plasma levels of inorganic mercury. The results suggest that the physiological changes during lactation alter the pharmacokinetics for methylmercury in mice, but not for inorganic mercury.

Organic Mercury. The fecal (biliary) pathway is the predominant excretory route for methylmercury, with less than one-third of the total mercury excretion occurring through the urine, following oral and inhalation exposure (Norseth and Clarkson 1970). In humans, nearly all of the total mercury in the feces after organic mercury administration is in the inorganic form. The conversion of methylmercury to inorganic mercury is a major step that is dependent on the duration of exposure and/or the duration after cessation of exposure.

In rats and nonhuman primates, methylmercury is secreted in the bile and can be reabsorbed in the intestine (Berlin et al. 1975; Norseth and Clarkson 1971; Urano et al. 1990). It is believed that methylmercury is complexed to nonprotein sulfhydryl compounds in the bile and reabsorbed in this form by a transport system (Ballatori and Clarkson 1982; Urano et al. 1990). In guinea pigs, hamsters, and monkeys, methyl-mercury, but not inorganic mercury, is extensively reabsorbed from the gall bladder, providing evidence for the biliary-hepatic recycling of this metal (Dutczak et al. 1991). The biliary-hepatic cycle probably contributes to the long biological half-life and toxicity of methylmercury. However, methylmercury can be converted into its inorganic form in the gastrointestinal lumen by intestinal flora (Nakamura et al. 1977;

Rowland et al. 1980), thus decreasing reabsorption and increasing the rate of fecal excretion (Berlin et al. 1975).

During the first few days after intravenous dosing, phenylmercury compounds are also eliminated primarily in the feces as a result of biliary secretion and its concentration in the gastrointestinal tract (mucosa and lumen) (Berlin and Ullberg 1963). The initial urinary excretion of phenylmercury represents primarily the parent compound (Gage 1964). Several days after exposure, however, elimination is primarily in the urine, which contains predominantly inorganic mercury (Gotelli et al. 1985).

Clearance half-times are longer with methylmercury than with inorganic compounds (see Table 2-5). Elimination of methylmercury compounds generally follows first-order kinetics because excretion is directly proportional to body burden and independent of the route of administration (oral or intraperitoneal) (Nielsen and Andersen 1991a). Furthermore, duration of exposure may affect the excretion process of mercury. A two-compartment model was established by Rice et al. (1989) for a single oral dose study in monkeys because of the appearance of an initial rapid elimination phase followed by a slower elimination phase. However, following repeated dosing for 2 years, a one-compartment model was considered a more reasonable fit for the data. Therefore, it was concluded that the average steady-state blood levels of mercury after chronic-duration exposure should not be estimated on the basis of short-term exposure data.

Elimination rates for methylmercury vary with species, dose, sex, and strain (Nielsen 1992). There is also evidence of sex-related differences in the elimination of methylmercury in humans (Miettinen 1973). The direction of the sex-related difference may differ for the fast and slow components of methylmercury elimination, with males excreting faster during the fast component and females excreting faster during the slow component. The net difference in elimination rates at time points distant from exposure indicates that females excrete methylmercury slightly faster than males. This net difference is seen in whole-body biological half-time derived by combining both fast and slow elimination components (Miettinen 1973). Clear sex-related differences were not reported for these volunteers for time points soon after exposure. In contrast, male mice excreted methylmercury much faster than females did for the first 14 days (i.e., primarily the fast component) (Nielsen 1992). Significant sex-related differences in elimination were also observed in rats dosed at 56 days of age (Thomas et al. 1982). As is apparently the case in humans, the difference was measured in the slow component only, with males excreting slightly slower than females. It should be noted that an insignificant difference in elimination was measured for the fast component of

Table 2-5. Elimination Constants for Methylmercury Measured in Blood and Hair

Reference	Clearance half-time in days	Elimination constant[a]	Number of subjects
Cox et al. 1989	48 (hair, women)	0.014	55
Miettenen et al. 1971	53 (blood)	0.013	15
Kershaw et al. 1980	52 (blood)	0.013	7
Sherlock et al 1984	51 (blood, women)	0.0136	6
Sherlock et al 1984	49 (blood, men)	0.0142	14
Bakir et al. 1973	65[b] (blood)	0.015	16

[a]Conversions between reported values for elimination constant and clearance half-time are based on the equation $T_{1/2}$= ln2/b, where $T_{1/2}$ is clearance half-time and b is elimination constant (WHO 1976).
[b]At least two of these individuals were young males (ages 6 and 10). The sex of the other 14 individuals was not reported.

Compiled from: Bakir et al. 1973; Cox et al. 1989; Kershaw et al. 1980; Miettenen et al. 1971; Sherlock et al. 1984

excretion in the rats, with males excreting slightly faster than females. Interestingly, a sex-difference elimination rate was not observed in rats dosed at 24 days or younger (Thomas et al. 1982).

The rate of mercury excretion was also slower in younger animals (7 or 15 days) than in older animals (24 and 56 days) (Thomas et al. 1982). This age-dependent difference in the rate of mercury excretion may reflect differences in the sites of mercury deposition (i.e., hair, red blood cells, skin). In neonatal rats, the excretion of methylmercury is longer than in adult rats because of the inability of the neonatal liver to secrete the toxicant into the bile. Therefore, the immaturity of the transport system in neonatal rats affects the elimination of mercury.

Methylmercury is also excreted in the breast milk of rats, humans, and guinea pigs (Sundberg and Oskarsson 1992; Yoshida et al. 1992). In pups exposed only through milk, approximately 80% of the total mercury in blood was present as methylmercury. Because suckling animals have a limited ability to demethylate methylmercury, the inorganic mercury present in the blood of the offspring probably originated from inorganic mercury in the milk. Since the dams were exposed only to methylmercury in their diet, some demethylation occurred in the dams, followed by the transport of the inorganic mercury to the sucklings via milk.

Sundberg et al. (1998) studied the elimination of radiolabeled methylmercury in lactating and nonlactating mice exposed to methylmercuric chloride via a single intravenous injection at 0.5 mg Hg/kg body weight. A comparison of the results for methylmercury with results for inorganic mercury is discussed in the section above on elimination of “Inorganic Mercury.” A three compartment pharmacokinetic model was used to fit the data. The values for the methylmercury kinetic parameters were significantly higher in lactating than nonlactating mice: plasma clearance (93.5 and 47.1 mL/hour/kg, respectively) and volume of distribution (18,500 and 9,400 mL/kg, respectively). The terminal half-life of methylmercury in plasma was 170 hours for lactating and 158 hours for nonlactating mice. The milk-to- plasma concentration ratios for total mercury after methylmercury administration were lower than those seen with inorganic mercury, and varied between 0.1 and 0.7, with a mean of 0.20. Mercury concentrations in milk were constant throughout the 9-day follow-up period postexposure. The results indicate that physiological changes during lactation alter the pharmacokinetics for methylmercury in mice.

2.3.5 Physiologically based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the

model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

PBPK models for mercury exist, and the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

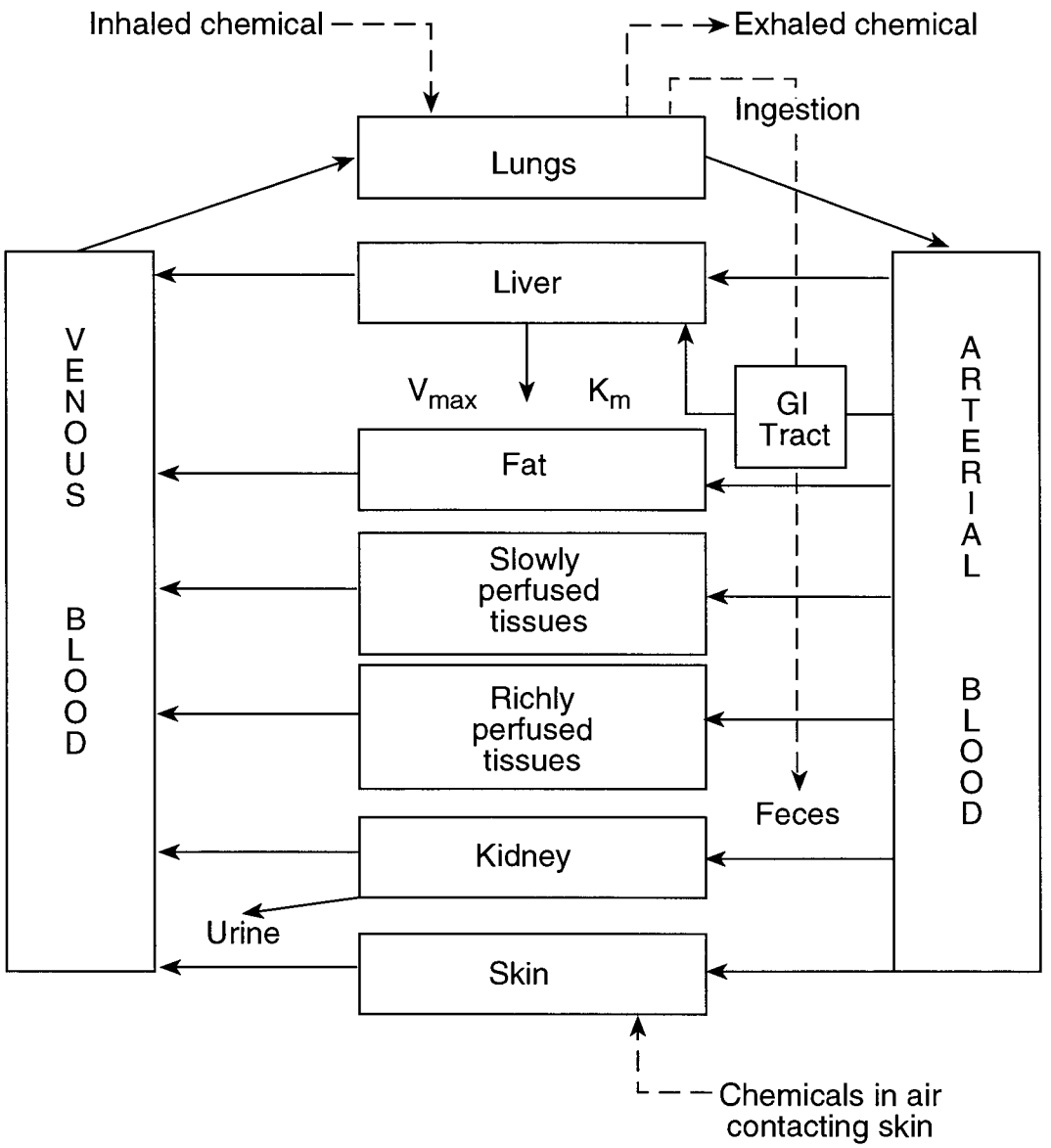
2.3.5.1 Summary of PBPK Models

Two physiologically based pharmacokinetic models have been developed recently that model the kinetics of methylmercury in rats. Farris et al. (1993) developed a PBPK model that simulates the long-term disposition of methylmercury and its primary biotransformation product, mercuric mercury, in the male Sprague-Dawley rat following a single oral nontoxic exposure. Gray (1995) developed a PBPK model that simulates the kinetics of methylmercury in the pregnant rat and fetus. The Gray model was developed to provide fetal and maternal organ methylmercury concentration-time profiles for any maternal dosing regimen. These model provide useful insight into the key physiological processes that determine the distribution and fate of mercury in the body, but neither model is currently being used in human risk assessment.

2.3.5.2 Mercury PBPK Model Comparison

Both the Farris et al. (1993) and the Gray (1995) PBPK models address the kinetics of methylmercury in rats. Both models provide useful insights into important physiological processes determining methyl-mercury distribution and changes in tissue concentrations. Also, both studies suggest further work to enhance the utility and accuracy of the models The Farris et al. model dealt more effectively with the conversion of methylmercury to mercuric mercury, while the Gray model specifically addressed fetal tissue concentrations as a function of maternal exposures and the extrapolation from short-term to continuous

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

dosing. The latter is of direct relevance to methylmercury risk assessments currently based on human studies of short-term exposures, while the general public exposure is more typically continuous. Neither model ran simulations nor validated against data for other species (including human). Nor did the models address high-to-low dose extrapolations or different routes of exposure.

2.3.5.3 Discussion of Models

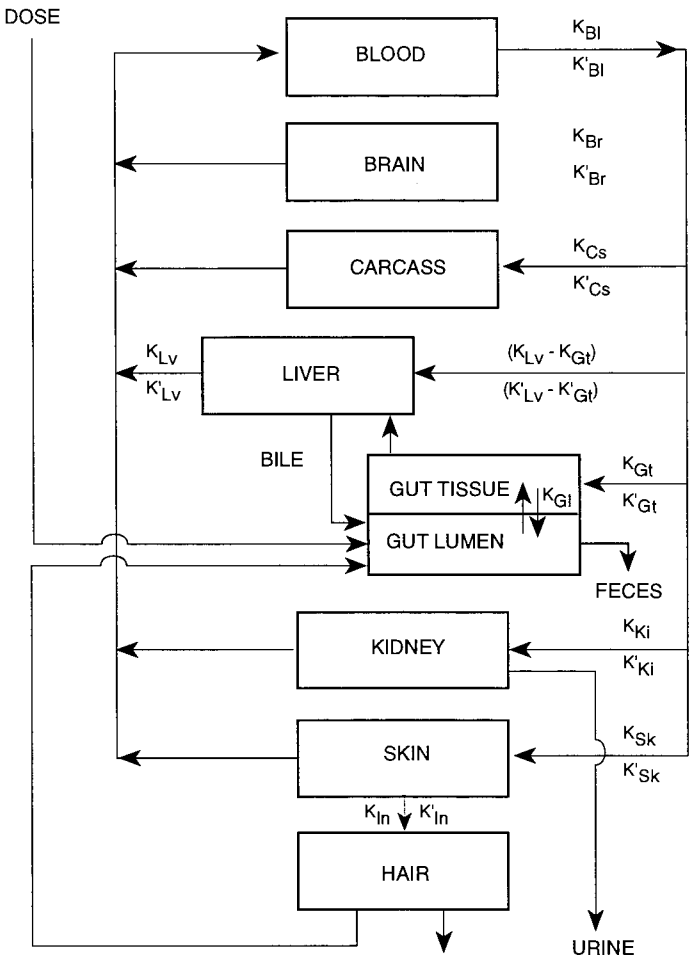
The Farris et al. Model for Methylmercury. The Farris et al. (1993) model is a physiologically based model that simulates the long-term disposition of methylmercury and its primary biotransformation product, mercuric mercury, in growing mammals following a single nontoxic oral dose of the parent compound. The test animal used to develop and validate the model was the male Sprague-Dawley rat. A tracer dose was used in the validation studies to preclude the possibility that the results would be biased by toxic or saturation effects. The model incorporates a number of features, including a time-dependent compartment for volume changes (i.e., the rats grew from 300 to 500 g in body weight over the 98-day time course of the validation study), compartment volume-dependent clearances, and the recycling of mercury from ingestion of hair by rats during grooming.

Risk assessment. The Farris et al. model has not been used in human risk assessment. The authors, however, suggest that the model would be useful in developing a better understanding of species differences and in predicting the affects of altered biochemical or physiological states on methylmercury pharmaco-kinetics. For example, the authors suggest that the model can be adapted to simulate data for neonatal animals or humans that are known to secrete glutathione poorly. It could also help elucidate the mercury kinetics for animals that have altered bile flow or that have nonabsorbable sulfhydryl-containing resins.

Description of the model. The Farris et al. model consists of nine lumped compartments, each of which represent a major site of mercury accumulation, elimination, or effect in mammals. The compartment labeled “carcass” is a residual compartment and consists of all tissues and organs not specifically represented by the other eight compartments in the model. A flow diagram of the model is shown in Figure 2-5. The interdepartmental mass transport parameters used in the model are shown in Table 2-6.

Methylmercury transport between all compartments except brain and hair is modeled as plasma flow limited (i.e., plasma levels rapidly equilibrate with erythrocytes). Mercuric mercury transport parameters

Figure 2-5. Compartmental Flow Diagram for a Pharmacokinetic Model of Methylmercury in the Growing Rat



The symbol K represents intercompartmental mass transport parameters. The subscripts Bl, Br, Cs, Gl, Gt, In, Ki, Lv, and Sk denote blood brain, carcass, gut lumen, gut tissue, integument, kidney, liver, and skin, respectively. Primed symbols designate inorganic mercury.

Source: Farris et al. 1993

Table 2-6. Intercompartmental Mass Transport Parameters Used to Model Methylmercury and Mercuric Mercury Pharmacokinetics in Rats

	Parameter	
Transport processes	Methylmercury	Inorganic mercury
Blood to brain K_{br}, K'_{Br}	3.4×10^{-5} [a,b]	3.2×10^{-5} [a,b]
Blood to carcass K_{Cs}, K'_{Cs}	7.7×10^{-4} [a,c]	3.1×10^{-4} [a,d]
Blood to liver $(L_{Lv} - K_{Gt})$, $(K'_{Lv} - K'_{Gt})$	9.1×10^{-4} [a,c,e]	9.1×10^{-2} [a,f]
Blood to kidney K_{Ki}, K'_{Ki}	2.0×10^{-2} [a,c]	8.4×10^{-3} [a,b]
Blood to skin K_{Sk}, K'_{Ki}	1.0×10^{-3} [a,c]	4.2×10^{-4} [a,d]
Blood to GI tissue G_{GT}, K'_{Gt}	8.6×10^{-3} [a,c]	3.5×10^{-3} [a,d]
GI tissue to lumen K_{Gi}, K'_{Gi}	1.0×10^{-1} [g]	2.0×10^{-4} [h]
Skin to hair K_{In}, K'_{In}	1.2×10^{-4} [j,i]	1.2×10^{-4} [b,i]

[a] Units are mL blood/min g tissue
[b] Estimated from experimental data
[c] Value is plasma flow rate to tissue divided by 100. Plasma flow rate is calculated from blood flow rate (Bonaccorsi et al.1978) assuming a hematocrit of 0.374
[d] Value is plasma flow rate to tissue divided by 250. Plasma flow rate is calculated as described in footnote[c].
[e] Based on flow via hepatic artery
[f] Hepatic artery plasma flow
[g] Value is based on assumption that transport from gut tissue represents about 79% of total methyl mercury transport to gut lumen. Units are mL tissue/min/g tissue.
[h] Value represents the average rate of GI mucosal cell exfoliation. Estimated from Bertalanffy (1960).
[i] Units are mL skin/min/g skin.

the carcass, gastrointestinal tissue, skin, and kidneys are assumed to follow a common mechanism and are based on the empirically estimated parameter for the kidneys. Transport of both organic and inorganic mercury to brain and hair compartments is assumed to be limited by the blood-brain barrier and the rate of hair growth. Recycled mercury from ingested hair during grooming was assumed available for reabsorption from the gut lumen at 100% for methylmercury and 10% for inorganic mercury.

The authors make the assumption that all of the inorganic mercury resulting from the demethylation of methylmercury is mercuric mercury. Farris et al. (1993) note that the precise site of demethylation is unknown, although the body's tissues and the lumen of the gastrointestinal tract seem most likely. For convenience, however, they modeled demethylation entirely in the liver compartment. Bidirectional and symmetric transport of methylmercury between the gut tissue and lumen is assumed and modeled accordingly. Biliary secretion of both methylmercury and inorganic mercury are modeled as undergoing low-molecular weight nonprotein sulfhydryl (NPSH) secretion d-dependent transport. Methylmercury secreted into the gut lumen, either from biliary secretion or from the gut tissue, is modeled as being readily reabsorbed. In line with previous studies, the model sets a value of 10% for resorption of inorganic mercury secreted into the lumen from bile or from exfoliation of the gastrointestinal mucosal cells.

The assumptions in the model were incorporated into a series of mass-balance differential equations that account for the changes in the amount of methylmercury and mercuric mercury in each compartment. The entire equation set was solved numerically using Gear's method for stiff differential equations (Gear 1971). The initial mercury dose was administered at 100% methylmercury, administered as a bolus to the gut lumen compartment. The mass transport parameters listed in Table 2-6 were multiplied by the time-dependent compartment volumes to give the mass transport parameters used in the model equations.

Validation of the model. The Farris et al. model simulations were compared to an extensive set of data collected by the authors on the metabolism and distribution of an orally dosed bolus of radiolabeled methyl-mercury in male Sprague-Dawley rats. In a distribution study, tissue samples were collected on days 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, and 98 post-dosing. In a metabolism study with the same dosing regimen, whole body counts and 24-hour feces and urine samples were collected daily for 15 days post-dosing, and then twice weekly.

The model simulations were in close agreement with the observed results from the distribution and metabolism studies. Physiological processes that were highlighted by the results and the discrepancies that

did occur include the probable active transport into the brain (versus passive diffusion) of a methylmercury-cysteine complex, the bidirectional transport of methylmercury between the gut lumen and gut tissue as a more important determinant of methylmercury fecal excretion than biliary secretion, the importance for the determination of methylmercury half-life in rats of the recycling of mercury from ingested hair, and the need for better estimates of the rate constants for the demethylation of methylmercury in order to adapt the model to other species.

No human data were presented to validate the model, and validation was not performed for other routes or duration of mercury exposure.

Target tissues. The target tissues for this model included the blood, liver, gut, kidneys, and brain.

Species extrapolation. The model was developed and validated using the male Sprague-Dawley rat. No other species were tested and data from other species were not used to validate the model. The authors, however, suggest that this model would prove useful in developing better rate constants or other important determinants of species differences (for example, demethylation rates, which differ based on differences in gut flora and tissue enzyme levels).

High-low dose extrapolations. Only the single nontoxic dose was evaluated. No data were presented to evaluate the utility of the model for high-to-low dose extrapolations.

Interroute extrapolation. Only the single oral dose was evaluated. No data were presented to evaluate the validity of the model in extrapolating from an oral to an inhalation or dermal dose. No compartment was included for the lungs. Although a skin compartment was included in the model, absorption from a dermal application of methylmercury was not addressed.

The Gray Model for Methylmercury.

The Gray (1995) PBPK model simulates the kinetics of methylmercury in the pregnant rat and fetus. The Gray model was developed to provide fetal and maternal organ methylmercury concentration-time profiles for any maternal dosing regimen.

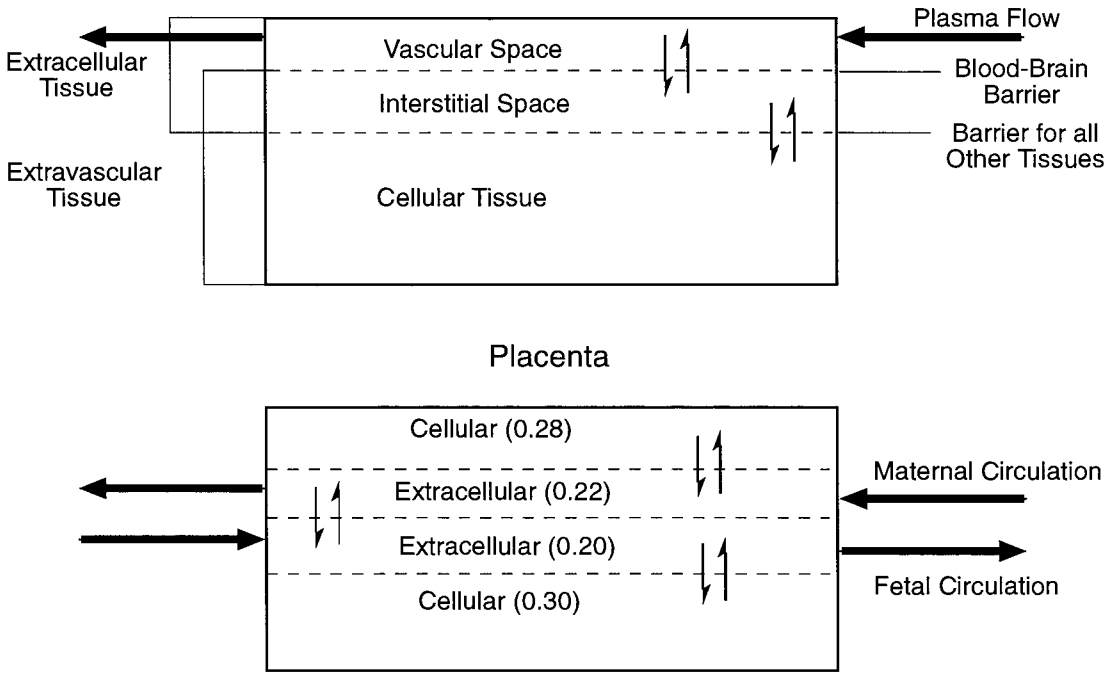
Risk assessment. The Gray model has not been used in human risk assessment. The author, however, suggests that the model would be useful to incorporate rat developmental toxicity data into the assessment of methylmercury risk. Specifically, the author suggests the model be used to convert the short-term exposure data from studies presently being used in risk assessments into continuous-exposure scenarios, which are more typical of the general public's likely exposure pattern.

Description of the model. The Gray model is a membrane-limited PBPK model for methylmercury developed using experimental data from the literature. The model parameters include constants for linear binding, membrane transfer, biliary transport, and gut reabsorption; and physiological parameters for tissue cellular and extracellular volumes and plasma flow rates. Mass balance equations were developed that describe the transport to all organ systems important to the distribution or toxicity of methylmercury to the pregnant rat or fetus. Mass balance equations were solved using an Advanced Continuous Simulation Language (ACSL) program developed by Mitchell and Gauthier Associates.

The compartments and barriers to methylmercury transport in the tissue compartments and placenta are shown in Figure 2-6. The cell membrane is assumed to be the barrier for methylmercury transport for all tissues except the brain and placenta. The barrier to methylmercury transport to the brain is the endothelial cell wall of the cerebral vascular system (the blood-brain barrier). The placenta is modeled as four compartments, with separate transfer constants for placental barrier and placental tissue transport. There is a tissue compartment for both the maternal and fetal sides of the placenta.

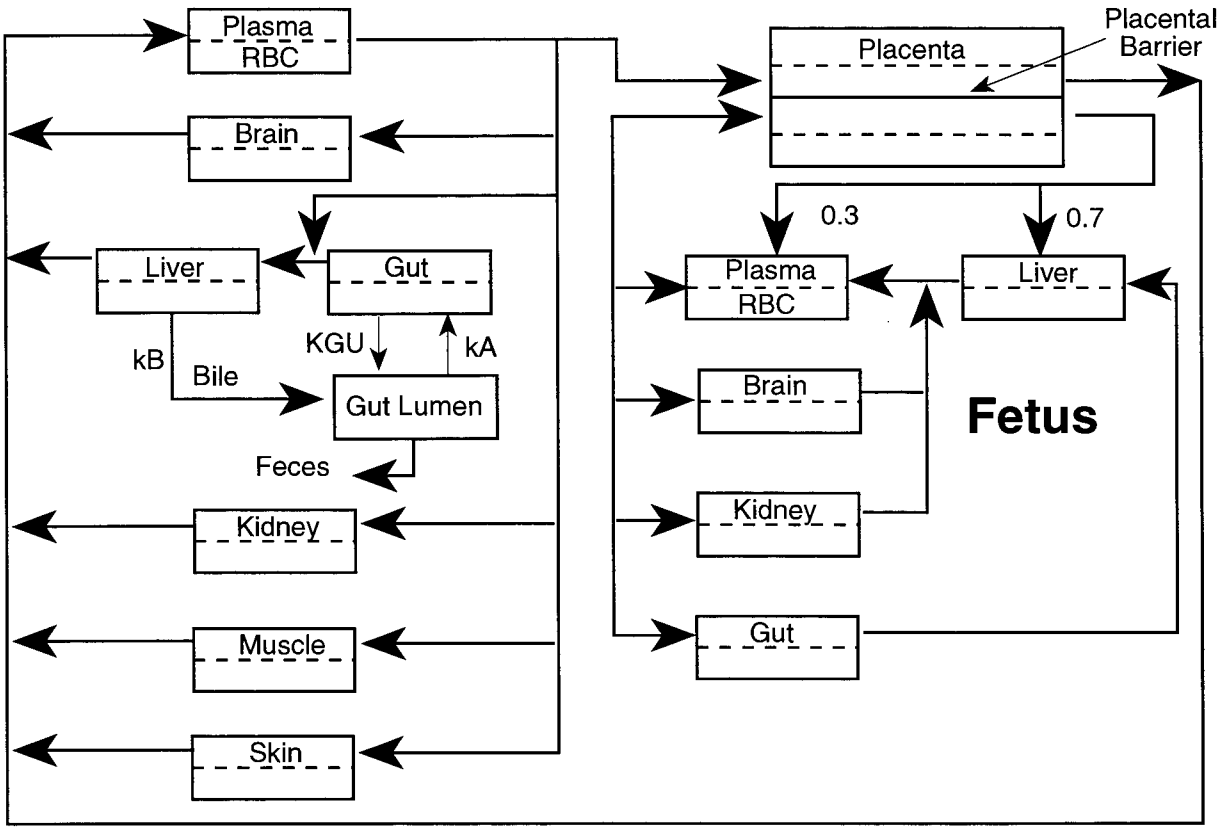
The flow chart shown in Figure 2-7 illustrates the transport pathways among the 8 compartments of the pregnant rat, the 5 compartments of the fetus, and the placental interface. The linear binding, membrane transfer transport, and secretion/reabsorption constants used in the Gray model are shown in Tables 2-7 and 2-8. The linear binding constants were estimated directly from *in vivo* tissue distribution studies using the ratio of tissue to plasma concentrations at pseudoequilibrium. They represent the degree to which methylmercury binds to intracellular sites. Because the skin (which includes the outer layers of hair and the pelt) contained excreted methylmercury that does not exchange with plasma, the linear binding constant for a typical organ (in this case the liver) was used as the constant for skin. No experimental data were available for fetal red blood cell (RBC) binding, so the author made the assumption that the fetal RBC binding constant would be equal to the maternal RBC binding constant. The conversion of methylmercury into mercuric mercury in the gut is not explicitly calculated in the Gray model; instead, the calculated

Figure 2-6. PBPK Model for Mercury in the Pregnant Rat



Source: Gray 1995

Figure 2-7. Model for Mercury Transport in the Pregnant Rat and Fetus



Source: Gray 1995

Table 2-7. Linear Binding and Membrane Transfer Constants

Tissue	Linear binding[a]	Membrane transfer (min^{-1})
Maternal		
Liver	14.2	0.56[b]
Kidney	164	1.55[b]
Brain	11.1	0.02[b]
Red blood cells	302	1.0[c]
Muscle	14.5	0.063[d]
Skin	14.2	0.506
Fetal		
Placenta	102[c]	0.064[c]
Placental barrier	—	0.33[f]
Liver	54.9	0.506
Kidney	21.3	1.55
Brain	23.7	0.028
Red blood cells	302	0.08[f]

[a] Wannag (1976)
[b] Thomas et al. (1986)
[c] Hirayama (9185)
[d] Berlin (1963)
[e] Mansour et al. (1974)
[f] Fit to Wannag (1976) data

Table 2-8. Secretion/Reabsorption Constants

Rate	Constant
Biliary secretion rate kB (excretion rate[a] /liver MeHg mass[b])	0.0021 min^{-1}
Gut resorption rate kA (resorption rate[a] /excretion rate x gut)	0.0026 min^{-1}
Gut volume[c]	24.4 mL
Fecal flow rate[c]	0.069 mL/min
Excretion rate[a] (average over 10 days)	8.68×10^{-6} mg/min
Reabsorption rate (average over 10 days)	7.99×10^{-6} mg/min

[a] Norseth and Clarkson 1971
[b] Wannag 1976
[c] Harrison and Gibaldi 1977

reabsorption rate of secreted or shed methylmercury in the gut implicitly accounts for the amount converted (i.e., the amount of demethylated mercury that subsequently would not be reabsorbed).

Published data were used directly or to estimate values for the maternal and fetal extracellular space, maternal plasma volume and flow expansion during pregnancy, and maternal and fetal organ volumes and plasma flow.

The model was run with a single intravenous bolus dose of 1 mg/kg at various times during a 22-day rat gestation period and compared with previously published (different author) maternal and fetal organ concentrations. The model was also run with a daily dosing for 98 days, ending on Gd 20, to simulate a typical human dietary exposure pattern for a frequent consumer of methylmercury-contaminated food.

Validation of the model. The Gray model simulations were validated against published values in the literature for mercury concentrations in maternal and fetal rat tissue from a variety of dosing patterns over the 22-day rat gestation period. Model-derived estimates of methylmercury half-life in red blood cells of 14.8 days for the rat were consistent with published values from 14 to 16 days. Consistent values were also obtained for the timing of the peak mercury concentration in the brain. Model estimates were in agreement with published values for most tissue mercury concentrations for dosing at various times, with percent differences generally <25%. Model estimates of maternal kidney methylmercury concentrations were consistently below published values, possibly due to an underestimate of the inorganic fraction of mercuric mercury in the kidneys.

The model results for a total fetal methylmercury concentration of 0.79% 24 hours after maternal methyl-mercury dosing on Gd 19 compare favorably with published values of 0.6 and 0.88% for administered doses on Gd 19 and 20, respectively.

No human data were presented to validate the model, and validation was not performed for other routes of mercury exposure.

Target tissues. The target tissues for this model included the blood, liver, gut, kidneys, and brain.

Species extrapolation. The model validated the use of published data for the rat. No other species were tested, and data from other species were not used to validate the model. The author, however,

suggests that generally good agreement between the model simulated results and the published values indicate that the model accurately reflects the underlying biological processes and that scaling factors for species-to-species extrapolations should be considered.

High-low dose extrapolations. No data were presented to evaluate the utility of the model for high-to-low dose extrapolations. A continuous exposure was simulated, but it was not validated against published data.

Interroute extrapolation. Only the intravenous route of exposure was evaluated. No data were presented to evaluate the validity of the model in extrapolating to an oral, inhalation, or dermal route of exposure. No compartment was included in the model for the lungs. Although a skin compartment was included in the model, absorption from a dermal application of methylmercury was not addressed.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

The absorption of metallic mercury through the lungs is by rapid diffusion. It is suggested that oral absorption of inorganic mercury compounds depends on their dissociation in the intestinal tract. In several cases, the underlying mechanism for the toxic effects of mercury has been attributed to the high affinity of mercury for protein-containing sulfhydryl or thiol groups.

The mechanism of absorption for metallic mercury vapors is rapid diffusion across alveolar membranes (Berlin et al. 1969; Clarkson 1989). Mercury distribution in the brains of mercury-sensitive SJL/N mice exposed for 10 weeks (5 days per week) to relatively high concentrations (0.5–1.0 mg/m^3) of mercury vapor was found to be affected by the magnitude of exposure (Warfvinge 1995). In animals exposed to 0.5 mg/m^3 for 19 hours a day or 1 mg/m^3 for 3 hours a day, mercury was found in almost the entire brain, whereas in those exposed to 0.3 mg/m^3 for 6 hours a day, mercury was primarily found in the neocortical layer V, the white matter, the thalamus, and the brain stem. In mice exposed to 1 mg/m^3 for just 1.5 hours a day, the white matter and brain stem were the targets for mercury accumulation. These findings in mice were generally in agreement with brain distribution patterns observed in mercury-sensitive rats (Schionning et al. 1991; Warfvinge et al. 1992), except that the white matter was not found to be a target for mercury accumulation.

Oral absorption of metallic mercury is low, possibly because of an *in vivo* conversion to divalent mercury and subsequent binding to sulfhydral groups, or possibly because of poor absorption of the elemental form. For inorganic mercuric compounds, the low absorption in the lungs is probably due to the deposition of particles in the upper respiratory system that should be cleared rapidly (Friberg and Nordberg 1973). Solubility and other chemical properties may also be factors in the absorption. The mechanism for intestinal absorption of inorganic mercuric mercury may also involve the process of diffusion, and the absorption rate is proportional to the concentration of mercury in the lumen of the intestines (Piotrowski et al. 1992). The extent of transport of inorganic mercury across the intestinal tract may depend on its solubility (Friberg and Nordberg 1973) or on how easily the compounds dissociate in the lumen (Endo et al. 1990). Absorption of mercurous compounds is less likely, probably because of solubility (Friberg and Nordberg 1973) or its conversion into the divalent cation in the gastrointestinal tract.

The divalent cation exists in both a nondiffusible form (tissues) and a diffusible form (blood) (Halbach and Clarkson 1978; Magos 1967) (see Section 2.3.2). The mechanism for the distribution of mercury and its compounds probably depends on the extent of uptake of the diffusible forms into different tissues or on the mercury-binding to protein-binding sites (sulfhydryl groups) in red cells and plasma proteins (Clarkson 1972b).

Mechanisms for the toxic effects of inorganic and organic mercury are believed to be similar. It has been suggested that the relative toxicities of the different forms of mercury (e.g., metallic, monovalent, and divalent cations and methyl- and phenylmercury compounds) are related, in part, to its differential accumulation in sensitive tissues. This theory is supported by the observation that mercury rapidly accumulates in the kidneys and specific areas of the central nervous system (Rothstein and Hayes 1960; Somjen et al. 1973).

The accumulation of methylmercury and inorganic mercury in the brain of female monkeys *(Macaca fascicularis)* was studied by Vahter et al. (1994). In this study, animals received oral doses of 50 µg/kg/day for either 6, 12, or 18 months. In normal-weight monkeys (2.4–4.1 kg), a steady-state blood concentration for total mercury was attained in approximately 4 months. The elimination half-life in the blood was found to be 26 days. Accumulation in the brain appeared to be biphasic, with an elimination half-life of 35 days for brain methylmercury in those monkeys exposed for 12 months. The elimination half-life of inorganic mercury, on the other hand, was reported be on the order of years. It was also found that inorganic mercury accounted for approximately 9% of the total brain mercury at 6–12 months, 18% at

18 months, and 74% 6 months after termination of exposure. The authors stated that the presence of inorganic mercury in the brain was thought to be the result of demethylation of methylmercury in the brain. In heavier monkeys, there was a limited distribution of mercury in the fat. A finding of higher brain concentrations in the heavy monkeys than in those of normal weight was probably due to higher blood mercury levels and a higher brain-to-blood distribution ratio. *In vivo* methylation of inorganic mercury, on the other hand, was not shown to occur in occupationally exposed workers (Barregard et al. 1994a, 1994b), contrary to the findings of previous *in vitro* studies.

Distribution of organic mercury is believed to involve complexes with proteins in the body. Methylmercury associates with water-soluble molecules (e.g., proteins) or thiol-containing amino acids because of the high affinity of the methylmercuric cation (CH_3Hg^+) for the sulfhydryl groups (SH-) (Aschner and Aschner 1990). Complexes of methylmercury with cysteine or glutathione have been identified in blood, liver, and bile (Aschner and Aschner 1990). The transport of methylmercury to the brain after subcutaneous injection appears to be closely linked to thiol-containing amino acids (Aschner and Clarkson 1988). The methylmercury cation can bind to the thiol group of the amino acid cysteine, forming a complex in which the valence bonds link the mercury atom to adjacent iron and sulfur atoms at an 180E angle, creating a chemical structure similar to that of the essential amino acid methionine (Clarkson 1995). In such a manner, methylmercury can cross the blood-brain barrier "disguised" as an amino acid via a carrier-mediated system (i.e., transport is not solely the result of methylmercury's lipid solubility). The uptake of methylmercury by the brain is inhibited by the presence of other amino acids such as leucine, methionine, phenylalanine, and other large neutral amino acids (Clarkson 1995).

The mechanism by which methylmercury crosses the blood-brain barrier has also been examined in the rat using a rapid carotid infusion technique (Kerper et al. 1992). The results of this study also showed that methylmercury may enter the brain as a cysteine complex. The uptake of Me_20_3Hg complexed with either L- or D-cysteine was measured as a function of Me_20_3Hg-cysteine concentration in the injection solution. There was a faster rate of uptake of Me_20_3Hg-L-cysteine as compared to the D-cysteine complex. The nonlinearity of Me_20_3Hg-L-cysteine uptake with the increasing concentration suggests that transport of this complex is saturable, while the D-cysteine complex is taken up by simple diffusion. The mechanism for the distribution in the brain of inorganic mercury (resulting from the demethylation of organic mercury) is not well understood.

Strain and sex differences in renal mercury content in mice are attributable, in part, to differences in tissue glutathione content and to differences in renal γ-glutamyltranspeptidase activity, which is controlled, at least in part, by testosterone (Tanaka et al. 1991, 1992). The correlation of hepatic glutathione (or plasma glutathione) with the rate of renal uptake of methylmercury suggests that methylmercury is transported to the kidneys as a glutathione complex (Tanaka et al. 1991). In addition to strain and sex differences in renal mercury content, it has also been demonstrated using mice (133–904 days old) that the ratio of mercury in the brain to that in the liver and the kidneys increased significantly with age (Massie et al. 1993).

In a study of the absorption of inorganic mercury by the rat jejunum, Foulkes and Bergman (1993) found that while tissue mercury could not be rigorously separated into membrane-bound and intracellular compartments (as can the heavy metal cadmium), its uptake into the jejunum includes a relatively temperature-insensitive and rapid influx into a pool readily accessible to suitable extracellular chelators. A separate, slower and more temperature-sensitive component, however, leads to the filling of a relatively chelation-resistant compartment. Nonspecific membrane properties, such as surface charge or membrane fluidity, might account for mucosal mercury uptake (Foulkes and Bergman 1993).

2.4.2 Mechanisms of Toxicity

High-affinity binding of the divalent mercuric ion to thiol or sulfhydryl groups of proteins is believed to be a major mechanism for the biological activity of mercury (Clarkson 1972a; Hughes 1957; Passow et al. 1961). Because proteins containing sulfhydryl groups occur in both extracellular and intracellular membranes and organelles, and because most sulfhydryl groups play an integral part in the structure or function of most proteins, the precise target(s) for mercury is not easily determined, if indeed there is a specific target. Possibilities include the inactivation of various enzymes, structural proteins, or transport processes (Bulger 1986); or alteration of cell membrane permeability by the formation of mercaptides (Sahaphong and Trump 1971). Binding may also occur to other sites (e.g., amine, carboxyl groups) that are less favored than sulfhydryl groups. A variety of mercury-induced alterations are being investigated, including increased oxidative stress, disruption of microtubule formation, increased permeability of the blood-brain barrier, disruption of protein synthesis, disruption of DNA replication and DNA polymerase activity, impairment of synaptic transmission, membrane disruption, impairment of the immune response, and disruption in calcium homeostasis. These alterations may be acting singly or in combination.

Mercury has been shown to affect hepatic microsomal enzyme activity (Alexidis et al. 1994). Intraperitoneal administration of mercuric acetate (6.2 µmol/kg/day) once daily for 6 days or once as a single dose of 15.68 µmol/kg resulted in an increase in kidney weight and a significant decrease in total cytochrome P-450 content. The single 15.68 µmol/kg injection resulted in the reduction of both microsomal protein level and P-450 content, possibly resulting from the generation of free radicals during the Hg^{++} intoxication process.

Through alterations in intracellular thiol status, mercury can promote oxidative stress, lipid peroxidation, mitochondrial dysfunction, and changes in heme metabolism (Zalups and Lash 1994). $HgCl_2$ has been shown to cause depolarization of the mitochondrial inner membrane, with a consequent increase in the formation of H_2O_2 (Lund et al. 1993). These events are coupled with a Hg^{++}-mediated glutathione depletion and pyridine nucleotide oxidation, creating an oxidant stress condition characterized by increased susceptibility of the mitochondrial membrane to iron-dependent lipid peroxidation. Lund et al. (1993) further postulated that mercury-induced alterations in mitochondrial calcium homeostasis may exacerbate Hg^{++}-induced oxidative stress in kidney cells. As a result of oxidative damage to the kidneys, numerous biochemical changes may occur, including the excretion of excess porphyrins in the urine (porphyrinuria). In a study of the mechanism of porphyrinogen oxidation by mercuric chloride, Miller and Woods (1993) found that mercury-thiol complexes possess redox activity, which promotes the oxidation of porphyrinogen and possibly other biomolecules.

The steps between thiol binding and cellular dysfunction or damage have not been completely elucidated, but several theories exist. Conner and Fowler (1993) have suggested that following entry of the mercuric or methylmercuric ion into the proximal tubular epithelial cell by transport across either the brush-border or basolateral membrane, mercury interacts with thiol-containing compounds, principally glutathione and metallothionein. This interaction initially produces alterations in membrane permeability to calcium ions and inhibition of mitochondrial function. Through unknown signaling mechanisms, mercury subsequently induces the synthesis of glutathione, various glutathione-dependent enzymes, metallothionein, and several stress proteins (Conner and Fowler 1993). In the kidneys, epithelial cell damage is believed to occur as the result of enhanced free radical formation and lipid peroxidation (Gstraunthaler et al. 1983). Treatment with mercury results in depletion of cellular defense mechanisms against oxidative damage such as glutathione, superoxide dismutase, catalase, and glutathione peroxidase (Gstraunthaler et al. 1983). Further, enhancement of glutathione peroxidase has been observed in mercury-treated rats in direct relationship with kidney mercury content (Guillermina and Elias 1995), but inhibition of renal redox cycle

enzymes *in vivo* did not appear to be a significant determinant of the increased lipid peroxidation observed during $HgCl_2$-induced nephrotoxicity. The selenium-dependent form of glutathione peroxidase is highly sensitive to inhibition by mercury, and it has been proposed that mercury interactions with selenium in the epithelial cells limit the amount of selenium available for this enzyme (Nielsen et al. 1991). Depletion of mitochondrial glutathione and increases in mitochondrial hydrogen peroxide at the inner mitochondrial membrane (Lund et al. 1991) may contribute to acceleration of the turnover of potassium and magnesium observed at this membrane (Humes and Weinberg 1983). Acute renal failure resulting from mercury exposure has been proposed to result from decreased renal reabsorption of sodium and chloride in the proximal tubules and increased concentrations of these ions at the macula densa (Barnes et al. 1980). This increase in ions at the macula densa, in turn, results in the local release of renin, vasoconstriction of the afferent arteriole, and filtration failure. These authors based this hypothesis on the observation that saline pretreatment of rats prior to mercuric chloride treatment did not prevent the proximal tubular damage but did prevent the acute renal failure. The saline pretreatment was suggested to have depleted the glomerular renin and thereby prevented the cascade of events occurring after accumulation of sodium and chloride ions at the glomerular macula densa (Barnes et al. 1980). A pivotal role for extracellular glutathione and membrane-bound γ-glutamyltransferase has also been identified in the renal incorporation, toxicity, and excretion of inorganic mercury ($HgCl_2$) in rats (Ceaurriz et al. 1994).

A similar mechanism for the promotion of neuronal degeneration by mercury has been proposed (Sarafian and Verity 1991). Increases in the formation of reactive oxygen species in several brain areas have been observed following intraperitoneal administration of methylmercuric chloride to rodents (Ali et al. 1992; LeBel et al. 1990, 1992). A dissociation between increases in lipid peroxidation and cytotoxicity has been demonstrated by showing inhibition of the lipid peroxidation with α-tocopherol without blocking the cytotoxicity (Verity and Sarafian 1991). These authors were able to show partial protection against the cytotoxicity with ethylene glycol tetra-acetate (EGTA), suggesting that increases in intracellular calcium may play a role in the cytotoxicity. They ultimately concluded that a synergistic interaction occurred between changes in intracellular calcium homeostasis and intracellular thiol status, culminating in lipoperoxidation, activation of Ca2+-dependent proteolysis, endonuclease activation, and phospholipid hydrolysis (Verity and Sarafian 1991). It has been suggested that neurons are highly sensitive to mercury either because of their low endogenous glutathione content or their inefficient glutathione redox activity. Inhibition of protein synthesis has been reported in neurons from rats exposed to methylmercury (Syversen 1977). However, it is unknown whether this inhibition is secondary to neuronal cytotoxicity.

At the functional level, both mercuric chloride and methylmercury have been shown to induce a slow inward current in patch-clamped dorsal root ganglion cells (Arakawa et al. 1991). The current does not appear to be mediated by either the sodium or calcium channels, but it may be activated by increases in intracellular calcium. Such slow inward currents suppress voltage- and neurotransmitter-activated currents. Studies of the effects of inorganic mercury, methylmercury, and phenylmercuric acetate on synaptic transmission in rat hippocampal slices (Yuan and Atchison 1994) revealed that the mechanisms that underlie the effects of various mercurials on central synaptic transmission differ with respect to the sites of action, the potency, and the reversibility of the effect. Inorganic mercury (Hg^{++}) appeared to act primarily on the postsynaptic neuronal membrane, whereas the action of methylmercury and phenylmercuric acetate was at both the pre- and postsynaptic sites but primarily on the postsynaptic membranes. Yuan and Atchison (1994) suggested that these differences may result, in part, from the differences in lipophilicity among the different mercurials studied. Differences in lipophilicity were also implicated by Roed and Herlofson (1994) as playing a role in the different effects produced by methylmercuric chloride and mercuric chloride. Roed and Herlofson (1994) suggested that the high lipid solubility of methylmercuric chloride may divert that organomercurial to the myelin of the nerve, where it very efficiently inhibits neuronal excitability. Further, they suggested that mercuric chloride probably causes inhibitory activity by binding to sulfhydryl groups in transport proteins that convey the messenger function of intracellular Ca^{++}. This, in turn, leads to both inhibition of muscle contraction and enhancement of $HgCl_2$-induced neuronal inhibition. The authors further suggest that $HgCl_2$ inhibits an internal Ca^{++} signal necessary for choline re-uptake and acetylcholine resynthesis.

Gallagher and Lee (1980) evaluated the similarity of inorganic and organic mercury toxicity to nervous tissue by injecting equimolar concentrations of both mercuric chloride and methylmercuric acetate directly into the cerebrum of rats, thereby circumventing systemic metabolic conversion pathways. The lesions induced by mercuric chloride were expected to have been much greater after the mercuric chloride injection, since this process circumvents the necessity for biotransformation. However, the lesions were only slightly larger than those seen after methylmercury injection, suggesting that there is a mechanism for organic mercury neurotoxicity that does not involve conversion into inorganic mercury. This suggestion is supported by the findings of Magos et al. (1985) who failed to establish a correlation between neuronal, cytoplasmic, mercuric ions and neuronal degeneration, or clinical evidence of neurotoxicity. These results do not, however, preclude the possibility that intracellular transport of mercuric mercury may be limited, and the limitations on transport may determine the effects observed.

Recent data from an *in vitro* study suggest that mercuric mercury may be more effective than methylmercury in some paradigms. Using patch-clamped dorsal root neurons, Arakawa et al. (1991) showed augmentation of the GABA-activated chloride current at extremely low mercuric chloride concentrations (0.1 µM), while a 1,000-fold higher concentration of methylmercury showed no such effect. The correlation between these effects observed *in vitro* and what may be occurring *in vivo*, however, is not known.

The experimental data concerning the mechanism of action of methylmercury on the developing nervous system indicate that effects on the microtubules and amino acid transport are disrupted in neuronal cells before overt signs of intoxication are observed. Vogel et al. (1985) demonstrated the potent inhibitory effects of methylmercury on microtubule assembly at ratios stoichiometric with the tubulin dimer. The effects were thought to be mediated through MeHg binding to free sulfhydryl groups on both ends and on the surface of microtubules, which would provide multiple classes of binding sites for MeHg. In subsequent *in vitro* studies, Vogel et al. (1989) identified a single high affinity class of binding sites on tubulin for methylmercury with 15 sites. The authors report that MeHg binds to tubulin stoichiometrically within microtubules, and does not induce microtubule disassembly at this low binding ratio. Free subunits of tubulin, however, will act as uncompetitive inhibitors for MeHg binding to the polymer, and MeHg binding to the multiple sites in the free dimer blocks subsequent assembly. In contrast, the stoichiometric polymer surface binding sites for MeHg in microtubules apparently do not interfere with subsequent polymerization. Mitotic inhibition from damage to microtubulin and binding to tubulin has also been reported by Sager et al. (1983).

Comparison of the effects of mercury on structural elements and enzyme activities (Vignani et al. 1992) suggests that effects on cytoskeletal elements may be observed at lower concentrations than on enzyme activities. In the *in vivo* study by Sager et al. (1982), it was concluded that methylmercury may be acting on mitotic spindle microtubules leading to cell injury in the developing cerebellar cortex. Cell injury observed in the external granular layer of the cerebellar cortex of 2-day-old rats was attributed to a reduced percentage of late mitotic figures (arrested cell division) due to the loss of spindle microtubules. Mitosis and migration of granule cells in the cerebellum end within weeks following birth; therefore, this observation may suggest potential differences in the sensitivities of children and adults to mercury-induced neurotoxicity. The toxic effects of methylmercury on the developing nervous system may also be due to deranged neuronal cell migration (Choi et al. 1978; Matsumoto et al. 1965). Examination of the brains of two infants who died following *in utero* exposure to methylmercury revealed an abnormal pattern in the

organization and a distorted alignment of neurons in the cerebral cortex. Exposures first occurred during the critical period of neuronal migration (from gestation week 7 into the third trimester) in the fetus. Both could result from a direct effect of mercury on microtubule proteins. Cell division and cell migration both require intact microtubules for normal functioning and, therefore, have been suggested as primary targets for methylmercury disruption in the developing nervous system. It is hypothesized by Aschner and Clarkson (1988) that the uptake of methylmercury through the blood-brain barrier in developing and mature animals is closely linked to amino acid transport and metabolism because of the infusion of L-cysteine enhanced ^{203}Hg uptake. The enhanced transport in the fetus may be a result of the immaturity of the transport systems in the blood-brain barrier or of possible physical immaturity of the barrier itself. Methylmercury has also been shown to increase intracellular Ca^{++} and inositol phosphate levels (Sarafian 1993). The observed stimulation of protein phosphorylation in rat cerebral neuronal culture was believed to be the result of elevation of intracellular second messengers (Ca^{++}, inositol phosphate) rather than to a direct interaction between methylmercury and protein kinase enzymes. This observation was considered to suggest a specific interference with neuronal signal transduction.

The mercuric ion is also an extremely potent inhibitor of microtubule polymerization, both *in vivo* and *in vitro* (Duhr et al. 1993). Duhr and his colleagues further reported that the ability of Hg^{++} to inhibit microtubule polymerization or to disrupt already formed microtubules not only cannot be prevented by binding with the chelating agents EDTA and EGTA, but that the binding of these two potent chelators potentiates the Hg^{++}-induced inhibition of tubulin polymerization by disrupting the interaction of GTP with the E-site of brain beta-tubulin, an obligatory step in the polymerization of tubulin.

Mercury has been shown to inhibit a variety of enzymes in the nervous system. The effects of mercuric chloride and methylmercuric chloride on the activity of protein kinase C in rat brain homogenate were studied by Rajanna et al. (1995). In this study, it was found that both forms of mercury inhibited protein kinase C activity in a dose-dependent manner at micromolar concentrations, with methylmercury being a more potent inhibitor than $HgCl_2$. Mercuric chloride has also been shown to cause the inhibition and ultrastructural localization of cerebral alkaline phosphatase (Albrecht et al. 1994) following a single intraperitoneal injection of 6 mg $HgCl_2$/kg body weight. The observed inhibition and subsequent translocation of alkaline phosphatase activity from the luminal to abluminal site and the accompanying ultrastructural alterations were reported to be typical of the formation of "leaky" microvessels known to be associated with damage to the blood-brain barrier. Mercuric chloride has also been demonstrated to block the uptake of [3H]-histamine by cultured rat astroglial cells and brain endothelial cells (Huszti and Balogh

1995). This effect was seen at mercury concentrations as low as 1 µM, and the inhibition was greater in astroglial cells than in the cerebral endothelial cells. At a concentration of 100 µM, however, $HgCl_2$ caused the stimulation of histamine uptake, which was greater in the cerebral endothelial than in the astroglial cells. The mechanisms of these dose-dependent effects were considered to be different, with the inhibition of histamine uptake associated with the loss of the transmembrane Na+ and/or K+ gradient and the stimulation of histamine uptake by the higher mercury concentration being possibly related to a direct effect on the histamine transporter.

Sekowski et al. (1997) used an intact human cell multiprotein complex (which they call a DNA synthesome) to evaluate the effects of mercuric chloride on DNA synthesome-mediated *in vitro* DNA replication and DNA synthesis. The authors state that the DNA synthesome has the advantage of providing the highly ordered environment in which DNA replication occurs while allowing more precise identification of the mechanism or site of effects than possible from the use of whole cells. The results showed that DNA replication and DNA polymerase activity, as well as DNA replication fidelity of the human cell synthesome, were specifically inhibited by mercuric ion at physiologically attainable concentrations. The results suggest that mercuric ions (at concentrations above 10 µM) actively inhibit the elongation stage of DNA replication.

It has been shown that Hg^{++} promotes dose-dependent toxic effects on heart muscle through actions on the sarcolemma, the sarcoplasmic reticulum, and contractile proteins (Oliveira et al. 1994). In this study, inorganic mercury ($HgCl_2$) was shown to have a dose-dependent effect on rat papillary muscle, with a concentration of 1 µM causing a small increase in the force of isometric contraction. Concentrations of 2.5, 5, and 10 µM produced a dose-dependent decrease in contractile force. The rate of force development, however, was effected differently, increasing at 1 and 2.5 µM Hg^{++} but decreasing to control levels at 5 and 10 µM concentrations. Oliveira et al. (1994) suggested that this response was due to an observed progressive reduction in the time to peak tension with increasing mercury concentrations, an effect they attributed to the binding of mercuric ions to SH groups inducing Ca^{++} release from the sarcoplasmic reticulum, the activity of which itself was depressed by mercury in a dose-dependent fashion. Further, tetanic tension did not change during treatment with 1 µM Hg^{++} but decreased with 5 µM, suggesting a toxic effect on the contractile proteins only at high Hg^{++} concentrations (Oliveira et al. 1994).

The molecular events leading to activation of the autoimmune response in susceptible individuals have yet to be fully elucidated. However, chemical modification of major histocompatibility complex (MHC) class

II molecules or modification of self peptides, T-cell receptors, or cell-surface adhesion molecules has been suggested (Mathieson 1992). The immune suppressive effect of mercury has been examined in human B-cells (Shenker et al. 1993). This study showed inhibition of B-cell proliferation, expression of surface antigens, and synthesis of IgG and IgM by both methylmercury and mercuric mercury. These chemicals caused a sustained elevation of intracellular calcium. Based on concurrent degenerative changes in the nucleus (hyperchromaticity, nuclear fragmentation, and condensation of nucleoplasm) in the presence of sustained membrane integrity, the author suggested that the increase in intracellular calcium was initiating apoptic changes in the B-cells, ultimately resulting in decreased viability.

The glomerulopathy produced by exposure of Brown-Norway rats to mercuric chloride has been related to the presence of antilaminin antibodies (Icard et al. 1993). Kosuda et al. (1993) suggest that both genetic background and immune regulatory networks (possibly acting through T-lymphocytes of the RT6 subset) may play an important role in the expression of autoimmunity after exposure to mercury. A strain (Brown-Norway) of rats known to be susceptible to mercury-induced production of autoantibodies to certain renal antigens (e.g., laminin) and autoimmune glomerulonephritis was compared to a nonsusceptible strain (Lewis). Different responses to subcutaneous injections of mercuric chloride regarding $RT6^+$ T-lymphocytes (a subpopulation of lymphocytes considered to have possible immunoregulatory properties) were observed. While a relative decrease in $RT6^+$ T-cells occurring with the development of renal autoantigen autoimmune responses was observed in the mercury-treated Brown-Norway rats, the Lewis rats did not develop renal autoimmunity and were found to have undergone significant change in the $RT6^+$-to-$RT6^+$ T-lymphocyte ratio. When Brown-Norway-Lewis F_1 hybrid rats were similarly dosed, effects similar to those in the Brown-Norway strain were seen, with the autoimmune responses to kidney antigens occurring concomitantly with a change in RT6 population proportionally in favor of T-lymphocytes that do not express the RT6 phenotype. Kosuda et al. (1993) proposed that there are both endogenous and exogenous components of mercury-induced autoimmunity. The endogenous (a genetically determined) component includes T-cell receptors, the major histocompatibility complex, and an immuno-regulatory network based upon a rather delicate balance between helper and suppressor (e.g., the $RT6^+$ T-lymphocytes) cells; whereas the exogenous component is represented by an environmental factor (e.g., mercury) capable of altering the balance within the immunoregulatory network. The manifestation of autoimmunity requires the presence and interaction of both of these components. In a similar study, Castedo et al. (1993) found that mercuric chloride induced $CD4^+$ autoreactive T-cells proliferate in the presence of class II^+ cells in susceptible Brown-Norway rats as well as in resistant Lewis rats. However, while those cells were believed to collaborate with B-cells in Brown-Norway rats to produce

autoantibodies, in Lewis rats they apparently initiate a suppressor circuit involving antiergotypic $CD8^+$ suppressor cells.

In Brown-Norway rats given 5 subcutaneous 1 mg/kg injections of mercuric chloride over a 10-day period, tissue injury (including vasculitis) was seen within 24 hours of the first injection (Qasim et al. 1995). The rapid onset of tissue injury suggests that cells other than T-cells may be involved in the primary induction of vasculitis typically seen as a response to mercuric chloride in this species. It is possible that this injury occurs through a direct action of $HgCl_2$ on neutrophils or through activation of mast cells, resulting in the release of TNF and IL8, which promote chemotaxis and activation of neutrophils. However, the changes in the Th2-like (CD4+CD45) T-cell subsets seen in this study were considered to provide support for the hypothesis that a rise in T helper cells drives the observed autoimmune syndrome, providing B-cell help, which leads to polyclonal activation and production of a range of antibodies.

Jiang and Moller (1995) found that mercuric chloride induced increased DNA synthesis *in vitro* (peak activity between days 4 and 6) in lymphocytes from several mouse strains and suggested a crucial role for helper T-cells in $HgCl_2$-induced immunotoxicity. The results of this study indicated that: (1) mercuric chloride activated CD4+ and CD8+ T-cells *(in vitro)* in a manner analogous to a specific antigen-driven response; (2) activation was dependent upon the presence of accessory cells; and (3) helper T-cells were induced to divide and transform in responder organ cells. This led Jiang and Moller (1995) to hypothesize that mercury binds to molecules on the antigen-presenting cell (APC) and transforms molecules on these cells to superantigens capable of activating T-cells with a particular set of antigen-binding receptors. In this manner, mercury could induce an internal activation of the immune system, which would in turn result in a variety of symptoms in predisposed individuals.

Both mercuric chloride (1 µM) and methylmercury (2 µM) have been shown to increase intracellular Ca^{++} concentrations in splenic lymphocytes in a concentration-dependent manner (Tang et al. 1993). The time course for the effect was, however, different for the two mercurials. In the case of methylmercury, the increase in intracellular Ca^{++} was rapid and the increased level was sustained over time, whereas the Ca^{++} rise caused by $HgCl_2$ was slower. While the effects of those mercurials did not appear to be associated with alterations of membrane integrity, both $HgCl_2$ and methylmercury did appear to cause membrane damage when the incubation time was extended. This study also found that methylmercury and mercuric chloride appear to exert their effects on internal lymphocyte Ca^{++} levels in different ways. Methylmercury increases intracellular Ca^{++} by both an apparent increase in the permeability of the membrane to

extracellular Ca^{++} and the mobilization of Ca^{++} from intracellular stores (perhaps the endoplasmic reticulum and mitochondria), whereas $HgCl_2$ causes only an increased influx of extracellular Ca^{++}.

2.4.3 Animal-to-Human Extrapolations

Mechanisms for the end toxic effects of inorganic and organic mercury are believed to be similar, and the differences in parent compound toxicity result from difference in the kinetics and metabolism of the parent compound. Animal models generally reflect the toxic events observed in humans (i.e., neurological for methylmercury toxicity and the kidneys for inorganic mercury); however, there are species and strain differences in response to mercury exposure. Prenatal exposures in animals result in neurological damage to the more sensitive developing fetus as is the case in humans. The observed inter- and intraspecies differences in the type and severity of the toxic response to mercury may result from differences in the absorption, distribution, transformation, and end tissue concentration of the parent mercury compound. For example, C57BL/6, B10.D2, B10.S inbred mice accumulated higher concentrations of mercury in the spleen than A.SW, and DBA/2 strains, subjected to the same dosage regimen. The higher concentration of splenic mercury in C57BL/6, B10.D2, B10.S correlated with the increased susceptibility of these strains to a mercury chloride-induced systemic autoimmune syndrome. The lower splenic mercury in A.SW, and DBA/2 strains resulted in more resistance to an autoimmune response (Griem et al. 1997).

A better understanding of certain physiological and biochemical processes affecting mercury kinetics may help explain these species differences. Specific processes that appear likely determinants include differences in demethylation rates affecting methylmercury fecal secretion, reabsorption, and membrane transport (Farris et al. 1993); differences in tissue glutathione content and renal γ-glutamyltranspeptidase activity (Tanaka et al. 1991, 1992), differences in antioxidative status (Miller and Woods 1993), differences in plasma cysteine concentrations compared with other thiol-containing amino acids (Aschner and Clarkson 1988; Clarkson 1995), and differences in factors that could affect gut lumenal uptake (Foulkes and Bergman 1993; Urano et al. 1990). Better controls and reporting of dietary factors, volume and timing of doses, and housing conditions would assist in the comparisons of effects among species and strains.

Further development of PBPK/PBPD models will assist in addressing these differences and in extrapolating animal data to support risk assessments for mercury exposure in humans.

2.5 RELEVANCE TO PUBLIC HEALTH

OVERVIEW

The nature and severity of the toxicity that may result from mercury exposure are functions of the magnitude and duration of exposure, the route of exposure, and the form of the mercury or mercury compound to which exposure occurs. Since the ultimate toxic species for all mercury compounds is thought to be the mercuric ion, the kinetics of the parent compound are the primary determinant of the severity of parent compound toxicity. It is differences in the delivery to target sites that result in the spectrum of effects. Thus, mercury, in both inorganic and organic forms, can be toxic to humans and other animals.

Ingestion of methylmercuric chloride, for example, is more harmful than ingestion of an equal amount of inorganic salts (e.g., mercuric chloride or mercuric acetate), since methylmercury is more readily absorbed through the intestinal tract (about 95%) than are mercuric salts (about 10–30%). In turn, ingestion of inorganic mercury salts is more harmful than ingestion of an equal amount of liquid metallic mercury, because of negligible absorption of liquid metallic mercury (about 0.01%) from the gastrointestinal tract. There is insufficient information to develop a complete matrix of effects for different mercury forms by route of exposure. The information on inhalation exposure to mercury is limited primarily to metallic mercury; only a few case studies are available for exposure to inorganic dusts or volatile organomercurials.

Inorganic salts of mercury do not readily cross the blood-brain barrier or the placenta. They are, therefore, ultimately less toxic to the central nervous system and the developing fetus than either absorbed metallic mercury or organic mercury compounds. Metallic mercury is more readily oxidized to mercuric mercury than is methylmercury, so its transport across the placenta and into the brain may be more limited than that of methylmercury. Once in the central nervous system, however, metallic mercury vapor is oxidized to the mercuric ion (Hg^{++}), which is then trapped in the central nervous system due to the limited ability of the mercuric ion to cross the blood-brain barrier. Mercurous salts are relatively unstable in the presence of sulfhydryl groups and readily transform to metallic mercury and mercuric mercury. Thus, mercurous forms of mercury will possess the toxic characteristics of both metallic and mercuric mercury. All mercury compounds may ultimately be oxidized to divalent (or mercuric) mercury, which preferentially deposits in the kidneys, and all mercury compounds may cause some degree of renal toxicity. While this is not

typically the first effect noted in all forms of mercury exposure, it can be an ultimate effect of either low-dose chronic intake or high-dose acute mercury exposure.

The most sensitive end point following oral exposure of any duration to inorganic salts of mercury appears to be the kidneys. Liquid metallic mercury can volatilize at ambient temperatures. The absorption of metallic mercury vapors from lungs is high (about 80%) (Hursh et al. 1976), and the most sensitive target following inhalation exposure to metallic mercury is the central nervous system. Absorbed metallic mercury crosses the placenta, and the fetal blood may concentrate mercury to levels 10 or more times the levels found in the maternal blood. Therefore, the developing fetal nervous system may be quite sensitive to maternal exposures to mercury vapors.

Salts of mercury and organic mercury compounds are far less volatile than liquid mercury under most conditions. Inhalation of mercury vapors from these forms is not considered a major source of exposure. While inhalation of particulate matter containing mercury salts and/or organic compounds is possible, intestinal absorption is a more likely route of exposure. The most sensitive end point for oral exposure to alkyl mercury compounds (e.g., methylmercuric chloride or ethylmercurials) is the developing nervous system, but toxicity to the adult nervous system may also result from prolonged low-dose exposures. Mercury may adversely affect a wide range of other organ systems, if exposures are sufficiently high. These effects may result from the mercuric ion’s affinity for sulfhydryl groups, which are ubiquitous in animal tissue.

Pharmacokinetic studies indicate that repeated or continuous exposure to any form of mercury can result in the accumulation of mercury in the body. Numerous studies using laboratory animals have shown that retention of mercury in the brain may persist long after cessation of short- and long-term exposures. Mercury is unusual in its ability to induce delayed neurological effects. This is especially prevalent with exposure to alkyl mercury compounds. In such cases, the onset of adverse effects may be delayed for months after the initial exposure. The delayed effects of methyl- and dimethylmercury reported in human poisonings are thought, in part, to result from binding to red blood cells, and subsequent slow release. Methylmercury also forms a complex in plasma with the amino acid cysteine, which is structurally similar to the essential amino acid methionine (Aschner and Clarkson 1988). Clarkson (1995) proposed that methylmercury can cross the blood-brain barrier "disguised" as an amino acid via a carrier-mediated system (i.e., transport is not solely the result of methylmercury’s lipid solubility).

Phenylmercuric acetate is another form of organic mercury to which the general public may be exposed. Although phenylmercury compounds are considered organomercurials, they are absorbed less efficiently by the gastrointestinal tract than is methylmercury. Once inside the body, phenylmercury is rapidly metabolized to Hg^{++}, and its effects are, therefore, similar to those of mercuric salts.

Dimethylmercury is an extremely toxic form of organic mercury, and very small exposures can cause se vere and irreversible delayed neurotoxicity, including death. Dimethylmercury is thought to be metabolized to methylmercury prior to crossing the blood-brain barrier. Dimethylmercury is used in the calibration of laboratory equipment, as a reagent, and in the manufacture of other chemicals. Unlike other forms of mercury, dimethylmercury is quickly absorbed through intact skin, and it will penetrate latex or polyvinyl gloves. It is highly volatile, will readily evaporate, and can be inhaled. Based on its vapor pressure of 58.8 mm at 23.7 EC, Toribara et al. (1997) estimated that a cubic meter of saturated air could hold more than 600 g of dimethylmercury. A recent case history of a chemist who died from an accidental spill of dimethylmercury is prompting calls for its removal as an analytical standard as a safety precaution to prevent further accidents.

Upon significant inhalation exposure to metallic mercury vapors, some people (primarily children) may exhibit a syndrome known as acrodynia, or pink disease. Acrodynia is often characterized by severe leg cramps; irritability; and erythema and subsequent peeling of the hands, nose, and soles of the feet. Itching, swelling, fever, tachycardia, elevated blood pressure, excessive salivation or perspiration, morbilliform rashes, fretfulness, sleeplessness, and/or weakness may also be present. It was formerly thought that this syndrome occurred exclusively in children, but recent reported cases in teenagers and adults have shown that these groups are also susceptible.

Occupational mercury exposures generally occur when workers inhale metallic mercury vapors. Some dermal absorption may occur from skin contact with contaminated air, but the rate is low (less than 3% of the inhaled dose). Dialkyl mercury compounds, which are not normally found in hazardous waste sites, are rapidly and extensively absorbed from both dermal and inhalation routes of exposure.

Mercury is a naturally occurring element in the earth’s crust. It is considered to have been a component of the lithosphere since the planet was formed approximately 4.5 billion years ago. However, levels of mercury at or near the earth’s surface (environmental background levels) are increasing as mercury continues to be released from the earth’s crust by both natural (weathering, volcanoes) and human (mining,

burning of fossil fuels) activities. Background levels, however, are considerable below harmful levels. There are a number of possible pathways for exposure to mercury. For a hazardous waste site that contains mercury that is being released to the environment, pathways that could result in human exposure to mercury include: (1) eating fish or wild game near the top of the food chain (i.e., larger fish, larger mammals) that have accumulated mercury in their tissues from living at or near the site; (2) playing on or in contaminated surface soils; (3) playing with liquid mercury from broken electrical switches, thermometers, blood pressure monitors etc.; or (4) bringing any liquid mercury or broken mercury device into the home, where vapors might build up in indoor air. Other potentially harmful exposure pathways include the excessive use of skin ointments or creams (e.g., skin lightening creams, antiseptic creams) that contain mercury compounds, the use of mercury fungicides (breathing vapors or contact of the skin with the fungicide), or the use of liquid mercury in herbal remedies or religious practices, especially if used indoors. If swallowed, liquid mercury is not very harmful, because it is not easily absorbed into the body from the gastrointestinal tract. However, small amounts of liquid mercury evaporate at room temperature, and the inhaled vapors are harmful.

The developing fetus and breast-fed infants are vulnerable to the harmful effects of mercury. The fetus can be exposed to mercury from the pregnant woman's body through the placenta, and infants may be exposed from the nursing woman's milk. Both inhaled mercury vapors and ingested methylmercury can cross the placenta. Inorganic mercury, and to a lesser extent elemental mercury and methylmercury, will move into breast milk. Pregnant women and nursing women need to be extra cautious in their use of consumer products containing mercury (such as some religious or herbal remedies or skin lightening creams); they should also pay attention to possible exposures to mercury at work and at home.

The primary pathways of mercury exposure for the general population are from eating fish or marine mammals that contain methylmercury, or from breathing in or swallowing very small amounts of mercury that are released from the dental amalgam used for fillings. The relative contribution of mercury from these two main sources will vary considerably for different individuals, depending upon the amount of fish consumed, the level of mercury in the fish, the number of amalgam fillings, eating and chewing habits, and a number of other factors.

Methylmercury levels vary considerably between species and within species of fish (depending on water conditions and size), so there are wide ranges in estimates of the average exposure levels to mercury in the general population from consumption of fish. Some researchers estimate that the typical daily exposure to

mercury is 0.49 µg/day for infants (aged 6–11 months), 1.3 µg/d for 2-year-old children, 2.9 µg/day for females aged 25–30 years, and 3.9 µg/day for males 25–30 years of age. Expressed on a per body weight basis, the intake for all age groups, except for 2-year-old children, was approximately 0.05 µg/kg/day (Clarkson 1990; Gunderson 1988). More recently, MacIntosh et al. (1996) estimated mean dietary exposure of 8.2 µg/d (range, 0.37–203.5 µg/day) for females and 8.6 µg/day (range, 0.22–165.7 µg/day) for males. For an average body weight of 65 kg for women and 70 kg for men, the daily intakes of mercury would be 0.126 µg/kg/day (range, 5.7–3,131 ng/kg/day) for women and 0.123 µg/kg/day (range, 3.1–2,367 ng/kg/day) for men, respectively. Lack of data about the actual amount of food consumed accounted for 95% of the total uncertainty for mercury. This was especially true for consumption levels of canned tuna and other fish (MacIntosh et al. 1996)

The Food and Drug Administration (FDA, 1996) has posted on the Internet advice for consumers recommending that pregnant women and women of childbearing age, who may become pregnant, limit their consumption of shark and swordfish to no more that one meal per month. This advice is given because methylmercury levels are relatively high in these fish species. The FDA's advice covers both pregnant women and women of child-bearing age who might become pregnant, since dietary practices immediately before the pregnancy could have a direct bearing on fetal exposure, particularly during the first trimester of pregnancy. The FDA also states that nursing women who follow this advice will not expose their infants to increased health risks from methylmercury (FDA 1996). For the general population (other than pregnant women and women of child-bearing age), the FDA advises limiting the regular consumption of shark and swordfish (which typically contain methylmercury at 1 ppm) to about 7 ounces per week (about one serving). This level of consumption results in methylmercury exposures below the U.S. FDA acceptable daily intake level for mercury. For fish species with methylmercury levels averaging 0.5 ppm, regular consumption should be limited to 14 ounces per week. Recreational and subsistence fishers who eat larger amounts of fish than the general population and routinely fish the same waters may have a higher exposure to methylmercury if these waters are contaminated (EPA 1995). People who consume greater than 100 grams of fish per day are considered high-end consumers. This is over 10 times the amount of fish consumed by members of the general population (6.5 g/day) (EPA 1995). No consumption advice is necessary for the top 10 seafood species, which make up about 80% of the seafood market: canned tuna, shrimp, pollock, salmon, cod, catfish, clams, flatfish, crabs, and scallops. The methylmercury in these species are generally less than 0.2 ppm, and few people eat more than the suggested weekly limit of fish (i.e., 2.2 pounds). More information on exposure to methylmercury and the levels in fish can be found in Section 5.5, General Population and Occupational Exposures.

Estimating mercury exposure from dental amalgams is also difficult because of high variability in the number of amalgam fillings per individual and the differences in chewing, eating, and breathing habits. Dental amalgams, however, would be the most significant source of mercury exposure in the absence of fish consumption or proximity to a waste site or incinerator. A report from the Committee to Coordinate Environmental Health and Related Programs (CCEHRP) of the Department of Health and Human Services determined a level of from 1 to 5 µg Hg/day from dental amalgam for people with 7–10 fillings (DHHS 1993). The World Health Organization reported a consensus average estimate of 10 µg amalgam Hg/day (range: 3–17 µg/day) (WHO 1991). Weiner and Nylander (1995) estimated the average uptake of mercury from amalgam fillings in Swedish subjects to be within the range of 4–19 µg/day. Skare and Engqvist (1994) estimated that the systemic uptake of mercury from amalgams in middle-aged Swedish individuals with a moderate amalgam load (30 surfaces) was, on the average, 12 µg/day, an amount said to be equivalent to a daily occupational air mercury exposure concentration of 2 $\mu g/m^3$. Other researchers have estimated the average daily absorption of Hg from amalgam at 1–27 µg/day, with levels for some individuals being as high as 100 µg/day (Björkman et al. 1997; Lorscheider et al. 1995).

Richardson et al. (1995) estimated total mercury exposure for Canadian populations of different ages to be 3.3 µg/day in toddlers (3–4 years old), 5.6 µg/day in children (5–11 years old), 6.7 µg/day in teens (12–19 years old), 9.4 µg/day in adults (20–59 years old), and 6.8 µg/day in seniors (aged 60+). Of this exposure, amalgam was estimated to contribute 50% to the total Hg in adults and 32–42% for other age groups. Estimates based on 2 independent models of exposure from amalgam alone were 0.8–1.4 µg/day in toddlers), 1.1–1.7 µg/day in children, 1.9–2.5 µg/day in teens; 3.4–3.7 µg/day in adults, and 2.1–2.8 µg/day in seniors (Richardson 1995).

Higher levels of mercury exposure can occur in individuals who chew gum or show bruxism, a rhythmic or spasmodic grinding of the teeth other than chewing and typically occurring during sleep (Barregard et al. 1995; Enestrom and Hultman 1995). Richardson (1995) reported a transient 5.3-fold increase in levels of mercury upon stimulation by chewing, eating, or tooth brushing. Sallsten et al. (1996) also reported over a 5-fold increase in plasma and urinary mercury levels (27 and 6.5 nmol/mmol creatinine versus 4.9 and 1.2 nmol/mmol creatinine, respectively) in a sample of 18 people who regularly chewed nicotine chewing gum (median values of 10 sticks per day for 27 months), compared to a control group.

Berdouses et al. (1995) studied mercury release from dental amalgams using an artificial mouth under controlled conditions of brushing and chewing and found that although the release of mercury during initial

nonsteady-state conditions was influenced by both the age of the amalgam and the amalgam type, the steady-state value of the mercury dose released by the amalgam was only 0.03 µg/day.

Sandborgh-Englund et al. (1998) evaluated the absorption, blood levels, and excretion of mercury in nine healthy volunteers (2 males, 7 females) exposed to 400 µg /m^3 mercury vapor in air for 15 minutes. This exposure corresponded to a dose of 5.5 nmol Hg/kg body weight. Samples of exhaled air, blood and urine were collected for 30 days after exposure. The median retention of elemental Hg was 69% of the inhaled dose. To evaluate the chronic exposure to mercury from dental amalgam in the general population, the daily Hg dose from fillings was estimated based on the plasma Hg levels of subjects with amalgam fillings and the plasma clearance obtained in this study. The daily dose was estimated to be from 5 to 9 µg/day in subjects with an "average" number (20–35 amalgam surfaces) of amalgam fillings (Sandborgh-Englund et al. 1998)

Halbach (1994) examined the data from 14 independent studies and concluded that the probable mercury dose from amalgam is less than 10 µg/day. When combined with the 2.6 µg/day background intake estimated by WHO (1990) for persons without amalgam fillings and with an estimated methylmercury intake of 5 µg/day from food, Halbach noted that the sum of all those inputs still falls within the WHO's 40 µg/day acceptable daily intake (ADI) level for total mercury. For the ADI of 40 µg total mercury exposure inhaled, approximately 30 µg would be absorbed, assuming 80% absorption (Halbach 1994; WHO 1976).

Whether adverse health effects result from exposure to mercury from amalgams at the levels reported above is currently a topic of on-going research and considerable discussion. A thorough review of this subject is beyond the scope of this profile. Readers are referred to the end of this section (see More on the Effects of Dental Amalgam) for a discussion of some recent reviews of this topic, and a few examples of studies on the putative toxic effects or the lack thereof from continued use of amalgam.

Other Uses of Metallic Mercury

A less well-documented source of exposure to metallic mercury among the general population is its use in ethnic religious, magical, and ritualistic practices, and in herbal remedies. Mercury has long been used for medicinal purposes in Chinese herbal preparations and is also used in some Hispanic practices for medical and/or religious reasons. Espinoza et al. (1996) analyzed 12 types of commercially produced herbal ball preparations used in traditional Chinese medicine. Mercury levels were found to range from 7.8 to

621.3 mg per ball. Since the minimum recommended adult dosage is 2 such balls daily, intake levels of up to 1.2 mg of mercury (presumed to be mercury sulfide) might be a daily dosage.

Some religions have practices that may include the use of metallic mercury. Examples of these religions include Santeria (a Cuban-based religion that worships both African deities and Catholic saints), Voodoo (a Haitian-based set of beliefs and rituals), Palo Mayombe (a secret form of ancestor worship practiced mainly in the Caribbean), and Espiritismo (a spiritual belief system native to Puerto Rico). Not all people who observe these religions use mercury, but when mercury is used in religious, folk, or ritualistic practices, exposure to mercury may occur both at the time of the practice and afterwards from breathing in contaminated indoor air. Metallic mercury is sold under the name "azogue" (pronounced ah-SEW-gay) in stores called “botanicas.” Botanicas are common in Hispanic and Haitian communities, where azogue may be sold as an herbal remedy or for spiritual practices. The metallic mercury is often sold in capsules or in glass containers. It may be placed in a sealed pouch to be worn on a necklace or carried in a pocket, or it may be sprinkled in the home or car. Some store owners may also suggest mixing azogue in bath water or perfume, and some people place azogue in devotional candles. The use of metallic mercury in a home or apartment not only threatens the health of the current residents, but also poses health risks to future residents, who may unknowingly be exposed to further release of mercury vapors from contaminated floors, carpeting, or walls.

Due to the increased number of reported metallic mercury poisonings and to the widespread potential for exposure to liquid/metallic mercury in school chemistry and science laboratories and other places accessible to the general public, the EPA and ATSDR issued a joint mercury alert in June 1997, alerting school and public health officials to the potential toxicity of this substance. This joint mercury alert also advised restricting access to mercury-containing spaces and storage rooms, and the use of alternative substances or chemicals for purposes for which liquid/metallic mercury is currently used.

Issues relevant to children are explicitly discussed in Sections 2.6, Children’s Susceptibility, and 5.6, Exposures of Children.

Minimal Risk Levels for Mercury

A common misconception is that health guidance values, such as the MRL, represent a level above which toxicity is likely to occur. This misconception has occasionally led to unwarranted concern and public

apprehension about relatively benign exposures to environmental substances. The MRL is neither a threshold for toxicity, nor a level beyond which toxicity is likely to occur. MRLs are established solely as screening tools for public health officials to use when determining whether further evaluation of potential exposure at a hazardous waste site is warranted. The relevance of the MRL to public health is discussed further in the following sections concerning the derivation of the respective mercury MRLs.

ATSDR has established a chronic inhalation MRL of 0.2 µg/m^3 for metallic mercury. Assuming a ventilation rate of 20 m^3/day for an average adult, and assuming complete absorption, exposure at the level of the MRL would result in a daily dose of 4 µg. This level of exposure is thought to represent no health risk to any element of the human population. No other inhalation MRLs have been derived for mercury or its compounds.

Oral MRLs have been established for acute (0.007 mg/kg/day) and intermediate (0.002 mg/kg/day) duration exposures to inorganic mercury. ATSDR has also established a chronic oral MRL of 0.0003 mg/kg/day (equivalent to 21 µg/day for a 70-kg adult) for methylmercury. This MRL is at least four times the estimated average daily intake level for methylmercury from the diet. The FDA has estimated that, on average, the intake rate for total mercury (both inorganic and organic) is 50–100 ng/kg/day (equivalent to 0.05–0.1 µg/kg/day or 3.5–7 µg/day for a 70-kg adult). This figure is based on the FDA total diet study of 1982–1984 (Gunderson 1988). Approximately 80–90% of the mercury in the FDA estimate would be expected to be in the form of methylmercury. A separate estimate of the average intake of methylmercury alone, based on a survey of fish eaters and on average levels of methylmercury in fish, places the average intake of methylmercury at 36 ng/kg/day (equivalent to 0.036 µg/kg/day or 2.52 µg/day for a 70-kg adult), with a 99% upper-bound estimate at 243 ng/kg/day (equivalent to 0.243 µg/kg/day or 17 µg/day for a 70-kg adult) (Clarkson 1990). These results indicate that an assessment of total methylmercury intake and body burden should be conducted when estimating exposure to mercury in populations (especially sensitive populations) living near hazardous waste sites that have the potential to release mercury to the environment.

Inhalation MRLs

No inhalation MRLs were derived for inorganic mercury salts or organic mercury compounds due to the absence of data or to the lack of sufficient information regarding exposure levels associated with the reported observed effects.

No MRLs were derived for acute- or intermediate-duration inhalation exposure to metallic mercury vapors. Available studies were either deficient in their reporting of details of experimental protocols and results, used an insufficient number of experimental animals, or tested only one dose/concentration level.

- An MRL of 0.0002 mg/m^3 has been derived for chronic-duration inhalation exposure (365 days or longer) to metallic mercury vapor.

A significant increase in the average velocity of naturally occurring tremors compared to controls was observed in a group of 26 mercury-exposed workers (from 3 industries) exposed to low levels of mercury for an average of 15.3 years (range, 1–41 years) (Fawer et al. 1983). To estimate an equivalent continuous exposure concentration, the average concentration assumed for the 8 hour/day exposures was multiplied by 8/24 and 5/7 (0.026 mg/m^3 x 8/24 hours/day x 5/7 days/week=0.0062 mg/m^3). Uncertainty factors of 10 for variability in sensitivity to mercury within the human population and 3 for use of a minimal-effect LOAEL in MRL derivation were then applied to the calculated 0.0062 mg/m^3 value, yielding a chronic inhalation MRL of 0.2 µg/m^3. Although this MRL is based on experimental data from an adult working population, there is no experimental or clinical evidence to suggest that it would not also be sufficiently protective of neurodevelopmental effects in developing embryos/fetuses and children, the most sensitive subgroups for metallic mercury toxicity.

Inhaled metallic mercury is quickly absorbed through the lungs into the blood, and 70–80% is retained. Its biological half-life in humans is approximately 60 days. The half-life is different for different physiological compartments (e.g., 21 days in the head versus 64 days in the kidneys) (Hursh et al. 1976). Since the duration of exposure influences the level of mercury in the body, the exposure level reported in the Fawer et al. (1983) occupational study was extrapolated from an 8-hour day, 40-hour workweek exposure to a level equivalent to a continuous 24 hour/day, 7 day/week exposure, as might be encountered near a hazardous waste site containing metallic mercury.

Gentry et al. (1998) used the neurobehavioral information on a control group and one exposure group from the Fawer et al. (1983) study to derive an inhalation MRL for elemental mercury based upon a benchmark dose (BMD) analysis. Dose-response analysis could be performed on four measures of hand tremor, with tasks performed both at rest and with a load. The exposure level of the exposed group to metallic mercury was assumed to be the mean TWA exposure of 0.026 mg/m^3. A physiologically based pharmacokinetic model for metallic mercury vapor was found to be linear through the region of concern from the LOAEL to

the MRL; that is, the relationship between inhaled concentration and target tissue concentration at the LOAEL and at lower levels (including the MRL) did not differ. Therefore, exposure concentrations were used directly for the analysis. Gentry et al. (1998) also assumed that 1% of the unexposed population would be considered in the adverse response range. The BMD_{10} was the dose at which the probability of exceeding the 1% adverse response level was 10% greater than in unexposed individuals, and the $BMDL_{10}$ is the 95% lower bound confidence level on that dose. A simple linear model sufficed to describe the dose-response. A $BMDL_{10}$ of 0.017 mg metallic mercury/m^3 was derived as a reasonable representation of the sparse data. This level would be equivalent to a NOAEL (i.e., no LOAEL to NOAEL uncertainty factor is needed). Using a PBPK model to estimate target tissue doses from inhaled mercury vapor and adjusting for continuous exposure and interhuman variability (with an uncertainty factor of 10), an MRL of 0.0004 mg/m^3 (based on target tissue dose) was derived which is about two times the ATSDR derived MRL of 0.0002 mg/m^3 based upon the Fawer et al. (1983) LOAEL.

The ability of long-term, low-level exposure to metallic mercury to produce a degradation in neurological performance was also demonstrated in other studies. One such study (Ngim et al. 1992) attributed adverse neurological effects to a lower average level of exposure than did the Fawer et al. (1983) study; however, this study was not used in deriving a chronic inhalation MRL due to uncertainties concerning the study protocol, including methodological and reporting deficiencies. In the Ngim et al. (1992) study, dentists with an average of 5.5 years of exposure to low levels of metallic mercury were reported to have impaired performance on several neurobehavioral tests. Exposure levels measured at the time of the study ranged from 0.0007 to 0.042 mg/m^3, with an average of 0.014 mg/m^3. Mean blood mercury levels among the dentists ranged from 0.6 to 57 µg/L, with a geometric mean of 9.8 µg/L. The performance of the dentists on finger tapping (measures digital motor speed), trail-making (measures visual scanning and motor speed), digit symbol (measures visuomotor coordination and concentration), digit span, logical memory delayed recall (measure of verbal memory), and Bender-Gestalt time (measures visual construction) tests was significantly poorer than controls. The exposed dentists also showed higher aggression than did controls. Furthermore, within the group of exposed dentists, significant differences were observed between a subgroup with high mercury exposure compared to a subgroup with lower exposure. These exposure severity subgroups were not compared to controls, and average exposure levels for the subgroups were not reported. The design and reporting of this study limits its usefulness in deriving an MRL for metallic mercury. The exposure status of the subjects was known to the investigator during testing, mercury levels were not reported for controls, and methods used to adjust for potential contributions other than mercury from amalgams to the study results (such as the possible use in this population of traditional medicines

containing mercury) were not reported. It was also unclear whether the results for the mercury exposure group were inordinately influenced or skewed by the individual dentists with the highest exposures and/or blood levels. These confounding factors precluded the use of the Ngim et al. (1992) study for the derivation of an MRL, but the study does provide support both for the premise that low-dose chronic exposure to metallic mercury can result in adverse health sequelae and for the chronic inhalation MRL that is based on the Fawer et al. (1983) study of occupationally exposed individuals.

Other occupational studies further support the ability of metallic mercury to induce neurological deficits. Several studies have reported significant effects on tremor or cognitive skills among groups exposed occupationally to comparable or slightly higher (up to 0.076 mg/m^3) levels (Ehrenberg et al. 1991; Piikivi et al. 1984; Roels et al. 1982). Difficulty with heel-to-toe gait was observed in thermometer plant workers subjected to mean personal breathing zone air concentrations of 0.076 mg/m^3 (range, 0.026–0.27 mg/m^3) (Ehrenberg et al. 1991). Tremors have also been reported in occupationally exposed workers with urinary mercury concentrations of 50–100 µg/g creatinine and blood levels of 10–20 µg/L (Roels et al. 1982). By comparison, blood mercury levels in the Fawer et al. (1983) study averaged 41.3 and 16.6 µmol Hg/L for the exposed and control groups, respectively. Urinary mercury levels for the exposed workers in the Fawer et al. (1983) study averaged 11.3 µmol Hg/mol creatinine (about 20 µg/g creatinine), compared with 3.4 µmol/mol creatinine in the controls. Piikivi et al. (1984) found decreases in performance on tests that measured intelligence (based upon a similarities test) and memory (evaluating digit span and visual reproduction) in chloralkali workers exposed for an average of 16.9 years (range, 10–37 years) to low levels of mercury, when compared to an age-matched control group. In this study, significant differences from controls were observed on these tests among 16 workers with blood levels ranging from 75 nmol/L to 344 nmol/L and urine levels ranging from 280 nmol/L (about 56 µg/L) to 663 nmol/L. Abnormal nerve conduction velocities have also been observed in chloralkali plant workers at a mean urine concentration of 450 µg/L (Levine et al. 1982). These workers also experienced weakness, paresthesias, and muscle cramps. Prolongation of brainstem auditory evoked potentials was observed in workers with urinary mercury levels of 325 µg/g creatinine (Discalzi et al. 1993). Prolonged somatosensory-evoked potentials were found in 28 subjects exposed to airborne mercury concentrations of 20–96 mg/m^3 (Langauer-Lewowicka and Kazibutowska 1989). All of these studies substantiate the ability of chronic, low- to moderate-level exposure to metallic mercury vapors to cause neurological deficiencies.

Employment of the Chronic Inhalation MRL for Metallic Mercury

ATSDR emphasizes that the MRL is not intended to be used as an estimation of a threshold level. Exceeding the MRL does not necessarily mean that a health threat exists. However, the greater the amount by which the MRL is exceeded and the longer or more frequent the individual exposures, the greater the likelihood that some adverse health outcome may occur. Secondly, the chronic inhalation MRL is, by definition, a level that is considered to be without appreciable (or significant) health risk over a lifetime of exposure at that level. It is further considered to be a "safe" level for all factions of the exposed human population, when exposure exists for 24 hours a day, 7 days a week for an extended period of years. The employment of the MRL, therefore, must be geared to the particular exposure scenario at hand. For example, people may be able to "tolerate" metallic mercury levels above the MRL for intermittent periods of exposure (e.g., 1 or 2 hours per day, 5 days per week) without any adverse health sequelae, either overt or covert. The use of the "contaminated area" (e.g., storage versus exercise room versus day care) will largely influence the use of the MRL. Finally, the MRL is intended primarily as a "screening value" for public health officials to use in their assessment of whether further evaluation of the potential risk to public health is warranted in a hazardous waste site scenario. The MRL is *not* intended, nor should it be indiscriminately used, as a clean-up or remediation level, or as a predictor of adverse health effects. While it is considered to afford an adequate degree of protection for the health of all potentially exposed individuals, it might be unnecessarily stringent for application to some exposure situations (i.e., higher air concentrations might afford a similar degree of protection in some exposure scenarios); thus, its relevance in any specific environmental situation is intended to be determined by an experienced public health or medical official.

Oral MRLs

Metallic Mercury

No oral MRLs were derived for metallic (elemental) mercury due to the lack of data. Oral exposure to liquid metallic mercury would be expected to present little health risk, since it is so poorly absorbed (<0.01%) through the healthy intestine. Sufficiently large quantities could, however, present a risk of intestinal blockage, and some could enter the systemic circulation (blood or lymphatic) through open lesions, presenting a risk of occlusion of smaller arteries, especially within the pulmonary circulation.

Inorganic Mercury

The acute- and intermediate-duration MRLs for oral exposure to inorganic mercury are based on kidney effects reported in a 1993 NTP study of mercuric chloride (NTP 1993). Most of the supporting studies of oral exposure to inorganic mercury also use mercuric chloride.

Mercuric sulfide (also known as cinnabar) is the predominant natural form of mercury in the environment and is a common ore from which metallic mercury is derived. Mercury released to the environment may be transformed into mercuric sulfide. Several studies suggest that the bioavailability of mercuric sulfide in animals is less than that of mercuric chloride (Sin et al. 1983, 1990; Yeoh et al. 1986, 1989). For example, Sin et al. (1983) found an increase in tissue levels of mercury in mice orally exposed to low doses of mercuric chloride, but elevated levels of mercury were not found in the tissues of mice fed an equivalent weight of mercuric sulfide. This finding indicates a difference in bioavailability between $HgCl_2$ and HgS in mice. However, a quantitative determination of the relative bioavailabilities of mercuric sulfide versus mercuric chloride has not been derived in the available studies, nor has the relative bioavailability of mercuric sulfide in humans been examined.

- An MRL of 0.007 mg Hg/kg/day has been derived for acute-duration oral exposure (14 days or less) to inorganic mercury.

The MRL was based on a NOAEL of 0.93 mg Hg/kg/day for renal effects in rats administered mercuric chloride 5 days a week for 2 weeks. The dose used in this study was duration-adjusted for a 5-day/week exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). Increased absolute and relative kidney weights were observed in male rats exposed to 1.9 mg Hg/kg/day as mercuric chloride (NTP 1993). At higher doses, an increased incidence and severity of tubular necrosis was observed.

Several other studies examining the effects of oral exposure to inorganic mercury salts have also shown renal toxicity in humans as a result of acute oral exposures. Kidney effects (i.e., heavy albuminuria, hypoalbuminemia, edema, and hypercholesterolemia) have been reported after therapeutic administration of inorganic mercury (Kazantzis et al. 1962). Acute renal failure has been observed in a number of case studies in which mercuric chloride had been ingested (Afonso and deAlvarez 1960; Murphy et al. 1979; Samuels et al. 1982). The autopsy of a 35-year-old man who ingested a lethal dose of mercuric chloride

and exhibited acute renal failure showed pale and swollen kidneys (Murphy et al. 1979). A case study reported acute renal failure characterized by oliguria, proteinuria, hematuria, and granular casts in a woman who ingested 30 mg Hg/kg body weight as mercuric chloride (Afonso and deAlvarez 1960). Another case study reported a dramatic increase in urinary protein secretion by a patient who ingested a single dose of 15.8 mg Hg/kg body weight as mercuric chloride (assuming a body weight of 70 kg) (Pesce et al. 1977). The authors of the report surmised that the increased excretion of both albumin and β_2-microglobulin were indicative of mercury-induced tubular and glomerular pathology. Acute renal failure that persisted for 10 days was also observed in a 19-month-old child who ingested an unknown amount of powdered mercuric chloride (Samuels et al. 1982). Decreased urine was also observed in a 22-year-old who attempted suicide by ingesting approximately 20 mg Hg/kg (Chugh et al. 1978).

- An MRL of 0.002 mg Hg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to inorganic mercury.

This MRL was based on a NOAEL of 0.23 mg Hg/kg/day for renal effects in rats administered mercuric chloride 5 days a week for 6 months (Dieter et al. 1992; NTP 1993). This dose was duration-adjusted for a 5 day/week exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). Increased absolute and relative kidney weights were observed in rats exposed to 0.46 mg Hg/kg/day, the next higher treatment level. At higher doses, an increased incidence of nephropathy (described as foci of tubular regeneration, thickened tubular basement membrane, and scattered dilated tubules containing hyaline casts) was observed. Renal toxicity is a sensitive end point for inorganic mercury toxicity, as seen in other intermediate-duration oral studies on rats and mice exposed to inorganic mercury (Carmignani et al. 1992; Jonker et al. 1993a; NTP 1993), as well as case reports of humans ingesting inorganic mercury for acute and chronic durations (Afonso and deAlvarez 1960; Davis et al. 1974; Kang-Yum and Oransky 1992; Nielsen et al. 1991; Pesce et al. 1977).

The relatively small difference between the acute-duration MRL (0.007 mg/kg/day) and the intermediate-duration MRL (0.002 mg/kg/day) is not meant, nor is it considered, to imply a high level of precision in the calculation of these health guidance values. Rather, this difference of 5 µg/kg/day reflects the increased toxicity of continued low-dose exposure for longer periods of time and is consistent with the known build-up of mercury levels in body tissues over a prolonged course of continued exposure. The actual precision of any derived (actually estimated) MRL is dependent upon an encompassing, but not sharply defined, area of uncertainty based upon the database used in its determination.

As a method of comparison to evaluate whether use of another method to derive an MRL might result in a different intermediate oral MRL value for inorganic mercury, ATSDR used the same data (Dieter et al. 1992; NTP 1993) to calculate a benchmark dose for inorganic mercury. Using the most sensitive end point identified in this study (relative kidney weight changes in rats), the experimental data were used to obtain a modeled dose-response curve. Benchmark doses were then determined for the 10% response level (0.38 mg/kg/day) and the 5% response level (0.20 mg/kg/day). After adjusting the 5-days/week exposures in the study to 7-days/week equivalent doses, the 10 and 5% response-base benchmarks became 0.27 and 0.15 mg/kg/day, respectively. Application of 10-fold uncertainty factors for each inter- and intraspecies variability resulted in estimated human benchmark doses of 0.003 mg/kg/day for the 10% response level and 0.002 mg/kg/day for the 5% response level. These values strongly support the current existing intermediate oral MRL of 0.002 mg/kg/day for inorganic mercury.

No MRL for chronic-duration oral exposure to inorganic mercury was derived, because the study results showed decreased survival rate for male rats at all LOAELs.

Organic Mercury

Acute, Intermediate, or Chronic Inhalation MRLs: No inhalation MRLs were derived for organic mercury compounds, due to the absence of data or to the lack of sufficient information regarding exposure levels associated with the reported observed effects.

Acute and Intermediate Oral MRLs: No MRLs were derived for acute or intermediate oral exposure to organic mercury compounds due to the absence of data or to the lack of sufficient information regarding exposure levels associated with the reported observed effects.

Chronic Oral MRL for Methylmercury: Hair levels are typically used as an index of exposure to methymercury. A number of studies report that hair mercury levels correlate with total intake levels and with organ-specific levels of mercury. Suzuki et al. (1993) analyzed 46 human autopsies in Tokyo, Japan and reported that hair mercury levels were highly significantly correlated with organ Hg levels in the cerebrum, cerebellum, heart, spleen, liver, kidney cortex, and kidney medulla, when the total mercury or methyl mercury value in the organ was compared with the hair total mercury or organic mercury, respectively.

Nakagawa (1995) analyzed total mercury in hair samples from 365 volunteers in Tokyo, and reported higher mercury levels in those who preferred fish in their diet, compared to those who preferred other foods (preference choices were fish, fish and meat, meat, and vegetables). The mean hair mercury levels were 4 ppm in men who preferred fish and 2.7 ppm in women who preferred fish. The lowest hair mercury levels were seen in men and women who preferred vegetables, 2.27 and 1.31 ppm, respectively. The mean hair level for the whole group was 2.23 ppm (median 1.98).

Drasch et al. (1997) assayed tissue samples of 150 human cadavers (75 males, and 75 females) from a "normal" European (German) population, i.e., there were no occupational or higher than average exposures to metals found in any of the biographies of the deceased. The objective was to evaluate the validity of blood, urine, hair, and muscle as biomarkers for internal burdens of mercury, lead, and cadmium in the general population. All individuals died suddenly and not as a result of chronic ailments. Age ranged from 16 to 93 years, and every decade was represented by approximately 10 males and 10 females. Tissues sampled included kidney cortex, liver, cerebral cortex, cerebellum, petrous portion of the temporal bone, (pars petrosis ossis temporalis), pelvic bone (spina iliaca anterior-superior), muscle (musculus gluteus), blood (heart blood), urine, and hair (scalp-hair). Statistically significant rank correlations between biomarker levels and tissues were observed, but with large confidence intervals for the regressions. The authors conclude that specific biomarkers relative to each metal are useful in estimating body burdens and trends in groups, but are not useful for determining the body burden (and therefore the health risks) in individuals. A notable exception was for correlation to brain mercury. By comparison to a generally poor correlation of cadmium, lead, and mercury between hair and tissue, there was a strong correlation between mercury in hair and mercury in brain (cerebrum and cerebellum). The authors state that this may be due to the high lipophilicity of elemental and short-chain alkyl mercury compounds. As seen in other studies comparing European to Japanese hair mercury levels, the mercury hair levels reported by Nakagawa (1995) of 2–4 ppm for a Japanese population are 10–20 times higher than total mercury levels observed in the Drasch et al. (1997) study (median, 0.247 µg/g in hair; range, 0.43–2.5 µg/g).

Other studies have confirmed a good correlation between hair mercury and brain mercury levels. In a study on the Seychelles Islands cohort, Cernichiari et al. (1995b) compared maternal hair levels, maternal blood levels, fetal blood levels, and fetal brain levels. Autopsy brains were obtained from infants dying from a variety of causes. The concentrations of total mercury in six major regions of the brain were highly correlated with maternal hair levels. This correlation was confirmed by a sequence of comparisons among the four measurements. Maternal hair levels correlated to maternal blood levels (r=0.82) and infant brain

levels (r=0.6–0.8). Concentrations in maternal blood correlated with infant blood levels (r=0.65); and infant blood levels correlated to infant brain levels (r=0.4–0.8).

Accordingly, ATSDR used maternal hair mercury levels as the exposure measurement to derive a chronic MRL for methylmercury. While hair analysis can be confounded by outside sources of contamination (e.g., as might occur in certain occupational settings) (Hac and Krechniak 1993), the study population used as the basis of the chronic oral MRL for methylmercury is far removed from external or industrial sources of mercury, effectively eliminating this as a consideration for the following analysis.

- An MRL of 0.0003 mg Hg/kg/day has been derived for chronic-duration oral exposure (365 days or longer) to methylmercury.

The chronic oral MRL for methylmercury is based upon the Seychelles Child Development Study (SCDS), in which over 700 mother-infant pairs have, to date, been followed and tested from parturition through 66 months of age (Davidson et al. 1998). The SCDS was conducted as a double-blind study and used maternal hair mercury as the index of fetal exposure. Enrollees were recruited by the head nurse/hospital midwife by asking the mothers if they wished to participate in the study when they arrived at the hospital for delivery. The first 779 who did not decline participation became the mothers in the study cohort. Of the initial 779 mothers enrolled in the study at parturition, 740 remained at the pre-determined child testing age of 6.5 months, 738 remained in the 19-month cohort, 736 remained at 29 months, and 711 remained for the 66-month neurobehavioral and developmental examinations.

The Seychellois were chosen as a study population for a number of reasons.

- (1) All fish contain some level of methylmercury (Davidson et al. 1998); and the Seychellois regularly consume a high quantity and variety of ocean fish, with 12 fish meals per week representing a typical methylmercury exposure.
- (2) The median total mercury concentration in 350 fish sampled from 25 species consumed by the Seychellois was <1 ppm (range, 0.004–0.75 ppm), comparable to the mercury concentration in commercially obtainable fish in the U.S. (It should be noted here that while the methylmercury levels in the Seychellois population are 10–20 times those in the U.S., it is not because they consume more highly contaminated fish, but rather because they consume more fish than the U.S. population.)
- (3) The Seychelles represents a relatively pristine environment, with no local industry for pollution, and are situated more than 1,000 miles from any continent or large population center.

- (4) The population is highly literate, cooperative, and has minimal immigration and emigration.

C (5) The Seychellois constitute a generally healthy population, with low maternal alcohol consumption and tobacco use (<2%).

C (6) The large sample size/study population (>700 mother-infant pairs).

C (7) Excellent retention of mother-infant pairs throughout the study (i.e., 711 of the initially enrolled 778 mother-infant pairs still participating at 66 months post-partum.

C (8) The use of standardized neurobehavioral tests.

The results of the 66-month testing in the SCDS revealed no evidence of adverse effects attributable to chronic ingestion of low levels of methylmercury in fish (Davidson et al. 1998). In this study, developing fetuses were exposed *in utero* through maternal fish ingestion before and during pregnancy (Davidson et al. 1998). Neonates continued to be exposed to maternal mercury during breastfeeding (i.e., some mercury is secreted in breast milk), and methylmercury exposure from the solid diet began after the gradual post-weaning shift to a fish diet. In the 66-month study cohort, the mean maternal hair level of total mercury during pregnancy was 6.8 ppm (range, 0.5–26.7 ppm; n=711), and the mean child hair level at the 66-month testing interval was 6.5 ppm (range, 0.9–25.8 ppm; n=708). The mean maternal hair mercury level in the highest exposed subgroup in the study was 15.3 ppm (range, 12–26.7; n=95). The 66-month test battery, which was designed to test multiple developmental domains, included the following primary measurements:

C (1) General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities (to estimate cognitive ability);

C (2) the Preschool Language Scale (PLS) total score (to measure both expressive and receptive language ability);

C (3) the Letter and Word Recognition and

C (4) Applied Problems subtests of the Woodcock-Johnson (W-J) Tests of Achievement (to measure reading and arithmetic achievement);

C (5) the Bender-Gestalt test (to measure visual-spatial ability); and

C (6) the total T score from the Child Behavior Checklist (CBCL) (to measure the child's social and adaptive behavior). Serum sampling revealed no detectable levels of PCBs (detection limit=0.2 ng/mL).

None of the tests indicated an adverse effect of methylmercury exposure. As evaluated through regression analyses, there was no reduction in performance with increasing maternal hair mercury levels for the neurobehavioral parameters examined. In contrast, scores were better for four of the six tests in the highest MeHg-exposed groups, compared with lower exposure groups for both prenatal and postnatal exposure (the four test were the (1) General Cognitive Index (GCI) of the McCarthy Scales of Children's `Abilities (to estimate cognitive ability); (2) the Preschool Language Scale (PLS) total score (to measure both expressive and receptive language ability); (3) the Letter and Word Recognition and (4) Applied Problems subtests of the Woodcock-Johnson (W-J) Tests of Achievement (to measure reading and arithmetic achievement). While the positive outcomes are not considered to indicate any beneficial effect of methylmercury on neurological development or behavior, they might be more appropriately attributed to the beneficial effects of omega-3 fatty acids or other constituents present in fish tissue, since the methylmercury levels in hair are known to correlate closely with fish intake. The slight decreases in the subjectively reported activity level of boys reported in the 29-month observations were not seen during the 66-month tests. The mean maternal hair level of 15.3 ppm in the highest exposed group in the 66-month test cohort is, therefore, considered a NOAEL for SCDS and is used by ATSDR as the basis for derivation of a chronic oral MRL for methylmercury. A related study (Myers et al. 1997) by some members of the same team of researchers from the University of Rochester examined the Seychellois children for attainment of the same developmental milestones reported to have been delayed in the Iraqi poisoning incident in the early 1970s (Cox et al. 1989); however, unlike the Iraqi study, no delays in the age of first walking and talking was seen in the Seychellois children exposed in utero.

Sensitivity of Neurobehavioral Measures /Reliability of Tests

The neurobehavioral test battery used in the 66-month Seychelles study was designed to assess multiple developmental domains (Davidson et al. 1998). The tests were considered to be sufficiently sensitive and accurate to detect neurotoxicity in the presence of a number of statistical covariates. On-site test administration reliability was assessed by an independent scorer, and mean interclass correlations for interscorer reliability were 0.96–0.97 (Davidson et al. 1998). The sample size was determined to be sufficient to detect a 5.7-point difference on any test with a mean (SD) of 100 (16) between low (0–3 ppm) and high (>12 ppm) hair mercury concentration groups for a 2-sided test (A = 0.05 at 80% power).

Supporting Studies

Crump et al. (1998) conducted benchmark dose (BMD) calculations and additional regression analyses of data collected in a study in which a series of scholastic and psychological tests were administered to children whose mothers had been exposed to methylmercury during pregnancy. Hair samples were collected from 10,970 new mothers in New Zealand in 1977 and 1978. High hair mercury levels were considered to be those over 6 ppm, which was the hair level predicted to result at steady state from consumption of mercury at the WHO/FAO Provisional Tolerable Weekly Intake of 0.3 mg total mercury/week and 0.2 mg methylmercury/week. By this criterion, 73 of approximately 1,000 mothers who had consumed fish more than 3 times/week during pregnancy were determined to have high hair mercury levels. In 1985, when the children were 6 to 7 years of age, 61 children (1 set of twins) of the 73 mothers in the high hair mercury group were located; these children constituted the high exposure group, which was matched with three control groups (one with 3–6 ppm maternal hair mercury levels, one with 0–3 ppm whose mothers had been high fish consumers, and one with 0–3 ppm whose mothers had not been high fish consumers). The entire study cohort consisted of 237 children. A battery of 26 psychological and scholastic tests were administered to the children at school during the year 1985. Mothers were interviewed at the time of test administration to obtain additional data on social and environmental factors. In the high exposure group of children, one boy's mother had a hair mercury level of 86 ppm, which was more than four times higher than the next highest hair mercury level of 20 ppm. BMDs (10% response rate) calculated from five tests ranged from 32 to 73 ppm, when the 86 ppm mother's child was included. This corresponded to a BMDL range of 17 to 24 ppm. Although none of the 86 ppm child's test scores was an outlier according to the definition used in the analyses, his scores were significantly influential in the analyses. When this child was omitted from the analyses, BMDs ranged from 13 to 21, with corresponding BMDLs of 7.4 to 10 ppm.

Developing fetuses in the SCDS were exposed through maternal fish ingestion before and during pregnancy. Each child was evaluated at 19 months and again at 29 months (±2 weeks) for infant intelligence (Bayley Scales of Infant Development [BSID] Mental and Psychomotor Scales), with a modified version of the BSID Infant Behavior Record to measure adaptive behaviors at 29 months (Davidson et al. 1995b). Testing was performed by a team of Seychellois nurses extensively trained in administration of the BSID. Maternal hair concentrations, measured in hair segments that corresponded to pregnancy, ranged from 0.5 to 26.7 ppm, with a median exposure of 5.9 ppm for the entire study group. The mean BSID Mental Scale Indices determined at both 19 and 29 months were found to be comparable

to the mean performance of U.S. children. The BSID Psychomotor Scale Indices at both measurement intervals were two standard deviation units above U.S. norms, but were still consistent with previous findings of motor precocity in children reared in African countries. The study found no effect that could be attributed to mercury on the BSID scores obtained at either the 19- or 29-month measurement/testing interval. The 29-month cohort represented 94% of the 779 mother-infant pairs initially enrolled in the study, and approximately 50% of all live births in the Seychelles in 1989.

The only observation in the 29-month testing that might be attributable to prenatal mercury exposure was a slight decrease in the activity level in boys (but not girls) as determined by the Bayley Infant Behavior Record (subjective observation). Whereas this decrease was significant in males ($p = 0.0004$), it was not statistically significant in females ($p = 0.87$). When the subjective activity scores for male and female children were evaluated collectively, no statistically significant or remarkable decrease in activity was apparent outside the >12 ppm maternal hair concentration group. The affect on activity level in boys is not considered an adverse effect by the authors of the study.

Grandjean et al. (1997b, 1998) reported another epidemiological study of methylmercury exposure for a population in the Faroe Islands. Although the Faroese are a fishing culture, the major source of methylmercury exposure for this population is pilot whale meat, which is intermittently consumed as part of the cultural tradition. The initial study cohort consisted of 1,022 singleton births occurring in a 21-month window during 1986-1987. At approximately 7 years of age, neurobehavioral testing was conducted on 917 of the remaining cohort members. No abnormalities attributable to mercury were found during clinical examinations or neurophysiological testing. A neuropsychological test battery was also conducted, which included the following: Finger Tapping; Hand-Eye Coordination; reaction time on a Continuous Performance Test; Wechsler Intelligence Scale for Children - Revised Digit Spans, Similarities, and Block Designs; Bender Visual Motor Gestalt Test; Boston Naming Test; and California Verbal Learning Test (Children). Neuropsychological tests emphasized motor coordination, perceptual-motor performance, and visual acuity. Pattern reversal visual evoked potentials (VEP) with binocular full-field stimulation, brain stem auditory evoked potentials (BAEP), postural sway, and the coefficient of variation for R-R inter-peak intervals (CVRR) on the electrocardiogram were all measured. The neuropsychological testing indicated mercury-related dysfunction in the domains of language, attention, memory, and visuospatial and motor function (to a lesser extent), which the authors considered to remain after the children of women with maternal hair mercury concentrations above 10 µg/g (10 ppm) were excluded. While this study represents a significant contribution to the human database for methylmercury exposure

and effects, a number of potentially influential factors not fully considered as possible covariates somewhat cloud the interpretation of the results.

These differences between the neuropsychological effects observed in the Faroe Island cohort and the absence of effects reported in the Seychelles Island cohort might result from a variety of factors. The Faroe Island children were older (7–8 years versus 5.5 in the SCDS). Some of the measurement instruments (i.e., the neuropsychological test administered) were also different. Since the first neuropsychological testing in the Faroe study was not conducted until 7 years of age, it is not known whether the observed effects might have been apparent at an earlier age. Ongoing and planned future testing of the Seychelles population will provide additional information on the progression of any observed effects. Further examination of the Seychelles population using the neuropsychological test that showed positive results in the Faroe Island population will also allow a more direct comparison of results.

The diet in the two studies was also considerably different. The majority of the mercury exposure to the Faroe Island population came from whale meat (estimated at about 3 ppm in muscle tissue) with a relatively small portion coming from fish. Some of the mercury in whale meat is in the form of inorganic mercury. In the Seychelles study, all of the mercury came from fish as methylmercury with concentrations of around 0.3 ppm. Whale meat blubber is widely consumed in the Faroe Islands and also contains polychlorinated biphenyls (PCBs). Grandjean et al. (1995b) estimated a daily intake of 200 µg of PCB. This value can be compared to the Tolerable Daily Intake of PCBs established by the FDA of 60–70 µg/day for an adult. Further statistical analysis of the possible influence of PCBs on the observed study results needs to be conducted (see the discussion below on Peer Panel 1Review of Key Studies for additional comments).

The primary biomarker used to estimate mercury exposure was also different in the two studies. The Faroe Island analysis used cord blood, and the Seychelles study used maternal hair level. The use of mercury in cord blood has the advantage of being a more direct measure of exposure to the fetus, but the levels at term may not reflect exposures at earlier developmental stages. While Grandjean et al. (1997) did report maternal hair mercury levels, the mean hair level for the interquartile range of 2.6–7.7 ppm was reported only as a geometric average (4.27 ppm). In contrast, the Seychelles study reported only an arithmetic mean level for the entire study population (6.8 ppm). While both are valid measures, a direct comparison of “average” values for the two studies is not possible without further statistical analysis of both data sets.

In the case of the Faroe study, no data were presented in the peer-reviewed publications to address variability of food/whale meat or blubber intake among the Faroe Islanders, making it difficult to evaluate the possibility of peak intake levels during critical development phases. Consumption data were reported only as <1 pilot whale meat meal/month and 1–2 fish meals per week. In contrast, the Seychelles dietary habits provide a relatively stable intake, and a high degree of correlation was found between mean hair levels in samples covering each trimester and levels in samples for the entire pregnancy (Cernichiari et al. 1995a). Cernichiari et al. (1995b) also report a good correlation between levels of total mercury in neonatal brain and levels in the corresponding maternal hair. While the contribution of continued mercury exposure through breast feeding or post-weaning diet was not fully addressed in the Seychelles study reports (Davidson 1995, 1998), that is not considered a significant drawback of the study, since no effects on neurobehavioral/neuropsychological testing were seen at any maternal hair level. In the Faroese assessment of latent neuropsychological effects from an *in utero* exposure to mercury, however, the role of continuing postnatal exposure to mercury either from breast milk or from ingestion of methylmercury-containing foods (e.g., pilot whale meat) is less clear. Specifically, it is not known what proportion, if any, of the neuropsychological effects reported in the Faroe Islands population could be attributed to 7 years of postnatal exposure to methylmercury in food. The variability and magnitude of this postnatal exposure should, therefore, be further evaluated.

Peer Panel Review of Key Studies

In addition to the traditional peer review process that precedes publication in most scientific journals, the studies considered by ATSDR for use in estimating a chronic oral MRL for methylmercury underwent two stringent reviews by recognized experts in the environmental health field.

On July 20 and 21, 1998, ATSDR assembled a panel of 18 experts from the scientific and medical communities to review current issues and the relevant literature on mercury and its compounds, including methylmercury (ATSDR 1999). Several members of each of the respective research teams that conducted the Iraqi, Seychelles, Faroe, and Madeira studies were included among the expert panelists, and provided extensive overviews of their studies. The presentations were followed by an open, wide-ranging scientific discussion of the merits and interpretations of the currently available studies. Topics of significant discussion included the relative merits of the respective study populations, exposure regimens, sensitivity of neurobehavioral measures, and determination of an uncertainty factor. While it was unanimously agreed that the Seychelles and Faroe studies were both excellent studies that provided a significant contribution to

the human database for methylmercury exposure and effects, a number of factors that could have contributed to the study results, but were not considered as possible statistical covariates, were discussed. In the case of the Faroe study, the consumption of whale blubber, which is known to be contaminated with PCBs, DDT, and possibly other organochlorines, introduces a potentially significant influence on the study results. Weihe et al. (1996) reported that the PCB and DDT concentrations in blubber of pilot whales taken in Faroese waters are about 30 ppm and 20 ppm, respectively. In contrast, the Seychellois population does not eat marine mammals at all. In addition, the Faroe study did not address other possible statistical covariates, such as the dietary and nutritional status of the study population and the use of tobacco during pregnancy, further complicating the interpretation of the neuropsychological test results.

On November 18–20, 1998, a workshop on Scientific Issues Relevant to the Assessment of Health Effects from Exposure to Methylmercury was conducted in Raleigh, North Carolina. The workshop was jointly sponsored by the U.S. Department of Health and Human Services (DHHS), the National Institute of Environmental Health Sciences (NIEHS), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the U.S. Environmental Protection Agency (EPA), the National Oceanic and Atmospheric Administration (NOAA), the Office of Science and Technology Policy (OSTP), the Office of Management and Budget (OMB), and ATSDR. The purpose of this workshop was to discuss and evaluate the major epidemiologic studies that associated methylmercury exposure and the results of an array of developmental measures in children. These studies monitored and evaluated exposed populations in Iraq, the Seychelles Islands, the Faroe Islands, and the Amazon River Basin. A number of animal studies were also considered in support of a human health risk assessment. Presentation of each study by the research team that conducted the study was followed by an expert panel evaluation that examined each study, taking into consideration the exposure data, experimental design and statistical analysis, potential confounders and variables, and neurobehavioral end points evaluated. A fifth panel evaluated the results of relevant animal studies. Significant issues that were discussed included the use of umbilical cord blood mercury levels versus hair mercury concentrations as an index of methylmercury exposure during pregnancy, the patterns of exposure, the dietary/health status of study populations, other potentially relevant exposures, other confounding influences, and the adjustments made for statistical covariates. All five panels at this workshop commended the efforts of the investigators and respective staffs of the Seychelles and Faroe studies for conducting highly sophisticated investigations under difficult conditions. However, specific findings of several of the panels raise issues that, at present, preclude the Faroe data from consideration as a starting point for MRL derivation.

In addressing the potential influence of concurrent PCB exposure on the Faroe results, the Confounders and Variables (Epidemiology) panel indicated that with respect to four of the prenatal outcomes (related primarily to verbal and memory performance), when PCBs were included in the model, only one of these outcomes is specifically related to mercury exposure. Concerning this matter, the panel wrote that "... the most likely explanation is that both (mercury and PCBs)... affect these three outcomes, but their relative contributions cannot be determined given their concurrence in this population." The Neurobehavioral Endpoints Panel also looked at this issue, and noted that "PCB exposure might act as an effect modifier, increasing the susceptibility to MeHg"; however, this panel further indicated that it did not believe that the effects seen in the Faroe Islands were due to uncontrolled confounding by PCBs. A third panel that addressed the issue of concurrent PCB exposures, the Statistics/Design Panel, noted that only 3 of 208 PCB congeners were measured in the Faroe study, and stated that it "seems likely that mercury was measured more accurately than the biologically relevant PCB exposure. Consequently even if the neurological effects seen in this study were caused entirely by PCBs, it is possible that mercury would still be more highly correlated with these effects than PCBs." The Statistics/Design Panel also said that "the best method to deal with this problem would be to study a population where exposure to PCBs is not an issue." This statement points directly to the Seychelles study as the study most appropriate for MRL derivation.

Another issue raised at Raleigh workshop concerned the taking of hair samples for determining pre-natal exposure. In the Seychelles, hair samples were collected 6 months post-partum, and segments corresponding to pregnancy were selected for analysis. In the case of the Faroese, hair samples were taken at the scalp. Regarding that, the Confounders and Variables (Epidemiology) panel stated that "Given the time it takes the Hg to be excreted into the hair, we can assume that samples collected at parturition do not cover the last 6 weeks of gestation, during which critically important neuronal proliferation and differentiation is taking place."

Regarding the Seychelles and Faroe studies, the Neurobehavioral Endpoints Panel found "no specific neurobehavioral signature injury from MeHg" in the data from either study (Seychelles or Faroe). The same panel also noted that episodic exposure in the Faroese (1–2 fish meals/week and <1 pilot whale meal/month) "may reduce the likelihood of detecting a consistent 'neurobehavioral signature injury' specific to MeHg and may account for different observations in children with the same average exposure."

Based upon the discussions at the Raleigh workshop and the individual panel findings, as well as the aforementioned Atlanta expert panel review, ATSDR has determined that the Seychelles study represents

the most appropriate and reliable database currently available for calculation of a chronic oral MRL from a population exposed only to methylmercury by a relevant route of exposure for the overall U.S. population.

Again, ATSDR would like to strongly emphasize that both the Seychelles study and the Faroese study represent credible scientific contributions by widely respected research teams. Similarly, both studies extend our knowledge base well beyond that provided by the Iraqi study and make significant contributions to our understanding of the effects of low-level exposure to methylmercury by an exposure route and vehicle (i.e., food) relevant to U.S. populations. The continuing monitoring and evaluation of the Seychellois and Faroese populations with more comparable neurobehavioral indices should help strengthen our understanding of the effects of low-level chronic methylmercury exposure and should reduce the uncertainty regarding the public health implications of exposure.

Other Key Studies Reviewed by ATSDR

Other epidemiology studies were also considered by ATSDR in evaluating the database on human exposure to methylmercury. Lebel et al. (1996) evaluated a fish-eating populations in the Amazon River Basin with a neurofunctional test battery and clinical manifestations of nervous system dysfunction in relation to hair mercury concentrations. The villagers examined live along the Tapajos River, a tributary of the Amazon. The study population consisted of 91 adult inhabitants 15–31 years of age. Hair mercury levels were below 50 µg/g (ppm). Clinical examinations were essentially normal, although persons displaying disorganized movements on an alternating movement task and those with restricted visual fields generally had higher hair mercury levels. Near visual contrast, sensitivity, and manual dexterity (adjusted for age) were found to decrease significantly with increasing mercury levels, while a tendency for muscular fatigue and decreasing strength were observed in women. The authors suggested that dose-dependent nervous system alterations might be associated with hair mercury levels below 50 ppm. This study, however, also had a number of potentially confounding factors. The impact of parasitic and other diseases endemic to the study area is of primary concern in the interpretation of the Lebel et al. (1996) results. In addition, the overall nutritional status of the study population was not known or reported, and the use of neuroactive drugs (from local herbs, plants, roots, or mushrooms) was not considered as a potential confounder or covariate. The previous mercury exposure history of the study cohort is also unclear. This is of particular importance because gold mining procedures that use metallic mercury have been commonly practiced along the Amazon Basin for decades. Finally, the end points of the Lebel et al. (1977) study evaluated adult toxicity and not effects in the developing fetus or the newborn (i.e., the most sensitive human population).

Myers et al. (1997) evaluated the population of the SCDS for developmental milestones similar to those determined in Iraq. As part of this ongoing study, cohort children were evaluated at 6.5, 19, 29, and 66 months of age. At 19 months care-givers were asked at what age the child walked (n=720 out of 738) and talked (n=680). Prenatal mercury exposure was determined by atomic absorption analysis of maternal hair segments corresponding to hair growth during the pregnancy. The median mercury level in maternal hair for the cohort in this analysis was 5.8 ppm, with a range of 0.5–26.7 ppm. The mean age (in months) at walking was 10.7 (SD=1.9) for females and 10.6 (SD=2.0) for males. The mean age for talking (in months) was 10.5 (SD=2.6) for females, and 11 (SD=2.9) for males. After adjusting for covariates and statistical outliers, no association was found between the age at which Seychellois children walked or talked and prenatal exposure to mercury. The ages for achievement of the developmental milestones were normal for walking and talking in the Seychellois toddlers following prenatal exposure to methylmercury from a maternal fish diet.

Clarkson (1995) raised some interesting issues concerning whether is it reasonable to apply health effects data based on an acute exposure to methylmercury fungicide eaten in homemade bread (in the 1971–1972 Iraq incident) to fish-eating populations having chronic exposure to much lower concentrations of methyl-mercury. He addressed two specific issues. The first regards the body's "defense mechanisms" that serve to mitigate the potential damage from mercury. One such mechanism in the case of methylmercury involves an enterohepatic cycling process in which methylmercury from dietary sources absorbed through the intestine is carried to the liver, where substantial quantities are secreted back into the bile and returned to the intestinal tract. During the residence time in the gut, microflora break the carbon-mercury bond, converting methylmercury into inorganic mercury, which in turn is poorly absorbed and is excreted in the feces. This creates an effective detoxification pathway for low-dose dietary exposures to methylmercury, but probably not for acute, high-dose exposures, such as occurred in Iraq. Secondly, the transport of methylmercury into brain tissue is inhibited by the presence of many amino acids, including leucine, methionine, and phenylalanine. Thus, it is possible that the rising plasma concentrations of amino acids from ingestion of fish protein may serve to depress the uptake of methylmercury by the brain.

While both of these issues need further laboratory/clinical investigation, they do raise appropriate questions concerning the relevance of the relatively short-term (i.e., about 6 weeks), high-level contaminated grain exposure scenario encountered in Iraq to the dietary methylmercury exposure scenarios encountered in many fish-eating populations (e.g., the Seychelles Islanders, Faroe Islanders, Peruvian villagers, and Inuit native people of Greenland). This position is supported by Cicmanec (1996), who reviewed data from the

Iraqi study, as well as data from studies of fish-consuming populations in the Faroe Islands, Seychelles Islands, and Peruvian fishing villages. Cicmanec concluded that the Iraqi population does not represent a sensitive subpopulation within a perinatal group; rather, the relatively lower threshold identified in that study was the result of confounders. Crump et al. (1995) reanalyzed the dose-response data from the Cox et al. (1989) report of the Iraqi incident and found the results to be potentially skewed by inadequacies in the study design and data-collection methods. Shortcomings or potentially confounding factors include: (1) the retrospective recall of developmental milestones by mothers and other family members; (2) the lack of precision in the determination of birth and other milestone dates; (3) and the possible biasing of the dose-response analysis by variation in symptom reporting and infant sex composition in the two study subcohorts. Crump et al. (1995) noted that perhaps the most serious limitation of the Iraqi study is the inability to assess the potential effects of low-level chronic-duration exposure to methylmercury, as these particular data are based on very high intake levels over a relatively brief period of time.

No increase in the frequency of neurodevelopmental abnormalities in early childhood was observed in a cohort of 131 infant-mother pairs in Mancora, Peru (Marsh et al. 1995b). The mean concentration of mercury in maternal hair was determined to be 8.3 ppm (range, 1.2–30 ppm), and the source of the mercury was believed to be from consumption of marine fish. Similarly, a study of 583 Faroe Island infants for the first 12 months after birth found no decrease in the age of attainment of sitting, creeping (crawling), and standing developmental milestones (Grandjean et al. 1995a). The age at which a child reached a particular developmental milestone was not only not found to be associated with prenatal mercury exposure, but infants that reached a milestone early were found to have significantly higher mercury concentrations in their hair at 12 months of age. It was also found that early milestone attainment was clearly associated with breast-feeding, which was in turn related to higher infant hair mercury levels. The authors (Grandjean et al. 1995a) concluded that the beneficial effects associated with breast-feeding seemed to overrule, or to compensate for, any neurotoxic effects on milestone development that could be due to the presence of contaminants (e.g., mercury) in human milk.

Additional studies have shown developmental toxicity after oral exposure of humans and animals to organic mercury compounds (Amin-Zaki et al. 1974; Bakir et al. 1973; Bornhausen et al. 1980; Cagiano et al. 1990; Elsner 1991; Engleson and Herner 1952; Fowler and Woods 1977; Guidetti et al. 1992; Harada 1978; Hughes and Annau 1976; Ilback et al. 1991; Inouye and Kajiwara 1988; Khera and Tabacova 1973; Lindstrom et al. 1991; McKeown-Eyssen et al. 1983; Nolen et al. 1972; Olson and Boush 1975; Rice 1992; Rice and Gilbert 1990; Snyder and Seelinger 1976; Stoltenburg-Didinger and Markwort 1990).

The accumulation of mercury is greater in larger fish and in fish higher in the food chain. The tendency for increased mercury concentration with increasing fish body weight is particularly noticeable in carnivorous fish species. Malm et al. (1995) analyzed mercury concentrations in 16 species of carnivorous fish from the Tapajos River basin in Brazil and hair samples from local populations who regularly ate such fish. Mercury levels in the fish averaged 0.55 ppm (range, 0.04–3.77 ppm), and the mercury levels in the hair of the affected fish-eating populations averaged approximately 25 ppm. In one population that consumed higher quantities of large carnivorous fish at the end of the local rainy season, 8 of 29 persons evaluated had hair mercury levels above 40 ppm, and one individual had a hair mercury concentration of 151 ppm. Some villages along the river can have per capita daily fish consumption rates around 200 g or more, which would greatly impact the human body burden and hair levels of mercury in such populations.

Hair-to-Blood Concentration Ratio

The hair:blood concentration ratio for total mercury is frequently cited as 250. However, a precise basis for this particular value is unclear. Ratios reported in the literature range from 140 to 416, a difference of more than a factor of 2.5 (see Table 2-9). Differences in the location of hair sampled (head versus chest, distance of sample from head or skin) may contribute to differences in observed ratios between studies. For example, as much as a 3-fold seasonal variation in mercury levels was observed in average hair levels for a group of individuals with moderate-to-high fish consumption rates, with yearly highs occurring in the fall and early winter (Phelps et al. 1980; Suzuki et al. 1992). Thus, it is important to obtain hair samples as close to the follicle as possible to obtain an estimate of recent blood levels. Large errors (the direction of which depends on whether samples were taken while blood levels were falling or rising) could result if hair samples are not taken close to the scalp. Several studies did not report the distance to the scalp for the hair samples taken. The high slope reported by Tsubaki (1971a) may have reflected the fact that mercury levels were declining at the time of sampling (Berglund et al. 1971), so the hair levels may reflect earlier, higher blood levels. Hair taken from different parts of the body also may yield different ratios. In 26 subjects with moderate-to-high fish consumption, axillary hair (i.e., from the armpit area) was found to contain an average of 23% less mercury than head hair (Skerfving et al. 1974).

Phelps et al. (1980) obtained multiple blood samples and sequentially analyzed lengths of hair from 339 individuals in Northwestern Ontario. The large sample size and the attention to sampling and analysis with regard to the hair:blood relationship make the results from this study the most appropriate to use for estimating the mercury blood levels of the Seychellois women during pregnancy. The actual ratio Phelps et

Table 2-9. Available Data on Hair:Blood Ratio (total Hg)

Reference	Hair to blood ratio	Number of subjects	Hg range in whole blood (µg/L)	Hg range in hair (ppm)	Hair sample	
					Length (mm)	Distance to scalp
Sumari et al. 1969[a]	140	50	5–270	1–56	–	–
Soria et al. 1992	218	16	2.4–9.1	0.15–20	–	At scalp
Tejning 1967[a]	230	51	4–110	1–30	–	Axillary
Skerfving 1974	230	60	44–550	1–142	5	At scalp
Haxton et al. 1979	250	173	0.4–26	0.1–11.3	20	–
Tsubaki 1971b[b]	260	45	2–800	20–325	–	–
Birke et al. 1972[b]	280[c]	12	4–650	1–180	5	At scalp
Den Tonkelaar et al. 1974	280	47	1–40.5	<0.5–13.2	–	–
Kershaw et al. 1980	292[d]	5	–	–	5	At scalp
Phelps et al. 1980	296	339	1–60	1–150	10	At scalp
Sherlock et al. 1982	367	98	1.1–42.3	0.2–21	24	–
Tsubaki 1971a[a]	370	≈25	–	–	"Longer tuft"[a]	–

[a] As cited in Berglund et al. 1971
[b] As cited in WHO 1976
[c] Ratio of methylmercury in hair to methylmercury in blood
[d] Based on repeated measurements at different time points (3–8 ratios per individual), of the ratio of 5 mm hair segments to corresponding 2-week average blood levels (assuming hair growth of 1.1 cm/month).

– = Not reported

al. (1980) observed between the total mercury concentration in hair taken close to the scalp and simultaneous blood sampling for this group was 296. To estimate the actual ratio, the authors assumed that blood and hair samples were taken following complete cessation of methylmercury intake. They also assumed a half-life of methylmercury in blood of 52 days and a lag of 4 weeks for appearance of the relevant level in hair at the scalp. Based on these assumptions, they calculated that if the actual hair:blood ratio were 200, they would have observed a ratio of 290 (i.e., essentially equivalent to the observed value of 296). Based on these and other considerations, Phelps et al. (1980) state that the actual ratio is "probably higher than 200, but less than the observed value of 296." As the authors point out, two-thirds of the study population were sampled during the falling phase of the seasonal variation and one-third or less in the rising phase. This fact would tend to result in a lower observed ratio; therefore, the actual average value is likely to be >200.

Phelps et al. (1980) also provide estimates assuming a 2-week lag for the appearance of the relevant level of mercury in the centimeter of hair nearest the scalp. For a 2-week lag time, an actual ratio of 250 would have resulted in an observed ratio of 301 (again, essentially identical to the observed value of 296). A study of ingestion of a large dose of mercuric chloride in one individual suggests that the lag time is longer than 2 weeks (Suzuki et al. 1992). Hair samples were taken at 41 and 95 days following ingestion of the mercuric chloride. In the 41-day hair sample, a large mercury peak occurred in the centimeter of hair closest to the scalp, with no elevation in mercury in the second centimeter of hair. Head hair grows at a rate of about 1.1 cm a month (Al-Shahristani and Shihab 1974; Cox et al. 1989). If emergence had occurred so that the elevation in mercury could be measured in the first centimeter of hair by 2 weeks after exposure, then by day 41 after exposure the peak should have moved into the second centimeter of hair, at least enough to raise the mercury level slightly in the second centimeter. Because no elevation was seen in the second centimeter of hair at 41 days, it would appear that emergence occurred at a lag of >2 weeks. In the hair sample taken at 95 days, the leading edge of the mercury peak occurred in the third centimeter of hair.

Based on the data presented in Phelps et al. (1980) and the lag time indicated in the individual studied by Suzuki et al. (1992), the actual average value is likely to be somewhere between 200 and 250. Because the data do not allow a more accurate determination of an average ratio, the value 250 is acceptable for the purpose of estimating average blood levels in the Seychellois population. Using 250 rather than a lower number results in a lower MRL. It should be noted that a wide range in hair:blood ratios has been reported for individuals in various studies: 137–342 in Soria et al. (1992), 171–270 in Phelps et al. (1980), 416 in

Cernichiari et al. (1995), and 137–585 in Birke et al. (1972). Therefore, this ratio (250) should not be used as the sole basis for determining levels of exposure and potential effect for individuals.

Calculation of dietary intake of mercury from blood concentration.

Fraction of mercury in diet that is absorbed (A_D). Radiolabeled methyl-mercuric nitrate was administered in water to three healthy volunteers (Aberg et al. 1969). The uptake was >95%. Miettinen et al. (1971) incubated fish liver homogenate with radiolabeled $MeHgNO_3$ to yield a methylmercury proteinate. The proteinate was then fed to fish that were killed after a week, cooked, and fed to volunteers after confirmation of the methylmercury in the fish. Mean uptake exceeded 94%. For the derivation of an MRL, an absorption factor of 0.95 is used.

Fraction of the absorbed dose that is found in the blood (A_B). The value 0.05 has been used for this parameter in the past (Berglund et al. 1971; WHO 1990). Three studies report observations of the fraction of the absorbed methylmercury dose distributed to blood volume in humans. Kershaw et al. (1980) report an average fraction of 0.059 of the absorbed dose in the total blood volume, based on a study of 5 adult male subjects who ingested methylmercury-contaminated tuna. In a group of 9 male and 6 female volunteers who had received ^{203}Hg-methylmercury in fish, approximately 10% of the total body burden was present in 1 L of blood in the first few days after exposure, dropping to approximately 5% over the first 100 days (Miettinen et al. 1971). In another study, an average value of 1.14% for the percentage of absorbed dose in 1 kg of blood was derived from subjects who consumed a known amount of methyl-mercury in fish over a period of 3 months (Sherlock et al. 1984). Average daily intake for the 4 groups observed in the study ranged from 43 to 233 µg/day. The authors report a dose-related effect on the estimated percentage of the absorbed dose in 1 kg of blood, with 1.26% of the absorbed dose in 1 kg of blood at an average daily intake of 43 µg/day and 1.03% of the absorbed dose in 1 kg of blood at an average daily intake of 233 µg/day. The average for all subjects in the study was 1.14%. When individual values for distribution to one kilogram of blood reported in the study are converted into the percentage of the absorbed dose in the total blood volume (assuming that blood is 7% of body weight [Best 1961] and using body weights reported for individuals in the study), the average value for A_B for all individuals is 0.056 (0.057 using the values for percentage in 1 kg normalized for body weight as reported in the study). The average value for A_B for 6 women as reported in Sherlock et al. (1984) is 0.048 (0.047 using values normalized for body weight). The average for 14 men is 0.059 (0.061 using values normalized for body weight).

The average values for A_B for all studies ranged from 0.047 to 0.061 (the values for women and men reported in Sherlock et al. [1984]). The data suggest that the average value of A_B for women may be lower than that for men, and they further suggest that 0.05 may be appropriate for modeling intake in a group of women (Sherlock et al. 1984). Based on these studies, the best estimate of A_B based on the available data is 0.05. Use of a higher value (i.e., 0.06 instead of 0.05) for this parameter would result in a lower MRL, but the sensitive populations are pregnant women and developing fetuses, making the 0.5 value more appropriate for the Seychelles study population.

Elimination constant (b). Reported clearance half-times for methylmercury from blood or hair range from 48 to 65 days (Table 2-5). The average elimination constant based on the six studies listed in Table 2-5 is 0.014. The average of the individual values for *b* reported for 20 volunteers ingesting 42–233 µg Hg/day in fish for 3 months (Sherlock et al. 1984) is also 0.014. Use of the value 0.014 for this parameter, rather than 0.01 (as used by WHO 1990), results in a higher MRL.

Volume of blood in body (V), and body weight. Blood volume is assumed to be 7% of body weight, with an increase to about 9% during pregnancy (Best 1961). Data for the body weight of the Seychelles Islands women were not found. Assuming an average body weight of 60 kg for women, the blood volume is 4.2 L (60 kg x 0.07 L/kg). The 9% of body weight value is not used because it is not representative of the blood volume throughout pregnancy. Blood volume does not begin to increase significantly from the 7% pre-pregnancy level until around the 27th week of pregnancy. It then sharply rises until week 40 or parturition (Guyton 1996). To use the 9% value would, therefore, be representative of the blood volume late in pregnancy (i.e., mid- to late- third trimester), but not throughout most of pregnancy. In contrast, the hair mercury level to which it is compared represents an average value throughout pregnancy. The use of the 9% value would result in a higher MRL, and is not considered appropriate in this instance.

Calculation of Exposure Dose

The concentration of mercury in hair is assumed to be 250 times the concentration in blood. ATSDR's peer-reviewed, published guidance for MRL derivation (Chou et al. 1998) calls for the use of the highest value at which no adverse effects were observed in the critical study. Using, therefore, the 15.3 ppm mean maternal hair (taken at parturition) value from the highest exposure group (range, 12–26.7 ppm) in the Seychellois test population as a NOAEL for the 66-month Seychelles testing (Davidson et al. 1998), the corresponding methylmercury concentration in blood would be: 1/250 x 15.3 µg/g x 1 mg/1,000 µg x 1,000 g/L = 0.061 mg/L.

Converting blood mercury concentration to daily intake.

The concentration of mercury in the blood may be converted to a daily intake by using the following equation from WHO (1990):

$$C = \frac{f \cdot d}{b \cdot V} \cdot \frac{A_D \cdot A_B \cdot d}{b \cdot V}$$

Where:

C = concentration in blood
f = fraction of the daily intake taken up by the blood
d = daily dietary intake
b = elimination constant
A_D = percent of mercury intake in diet that is absorbed
A_B = percent of the absorbed amount that enters the blood
V = volume of blood in the body

where:

C = (0.95 x 0.05 x d)/(0.014 x 4.2)
C = 0.81 d
0.061 mg = 0.81 d
d = 0.075 mg/day

Using the assumed body weight of 60 kg for women, the estimated dose that would result in a hair level of 15.3 ppm is 0.075/60 kg = 0.0013 mg/kg/day. Therefore, the NOAEL derived from the highest exposure group (n = 95) at 66 months is 0.0013 mg/kg/day.

Consideration of Uncertainty

The standard/traditional areas of uncertainty addressed in any duration-specific MRL are: (1) interspecies variability (i.e., cross-species extrapolation of a NOAEL or LOAEL); (2) intra-human variability (i.e., differences in susceptibility to a substance or effect within the human population); (3) use of an LOAEL for MRL derivation when an NOAEL for the critical effect is not available; and (4) extrapolation from subchronic to chronic duration. In addition, a modifying factor may also be used when special circumstances exist that may contribute to, or introduce, uncertainty into the calculated health guidance value (MRL) in an area not typically covered by the traditional uncertainty factor approach.

The NOAEL of 15.3 ppm mercury in maternal hair from Davidson et al. (1998) used as the starting point for MRL derivation was based upon an unusually large study cohort of the population considered most sensitive to the neurodevelopmental effects of methylmercury, i.e., pregnant women and their developing fetuses. The negative results of this study are strongly supported by the BMD NOAEL range of 13 to 21 ppm calculated for the New Zealand cohort of 237 mother-child pairs (Crump et al. 1998). Consequently, much of the uncertainty normally present in the MRL derivation process does not exist in the case of methylmercury. Nonetheless, in view of the nature of the most susceptible group (developing fetuses) and some questions raised in the vast human data base for this chemical, an aggregate value of 4.5 was employed.

This value (4.5) was based upon three separate components, two of which are interrelated and the other independent. For the Seychelles data, a value of 1.5 was used to address variability in hair-to-blood ratios among women and fetuses in the U.S. population, as determined by pharmacokinetic modeling of actual data by Clewell et al. (1998); a second value of 1.5 was applied to address the remainder of any inter-individual variability (i.e., pharmacodynamics) in the U.S. population. A third, and independent, factor of 1.5 was employed to account for the possibility that the domain-specific tests, as employed extensively in the Faroe Islands, but not the Seychelles (which used primarily neurobehavioral tests of global function) might be able to detect very subtle neurological effects not tested for in the 66-month Seychelles cohort.

The World Health Organization (WHO, 1993, 1996) has defined the -kinetic and -dynamic components of intrahuman variability as being equal contributors to, and collectively constituting the total of, human variability. In order to assure a conservative approach, these two interdependent components were added to give a composite uncertainty factor of three (i.e., 1.5 + 1.5 = 3) to account for the full range of variability attributable to mercury in the Seychelles study. A modifying factor of 1.5 was also used to account for the possibility of domain-specific effects, as were seen in the Faroe study, being attributable to mercury. Since these effects were considered to be entirely separate or “independent” events, this modifying factor of 1.5 was multiplied by the uncertainty factor of 3.0 (for uncertainty attributable solely to the Seychelles study) to yield an aggregate uncertainty of 4.5 for chronic oral exposure to methylmercury.

While domain-specific tests from the Seychelles were reviewed at the North Carolina meeting in November 1998 and the results failed to demonstrate effects, the tests do not represent the full range of domain-specific tests that were administered in the Faroe Islands. For these reasons, and based on our consultation with our Board of Scientific Counselors about concerns for “missing” data sets (i.e., in relation to the Executive Order of children’s health and the agency’s efforts to protect the health of children, including the developing fetus), ATSDR determined that an additional factor of 1.5 should be used since the full range of

domain-specific neuropsychological test results from the Seychelles are not yet available. When these results become available and if they fail to show domain-specific effects, this additional factor of 1.5 would no longer be needed. At that time ATSDR will re-evaluate its MRL, as well as all other relevant data, in compliance with the agency's mandates and authorities.

Therefore, in the calculation of the chronic oral MRL for methylmercury, the NOAEL of 0.0013 mg/kg/day from the 66-month study (Davidson et al. 1998) is divided by 4.5, giving a chronic oral MRL for methylmercury of 0.0003 mg/kg/day [0.0013 mg/kg/day / 4.5 (UF) = 0.0003 mg/kg/day].

Alternative Derivations of the MRL

To ensure a health guidance value based upon the best use of the Seychelles study data (widely considered the most relevant data available), ATSDR evaluated alternate MRL derivation methods for methylmercury. One such approach is to use the mean total mercury level of 6.8 ppm in maternal hair for the entire Seychellois study cohort. Using the same formula as in the previous MRL calculation,

$C = (0.95 \times 0.05 \times d) / (0.014 \times 4.2)$

$C = 0.81\ d$

$(1/250 \times 6.8) = 0.027$

$0.027\ mg/L = 0.81\ d$

$d = 0.034\ mg/day$

$0.034\ mg/day / 60\ kg = 0.0006\ mg/kg/day$

In consideration of uncertainty factors for this MRL approach, multiple factors also apply. In this case, the mean value of 6.8 ppm for the NOAEL is for the entire study cohort at 66 months (n = 711). An uncertainty factor of 1.5 was used to account for the pharmacokinetically based variability of hair-to-blood ratios (95% confidence level) in pregnant women and fetuses in the U.S. population (Clewell et al. 1998, 1999). The extremely large size of the study population (n=711), in combination with an uncertainty factor of 1.5, is considered adequate to encompass the full range of pharmacokinetic and pharmacodynamic variability within the human population. An independent modifying factor of 1.5 was also used to take into consideration the positive results of the domain-specific tests administered in the Faroe study (Grandjean et al. 1997, 1998). The uncertainty factor of 1.5, multiplied by the modifying factor of 1.5, yields a total aggregate value of 2.25. Applying the factor of 2.25 to the daily intake calculated from the 6.8 ppm

NOAEL yields a chronic oral MRL value of 0.0003 mg/kg/day for methylmercury (0.0006 mg/kg/day divided by 2.25 = 0.0003 mg/kg/day).

A third approach to deriving a health guidance value is the use of bench mark dose (BMD) modeling. Clewell et al. (1998) used a benchmark dose analysis to determine a reference dose (RfD, a health guidance value used by the Environmental Protection Agency and, in some ways, the equivalent of ATSDR's chronic oral MRL). Clewell et al. (1998) used the data from the 29-month test in the Seychellois population (Davidson et al. 1995b) for their analysis (i.e., the 66-month study had not been published at the time of their benchmark dose analysis). The BMD is calculated by fitting a mathematical dose-response model to dose-response data. The bench mark dose level (BMDL) is a lower statistical confidence bound on the BMD and replaces the NOAEL in the calculation of a health guidance value. The BMD approach has been proposed as superior to the use of "average" or "grouped" exposure estimates when dose-response information is available, as is the case for the Seychelles study. Clewell et al. (1998) note that the Faroe Islands study reported by Grandjean et al. (1997b) could not be used for dose-response modeling due to inadequate reporting of the data and the confounding influence of co-exposure to PCBs.

For the 29-month Seychelles data, Clewell et al. (1998) used the 95% lower bound on the 10% benchmark dose level (BMDL), which represents a conservative estimate of the traditional NOAEL. The benchmark dose modeling over the entire range of neurological endpoints reported by Davidson et al. (1995b) yielded a lowest $BMDL_{10}$ of 21 ppm methylmercury in maternal hair. This $BMDL_{10}$ was then converted to an expected distribution of daily ingestion rates across a population of U.S. women of child-bearing age by using a Monte Carlo analysis with a physiologically based pharmacokinetic (PBPK) model of methyl-mercury developed by Gearhart et al. (1995). This analysis addresses the impact of interindividual pharmacokinetic variability on the relationship between ingestion rate and hair concentration for methyl-mercury. The resulting distribution had a geometric mean value of 0.00160 mg/kg/day (S.D. 0.00133). The 1st, 5th, and 10th percentiles of that distribution were 0.00086, 0.00104, and 0.00115 mg/kg/day, respectively. Clewell et al. (1998) suggested that the 5th percentile of 0.00104 mg/kg/day provides a scientifically based, conservative basis that incorporates the pharmacokinetic variability across the U.S. population of child-bearing women and that no other uncertainty factor for interindividual variability would be needed. To the benchmark-estimated NOAEL of 21 ppm derived from the Seychelles 29-month data, Clewell et al. (1998) applied an uncertainty factor of 3 to account for data base limitations. (Note: The 66-month Seychelles data was not yet published at the time; hence the reliance on the 29-month Seychelles

data for the benchmark analysis.) Consequently, Clewell et al. (1998) concluded that using a NOAEL of 7 ppm (21 ppm / 3 (UF) provides additional protection against the possibility that effects could occur at lower concentrations in some populations. Based upon this reasoning, Clewell and his colleagues recommended a health guidance value (i.e., an RfD) of 0.0004 mg/kg/day. If a modifying factor of 1.5 is used to further address the domain-specific findings in the Faroe study, a final MRL of 0.3 µg/kg/day results.

The above benchmark analysis of 29-month data from the Seychelles Child Development Study strongly supports the MRL of 0.0003 mg/kg/day calculated by ATSDR in this profile. Similarly, addressing the Seychellois 66-month data from the perspective of using the mean value (15.3 ppm) of the highest exposure group in the study, a method prescribed in ATSDR's published guidance for MRL development (Chou et al. 1998), also results in an identical MRL. ATSDR therefore has high confidence that this level is protective of the health of all potentially exposed human populations.

Employment of the Chronic Oral MRL for Methylmercury

It should be emphasized that the MRL is considered by ATSDR to be a level of exposure to a single chemical/substance which is considered "safe" for all potentially exposed populations for a specified duration of time (acute, intermediate, or chronic). It is not considered be a threshold for adverse effects, and not address the likelihood of adversity at any incremental level above the MRL value. ATSDR notes that the 0.3 µg/kg/day chronic oral MRL for methylmercury is in close agreement with the tolerable daily intake (ADI) levels of 0.47 and 0.48 µg/kg/day established by the FDA and WHO, respectively.

MRLs are, by definition (Chou et al. 1998), substance-specific and do not include effects attributable to interaction (whether additive, synergistic, or antagonistic) with other chemicals or environmental substances. Their relevance to the mission of ATSDR is to assist public health officials in the identification of chemicals/elements of potential health concern at hazardous waste sites. The ATSDR MRL is not intended to be used in the regulatory or site clean-up process, but is instead intended to serve as a basis of comparison with actual measured levels of environmental exposure. Further, the role of informed biomedical judgment is crucial in the application of any MRL, or the media-specific health guidance values (HGVs) derived from them, in any given exposure scenario (Risher and De Rosa 1997). MRLs for a particular substance are based upon the most sensitive effect/endpoint in that portion of the human population considered to be most susceptible to injury from exposure to that substance. Thus, the MRL has never been intended as a one-size-fits-all tool for all hazardous waste site exposure scenarios; rather, it is merely a starting point for further examination of potential health risk. Therefore, at sites

where methylmercury is present in combination with other known or suspected neurodevelopmental toxicants, such as lead or polychlorinated biphenyls (PCBs), and in which exposure is primarily episodic in nature, the health assessor might consider using a value below the chronic oral MRL for methylmercury as a starting point for determination of further site investigation. (A more complete description of the uses of MRLs and other HGVs can be found in Chou et al. 1998 and Risher and De Rosa 1997.)

Background and general population exposures relevant to the oral MRL for methylmercury

Mercury hair levels have been monitored in a variety of populations and generally range from 1 to 4 ppm, depending upon the level of fish consumption. Table 2-10 summarizes the mean (or median) values and the maximum value from a number of these studies.

Diet. Based on the FDA total diet study of 1982–1984 (Gunderson 1988), FDA estimated that the average intake for total mercury (both inorganic and organic) is 50–100 ng/kg/day. Based on the more recent 1989–1990 FDA total diet study, the estimated intake of total mercury is 27–60 ng/kg/day (Cramer 1994). An estimated 86% of the mercury in the total diet study is derived from fish (Tollefson and Cordle 1986). A separate estimate of the average intake of methylmercury alone, based on a survey of fish eaters and average levels of methylmercury in fish, places the average intake of methylmercury at 36 ng/kg/day, with a 99% upper bound at 243 ng/kg/day (Clarkson 1990).

Potential protective effect of selenium in fish. Selenium is known to bioconcentrate in fish, and selenium has been observed to correlate with mercury levels in the blood of fish consumed (Grandjean et al. 1992). Furthermore, there is evidence suggesting that consumption of methylmercury from fish, in conjunction with other beneficial constituents in fish (e.g., omega-3 fatty acids) may not result in the same toxicity dose-response relationship observed with methylmercury exposure from consumption of contaminated grain (as in the Iraqi population) (Davidson et al. 1998).

Regarding the bioavailability of methylmercury in fish, the available data indicate that methylmercury uptake is not affected by its presence in fish. Experimental studies on the metabolism of methylmercury in humans following the ingestion of contaminated fish (using methylmercury bound to fish muscle protein) have shown that absorption is almost complete (95% absorbed) (Miettinen 1973). Animal studies also support this absorption value. Data on cats given fish homogenates indicate absorptions of $90% of methylmercury, whether added to the homogenate, accumulated by fish *in vivo*, or from methylmercury proteinate (Berglund et al. 1971). Using blood and tissue levels as evidence of absorption, Charbonneau et al. (1976) concluded that there was no difference in the biological availability of methylmercury

Table 2-10. Concentration of Total Mercury in Hair

Mean (M) or median (m) (ppm)	Maximum (ppm)	N	Description of population	Reference
1.4 (M)	27.4	942	United Kingdom. Area chosen for "above average fish consumption"	Sherlock et al. 1982
1.35 (M)	5.8	55	United Kingdom. Fishing community, area with lesser contamination	Haxton et al. 1979
1.48 (M)	3.28	34	Islands of the central Adriatic (Yugoslavia). Women; degree of fish consumption not reported. Hair sampled at end of pregnancy	Horvat et al. 1988
2.0 (M)	11.3	119	United Kingdom. Fishing community, area with greater contamination. Fish consumption range 10–225 g/day with 50% eating greater than 50 g/day	Haxton et al. 1979
2.85 (M)	20	50	Spain. Women; degree of fish consumption not reported. Hair sampled at end of pregnancy	Soria et al. 1992
3.2 (M)	10.8	50	Sweden. High consumption of freshwater fish. Mercury levels in fish generally below 1 ppm	Oskarsson et al. 1990
3.9 (M)	21	98	United Kingdom. Consumed an average of 0.36 kg fish/week	Sherlock et al. 1982
5.6 (M)	20	35	Japan. Fish consumption not known	Suzuki et al. 1993
0.8 (m)	2[a]	18	Faroe Islands. No fish consumption	Grandjean et al. 1992
1.61 (m)	3.7	49	1 fish meal per week	
2.5 (m)	4.7	75	2 fish meals per week	
2.1 (m)	3.6	49	3 fish meals per week	
5.2 (m)	8	17	4 fish meals per week	
1.4 (M)			Eat fish once a month	Airey 1983b
1.9 (M)			Eat fish once every 2 weeks	
2.5 (M)			Eat fish once a week	
11.6 (M)			Eat fish once a day	
0.247 (m)	2.5	150	German sample from 150 cadavers (75 males, 75 females) from the general population (i.e., no occupational or unusual expsoures to metals.)	Drasch et al. 1997

[a] The "maximums" reported in this column for Grandjean et al. 1992 are the upper values for the "50% range" as reported in Grandjean et al. (1992).

administered to adult cats (0.003, 0.0084, 0.020, 0.046, 0.074, or 0.176 mg Hg/kg/day, 7 days a week for 2 years), either as pure methylmercuric chloride in corn oil added to a diet containing uncontaminated fish or as methylmercury-contaminated fish. In the two highest dose groups (0.074 and 0.176 mg Hg/kg body weight at 100 weeks of exposure), no significant differences were seen in total mercury concentrations in the blood between groups receiving the dose as methylmercuric chloride or as contaminated fish at the same dose level. In addition, monthly blood levels were comparable for all dose groups. No significant differences were seen at 100 weeks in total mercury concentrations in nervous tissue or other tissues (renal cortex, renal medulla, liver, spleen, adrenal, bladder, atria, ventricle, ovary, testis, muscle) between the two highest dose groups receiving the dose as methylmercuric chloride or as contaminated fish at the same dose level.

Regarding the effect of selenium on methylmercury toxicity, most studies have shown that the simultaneous administration of mercury and selenium in equimolar doses to animals has resulted in decreased toxicity of both elements for acute- and chronic-duration exposures. This effect has been observed with inorganic and organic mercury and with either inorganic or organic selenium compounds, although inorganic forms of selenium appear to be more effective than organic forms (Chang 1983; Skerfving 1978). Selenium protects against the acute nephrotoxicity of the mercuric ion and methylmercuric ion in rats (Ganther et al. 1972, 1980; Hansen 1988; Magos et al. 1987; Parizek and Ostadolva 1967) and possibly against acute neurotoxicity of methylmercuric ion in rats (Ohi et al. 1980).

Somewhat paradoxically, the protective effect of selenium has been associated with a higher whole-body retention of mercury (Hansen 1988; Magos et al. 1987). In a study of selenium excretion in workers exposed to low levels of metallic mercury vapor in a chloralkali plant, Ellingsen et al. (1995) found that even in a low-to-moderate occupational exposure, mercury may reduce the urinary selenium concentration in humans in a manner that is not yet fully known. Evidence from human autopsy tissues suggests that distribution of mercury throughout the body may be influenced by the presence of selenium (Suzuki et al. 1993). In this study, however, the level of selenium was found to negatively correlate with the level of mercury in some tissues including the cerebrum, spleen, and kidney cortex. Suzuki et al. (1993) also report that hair selenium values negatively correlated with total organ mercury and inorganic mercury levels. The association between concentrations of inorganic mercury and selenium in both the occipital lobe and the thalamus of the brains of methylmercury-exposed female monkeys was reported by Bjorkman et al. (1995). These authors observed a tendency to a "hockey stick-shaped" relationship between concentrations of selenium and inorganic mercury in the thalamus of monkeys with ongoing exposure to methylmercury, and

they postulated an important role for selenium in the retention of mercury in the brain. These studies indicate that selenium has an effect on mercury toxicokinetics, although more study is needed to determine the nature of the interaction with respect to different organs and exposure regimens.

Although the specific mechanism for the protection is not well understood, possible mechanisms for selenium's protective effect include redistribution of mercury (Mengel and Karlog 1980), competition by selenium for mercury-binding sites associated with toxicity, formation of a mercury-selenium complex that diverts mercury from sensitive targets (Hansen 1988; Magos et al. 1987; Naganuma and Imura 1981), and prevention of oxidative damage by increasing selenium available for the selenium-dependent glutathione peroxidase (Cuvin-Aralar and Furness 1991; Imura and Naganuma 1991; Nylander and Weiner 1991). One laboratory study showed that selenium-treated animals can remain unaffected, despite an accumulation of mercury in tissues to levels that are otherwise associated with toxic effects (Skerfving 1978). Support for the proposal that an inert complex is formed comes from the 1:1 ratio of selenium and mercury found in the livers of marine mammals and in the bodies of experimental animals administered compounds of mercury and compounds of selenium, regardless of the ratio of the injected doses (Hansen 1988).

Southworth et al. (1994) evaluated the elimination of slurried fly ash discharges into a water-filled quarry and found that the discharge was followed by a steady increase in concentrations of mercury in the axial muscle of resident largemouth bass *(Micropterus salmoides)*, increasing from 0.02 to 0.17 µg/g in a period of just 3 years. These authors also found that while selenium concentrations in the quarry decreased from 25 to <2 µg/L during the same period, selenium concentrations in bass remained at about 3 times the background levels. Southworth and his co-authors concluded that the results of their study suggest that selenium may also be effective at blocking the accumulation of methylmercury in harder, more alkaline waters.

SPECIFIC ADVERSE EFFECTS ATTRIBUTABLE TO MERCURY EXPOSURE

Death. Inhalation of sufficiently high concentrations of metallic and organic mercury vapors, ingestion of sufficiently high doses of organic and inorganic mercury, and exposure to dialkyl mercurials by any route can be fatal to humans and animals. In the cases of both inhalation and dermal exposure to dialkyl-organomercurials (e.g., diethyl- and dimethylmercury), acute exposures that appear innocuous or unremarkable at the time of exposure can result in death following a delay period of weeks or months. The tragic case of a delayed neurotoxicity and ultimately fatal poisoning 9 months after an acute dermal

exposure to only a few drops of dimethylmercury is striking example of the danger of these forms of organic mercury (Blayney et al. 1997; Nierenberg et al. 1998). At least 5 other deaths have been reported due to alkyl mercury exposure since its first synthesis in the mid-19th century (Toribara et al. 1997). These accidental poisoning cases also reveal a latency period of some months between the exposure and the onset of symptoms. In such cases, irreversible brain damage has already occurred by the time the first symptoms appeared.

No information was located regarding specific concentrations of elemental mercury vapor that may be lethal; however, lethal exposures have generally occurred as a result of exposure under conditions in which exposure levels are likely to be quite high (e.g., heating metallic mercury in a closed space). Death in these cases has generally been attributed to respiratory failure (Campbell 1948; Kanluen and Gottlieb 1991; Matthes et al. 1958; Rowens et al. 1991; Soni et al. 1992; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961). Deaths resulting from inhalation exposure to organic mercury compounds have also been reported (Brown 1954; Hill 1943; Hook et al. 1954; Lundgren and Swensson 1949). Although the cause of death following inhalation of organic mercury was not reported, severe neurological dysfunction was observed prior to death.

Lethal doses for acute oral exposure to inorganic mercury have been estimated to be 29–50 mg Hg/kg (Troen et al. 1951). Deaths resulting from oral exposure to inorganic mercury have been attributed to renal failure, cardiovascular collapse, and severe gastrointestinal damage (Gleason et al. 1957; Kang-Yum and Oransky 1992; Troen et al. 1951).

Deaths from consumption of methylmercury-contaminated foods are well documented in outbreaks in Japan and Iraq, and lethal doses of 10–60 mg Hg/kg have been estimated from tissue concentrations (Bakir et al. 1973; Tsubaki and Takahashi 1986). Fatalities were attributed to central nervous system toxicity (Bakir et al. 1973; Tamashiro et al. 1984). Pneumonia and nonischemic heart disease were prominent secondary causes of death in the Japan epidemic (Tamashiro et al. 1984). Case reports of deaths associated solely with dermal mercury exposure to inorganic mercury are limited to a woman who died after inserting a mercuric chloride tablet into her vagina (Millar 1916) and a man who died after a 2-month treatment with a topical medicine containing mercurous chloride (Kang-Yum and Oransky 1992). Death was attributed to renal failure in one of these cases (Kang-Yum and Oransky 1992), and severe renal damage was noted at the autopsy in the other (Millar 1916).

Animal data support the findings from human studies and provide somewhat more information regarding lethal exposure levels. Deaths associated with acute-duration inhalation exposure to metallic mercury vapor have been observed in rats and rabbits at about 27–29 mg/m^3 (Ashe et al. 1953; Livardjani et al. 1991b). Severe pulmonary edema has been reported as the cause of death following such exposures (Christensen et al. 1937). Severe ataxia occurred prior to death in rats exposed to methylmercury iodide vapor for intermediate durations (Hunter et al. 1940). Acute oral LD_{50} values for inorganic mercury ranged from 25.9 to 77.7 mg Hg/kg, with the most sensitive LD_{50} for 2-week-old rats (Kostial et al. 1978). Increased mortality in chronic-duration oral studies has been observed at 1.9 mg Hg/kg in male rats gavaged 5 days a week (NTP 1993). Early deaths were attributed to renal toxicity. Oral exposure to methylmercuric compounds has resulted in increased mortality at 16 mg Hg/kg (single dose) (Yasutake et al. 1991b), 3.1 mg Hg/kg/day for 26 weeks (Mitsumori et al. 1981), and 0.69 mg Hg/kg/day for up to 2 years (Mitsumori et al. 1990).

Systemic Effects

Respiratory Effects. The evidence from case report studies suggests that inhalation of metallic mercury vapor may result in clinical respiratory symptoms (e.g., chest pains, dyspnea, cough, reduced vital capacity) (Bluhm et al. 1992a; Gore and Harding 1987; Haddad and Sternberg 1963; Hallee 1969; Kanluen and Gottlieb 1991; King 1954; Lilis et al. 1985; Matthes et al. 1958; McFarland and Reigel 1978; Milne et al. 1970; Rowens et al. 1991; Snodgrass et al. 1981; Soni et al. 1992; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961). In the more severe cases, respiratory distress, pulmonary edema, lobar pneumonia, fibrosis, desquamation of the bronchiolar epithelium, and death due to respiratory failure have been observed (Campbell 1948; Gore and Harding 1987; Jaffe et al. 1983; Kanluen and Gottlieb 1991; Matthes et al. 1958; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961). Acute- and intermediate-duration studies in rabbits appear to corroborate clinical symptoms observed in humans following inhalation exposure to metallic mercury vapors. Mild-to-moderate pathological changes (unspecified) were exhibited in the lungs of rabbits exposed to 6–28.8 mg/m^3 mercury vapor for up to 11 weeks (Ashe et al. 1953), and death due to asphyxiation has been observed in rats exposed to 27 mg/m^3 for 2 hours (Livardjani et al. 1991b). Lung congestion was observed after 100 hours of continuous exposure of rats to 1 mg/m^3 (Gage 1961). The potential for oral exposure was not quantified; however, it is likely that most of the exposure was through inhalation. Inconclusive evidence is available regarding respiratory effects due to inhalation of organic mercury (Brown 1954; Hunter et al. 1940), and there is no conclusive evidence indicating that oral or dermal exposure to inorganic or organic forms of mercury is

directly toxic to the respiratory system. Based on these results, it would appear that acute inhalation exposure of humans to high levels of metallic mercury may result in pulmonary effects.

Cardiovascular Effects. The evidence from clinical, occupational, and general population studies suggests that inhalation of metallic mercury may affect the cardiovascular system in humans, producing elevations in blood pressure and/or heart rate (Aronow et al. 1990; Bluhm et al. 1992a; Campbell 1948; Fagala and Wigg 1992; Foulds et al. 1987; Friberg et al. 1953; Haddad and Sternberg 1963; Hallee 1969; Jaffe et al. 1983; Karpathios et al. 1991; Siblerud 1990; Smith et al. 1970; Snodgrass et al. 1981; Soni et al. 1992; Taueg et al. 1992; Teng and Brennan 1959). Studies of workers chronically exposed to elemental mercury vapor have shown increased incidences of palpitations (Piikivi 1989), high incidences of hypertension (Vroom and Greer 1972), and increased likelihood of death due to ischemic heart and cerebrovascular disease (Barregard et al. 1990). Of particular interest is the study showing slightly higher blood pressure in persons with dental amalgams than in those with no mercury-containing amalgams (Siblerud 1990). Less information is available regarding inhalation of organic mercury, but one study showed elevated blood pressure in two men occupationally exposed to methylmercury compounds (Hook et al. 1954). Electrocardiographic abnormalities (ventricular ectopic beats, prolongation of the Q–T interval, S–T segment depression, and T-wave inversion) were reported in persons who ate foods contaminated with ethylmercury compounds or who ingested a large dose of mercuric chloride (Chugh et al. 1978; Cinca et al. 1979; Jalili and Abbasi 1961). It is unclear whether these electrocardiographic abnormalities were the result of direct cardiac toxicity or whether they were secondary to other toxicity.

A number of the above cases of mercury-related tachycardia and elevated blood pressure in children inhaling metallic mercury vapors (Aronow et al. 1990; Fagala and Wigg 1992; Foulds et al. 1987; Karpathios et al. 1991) are associated with acrodynia, a nonallergic hypersensitive reaction in children to mercury exposure. Similar elevations in heart rate and blood pressure have been reported in children ingesting mercurous chloride (calomel)-containing medications and in children dermally exposed to ammoniated mercury-containing ointments or diapers that had been rinsed in a mercuric chloride-containing solution (Warkany and Hubbard 1953).

Limited animal data are available regarding inhalation exposure to mercury, but studies indicate that mercury may have a toxic effect on the heart. Effects ranging from mild pathological changes to marked cellular degeneration of heart tissue were exhibited in rabbits inhaling 0.86–28.8 mg/m^3 mercury vapor for

acute and intermediate durations (Ashe et al. 1953). However, it is unclear whether these changes represent direct toxic effects on the heart or whether they were secondary to shock.

The bulk of information available regarding cardiovascular effects after oral exposure of animals to mercury generally supports findings seen in human inhalation studies. Oral administration of 7 mg Hg/kg/day as inorganic mercury (mercuric chloride) for a year or 0.4 mg Hg/kg/day as organic mercury (methylmercuric chloride) for up to 28 days in rats resulted in elevated blood pressure (Carmignani et al. 1989; Wakita 1987). At higher concentrations (28 mg Hg/kg/day as mercuric chloride for 180 days), decreases in cardiac contractility were observed; these effects were suggested to be due to direct myocardial toxicity (Carmignani et al. 1992). Biphasic effects on myocardial tissue have been demonstrated on isolated papillary muscles from rat ventricles (Oliveira and Vassallo 1992). At low mercury concentrations, an increase in contractile force was observed, whereas at 5–10-fold higher concentrations dose-related decreases in contractile force were observed. The increases in contractile force were suggested to be due to inhibition of Na+-K+-ATPase, and the decreases were suggested to be due to inhibition of Ca2+-ATPase of the sarcoplasmic reticulum. Based on these results, it would appear that children with hypersensitivity to mercury may exhibit tachycardia and elevated blood pressure following inhalation, oral, or dermal exposure to mercury or to mercury-containing compounds. In addition, low-level exposure to mercury for extended periods may cause elevated blood pressure in exposed populations. Chronic-duration inhalation exposures or intermediate-duration oral exposures may also be associated with increased mortality due to ischemic heart or cerebrovascular disease; however, the data supporting this conclusion are more limited.

Gastrointestinal Effects. Both inhalation and oral exposures to mercury have resulted in gastrointestinal toxicity. Mercurial stomatitis (inflammation of the oral mucosa, occasionally accompanied by excessive salivation) is a classic symptom of mercury toxicity and has been observed following inhalation exposure to both inorganic and organic mercury (Bluhm et al. 1992a; Brown 1954; Campbell 1948; Fagala and Wigg 1992; Garnier et al. 1981; Haddad and Sternberg 1963; Hallee 1969; Hill 1943; Hook et al. 1954; Karpathios et al. 1991; Sexton et al. 1976; Snodgrass et al. 1981; Tennant et al. 1961; Vroom and Greer 1972).

Mercuric chloride is caustic to the tissues of the gastrointestinal tract, and persons who have ingested large amounts of this form of mercury have exhibited blisters, ulceration, and hemorrhages throughout the gastro-intestinal tract (Afonso and deAlvarez 1960; Chugh et al. 1978; Murphy et al. 1979; Samuels et al.

1982). In some cases, gastrointestinal lesions have been observed after inhalation exposure to high concentrations of metallic mercury vapors. The autopsy of a young child who inhaled metallic mercury vapor revealed necrosis in the mucosa of the stomach and duodenum (Campbell 1948). Irritation of the oral mucosa has also been observed at the site of contact with dental amalgams that contain mercury (Veien 1990). However, this type of response appears to be a combination of stomatitis and a contact dermatitis.

Symptoms of abdominal cramps, diarrhea, and nausea have been reported following acute- and/or intermediate-duration inhalation, oral, and dermal exposures of persons to mercury (Afonso and deAlvarez 1960; Bluhm et al. 1992a; Campbell 1948; Cinca et al. 1979; Haddad and Sternberg 1963; Hallee 1969; Jalili and Abbasi 1961; Kang-Yum and Oransky 1992; Kanluen and Gottlieb 1991; Lilis et al. 1985; Milne et al. 1970; Sexton et al. 1976; Snodgrass et al. 1981; Soni et al. 1992; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961; Warkany and Hubbard 1953).

Rabbits displayed mild pathological changes to marked cellular degeneration and some necrosis in the colon tissue after inhaling 28.8 mg/m^3 mercury for 4–30 hours (Ashe et al. 1953). Inflammation and necrosis of the glandular stomach were observed in mice given 59 mg Hg/kg as mercuric chloride by gavage 5 days a week for 2 weeks (NTP 1993). An increased incidence of forestomach hyperplasia was observed in male rats exposed to 1.9 mg Hg/kg/day as mercuric chloride for 2 years (NTP 1993). Necrosis and ulceration of the cecum have been observed in rats after chronic-duration exposure to 4.2 mg Hg/kg/day as phenylmercuric acetate in the drinking water (Fitzhugh et al. 1950; Solecki et al. 1991). Ulceration of the glandular stomach was observed in mice after 2 years of exposure to methylmercuric chloride (0.86 mg Hg/kg/day) in the diet. Acute-duration inhalation exposure or chronic-duration oral exposure to inorganic and organic mercury may, therefore, result in various gastrointestinal symptoms in humans, with possible damage to intestinal tissues.

Hematological Effects. Leukocytosis associated with a metal fume fever-like syndrome has been observed in persons exposed to high concentrations of metallic mercury vapor (Campbell 1948; Fagala and Wigg 1992; Haddad and Sternberg 1963; Hallee 1969; Jaffe et al. 1983; Lilis et al. 1985; Matthes et al. 1958; Rowens et al. 1991). It is probable that this effect is specific to inhalation exposure to mercury. Because of the high concentrations of mercury that have been involved in the studies reviewed, it is unlikely that persons exposed to mercury vapors at hazardous waste sites would be exposed to sufficiently high concentrations of mercury to result in leukocytosis. Other hematological effects associated with exposure to mercury include decreased hemoglobin and hematocrit in persons with dental amalgams (Siblerud 1990)

and decreased δ-aminolevulinic acid dehydratase activity in erythrocytes or increased serum proteins involved in the storage and transport of copper in workers exposed to mercury vapor (Bencko et al. 1990; Wada et al. 1969). Anemia was found in a man who ingested a lethal amount of mercuric chloride (Murphy et al. 1979). However, the anemia was most likely the result of massive gastrointestinal hemorrhaging. No reports of effects on blood parameters in humans were located after oral exposure to organic mercury. A decrease in red cell count, hemoglobin, and hematocrit and rupture of erythrocytes were observed after intraperitoneal injection of mice with 19.2 mg Hg/kg as methylmercuric chloride (Shaw et al. 1991). A decrease in hemoglobin, hematocrit, and red blood cell count was observed in rats that received phenylmercuric acetate in their drinking water for 2 years (Solecki et al. 1991). However, this effect was probably due to blood loss associated with intestinal ulcers. Thus, there is limited information that suggests that prolonged exposure of humans to high levels of mercury, possibly from living in the vicinity of hazardous waste sites, may result in hematological changes.

Musculoskeletal Effects. Increases in tremors, muscle fasciculations, myoclonus, or muscle pains have been reported in persons exposed to unspecified concentrations of elemental mercury vapor (Adams et al. 1983; Albers et al. 1982, 1988; Aronow et al. 1990; Barber 1978; Bidstrup et al. 1951; Bluhm et al. 1992a; Chaffin et al. 1973; Chapman et al. 1990; Fawer et al. 1983; Karpathios et al. 1991; McFarland and Reigel 1978; Sexton et al. 1976; Smith et al. 1970; Taueg et al. 1992; Verberk et al. 1986; Vroom and Greer 1972; Williamson et al. 1982), in individuals inhaling alkyl mercury compounds (Brown 1954; Hook et al. 1954; Hunter et al. 1940), and in persons ingesting mercurous chloride (Warkany and Hubbard 1953) or ethyl-mercury compounds (Jalili and Abbasi 1961). These muscular effects are probably the result of peripheral nervous system dysfunction. It is probable that persons exposed to sufficiently high concentrations of mercury in the air or in foodstuffs (e.g., contaminated fish) at hazardous waste sites may also experience symptoms of tremors, myoclonus, muscle fasciculations, or muscle pains. A single report was identified that found evidence of rhabdomyolysis (destruction of the skeletal muscle) in a 22-year-old man who attempted suicide by ingesting 2 g of mercuric chloride (Chugh et al. 1978). It is extremely unlikely that persons at hazardous waste sites would be exposed to similarly high concentrations of mercuric chloride.

Hepatic Effects. Elevated serum glutamic pyruvic transaminase (SGPT), ornithine carbamyl transferase, and serum bilirubin, as well as evidence of decreased synthesis of hepatic coagulation factors, were reported in a case study of a child who inhaled an unspecified concentration of metallic mercury vapor (Jaffe et al. 1983). Similarly, hepatomegaly and hepatocellular vacuolation were observed in a man who

died following acute-duration, high-level exposure to elemental mercury vapor (Kanluen and Gottlieb 1991; Rowens et al. 1991). A lethal oral dose of mercuric chloride in a 35-year-old man also resulted in jaundice, an enlarged liver, and elevated aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, and bilirubin (Murphy et al. 1979).

Inhalation of 6–28.8 mg/m^3 mercury vapor for 6 hours to 11 weeks by rabbits produced effects ranging from mild pathological changes to severe necrosis in the liver, including necrosis and degeneration; effects were less severe at the shorter durations (Ashe et al. 1953). Intermediate-duration oral exposure to inorganic mercury has also been associated with increases in hepatic lipid peroxidation (Rana and Boora 1992) and in serum alkaline phosphatase (Jonker et al. 1993a). It is unclear to what extent these effects were due to the direct toxic effects of mercury on the liver or were secondary to shock in the exposed animals. Reliable information regarding hepatic effects following organic mercury exposure was not located. These limited data suggest the potential hepatic toxicity of short-term inhalation of high concentrations of mercury vapor to humans. It is unlikely that persons at hazardous waste sites would ingest sufficiently large amounts of mercuric chloride to cause hepatic toxicity.

Renal Effects. The kidney is one of the major target organs of mercury-induced toxicity. Adverse renal effects have been reported following exposure to metallic, inorganic, and organic forms of mercury in both humans and experimental animals. The nephrotic syndrome in humans associated with the ingestion, inhalation, or dermal application of mercury is primarily identified as an increase in excretion of urinary protein, although depending on the severity of the renal toxicity, hematuria, oliguria, urinary casts, edema, inability to concentrate the urine, and hypercholesterolemia may also be observed (Agner and Jans 1978; Afonso and deAlvarez 1960; Anneroth et al. 1992; Barr et al. 1972; Buchet et al. 1980; Campbell 1948; Cinca et al. 1979; Danziger and Possick 1973; Dyall-Smith and Scurry 1990; Engleson and Herner 1952; Friberg et al. 1953; Hallee 1969; Jaffe et al. 1983; Jalili and Abbasi 1961; Kang-Yum and Oransky 1992; Kanluen and Gottlieb 1991; Kazantzis et al. 1962; Langworth et al. 1992b; Murphy et al. 1979; Pesce et al. 1977; Piikivi and Ruokonen 1989; Roels et al. 1982; Rowens et al. 1991; Samuels et al. 1982; Snodgrass et al. 1981; Soni et al. 1992; Stewart et al. 1977; Tubbs et al. 1982). These effects are usually reversible. However, in the most severe cases, acute renal failure has been observed (Afonso and deAlvarez 1960; Davis et al. 1974; Jaffe et al. 1983; Kang-Yum and Oransky 1992; Murphy et al. 1979; Samuels et al. 1982). Renal biopsies and/or autopsy results have primarily

Rowens et al. 1991), but glomerular changes have also been reported (Kazantzis et al. 1962; Tubbs et al. 1982).

Although the primary effect of mercury on the kidneys appears to be a direct toxic effect on the renal tubules, there is also evidence that implicates an immune mechanism of action for mercury-induced glomerular toxicity in some persons. In support of this theory, a few human case studies have reported deposition of IgG, immune complexes, and/or complement C3 along the glomerular basement membrane (Lindqvist et al. 1974; Tubbs et al. 1982).

Studies in animals support the conclusion that the primary toxic effect of both inorganic and organic mercury in the kidneys is on the epithelial cells of the renal proximal tubules. The changes observed in these studies were comparable with those observed in humans (i.e., proteinuria, oliguria, increases in urinary excretion of tubular enzymes, proteinaceous casts, decreased ability to concentrate the urine, decreased phenolsulfonphthalein excretion, increased plasma creatinine) (Bernard et al. 1992; Chan et al. 1992; Dieter et al. 1992; Girardi and Elias 1991; Jonker et al. 1993a; Kirschbaum et al. 1980; Nielsen et al. 1991; NTP 1993; Yasutake et al. 1991b). In addition, the animal studies provided detailed information regarding the histopathological changes occurring in the kidneys (Carmignani et al. 1989, 1992; Chan et al. 1992; Dieter et al. 1992; Falk et al. 1974; Fitzhugh et al. 1950; Fowler 1972; Goering et al. 1992; Hirano et al. 1986; Jonker et al. 1993a; Klein et al. 1973; Magos and Butler 1972; Magos et al. 1985; Mitsumori et al. 1990; Nielsen et al. 1991; NTP 1993; Yasutake et al. 1991b). The progression of renal toxicity included initial degenerative changes in the epithelial cells of the proximal tubules (nuclear swelling, increased eosinophilia/basophilia, vacuolization, and cellular hypertrophy). In the early stages, these degenerative changes were accompanied by tubular regeneration. Occasionally, when there is minor toxic damage, only the regenerative changes were observed. As the lesions progressed, tubular dilation, desquamation of the epithelial cells, and thickening of the tubular basement membrane were observed. Fibrosis, inflammation, necrosis, and atrophy of the tubules and glomerular changes (i.e., hypercellularity, thickening of the glomerular basement membrane) were then observed.

Several investigators have suggested that the renal toxicity exhibited after administration of organic forms of mercury (e.g., methylmercury) may actually result from the *in vivo* metabolism of this form to inorganic mercury (Fowler 1972; Klein et al. 1973; Magos et al. 1985). This hypothesis is supported by the increase in the smooth endoplasmic reticulum, a potential site for this metabolic conversion, and the measurement of

substantial levels of inorganic mercury in the kidneys following exposure to methylmercury (Fowler 1972; Klein et al. 1973).

In New Zealand White rabbits and in certain strains of mice and rats, a membranous glomerulonephropathy was the predominant finding in the absence of significant tubular damage. This syndrome was characterized by proteinuria, deposition of immune material (i.e., IgG and complement C3) in the renal mesangium and glomerular blood vessels, and minimal glomerular cell hyperplasia (Aten et al. 1992; Druet et al. 1978; Hirszel et al. 1985; Hultman and Enestrom 1992; Matsuo et al. 1989; Michaelson et al. 1985; Pelletier et al. 1990; Pusey et al. 1990; Roman-Franco et al. 1978; van der Meide et al. 1993). Deposition of antiglomerular basement membrane antibodies has been observed in a susceptible strain of rat at subcutaneous doses of mercuric chloride as low as 0.15 mg Hg/kg 4 days a week for 2 weeks (Michaelson et al. 1985). Increases in urinary protein were not observed until 0.74 mg Hg/kg 4 days a week for 2 weeks. In mice, autoantibodies to glomerular basement membrane were not observed, but deposition of IgG in the kidneys occurs as a result of autoantibodies to nucleolar antigens (Hultman and Enestrom 1988). The immune basis for these responses is covered in the section on immunological effects below. The susceptibility to this form of renal toxicity appears to be governed by both MHC genes and nonMHC genes (Aten et al. 1991; Sapin et al. 1984). Among rat strains, Brown-Norway, MAXX, and DZB strains showed susceptibility to renal damage, whereas Lewis, M520, and AO rats did not (Aten et al. 1991; Druet et al. 1978; Michaelson et al. 1985). Among mouse strains, SJL/N mice are susceptible to renal toxicity, whereas DBA, C57BL, and Balb/c mice are not (Hultman and Enestrom 1992; Hultman et al. 1992). The apparent genetic basis for susceptibility to mercury-induced nephrotoxicity in experimental animals has important implications with regard to susceptible subpopulations of humans.

Based on the above information, it is likely that persons exposed to sufficiently high concentrations of mercury may experience renal tubular toxicity. Certain persons who are genetically predisposed may also develop an immunologically based membranous glomerulonephritis.

Dermal Effects. Dermal reactions have been observed in persons exposed to inorganic and organic mercury following inhalation, oral, and/or dermal exposures. The predominant skin reaction is erythematous and pruritic skin rashes (Al-Mufti et al. 1976; Aronow et al. 1990; Bagley et al. 1987; Biro and Klein 1967; Bluhm et al. 1992a; Engleson and Herner 1952; Faria and Freitas 1992; Foulds et al. 1987; Goh and Ng 1988; Hunter et al. 1940; Jalili and Abbasi 1961; Kang-Yum and Oransky 1992; Karpathios et al. 1991; Morris 1960; Pambor and Timmel 1989; Schwartz et al. 1992; Sexton et al. 1976;

Tunnessen et al. 1987; Veien 1990; Warkany and Hubbard 1953). In many of the dermal cases, a contact dermatitis type of response was observed. However, a nonallergic pruritus is characteristic of acrodynia, a hypersensitive reaction to mercury exposure observed primarily in children, and several of the above cases may have been attributable to this syndrome (Aronow et al. 1990; Engleson and Herner 1952; Foulds et al. 1987; Jalili and Abbasi 1961; Karpathios et al. 1991; Tunnessen et al. 1987; Warkany and Hubbard 1953). Other dermal reactions characteristic of acrodynia include heavy perspiration (Aronow et al. 1990; Fagala and Wigg 1992; Karpathios et al. 1991; Sexton et al. 1976; Warkany and Hubbard 1953) and itching, reddened, swollen and/or peeling skin on the palms of the hands and soles of the feet (Aronow et al. 1990; Fagala and Wigg 1992; Jalili and Abbasi 1961; Karpathios et al. 1991; Tunnessen et al. 1987; Warkany and Hubbard 1953). No animal studies were located to support these findings. However, these results demonstrate that two populations may experience dermal effects as a result of mercury exposure. One is those persons who develop an allergic reaction to mercury. The other is those who are hypersensitive to mercury and who develop acrodynia upon exposure. It is unknown whether sufficiently high concentrations of inorganic mercury in soil or methylmercury in fish may exist at hazardous waste sites to trigger allergic dermatitis in sensitive persons or acrodynia in those predisposed to develop this syndrome.

Ocular Effects. Ocular effects have been observed in persons exposed to high concentrations of metallic mercury vapors. These effects are probably due to direct contact of the mercury vapor with the eyes. The observed effects include red and burning eyes, conjunctivitis (Bluhm et al. 1992a; Foulds et al. 1987; Karpathios et al. 1991; Schwartz et al. 1992; Sexton et al. 1976), and a yellow haze on the lenses of the eye (Atkinson 1943; Bidstrup et al. 1951; Locket and Nazroo 1952). The yellow haze was associated with long-term occupational exposures. Animal studies were not available to support these findings. However, the evidence suggests that exposure to high levels of mercury vapor may result in ocular irritation.

Other Systemic Effects. Studies of workers exposed to mercury vapor found no effect on serum levels of thyroid-stimulating hormone (Erfurth et al. 1990; McGregor and Mason 1991). However, an enlarged thyroid, with elevated triiodothyronine and thyroxine, as well as reduced thyroid-stimulating hormone developed in a 13-year-old boy exposed to mercury vapor for 2 weeks (Karpathios et al. 1991). Animal studies generally support an effect of acute-duration high-level exposure on the thyroid, although the results have been somewhat variable (Goldman and Blackburn 1979; Sin and The 1992; Sin et al. 1990). A single intramuscular injection of 14.8 mg Hg/kg in rabbits resulted in increased thyroid peroxidase and triiodo-thyronine and decreased thyroxine (Ghosh and Bhattacharya 1992). A study in which rats received three

daily subcutaneous doses of methylmercuric chloride showed slight increases in thyroid weight and basal levels of thyroid-stimulating hormone and thyroxine (Kabuto 1991). However, it was unclear whether these changes were statistically significant. In contrast, a single subcutaneous dose of 6.4 mg/Hg as methyl-mercuric chloride resulted in significant decreases in serum thyroxine (Kabuto 1987). At higher doses (9.6 and 12.8 mg mercury), increases in prolactin and thyroid-stimulating hormone were observed. The reason for these differences is unclear, but the data suggest that thyroid function may be affected if persons are exposed to sufficiently high concentrations of mercury.

Animal studies also provide evidence of mercury-induced effects on the corticosteroid levels. Increased adrenal and plasma corticosterone levels were reported in rats receiving 2.6 mg Hg/kg/day as mercuric chloride in drinking water after 120 days (Agrawal and Chansouria 1989). At 180 days of exposure, these effects were not evident in the animals. The investigators suggested that mercuric chloride is a dose- and duration-dependent chemical stressor. Subchronic administration of methylmercury to rats caused a diminished secretory response of corticosterone and testosterone serum levels following adrenocorticotropin (ACTH) and human chorionic gonadotropin (HCG) stimulation, respectively (Burton and Meikle 1980). The adrenal glands showed marked hyperplasia and increased weight, and basal levels of these hormones were also depressed. The treated animals exhibited stress intolerance and decreased sexual activity. These results suggest that methylmercury may have an adverse effect on steroidogenesis in the adrenal cortex and testes. Based on these animal studies, inorganic and organic mercury may also act on the corticosteroid system to alter hormonal levels. It is unclear to what extent the effects observed are the result of generalized stress or direct toxic effects on the endocrine system regulating corticosteroid levels.

Inhalation of metallic mercury vapor may result in a metal fume fever-like syndrome characterized by fatigue, fever, chills, cough, and an elevated leukocyte count (Bluhm et al. 1992a; Garnier et al. 1981; Lilis et al. 1985; McFarland and Reigel 1978; Milne et al. 1970; Schwartz et al. 1992; Snodgrass et al. 1981). Also, children with acrodynia frequently exhibit low-grade intermittent fevers (Aronow et al. 1990; Warkany and Hubbard 1953). Animal data are not available to support this finding, but the human data suggest that exposure to sufficiently high concentrations of metallic mercury vapor may result in transient fever (see Hematological Effects).

Immunological Effects. As indicated in the section on dermal effects, allergic dermatological reactions occurred in persons exposed to inorganic mercury from dental amalgams, tattoos, or breakage of medical instruments (Anneroth et al. 1992; Bagley et al. 1987; Biro and Klein 1967; Faria and Freitas

1992; Goh and Ng 1988; Pambor and Timmel 1989; Skoglund and Egelrud 1991; Veien 1990). Additionally, mercury may cause either decreases in immune activity or an autoimmune response, depending on the genetic predisposition of the individual exposed. The human data are very limited, and only decreased IgG production has been observed in workers chronically exposed to metallic mercury vapor at chloralkali and ore production plants (Bencko et al. 1990; Moszczynski et al. 1990b). Neither of these studies, however, adjusted for smoking or alcohol. Increases in serum immunoglobulins (IgA, IgG, IgE, or IgM) and autoantibody titres (antilaminin or antiglomerular basement membrane antibodies) have not been observed in similarly exposed populations (Bernard et al. 1987; Cardenas et al. 1993; Langworth et al. 1992b). There is limited information in humans that suggests that certain individuals may develop an autoimmune response when exposed to mercury. Deposition of IgG and complement C3 have been observed in the glomeruli of two workers with mercury-induced proteinuria (Tubbs et al. 1982). Also, increased antiglomerular basement membrane antibodies and elevated antinuclear antibodies have been observed in a few persons with exposure to mercury in dental amalgams (Anneroth et al. 1992). After removal of one dental amalgam, a significant decrease in IgE levels was observed. Within the populations described above that showed no overall increase in immune parameters, individuals in these groups showed either increases in anti-DNA antibody titres or antiglomerular basement membrane responses (Cardenas et al. 1993; Langworth et al. 1992b). Moszczynski et al. (1995) studied workers exposed to mercury vapor and reported a positive correlation between the T-helper cell count and the duration of exposure. The combined stimulation of the T-cell line and an observed decrease in the helper/suppressor ratio were suggestive of an autoimmune response.

The immune system reaction to mercury has been extensively studied in animals. Although it has not been completely described, a great deal of information exists about the changes that occur in the immune system in response to mercury exposure (Bigazzi 1992; Goldman et al. 1991; Mathieson 1992). Animal strains that are susceptible or predisposed to develop an autoimmune response show a proliferation of autoreactive T-cells (specifically CD4+ T-cells) (Pelletier et al. 1986; Rossert et al. 1988). The fundamental change caused by mercury that results in the autoimmune response appears to be in these autoreactive T-cells, since transfer of these cells to an unexposed animal results in the development of the autoimmune response in the unexposed animal (Pelletier et al. 1988). A subset of the CD4+ T-cells, the Th2 cells, are activated and induce polyclonal B-cell activation (possibly through the release of interleukin-4 [IL-4]), which results in IgE production by the B-cells (Ochel et al. 1991). The increases in serum IgE are paralleled by increases in MHC molecule expression on the B-cells (Dubey et al. 1991a). These changes are accompanied by enlargement of the spleen and lymph nodes, an increase in the number of spleen cells

(thought to be associated with the B-cell proliferation) (Hirsch et al. 1982; Matsuo et al. 1989), and marked increases in serum levels of IgE (Dubey et al. 1991b; Hirsch et al. 1986; Lymberi et al. 1986; Prouvost-Danon et al. 1981). Increases in the production of autoantibodies (IgG) to glomerular basement membrane, thyroglobulin, collagen types I and II, and DNA also occur (Pusey et al. 1990). Immune complex deposits occur in blood vessels in several organs (Hultman et al. 1992), and deposition of these autoantibodies and complement in the renal glomerulus ultimately lead to membranous glomerulonephropathy, although the deposition of the IgG alone does not appear to be sufficient to induce renal dysfunction (Michaelson et al. 1985). In rodents, the autoimmune response spontaneously resolves within a few weeks. The mechanism underlying the resolution is unknown, but antiidiotypic antibodies and a change in the balance between Th2 and Th1 (another subset of the CD4+ T-cells) cell activation (see below) have been proposed (Mathieson 1992). After this resolution phase has occurred, affected individuals develop a resistance to future autoimmune toxicity (Bowman et al. 1984). The resistance appears to be mediated by CD8+ T-cells, since depletion of these cells reverses the resistance (Mathieson et al. 1991).

The so-called resistant strains, however, show a different response to mercury exposure. These resistant strains also show an increase in MHC expression molecules on B-cells, but this response is extremely short-lived, and increases in serum IgE were not observed (Dubey et al. 1991a; Prouvost-Danon et al. 1981). The difference in the responses of the so-called resistant and susceptible strains may be found in the activation of Th1 cells and the increase in secretion of γ-interferon by the Th1 cells of resistant animals (van der Meide et al. 1993). The susceptible strains do not show an increase in γ-interferon production with mercury exposure. Because γ-interferon inhibits the proliferation of Th2 cells, the absence of this response in the susceptible strains may allow the Th2 cell-stimulated production of autoantibodies to occur, whereas in the resistant strains the production of antibodies is curtailed. Thus, differences in the activation of Th1 versus Th2 cells may underlie the differences in susceptibility of various individuals. Studies using in-bred strains of mice and rats have determined that the susceptibility to the different immune reactions is governed by both MHC genes as well as other genes (Aten et al. 1991; Druet et al. 1977; Mirtcheva et al. 1989; Sapin et al. 1984). As indicated in the section on renal effects, Brown-Norway, MAXX, and DZB rat strains showed susceptibility, whereas Lewis, M520, and AO rats did not (Aten et al. 1991; Druet et al. 1978; Michaelson et al. 1985). Among mouse strains, SJL/N mice are susceptible and DBA, C57BL, and Balb/c mice are not (Hultman and Enestrom 1992; Hultman et al. 1992). In a resistant strain, the Balb/c mouse, immune suppression was manifested as decreased natural killer cell activity in mice administered a diet containing 0.5 mg Hg/kg/day as methylmercury (Ilback 1991).

Neurological Effects. The nervous system is the primary target organ for elemental and methylmercury-induced toxicity. Neurological and behavioral disorders in humans have been observed following inhalation of metallic mercury vapor and organic mercury compounds, ingestion or dermal application of inorganic mercury-containing medicinal products (e.g., teething powders, ointments, and laxatives), and ingestion or dermal exposure to organic mercury-containing pesticides or ingestion of contaminated seafood. A broad range of symptoms has been reported, and these symptoms are qualitatively similar, irrespective of the mercury compound to which one is exposed. Specific neurotoxic symptoms include tremors (initially affecting the hands and sometimes spreading to other parts of the body), emotional lability (characterized by irritability, excessive shyness, confidence loss, and nervousness), insomnia, memory loss, neuromuscular changes (weakness, muscle atrophy, and muscle twitching), headaches, polyneuropathy (paresthesias, stocking-glove sensory loss, hyperactive tendon reflexes, slowed sensory and motor nerve conduction velocities), and performance deficits in tests of cognitive and motor function (Adams et al. 1983; Albers et al. 1982, 1988; Aronow et al. 1990; Bakir et al. 1973; Barber 1978; Bidstrup et al. 1951; Bluhm et al. 1992a; Bourgeois et al. 1986; Chaffin et al. 1973; Chapman et al. 1990; Choi et al. 1978; Cinca et al. 1979; Davis et al. 1974; DeBont et al. 1986; Discalzi et al. 1993; Dyall-Smith and Scurry 1990; Ehrenberg et al. 1991; Fagala and Wigg 1992; Fawer et al. 1983; Foulds et al. 1987; Friberg et al. 1953; Hallee 1969; Harada 1978; Hook et al. 1954; Hunter et al. 1940; Iyer et al. 1976; Jaffe et al. 1983; Jalili and Abbasi 1961; Kang-Yum and Oransky 1992; Karpathios et al. 1991; Kutsuna 1968; Langauer-Lewowicka and Kazibutowska 1989; Kutsuna 1968; Langolf et al. 1978; Langworth et al. 1992a; Levine et al. 1982; Lilis et al. 1985; Lundgren and Swensson 1949; Matsumoto et al. 1965; McFarland and Reigel 1978; Melkonian and Baker 1988; Miyakawa et al. 1976; Ngim et al. 1992; Piikivi and Hanninen 1989; Piikivi and Tolonen 1989; Piikivi et al. 1984; Roels et al. 1982; Sexton et al. 1976; Shapiro et al. 1982; Snodgrass et al. 1981; Smith et al. 1970; Tamashiro et al. 1984; Taueg et al. 1992; Tsubaki and Takahashi 1986; Verberk et al. 1986; Vroom and Greer 1972; Warkany and Hubbard 1953; Williamson et al. 1982). Some individuals have also noted hearing loss, visual disturbances (visual field defects), and/or hallucinations (Bluhm et al. 1992a; Cinca et al. 1979; Fagala and Wigg 1992; Jalili and Abbasi 1961; Locket and Nazroo 1952; McFarland and Reigel 1978; Taueg et al. 1992). Although improvement has often been observed upon removal of persons from the source of exposure, it is possible that some changes may be irreversible. Autopsy findings of degenerative changes in the brains of poisoned patients exposed to mercury support the functional changes observed (Al-Saleem and the Clinical Committee on Mercury Poisoning 1976; Cinca et al. 1979; Davis et al. 1974; Miyakawa et al. 1976). Limited information was located regarding exposure levels associated with the above effects, but increased tremors and cognitive difficulties are sensitive end points for chronic low-level exposure to metallic mercury vapor (Fawer et al.

1983; Ngim et al. 1992). Photophobia has been reported exclusively in children with acrodynia (Fagala and Wigg 1992; Warkany and Hubbard 1953). The physiological basis for the photophobia is unknown.

The neurotoxicity of inorganic and organic mercury in experimental animals is manifested as functional, behavioral, and morphological changes, as well as alterations in brain neurochemistry (Arito and Takahashi 1991; Ashe et al. 1953; Berthoud et al. 1976; Burbacher et al. 1988; Cavanaugh and Chen 1971; Chang and Hartmann 1972a, 1972b; Chang et al. 1974; Charbonneau et al. 1976; Concas et al. 1983; Evans et al. 1977; Fukuda 1971; Fuyuta et al. 1978; Ganser and Kirschner 1985; Inouye and Murakami 1975; Jacobs et al. 1977; Kishi et al. 1978; Lehotzky and Meszaros 1974; Leyshon and Morgan 1991; MacDonald and Harbison 1977; Magos and Butler 1972; Magos et al. 1980, 1985; Mitsumori et al. 1981; Miyama et al. 1983; Post et al. 1973; Rice 1989c; Rice and Gilbert 1982, 1992; Salvaterra et al. 1973; Sharma et al. 1982; Tsuzuki 1981; Yip and Chang 1981).

Animal studies have shown damage to the cerebellar cortex and dorsal root ganglion cells following both mercuric chloride and methylmercuric chloride exposure (Chang and Hartmann 1972b). These structures appear to be especially sensitive to the toxic effects of mercury (Chang and Hartmann 1972a, 1972b; Chang et al. 1974; Charbonneau et al. 1976; Falk et al. 1974; Hirano et al. 1986; Jacobs et al. 1977; Leyshon and Morgan 1991; MacDonald and Harbison 1977; Magos and Butler 1972; Magos et al. 1980, 1985; Mitsumori et al. 1990; Yip and Chang 1981), although other areas (e.g., the cerebral cortex, corpus striatum, thalamus, hypothalamus, organ of Corti, and peripheral nerves) have also shown degenerative changes after exposure to methylmercury (Berthoud et al. 1976; Chang et al. 1974; Charbonneau et al. 1976; Falk et al. 1974; Fehling et al. 1975; Jacobs et al. 1977; Miyakawa et al. 1974, 1976; Yip and Chang 1981). Cats and monkeys appear to be more sensitive to the toxic effects than rodents and have shown signs of neurotoxicity at approximately 10-fold lower doses (0.05 mg Hg/kg/day) following long-term exposure to methylmercuric chloride (Charbonneau et al. 1976; Rice 1989c; Rice and Gilbert 1982, 1992).

Although it is unclear whether changes in neurochemical parameters are primary targets of mercury or whether the changes are secondary to degenerative changes in neurons, several neurotransmitter systems have been shown to be affected by mercury exposure. Cholinergic transmission at the neuromuscular junction has been shown to be affected by mercury exposure (Eldefrawi et al. 1977; Sager et al. 1982). Changes in GABA receptor activity and number have also been observed (Arakawa et al. 1991; Concas et al. 1983). Changes in the activities of enzymes involved in cholinergic, adrenergic, dopaminergic, and

serotonergic synthesis and/or catabolism have also been observed following mercury exposure (Sharma et al. 1982; Tsuzuki 1981).

Collectively, the above information shows the high sensitivity of the nervous system to mercury toxicity and indicates that persons exposed to sufficiently high amounts of mercury may experience adverse neurological symptoms.

Reproductive Effects. Studies in humans indicate that metallic mercury vapor does not cause infertility or malformations following paternal exposure (Alcser et al. 1989; Lauwerys et al. 1985) but may cause an increase in the rate of spontaneous abortions (Cordier et al. 1991). No correlation was observed between levels of testosterone, luteinizing hormone, or follicle-stimulating hormone and occupational exposure to metallic mercury vapor, indicating that the pituitary control of testosterone secretion was not affected (Erfurth et al. 1990; McGregor and Mason 1991). However, *in vitro* studies have shown that mercury can adversely affect human spermatozoa. Inorganic (mercuric chloride) and organic (methylmercuric chloride) mercury decreased the percentage of motile spermatozoa *in vitro* (Ernst and Lauritsen 1991). Incubation of human spermatozoa with inorganic mercury resulted in mercury deposits localized in the membranes of the midpiece and tailpiece. The lack of mercury grains in spermatozoa with methylmercury exposure may be due to the inability of spermatozoa or the semen plasma to demethylate methylmercury in the 15-minute incubation period (Ernst and Lauritsen 1991).

Female dentists and dental assistants exposed to metallic mercury vapors had increased reproductive failures (spontaneous abortions, stillbirths, and congenital malformations) and irregular, painful, or hemorrhagic menstrual disorders (Sikorski et al. 1987). Correlations were observed between the incidence of these effects and hair mercury levels.

Rowland et al. (1994) report that female dental assistants with a high occupational exposure to mercury were found to be less fertile than controls. The probability of conception with each menstrual cycle (called "fecundability" by the authors) in women who prepared 30 or more amalgams per week and who were evaluated as having 4 or more poor mercury-hygiene practices was only 63% of that of unexposed controls. Hygiene was incorporated into the evaluation of the results of this study because occupational groups with roughly the same potential for exposure often contain subjects whose actual exposures are quite different, depending on their particular work environment and their work (and personal) hygiene practices within that environment. Rowland et al. (1994) found that 20% of the women in their final evaluation who prepared

more than 30 amalgams a week had 4 or more poor mercury-hygiene factors. Among women preparing a comparable number of amalgams, there were differences in "fecundability," based on the number of self-reported poor hygiene factors. The study is limited in that a group of unexposed women had lower fertility than the low exposed group suggesting other unaccounted for exposures or confounding factors.

Animal data suggest that mercury may alter reproductive function and/or success when administered to either males or females. In males, mercury exposure results primarily in impaired spermatogenesis, sperm motility, and degeneration of seminiferous tubules. Oral administration of methylmercury to males has resulted in decreases in litter size due to preimplantation loss (presumably due to defective sperm) in rats (Khera 1973), decreases in sperm motility in monkeys (at 0.025 mg Hg/kg/day for 20 weeks) (Mohamed et al. 1987), and tubular atrophy and decreased spermatogenesis in mice after prolonged exposure (Hirano et al. 1986; Mitsumori et al. 1990). Parenteral administration of methylmercury has shown similar results. A single intraperitoneal injection of 10 mg/kg of methylmercury in male mice resulted in decreased implantations in females (Suter 1975), and a single intraperitoneal injection of 1 mg/kg of methylmercury resulted in a reversible failure of spermatogenesis and infertility in male mice (Lee and Dixon 1975). Repeated intraperitoneal injections of methylmercury (3.5 mg Hg/kg/day for 6 weeks) in male rats resulted in decreased sexual activity, depression of testosterone levels (Burton and Meikle 1980), and decreased spermatogenesis (0.004 mg Hg/kg/day for 15–90 days) (Vachhrajani et al. 1992). Less is known about the effects of inorganic mercury on the male reproductive system, but a single intraperitoneal injection of mercuric chloride (1 mg Hg/kg) in male rats resulted in decreased conceptions in females (Lee and Dixon 1975), and 0.74 mg Hg/kg resulted in tubular degeneration (Prem et al. 1992). An *in vitro* study (Mohamed et al. 1987) suggested that the decrease in sperm motility observed in monkeys may be due to interference with microtubule assembly or dynein/microtubule sliding function.

In females, mercury exposure results primarily in increases in resorptions and decreases in implantations. Inhalation exposure of female rats to metallic mercury vapor (2.5 mg/m^3, 6 hours a day, 5 days a week for 21 days) resulted in a prolongation of the estrous cycle (Baranski and Szymczyk 1973). Oral administration of mercuric acetate (22 mg Hg/kg) to pregnant hamsters resulted in an increase in resorptions (Gale 1974). Oral administration of methylmercury to pregnant guinea pigs (11.5 mg Hg/kg) resulted in an increase in abortions (Inouye and Kajiwara 1988), and 3 mg Hg/kg resulted in a decrease in the number of pups in the litter from pregnant mice (Hughes and Annau 1976). Pregnant mice given a single dose of 20 mg Hg/kg as methylmercuric chloride had increased resorptions, decreased live fetuses, and decreased fetuses per litter (Fuyuta et al. 1978). Repeated oral administration of methylmercury

(0.06 mg Hg/kg/day) to female monkeys resulted in an increase in the number of abortions and a decrease in conceptions (Burbacher et al. 1988). No effect on the monkeys' menstrual cycles was observed. Intraperitoneal administration of mercuric chloride (1.48 mg Hg/kg) to female mice resulted in decreases in litter size and number of litters/female and an increase in dead implants in some strains of mice, but these effects were strain-specific (Suter 1975). In female mice administered a single intraperitoneal dose of 1 mg Hg/kg as mercuric chloride, a decrease in mean implantation sites was observed (Kajiwara and Inouye 1992). Subcutaneous injection of female hamsters with 6.2–8.2 mg Hg/kg as mercuric chloride for 1–4 days resulted in a disruption of estrous (Lamperti and Printz 1973). Inhibition of follicular maturation and normal uterine hypertrophy, morphological prolongation of the corpora lutea, and alteration of progesterone levels were observed. Collectively, these results suggest that at sufficiently high mercury concentrations, men may experience some adverse effects on testicular function and women may experience increases in abortions, decreases in conceptions, or development of menstrual disorders.

Developmental Effects. Mercury is considered to be a developmental toxicant. Extremely limited information was located regarding human developmental effects associated with exposure to inorganic mercury (Alcser et al. 1989; Derobert and Tara 1950; Melkonian and Baker 1988; Thorpe et al. 1992). However, developmental toxicity in humans associated with oral exposure to organic forms of mercury is well recognized (Amin-Zaki et al. 1974; Bakir et al. 1973; Cox et al. 1989; Engleson and Herner 1952; Harada 1978; Marsh et al. 1980, 1981, 1987; McKeown-Eyssen et al. 1983; Snyder and Seelinger 1976). The symptoms observed in offspring of exposed mothers are primarily neurological in origin and have ranged from delays in motor and verbal development to severe brain damage. Subtle changes, such as small changes in intelligence or learning capacity are currently being tested in populations with low-level, chronic exposure to mercury in the diet (Davidson et al. 1998; Grandjean et al. 1997b, 1998). MRLs for acute- and intermediate-duration exposure to methylmercury have been developed based on the lowest observed peak hair level in a mother whose child was reported to have a delayed onset of walking (14 ppm in hair) (Cox et al. 1989; WHO 1990).

Animal studies suggest that both inorganic mercury and organic mercury cause developmental toxicity. Metallic mercury vapor may be transferred across the placenta (Greenwood et al. 1972). The placental transport of mercury in pregnant mice and its localization in the embryo and fetus were studied by autoradiography and gamma counting (Khayat and Dencker 1982). Retention of ^{203}Hg vapor following inhalation was compared to intravenous injection of ^{203}Hg as mercuric chloride. The authors reported that inhalation of mercury vapor resulted in a mercury concentration that was four times higher than the

concentration resulting from injection of mercuric chloride. Furthermore, the authors reported that metallic mercury appeared to oxidize to Hg^{+2} in the fetal tissues. Evidence that inhalation exposure may result in developmental toxicity comes from a study in which neonatal rats were exposed to metallic mercury vapor during a period of rapid brain development (this occurs postnatally in rodents but prenatally in humans), resulting in impaired spatial learning (Fredriksson et al. 1992). Oral administration of inorganic mercury salts to pregnant hamsters has been observed to produce an increase in the number of resorptions and small and edematous embryos (Gale 1974). Mercury-induced embryotoxicity in one non-inbred and five inbred stains of female hamsters was investigated by Gale and Ferm (1971). A single subcutaneous injection of 9.5 mg Hg/kg as mercuric acetate to dams on Gd 8 produced a variety of malformations, including cleft palate, hydrocephalus, and heart defects, and statistically significant interstrain differences in the embryotoxic response. Single doses of 1.3–2.5 mg Hg/kg as mercuric acetate injected intravenously into pregnant hamsters on Gd 8 produced growth retardation and edema of the fetuses at all 3 dose levels, while an increase in the number of abnormalities was detected at the two higher doses (Gale and Ferm 1971). The relative effectiveness of different exposure routes in hamsters was compared by Gale (1974). The following sequence of decreasing efficacy was noted for mercuric acetate: intraperitoneal > intravenous > subcutaneous > oral. The lowest doses used (2 mg/kg for intraperitoneal and 4 mg/kg for the other 3 routes) were all effective in causing increased resorption and an increased percentage of abnormalities. Intravenous injection of 1.5 mg Hg/kg/day as mercuric chloride also resulted in a significant increase in the number of abnormal preimplantation embryos (Kajiwara and Inouye 1986).

In animals, embryolethal, anatomical, and behavioral effects have been reported following oral exposure of pregnant dams to methylmercury (Bornhausen et al. 1980; Cagiano et al. 1990; Elsner 1991; Fowler and Woods 1977; Fuyuta et al. 1978, 1979; Guidetti et al. 1992; Gunderson et al. 1988; Hughes and Annau 1976; Ilback et al. 1991; Inouye and Kajiwara 1988; Inouye and Murakami 1975; Inouye et al. 1985; Khera and Tabacova 1973; Lindstrom et al. 1991; Nolen et al. 1972; Olson and Boush 1975; Reuhl et al. 1981a, 1981b; Rice 1992; Rice and Gilbert 1990; Stoltenburg-Didinger and Markwort 1990; Yasuda et al. 1985). Thus far, the most sensitive animal assay for developmental neurotoxicity has been a behavioral paradigm that examined the number of rewarded responses to differential reinforcement at high rates (Bornhausen et al. 1980). At doses of 0.008 mg Hg/kg/day and above, a dose-related decrease in rewarded responses was observed in 4-month-old offspring of rats treated on Gd 6–9. The effect was more pronounced in male offspring than females. Foster mothers were used to preclude consumption of contaminated milk during lactation.

Developmental toxicity has also been observed with parenteral exposure to methylmercury in pregnant dams during gestation. In mice given methylmercuric hydroxide subcutaneously daily from Gd 7–12, significant dose-related increases in the percentage of litters with resorptions were seen in groups receiving 3.45–8.6 mg Hg/kg/day (Su and Okita 1976). The frequency of cleft palate increased significantly in litters of the 3.45 and 4.3 mg Hg/kg/day groups only. A high incidence of delayed palate closure and cleft palate was also reported in mice injected subcutaneously with 5 mg Hg/kg of methylmercuric chloride on Gd 12 (Olson and Massaro 1977). Gross incoordination and decreased frequencies of defecation and urination in pups were observed following intraperitoneal administration of a single dose of methylmercury dicyandiamide (8 mg/kg/day) to pregnant mice on day 7 or 9 of pregnancy (Spyker et al. 1972). Degenerative changes were observed in the cerebellum and cerebral cortex of rat pups of maternal rats injected with 4 mg Hg/kg as methylmercuric chloride on Gd 8 (Chang et al. 1977). Degenerative renal changes (in epithelial cells of proximal tubules and Bowman's capsule of glomeruli) were reported in rat fetuses of dams exposed intraperitoneally to methylmercuric chloride during Gd 8 (Chang and Sprecher 1976). The studies by Spyker and Smithberg (1972) demonstrated strain differences in susceptibility to the developmental effects of methylmercury dicyandiamide. Intraperitoneal administration of single doses of methylmercury dicyandiamide (2, 4, or 8 mg/kg) to pregnant mice of strains 129 Sv/S1 and A/J during gestation resulted in retardation of fetal growth and increased resorption of implants in both strains. Teratogenic effects, primarily of the palate and jaw, were detected at all dose levels in 129 Sv/S1 mice, but only at the highest dose in strain A/J. The differential effects of methylmercury were dependent on the strain, the dose of the agent, and the stage of embryonic development.

Antilaminin antibodies induced by mercuric chloride have been demonstrated to be detrimental to the development of cultured rat embryos (Chambers and Klein 1993). Based upon that observation, those authors suggested that it might be possible for an autoimmune disease induced by a substance such as mercury at an early age to persist into later life, acting as a teratogen independent of both dose-response relationships and time of exposure, but that possibility remains to be experimentally demonstrated.

One developmental study of phenylmercury compounds was reported by Gale and Ferm (1971) in which hamsters were injected intravenously with phenylmercuric acetate at doses ranging from 5 to 10 mg/kg on Gd 8. With the exception of the lowest dose, all other doses induced increased resorption rates and edema, along with a few miscellaneous abnormalities including cleft palate and exencephaly.

The above information clearly indicates the possibility of developmental toxicity in offspring of mothers that ingest sufficient amounts of organic mercury. The animal data also suggest that exposure to sufficient amounts of inorganic mercury by inhalation of metallic mercury vapor or ingestion of inorganic mercury may result in developmental toxicity.

Genotoxic Effects. The overall findings from cytogenetic monitoring studies of workers occupationally exposed to mercury compounds by inhalation (Anwar and Gabal 1991; Barregard et al. 1991; Mabille et al. 1984; Popescu et al. 1979; Verschaeve et al. 1976, 1979) or accidentally exposed through ingestion (Wulf et al. 1986) provided no convincing evidence that mercury adversely affects the number or structure of chromosomes in human somatic cells. Studies reporting a positive result (Anwar and Gabal 1991; Barregard et al. 1991; Popescu et al. 1979; Skerfving et al. 1970, 1974; Verschaeve et al. 1976; Wulf et al. 1986) were compromised either by technical problems, a lack of consideration of confounding factors, or a failure to demonstrate a relationship between mercury exposure and induced aberrations. Therefore, none of these studies can be used to predict the potential genetic hazard to humans associated with exposure to mercury or mercury compounds.

A dose-related increase in chromosome aberrations was observed in the bone marrow of mice administered a single oral dose of mercuric chloride at levels of at least 4.4 mg Hg/kg (Ghosh et al. 1991). By contrast, there was no valid evidence of a genotoxic effect on somatic cells of cats chronically exposed to methyl-mercury orally (Miller et al. 1979). However, only minimal toxicity was observed at the high dose (0.046 mg Hg/kg/day) in this study. Doses of 0.86, 1.7, or 3.4 mg Hg/kg as methylmercury hydroxide administered once by intraperitoneal injection to groups of 2 male CBA mice did not cause an increase in micronucleated polychromatic erythrocytes harvested from bone marrow cells 24 hours after treatment (Jenssen and Ramel 1980). Similarly, there was no increase in structural chromosome aberrations in bone marrow cells collected from male Swiss OF_1 mice (3–4/group) 12, 24, 36, or 48 hours postexposure to single intraperitoneal doses of 0.7, 1.5, 3.0, or 4.4 mg Hg/kg as mercuric chloride (Poma et al. 1981). The lack of a clastogenic response, particularly with mercuric chloride, should not be viewed as a possible inability of this compound to penetrate somatic cell membranes. There are data from the study of Bryan et al. (1974) indicating that mercuric chloride can bind to chromatin in the livers of mice challenged with 38 mg Hg/kg/day as mercuric chloride for 1 month. Although the overall data are mixed, the findings from a well conducted study using oral dosing suggests that mercury can be clastogenic for somatic cells (Ghosh et al. 1991).

The intraperitoneal administration of mercuric chloride at levels comparable to those described above did not induce a clastogenic response in the spermatogonia of the same mouse strain (Poma et al. 1981). Structural chromosome aberrations were not produced in metaphase II oocytes of 15 virgin Syrian hamsters receiving a single intraperitoneal injection of 7.4 mg Hg/kg as methylmercury chloride (Mailhes 1983). However, the frequency of hyperploid cells in the treated animals was significantly ($p<0.01$) increased compared to the control. A borderline significant increase in hypoploid cells was also seen. By contrast, Jagiello and Lin (1973) found no evidence of aneuploidy in the oocytes of Swiss/Webster mice (6–8/group) for 3 days after receiving a single intravenous injection of dimethylmercury (140 mg Hg/kg) or mercuric acetate (2, 5, or 10 mg Hg/kg). The lack of concordance between these two studies could be related to the different mercurials that were utilized, the different routes of exposure, or the possible differences in species sensitivity. There are data from a series of dominant lethal assays suggesting that variable strain sensitivity to mercury compounds can affect the outcome of germinal cell cytogenetic investigations (Suter 1975). In this study, two strains of male mice, $(101\times C3H)F_1$ and $(SEC\times C57BL)F_1$, and one strain of female mice, $(101\times C3H)F_1$, received single intraperitoneal injections of 8.6 mg Hg/kg as methylmercuric hydroxide. An additional group of females was injected intraperitoneally with 1.5 mg Hg/kg as mercuric chloride. Males were sequentially mated with untreated females over the entire spermatogenic cycle; treated females were mated once with untreated males. Methylmercuric hydroxide had no effect on fertility and did not induce a clastogenic response in $(101\times C3H)F_1$ males. However, a comparable dose administered to $(SEC\times C57BL)F_1$ males adversely affected fertility and caused significant reductions in total and live implants accompanied by increases in the percentage of dead implants following the first two mating cycles. Suggestive evidence of poor reproductive performance and a dominant lethal effect was also seen in female $(101\times C3H)F_1$ mice treated with methylmercuric hydroxide (8.6 mg Hg/kg) and mercuric chloride (1.5 mg Hg/kg). It was noteworthy that an independent phase of the investigation examined reproduction in females in two additional strains, $(SEC\times C57BL)F_1$ and a mixed stock obtained by crossing $(SEC\times C57BL)F_1$ females with XGSY males. Neither compound had a detrimental effect on the fertility of these females. The single dominant lethal assay conducted with rats (strain not specified) showed that mercuric chloride, administered orally for 12 months (1.8×10^{-3} to 1.8×10^{-4} mg Hg/kg), induced a dose-related increase in dominant lethal mutations, as indicated by increased embryonic death (Zasukhina et al. 1983).

The overall findings from *in vivo* germinal cell assays suggest that mercury compounds are clastogenic for mammalian germ cells. However, the apparent differences in species sensitivity and, in some cases, strain

sensitivity preclude an extrapolation of the relevance of these findings to humans. Refer to Table 2-11 for a further summary of these results.

Several *in vitro* assays employing human cells were located. Both structural and numerical chromosomal aberrations were observed following the exposure of human lymphocytes to methylmercury chloride or dimethylmercury *in vitro* (Betti et al. 1992). Although the smoking status of the donor was not reported, all of the cells came from the same donor, and no aberrations were observed in the control cultures. Mercuric acetate caused single-strand breaks in DNA from human KB-cells (Williams et al. 1987). Methylmercuric chloride treatment of human lymphocytes resulted in the formation of chromosome and chromatid aberrations (Betti et al. 1993b). Further, it was found to be a weak inducer of sister chromatid exchange, but that effect did not increase with an increasing dosage. Methylmercuric chloride was also found to be capable of producing aneuploidy (particularly hyperdiploidy). At low doses, more chromosomal aberrations were observed in the second metaphases than in the first, suggesting that several premutational lesions induced by that organomercurial survived through one cell cycle. Thus, the damage produced by methylmercuric chloride appeared to be stable and could lead to chromosome segregation errors. Betti et al. (1993b) concluded that methylmercuric chloride was capable of producing long-lasting damage, which in turn gives rise to both structural and numerical chromosome abnormalities. Bala et al. (1993) reported that methyl-mercuric chloride in concentrations of 10^{-5}, 10^{-6}, and 10^{-7} M induced aberrant metaphases (including gaps) in cultured human peripheral lymphocytes in a dose-dependent manner ($p<0.05$). Methylmercuric chloride at the higher concentrations also induced a significant number of breaks. Further, methylmercuric chloride induced a significant number of SCEs per cell in a dose-dependent manner. However, cultures treated with gamma linolenic acid (GLA), a derivative of dietary essential fatty acid, did not differ from controls with respect to aberrations, and GLA reduced the frequency of SCEs induced by methylmercuric chloride in a dose-dependent manner ($p<0.05$).

Mercuric chloride was not mutagenic in the *Salmonella typhimurium* plate incorporation assay (Wong 1988). These negative results are not unexpected because the Ames test is not suitable for the detection of heavy metal mutagens. Oberly et al. (1982) reported, however, that doses of mercuric chloride (4.4 and 5.9 µg Hg/mL) approaching severely cytotoxic levels induced a weak mutagenic response in mouse lymphoma L5178Y cells but only in the presence of auxiliary metabolic activation.

In an *in vitro* study of the clastogenic effects of mercurials in animal cells, Howard et al. (1991) observed a dose-related increase in chromosome aberrations in Chinese hamster ovary (CHO) cells treated with

Table 2-11. Genotoxicity of Mercury *In Vivo*

Species (test system)	End point	Results	Reference
Somatic cells:			
CBA mouse (bone marrow cells)	Micronuclei induction	–	Jenssen and Ramel 1980
Swiss mouse (bone marrow cells)	Chromosome aberrations	–	Poma et al. 1981
Swiss mouse (bone marrow cells)	Chromosome aberrations	+	Ghosh et al. 1991
Swiss mouse (liver chromatin)	Chromatid binding	+	Bryan et al. 1974
Cat (bone marrow cells)	Chromsome aberrations	(+)	Miller et al. 1979
Human (peripheral lymphocytes)	Structural chromosome aberrations	(+)	Skerfving et al. 1970
	Aneuploidy	(+)	Skerfving et al. 1974
Human (peripheral lymphocytes)	Structural chromosome aberrations	(+)	Skerfving et al. 1974
	Aneuploidy	(+)	Skerfving et al. 1974
Human (peripheral lymphocytes)	Structural chromosome aberrations	(+)	Popescu et al. 1979
	Aneuploidy	–	Popescu et al. 1979
Human (peripheral lymphocytes)	Structural chromosome aberrations	(+)	Verschaeve et al. 1976
	Aneuploidy	(+)	Verschaeve et al. 1976
Human (peripheral lymphocytes)	Structural chromosome aberrations	–	Verschaeve et al. 1979
	Aneuploidy	–	Verschaeve et al. 1979
Human (peripheral lymphocytes)	Structural chromosome aberrations	–	Mabille et al. 1984
Human (peripheral lymphocytes)	Micronuclei induction	+[a]	Barregard et al. 1991
Human (peripheral lymphocytes)	Structural chromosome aberrations	+[b]	Anwar and Gabal 1991
	Micronuclei induction	+[b]	Anwar and Gabal 1991
	Aneuploidy	–	Anwar and Gabal 1991
Human (peripheral lymphocytes)	Sister chromatid exchange	(+)	Wulf et al. 1986

Table 2-11. Genotoxicity of Mercury *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Germinal cells:			
Swiss mouse (spermatogonia)	Aneuploidy	–	Poma et al. 1981
Swiss mouse (oocytes)	Aneuploidy	–	Jagiello and Lin 1973
$(101\times C_3H)F_1$ mouse (spermatogonia)	Dominant lethal	–	Suter 1975
$(SEC\times C_{57}BL)F_1$ mouse (spermatogonia)	Dominant lethal	+	Suter 1975
$(101\times C_3H)F_1$ mouse (oocytes)	Dominant lethal	+/–	Suter 1975
Rat (spermatogonia)	Dominant lethal	+	Zasukhina et al. 1983
Syrian hamsters (oocytes)	Structural aberrations	–	Mailhes 1983
	Aneuploidy	+	Mailhes 1983

[a]Positive response only in stimulated T-lymphocytes
[b]Positive response but no correlation to urinary mercury levels or duration of exposure

– = negative results; + = positive results; (+) = reported as positive but study was either seriously compromised or findings did not provide valid evidence of a positive response; +/– = inconclusive

mercuric chloride. In a study of the potentiating effects of organomercurials on clastogen-induced chromosomal aberrations in cultured Chinese hamster cells, Yamada et al. (1993) investigated the effects of five organomercurial compounds (methylmercuric chloride, ethylmercuric chloride, phenylmercuric chloride, dimethylmercury, and diethylmercury) and found all to produce remarkable cytotoxicity. Fifty percent or more depression in the mitotic index was observed following treatment with methylmercuric chloride (2.5 µg/mL), ethylmercuric chloride (2.5 µg/mL), phenylmercuric chloride (1.25 µg/mL), and HgCl and $HgCl_2$ ($1.25 µg/mL). Post-treatment with methylmercuric chloride and ethylmercuric chloride increased the number of breakage and exchange-type aberrations induced by 4-nitroquinoline 1-oxide and methylmethane sulfonate but they did not show any clastogenic effects by themselves. Dimethylmercury, diethylmercury, mercurous chloride, and mercuric chloride did not show any potentiating effects. Following pretreatment with the 4-nitroquinoline 1-oxide or the DNA cross-linking agent mitomycin C, treatment with methylmercuric chloride during the G1 phase resulted in the enhancement of both breakage- and exchange-type aberrations. Ethylmercuric chloride treatment during the G1 phase also enhanced both types of aberrations induced by 4-nitroquinoline 1-oxide, but did not show any potentiating effect. When treatment was during the G2 phase, however, both methylmercuric chloride and ethylmercuric chloride enhanced breakage-type aberrations only. In the Yamada et al. (1993) study, the dialkyl mercury compounds dimethylmercury and diethylmercury did not show any cytotoxicity at 5–40 µg/mL, but they did cause a significant increase in the frequency of aberrant cells at the 40 µg/mL concentration. The authors of this study suggested three possible mechanisms for the observed potentiation of clastogenicity by monoalkylated mercurials: (1) they interfere with the repair of base lesions induced by 4-nitroquinoline 1-oxide and mitomycin C during the prereplication stage, thus increasing unrepaired DNA lesions that subsequently convert into DNA double-strand breaks in the S phase; (2) methylmercuric chloride (but not ethylmercuric chloride) inhibits the repair of cross-linking lesions during the prereplication stage; and (3) their G2 effects enhance breakage-type aberrations only. Yamada et al. (1993) concluded that because mercury compounds are known to react with protein thiol groups to inhibit protein activity, it is possible that they also inhibit some protein activities involved in the DNA repair process. The specific target protein for organomercurials and why the potentiation activities of methylmercury chloride and ethylmercury chloride differ remain to be identified.

There is a sizable database of studies investigating the DNA-damaging activity of mercuric chloride. The finding that mercuric chloride can damage DNA in rat and mouse embryo fibroblasts (Zasukhina et al. 1983), supports the *in vivo* evidence of species- and intraspecies-specific sensitivity to the genotoxic action of mercuric chloride. Marked conversion of DNA into the single-stranded form occurred at 10^{-6} M

mercuric chloride in rat fibroblasts, while 5×10^{-6} M mercuric chloride produced a comparable response in C57BL/6 mouse cells; at this level, the response in CBA mouse cells was marginal. Mercuric chloride can also bind to the chromatin of rat fibroblasts (Rozalski and Wierzbicki 1983) and Chinese hamster ovary cells (Cantoni et al. 1984a, 1984b; Christie et al. 1984, 1985). Using the alkaline elution assay with intact Chinese hamster ovary cells, several studies have demonstrated that mercuric chloride induces single-strand breaks in DNA (Cantoni and Costa 1983; Cantoni et al. 1982, 1984a, 1984b; Christie et al. 1984, 1985). Furthermore, Cantoni and Costa (1983) found that the DNA-damaging potential of mercuric chloride is enhanced by a concurrent inhibition of DNA repair mechanisms. Methylmercuric chloride induced single-strand breaks in the DNA of intact rat glioblastoma cells, Chinese hamster V79 (fetal lung) cells, human lung cells, and human nerve cells (Costa et al. 1991). Results of the *Bacillus subtilis* rec-assay (Kanematsu et al. 1980) and the sister chromatid exchange assay (Howard et al. 1991) provide additional support to the body of evidence suggesting that mercuric chloride is genotoxic. However, there is no clear evidence that mercury would cause DNA damage *in vivo*.

Two organic mercury compounds (methylmercury chloride at 0.08–0.4 µg Hg/mL and methoxyethyl mercury chloride at 0.04–0.23 µg Hg/mL) induced weak but dose-related mutagenic responses in Chinese hamster V-79 cells near the cytotoxic threshold (Fiskesjo 1979). Methylmercury was neither mutagenic nor caused recombination in *Saccharomyces cerevisiae*, but it did produce a slight increase in the frequency of chromosomal nondisjunction (Nakai and Machida 1973). Both methylmercury and phenylmercuric acetate induced primary DNA damage in the *B. subtilis* rec-assay (Kanematsu et al. 1980).

In contrast, high concentrations of methylmercury (1 or 2 µm) did not increase the frequency of sister chromatid exchanges in cultured blastocysts of early ICR mouse embryos (Matsumoto and Spindle 1982). Severe toxicity, which was more intense in blastocysts than in morulae, consisted of cessation of preimplantation development, blastocoel collapse, and mitotic delay.

In summary, the body of evidence showing the induction of primary DNA damage in mammalian and bacterial cells and weak mutagenesis in mammalian cells suggests that inorganic and organic mercury compounds have some genotoxic potential. Although the data on clastogenesis are less consistent, recent well conducted studies suggest that mercury compounds can be clastogenic. Refer to Table 2-12 for a further summary of these results.

Table 2-12. Genotoxicity of Mercury *In Vitro*

Species (test system	End point	Results: With activation	Results: Without activation	Reference
Inorganic Mercury Compounds				
Prokaryotic organisms:				
Salmonella typhimurium (TA1535, TA1537, TA98, TA102)	Gene mutation	–	–	Wong 1988
Bacillus subtilis (H17, M45)	DNA damage	NT	+	Kanematsu et al. 1980
Eukaryotic organisms: Mouse lymphoma cells L5178Y	Gene mutation	(+)	–	Oberly et al. 1982
Mouse embryo fibroblasts	DNA damage	NT	+	Zasukhina et al. 1983
Rat embryo fibroblasts	DNA damage	NT	+	Zasukhina et al. 1983
Chinese hamster ovary cells	Chromosome aberrations	NT	+	Howard et al. 1991
Chinese hamster ovary cells	Sister chromatid exchange	NT	+	Howard et al. 1991
Chinese hamster ovary cells	DNA damage	NT	+	Cantoni and Costa 1983
Chinese hamster ovary cells	DNA damage	NT	+	Cantoni et al. 1982, 1984a,b
Chinese hamster ovary cells	DNA damage	NT	+	Christie et al. 1984, 1986
Human KB cells	DNA damage	NT	+	Williams 1987
Rat embryo fibroblasts	Chromatin binding	NT	+	Rozalski and Wierzbicki 1983
Chinese hamster ovary cells	Chromatin binding	NT	+	Cantoni et al. 1984
Organic Mercury Compounds				
Prokaryotic organisms:				
B. subtilis (H17, M45)	DNA damage	NT	+	Kanematsu et al. 1980
Eukaryotic organisms:				
Early mouse embryos (blastocysts)	Sister chromatid exchange	NT	–	Matsumoto and Spindle 1982
Chinese hamster V79 cells	Gene mutation	NT	(+)	Fiskesjo 1979
Chinese hamster V79 cells	DNA damage	NT	+	Costa et al. 1991
Rat glioblastoma cells	DNA damage	NT	+	Costa et al. 1991
Saccharomyces cerevisiae	Gene mutation	NT	–	Nakai and Machida 1973

Table 2-12. Genotoxicity of Mercury *In Vitro* (continued)

Species (test system	End point	Results		Reference
		With activation	Without activation	
S. cerevisiae/intragenic and intergenic recombination	Recombination	NT	–	Nakai and Machida 1973
S. cerevisiae	Chromosome nondisjunction	NT	(+)	Nakai and Machida 1973
Human (peripheral lymphocytes)	Structural chromosome aberrations	NT	+	Betti et al. 1992
Human (peripheral lymphocytes)	Aneuploidy	NT	+	Betti et al. 1992
Human (nerve cells)	DNA damage	NT	+	Costa et al. 1991
Human (lung cells)	DNA damage	NT	+	Costa et al. 1991

(+) = weakly positive or marginal result; – = negative result; + = positive result; DNA = deoxyribonucleic acid; NT = not tested

Cancer. Mercury has not been determined to be carcinogenic in humans (Cragle et al. 1984; Kazantzis 1981). An excess of lung cancer (type not specified) was found in Swedish chloralkali workers, but these workers had also been exposed to asbestos (Barregard et al. 1990). A significant association between the farm use of mercury-containing fungicides and lymphocytic leukemia in cattle was presented by Janicki et al. (1987). However, this study is limited because exposure to other chemicals was not adequately addressed and risk estimates were not adjusted for other risk factors for leukemia.

Animal data, however, suggest that mercuric chloride, and methylmercuric chloride, phenylmercuric acetate are tumorigenic in rats and/or mice. In a 2-year NTP (1993) study, male Fischer 344 rats administered mercuric chloride by gavage had an increased incidence of squamous cell papillomas of the forestomach and an increased incidence of thyroid follicular cell carcinomas at 3.7 mg Hg/kg/day. There is equivocal evidence of carcinogenicity in female rats (a nonsignificant incidence of squamous cell papillomas) and in male $B6C3F_1$ mice (a nonsignificant incidence of renal tubule adenomas and carcinomas). Dietary exposure of ICR and $B6C3F_1$ mice to methylmercuric chloride resulted in significant increases in the incidences of renal epithelial cell adenomas and/or carcinomas in males at doses as low as 0.69–0.73 mg Hg/kg/day (Hirano et al. 1986; Mitsumori et al. 1981, 1990). Similar increases were not observed in females. Renal cell adenomas were also significantly increased in male Wistar rats that received 4.2 mg Hg/kg/day as phenylmercuric acetate in their drinking water (Solecki et al. 1991). This study is limited, however, because an insufficient number of animals were tested to adequately assess carcinogenicity.

Swiss mice were exposed for 15 weeks to drinking water containing methylmercuric chloride at concentrations of 0.038, 0.095, and 0.38 mg Hg/kg/day (Blakley 1984). Urethane (1.5 mg/g) was subsequently given intraperitoneally to the mice at week 3 of the study. Methylmercury exposures of 0.038 and 0.095 mg Hg/kg/day produced a significant increase in the incidence of urethane-induced pulmonary adenomas. The author suggested that methylmercury enhances the formation of pulmonary adenomas and that the immunosuppressive activity of methylmercury may be partially responsible for this tumor-enhancing effect. No other studies were located regarding carcinogenic effects in animals following oral exposure to mercury.

The Department of Health and Human Services (DHHS), and the International Agency for Research on Cancer (IARC) have not classified mercury as to its human carcinogenicity. The Environmental Protection Agency has determined that mercury chloride and methylmercury are possible human carcinogens.

More on Health Effects and Dental Amalgam.

A number of government sponsored scientific reviews of the literature on the health effects associated with the use of dental amalgam have concluded that the data do not demonstrate a health hazard for the large majority of individuals exposed to mercury vapor at levels commonly encountered from dental amalgam (DHHS 1993; Health Canada 1997). Governments that have restricted the use of amalgam or recommend limited use (e.g., Germany, Sweden, Denmark, and Canada) cite the need to minimize human exposure to all forms of mercury as much as possible and to reduce the release of mercury to the environment (DHHS 1993; Health Canada 1997). The restrictive actions, however are prospective, and none of the government reports recommend removing existing fillings in people who have no indication of adverse effects attributable to mercury exposure. Removal of existing amalgams, if improperly performed or not indicated, may result in unnecessarily high exposure to mercury. Levels of mercury release for various dental procedures have been reported by Eley (1997). Chelation therapy (used to remove metals from the body tissues) also may have adverse health effects (and varying levels of effectiveness), and should be considered only in consultation with a qualified physician.

In 1990 in the United States, over 200 million restorative procedures were provided of which dental amalgam accounted for roughly 96 million (DHHS 1993). In the 1970s, the use of amalgam was 38% higher. The use of mercury amalgam has been steadily declining and is expected to continue to decline due to improvements in dental hygiene and preventive care. Approximately 70% of the restorations placed annually are replacements. Advocates of the safety of amalgam emphasize the long history of use (over 150 years) and the large exposed population without apparent adverse effects as strong support for their position (ADA 1997). They also underscore the poor quality of the studies in the literature reporting adverse effects attributable to amalgam. Researchers concerned about the safety of mercury amalgams counter that sample sizes in the studies that support the safety of amalgams are also too small to detect low frequency effects in the general population, and that the absence of high quality studies simply reflects the relatively small amount of research effort that has gone into resolving this very important issue (Richardson 1995; Weiner et al. 1990).

The general public is also clearly concerned about the placement of mercury, a substance with demonstrated toxic effects, into their mouths. A survey conducted by the American Dental Association in 1991 demonstrated that nearly half of the 1,000 American adults surveyed believed that health problems could develop as a result of dental amalgam (ADA 1991). Increases in life expectancy and increases in the

numbers of older adults who still have their permanent teeth will result in longer mercury exposure durations from dental amalgam, which may result in new or increased severity of effects. Recent improvements in neurological measures of performance (especially cognitive and behavior tests) as well as immunological assays have also improved the ability to resolve more subtle or preclinical effects. In this context, DHHS (1993) and other summary reports on the health risks from the use of mercury amalgam generally support the need for further investigations.

Additional recommendations concerning the use of dental amalgam include minimizing exposure to populations susceptible to mercury toxicity including pregnant women and nursing women (to minimize the exposure to their developing young), young children up to the age of 6 (and especially up to the age of 3), people with impaired kidney function, and people with hypersensitive immune response to mercury. People who have higher than average exposures to mercury from other sources (e.g., people who consume large quantities of fish or who work in professions that expose them to mercury) should also consider their total mercury exposure in making their life style and health care decisions. In all cases, the choice not to use mercury amalgam should be made in consultation with a qualified dentists (and/or physician) and weighed against the risk of alternative practices and materials.

The DHHS (1993) report also strongly recommends educating the public on the risks and benefits of dental amalgam. To prevent misleading or unduly alarming the public, the layperson should be informed that the presence of metallic mercury in dental amalgams is, in itself, not sufficient to produce an adverse health effect. Toxic levels of mercury must first be released from the filling, absorbed into the body, and transported to target tissues where adverse effects are produced. What constitutes a “toxic level” from an amalgam exposure has been the focus of recent research. Uncertainty continues concerning the presence or absence of a threshold for adverse effects from low level chronic exposure to mercury. The above mentioned inadequacies in study size, the measures used for effects, the reproducibility of the results, and the subjective nature of some of the low level effects have precluded a consensus in the scientific community on the safety of mercury amalgam. In the absence of clearly defined toxicity from low level exposures, one approach has been to focus upon determining exposure levels from mercury amalgam, and whether these levels exceed recommended guidelines or regulations. Since these guidelines and regulations (including the MRL) are themselves extrapolated from the hazardous effects literature, there is some circularity in the argument that exposures of mercury from amalgam that exceed guidelines like the MRL (or other standard) “support” the position that mercury amalgams pose a health risk. This aspect of the

controversy will only be satisfactorily resolved with better toxicity and pharmacokinetic data for chronic low level mercury exposure from amalgams.

People who are concerned that their mercury exposure may be causing adverse effects can be tested for allergies to mercury or to other metals, or for the amount of mercury in their body. Tests that measure the amounts of mercury in hair and urine are available and provide some indication of the potential for adverse effects from mercury. For more information about the tests that are available, see Section 2.7, Biomarkers of Exposure and Effects.

The following studies supporting or refuting the adverse health effects from exposure to dental amalgam provide some examples from the recent literature of effects being evaluated and the procedures that are being used. Some of the studies depend upon the self-reporting of symptoms or may be weakly blinded (i.e., the patients were not completely unaware of the assignment to different exposure groups) which could bias the outcome, especially with respect to some of the end points. An exhaustive analysis of the results presented below, however, is beyond the scope of this profile, and the reader is referred to the cited references for a more complete discussion of the issues concerning the potential adverse effects from exposure to dental amalgam.

Studies reporting no association between adverse effects and mercury amalgam.

Berglund and Molin (1996) evaluated whether a group of patients with symptoms, self-related to their amalgam restorations, experienced an exposure to mercury vapor from their amalgam restorations that reached the range at which subtle symptoms have been reported in the literature. They further evaluated whether the mercury exposure for these patients was significantly higher than for controls with no reported health complaints. The symptom group consisted of 10 consecutively selected patients from a larger group. The larger group consisted of patients who were referred by their physicians for an investigation of a correlation between subjective symptoms and amalgam restorations. The control group consisted of 8 persons with no reported health complaints. The intra-oral release of mercury vapor was measured between 7:45 a.m. and 9:00 p.m. at intervals of 30–45 minutes, following a standardized schedule. The mercury levels in plasma, erythrocytes, and urine were also determined. The calculated daily uptake of inhaled mercury vapor, released from the amalgam restorations, was less than 5% of the daily uptake calculated at the lower concentration range given by the WHO (1991), at which subtle symptoms have been found in particularly sensitive individuals. The symptom group had neither a higher estimated daily uptake

of inhaled mercury vapor nor a higher mercury concentration in blood and urine than in the control group. The study provided no scientific support for the belief that the symptoms of the patients examined originated from an enhanced mercury release from their amalgam restorations.

Bagedahl-Strindlund et al. (1997) evaluated Swedish patients with illnesses thought to be causally related to mercury release during dental restorations, and mapped the psychological/psychiatric, odontological, and medical aspects of the patients and their purportedly mercury-induced symptoms. A total of 67 consecutive patients and 64 controls matched for age, sex, and residential area were included in the study. Questionnaires were completed and a semi-structured psychiatric interview performed. The Comprehensive Psychopathological Rating Scale was used to record psychopatholgical symptoms. The Karolinska Scales of Personality (KSP) set was used to assess personality traits. The Toronto Alexithymia Scale and the Schalling-Sifneos Personality Scale were completed. The Whitely Index was used to assess hypochondriacal attitudes. The type and number of amalgam-filled surfaces was determined. The most striking result was the high prevalence of psychiatric disorders (predominantly somatoform disorders) in the patients (89%) compared to the controls (6%). The personality traits differentiating the patients according to the Karolinska Scales of Personality were somatic anxiety, muscular tension, psychasthenia, and low socialization. More patients than controls showed alexithymic traits. The prevalence of diagnosed somatic diseases was higher, but not sufficiently so to explain the large difference in perceived health. The multiple symptoms and signs of distress displayed by the patients could not be explained either by the odontological data or by the medical examination. These data indicate that the patients show sociodemographic and clinical patterns similar to those of somatizing patients. The number of amalgam-filled surfaces did not differ significantly between patients and controls; 19% of the patients lacked amalgam fillings.

Grandjean et al. (1997a) evaluated the effects of chelation therapy versus a placebo on patient improvement for patients who attribute their environmental illness to mercury from amalgam fillings. Succimer (meso-2, 3-dimercaptosuccinic acid) was given at a daily dose of 30 mg/kg for 5 days in a double-blind, randomized placebo-controlled trial. Treatment of patients who attribute their environmental illness to mercury from amalgam fillings is largely experimental. On the Symptom Check List, overall distress, and somatization, obsessive-compulsive, depression, and anxiety symptom dimensions, were increased in 50 consecutive patients examined, and Eysenck Personality Questionnaire scores suggested less extroversion and increased degree of emotional lability. Urinary excretion of mercury and lead was considerably increased in the patients who received the chelator. Immediately after the treatment and 5–6 weeks later, most distress

dimensions had improved considerably, but there was no difference between the succimer and placebo groups. These findings suggest that some patients with environmental illness may substantially benefit from placebo.

Stoz et al. (1995) studied 185 mothers with tooth amalgam filling surfaces ranging from 0 to 780 mm^2 and found no relationship between the blood values of the women and their children and the size of the surfaces of the amalgam fillings. All mothers gave birth to healthy children. Malt et al. (1997) evaluated the physical and mental symptomatology of 99 self-referred adult patients complaining of multiple somatic and mental symptoms attributed to dental amalgam fillings. These patients were compared with patients with known chronic medical disorders seen in alternative (n=93) and ordinary (n=99) medical family practices and patients with dental amalgam fillings (n=80) seen in an ordinary dental practice. The assessments included written self-reports, a 131-item somatic symptom checklist, Eysenck Personality Questionnaire, the General Health Questionnaire, and Toronto Alexithymia Scale. Somatic symptom complaints were categorized by exhaustion, and musculoskeletal, cardiovascular, and gastrointestinal effects. The mean number of silver fillings surfaces were 40.96 in self-referrents as compared to 36.61 in the dental practice patients. No correlation between number of dental fillings and symptomatology was found. Self-reports suggested that 62% suffered from chronic anxiety. Forty-seven percent suffered from major depression compared with none in the dental control sample. Symptoms suggesting somatization disorder were found in 29% of the dental amalgam sample compared with only one subject in the 272 comparison subjects; 37.5% of the dental amalgam patients reported symptoms of chronic fatigue syndrome compared with none in the dental control sample and only 2 and 6%, respectively, in the two clinical comparison samples. The dental amalgam group reported higher mean neuroticism and lower lie scores than the comparison groups. The authors concluded that self-referred patients with health complaints attributed to dental amalgam are a heterogeneous group of patients who suffer multiple symptoms and frequently have mental disorders. The authors report a striking similarity with the multiple chemical sensitivity syndrome.

An ad hoc review group of the DHHS Working Group on Dental Amalgam examined 175 literature articles concerning mercury amalgam (DHHS, 1997). The articles represented an assortment of literature from peer-reviewed journals and a variety of other print media. None of the 12 expert reviewers evaluating the articles suggested that any study under review would indicate that individuals with dental amalgam restorations would experience adverse health effects. Many of the reviewed articles were reported to suffer from inadequacy of experimental control, lack of dose-response information, poor measurement of exposure, and a variety of other experimental design inadequacies.

Studies that report an association between dental amalgam and adverse effects.

Echeverria et al. (1995) evaluated the behavioral effects of low-level exposure to Hg among dentists who had either been exposed to mercury or not as measured in a selection procedure where the exposed group was defined as those with urinary mercury levels greater than 19 µg/L. Exposure thresholds for health effects associated with elemental mercury exposure were examined by comparing behavioral test scores of 19 exposed (17 males, 2 females) with those of 20 unexposed dentists (14 males, 6 females). The mean urinary Hg of exposed dentists was 36.4 µg/L, which was 7 times greater than the 5 µg Hg/L mean level measured in a national sample of dentists (urinary Hg was below the level of detection in unexposed dentists for this study). To improve the distinction between recent and cumulative effects, the study also evaluated porphyrin concentrations in urine, which are correlated with renal Hg content (a measure of cumulative body burden). Significant urinary Hg dose-effects were found for poor mental concentration, emotional lability, somatosensory irritation, and mood scores (tension, fatigue, confusion). Individual tests evaluating cognitive and motor function changed in the expected directions but were not significantly associated with urinary Hg. However, the pooled sum of rank scores for combinations of tests within domains were significantly associated with urinary Hg, providing evidence of subtle preclinical changes in behavior associated with Hg exposure. Coproporphyrin, one of three urinary porphyrins altered by mercury exposure, was significantly associated with deficits in digit span and simple reaction time. Exposed dentists placed significantly more amalgams per week (28.0) than unexposed dentists (19.8). No significant differences were found between exposed and unexposed dentists for the overall number of years in practice or the number of amalgams removed per week.

Altmann et al. (1998) compared visual functions in 6-year-old children exposed to lead and mercury levels, in a cohort of 384 children (mean age 6.2 years) living in three different areas of East and West Germany. After adjusting for confounding effects, statistically significant lead-related changes were found only for some of the visually evoked potentials (VEP) interpeak latencies, while some of the contrast sensitivity values were significantly reduced with increasing mercury concentrations. All other outcome variables were not significantly related to lead or mercury levels. The authors concluded that even at blood lead levels in the range of 14–174 µg/L and at very low urinary mercury levels subtle changes in visual system functions can be measured. The geometric means of urinary mercury concentrations were 0.161, 0.203, and 0.075 µg Hg/24 hours for subjects of the three study areas (0.157 µg Hg/24 hours for the total study); the average numbers of amalgam fillings were 0.76, 1.10, and 1.88, respectively (1.15 amalgam fillings for the total study).

Siblerud and Kienholz (1997) investigated whether mercury from silver dental fillings (amalgam) may be an etiological factor in multiple sclerosis (MS). Blood findings were compared between MS subjects who had their amalgams removed (n=50) and MS subjects with amalgams (n=47). All subjects filled out a health survey, an MS health questionnaire, and a psychological profile; the MS amalgam removal group completed a health questionnaire comparing their health before and after amalgam removal. MS subjects with amalgams were found to have significantly lower levels of red blood cells, hemoglobin, and hematocrit compared to MS subjects with amalgam removal. Thyroxine (T-4) levels were also significantly lower in the MS amalgam group, which had significantly lower levels of total T-lymphocytes and T-8 (CD8) suppressor cells. The MS amalgam group had significantly higher blood urea nitrogen (BUN) and BUN/creatinine ratio, and lower serum IgG. Hair mercury was significantly higher in the MS subjects compared to the non-MS control group (2.08 versus 1.32 ppm). A health questionnaire found that MS subjects with amalgams had significantly more (33.7%) exacerbations during the past 12 months compared to the MS volunteers with amalgam removal: 31% of MS subjects felt their MS got better after amalgam removal, 7% felt it was eliminated, 33% felt no change, and 29% believed the condition got worse. In addition, 17% of the MS with amalgam group had more neuromuscular symptoms compared to the amalgam removal group.

Björkman et al. (1997) examined the mercury concentrations in saliva, feces, urine, whole blood, and plasma before and after removal of dental amalgam fillings in 10 human subjects. Before removal, the median mercury concentration in feces was more than 10 times higher than in samples taken from an amalgam-free reference group of 10 individuals. Two days following removal of all amalgams, a considerable increase in mercury appeared in the feces. This initial increase was followed by a significant decrease. In saliva, there was an exponential decline in the mercury concentration during the first 2 weeks after amalgam removal ($t_{1/2}$ of 1.8 days). The authors concluded that while mercury amalgam fillings are a significant source of mercury in saliva and feces, those levels decrease considerably following amalgam removal. Further, the gastrointestinal uptake of mercury seen in conjunction with removal of amalgam fillings appears to be low. Of 108 patients (all with amalgam dental fillings) presenting to an environmental toxicology service, the average salivary mercury level was 11 µg/L (range, <1–19 µg/L) before chewing and 38 µg/L (range, 6–500 µg/L) after chewing. Six of the 108 patients had salivary mercury concentrations >100 µg/L. Of 58 patients with suspected allergic disease, an epicutaneous test for amalgam was positive in 32 of them; however, direct involvement of dental amalgams in these sensitivities was not mentioned. Seventy-five of the total patients presenting with symptoms felt that amalgam fillings

or other dental materials were responsible, at least in part, for their symptoms, although no causal relationship was borne out by medical evaluation.

Bratel et al. (1996) investigated (1) healing of oral lichenoid reactions (OLR) following the selective replacement of restorations of dental amalgam, (2) whether there were differences in healing between contact lesions (CL) and oral lichen planus (OLP), and (3) whether there was a difference in healing potential when different materials were selected as a substitute for dental amalgam. Patients included in the study presented with OLR confined to areas of the oral mucosa in close contact with amalgam restorations (CL; n=142) or with OLR which involved other parts of the oral mucosa as well (OLP; n=19). After examination, restorations of dental amalgam which were in contact with OLR in both patient groups were replaced. The effect of replacement was evaluated at a follow-up after 6–12 months. In the CL group, the lesions showed a considerable improvement or had totally disappeared in 95% of the patients after replacement of the restorations of dental amalgam (n=474). This effect was paralleled by a disappearance of symptoms, in contrast to patients with persisting CL (5%) who did not report any significant improvement. The healing response was not found to correlate with age, gender, smoking habits, subjective dryness of the mouth or current medication. However, the healing effect in patients who received gold crowns was superior than in patients treated with metal-ceramic crowns (MC) ($p<0.05$). In the OLP group (n=19), 63% of the patients with amalgam-associated erosive and atrophic lesions showed an improvement following selective replacement. OLP lesions in sites not in contact with amalgams were not affected. Most of the patients (53%) with OLP reported symptoms also after replacement. From these data the authors conclude that in the vast majority of cases, CL resolves following selective replacement of restorations of dental amalgam, provided that a correct clinical diagnosis is established. The authors note that MC crowns did not facilitate healing of CL to the same extent as gold crowns.

Hultman et al. (1994) studied the effects of dental amalgams in in-bred mice genetically susceptible to mercury-induced immunotoxic effects. Following intraperitoneal implantation of a silver amalgam and observation for up to 6 months, chronic hyperimmunoglobulinemia, serum IgG autoantibodies targeting the nucleolar protein fibrillarin, and systemic immune-complex deposits developed in both a time- and dose-dependent manner. The functional capacity of splenic T- and B-cells was affected in a dose-dependent fashion. In this study, not only did the dental amalgam implantation cause chronic stimulation of the immune system with induction of systemic autoimmunity, but the implantation of silver alloy not containing mercury also induced autoimmunity, suggesting that other metals have the potential to induce autoimmunity in that genetically susceptible strain of mice. Accumulation of heavy metals from dental amalgams, as well

as from other sources, may lower the threshold of an individual metal to elicit immune aberrations, which could lead to overt autoimmunity.

2.6 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996).

Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

Adverse health effects from different forms of mercury differ primarily because of differences in kinetics rather than mode of action. As discussed in the introduction to this section, children have different, and sometimes dramatically different, morphology or physiology that alters the way toxic compounds are absorbed and distributed throughout their bodies. For mercury compounds, preventing entry into the systemic circulation is the best means to prevent adverse effects. Once mercury enters the circulation, the tissues that end up as target sites are those that accumulate the most mercuric ion or the ones that are most often exposed to mercuric ion. That is why the kidney is a prime target site, for in fulfilling its major role of filtering and purifying the blood, the kidney is continually exposed to ionic mercury. The central nervous system is a major target site because mercuric ion also concentrates in the brain compartment. Ironically, it may be the blood-brain barrier that contributes to, rather than prevents, mercuric ion "trapping" in the brain. A current hypothesis is that once lipophilic forms of mercury cross the blood-brain barrier, they are oxidized to more hydrophilic species and become trapped inside the brain compartment. This "one way" only kinetic pathway results in continually increasing brain mercuric ion levels, as long as nonpolar forms are in the blood stream. Even small amounts of nonpolar mercury (<2 g) in the body may eventually lead to central nervous system damage (Neirenberg et al. 1998). The low capacity for central nervous system tissues to regenerate and the fact that even subtle damage to small areas of the brain can have profound overall effects, makes this tissue very susceptible to the highly toxic mercuric ion. These factors, and a slow but inevitable trapping of mercuric ions may lead to the mercury-induced delayed central nervous system toxicity observed months to years after exposure ceases (Neirenberg et al. 1998, Rice 1996a). Even potent chelators have not been effective in interfering with progressive central nervous

system damage once a nonpolar mercury compound gains access to the circulatory system and begins to concentrate in tissues (Neirenberg et al. 1998, Taueg et al. 1992).

For similar routes and forms of mercury, the adverse health effects seen in children are similar to the effects seen in adults. For example, a young child who was intoxicated with mercury vapor, died of pulmonary edema and had a grayish, necrotic mucosa of the stomach and duodenum (Campbell 1948). These effects are similar to those seen in adult populations occupationally exposures to inhaled metallic mercury vapors. Respiratory effects in adults from inhalation of metallic mercury vapor include pulmonary edema, lobar pneumonia, fibrosis, desquamation of the bronchiolar epithelium, and death in severe cases due to respiratory failure (Gore and Harding 1987; Jaffe et al. 1983; Kanluen and Gottlieb 1991; Matthes et al. 1958; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961).

The majority of the information regarding cardiovascular effects comes from reports of children who were treated with mercurous chloride tablets for worms or mercurous chloride-containing powders for teething discomfort (Warkany and Hubbard 1953). These authors described multiple cases in which tachycardia and elevated blood pressure were observed in the affected children.

Electrocardiography in four family members who ate meat from a hog that had consumed seed treated with ethylmercuric chloride showed abnormal heart rhythms (ST segment depression and T wave inversion) (Cinca et al. 1979). Death of the two children in the family was attributed to cardiac arrest, and autopsy of these boys showed myocarditis. Cardiovascular abnormalities were also observed in severe cases of poisoning in the Iraqi epidemic of 1956, when widespread poisoning resulted from eating flour made from seed grains treated with ethylmercury *p*-toluene sulfonanilide (Jalili and Abbasi 1961). These abnormalities included irregular pulse, occasionally with bradycardia, and electrocardiograms showing ventricular ectopic beats, prolongation of the Q-T interval, depression of the S-T segment, and T inversion.

Several children who were treated with mercurous chloride for constipation, worms, or teething discomfort had swollen red gums, excessive salivation, anorexia, diarrhea, and/or abdominal pain (Warkany and Hubbard 1953). They also experienced muscle twitching or cramping in the legs and/or arms, but these muscular effects were probably secondary to changes in electrolyte balance (i.e., potassium imbalance due to fluid loss or renal wasting).

Acute renal failure that persisted for 10 days was observed in a 19-month-old child who ingested an unknown amount of powdered mercuric chloride (Samuels et al. 1982). Several children who were treated with medications containing mercurous chloride for constipation, worms, or teething discomfort exhibited flushing of the palms of the hands and soles of the feet (Warkany and Hubbard 1953). The flushing was frequently accompanied by itching, swelling, and desquamation of these areas. Morbilliform rashes, conjunctivitis, and excessive perspiration were also frequently observed in the affected children. Patch tests conducted in several children revealed that the rashes were not allergic reactions to the mercury. They also had irritability, fretfulness, sleeplessness, weakness, photophobia, muscle twitching, hyperactive or hypoactive tendon reflexes, and/or confusion.

A 13-month-old child who ingested porridge made from flour that had been treated with an alkyl mercury compound (specific mercury compound not reported) developed a measles-like rash, fever, and facial flushing (Engleson and Herner 1952). A 4-year-old boy who had been given a Chinese medicine containing mercurous chloride for 3 months developed drooling, dysphagia, irregular arm movements, and impaired gait (Kang-Yum and Oransky 1992). A number of children who were treated with an ammoniated mercury ointment or whose diapers had been rinsed in a mercuric chloride solution experienced tachycardia and elevated blood pressure, and anorexia (Warkany and Hubbard 1953).

In addition, rashes, conjunctivitis, and/or excessive perspiration were observed. These dermal and ocular reactions were not attributed to allergic-type reactions to the mercury. A 23-month-old boy who was exposed to an unspecified form of mercury also developed a "diffuse, pinpoint, erythematous, papular rash" and bright red finger tips "with large sheets of peeling skin" (Tunnessen et al. 1987).

A woman chronically exposed to an undetermined concentration of mercury vapor reported that her first pregnancy resulted in spontaneous abortion, and her second resulted in the death of the newborn soon after birth (Derobert and Tara 1950). It is unclear whether the reproductive toxicity experienced by the woman was due to the mercury exposure. However, after recovery from overt mercury poisoning, she gave birth to a healthy child. Not all exposures lead to immediate adverse effects. A woman occupationally exposed to mercury vapors for 2 years prior to pregnancy and throughout pregnancy was reported to have delivered a viable infant at term (Melkonian and Baker 1988). Urinary mercury in the woman at 15 weeks of pregnancy was 0.875 mg/L (normal levels are approximately 0.004 mg/L). A case report of a woman exposed to mercury vapors in her home during the first 17 weeks of pregnancy reported that the woman delivered a normal child who met all developmental milestones (although the child was not formally tested

for psychological development) (Thorpe et al. 1992). Mercury exposure was not measured, but the child was born with hair levels of 3 mg/kg (3 ppm) of mercury. This hair level was comparable to that observed in populations consuming fish once a week (WHO 1990) and suggests that exposure in this case may have been relatively low.

In the *in vivo* study by Sager et al. (1982), it was concluded that methylmercury may be acting on mitotic spindle microtubules leading to cell injury in the developing cerebellar cortex. Cell injury observed in the external granular layer of the cerebellar cortex of 2-day-old rats was attributed to a reduced percentage of late mitotic figures (arrested cell division) due to the loss of spindle microtubules. Mitosis and migration of granule cells in the cerebellum end within weeks following birth; therefore, this observation may suggest potential differences in the sensitivities of children and adults to mercury-induced neurotoxicity.

Regardless of whether mercury exposure is through inhalation of mercury vapors, ingestion of organic mercury or mercury salts, or dermal application of mercury-containing ointments, patients (primarily children) may exhibit a syndrome known as acrodynia, or pink disease. Acrodynia is often characterized by severe leg cramps; irritability; and erythema and subsequent peeling of the hands, nose, and soles of the feet. Itching, swelling, fever, tachycardia, elevated blood pressure, excessive salivation or perspiration, morbilliform rashes, fretfulness, sleeplessness, and/or weakness may also be present. It was formerly thought that this syndrome occurred exclusively in children, but recent reported cases in teenagers and adults have shown that these groups are also susceptible.

Developmental effects from prenatal or postnatal exposures to mercury are unique to children. During critical periods of structural and functional development in both prenatal and postnatal life, children are especially vulnerable to the toxic effects of mercury. Inhalation exposures are relatively rare outside of the occupational setting so the exposure route and form of mercury most commonly associated with a risk for development effects is the ingestion of methylmercury on the surface of contaminated foods (methylmercury used as a fungicide on seed grain) or accumulated within the food (methylmercury in fish, wild game, and marine mammals). The exposure route and form of mercury most commonly associated with maternal exposures is to foods contaminated with methylmercury fungicides (Bakir et al. 1973) or foods that contain high levels of methylmercury (Grandjean et al. 1997b, 1998; Tsubaki and Takahashi 1986).

The first such incident was reported in Sweden in 1952 when flour from grain treated with an unspecified alkyl mercury compound ingested by a pregnant woman was associated with developmental toxicity. An

apparently normal infant was born, but the infant later displayed brain damage manifested by mental retardation, incoordination, and inability to move (Engleson and Herner 1952). A 40-year-old woman, 3 months pregnant, consumed methylmercury-contaminated meat for an unspecified duration and subsequently delivered a male infant with elevated urinary mercury levels (Snyder and Seelinger 1976). At 3 months, the infant was hypotonic, irritable, and exhibited myoclonic seizures. At 6 years of age, the child displayed severe neurological impairment (e.g., blindness, myoclonic seizures, neuromuscular weakness, inability to speak) (Snyder and Seelinger 1976).

Another incidence of neurodevelopmental effects occurring as a result of *in utero* exposure to methylmercury was reported by Cox et al. (1989) and WHO (1990). The effect of concern was the delayed onset of walking in offspring in Iraqi children whose mothers were exposed to methylmercury through the consumption of seed grain treated with methylmercury as a fungicide (Al-Mufti et al. 1976; Bakir et al. 1973; Cox et al. 1989; Marsh et al. 1981, 1987).

A New Mexico family, including a pregnant woman, a 20-year-old female, and 2 children (a 13-year-old male and an 8-year-old female) ate meat from a hog inadvertently fed seed grain treated with a fungicide containing methylmercury and experienced severe, delayed neurological effects (Davis et al. 1994). Several months after the exposures, the children developed symptoms of neurological dysfunction. The newborn child of the exposed mother showed signs of central nervous system disorder from birth. Twenty-two years after the 3-month exposure period, the people who were 20 and 13 years old at time of exposure had developed cortical blindness or constricted visual fields, diminished hand proprioception, choreoathetosis, and attention deficits. MRI examination of these two revealed residual brain damage in the calcarine cortices, parietal cortices, and cerebellum. The brain of the person who was exposed at age 8 (who died of aspiration pneumonia with a superimposed *Klebsiella* bronchopneumonia and sepsis at age 29) showed cortical atrophy, neuronal loss, and gliosis, most pronounced in the paracentral and parieto-occipital regions. Regional brain mercury levels correlated with the extent of brain damage. The youngest (*in utero* at the time of exposure) developed quadriplegia, blindness, severe mental retardation, choreoathetosis, and seizures, and died at age 21. Since inorganic mercury crosses the blood-brain barrier poorly, biotransformation of the methylmercury to inorganic mercury may have occurred after the methylmercury crossed the blood-brain barrier, accounting for its observed persistence in the brain and its possible contribution to the brain damage.

More recently, Grandjean et al. (1997b, 1998) evaluated a cohort of 1,022 consecutive singleton births generated during 1986–1987 in the Faroe Islands. Increased methylmercury exposure from maternal consumption of pilot whale meat was indicated by mercury concentrations in cord blood and maternal hair. Neurophysiological tests emphasized motor coordination, perceptual-motor performance, and visual acuity; pattern reversal visual evoked potentials (VEP) with binocular full-field stimulation, brain stem auditory evoked potentials (BAEP), postural sway, and the coefficient of variation for R-R interpeak intervals (CVRR) on the electrocardiogram were measured. Clinical examination and neurophysiological testing did not reveal any clear-cut mercury-related abnormalities. However, mercury-related neuropsychological dysfunctions were most pronounced in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions. These associations remained after adjustment for covariates and after exclusion of children of mothers with maternal hair mercury concentrations above 10 μg/g (50 nmol/g). The effects on brain function associated with prenatal methylmercury exposure appear widespread, and early dysfunction is detectable at exposure levels currently considered safe.

There are differences in the outcomes of these epidemiology studies on low level chronic exposures to methylmercury in foods. Davidson et al. (1998) report no adverse developmental effects associated with prenatal and postnatal exposure to methylmercury in fish in a Seychelles Island cohort of children at age 66 months (n=708). The exposure levels are reflected in maternal hair levels of 6.8 ppm for the prenatal exposure (SD=4.5, n=711) and children's hair levels of 6.5 ppm (SD=3.3, n=708) for both the prenatal and subsequent postnatal exposure. The age-appropriate main outcome measures included: (1) the McCarthy Scales of Children's Abilities, (2) the Preschool Language Scale, (3) the Woodcock-Johnson Tests of Achievement - Letter and Word Recognition, (4) Woodcock-Johnson Tests of Achievement - Applied Problems and, (5) the Bender Gestalt test, and (6) the Child Behavior Checklist. The test results were similar to what would be expected from a healthy, well-developing U.S. population. No test indicated a deleterious effect of methylmercury from the exposure levels received in this population. Four of the six measures showed better scores in the highest MeHg groups compared with lower groups for both prenatal and postnatal exposure. This result is likely due to the benefits of increased levels of fish in the diet, possibly because of increased consumption of omega-3-fatty acids. Serum from a subset of 49 of the children was sampled for polychlorinated biphenyl levels (PCBs). None of the samples had detectable levels (detection limit 0.2 ng/mL) for any of the 28 congeners assayed (from congener 28 to 206) indicating that was no concurrent (i.e, potentially confounding) exposure to PCBs in this population. The median level of total mercury for each of 25 species sampled was 0.004–0.75 ppm, with most medians in the range of 0.05–0.25 ppm, levels that are comparable to fish in the U.S. market. The authors conclude that this

most recent NOAEL of 6.8 ppm for the Seychelles cohort at 66 months of age strongly supports the findings at earlier ages, and that the benefits of eating fish outweigh the small risk of adverse effects from an increased exposure to methylmercury for this exposure pathway.

The differences in these studies highlight the importance of interpreting epidemiology results and, indeed, all study results on mercury toxicity within a fairly comprehensive context of the numerous factors that might affect the toxicokinetics and the amount absorbed (e.g., form of mercury, route of exposure, age, diet of population exposed, health status, other potential sources of exposure to mercury, dose duration, constancy of dose amount over time, etc.)

A route of exposure unique to children is breast milk. Both organic and inorganic mercury can move into breast milk from a nursing woman's body, and children will readily absorb this mercury. Oskarsson et al. (1996) assessed the total and inorganic mercury content in breast milk and blood in relation to fish consumption and amalgam fillings (an exposure source for older children). Total mercury concentrations were evaluated in breast milk, blood, and hair samples collected 6 weeks after delivery from 30 lactating Swedish women. In breast milk, about half of the total mercury was inorganic and half was methylmercury, whereas in blood only 26% was inorganic and 74% was methylmercury. That is because, unlike the placental barrier, which is crossed more easily by methylmercury than by inorganic mercury, inorganic mercury moves more easily into breast milk. Some researchers think that a carrier mediated process is involved (Sundberg et al 1998).

For the Swedish population in the study, Oskarsson et al. (1996) reports that there was an efficient transfer of inorganic mercury from blood to breast milk and that mercury from amalgam fillings was probably the main source of mercury in breast milk, while methylmercury levels in blood did not appear to be efficiently transferred to breast milk . Exposure of the infant to mercury in breast milk was calculated to range up to 0.3 µg/kg/day of which approximately one-half was inorganic mercury. This exposure corresponds to approximately one-half the tolerable daily intake of total mercury for adults recommended by the World Health organization. The authors concluded that efforts should be made to decrease total mercury burden in women of reproductive age Oskarsson et al. (1996).

The metabolism of mercury is relatively straightforward compared, for example, to pesticides or some organic solvents. No information was identified to indicate that metabolic pathways are different for children and adults, or that children have unique metabolites. Once absorbed, metallic and inorganic

mercury enter an oxidation-reduction cycle. Metallic mercury is oxidized to the divalent inorganic cation in the red blood cells and lungs of humans and animals. Evidence from animal studies suggests the liver as an additional site of oxidation. Absorbed divalent cation from exposure to mercuric mercury compounds can, in turn, be reduced to the metallic or monovalent form and released as exhaled metallic mercury vapor. In the presence of protein sulfhydryl groups, mercurous mercury (Hg^{+}) disproportionates to one divalent cation (Hg^{+2}) and one molecule at the zero oxidation state (Hg^{0}). The conversion of methylmercury or phenylmercury into divalent inorganic mercury can probably occur soon after absorption, also feeding into the oxidation-reduction pathway.

A number of good physiologically based pharmacokinetic models are currently available for mercury, including some that address developmental toxicity and maternal/fetal transfer. Two models were constructed based upon data from the kinetics of methylmercury in rats. Farris et al. (1993) developed a PBPK model that simulates the long-term disposition of methylmercury and its primary biotransformation product, mercuric mercury, in the male Sprague-Dawley rat following a single oral nontoxic exposure. Gray (1995) developed a PBPK model that simulates the kinetics of methylmercury in the pregnant rat and fetus. The Gray model was developed to provide fetal and maternal organ methylmercury concentration-time profiles for any maternal dosing regimen. Sundberg et al. (1998) fitted a three compartment model to the elimination kinetics of methylmercury and inorganic mercury transfer to milk in lactating and nonlactating mice. Luecke et al. (1997) developed a model based on human physiology but extended to simulate animal data that depict internal disposition of two chemicals (singly or in combination) during pregnancy in the mother and the embryo/fetus. Leroux et al. (1996) developed a biologically based-dose-response model to describe the dynamics of organogenesis, based on the branching process models of cell kinetics. Gearhart et al. (1995) developed a PBPK model to coherently describe methylmercury pharmacokinetics in a variety of species (adult rat, monkey, and human), and to predict fetal levels of methylmercury from an i*n utero* exposure.

No information was identified on biomarkers of exposure for children. Mercury levels in hair, urine, and blood are the standard measures of exposure. There are biomarkers for developmental effects that are unique to specific ages and stages of development throughout the child's developmental process. Developing the best measures for evaluation of cognitive functions is an area of intense debate and on-going research.

Concerning interactions with other chemicals, there is an ongoing debate about the value of fish in the diet versus the risk from increased exposure to methylmercury that may be in the fish. One recent study reported a beneficial effect from increased fish consumption even though mercury body burdens were increased to some extent (Davidson et al. 1998). One possible factor in the fish that could improve health is omega 3-fatty acid. Children and adults both benefit from a healthy diet, but there may more emphasis on the benefits to growing children. Other interactions for mercury include the effect of various substances on its gastrointestinal absorption (e.g., iron, zinc) or possibly protective effects from prevention or repair of mercury related oxidative damage (e.g., interactions with selenium as an antioxidant). No information was identified that specifically addresses differences in these interactions for children compared to adults.

The methods used to reduce peak absorption and to reduce body burdens in exposed adults (i.e., chelation therapy) are also used for exposures in children.

No information was identified on parental exposures affecting children in areas of parental germ cells or germ line mutations. The topic of exposure pathways for mercury via nursing or pregnant women who have been exposed is of main concern and has been addressed earlier in this section.

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biological systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s), that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biological half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed

to hazardous substances that are commonly found in body tissues and fluids (essential mineral nutrients [e.g., copper, zinc, and selenium]). Biomarkers of exposure to mercury are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiological, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathological changes in female genital epithelial cells), as well as physiological signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but they can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by mercury are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a pre-existing disease that results in an increase in the absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8 (Populations That Are Unusually Susceptible).

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Mercury

Blood and urine mercury concentrations are commonly used as biomarkers of exposure to mercury. Hair has been used as a biomarker of exposure to methylmercury. Occupational studies show that recent mercury exposure is reflected in blood and urine (Naleway et al. 1991; WHO 1991). However, at low exposure levels (<0.05 mg Hg/m^3), correlation to blood or urine mercury levels is low (Lindstedt et al. 1979). Blood levels of mercury peak sharply during and soon after short-term exposures, indicating that measurements should be made soon after exposure (Cherian et al. 1978). The specific time frame at which measurements become less reliable has not been determined. Workers exposed for a chronic duration, however, may have a high body burden of mercury, therefore, mercury levels would probably still be elevated in the urine and blood for a long period of time after cessation of exposure (Lindstedt et al. 1979). The following discussion of blood and urine mercury levels generally refers to measurements taken immediately or within a few days following the last exposure.

The mean total mercury levels in whole blood and urine of the general population are approximately 1–8 µg/L and 4–5 µg/L, respectively (Gerhardsson and Brune 1989; WHO 1990). Recently, the International Commission on Occupational Health (ICOH) and the International Union of Pure and Applied Chemistry (IUPAC) Commission on Toxicology determined that a mean value of 2 µg/L was the background blood level of mercury in persons who do not eat fish (Nordberg et al. 1992). These blood and urine levels are "background" in the sense that they represent the average levels in blood in the general population and are not associated with a particular source for mercury. However, the intra- and inter-individual differences in these biomarkers are substantial, possibly due to dental amalgams (urine) and ingestion of contaminated fish (blood) (Verschoor et al. 1988; WHO 1991). Long-term consumption of fish is the source of nearly all of the methylmercury measured in the general population, and individuals in communities with high fish consumption rates have been shown to have blood levels of 200 µg/L, with daily intake of 200 µg mercury (WHO 1990). However, acute inhalation exposure to low levels of metallic mercury resulted in much lower levels in the blood (0.028 and 0.18 µg/100 mL) and urine (from 94 to >438 µg/L) (Kanluen and Gottlieb 1991; Rowens et al. 1991).

Urine mercury measurement is reliable and simple, and it provides rapid identification of individuals with elevated mercury levels (Naleway et al. 1991). It is a more appropriate marker of inorganic mercury, because organic mercury represents only a small fraction of urinary mercury. Yoshida (1985) found that urinary mercury levels were better correlated with exposure than were blood inorganic mercury concentrations in workers exposed to metallic mercury vapor.

Several studies have reported a correlation between mercury in blood and urine; however, results vary, and it is not known whether the ratio between concentrations in urine and blood remains constant at different exposure levels (Lindstedt et al. 1979; Roels et al. 1987; Smith et al. 1970). Significant correlations between occupational exposure to mercury vapor and mercury levels in the blood and urine of 642 workers in 21 chloralkali facilities were reported by Smith et al. (1970). According to the investigators, an air concentration (8-hour TWA) of 0.1 mg/m^3 was associated with blood levels of 6 µg/100 mL and urine levels of 220 (not corrected for specific gravity), 200, or 260 µg/L (corrected to specific gravities of 1.018 or 1.024, respectively). It is likely that current worker exposure is significantly less than this study indicates, because practices such as requiring showers after workshifts and cleaning work clothes after use have been implemented since 1970, when the Smith study was conducted. Another group of investigators, Henderson et al. (1974), found the concentrations reported in Smith et al. (1970) to be 2–10 times higher than those found 2 years later. As suggested by Roels et al. (1982), the actual mercury absorption by

workers exposed to the same air concentration may vary; therefore, researchers should report urine mercury levels together with estimated exposure concentrations to address the issue of variance between individuals.

Studies assessing mercury vapor exposure have suggested various ratios relating the concentration of mercury in the air (in µg/m^3) to the levels of mercury in the urine (in µg/L). Such estimates include 1:1 (Bell et al. 1973), 1:1.22 (Roels et al. 1987), and 1:2.5 (Lindstedt et al. 1979; Rosenman et al. 1986). Urinary metallic mercury levels ranging from 0.05 to 1.7 µg/L were detected in the urine of workers exposed to mercury vapor (>0.1 mg/m^3); this elemental mercury represented <1% of the inorganic mercury content of the urine (Yoshida and Yamamura 1982). With increased exposure to mercury vapor (0.47–0.67 mg/m^3), the amount of elemental mercury in the urine increased. A "rough" correlation between levels of metallic mercury vapor in air and mercury levels in blood and urine was established by Rosenman et al. (1986). They associated levels of 50 µg/100 mL in blood and 250 µg/L in urine with a mercury level in air of approximately 0.1 mg/m^3 (8-hour TWA), and 28 µg/100 mL in blood and 100 µg/L in urine with a TWA of 0.05 mg/m^3. Roels et al. (1987) found a correlation between daily mercury vapor exposure and blood or urine mercury levels in 10 workers employed for at least 1 year at an alkaline battery plant. The mercury levels in the air and the pre- or post-workshift levels of blood and urinary mercury correlated well (r=0.79–0.86 [blood] and r=0.70–0.80 [urine]). Based on a ratio of 1:0.045:1.22 (mercury in air:blood mercury:urinary mercury), Roels et al. (1987) concluded that exposure to 0.05 mg/m^3 mercury vapor would result in a blood mercury of 2.26 µg/100 mL and a urinary mercury of 61 µg/g creatinine. This correlation differed from that reported by Rosenman et al. (1986), possibly because fewer subjects were evaluated and determination of mercury vapor concentration by Roels et al. (1987) was based on air sampling collection during 5 consecutive days at 10 different workplaces.

Expired air samples have been considered as possible biomarkers of exposure for mercury. Following inhalation of metallic mercury vapor, some of the mercury may be eliminated in the expired air, but excretion from this pathway is negligible 5–7 days after exposure (Cherian et al. 1978; Hursh et al. 1976). Thus, expired air as a measure of mercury exposure can only be used soon after short-term exposure to mercury vapor. There is no information on the amount of mercury in expired air following long-term exposure to mercury.

Nonoccupational exposure to mercury includes the use of mercury-containing products and consumption of mercury-contaminated food. Urine samples from young women using skin-lightening creams containing

5–10% mercuric ammonium chloride had a mean mercury concentration of 109 µg/L, compared to 6 µg/L for urine samples from women who had discontinued use and to 2 µg/L for women who had never used the creams (Barr et al. 1973). Increased urinary excretion and blood levels of mercury were observed in volunteers who used phenylmercuric borate solutions or lozenges intended for the treatment of mouth or throat infections (Lauwerys et al. 1977). Swedes consuming fish contaminated with 0.3–7 mg Hg/kg (0.3-7 ppm) had blood cell levels of total mercury ranging from 8 to 390 ng/g (Skerfving 1974). Long-term exposure to methylmercury at 4 µg Hg/kg/day was associated with a mercury level in blood cells of approximately 300 ng/g (Skerfving 1974). The steady-state concentration of methylmercury in blood may be related to daily intake in the following equation (Task Group on Metal Accumulation 1973; WHO 1990):

$$C = \frac{f \cdot d}{b \cdot V} \cdot \frac{A_D \cdot A_B \cdot d}{b \cdot V}$$

Where:

C	=	concentration in blood
f	=	fraction of the daily intake taken up by the blood
d	=	daily dietary intake
b	=	elimination constant
A_D	=	percent of mercury intake in diet that is absorbed
A_B	=	percent of the absorbed amount that enters the blood
V	=	volume of blood in the body

Hair is a biomarker of long-term exposure to methylmercury. Once mercury is incorporated into hair, it remains unchanged (Clarkson et al. 1973; Nielsen and Andersen 1991a, 1991b). A number of studies have examined the level of mercury in hair relative to the amount of fish consumed (see Table 2-10) (Airey 1983b; Haxton et al. 1979; Oskarsson et al. 1990; Sherlock et al. 1982). A fairly strong correlation has been demonstrated by these studies between the amount of fish consumed, the level of mercury in the fish, and the level of mercury in hair. Furthermore, the relationship between hair levels and blood levels has been well studied (see Table 2-9) (Amin Zaki et al. 1976; Den Tonkelaar et al. 1974; Haxton et al. 1979; Kershaw et al. 1980; Phelps et al. 1980; Sherlock et al. 1982; Skerfving 1974; Soria et al. 1992).

A number of studies report that hair mercury levels correlate with total intake levels and with organ-specific levels of mercury. Suzuki et al. (1993) analyzed 46 human autopsies in Tokyo, Japan and reported that hair mercury levels were highly significantly correlated with organ Hg levels in the cerebrum, cerebellum, heart, spleen, liver, kidney cortex, and kidney medulla, when the total mercury or methyl mercury value in the organ was compared with the hair total mercury or organic mercury, respectively.

When the inorganic mercury value was tested, significant correlations remained, with weaker coefficients in all the organs but the spleen. Stepwise multiple regression analysis indicated that hair organic mercury value was the major correlating variable for the organ total mercury or organ methyl mercury value in all the organs. With respect to the organ inorganic mercury value, the hair organic mercury value was the major correlate for the cerebrum and kidney (both cortex and medulla), the hair inorganic mercury value was the major variable for the cerebellum and heart, and the hair phosphorous and hair organic mercury were the major variables for the liver. No explanatory variable existed for the spleen. Auxiliary correlating variables accounted for the organ total mercury and inorganic mercury levels, among which the hair selenium value was conspicuous and with negative regression coefficients.

Nakagawa (1995) analyzed total mercury in hair samples from 365 volunteers in Tokyo, and reported higher mercury levels in those who preferred fish in their diet, compared to those who preferred other foods (preference choices were fish, fish and meat, meat, and vegetables). The mean hair mercury levels were 4 ppm in men who preferred fish and 2.7 ppm in women who preferred fish. The lowest hair mercury levels were seen in men and women who preferred vegetables, 2.27 and 1.31 ppm, respectively. The mean hair level for the whole group was 2.23 ppm (median 1.98).

Drasch et al. (1997) assayed tissue samples of 150 human cadavers (75 males, 75 females) from a “normal” European (German) population, i.e., there were no occupational or higher than average exposures to metals found in any of the biographies of the deceased. The objective was to evaluate the validity of blood, urine, hair, and muscle as biomarkers for internal burdens of mercury, lead, and cadmium in the general population. All individuals died suddenly and not as a result of chronic ailments. Age ranged from 16 to 93 years, and every decade was represented by approximately 10 males and 10 females. Tissues sampled included kidney cortex, liver, cerebral cortex, cerebellum, petrous portion of the temporal bone, (pars petrosis ossis temporalis), pelvic bone (spina iliaca anterior-superior), muscle (musculus gluteus), blood (heart blood), urine, and hair (scalp-hair). Statistically significant rank correlations between biomarker levels and tissues were observed but with large confidence intervals for the regressions. The authors conclude that specific biomarkers relative to each metal are useful in estimating body burdens and trends in groups, but are not useful for determining the body burden (and therefore the health risks) in individuals. A notable exception was, that in comparison to a generally poor correlation of cadmium, lead, and mercury between hair and tissue, there was a strong correlation between mercury in hair and mercury in brain (cerebrum and cerebellum). The authors state that this may be due to the high lipophilicity of elemental and short-chain alkyl mercury compounds. As seen in other studies comparing European to

Japanese hair mercury levels, the hair levels reported by Nakagawa (1995) of 2–4 ppm for a Japanese population are 10–20 times higher than levels observed in the Drasch et al. (1997) study (median, 0.247 µg/g in hair; range, 0.43-2.5 µg/g).

Other studies have confirmed a good correlation between hair mercury and brain mercury levels. In a study on the Seychelles Islands cohort, Cernichiari et al. (1995b) compared maternal hair levels, maternal blood levels, fetal blood levels, and fetal brain levels. Autopsy brains were obtained from infants dying from a variety of causes. The concentrations of total mercury in six major regions of the brain were highly correlated with maternal hair levels. This correlation was confirmed by a sequence of comparisons among the four measures. Maternal hair correlated to maternal blood (r=0.82) and infant brain level (r=0.6–0.8). Maternal blood correlated to infant blood (r=0.65); and infant blood correlated to infant brain (r=0.4–0.8).

There are potential confounding factors and other factors to consider when assessing mercury exposure based upon mercury hair levels. Mercury may be deposited to hair from the air when significant sources of mercury are present in the air or when certain hair treatments are used (Hac and Krechniak 1993; WHO 1991). Potential sources of external mercury exposure should, therefore, be evaluated as part of an exposure assessment. Some studies also report a sex related difference in mercury tissue levels. Nielson et al. (1994) observed a significant sex-related differences in the toxicokinetics of methylmercury in mice following administration of a single radiolabeled dose. Drasch et al. (1997) reported that mercury levels in all tissues assayed in their human cadaver study had higher levels compared to male tissues. The difference was significant for the kidney (median female kidney mercury level=92.0 ng/g, males=40.8 ng/g; p=0.002). In blood and urine there was a similar trend. In contrast, the authors report that mercury hair levels in females were significantly lower than in males (median females=205 ng/g, males 285 ng/g; p=0.02). Nakagawa (1995) also report higher mean mercury hair levels in males (2.98 µg/g) compared with females (2.02 µg/g) in a Japanese population. Further research is, therefore, needed to characterize potential sex related difference in the toxicokinetics of mercury under different exposure scenarios.

Eide and Wesenberg (1993) studied mercury concentrations in various organs and tissues in rats exposed to mercury vapor for approximately 2 months and proposed that human deciduous teeth may be useful indicators of chronic mercury exposure, as well as indicators of mercury uptake in organs such as the kidneys and the brain.

Other potential biomarkers of exposure include renal dysfunction parameters, neurological effects, and increased urinary porphyrins, and are discussed below in Section 2.7.2.

2.7.2 Biomarkers Used to Characterize Effects Caused by Mercury

Several potential biomarkers of effect for mercury have been evaluated, usually for neurological and renal dysfunction. Many of these toxic effects have been correlated with blood and urine levels (see Table 2-13). However, most indicators are nonspecific and may have resulted from other influences. As discussed in Section 2.2, many studies have examined the relationship between urine mercury levels and specific renal and neurological effects. Renal dysfunction has been studied extensively as a potential sensitive measure of mercury exposure. Signs of renal dysfunction at mercury air concentration of 0.1 mg/m^3 were reported by Stewart et al. (1977). Case reports have associated the therapeutic use of inorganic mercury salts with the occurrence of nephrotic syndrome (Kazantzis et al. 1962).

Several different biomarkers have been evaluated for assessing renal damage; however, renal parameters are interdependent (Verschoor et al. 1988). Furthermore, these markers are not specific for mercury exposure and may be a consequence of other concurrent chemical exposures. Markers for renal toxicity may indicate decreased function, cytotoxicity, or biochemical changes (Cardenas et al. 1993). Biomarkers for decreased function include increases in urinary proteins and elevation of serum creatinine or β_2-microglobulin. Biomarkers for renal cytotoxicity include increases in urinary excretion of antigens and enzymes located within renal tissues. Biomarkers for biochemical changes occurring within the kidneys include eicosanoids, fibronectin, kallikrein activity, and glycosaminoglycans in urine. Glomerular changes resulting from mercury exposure have predominantly been reported as increases in high-molecular weight proteinuria (Buchet et al. 1980; Kazantzis et al. 1962; Stonard et al. 1983; Tubbs et al. 1982). Renal tubular changes in workers exposed to mercury include increased urinary excretion of *N*-acetyl-β-D-glucosaminidase (NAG), β-galactosidase, and retinol binding protein (Barregard et al. 1988; Langworth et al. 1992b; Rosenman et al. 1986). Elevated urinary NAG levels occurred with urinary mercury levels of 100–250 µg/L in a study population of mixed ethnic background (Rosenman et al. 1986), with urinary levels of 35 µg/g creatinine in chloralkali workers (Barregard et al. 1988), with urinary mercury levels >25 µg/g creatinine in chloralkali workers (Langworth et al. 1992b), and with urinary mercury levels >50 µg/g creatinine in another group of chloralkali workers (Cardenas et al. 1993). NAG levels were not affected in chloralkali workers with urinary mercury levels of 15 µg/g creatinine (Piikivi and Ruokonen 1989). No significant increase of proteinuria, albuminuria, and other indicators of renal

Table 2-13. Health Effects Associated with Mercury Levels in Human Blood and Urine

Parameter	Normal levels found in tissue	Observed effect levels	Effect	Reference
Blood (whole)	<0.5–2 µ/100 mL			Iyengar et al. 1978
		<1–>10 µg/100 mL	Increased tremors	Verbeck et al. 1986
		>1.5 µg/100 mL	Disturbances in tests on verbal intelligence and memory. No effect level for proteinuria	Piikivi et al. 1984
		1.6 µg/100 mL	No effect level for proteinuria	Lauwreys et al. 1983
		1–2 µg/100 mL	Increased prevalence of abnormal psychomotor scores	Roels et al. 1982
		12 µg/100 mL	Increased tremors. Impaired eye-hand coordination	Smith et al. 1970
		>3 µg/100 mL	(Estimated threshold level): Increased urinary excretion of β-galactosidase and high molecular weight proteins	Buchet et al. 1980
Urine	0.43–11.4			Iyengar et al. 1978
		2–472 µg/g creatinine	Decreased delta-aminolevulinic acid dehydratase and cholinesterase activity. Increased urine coproporphyrin levels	Wade et ad. 1969
		3–272 µg/g creatinine	Increased anti-laminin antibodies (implicated in the etiology of autoimmune glomerulo-nephritis)	Lauwreys et al. 1983
		50–100 µg/g creatinine	Increased tremors. Impaired eye-hand coordination	Smith et al. 1970
		50 µg/g creatinine	(Estimated threshold level): Increased urinary excretion of β-galactosidase and high molecular weight proteins	Buchet et al. 1980

Table 2-13. Health Effects Associated with Mercury Levels in Human Blood and Urine (continued)

Parameter	Normal levels found in tissue	Observed effect levels	Effect	Reference
Urine (cont.)		56 µg/g creatinine	No effect level for proteinuria	Lauwreys et al. 1983
		7–1,101 µg/24 hours	Abnormal memory tests; decreased tibial nerve velocity; increased median nerve latency in both motor and sensory nerves	Vroom and Greer 1972
		0–510 µg/L	Short-term memory loss	Smith et al. 1983
		5–1,000 µg/L	Increased tremor frequency and reaction time; impaired eye-hand coordination	Miller et al. 1975
		<10–>1,000 µg/L	Increased tremors	Verbeck et al. 1986
		20–450 µg/L	Increased motor and sensory nerve latency	Levine et al. 1982
		>56 µg/L	Disturbances in tests on verbal intelligence and memory	Piikivi et al. 1984
		100–250 µg/L	Increased acetyl β-D-glucosaminidase (NAG) enzyme levels in urine	Rosenman et al. 1986
		>200 µg/L	Increased tremors; impaired eye-hand coordination	Williamson et al. 1982
		300–1,400 µg/L	Nephrotic syndrome; albuminuria; hypercholesterolemia	Kazantis et al. 1962

dysfunction was evident in 62 mercury workers with average blood mercury levels of 1.6 µg/100 mL (range, 0.25–7.56 µg/100 mL) and average urine mercury levels of 56 µg/g creatinine (range, 3–272 µg/g creatinine) (Lauwerys et al. 1983). Another renal parameter evaluated is β-microglobulin, which has a normal range of 0.004–0.37 mg/L (Naleway et al. 1991). No statistically significant relationship was found between urinary β-microglobulin levels and elevated urinary mercury concentrations (Ehrenberg et al. 1991; Naleway et al. 1991). Examination of a wide range of biomarkers for renal toxicity in a group of chloralkali workers identified several other changes at low urinary mercury levels (Cardenas et al. 1993). Workers with urinary mercury levels in the range of 5–50 µg/g creatinine showed statistically significant increases in urinary Tamm-Horsfall glycoprotein (localized in the epithelial cells of the convoluted tubules) and decreases in urinary prostaglandins E2 and F2α. In workers with >50 µg/g creatinine, increased NAG, tubular brush border antigens, alkaline phosphatase, thromboxane B2, and glycosaminoglycans were also observed. Urinary porphyrins, which are intermediates in the biosynthesis of heme, may be another potential biomarker of effect for mercury exposure. A correlation was observed between urinary mercury and urinary coproporphyrin (Wada et al. 1969). Correlations were also observed for decreases in δ-aminolevulinic acid-dehydratase and cholinesterase activity with increases in urinary mercury. Porphyrins are considered a nonspecific measure of effect because they are influenced by other metal exposures. Woods et al. (1991) present data suggesting that there is a specific urinary porphyrin profile that may serve as a biomarker of mercury accumulation in the kidneys during prolonged inorganic and organic mercury exposure. A urinary porphyrin pattern, characterized by elevated coproporphyrin, pentacarboxyl porphyrin, and precoproporphyrin, for methylmercury hydroxide exposure was observed in mice for up to 30 weeks. This profile is observed at variable dose levels, as well as up to at least 40 weeks after cessation of exposure. The time course of the profile during prolonged treatment is closely associated with divalent inorganic mercury (Hg^{+2}), suggesting that the effects are mediated by this cation because it inhibits the heme pathway (Woods et al. 1991). Specificity may be a problem unless the porphyrin levels are analyzed at the same time as urinary mercury measurements.

The neurophysiological and neuropsychological health effects of mercury have been extensively studied in occupationally exposed individuals in an effort to monitor body levels and to determine a threshold value below which these effects are unlikely to occur. As with other biomarkers of effect, neurological changes induced by mercury may resemble exposure to other chemicals that can cause damage to the brain.

Case studies have associated exposure to mercury vapor with neurological effects (e.g., tremors, insomnia, shyness, emotional instability, decreased motor function and muscle reflexes, headaches, and abnormal

EEGs) (Davis et al. 1974; Jaffe et al. 1983; McFarland and Reigel 1978). Some studies have examined the relationship between nerve function and mercury levels in blood, urine, and tissue. Tissue levels of mercury have also been found to correlate with impaired nerve function. Among 23 dentists with mercury levels greater than 20 µg/g (measured in wrist tissue), 30% exhibited reduced nerve conduction velocity when compared with dentists with tissue levels of mercury below 20 µg/g (Shapiro et al. 1982). The decrease in nerve conduction velocity was observed in both sensory and motor nerves.

A dose-response relationship has also been reported for the association between paresthesia and blood mercury concentrations in an Iraqi population exposed to methylmercury. At a blood mercury level of 24 µg/100 mL 65 days after cessation of exposure, the incidence of paresthesia caused by methylmercury rose significantly (Clarkson et al. 1976). Below this concentration, any incidence of paresthesia was assumed to be related to other causes, according to the investigators. As a result of the reported blood mercury half-life of 65 days in this population, the maximum blood mercury concentration was likely to have been 48 µg/100 mL at the end of the exposure. Some evidence of paresthesia, sensory impairment, general ataxia, and visual field effects in exposed Swedes was reported; however, no significant increases in occurrence were found in Swedes with high levels of mercury in blood cells (82–1,100 ng/g) as compared to Swedes with lower blood cell mercury levels (12–75 ng/g) (Skerfving 1974). The study did not include a matched control group.

Many possible biomarkers of effect for mercury exposure have been correlated with urinary mercury levels. Workers exposed to elemental mercury vapor with urinary mercury excretion levels ranging from 7 to 1,101 µg/day exhibited significantly reduced tibial nerve velocity and increased median nerve latency in both motor and sensory nerves as compared with controls (Vroom and Greer 1972). Prolonged motor and sensory nerve latency was also associated with urine mercury levels ranging from 20 to 450 µg/L in 18 male workers exposed to elemental mercury vapor at a mercury cell chlorine plant (Levine et al. 1982). Urine mercury levels exceeding 200 µg/L have been reported to be associated with tremors and poor eye-hand coordination (Williamson et al. 1982). Twelve workers chronically exposed to elemental mercury vapor had urinary mercury levels ranging from <10 to 670 µg/L. A significant relationship between urine mercury and hand steadiness was reported. Increased tremor frequency, increased reaction time, and reduced eye-hand coordination were observed as urine mercury levels increased from 5 to 1,000 µg/L in 77 exposed individuals (Miller et al. 1975). A weak but significant quantitative relationship between urine mercury levels and finger tremors was elucidated by Verberk et al. (1986). The relationship between acceleration of finger tremors and excretion of mercury in the urine of 20 workers exposed to metallic

mercury was expressed by the equation 10 log (acceleration)=G0.888 + 0.0059 (urine mercury) (r=0.39, p<0.05, n=20). Tremors have also been reported in 567 workers from chloralkali production facilities whose blood mercury levels ranged from <1 to >10 µg/100 mL and whose urine mercury levels ranged from <10 to >1,000 µg/L. Increased tremors and reduced eye-hand coordination were associated with blood mercury levels of 1–2 µg/100 mL and urine mercury levels of 50–100 µg/g creatinine (Smith et al. 1970). Cavalleri et al. (1995) have suggested that exposure to elemental mercury vapors at levels producing urine mercury concentrations >50 µg/g creatinine can cause a dose-related loss of color vision.

An association between urine mercury levels and performance on memory tests and verbal intelligence tests has been established. Abnormal results on memory tests were reported for 9 workers exposed to mercury in the production of thermometers; urinary mercury excretion levels were 7–1,101 µg/24 hours (Vroom and Greer 1972). The short-term memory span of 26 workers was examined by Smith et al. (1983) and found to decrease with increasing urine mercury levels. The range of mercury found in the urine of these workers was 0–510 µg/L. A significant linear relationship was reported between subjects' 50% memory threshold spans and 12-month urinary mercury concentrations. Disturbances on tests of verbal intelligence and memory were more frequent among individuals with mercury blood levels above 1.5 µg/100 mL and mercury urine levels above 56 µg/L in 36 male chloralkali workers (Piikivi et al. 1984).

Potential biomarkers for the autoimmune effects of mercury include measurement of antiglomerular basement membrane antibodies, anti-DNA antibodies, serum IgE complexes, and total IgE (Cardenas et al. 1993). Elevated IgE, antiglomerular basement membrane antibodies, and anti-DNA antibodies have been observed in a few persons with exposure to mercury from dental amalgams (Anneroth et al. 1992). Other individuals have also been shown to have elevated anti-DNA or antiglomerular basement membrane antibodies (Cardenas et al. 1993; Langworth et al. 1992b).

Recent data regarding the action of low-level mercury exposure on receptors and signal transduction pathways in peripheral lymphocytes suggest potential applications of certain surrogate markers in mechanistic studies of neurotoxicity and, possibly, in assessing early biochemical effects of neurotoxicants in humans (Manzo et al. 1995). Additional biomarkers for effects on the immune, renal, hepatic, and neurological systems are presented in the CDC/ATSDR (1990) and OTA (1990) reports. See Section 2.2 for a more detailed discussion of the effects caused by mercury.

2.8 INTERACTIONS WITH OTHER CHEMICALS

As with many other metals, both toxic and nontoxic, interrelationships exist that can influence and alter the absorption, distribution, excretion, and toxicity of one or more of the component metals. For example, the zinc status of an individual can affect mercury toxicity. Pretreatment with zinc provides some protection from the nephrotoxic effects of inorganic mercury in rats (Zalups and Cherian 1992). The data indicate that zinc-induced metallothionein binds mercury in the renal cortex and shifts the distribution of mercury from its site of toxicity at the epithelial cells of the proximal tubules. Thus, the renal content of mercury is increased, yet less is available to cause toxicity. In contrast, the renal toxicity of mercuric chloride is exacerbated in zinc-deficient animals (Fukino et al. 1992). In the zinc-deficient state, less mercury accumulates in the kidneys, but the toxicity is greater. The mechanism of the protection appears to involve more than simply a redistribution of renal mercury, because in the absence of mercury exposure, zinc deficiency increases renal oxidative stress (increased lipid peroxidation, decreased reduced ascorbate). When mercury exposure occurs, the oxidative stress is compounded (increased lipid peroxidation and decreased glutathione and glutathione peroxidase). Thus, zinc appears to affect the biochemical protective mechanisms in the kidneys as well.

Similarly, in most studies, the simultaneous administration of mercury and selenium in equimolar doses to animals has resulted in decreased toxicity of both elements in acute and chronic exposure studies. This effect has been observed with inorganic and organic mercury and with either inorganic or organic selenium compounds, although inorganic forms of selenium appear to be more effective than organic forms (Chang 1983; Skerfving 1978). Selenium protects against the acute nephrotoxicity of the mercuric ion and the methylmercuric ion in rats (Ganther 1980; Ganther et al. 1972; Hansen 1988; Magos et al. 1987; Parizek and Ostadolva 1967) and possibly against acute neurotoxicity of methylmercuric ion in rats (Ohi et al. 1980). The protective effect of selenium has been associated with a higher whole-body retention of mercury rather than with increased mercury excretion (Hansen 1988; Magos et al. 1987). Mercury-selenium complexes are formed when these chemicals are co-administered. Mercuric mercury forms a complex with selenium and a high-molecular weight protein (Naganuma and Imura 1981). Methylmercury forms a bismethyl-mercury selenide complex. Although the specific mechanism for the protection is not well understood, possible mechanisms for selenium's protective effect include redistribution of mercury (Mengel and Karlog 1980), competition by selenium for mercury-binding sites associated with toxicity, formation of a mercury-selenium complex that diverts mercury from sensitive targets (Hansen 1988; Magos et al. 1987; Naganuma and Imura 1981), and prevention of oxidative damage by increasing

selenium available for the selenium-dependent glutathione peroxidase (Cuvin-Aralar and Furness 1991; Imura and Naganuma 1991; Nylander and Weiner 1991). Selenium-treated animals can remain unaffected despite an accumulation of mercury in tissues to levels that are otherwise associated with toxic effects (Skerfving 1978). Support for the proposal that an inert complex is formed comes from the 1:1 ratio of selenium and mercury found in the livers of marine mammals and in the bodies of experimental animals administered compounds of mercury and compounds of selenium, regardless of the ratio of the injected doses (Hansen 1988). Mercuric mercury has been shown to form a complex with selenium and a high-molecular weight protein (Naganuma and Imura 1981). Methylmercury forms a bismethyl-mercury selenide complex.

Although the fetotoxicity of methylmercuric chloride has been shown to be enhanced by the feeding of a selenium-deficient diet in mice (Nishikido et al. 1987), additional selenium administration does not appear to protect against teratogenic effects (i.e., cleft palate) of methylmercuric chloride in mice (Lee et al. 1979). High doses of selenium administered as selenite for 30 days prior to gestation and through Gd 18 to mice fed a diet containing high doses of methylmercuric chloride increased the incidence of cleft palate (Nobunaga et al. 1979). It is possible that cleft palate induction by methylmercury is the result of a suppression of growth rather than a tissue-specific teratogenic action (Lee et al. 1979). If this were the case, high doses of selenium that inhibit growth could potentiate the induction of cleft palate by methyl-mercury administration. Further discussion of selenium-mercury interactions can be found in Section 2.3.1.2.

Ethanol promotes an increase in the respiratory excretion of metallic mercury by inhibiting the enzyme catalase, which is responsible for oxidizing metallic mercury to mercuric mercury. This process was shown in workers who ingested a moderate dose of alcohol and experienced a 50% decrease in mercury retention upon inhalation exposure to metallic mercury vapor (Nielsen-Kudsk 1973). Also, ethanol increased the amount of mercury exhaled by people who inhaled metallic mercury vapor or received trace doses of mercuric chloride (Nielsen-Kudsk 1965). Therefore, less mercury should reach the kidneys and less renal toxicity should be observed (Nielsen-Kudsk 1965). However, ethanol also allows elemental mercury to persist longer in the plasma, resulting in prolonged diffusion of elemental mercury throughout the body (Nielsen-Kudsk 1965). Therefore, ethanol can cause mercury to distribute more easily across the blood-brain barrier and the placenta, thereby increasing the risk of mercury toxicity to the brain and the developing fetus. In addition, the oxidation of ethanol with concurrent NADPH generation enhances

the reduction of the mercuric ion to metallic mercury, thereby making it more favorable for permeating the placenta (Khayat and Dencker 1982).

Ethanol also potentiates the toxicity of methylmercury (Rumbeiha et al. 1992; Tamashiro et al. 1986; Turner et al. 1981). Studies in animals have shown increased mortality (Tamashiro et al. 1986), increased severity and decreased time to onset of neurotoxicity (hind-limb ataxia) (Tamashiro et al. 1986; Turner et al. 1981), and increased renal toxicity (increased hematuria, renal weight, blood urea nitrogen, and oliguria) (Rumbeiha et al. 1992; Tamashiro et al. 1986) when methylmercury exposure occurred concomitant with ethanol ingestion. Although increased mercury concentrations were observed in the brain and kidneys, the changes in mercury content were insufficient to fully explain the observed potentiation of toxicity (Tamashiro et al. 1986), suggesting that ethanol may enhance the toxic mechanisms of methylmercury. The mechanism for this enhancement is unknown.

Atrazine and potassium dichromate have also been demonstrated to enhance the toxicity of inorganic mercury. Administration of atrazine, a widely used herbicide, with methylmercury in the diet resulted in a higher deposition of mercury in the liver and an earlier onset of neurotoxicity (Meydani and Hathcock 1984). The mechanism underlying this interaction was unclear. Parenteral administration of minimally toxic doses of potassium dichromate and mercuric chloride resulted in a synergistic inhibition of the renal transport of organic ions *p*-aminohippurate and tetraethylammonium (Baggett and Berndt 1984). Although the mechanism underlying this interaction was not examined, it may be associated with the fact that both mercury and potassium dichromate are both toxic to the renal proximal tubule (Biber et al. 1968).

Agents that deplete nonprotein sulfhydryls may increase the toxicity of mercury. Depletion of glutathione levels with diethylmaleate in rats resulted in greatly increased renal toxicity of mercury chloride (Girardi and Elias 1991). Greater decreases in glomerular filtration and increases in fractional excretion of sodium and lithium, urinary γ-glutamyltransferase, and lipid peroxidation were observed. Conversely, chemicals that protect against oxidative damage may decrease the toxic effects of mercury. Increased survival and decreased toxicity were observed in rats given vitamin E (α-tocopherol) during treatment with methylmercury (Welsh 1979). It is probable that the mechanism for the protection involved the antioxidant properties of vitamin E.

The exogenous application of the monothiols glutathione or its, precursor N-acetyl-DL-homocysteine thiolactone (NAHT), or B-complex and E vitamins to mice exposed to methylmercuric chloride injected

at dosages of 1 mg/kg/day was reported by Bapu et al. (1994). Therapy with both B-complex vitamins and vitamin E was found to mobilize a significant amount of mercury from all tissues examined (brain, spinal cord, liver, and kidneys), with the maximum mobilization (about 63%, compared with controls) being recorded in the spinal cord following vitamin E treatment. NAHT treatment also produced significant mobilization of mercury from nervous tissue but caused an increase in mercury concentration in non-nervous tissue.

Another group of compounds that combines with mercury (and other divalent cation species) is comprised by those used in chelation therapy to reduce the body burden of mercury by enhancing its elimination from the body. Such chelators include: ethylenediaminetetraacetic acid (EDTA); ethylene glycol bis(beta-aminoethyl ether)N,N,N',N'-tetraacetic acid (EGTA); 2,3-dimercaptopropane-1-sulphonate (DMPS); 2,3-dimercaptosuccoinic acid (DMSA); 2,3-dimercaptopropanol (British anti-Lewisite [BAL]; sometimes called dimercaprol); and N-acetylpenicillamine (NAP). While these chelating agents have a very high affinity for Hg^{++}, which makes them effective mercury chelators, they also have an affinity for other divalent cations, many of which are essential for normal physiological function.

BAL was the first chelating agent used for mercury toxicity, and it is still widely used today for inorganic mercury poisoning (ATSDR 1992). BAL is also believed to be effective in treating phenylmercury poisoning, because of the rapid *in vivo* oxidization of phenylmercuric acetate to Hg^{++}, thereby rendering phenylmercury similar in behavior to inorganic mercury. BAL is <u>contraindicated</u> for cases of methyl-mercury poisoning, however, because it has been demonstrated to increase the concentration of methyl-mercury in the brain. Possible side effects of BAL include nausea, vomiting, headache, tachycardia, fever, conjunctivitis, blepharospasm, and lacrimation. As an adjunct or alternative to parenterally administered BAL, oral NAP may be used (ATSDR 1992). Side effects of NAP may include fever, rash, leukopenia, eosinophilia, and thrombocytopenia.

DMPS and DMSA are derivatives of BAL, but they have been found to be more effective than BAL in experimental studies. Although still considered an investigational drug, DMPS decreased the mercury excretion half-life from 33.1 to 11.2 days in 2 workers exposed to high levels of mercury vapor (ATSDR 1992). In a study of the influence of DMPS and DMSA on renal deposition of mercury in rats, both chelating agents were found to cause a significantly increased urinary excretion of mercury (Zalups 1993), although significant differences in the extrarenal handling of these two chelators were found. DMPS was also shown to increase the urinary excretion of mercury 7.6-fold in a group of former chloralkali workers

3 years after cessation of occupational exposure (Sallsten et al. 1994), probably reflecting the excretion of mercury stored in the kidneys. In a case report of two human mercury vapor intoxication incidents, treatment with BAL followed by DMSA was found to decrease plasma inorganic mercury uptake at concentrations <50 µg/L. However, relatively high concentrations of mercury remained in the plasma for a very long time, possibly due to the progressive release of mercury from red blood cells and tissues after oxidation.

EDTA and EGTA also effectively form complexes with Hg^{++}, and enhance its excretion from the body, in what is typically considered a relatively benign or biologically inert fashion. In a study using human brain homogenates from autopsy samples from apparently healthy brains, Duhr et al. (1993) demonstrated that not only is the inhibition of microtubule polymerization and the disruption of already-formed microtubules not prevented by the addition of EDTA and EGTA (which bind Hg^{++} with very high affinity) but, to the contrary, these two chelating agents potentiate the Hg^{++}-induced inhibition of tubulin polymerization. Duhr et al. (1993) further reported that the mercury-EDTA and mercury-EGTA complexes cause the inhibition of tubulin polymerization by disrupting the interaction of GTP with the E-site of brain beta-tubulin, an obligatory step in the polymerization of tubulin.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to mercury than will most people exposed to the same level of mercury in the environment. Reasons include genetic makeup, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects on clearance rates and any resulting end-product metabolites). Populations more susceptible to the toxic effects of mercury than a healthy young adult include: the elderly because of declining organ function, higher levels of persistent heavy metals (e.g., cadmium) that also accumulate in the kidney, and potentially higher brain to liver or kidney mercury concentrations; people with pre-existing disease (e.g., renal or neurological disease); and the youngest of the population because of their immature and developing organs. Populations at greater risk due to unusually high exposure are discussed in Section 5.7 (Populations With Potentially High Exposure).

Probably the most widely recognized form of hypersensitivity to mercury is the occurrence of acrodynia, or pink disease, in persons exposed to mercury. Acrodynia is characterized by itching, flushing, swelling, and/or desquamation of the palms of the hands or soles of the feet, morbilliform rashes, excessive sweating and/or salivation, tachycardia, elevated blood pressure, insomnia, weakness, irritability, fretfulness, and peripheral sensory disturbances (Warkany and Hubbard 1953). The occurrence of acrodynia was determined to be an idiosyncratic reaction to mercury exposure. Despite widespread exposure of children to mercury-containing laxatives, antiascariasis medications, and teething powders in the 1940s and 1950s, only a few children developed acrodynia. The affected population was not the most highly exposed; numerous reports identified higher exposures in others with no evidence of the disease. The physiological basis for this hypersensitivity is unknown, but patch testing indicated that it is not an allergic response to mercury exposure.

Animal studies (Aten et al. 1992; Druet et al. 1978; Hirszel et al. 1985; Hultman and Enestrom 1992; Matsuo et al. 1989; Michaelson et al. 1985; Pelletier et al. 1990; Pusey et al. 1990; Roman-Franco et al. 1978; van der Meide et al. 1993) and limited human data (Lindqvist et al. 1974; Tubbs et al. 1982) also indicate that there may be persons with a genetic predisposition to develop an autoimmune glomerulo-nephritis upon exposure to mercury. In this form of renal toxicity, proteinuria is observed following the reaction of autoantibodies with renal tissues and deposition of immune material (i.e., IgG and complement C3) in the renal mesangium and glomerular blood vessels. Both susceptible and resistant mouse and rat strains have been identified, and susceptibility appears to be governed by both MHC genes and nonMHC genes (Aten et al. 1991; Druet et al. 1978; Hultman and Enestrom 1992; Hultman et al. 1992; Michaelson et al. 1985; Sapin et al. 1984).

Unborn children are another known susceptible population to the toxic effects of mercury (see Section 2.2.2.4). Data from large-scale poisonings in Japan (Harada 1978) and Iraq (Marsh et al. 1987) indicate that infants exposed *in utero* to alkyl mercury compounds developed severe neurological toxicity whereas their mothers may have experienced no or only mild toxicity. This difference may be due to methylmercury binding to tubulin (Vogel et al. 1985, 1989) and the role of microtubules in neuronal cell division and migration in the developing nervous system (Sager et al. 1982). There is evidence indicating that the developing male fetus may be more susceptible to methylmercury exposure than the female fetus (Buelke-Sam et al. 1985; Grant-Webster et al. 1992; Sager et al. 1984).

Neonates may also be especially susceptible to mercury toxicity. Both inorganic and organic forms of mercury are excreted in the milk (Sundberg and Oskarsson 1992; Yoshida et al. 1992). Furthermore, suckling rats exhibit a very high absorption of inorganic mercury as a percentage of the diet (30–40%) compared to adult rats, which absorb approximately 1% of the inorganic mercury from the diet (Kostial et al. 1978). The highest oral toxicity to inorganic mercury as expressed by the LD_{50} was for 2-week-old rats; by 3–6 weeks of age, rats showed a dramatic drop in sensitivity to inorganic mercury poisoning (Kostial et al. 1978). The transfer of mercury to suckling rats through milk was found to result in greater concentrations of the metal in the brains of the offspring than in the mother (Yang et al. 1973). Developmental neurotoxicity, similar to that seen with *in utero* exposure, has been observed in an infant exposed to alkyl mercury only after birth (Engleson and Herner 1952).

Individuals with diseases of the liver, kidneys, lungs, and nerves are considered to be at greater risk of suffering from the toxic effects of both organic and inorganic mercury. Individuals with a dietary insufficiency of zinc, glutathione, antioxidants, or selenium or those who are malnourished may be more susceptible to the toxic effects of mercury poisoning because of the diminished ability of these substances to protect against mercury toxicity (see Section 2.8).

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section describes clinical practice and research concerning methods for reducing toxic effects of exposure to mercury. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for the treatment of exposures to mercury. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Although there are a number of treatments currently available, none are completely satisfactory and additional development of treatment drugs and protocols is needed. The recent death of a researcher poisoned with dimethylmercury is a case in point (Nierenberg et al 1998; Toribara et al. 1997). In spite of prompt action and excellent medical care and monitoring, the clinical course in this patient continued to decline, and ultimately ended in death.

In general, even the inorganic mercurials, that are considered to be more easily chelated, are difficult to remove from the body and are not treated without some side effects. Infants and young children are

particularly difficult to treat, sometimes requiring exchange transfusion or other more elaborate measures. Reducing the body burden or toxic effects of mercury in pregnant women presents an even greater challenge (i.e., treatment must be effective for both the mother and the developing child), and specific treatment protocols are needed.

2.10.1 Reducing Peak Absorption Following Exposure

Strategies used to reduce absorption of mercury may differ depending on the route of exposure and the specific chemical to which one is exposed. Elemental mercury and certain organic forms of mercury have high vapor pressures and are readily absorbed by the lungs; inhalation of these chemicals may be the major exposure of concern. Because ingestion of most chemical forms of mercury is possible, strategies for limiting absorption from the gastrointestinal tract would be of utmost concern in such situations. The organic mercury compounds have greater absorption from the gut than elemental and inorganic mercury; thus, strategies differ depending on the form of mercury ingested. Dermal absorption of the various forms of mercury is also possible, so strategies should also consider limiting dermal absorption.

The first step in mitigating the toxic effects of inhalation and dermal exposures to mercury or its compounds is removal from the contaminated area or source (Bronstein and Currance 1988; Gossel and Bricker 1984; Haddad and Winchester 1990; Stutz and Janusz 1988). Since continued exposure may occur when clothing is contaminated, clothing may be removed as well (Bronstein and Currance 1988; Stutz and Janusz 1988). If dermal or ocular exposure has occurred, thoroughly washing the exposed areas with water has been suggested; treatment protocols recommend the use of Tincture of Green® soap a disinfectant) for the skin and normal saline for the eyes (Bronstein and Currance 1988; Stutz and Janusz 1988).

Several treatments have been suggested to reduce absorption of mercury from the gastrointestinal tract; however, most refer to the inorganic forms of mercury. It is likely that strategies that are effective in reducing the absorption of inorganic forms may also have some efficacy for organic forms. Several procedures that have been recommended for trapping mercury in the gastrointestinal tract are based on the mercury's affinity for binding to sulfhydryl groups. For example, oral administration of a protein solution (e.g., milk or egg whites) has been suggested to reduce absorption (Gossel and Bricker 1984; Haddad and Winchester 1990; Stutz and Janusz 1988). Salt-poor albumin administration has also been suggested (Haddad and Winchester 1990). Nonabsorbable agents (e.g., polystyrene resins containing sulfhydryl

groups) have been used to decrease the absorption rate of methylmercury (Clarkson et al. 1973). The oral administration of activated charcoal has also been suggested (Gossel and Bricker 1984; Stutz and Janusz 1988). Rapid removal of mercury from the gastrointestinal tract may be indicated in some acute, high-dose situations. In such situations, immediate emesis or gastric lavage has been suggested (Goldfrank et al. 1990; Haddad and Winchester 1990). Inclusion of salt-poor albumin or sodium formaldehyde sulfoxylate in the lavage fluid to convert the mercuric ion into the less soluble mercurous ion in the stomach has also been recommended (Haddad and Winchester 1990). Emesis is contraindicated following the ingestion of mercuric oxide, presumably because of the risk of damage to the esophagus as the potentially caustic compound is ejected. A saline cathartic, such as magnesium sulfate, to speed removal from the gastrointestinal tract has also been recommended unless diarrhea has already begun (Haddad and Winchester 1990; Stutz and Janusz 1988). Giving CaNa2-EDTA is contraindicated because it binds poorly to mercury, may be toxic to the kidneys, chelates other essential minerals, and may cause redistribution of mercury in the body (Gossel and Bricker 1984).

2.10.2 Reducing Body Burden

Since the main source of mercury exposure for the general public is organic mercury in the diet, minimizing the consumption of mercury-laden fish and shellfish is an effective means of reducing the body burden. The amount of inhaled mercury vapor from accidental spills of metallic mercury (e.g., from broken thermometers or electrical switches) can be minimized by informing the general public of the potential dangers and volatility of liquid mercury, and by prompt and thorough clean-up of liquid mercury spills.

Following exposure and absorption, metallic mercury is distributed primarily to the kidneys. Elemental mercury is highly soluble in lipids and easily crosses cell membranes (Gossel and Bricker 1984), particularly those of the alveoli (Florentine and Sanfilippo 1991). Once in the blood, this form of mercury can distribute throughout the body, as well as penetrate the blood-brain barrier, thus accumulating in the brain (Berlin et al. 1969). The body burden half-life of metallic mercury is about 1–2 months (Clarkson 1989). The kidney is also the primary organ of accumulation for compounds of inorganic mercury, but the liver, spleen, bone marrow, red blood cells, intestine, and respiratory mucosa are target tissues as well (Haddad and Winchester 1990; Rothstein and Hayes 1964). Inorganic mercury is excreted primarily through the kidneys; its half-life ranges from 42–60 days (Hursh et al. 1976; Rahola et al. 1973). As with elemental mercury, organic mercury compounds accumulate throughout the body (Aberg et al. 1969; Miettinen 1973). Accumulation of organic mercury also occurs in the liver, where it

is metabolized, excreted through the bile, and often reabsorbed in the gastrointestinal tract (Florentine and Sanfilippo 1991; Haddad and Winchester 1990). The half-life of lower alkyl mercurials is about 70–79 days (Aberg et al. 1969; Miettinen 1973).

For several years, diaphoresis (excretion through perspiration) was used to lower the body burden of mercury in miners exposed to mercury vapors (Sunderman 1978). Recently, this method of therapy has also been used to lower tissue levels of mercury in a patient exposed to metallic mercury in the manufacture of thermometers (Sunderman 1978).

Chelation therapy is presently the treatment of choice for reducing the body burden of mercury. There are currently a number of chelators that are either in practical use or under investigation in *in vivo* and *in vitro* studies (Florentine and Sanfilippo 1991; Gossel and Bricker 1984; Haddad and Winchester 1990). These chelators differ in their efficacy for various forms of mercury, routes of administration, side effects, and routes of excretion. Depending on the chemical to which one has been exposed and the health status of the individual, different chelators may be indicated. One popularly used chelator, dimercaprol or BAL, has two sulfhydryl groups that can bind mercury and compete with its binding to sulfhydryl groups in body tissues (Florentine and Sanfilippo 1991; Haddad and Winchester 1990). BAL is one of the more effective chelators for inorganic mercury salts. BAL is administered intramuscularly and is the preferred chelator when oral dosing is impractical (Florentine and Sanfilippo 1991; Gossel and Bricker 1984; Haddad and Winchester 1990). Approximately 50% of the dimercaprol-mercury complex is excreted through the kidneys, while the remainder is eliminated in the bile and feces. Thus, this chelator is preferred when renal impairment has occurred. BAL therapy, however, has several limitations. Significant reabsorption of mercury from the bile occurs (Shimada et al. 1993). Also, multiple toxic side effects including urticaria, elevated blood pressure and heart rate, nausea and vomiting, headache, conjunctivitis, lacrimation, and paresthesias have been reported (Goldfrank et al. 1990). Children may develop fevers, and individuals with a glucose-6-phosphatase deficiency may develop hemolysis. BAL treatment is contraindicated for elemental and organic mercury compounds because it has been shown to increase brain levels of mercury in animal studies when used to treat exposures to phenylmercury or methoxyethylmercury compounds (Berlin 1986; Berlin and Rylander 1964) or elemental mercury vapor (Goldfrank et al. 1990), indicating the possibility of increased neurotoxicity.

Another currently used mercury chelator is D-penicillamine. This drug has been used somewhat effectively to reduce the toxicity of elemental and inorganic mercury exposures. It can be taken orally, and its

metabolism is slight in humans. Penicillamine is removed though the kidneys (Florentine and Sanfilippo 1991). However, acute allergic reactions to penicillamine may occur (Goldfrank et al. 1990). An experimental drug, *N*-acetyl-D,L-penicillamine (NAP), is very similar to its analog, penicillamine, in its properties of absorption, metabolism, and excretion; however, it may be more mercury-specific in its chelating abilities and less toxic (Goldfrank et al. 1990; Haddad and Winchester 1990). A high success rate (88%) has been reported by investigators using NAP to treat victims of mercury inhalation (Florentine and Sanfilippo 1991).

2,3-Dimercaptosuccoinic acid (DMSA), an analogue of BAL, is another experimental chelating agent. DMSA can be given orally and is primarily excreted through the kidneys (Aposhian et al. 1992b). It has been shown to be an effective chelator for both inorganic and methylmercury (Magos 1967). Comparative studies have demonstrated that DMSA is as effective, if not more so, as dimercaprol, penicillamine, and NAP. Data also suggest that this chelating drug produces fewer adverse effects than NAP (Florentine and Sanfilippo 1991). 2,3-Dimercaptopropane-1-sulfonate (DMPS) is another BAL analogue that is an orally effective chelator for mercury. Reports differ with respect to which of these analogues is less toxic (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Jones 1991; Karagacin and Kostial 1991). Better results were obtained in rats with DMPS than with DMSA when the chelating agent was administered at least 24 hours following exposure to mercuric chloride. However, early oral administration of DMPS (within 24 hours) resulted in increased mercury retention (Karagacin and Kostial 1991). In contrast, DMSA resulted in decreased mercury retention irrespective of when it was administered.

Hemodialysis with infusion of a chelator (cysteine, *N*-acetylcysteine, NAP) has been reported to be effective in some severe cases of poisoning where renal failure is a complication (Berlin 1986; Goldfrank et al. 1990; Haddad and Winchester 1990). It has been reported to be advantageous to begin the hemodialysis before substantial renal damage has occurred (Haddad and Winchester 1990).

Because methylmercury undergoes enterohepatic recirculation, nonabsorbable agents have been used to "trap" methylmercury excreted into the bile (Lund et al. 1984). A polystyrene resin containing sulfhydryl groups added to food at a concentration of 1% doubled the elimination rate of methylmercuric chloride when administered to mice. The elimination half-life decreased from 65 to 20 days (Clarkson et al. 1973). Excretion of methylmercury may also be enhanced by bile drainage either through catheterization and drainage of the choledochal duct or by surgical establishment of gallbladder drainage (Berlin 1986). However, this method has not been used therapeutically.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The majority of metallic mercury vapor and organic mercury absorbed by the body is rapidly oxidized to the more toxic and soluble mercuric ion in the blood and tissues through a hydrogen peroxide catalase pathway (Clarkson 1989; Halbach and Clarkson 1978). It is believed that the high affinity of the cation for protein-containing sulfhydryl or thiol groups is the underlying mechanism for the biological activity of mercury (Clarkson 1972a; Hughes 1957; Passow et al. 1961). In a process that is not yet completely understood, mercury disrupts the intracellular sulfhydryl status, resulting in oxidative stress, followed by activation of catabolic enzymes (i.e., proteases, endonucleases), and ultimately in cellular injury (Verity and Sarafian 1991). Treatment with agents that reduce oxygen radical-producing reactions may be effective in reducing mercury-induced oxidative cell damage. For example, pretreatment of rats with deferoxamine, a potent iron chelator and inhibitor of iron-catalyzed oxygen radical-producing reactions, reduced the increase in reactive oxygen species seen in the cerebellum after methylmercury exposure (LeBel et al. 1992; Sarafian and Verity 1991). Similarly, treatment with *N*-acetylcysteine, an antioxidant, resulted in increased survival time and less severe lung lesions in rats following exposure to mercury vapor (Livardjani et al. 1991b). Vitamin E (alpha tocopherol) and *N*,*N*'-diphenyl-*p*-phenylenediamine therapy have antioxidant effects and have been shown to be effective in protecting against methylmercury-induced toxicity (Ganther 1980; Welsh 1979).

Strategies to block the oxidation of elemental mercury to mercuric ion through the hydrogen peroxide catalase pathway do not appear to be a viable method for mitigating the effects of mercury exposure because treatment with chemicals (e.g., ethanol) that have been shown to block this reaction (Nielsen-Kudsk 1965) result in higher levels of blood mercury and increased renal toxicity (Rumbeiha et al. 1992). Another option would be to reduce the oxidized mercury ions to the monovalent mercurous form. A treatment of this nature has been suggested for ingested inorganic mercury.

Metals and chemicals shown to be antagonistic to the toxic effects of mercury may offer a possible method of interfering with the mercury's mechanism of action. Selenium, as sodium selenite, has been used in counteracting mercury poisoning, although the specific mechanism is not understood (Mengel and Karlog 1980; Naganuma and Imura 1981). The efficacy of selenium administration also appears to be dependent on the form of mercury to which one is exposed. Co-administration of sodium selenite with mercuric chloride resulted in decreased renal toxicity, whereas co-administration with methylmercuric chloride had no effect on renal toxicity (Yasutake et al. 1991b). The nephrotoxic effects of inorganic mercury may be

protected against by pretreatment with zinc (Zalups and Cherian 1992). Data in rats suggest that zinc can induce metallothionein in the renal cortex and cause mercury accumulation in the kidneys to shift from the outer medulla to the cortex, where a greater percentage is bound to the induced metallothionein. However, despite its potential use for interfering with the mercury-induced renal effects, zinc also prolongs retention in the body.

2.11 ADEQUACY OF THE DATABASE

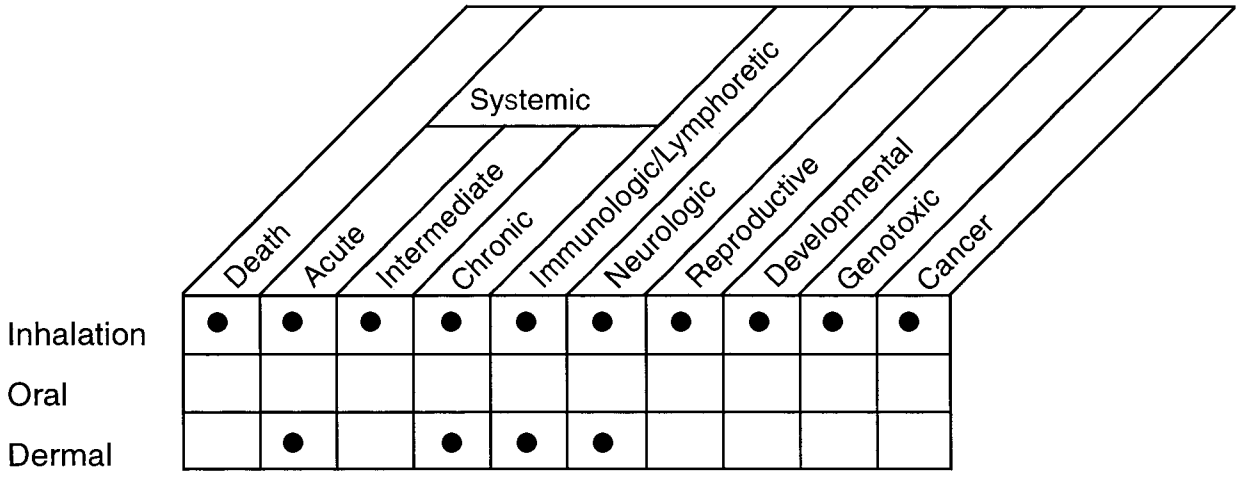
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of mercury is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of mercury.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

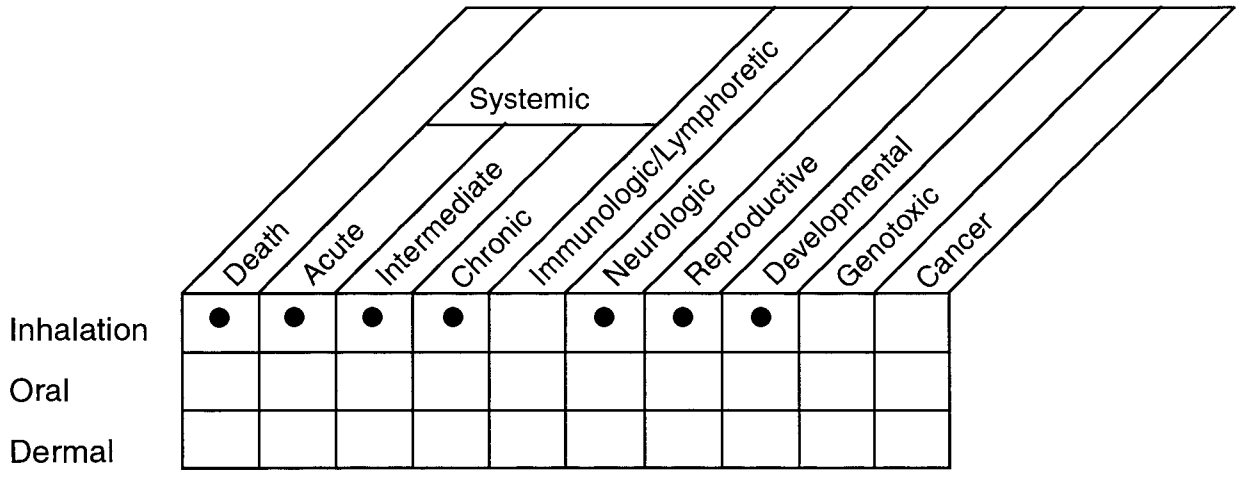
2.11.1 Existing Information on Health Effects of Mercury

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to inorganic and organic mercury are summarized in Figures 2-8 to 2-11. The purpose of these figures is to illustrate the existing information concerning the health effects of inorganic and organic mercury. Each dot in the figures indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 2-8. Existing Information on Health Effects of Metallic Mercury



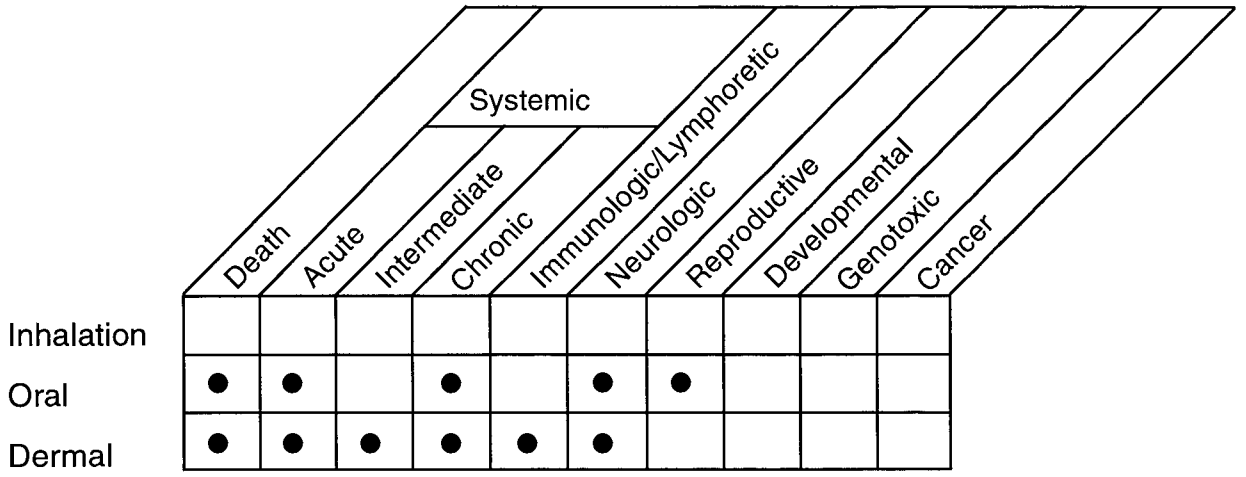
Human



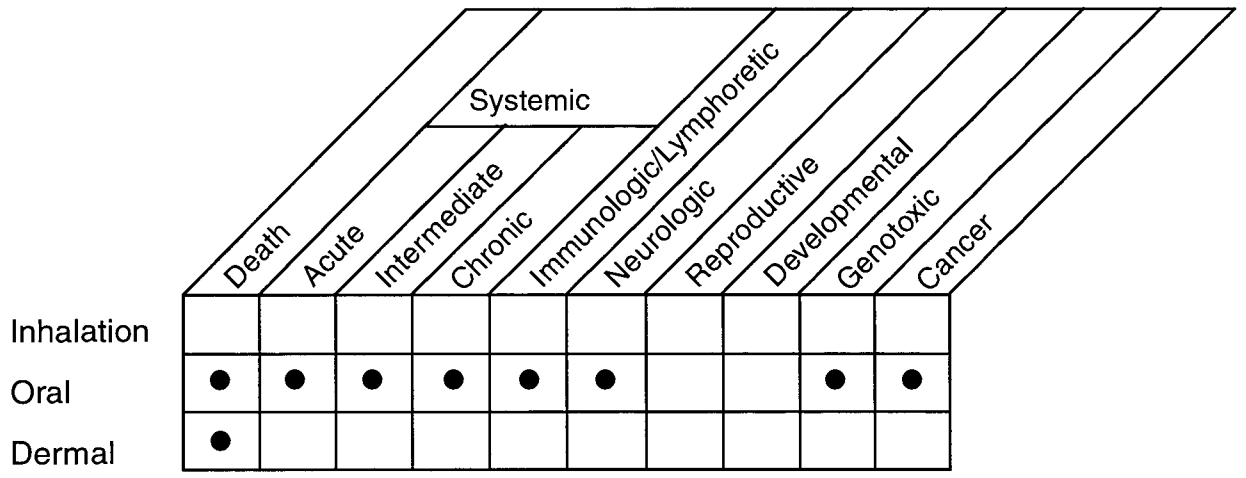
Animal

● Existing Studies

Figure 2-9. Existing Information on Health Effects of Inorganic Mercury Salts



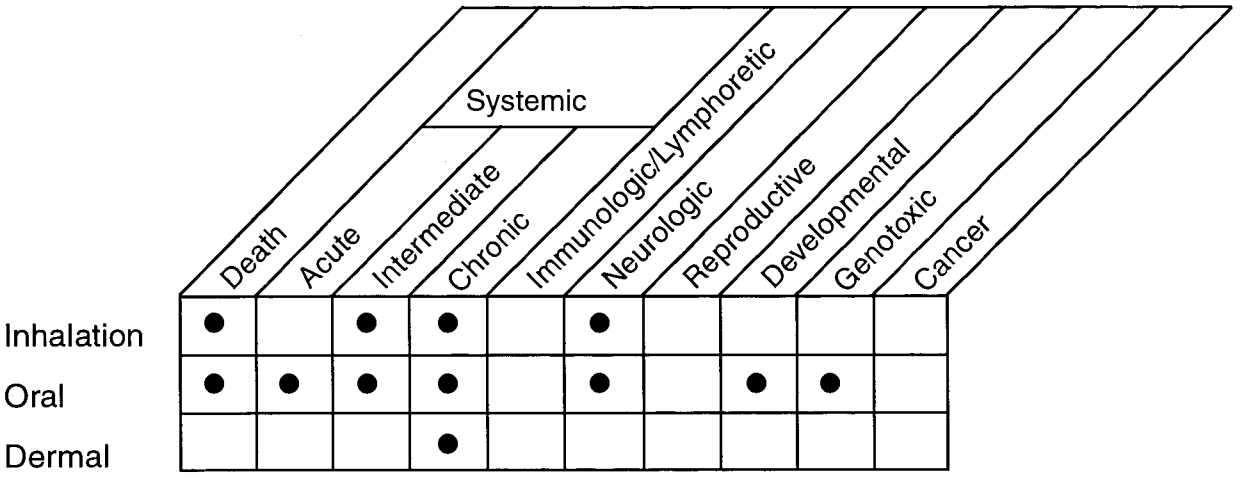
Human



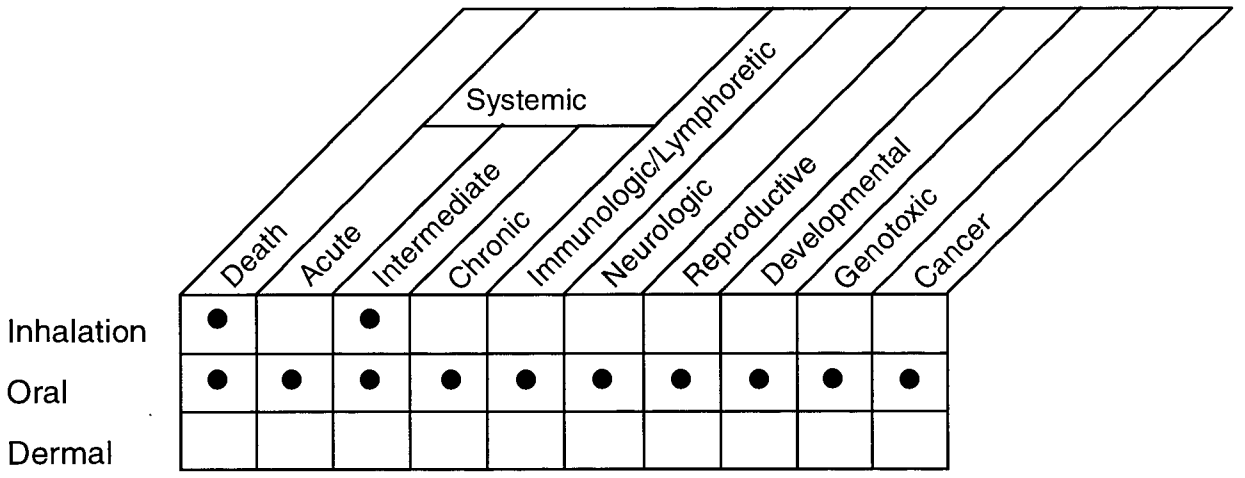
Animal

● Existing Studies

Figure 2-10. Existing Information on Health Effects of Methylmercuric Mercury



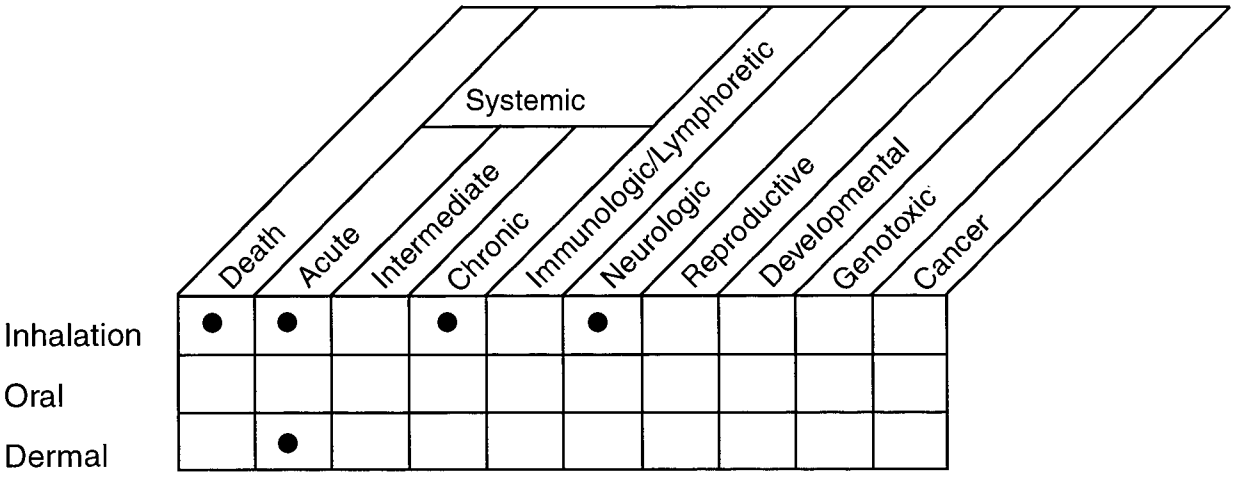
Human



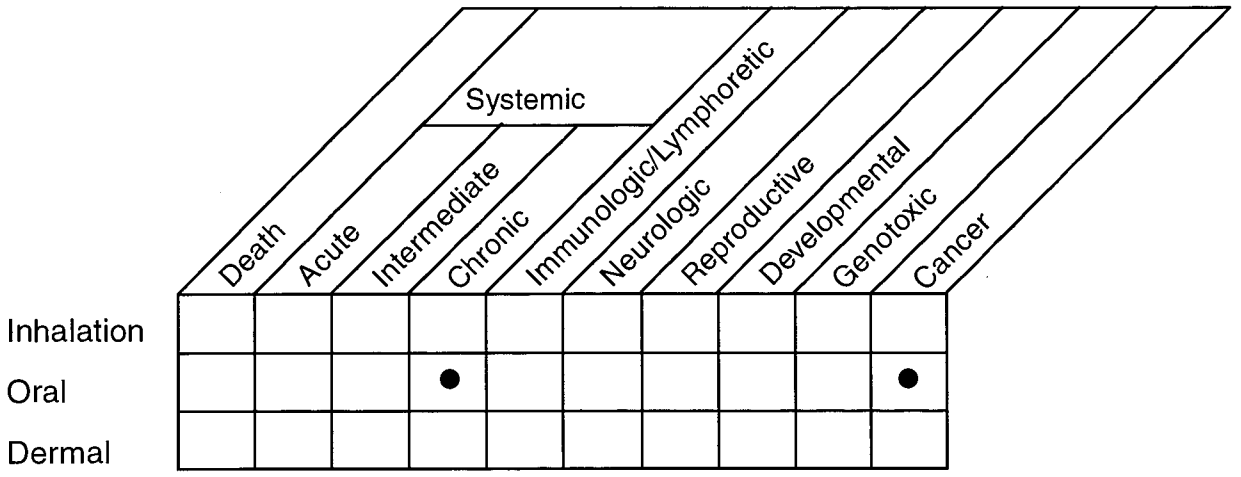
Animal

● Existing Studies

Figure 2-11. Existing Information on Health Effects of Phenylmercuric Mercury



Human



Animal

● Existing Studies

Information concerning metallic mercury exists primarily for the inhalation route of exposure in humans and animals (see Figure 2-8). Human data exist for all categories of effect following inhalation exposure to metallic mercury vapor. The results from inhalation studies in animals have been reported for all end points except immunological and genotoxic effects, and cancer. With the exception of case studies on contact dermatitis and neurological effects after acute and occupational dermal exposure to metallic mercury in humans, no studies were located for either the oral or dermal routes of exposure for either humans or animals.

Existing information on inorganic mercury salts is shown in Figure 2-9. No studies were found on the health effects from inhaled mercury salts in humans or animals. A number of case histories for acute or chronic oral exposure to mercury salts provide information on systemic and neurological effects and death. Some case histories and occupational studies provide information on dermal exposures to mercury salts at acute, intermediate, and chronic exposures leading to death, immunologic, neurologic, and systemic effects. No animal inhalation studies for inorganic mercury salts were identified, and only one acute study provides limited information on death from dermal exposure. A number of animal studies that have investigated the effects from oral exposure to mercury salts provide good information on systemic effects; limited information on cancer, neurologic, immunologic, and genotoxic effects; and no information on reproductive or developmental effects.

Information on methylmercuric and phenylmercuric mercury is presented in Figures 2-10 and 2-11. These two forms of organic mercury were chosen to represent the group of organic mercurials because they have been detected at Superfund sites, and because methylmercury is the predominant form of organic mercury in the environment. There is a paucity of information on phenylmercury. Only a few case histories are available for effects following inhalation exposure (death, acute or chronic systemic effects, and neurologic effects), and the information from these reports is very limited. Only one case history for acute systemic effects following dermal exposure to phenylmercury was identified. One chronic oral study in rats and a cancer study in rats and mice provide the only animal data for phenylmercury. In contrast, there are a number of human studies on systemic, neurologic, and developmental effects resulting from an oral exposure to methylmercury. No human toxicity data were identified for immunologic, reproductive, or genotoxic effect, nor for carcinogenicity. The human data for methylmercury are accompanied by a relatively large number of animal studies representing all three exposure durations and providing some, although often limited, information for all health effects categories. As with phenylmercury, there are only a few case histories for inhalation and dermal exposures, with limited information on neurologic and

systemic effects or death from acute poisonings. The animal data for inhalation exposure to methylmercury is equally scarce and nonexistent for dermal exposures.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. The human toxicity information for acute duration exposures to mercury is limited to qualitative data and case histories following oral, inhalation, and dermal routes of exposure. Several case reports described death due to respiratory impairment from inhaled metallic mercury (Campbell 1948; Kanluen and Gottlieb 1991; Soni et al. 1992; Taueg et al. 1992). Respiratory, cardiovascular, gastrointestinal, hematological, and renal effects have been observed after acute-duration inhalation exposure to metallic mercury vapors (Bluhm et al. 1992a, 1992b; Campbell 1948; Garnier et al. 1981; Haddad and Sternberg 1963; Hallee 1969; Jaffe et al. 1983; Kanluen and Gottlieb 1991; Karpathios et al. 1991; Lilis et al. 1985; McFarland and Reigel 1978; Milne et al. 1970; Snodgrass et al. 1981; Soni et al. 1992; Taueg et al. 1992). Acute exposure to ingested inorganic mercury salts has also resulted in gastrointestinal and renal symptoms (Afonso and deAlvarez 1960; Kang-Yum and Oransky 1992). Tremors, irritability, and decreased motor function and reflexes are common neurological symptoms following high-level acute duration exposures to metallic mercury vapors (Adams et al. 1983; Bluhm et al. 1992a; Hallee 1969; Jaffe et al. 1983; McFarland and Reigel 1978; Snodgrass et al. 1981). Acute exposure to ingested methylmercury has resulted in both neurological and developmental toxicity (Al-Mufti et al. 1976; Amin-Zaki et al. 1974; Bakir et al. 1973; Cox et al. 1989; Engleson and Herner 1952; Harada 1978; Marsh et al. 1980, 1981, 1987; Snyder and Seelinger 1976). Information on short term dermal exposures in humans to inorganic mercury are from case studies, and provide some information on renal, neurological, immunological, and dermatological effects (Bagley et al. 1987; Bourgeois et al. 1986; DeBont et al. 1986; Faria and Freitas 1992; Kawahara et al. 1993; Millar 1916; Pambor and Timmel 1989).

Dermal effects from acute duration dermal exposures to organic mercury compounds have also been reported to a limited extent (Morris 1960). In a highly publicized poisoning, a laboratory researcher was thought to have received a single dermal exposure to the organomercurial, dimethylmercury (estimated at between 0.1 and 0.5 mL at a density of 3 g/mL), that apparently penetrated the researcher’s latex safety gloves and resulted in a severe neurotoxicty 5 months later that subsequently ending with death (Blayney et al. 1997; Nierenberg et al. 1998; Toribara et al. 1997). Additional studies on dermal absorption of organic mercury, especially dimethylmercury, are needed to further evaluate the risk to human health.

Acute inhalation exposure to metallic mercury in rats and rabbits have resulted in death, respiratory, gastrointestinal, hepatic, renal, neurological, and/or developmental effects (Ashe et al. 1953; Fredriksson et al. 1992; Livardjani et al. 1991b). Acute oral exposures to inorganic mercury have resulted in renal, gastrointestinal, and thyroid effects in rats and/or mice (Dieter et al. 1992; Nielsen et al. 1991; NTP 1993; Sin et al. 1990) and neurological effects in rats (Chang and Hartmann 1972a, 1972b). An acute oral MRL was derived for inorganic mercury based on renal effects in rats (NTP 1993). Acute oral exposures to organic mercury have resulted in renal, neurological, developmental, and reproductive effects in rats, mice, guinea pigs, and rabbits (Arito and Takahashi 1991; Bornhausen et al. 1980; Cagiano et al. 1990; Chang and Hartmann 1972b; Guidetti et al. 1992; Hughes and Annau 1976; Inouye and Kajiwara 1988; Jacobs et al. 1977; Khera 1973; Khera and Tabacova 1973; Magos et al. 1985; Nolen et al. 1972; Post et al. 1973; Stoltenburg-Didinger and Markwort 1990; Yasutake et al. 1991b). Well conducted animal studies on neurological effects from an acute inhalation exposure to metallic mercury or to an acute dermal exposure to organic mercury are needed because of the potential for these kinds of exposures to populations near hazardous waste sites. The potential for latent or delayed expression of toxicity after an acute exposure to mercury from all the most likely routes and forms (especially for a dermal exposure to dimethylmercury) needs to be addressed.

Intermediate-Duration Exposure. Inhalation data on intermediate-duration exposure to metallic mercury vapors are limited to case reports of individuals exhibiting cardiovascular, gastrointestinal, hematological, renal, dermal, immunological, and neurological effects similar to acute exposures (Anneroth et al. 1992; Barber 1978; Fagala and Wigg 1992; Foulds et al. 1987; Friberg et al. 1953; Schwartz et al. 1992; Sexton et al. 1976; Taueg et al. 1992). Workers inhaling diethylmercury vapors developed gastrointestinal and neurological symptoms prior to death (Hill 1943). No inhalation exposure data are available on intermediate-duration exposure to mercuric mercury. Information on intermediate-duration oral exposure to inorganic mercury is limited to the observation of neurological symptoms in a boy who ingested Chinese medicine containing mercurous mercury for several months (Kang-Yum and Oransky 1992). Intermediate-duration oral exposure to organic mercury has resulted in dermal, neurological, and developmental toxicity (Al-Mufti et al. 1976; Amin-Zaki et al. 1974; Bakir et al. 1973; Cox et al. 1989; Harada 1978; Marsh et al. 1980, 1981, 1987; Snyder and Seelinger 1976). Intermediate-duration dermal exposure to inorganic mercury has resulted in adverse gastrointestinal, renal, and immunological health effects (Anneroth et al. 1992; Kang-Yum and Oransky 1992). No studies were located that examined effects resulting from intermediate-duration dermal exposure to organic mercury.

Inhalation exposure to metallic mercury vapors for an intermediate duration has resulted in renal and/or neurological effects in rabbits (Ashe et al. 1953) and rats (Fukuda 1971; Kishi et al. 1978). No studies were located regarding effects in animals after intermediate-duration inhalation exposure to organic mercury. An intermediate inhalation MRL was not derived for metallic mercury because studies were considered inadequate. Following intermediate-duration oral exposure to inorganic mercury, adverse cardiovascular, hepatic, and renal health effects have were observed in rats and mice exposed to mercuric chloride (Andres 1984; Carmignani et al. 1992; Dieter et al. 1992; Hultman and Enestrom 1992; Jonker et al. 1993a; NTP 1993; Rana and Boora 1992). Immunological and neurological health effects were also observed (Chang and Hartmann 1972a; Dieter et al. 1983; Hultman and Enestrom 1992). An intermediate oral MRL was derived for inorganic mercury based on increased kidney weight in rats (NTP 1993). Intermediate-duration oral exposure to organic mercury has resulted in adverse cardiovascular, renal, immunological, neurological, and developmental health effects in rats, mice, cats, and monkeys (Berthoud et al. 1976; Burbacher et al. 1988; Chang and Hartmann 1972a; Chang et al. 1974; Concas et al. 1983; Elsner 1991; Evans et al. 1977; Fowler 1972; Fowler and Woods 1977; Ganser and Kirschner 1985; Hirano et al. 1986; Ilback 1991; Khera and Tabacova 1973; Leyshon and Morgan 1991; Lindstrom et al. 1991; MacDonald and Harbison 1977; Magos and Butler 1972; Mitsumori et al. 1981; Olson and Boush 1975; Sharma et al. 1982; Tsuzuki 1981; Wakita 1987; Yip and Chang 1981). The data were insufficient to derive an intermediate-duration MRL for oral exposure to organic mercury because serious adverse health effects (e.g., neurological degeneration, behavioral changes) were observed at the lowest doses (Burbacher et al. 1988; Chang et al. 1974; Chang and Hartmann 1972a). No studies were located regarding intermediate-duration dermal exposure in animals. Because populations surrounding hazardous waste sites might be exposed to higher-than-normal levels of mercury for an intermediate duration, more quantitative information on metallic and organic mercury toxicity, specifically neurotoxicity, following inhalation and oral exposure in humans and animals is needed. The potential for latent or delayed expression of toxicity after an exposure of intermediate duration needs to be addressed.

Chronic-Duration Exposure and Cancer. Occupational exposure to metallic mercury vapors has been reported to result in adverse cardiovascular, gastrointestinal, renal, ocular, immunological, and reproductive health effects (Barregard et al. 1988, 1990; Bencko et al. 1990; Bidstrup et al. 1951; Buchet et al. 1980; Cardenas et al. 1993; Cordier et al. 1991; Danziger and Possick 1973; Ehrenberg et al. 1991; Kazantzis et al. 1962; Langworth et al. 1992b; Lille et al. 1988; Moszczynski et al. 1990b; Piikivi 1989; Piikivi and Hanninen 1989; Roels et al. 1982; Schuckmann 1979; Siblerud 1990; Smith et al. 1970; Stewart et al. 1977; Tubbs et al. 1982; Vroom and Greer 1972). Substantial evidence indicates that

chronic inhalation of metallic mercury vapors results in neurotoxicity (Albers et al. 1988; Bidstrup et al. 1951; Chapman et al. 1990; Discalzi et al. 1993; Ehrenberg et al. 1991; Fawer et al. 1983; Langauer-Lewowicka and Kazibutowska 1989; Langworth et al. 1992a; Levine et al. 1982; Melkonian and Baker 1988; Ngim et al. 1992; Piikivi and Hanninen 1989; Piikivi and Tolonen 1989; Piikivi et al. 1984; Shapiro et al. 1982; Smith et al. 1970; Verberk et al. 1986; Vroom and Greer 1972; Williamson et al. 1982). A chronic inhalation MRL was derived for neurological effects observed in workers chronically exposed to metallic mercury (Fawer et al. 1983). Very limited information is available indicating that chronic-duration inhalation of organic mercury (sometimes unspecified) causes adverse cardiovascular, gastrointestinal, renal, and neurological health effects (Brown 1954; Hook et al. 1954; Hunter et al. 1940; Williamson et al. 1982). Chronic-duration ingestion of mercurous chloride resulted in dementia and irritability (Davis et al. 1974). Qualitative and quantitative data on organic mercury exposure are provided by the neurological disorders associated with ingestion of methylmercury-contaminated fish, but the length of exposure is unknown (Kutsuna 1968). Chronic occupational exposure to alkyl mercury compounds caused neurological changes in humans (Lundgren and Swensson 1949). The available evidence indicates that the differences in toxicity between inorganic and organic mercury forms are largely the result of the differences in their distribution in the body. Information concerning methyl-mercury is much more extensive than that for phenylmercury, especially considering the outbreaks of methylmercury poisoning that have occurred in Japan and Iraq.

Cardiovascular and renal health effects in rats and mice after chronic-duration ingestion of inorganic mercury have been reported (Carmignani et al. 1989; Fitzhugh et al. 1950; NTP 1993). An intermediate oral MRL based on renal effects was derived for intermediate oral exposure to inorganic mercury (NTP 1993). Chronic-duration oral exposure to organic mercury has resulted in adverse gastrointestinal, renal, developmental, neurological, and reproductive health effects in rats, mice, cats, and monkeys (Charbonneau et al. 1976; Fitzhugh et al. 1950; Hirano et al. 1986; Mitsumori et al. 1981, 1990; Rice 1989c, 1992; Rice and Gilbert 1982, 1990, 1992; Solecki et al. 1991). A chronic MRL for oral exposure to organic mercury was derived based on a study of prenatal exposures in a fish-consuming population on the Seychelles Islands (Davidson et al. 1998). Additional chronic-duration data on neurological disorders following metallic and organic mercury exposure are needed because they are a sensitive end point. Furthermore, there is a potential for chronic exposure to higher-than-normal levels of mercury in populations living in the vicinity of hazardous waste sites.

Additional chronic-duration oral exposure information in animals concerning renal effects following inorganic mercury exposure is needed to evaluate the threshold of this effect in humans following chronic exposure. The data would be useful if populations living near hazardous waste sites were to be exposed chronically to inorganic mercury that leached into near-by wells or water supplies.

Forestomach squamous cell papillomas and thyroid follicular cell carcinomas have been observed in rats and renal tubule tumors have been observed in mice following oral exposure to mercuric chloride (NTP 1993). Renal tumors have also been observed in rats and mice after oral exposure to organic mercury (Hirano et al. 1986; Mitsumori et al. 1981, 1990; Solecki et al. 1991). These results suggest the potential carcinogenicity of mercury to humans. Therefore, additional chronic-duration animal studies on metallic, inorganic, and organic mercury are needed to confirm the findings of the NTP study. Additional long-term follow-up studies examining carcinogenicity in highly exposed populations (i.e., those involved in mercury mining, or the exposed Iraqi or Japanese populations) are needed to evaluate the likelihood of tumors appearing in humans.

Genotoxicity. Although there are data from several *in vivo* studies on rats (oral exposure) and mice (intraperitoneal) indicating that inorganic and organic mercury compounds can cause clastogenic effects in mammalian germinal cells, the differences in species sensitivity, and in some cases strain sensitivity, do not permit the use of these findings for predicting a potential hazard to human genetic material (Suter 1975; Zasukhina et al. 1983). Epidemiological studies of humans occupationally or accidentally exposed to mercurials were inconclusive, but the combined results from these studies did not suggest that metallic mercury and organic mercury are clastogens for human somatic cells (Anwar and Gabal 1991; Barregard et al. 1991; Mabille et al. 1984; Popescu et al. 1979; Verschaeve et al. 1976, 1979; Wulf et al. 1986). There is, however, convincing evidence that inorganic and organic mercury compounds can interact with and damage DNA *in vitro* (Williams et al. 1987). The outcome of this damage has not been characterized, but there is some indication that mercury compounds are weak mutagens for cultured mammalian cells. In addition, *in vitro* results with human cells (Betti et al. 1992) and animal cells (Howard et al. 1991) and *in vivo* data in mice (Ghosh et al. 1991) suggest that mercury compounds can cause clastogenic effects in somatic cells. Considering the problems stated above in using the whole animal data, and the apparent species- and strain-specific responses noted in the DNA damage tests with cultured mammalian cells, the *in vitro* data, while of interest, are probably not reliable indicators of potential adverse effects in humans exposed to mercury. Well controlled human epidemiological studies are needed to determine the genetic hazard of mercury compounds to humans.

Reproductive Toxicity. Occupational exposure to metallic mercury has not been shown to result in statistically significant effects on male fertility (Alcser et al. 1989; Lauwerys et al. 1985). However, an increase in the rate of spontaneous abortions may occur (Cordier et al. 1991). A spontaneous abortion occurred in a female after ingesting an acute dose of mercuric chloride (Afonso and deAlvarez 1960). There were no studies available on dermal exposure to metallic, inorganic, or organic mercury. Additional epidemiological studies on inhalation and dermal exposure to mercury are needed to evaluate the threshold of reproductive effects in workers (including dentists and dental assistants).

Inorganic mercury exposure caused a significant increase in the incidence of resorptions in hamsters (Gale 1974). Abortions and decreased mean litter size have been observed in rats, mice, guinea pigs, and monkeys following oral exposure to organic mercury (Burbacher et al. 1988; Hughes and Annau 1976; Inouye and Kajiwara 1988; Khera 1973). There was a decrease in conceptions and an increase in early abortions and stillbirths in female monkeys exposed orally to methylmercury for 4 months, but the menstrual cycle length was not affected (Burbacher et al. 1988). However, prolonged estrous cycles were found in rats inhaling metallic mercury (Baranski and Szymczyk 1973). Adverse effects on spermatogenesis and on histopathology of the testes have been reported in several studies in animals exposed to methylmercury (Hirano et al. 1986; Mitsumori et al. 1990; Mohamed et al. 1987). There was no information on reproductive effects following dermal exposure to mercury in animals. A 90-day study is needed to provide reproductive organ pathology data on male and female animals. Multigenerational studies for inorganic and organic mercury are also needed. Additional reproductive studies are needed because reproductive-aged populations near hazardous waste sites might be exposed to mercury.

Developmental Toxicity. Occupational exposure to metallic mercury in males did not result in statistically significant effects on malformations or the number of children born (Alcser et al. 1989; Lauwerys et al. 1985). The results from an inhalation developmental rat study (Baranski and Szymczyk 1973) suggest that metallic mercury vapors may cause a higher incidence of fetal malformations, resorptions, and deaths. Dermal studies on metallic mercury in humans and animals were not available. Additional well-conducted inhalation and dermal studies on metallic mercury in animals are needed to evaluate the potential for adverse developmental effects to humans from mercury.

Inorganic mercury exposure caused a significant increase in the incidence of resorptions in hamsters (Gale 1974). No other human or animal studies were available on developmental effects following inorganic mercury exposure. Therefore, additional studies for inhalation, oral, and dermal exposures are

needed to evaluate the potential developmental toxicity of inorganic mercury to populations, specifically young children, living near hazardous waste sites. Longitudinal studies for higher dose level acute and intermediate exposures are needed to determine the potential delayed expression of toxicity.

Prenatal exposure to methylmercury from contaminated food during the early stages of pregnancy has caused neurological damage in humans (Amin-Zaki et al. 1974; Bakir et al. 1973; Choi et al. 1978; Cox et al. 1989; Engleson and Herner 1952; Harada 1978; Marsh et al. 1980, 1981, 1987; Matsumoto et al. 1965; McKeown-Eyssen et al. 1983; Snyder and Seelinger 1976). Severe neurological impairment developed in a child exposed *in utero* to methylmercury, and effects were still present at 6 years of age (Snyder and Seelinger 1976). In animals, numerous oral exposure studies on the developmental effects of organic mercury have been conducted. Disruptions in the development of the nervous system in rats, mice, hamsters, and guinea pigs (Chang et al. 1977; Inouye and Kajiwara 1988; Khera and Tabacova 1973; Reuhl et al. 1981a, 1981b) and in the immune system in rats (Ilback et al. 1991) have been reported. Behavioral changes were also observed in rats and mice (Bornhausen et al. 1980; Hughes and Annau 1976; Olson and Boush 1975). Additional long-term inhalation, oral, and dermal studies for inorganic and organic mercury are needed to evaluate the threshold of developmental effects in workers chronically exposed to mercury or in populations living near hazardous waste sites.

Immunotoxicity. The results from two occupational studies indicate a decreased serum IgG levels in workers to inhaled metallic mercury vapors (Bencko et al. 1990; Moszczynski et al. 1990b), but these studies are limited and did not evaluate potential confounders (smoking and alcohol). Other studies in similarly exposed populations did not observe an increases in serum immunoglobulins (IgA, IgG, IgE, or IgM) and autoantibody titres (antilaminin or antiglomerular basement membrane antibodies) (Bernard et al. 1987; Cardenas et al. 1993; Langworth et al. 1992b). There is limited information in humans that suggests that certain individuals may develop an autoimmune response (Tubbs et al. 1982; Moszczynski et al. 1995). Data on immunological effects following oral exposure to organic mercury compounds in humans are not available. Oral exposures to inorganic and organic mercury in animals indicate that the immune system may be a target organ for mercury. Immune deposits were observed in the intestines and kidneys of rats exposed to mercuric chloride for 2 months, but no functional changes were evident in these tissues (Andres 1984). Suppression of the lymphoproliferative response occurred at a higher dose of mercury in mice exposed to mercuric chloride for 7 weeks (Dieter et al. 1983). Reduced natural killer cell activity in spleen and blood was exhibited in mice administered a diet containing methylmercury for 12 weeks (Ilback 1991). It is unknown how an adverse effect on the immune system from exposure to one form of mercury

might affect the response to other forms or other routes of exposure (e.g., how an adverse immune effect induced by inhalation of mercury vapor from dental amalgam might effect the dose-response from exposure to ingested methylmercury). Therefore, the potential for immunotoxic effects from exposure to mercury vapor, mercury salts, or methylmercury separately or in combination is of considerable importance and warrants further research, especially from low level chronic exposures.

Neurotoxicity. The nervous system is the major target organ for metallic and organic mercury through inhalation and oral routes, respectively. In humans, the neurological effects of metallic mercury have been observed primarily after acute high-concentration exposures (accidental) to intermediate and chronic low-concentration exposures (occupational). Tremors and irritability are the most prominent symptoms of inhaled metallic mercury in humans (Albers et al. 1988; Bidstrup et al. 1951; Fawer et al. 1983; Piikivi et al. 1984). Information on effects in humans from oral exposure includes case histories, for example, a chronic oral exposure to a laxative containing mercurous chloride (Davis et al. 1974), acute to intermediate duration ingestion of high levels of methylmercury-contaminated food (Bakir et al. 1973; Kutsuna 1968), or to chronic low-level exposures from fish or marine mammals containing methylmercury (Davidson et al. 1995aa, 1995b; Grandjean et al. 1997b, 1998). Case histories of dermal exposure to inorganic mercury cite similar neurological effects from acute (Bourgeois et al. 1986; DeBont et al. 1986) or chronic exposures (Dyall-Smith and Scurry 1990).

The neurotoxicity of inhaled metallic mercury has been studied in animals for acute and intermediate exposures (Ashe et al. 1953; Ganser and Kirschner 1985; Kishi et al. 1978). Behavioral, motor, and cognitive effects, as well as histopathological changes in the brain, were reported in rats, rabbits, and mice. Neurological disturbances in rats and mice resulted from acute, intermediate, and chronic oral exposures to mercuric mercury (Chang and Hartmann 1972b; Ganser and Kirschner 1985). Oral exposure to organic mercury in animals produced a range of neurological changes (Charbonneau et al. 1976; Evans et al. 1977; Magos and Butler 1972; Rice and Gilbert 1982; Sharma et al. 1982; Tsuzuki 1981). A chronic inhalation MRL was derived for metallic mercury. Additional animal studies are needed, however, to evaluate the neurotoxicity of inorganic mercuric salts to resolve some of the conflicting findings from pervious work (Chang and Hartmann 1972b; Ganser and Kirschner 1985; Goldman and Blackburn 1979; NTP 1993). *In vivo* studies are needed to evaluate the mechanisms of neurotoxic effects seen in *in vitro* studies, i.e., the lipoperoxidation and cell injury in methylmercury-exposed cerebellar granule cells (Sarafian and Verity 1991). Further evaluation is needed in humans and animal models of the potential for neurological effects and delayed neurotoxicity from chronic low level exposures to organic and inorganic mercury, especially

from multiple sources (i.e., organic mercury from fish consumption in conjunction with metallic mercury released from dental amalgam).

Epidemiological and Human Dosimetry Studies. There have been a number of occupational studies on workers chronically exposed to metallic mercury vapors. Mercury exposure (as measured by urine or blood mercury levels) and neurological effects have been evaluated (Adams et al. 1983; Miller et al. 1975; Roels et al. 1982; Smith et al. 1970). The most obvious deficiency in these epidemiological studies is the absence of good measures of exposure. Additional data are needed on the potential health effects for populations near hazardous waste sites based upon specific identification of the form of mercury and the pathways of exposure (i.e., the levels of exposure that populations near waste sites may actually experience from inorganic mercury in the air, water, and soil, or methylmercury in contaminated food). An area of considerable controversy, which is in need of good epidemiological data, is the potential for adverse effects from the mercury released from dental amalgam. Although this is not an exposure pathway associated with hazardous waste sites, mercury from amalgam represents a major contributor to the total body burden for a large percentage of the population, and thus must be factored into an assessment of the toxicokinetic behavior and toxic effects of mercury originating from a waste site. Long term longitudinal studies are needed for all dose durations and forms to evaluate delayed or persistent expression of mercury toxicity.

Biomarkers of Exposure and Effect

Exposure. Blood and urine mercury levels have been used as biomarkers of high level exposure in acute and chronic studies for both inorganic and organic mercury (Akesson et al. 1991; Naleway et al. 1991; Verschoor et al. 1988). Hair has been used as a biomarker for chronic low level organic mercury exposure (Nielsen and Andersen 1991a, 1991b; Oskarsson et al. 1990), with an awareness of the potential for external contamination (Clarkson et al. 1983). Further development of more sensitive tests to measure mercury in expired air and retention in hair are needed for monitoring short- and long-term exposures, respectively, for populations at risk.

As seen in other studies comparing European to Japanese hair mercury levels, the hair levels reported by Nakagawa (1995) of 2–4 ppm for a Japanese population are 10–20 times higher than levels observed in the Drasch et al. (1997) study (median, 0.247 µg/g in hair; range, 0.43–2.5 µg/g). These differences in the mercury exposure may affect not only the mercury hair levels but also the mercury hair-to-tissue

correlations. Further study is needed on the effects that the exposure level of methylmercury (as well as other forms of mercury) has on tissue distributions and the correlation to biomarkers of exposure.

There are potential confounding factors and other factors to consider when assessing mercury exposure based upon mercury hair levels. Mercury may be deposited to hair from the air when significant sources of mercury are present in the air or when certain hair treatments are used (Hac and Krechniak 1993; WHO 1991). Potential sources of external mercury exposure should, therefore, be evaluated as part of an exposure assessment. Some studies also report a sex related difference in mercury tissue levels. Nielson et al. (1994) observed a significant sex-related differences in the toxicokinetics of methylmercury in mice following administration of a single radiolabeled dose. Drasch et al. (1997) reported that mercury levels in all tissues assayed in their human cadaver study had higher levels compared to male tissues. The difference was significant for the kidney (median female kidney mercury level=92.0 ng/g, males=40.8 ng/g; p=0.002). In blood and urine there was a similar trend. In contrast, the authors report that mercury hair levels in females were significantly lower than in males (median females=205 ng/g, males 285 ng/g; p=0.02). Nakagawa (1995) also report higher mean mercury hair levels in males (2.98 µg/g) compared with females (2.02 µg/g) in a Japanese population. Further research is, therefore, needed to characterize potential sex related difference in the toxicokinetics of mercury under different exposure scenarios.

Further research on other biomarkers of mercury does not warrant a high priority.

Of particular importance is the collection of pharmacokinetic data showing the relationship between low-level exposure (acute, intermediate, and chronic) and blood and urine levels throughout the study .duration. Also tissue levels at necropsy should be taken immediately after cessation of dosing. In animal studies, a similar group of animals should be followed for urine (and blood, but not as important here) mercury levels for periods of 30, 60, 90, and 120 days postdosing to examine whole-body excretion, and necropsy tissue samples should also be taken from several animals at 30, 60, 90, and 120 days postdosing. Primates would be the best animal model, but rodent models could suffice.

A needed study is a longitudinal epidemiology study that tracked daily individual exposure levels in chloralkali industry workers, fluorescent lightbulb manufacturers, or other mercury utilizing industries, and associated these exposure levels with weekly urine and blood samples for a period of 1–2 years. Neurobehavioral testing (using tests from ATSDR’s recommended test battery for adults) should be used

conducted at 6-month intervals. Workers new to these industries would be the best subjects, since their pre-exposure blood and urine levels could be used as reference values.

A biomarker/exposure could also be conducted in persons with dental amalgam fillings. Urine levels should be tracked in those with fillings and in those with removed or replaced amalgam fillings. There are a number of confounding factors and logistical difficulties in conducting such studies, and new study protocols should be developed to address the problems encountered in previous studies.

Effect. Potential biomarkers of effect for mercury-induced renal toxicity have been well described (Cardenas et al. 1993; Lauwerys et al. 1983; Rosenman et al. 1986; Verschoor et al. 1988). Biomarkers for neurological changes (e.g., paresthesia, decreased motor function, and impaired nerve conduction) have also been described (Clarkson et al. 1976; Shapiro et al. 1982). There is long history of evaluation of the neurophysiological and neuropsychological effects associated with mercury levels in blood, urine, and (Levine et al. 1982; Vroom and Greer 1972; Williamson et al. 1982). More recently, studies are evaluating cognitive and neurobehavioral effects with increasing sophistication in the assays and analyses that are used (Davidson et al. 1998; Grandjean et al. 1997b, 1998). Additional biomarkers are needed in this continuing effort to resolve subtle cognitive or neurobehavioral effects, and immune system effects from chronic low level exposures to methylmercury in food or metallic mercury released from dental amalgam, especially in sensitive populations.

Absorption, Distribution, Metabolism, and Excretion. Limited data are available to assess the relative rate and extent of absorption in humans following inhalation exposure to metallic mercury (Barregard et al. 1992; Berlin et al. 1969; Friberg and Vostal 1972; Hursh et al. 1976; Teisinger and Fiserova-Bergerova 1965) and in humans and animals following oral exposure to both inorganic salts and organic mercury (Aberg et al. 1969; Clarkson 1971, 1972a, 1989; Endo et al. 1989, 1990; Fitzhugh et al. 1950; Friberg and Nordberg 1973; Kostial et al. 1978; Miettinen 1973; Nielsen 1992; Nielsen and Andersen 1992; Rice 1989b; Suzuki et al. 1992; Urano et al. 1990; Weiss et al. 1973; Yeoh et al. 1989). Indirect evidence of absorption following inhalation exposure in humans and animals is reported for inorganic and organic mercury (Clarkson 1989; Ostlund 1969; Warfvinge et al. 1992; Yoshida et al. 1990, 1992). Only limited quantitative data were located regarding dermal uptake of metallic mercury in humans (Hursh et al. 1989). Information is needed regarding the rate and extent of dermal absorption of inorganic and organic mercury in humans and animals. Quantitative information concerning the inhalation and oral absorption of mercury (all forms)are needed.

In general, quantitative data are available to evaluate the rate and extent of distribution, metabolism, and elimination of mercury in humans and animals following inhalation and oral exposure. Data on distribution, metabolism, and excretion following dermal exposure are lacking for all forms of mercury. The distribution data for metallic, inorganic and organic mercury are similar in humans and animals (Aschner and Aschner 1990; Berlin 1963; Cherian and Clarkson 1976; Cherian et al. 1978; Clarkson 1989; Clarkson and Magos 1978; Danscher et al. 1990; Grandjean et al. 1992; Nielsen and Andersen 1990, 1991a, 1991b; Nordberg 1976; Schionning et al. 1991; Sin et al. 1983; Suzuki et al. 1992; Warfvinge et al. 1992; Yeoh et al. 1989; Yoshida et al. 1990, 1992). No quantitative distribution data were located for organic mercury compounds following inhalation exposure. The oxidation and reduction reactions that control the disposition of elemental mercury were identified in both animals and humans (Clarkson 1989; Halbach and Clarkson 1978; Nielsen-Kudsk 1973). Quantitative data on the biotransformation of organic mercury are limited (Norseth and Clarkson 1970). Reliable quantitative evidence on excretion of metallic and inorganic mercury in humans and animals following inhalation exposure is available (Cherian et al. 1978; Hursh et al. 1976; Joselow et al. 1968b; Lovejoy et al. 1974).

As discussed in the section on data needs for biomarkers, further study is needed on the effects that the exposure level of methylmercury (as well as other forms of mercury) has on tissue distributions and the correlation to biomarkers of exposure. Age appears to be a factor in the elimination of mercury in rats following inorganic and organic mercury exposures (Daston et al. 1986; Thomas et al. 1982). Elimination of methylmercury in rats may also be sex-related (Ballatori and Clarkson 1982). Nielson et al. (1994) observed a significant sex-related differences in the toxicokinetics of methylmercury in mice following administration of a single radiolabeled dose. Drasch et al. (1997) reported that mercury levels in all tissues assayed in their human cadaver study had higher levels compared to male tissues. Nakagawa (1995) also report higher mean mercury hair levels in males (2.98 µg/g) compared with females (2.02 µg/g) in a Japanese population. Further research is, therefore, needed to characterize potential sex related difference in the toxicokinetics of mercury under different exposure scenarios.

Insufficient data are available to assess whether or not there are any differences in absorption, distribution, metabolism, and excretion of mercury with respect to time or dose (i.e., if saturation phenomena occur). The majority of the available toxicokinetic data involve acute exposures to single doses. For all three routes, studies are needed that compare various dose levels and durations in order to determine if there are any differences in the toxicokinetics of mercury. Little is known about how mercurials are eliminated from specific organs. In particular, the mechanism by which mercury is eliminated from the brain is

unknown. This information is needed to design better treatment drugs and protocols. Mechanistic studies are needed on how mercury (in its various forms) is excreted and how such activities can be enhanced.

An important priority research and data need is a study of the effects of dietary selenium on the absorption and toxicity of methylmercury. Primates would be the most appropriate species for such a study. Oral dosage levels (in food) should cover an sufficient dose range to provide useful information for high fish consuming populations. Mercury excretion should also be measured and compared with controls at least weekly, with the entire study length being not less than 6 months, and preferably one to two years in duration. Concurrent neurobehavioral testing should be included, if possible, and be conducted at fixed intervals depending upon the duration of the study.

Comparative Toxicokinetics. There is only limited data available on species differences in absorption rates following oral exposures to all forms of mercury, and the results are negative (i.e., no differences) (Clarkson 1971, 1972a; Friberg and Nordberg 1973; Nielsen and Andersen 1990; Rice 1989b). There are data concerning inhalation absorption of metallic and inorganic mercury (Berlin et al. 1969; Cherian et al. 1978; Clarkson 1989; Hursh et al. 1976); however, the data are insufficient to allow for interspecies comparisons (Ostlund 1969). Studies comparing the inhalation absorption of all forms of mercury in humans and animals are needed to improve the utility of animal data in assessing human risk. The limited information available on dermal exposure suggests that dermal absorption of both inorganic and organic mercury compounds occurs in humans and animals, although no comparison of the rate or extent of absorption can be made between species (Gotelli et al. 1985; Hursh et al. 1989; Laug and Kunze 1949; Schamberg et al. 1918). As with inhalation exposure, studies comparing the dermal absorption of all forms of mercury in humans and animals are needed to improve the utility of animal data for assessing human risk.

The distribution of mercury in humans and animals appears to be similar. The lipophilic nature of metallic mercury results in its distribution throughout the body in humans (Takahata et al. 1970) and in animals (Berlin and Johansson 1964; Berlin et al. 1966). Distribution of inorganic mercury compounds resembles that of metallic mercury; however, human distribution is preferentially to the kidneys, liver, and intestines. Also, levels in the brain are substantially lower, as these compounds have a lower lipophilicity. Distribution of organic mercury compounds is also similar to that of metallic mercury. The ability of methylmercuric compounds to cross the blood-brain and placental barriers enables ready distribution to all tissues, although, again, the highest levels are found in the kidneys. Phenylmercuric compounds are

initially distributed in a similar manner to methylmercury; however, the distribution eventually resembles that of inorganic mercury.

The available evidence suggests that feces and urine constitute the main excretory pathways of metallic mercury and inorganic mercury compounds in both humans and animals. Additional excretory routes following metallic and inorganic mercury exposure include exhalation and secretion in saliva, sweat, bile, and breast milk (Joselow et al. 1968b; Lovejoy et al. 1974; Rothstein and Hayes 1964; Sundberg and Oskarsson 1992; Yoshida et al. 1992). Excretion following exposure to organic mercury is considered to be predominantly through the fecal route in humans. Evidence from studies in humans and animals (mice, rats) suggests that exposure to methylmercury leads primarily to biliary secretion, while excretion is initially through the bile; it then shifts to the urine following phenylmercury exposure (Berlin and Ullberg 1963; Berlin et al. 1975; Gotelli et al. 1985; Norseth and Clarkson 1971). No further comparative studies on excretion are warranted because there is no apparent difference in the excretion of mercury in any form in humans and animals.

Two PBPK models have recently been published on the pharmacokinetics of methylmercury in rats (Farris et al. 1993; Gray 1995). Additional PBPK studies are needed to support species and dose extrapolations, and a better understanding of the underlying toxic and kinetic mechanisms is needed in support of human risk assessments.

Validation of *in vitro* data is a major need. Much of the data from *in vitro* experimentation is based on unrealistic concentrations of the toxicant or is derived from studies using non-physiological designs. In particular, more validation is needed for immunotoxicity studies and biochemical studies.

Methods for Reducing Toxic Effects. Nonspecific methods or treatments for reducing absorption following mercury exposure include the administration of chelators or protein solutions to neutralize and bind to inorganic mercury compounds (Bronstein and Currance 1988; Florentine and Sanfilippo 1991; Gossel and Bricker 1984). The use of a particular chelator is dependent upon the type of mercury exposure (Gossel and Bricker 1984). Chelation therapy is the treatment of choice for reducing the body burden of mercury (Florentine and Sanfilippo 1991; Gossel and Bricker 1984; Haddad and Winchester 1990). However, chelation releases mercury from soft tissues that can then be redistributed to the brain. Additional research is needed to elucidate the mechanisms of absorption and distribution of inorganic and organic mercury. Animal studies suggest that antioxidants may be useful for decreasing the toxicity of

mercury. Additional work studying the effectiveness of prophylactic administration of vitamin E (or other antioxidants) and of proper diet are needed. Improved chelation and drug therapies for treating acute and chronic mercury poisonings are greatly needed.

Children's Susceptibility. The systemic health effects from different forms of mercury and exposure routes have been fairly well characterized (EPA 1997; Sue 1994; WHO 1990). There is generally sufficient information on the symptoms to resolve the form and route of exposure when children are exposed to high levels of mercury. There is less information to assist the physician or public health official in recognizing the symptoms that might arise from lower level exposure to multiple forms of mercury (e.g., dental amalgam and fish) and multiple pathways (inhalation and ingestion). Whether concurrent exposures would result in a different presentation of symptoms would be important information in determining the best therapeutic treatment. Some health effects categories are not well defined (e.g., immune responses). Earlier identification of immunotoxicity is of concern for children because of the progressive nature of hypersensitization to environmental pollutants, and the burden that a compromised immune system can place on a person's long-term health.

There are not presently adequate measures for neurologic development. Delayed developmental effects are of grave concern for children exposed to mercury; methods for early determination and detection of progressively worsening changes in a child's behavioral or cognitive function are needed. For the measures to be truly useful they should in some way be integrated into a more directed exposure assessment and body burden analysis and to resolve the contribution from other influences on cognitive abilities and behaviors. Other data needs related to developmental effects are discusses above under Developmental Toxicity.

Pharmacokinetics are different for children, and more data are needed to improve chelation therapies for both acute high-level poisoning and for chronic low-level exposures. This is perhaps the area that deserves the most attention because accidental poisonings continue to occur and there are virtually no therapies to ameliorate the inevitable progression of mercury intoxication. Since environmental levels of mercury are also continuing to rise, and levels in food will concurrently rise, strategies to boost the body's ability to eliminate absorbed mercury are going to become increasingly important (i.e., the alternative is to change dietary patterns, i.e., eat less fish, and the risk/benefits of doing that are already being hotly debated).

There appears to be adequate information on the metabolism of mercury, and there are no special metabolites or metabolic pathways that are unique to children and require further evaluation.

The mechanism of mercury toxicity is still largely unknown. It is not known whether there are unique mechanisms of action for the toxic effects in children that would require special consideration for treatment modalities, but at present it appears that target site is determined more by the pharmacokinetics (i.e., which tissues end up with the highest levels) than by a specific mechanism of action (e.g., a receptor binding-process initiating type of mechanism).

The results of a number of accidental food poisonings indicate that children are more vulnerable, and this vulnerability may be a function of easier access of mercury to the systemic circulation and brain, or it may be because disruption of cell growth and organization is more critical for children in developmental stages of growth. More data are needed to determine if the vulnerability of children is due to less plasticity to insult of analogous target tissue in adults, or because target tissues actually receive more toxic agent.

There are not adequate biomarkers of exposure nor adequate access to biomarkers of exposure. Hair, urine, and blood levels are gross measures of body burden and do not provide the essential information about levels of mercury at target tissues. Research is needed into better (preferably noninvasive) monitoring tools. Research is also needed on how to make monitoring tests readily and inexpensively available to the general public. Mercury is one of the top ten most hazardous substances, and its levels are increasing in the environment. There is considerable anxiety present in the general population about potential mercury toxicity from dental amalgam, but this occurs in the absence of good information on actual body burdens. The general public and health officials would benefit from readily available ways for individuals to measure personal and family member mercury body burdens.

The interactions of immediate interest are those that either affect absorption from the gastrointestinal tract or that prevent or reduce mercury toxicity. No information was identified to indicate that mercury interacts differently with iron or zinc, for example, in a child’s body then it would in an adult, although the difference in children’s physiology and morphology may result in a different response to that interaction. Except for the latter, which is again a toxicokinetic question, chemical interactions do not appear to be a data need.

There is a data need to develop better chelation therapies, better ways to prevent absorption of mercury into the body of children, and better ways to interfere with the mechanism of action, especially for damage to the nervous system. The current literature continues to grow with case histories of poisonings where

supportive therapy and passive observation of a progressively deteriorating health status are the best that can be done.

No information was found that parental exposure to mercury results in heritable defects or deficits in germ cell function that would be translated to the offspring. There is considerable information on the transfer of mercury from the mother to the developing child, both during the prenatal period via the placenta and during postnatal nursing; both inorganic mercury and organic mercury pass from mother to child. This is an area of active research primarily to characterize the dose, duration, and form of mercury to which the child is being exposed. Further work in this area is needed.

Child health data needs related to exposure are discussed in Section 5.8.1, Data Needs: Exposure of Children.

2.11.3 Ongoing Studies

Ongoing studies regarding mercury's health effects and mechanisms of action were reported in the Federal Research In Progress (FEDRIP 1998) database. Table 2-14 lists these studies.

Table 2-14. Ongoing Studies on Health Effects of Mercury

Author	Affiliation	Title	Sponsor
Tan, KH	Winston-Salem State University Winston-Salem, NC	Pilot study--astrocyte gene expression and methyl mercury neurotoxicity.	NCRR
Opella, SJ	University of Pennsylvania Philadelphia, PA	Structural studies of mercury transport protein.	NCRR
Prusiner, SB	University of California-SF San Francisco, CA	Nmr structures of recombinant prps.	National Institute of Neurological Disorders
Agre, PC	Johns Hopkins University Baltimore, MD	Red cell aquaporin-1 water transport protein.	National Heart, Lung, and Blood Institute
Rajanna, B	Alcorn State University Lorman, MS	Developmental neurotoxicity of lead and methyl nercury.	NIGMS
Mitra, AK	Scripps Research Institute San Diego, CA	Structure and function of the chip28 water channel.	NIGMS
Miller, S	University of California-SF San Francisco, CA	Cause and effect of dimer asymmetry in mercuric reductase.	NIGMS
Jensen, JL	California State University-LB Long Beach, CA	Reactivity of heavy metal ions with organosulfur moieties.	NIGMS
Rowland, AS		Effects of dental treatment during pregnancy on childhood development.	NIEHS
Rowland, AS		Chronic disease risks associated with mercury vapor exposure.	NIEHS
Longnecker, MP		Validity of toenail element levels as a surrogate measure of exposure.	NIEHS
Kamel, F		Lead and other neurotoxins as risk factors for amyotrophic lateral sclerosis.	NIEHS
Baird, DD		Environmental effects on fertility.	NIEHS
Morgan, DL		Prenatal effects of chemicals on the respiratory tract.	NIEHS
Knudsen,	Thomas Jefferson University Philadelphia, PA	Environmental impact on the embryonic mtdna genome.	NIEHS
Kono, DH	Scripps Research Institute San Diego, CA	Heavy metal induced autoimmunity.	NIEHS

Table 2-14. Ongoing Studies on Health Effects of Mercury (continued)

Author	Affiliation	Title	Sponsor
Frumkin, H	Emory University Atlanta, GA	Cohort study of former employees of a chloralkali plant.	NIEHS
Nelson, LM	Stanford University Stanford, CA	Exogenous toxicants and genetic susceptibility in als.	NIEHS
Weiss, B	University of Rochester Rochester, NY	Developmental neurotoxicity of metallic mercury.	NIEHS
Pollard, KM	Scripps Research Institute San Diego, CA	Immunotoxicology of a heavy metal.	NIEHS
Pollard, KM	Scripps Research Institute San Diego, CA	Mercury induced autoimmunity.	NIEHS
Aschner, M	Wake Forest University Winston-Salem, NC	Mechanisms of methylmercury induced neuronal toxicity.	NIEHS
Ballatori, N	University of Rochester Rochester, NY	Methylmercury transport across cell membranes.	NIEHS
Newland, MC	Auburn University at Auburn Auburn, AL	Behavioral teratology of methylmercury.	NIEHS
Kane, AS	University of Maryland Baltimore Baltimore, MD	Mechanisms underlying segment-specific nephrotoxicity.	NIEHS
Zalups, RK	Mercer University Macon Macon, GA	Transport and toxicity of mercury in the nephron.	NIEHS
Korrish, SM	Harvard University Boston, MA	*In utero* PCB and metal exposure and infant development.	NIEHS
Clarkson, TW	University of Rochester Rochester, NY	Dosimetry.	NIEHS
Myers, GI	University of Rochester Rochester, NY	Child development following prenatal methyl mercury exposure via fish diet.	NIEHS
Clarkson, TW	University of Rochester Rochester, NY	Health hazards of methylmercury.	NIEHS
Zalups, RK	Mercer University Macon Macon, GA	Mercury nephrotoxicity after a reduction of renal mass.	NIEHS
Reuhl, KR	Rutgers The State Univ New Brunswick New Brunswick, NJ	Mechanisms of mehg neurotoxicity during development.	NIEHS

Table 2-14. Ongoing Studies on Health Effects of Mercury (continued)

Author	Affiliation	Title	Sponsor
Gandolfi, AJ	University of Arizona Tucson, AZ	Metal-metal interactions in the kidney.	NIEHS
Schell, LM	State University of New York a Albany, NY	PCBs and well being of Mohawk children and youth--growth, development, cognition.	NIEHS
Checkoway, H	University of Washington Seattle, WA	Environmental and biochemical risk factors for Parkinson's disease.	NIEHS
Woods, JS	University of Washington Seattle, WA	Porphyrin profiles as biomarkers of trace metal exposure and toxicity.	NIEHS
Silva, P	Mount Desert Island Biological Salsbury Cove, ME	Mercury in chloride transport in shark rectal gland and rabbit thick ascending limb.	NIEHS
Preston, RL	Mount Desert Island Biological Salsbury Cove, ME	Mercury interaction with the taurine transport system of red blood cells.	NIEHS
Kinne, R	Mount Desert Island Biological Salsbury Cove, ME	Effects of cadmium and mercury on na-k-cl cotransporter in shark rectal gland.	NIEHS
Dawson, DC	Mount Desert Island Biological Salsbury Cove, ME	Effect of mercury on thiazide-sensitive sodium chloride cotransporter in flounder.	NIEHS
Boyer, J	Mount Desert Island Biological Salsbury Cove, ME	Mercury impairment of cell volume registration in skate hepatocytes.	NIEHS
Burbacher, TM	University of Washington Seattle, WA	Developmental effects of methylmercury.	NIEHS
Atchison, WD	Michigan State University East Lansing, MI	Neurotoxic mechanisms of methylmercury poisoning.	NIEHS
Bigazzi, PE	University of Connecticut Farmington, CT	Immune effects of metals--mercury-induced autoimmune disease.	NIEHS
Lawrence, DA	Wadsworth Center Albany, NY	Immunotoxicity of heavy metals.	NIEHS
Crawford, S	New England Research Institute Watertown, MA	Contribution of amalgam restoration to total body burden.	NIDCR
Janoff, EE	University of Washington Seattle, WA	Influence of dental amalgams on mercury and antibiotic resistant bacteria.	NIDCR

Table 2-14. Ongoing Studies on Health Effects of Mercury (continued)

Author	Affiliation	Title	Sponsor
De Rouen, TA	University of Washington Seattle, WA	Casa Pia study of dental amalgams in children.	NIDCR
Crawford, SL	New England Research Institute Watertown, MA	Health effects of dental amalgams in children.	NIDCR
Echeverria, D	Battelle Memorial Institute Columbus, OH	Neurologic effects of HgO exposure in dental personnel.	NIDCR
Factor-litvak, P	Columbia University Health Sci New York, NY	Dental amalgams and neuropsychological function.	NIDCR
Shenker, BJ	University of Pennsylvania Philadelphia, PA	Immunotoxic properties of mercuric compounds.	NIDCR
Kingman, A		Correlations between amalgam exposure and mercury levels in urine and blood.	NIDCR
Kingman, A		The NIDR amalgam study and health effects protocol.	NIDCR
Winn, DM		Occupation and reproductive health of women dentists.	NIDCR
Barron, DJ	University of Rochester Rochester, NY	Mercury toxicity and the blood-brain factor.	NIDCR
Sobel, ES	University of Florida Gainesville, FL	Hgc12 induction of systemic autoimmune disease in mice.	National Instute of Arthritis and Musculoskeletal and Skin
Casiano, CA	Loma Linda University Loma Linda, CA	Autoantigen cleavage during apoptosis and necrosis.	National Institute of Allergy and Infectious Diseases
Markesbery, WR	University of Kentucky Lexington, KY	Oxidative, antioxidant and trace element studies in the alzheimer's brain.	National Institute on Aging
Smith DE	North Carolina State University Raleigh, NC	Effects of metal ions on in vitro estrogen action in the rat uterus.	U. S. Department of Agriculture

NCRR = National Center for Research Resources; NIDCR = National Instute of Arthritis and Musculoskeletal Research; NIEHS = National Institute of Environmental Health Science; NIGMS = National Institute of General Medical Sciences

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of mercury compounds is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of mercury compounds is located in Table 3-2. Mercuric acetate has been included as an organic form of mercury. However, the bonds of the salt are not covalent and, in aqueous solution, the mercury behaves like an inorganic form.

Table 3-1. Chemical Identity of Selected Inorganic and Organic Mercury Compounds[a]

		Inorganic	
Characteristic	Mercury	Mercuric (II) chloride	Mercuric (II) sulfide
Chemical name	Mercury	Mercuric (II) chloride	Mercuric (II) sulfide
Synonym(s)	Colloidal mercury; liquid silver; mercury, metallic (DOT); quicksilver; metallic mercury[b]; hydrargyrum[c]	Bichloride of mercury; mercury bichloride[d]; mercury chloride[d]; mercury dichloride; mercury perchloride; mercury (II) chloride; perchloride of mercury; corrosive sublimate[d]; corrosive mercury chloride; dichloromercury	Etiops mineral[c]; mercury sulfide, black[d]; vermilion; chinese red; C.I. Pigment Red 106; C.I.77766[c]; quicksilver vermilion; chinese vermilion; red mercury sulfide; artificial cinnabar; red mercury sulfuret[d]
Registered trade name(s)	No data	Calochlor; Fungchex; TL 898	No data
Chemical formula	Hg[c]	$HgCl_2$[c]	HgS[c]
Chemical structure	Hg[c]	Hg^{++} Cl^- Cl^-	Hg ═ S
Identification numbers:			
CAS registry	7439-97-6[c]	7487-94-7[c]	1344-48-5[c]
NIOSH RTECS	OVA4550000	OV9100000	No data
EPA hazardous waste	U151;D009	D009	No data
OHM/TADS	7216782	No data	No data
DOT/UN/NA/IMCO shipping	UN 2024 (mercury compounds, liquid); UN 2025 (mercury compounds, solid); IMO 6.1 (mercury compounds, liquid or solid); UN 2809 (DOT)[b]	UN 1624 (mercuric chloride) IMO 6.1 (mercuric chloride)	No data
HSDB	1208	33	No data
NCI	C60399[b]	C60173	No data
STCC	49 232 69 (mercury compound, solid), 49 443 25 (mercury, metallic)	49 232 45 (mercuric chloride) 49 232 71 (mercuric chloride, solid)	No data

Table 3-1. Chemical Identity of Selected Inorganic and Organic Mercury Compounds[a] (continued)

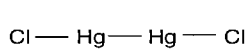
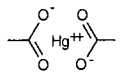
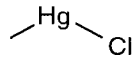
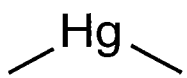
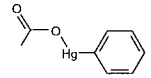
	Inorganic (continued)	Organic	
Characteristic	Mercurous (I) chloride	Mercuric (II) acetate[f]	Methylmercuric chloride
Chemical name	Mercurous (I) chloride	Mercuric (II) acetate	Methylmercuric chloride
Synonym(s)	Calomel; mild mercury chloride; mercury monochloride; mercury protochloride; mercury subchloride; calogreen; cyclosan[c]; mercury chloride[d]	Acetic acid, mercury (2+) salt; bis(acetyloxy) mercury; diacetocymercury; mercury diacetate; mercuriacetate; mercury (II) acetate; mercury (2+) acetate; mercury acetate[d]	Chloromethylmercury; monomethyl mercury chloride; methylmercury chloride; methylmercury monochloride[b]
Registered trade name(s)	Calogreen; Calomel Calotab; Cylcosan	No data	Caspan
Chemical formula	Hg_2Cl_2[b]	$HgC_4H_6O_4$[b]	CH_3HgCl[e]
Chemical structure			$(CH_3)^-Hg^{2+}Cl^-$ 
Identification numbers:			
CAS registry	10112-91-1[c]	1600-27-7	115-09-3[e]
NIOSH RTECS	OV8750000[b]	A18575000	OW1225000
EPA hazardous waste	No data	D009	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	UN 1629 (mercury acetate); IMO 6.1 (mercury acetate)	No data
HSDB	No data	1244	No data
NCI	77764[b]	No data	No data
STCC	No data	49 232 41	No data

Table 3-1. Chemical Identity of Selected Inorganic and Organic Mercury Compounds[a] (continued)

	Organic (continued)	
Characteristic	Dimethyl mercury	Phenylmercuric acetate
Chemical name	Dimethyl mercury	Phenylmercuric acetate
Synonym(s)	Mercury, dimethyl; methyl mercury[c]	(Acetato)phenylmercury; acetoxyphenylmercury; phenylmercury acetate[c]; acetoxyphenylmercury; mercury (II) acetate, phenyl-; mercury, (acetato)phenyl-; phenylmercuric acetate; phenylmercuriacetate
Registered trade name(s)	No data	PMA; PMAC; Pmacetate;Cerasan Slaked Lime; Gollitox; liquiphene; Mersolite; Tag Fungicide; Tag HL-331; Nylmerate; Scutl; Riogen; PMAS
Chemical formula	C_2H_6Hg[c]	$C_8H_8HgO_2$[c]
Chemical structure		
Identification numbers:		
CAS registry	593-74-8[c]	62-38-4[c]
NIOSH RTECS	No data	OV6475000
EPA hazardous waste	No data	PO92
OHM/TADS	No data	7216544
DOT/UN/NA/IMCO shipping	No data	UN 1674 (phenylmercuric acetate); IMO 6.1 (phenylmercuric acetate)
HSDB	No data	1670
NCI	No data	No data
STCC	No data	29 216 53

[a] All information obtained from HSDB 1997, except where noted. [b]RTECS 1997 [c]Merck 1989 [d]Lewis 1993 [e]ASTER 1997 [f] Although organic moieties are associated with the Hg atom, the mercury-carbon bonds are ionic, not covalent, in nature and in aqueous solution, Hg^{2+} is released.

CAS = Chemical Abstracts Service; DOT/UN/NA/IMO = Dept. of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-2. Physical and Chemical Properties of Selected Inorganic and Organic Mercury Compounds[a]

		Inorganic		
Property	Mercury	Mercuric (II) chloride	Mercuric (II) sulfide	Mercurous (I) chloride
Molecular weight	200.59	271.52	232.68	472.09
Color	Silver-white (liquid metal); tin-white (solid mercury)	White	Black or grayish-black (mercuric sulfide, black); bright scarlet-red blackens on exposure to light (mercuric sulfide, red)	White
Physical state	Heavy, mobile, liquid metal; Solid mercury is ductile, maleable mass which may be cut with a knife	Crystals, granules or powder; rhombic crystals, crystalline solid[c]	Heavy amorphous powder, also occurs as black cubic crystals (mercuric sulfide, black); powder, lumps, hexagonal crystals (mercuric sulfide, red)	Heavy powder; rhombic crystals or crystalline powder[b]
Melting point	-38.87 °C	277 °C	Transition temp (red to black) 386 °C; 583 , sublimes at 446 °C (mercuric sulfide, black)[b]; sublimes at 583 °C (mercuric sulfide, red)	Sublimes at 400–500 °C without melting; 302 °C[b]
Boiling point	356.72 °C	302 °C	No data	384 °C[b]
Density at °C	13.534 g/cm^3 at 25 °C	5.4 g/cm^3 at 25 °C	7.55-7.70 (mercuric sulfide, black), 8.06-8.12 g/cc (mercuric sulfide, red)[b]	7.15 g/cc; 6.993 g/cc[b]
Odor	Odorless[c]	Odorless[b]	Odorless	Odorless
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	0.28 µmoles/L at 25 °C	1 g/35 mL, 1 g/2.1 mL boiling H_2O; 6.9 g/100 cc H_2O at 20 °C[c], 48 g/100 cc at 100 °C[c]	Insoluble (mercuric sulfide, black), soluble in aqua regia with separation of S, in warm hydriodic acid with evolution of H_2S (mercuric sulfide, red)	2.0x10^{-4} g/100mL at 25 °C

Table 3-2. Physical and Chemical Properties of Selected Inorganic and Organic Mercury Compounds[a] (continued)

		Inorganic		
Property	Mercury	Mercuric (II) chloride	Mercuric (II) sulfide	Mercurous (I) chloride
Solubility:				
Organic solvents	Soluble in H_2SO_4 upon boiling, in lipids, readily soluble in HNO_3, insoluble in HCL[b]; soluble in 2.7 mg/L pentane[c]	1 g/3.8 mL alcohol, 1 g/200 mL C_6H_6, 22 mL ether, 12 mL glycerol, 40 mL CH_3COOH, acetone, CH_3OH, ethyl acetate; 33 g/100 cc alcohol at 25 °C, slightly soluble in carbon disulfide, pyridine[c]	Insoluble in alcohol, dilute mineral acids	Insoluble in alcohol, ether
Partition coefficients:				
Log K_{ow}	5.95[g]	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	$2x10^{-3}$ mm Hg at 25 °C	1 mm Hg at 136.2 °C	No data	No data
Henry's law constant at 24.8 °C	No data	No data	No data	No data
Degradation reaction rate constant	Gas-phase reaction with O_3 = $1.7x10^{-18}$ $cm^3/mol/s$[j]; $8 x10^{-19}$ $cm^3/mol/s$[k]	No data	No data	No data
Autoignition temperature	Not flammable[c]	No data	No data	No data
Flashpoint	Not flammable[c]	Not flammable[c]	No data	No data
Flammability limits in air	Not flammable[c]	Not flammable[c]	No data	No data
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 °C	1 ppm = 8.18 mg/m^3	No data	No data	No data
mg/m^3 to ppm (v/v) in air at 25 °C	1 mg/m^3 = 0.122 ppm	No data	No data	No data
Explosive limits	Non-combustible[c]	Non-combustible[c]	No data	No data
Valence states	+1, +2	+2	+2	+2

Table 3-2. Physical and Chemical Properties of Selected Inorganic and Organic Mercury Compounds[a] (continued)

	Organic			
Property	Mercuric (II) acetate	Methylmercuric chloride[l]	Dimethyl mercury	Phenylmercuric acetate
Molecular weight	318.70	251.1[d]	230.66	336.75
Color	White[b]	White[f]	Colorless	White to cream[b]
Physical state	Crystals or crystalline powder; Solid at 25 °C and 1 atm[c]	Crystals[f]	Liquid	Small lustrous prisms; crystalline powder, small prisms or leaflets[c]
Melting point	178–180 °C	170 °C[d]	No data	149 °C; 148-150 °C[b]
Boiling point	No data	No data	92 °C	No data
Density at °C	3.28 g/cm^3	4.06 g/mL at 25 °C[f]	3.1874 g/mL at 20 °C	No data
Odor	Slight acetic odor	No data	No data	Odorless[e]
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 25 °C	1 g in 2.5 mL cold, 1 mL boiling H_2O; 25 g/100 mL at 10 °C, 100 g/100 mL at 100 °C[c]	<0.1 mg/mL at 21 °C[f]	Insoluble; 1.00x10^3 mg/L[d]	Soluble in about 600 parts H_2O; 1 g/180 mL[c]
Organic solvents	Soluble in alcohol; acetic acid[c]	DMSO >=100 mg/mL at 27°C, 95% C_2H_5OH 10–50 mg/mL at 27 °C; acetone >= 100 mg/mL at 27 °C[f]	Easily soluble in ether, alcohol	Soluble in alcohol, benzene, acetone; 6.8 mL $CHCl_3$, 200 mL ether[c]
Partition coefficients:				
Log K_{ow}	No data	No data	2.28[h]	No data
Log K_{oc}	No data	No data	2.73[d]	1.72[d]
Vapor pressure at 25 °C	No data	0.0085 mm Hg at 25 °C[f]	No data	9x10^{-4} mm Hg at 35 °C[f]; 1.20x10^{-4} mm Hg at 25 °C[c]; <1mm Hg at 35 °C[e]
Henry's law constant °C	No data	No data	No data	1.22x10^{-8} atm m^3/mol[c]
Degradation reaction rate constant	No data	No data	Volatilizes to air where it photolyzes to CH_4 and Hg or is oxidized by the OH radical[i]	No data
Autoignition temperature	No data	probably nonflammable[f]	Easily inflammable	No data

Table 3-2. Physical and Chemical Properties of Selected Inorganic and Organic Mercury Compounds[a] (continued)

		Organic		
Property	Mercuric (II) acetate	Methylmercuric chloride[l]	Dimethyl mercury	Phenylmercuric acetate
Flashpoint	Not flammable[c]	probably nonflammable[f]	Easily inflammable	>38 °C[e]
Flammability limits in air	Not flammable[c]	probably nonflammable[f]	Easily inflammable	No data
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 °C	No data	1 ppm = 10.27 mg/m^3	1 ppm = 9.43 mg/m^3	No data
mg/m^3 to ppm (v/v) in air at 25 °C	No data	1 mg/m^3 = 0.0974 ppm	1 mg/m^3 = 0.106 ppm	No data
Explosive limits	Non-combustible[c]	No data	No data	Probably combustible[f]
Valence state	+2	+2	+2	+2

[a] All information obtained from Merck 1989 except where noted.
[b] All information obtained from Lewis 1993
[c] HSDB 1997
[d] Aster 1997
[e] NFPA 1994
[f] NTP Chemical Repository 1997 (Radian Corporation)
[g] Stein et al. 1996
[h] Wasik 1978
[i] Bodek et al. 1988 (to be verified)
[j] Schroeder et al. 1991
[k] Signeur et al. 1994
[l] Commonly occuring form of methyl mercury; proprietary names include bis-methylmercuric sulfate (cerewet), methylmercury cyanoguanidine or methylmercury dicyanodiamide (agrosol, morsodren, panogen, panospray), methylmercury nitrile (chipcote) and methylmercury propionate (metasol MP)
[m] Iverfeldt and Lindquist 1984
[n] Although organic moieties are associated with the Hg atom, the bonds are ionic, not covalent, in nature. In aqueous solution, Hg^{2+} is released.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Mercury is a naturally occurring element that is usually found as mercuric sulfide (cinnabar), an insoluble, stable compound. It occurs in the earth's crust at levels averaging 0.5 ppm, but the actual concentration varies considerably depending on location (Merck 1989; Sidle 1993). Mercury is mined using both open pit (10% of production) and underground mining techniques (90%) (Drake 1981).

Mercury ores are processed inexpensively to produce metallic mercury. Due to the low boiling point of elemental mercury, mercury can be refined by heating the ore and condensing the vapor to form metallic mercury. This method is 95% efficient and yields mercury that is 99.9% pure. The methods used to refine mercury ores are uncomplicated. Smaller refineries use simple firing and condensing equipment, while larger operations use continuous rotary kilns or mechanically feeding and discharging multiple-hearth furnaces (Carrico 1985).

Table 4-1 lists the facilities in each state that manufacture or process mercury, the intended use, and the range of maximum amounts of mercury that are stored on site. There are currently 34 facilities that produce or process mercury in the United States. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TRI96 1998). Since only certain types of facilities are required to report (EPA 1996d), this is not an exhaustive list.

With the closure of the McDermitt Mine in Nevada in 1990, mercury ceased to be a principal product of U.S. industry (USGS 1997). The figures for the total output of this mine have been withheld by the Bureau of Mines to avoid disclosure of company proprietary data (see Table 4-2). As of 1995, eight mines in California, Nevada, and Utah produced mercury as a by-product from gold mining operations. Metals in the gold ores are extracted with an aqueous cyanide solution, with typical mercury recoveries of between 10 and 20% (Jasinski 1993; USGS 1997). Approximately 58 metric tons of mercury were produced as a by-product from 8 mines in 1991 and 64 metric tons were produced as a by-product from 9 mines in 1992. Since then, production volumes have been withheld to avoid disclosing company proprietary data.

Although most of the world production of mercury is generated by mercury mines, most of the mercury produced in the United States comes from secondary production sources (recycling) (EPA 1997).

Table 4-1. Facilities That Manufacture or Process Mercury

FACILITY	LOCATION [a]	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS	ACTIVITIES AND USES
OCCIDENTAL CHEMICAL CORP.	MUSCLE SHOALS , AL	100,000 - 999,999	CHEMICAL PROCESSING AID
TUSCALOOSA STEEL CORP.	TUSCALOOSA , AL	0 - 99	ARTICLE COMPONENT
OCCIDENTAL CHEMICAL CORP.	NEW CASTLE , DE	100,000 - 999,999	CHEMICAL PROCESSING AID
OLIN CHLOR-ALKALI PRODS.	AUGUSTA , GA	100,000 - 999,999	CHEMICAL PROCESSING AID
ALEXANDER MFG. CO.	MASON CITY , IA	0 - 99	IMPORT , ON-SITE USE/PROCESSING , ARTICLE COMPONENT
MICRO SWITCH	FREEPORT , IL	10,000 - 99,999	ARTICLE COMPONENT
VALSPAR CORP.	ROCKFORD , IL	10,000 - 99,999	FORMULATION COMPONENT
DURAKOOL INC.	ELKHART , IN	10,000 - 99,999	ARTICLE COMPONENT
HERMASEAL CO.	ELKHART , IN	10,000 - 99,999	ARTICLE COMPONENT
U.S. STEEL	GARY , IN	10,000 - 99,999	PRODUCE , BYPRODUCT
UNITED TECHS. AUTOMOTIVE INC.	EDINBURGH , IN	10,000 - 99,999	ARTICLE COMPONENT
KOCH SULFUR PRODS. CO.	DE SOTO , KS	0 - 99	ANCILLARY/OTHER USE
BF GOODRICH CO.	CALVERT CITY , KY	100,000 - 999,999	CHEMICAL PROCESSING AID
DU PONT	LOUISVILLE , KY		
BORDEN CHEMICALS & PLASTICS	GEISMAR , LA	100,000 - 999,999	IMPORT , ON-SITE USE/PROCESSING , CHEMICAL PROCESSING AID
DOW CHEMICAL CO.	PLAQUEMINE , LA	1,000 - 9,999	PRODUCE , BYPRODUCT
PIONEER CHLOR ALKALI CO. INC.	SAINT GABRIEL , LA	100,000 - 999,999	CHEMICAL PROCESSING AID
PPG IND. INC.	LAKE CHARLES , LA	100,000 - 999,999	CHEMICAL PROCESSING AID
HOLTRACHEM MFG.	ORRINGTON , ME	100,000 - 999,999	CHEMICAL PROCESSING AID
ELM PLATING CO.	JACKSON , MI	0 - 99	ARTICLE COMPONENT
KERR CORP.	ROMULUS , MI	1,000 - 9,999	REPACKAGING
HOLTRACHEM MFG. CO. L.L.C.	RIEGELWOOD , NC	100,000 - 999,999	CHEMICAL PROCESSING AID
MERCURY REFINING CO. INC.	ALBANY , NY	10,000 - 99,999	PRODUCE , SALE/DISTRIBUTION , REPACKAGING , ANCILLARY/OTHER USE
ASHTA CHEMICALS INC.	ASHTABULA , OH	10,000 - 99,999	CHEMICAL PROCESSING AID
COMPONENT REPAIR TECHS.	MENTOR , OH		
SINCLAIR OIL CORP.	TULSA , OK	100 - 999	PRODUCE , BYPRODUCT
ADVANCED ENVIRONMENTAL	ALLENTOWN , PA	10,000 - 99,999	PRODUCE , SALE/DISTRIBUTION
BETHLEHEM APPARATUS CO. INC.	HELLERTOWN , PA	100,000 - 999,999	PRODUCE , IMPORT , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , REPACKAGING
ZINC CORP. OF AMERICA	MONACA , PA	10,000 - 99,999	PRODUCE , IMPURITY
OLIN CORP.	CHARLESTON , TN	100,000 - 999,999	CHEMICAL PROCESSING AID
OCCIDENTAL CHEMICAL CORP.	DEER PARK , TX	100,000 - 999,999	CHEMICAL PROCESSING AID
GEORGIA-PACIFIC WEST INC.	BELLINGHAM , WA	100,000 - 999,999	CHEMICAL PROCESSING AID
VULCAN MATERIALS CO.	PORT EDWARDS , WI	100,000 - 999,999	CHEMICAL PROCESSING AID
PPG IND. INC.	NEW MARTINSVILLE , WV	100,000 - 999,999	CHEMICAL PROCESSING AID

Source: TRI96 1998

[a] Post Office state abbreviations used

blank = not available

Table 4-2. U.S. Mercury Supply Demand, Imports, and Exports (metric tons)

Category	1987	1988	1989	1990	1991	1992	1993	1994	1995
Supply									
Mine production[a]		379	414	448	0	0	0		
By-product production[b]		W[c]	W	114	58	64	W		
Industrial recovery		278	137	108	165	176	350	466[e]	534[e]
DLA sales		52	170	52	103	267	543		
DOE sales		214	180	193	215	103	0		
Imports	636[e]	329	131	15	56	92	40		
Total supply	**NA[d]**	**1,252**	**1032**	**930**	**597**	**702**	**933**	**NA[d]**	**NA[d]**
Subtotal: federal sales	NA[d]	266	350	245	318	370	543	NA[d]	NA[d]
Federal sales as % of total supply	NA[d]	21.2%	33.9%	26.3%	53.3%	52.7%	58.1%	NA[d]	NA[d]
Demand	**NA[d]**	**1,503**	**1,212**	**720**	**554**	**621**	**558**	**NA[d]**	**NA[d]**
Federal sales as % of demand	NA[d]	17.6%	0.29%	34%	57.4%	59.6%	0.97%	NA[d]	NA[d]
Imports	**636[e]**	**329**	**131**	**15**	**56**	**92**	**40**	**129[e]**	**277[e]**
Exports	**NA[d]**	**N/A[d]**	**221**	**311**	**786**	**977**	**389**	**316[e]**	**179[e]**

[a] Mercury production from McDermitt mine; closed November 1990
[b] Mercury by-product from 9 gold mining firms
[c] Withheld for proprietary reasons
[d] Not available
[e] Information from USGS 1997

Source: EPA 1996b

Secondary production of mercury includes the processing of scrapped mercury-containing products, and industrial waste and scrap (EPA 1997). As a result of the increasingly stricter regulations that have been placed on the disposal of mercury-containing products, secondary production using recycled mercury has increased from 165 metric tons in 1991 to 176 metric tons in 1992, 350 metric tons in 1993, 466 metric tons in 1994, and 534 metric tons in 1995. Mercury was recovered from various waste materials, including mercury batteries, dental amalgams, switches (including thermostats), manometers, chloralkali wastewater sludges, chemical solutions, and fluorescent light tubes. Refining of the recycled mercury was dominated by three companies: Bethlehem Apparatus Co., Hellertown, Pennsylvania; D.F. Goldsmith Co., Evanston, Illinois; and Mercury Refining Co., Albany, New York (USGS 1997).

4.2 IMPORT/EXPORT

Until 1989, the United States was a net importer of mercury. After that, market values of mercury fluctuated and consumption diminished, leading to a decreased need for imported mercury (Carrico 1985; Drake 1981). U.S. imports of mercury fell sharply between 1987 and 1990 (Jasinski 1993; Reese 1990). The import volumes decreased drastically during the period from 1987 to 1990: 636 metric tons in 1987, 329 metric tons in 1988, 131 metric tons in 1989, and 15 metric tons in 1990 (see Table 4-2). However, import figures generally have increased substantially since 1990: 56 metric tons in 1991, 92 metric tons in 1992, 40 metric tons in 1993, 129 metric tons in 1994, and 277 metric tons in 1995 (USGS 1997). The major reason for the recent escalation in mercury imports is the suspension of mercury sales from the National Defense Stockpile (NDS) in 1994, which had been the major supplier of mercury to the domestic market in recent years. The suspension was imposed by Congress after the EPA raised questions about potential problems associated with the release of mercury. Also, there was concern about the export of NDS mercury for uses banned in the United States (USGS 1997).

From 1978 to 1988, figures were unavailable for the amount of mercury exported by the United States. The U.S. export figures for mercury from 1989 to 1992 are: 221 metric tons in 1989, 311 metric tons in 1990, 786 metric tons in 1991 (Jasinski 1993; Reese 1990), 977 metric tons in 1992, 389 metric tons in 1993, 316 metric tons in 1994, and 179 metric tons in 1995 (USGS 1997) (see Table 4-2). General trends in exportation of mercury are difficult to characterize because the data are unavailable for the 11 years prior to 1989. However, the decline of exports in 1995 is largely due to the suspension of sales from the NDS (USGS 1997).

Major mercury producing countries (primary production from mining operations) in the world currently include Algeria, China, Czechoslovakia, Finland, Kyrgyzstan, Mexico, Morocco, Russia, Slovakia,

Slovenia, Spain, Turkey, and the Ukraine (USGS 1997). The world reserves of mercury are estimated to be sufficient to supply enough product for 100 years, given current production and consumption estimates (Jasinski 1993).

4.3 USE

Mercury has many applications in industry due to its unique properties, such as its fluidity, its uniform volume expansion over the entire liquid temperature range, its high surface tension, and its ability to alloy with other metals. However, domestic consumption of mercury has shown a downward trend since the early 1970s. In 1995, consumption was 463 metric tons, down 10% from 1994. The largest commercial use of mercury in the United States was for electrolytic production of chlorine and caustic soda in mercury cells, accounting for 35% of domestic consumption. Manufacture of wiring devices and switches accounted for 19%, measuring and control instruments for 9%, dental equipment and supplies used 7%, electric lighting used 7%, and other uses used 21% (EPA 1997; USGS 1997). Due to the high toxicity of mercury in most of its forms, many applications have been canceled as a result of attempts to limit the amount of exposure to mercury waste.

Electrical applications. Mercury is a critical element in alkaline batteries. In the past, excess amounts of mercury were used in batteries; however, alkaline battery manufacturers in Europe, Japan, and the United States are now reducing the mercury load from 0.1% to 0.025% of battery content. This reduction will ultimately limit the amount of mercury needed in the battery industry to below 4 metric tons per year (Cole et al. 1992; Reese 1990). Mercuric oxide has become increasingly important commercially in the production of galvanic cells with mercuric oxide anodes in combination with zinc or cadmium cathodes. The voltage for these small, button-shaped batteries remains constant during discharge. The batteries are used in hearing devices, digital watches, exposure meters, pocket calculators, and security installations (IARC 1993), but their use has been declining as non-mercury replacement battery production has increased. Some electrical lamps use mercury vapors in discharge tubes. These lamps are efficient, long-lasting, and produce more lumens per watt than most other industrial lamps (Drake 1981). Wiring and switching devices, such as thermostats and cathode tubes, use mercury because of its predictable contact resistance, thermal conductivity, and quiet operation (Carrico 1985; Drake 1981). In 1985, 64% of the mercury used in the United States was for electrical applications. This use declined to 29% in 1992 (IARC 1993).

Medical applications. Metallic mercury is used in dental restorations because of its ability to alloy with other metals. The World Health Organization (WHO 1991) estimated that, in industrialized countries, about 3% of the total mercury consumption is for dental amalgams. Based on 1992 dental manufacturer specifications, amalgam (at mixing) contains approximately 50% metallic mercury, 35% silver, 9% tin, 6% copper, and trace amounts of zinc. Estimates of annual mercury usage by United States dentists range from approximately 100,000 kg in the 1970s to 70,000 kg in 1995. More than 100 million fillings are replaced each year in the United States (Lorscheider et al. 1995). Until 30 years ago, mercury compounds were used extensively in pharmaceuticals. Mercury salts were components of antiseptics (e.g., merthiolate, mercurochrome), diuretics, skin lightening creams, and laxatives (calomel). Organic mercury compounds were employed in antisyphilitic drugs and some laxatives. Phenylmercury acetate was used in contraceptive gels and foams and as a disinfectant (IARC 1993). Since then, more effective and less toxic alternatives have replaced most pharmaceutical uses of mercury. Medical equipment, such as thermometers and manometers, use metallic mercury to measure temperature and pressure (Carrico 1985).

Chemical/mining applications. Mercury is a catalyst in reactions to form polymers, such as vinyl chloride and urethane foams. The preparation of chlorine and caustic soda (NaOH) from brines also uses mercury as a catalyst. In this process, mercury is used as a moving cathode to separate sodium and chlorine (Rieber and Harris 1994). This mercury can be recycled with 95% efficiency (Drake 1981). Consumption occurs as mercury is lost in wastewater treatment, is recaptured, reprocessed, and sent to landfills (Rieber and Harris 1994). Mercuric oxide and mercuric sulfide are used as pigments in paints (Winship 1985). Gold mining operations use mercury to extract gold from ores through amalgamation (Carrico 1985).

Other applications. Phenylmercuric acetate has been used in aqueous preparations such as inks, adhesives, and caulking compounds, as a catalyst for the manufacture of certain polyurethanes, and as a fungicide in seed dressings and interior and exterior paints (IARC 1993; Reese 1990). Dimethylmercury is used to prepare mercury nuclear magnetic resonance standards (Blayney et al. 1997) and mass spectrometer mercury calibration standards (Toribara et al. 1997).

Discontinued applications. The use of phenylmercuric acetate as a fungicide in interior latex paints was banned in 1990 (Reese 1990), and its use in exterior paint was banned in 1991 (Hefflin et al. 1993). Both of these bans were prompted because of releases of mercury vapors as the paint degraded. Alkyl mercurial

compounds were used until the mid-1970s as a treatment to disinfect grain seeds. Most other agricultural applications of mercury compounds in bactericides and fungicides have been banned due to the toxicity of mercury. Mercuric nitrate was used in the production of felt hats to hydrolyze rabbit fur. The use of mercury as a wood preservative has ceased due to the use of polyurethane (Drake 1981).

4.4 DISPOSAL

Mercury is an element, and therefore its chemical structure cannot be further broken down. In its elemental form, mercury is highly toxic when inhaled. Therefore, incineration of mercury is not recommended as a disposal method. Mercury-containing waste products include waste effluents from chloralkali plants and discarded mercury-containing mechanical and electrical devices (Carrico 1985). Under current federal guidelines, mercury and its compounds are considered hazardous substances, and various regulations are in effect to control the emission of mercury into the environment (especially organic compounds) (Carrico 1985). Emissions from mercury ore processing facilities and mercury cell chloralkali plants are limited to 2.3 kg/day/facility. Emissions of mercury from the incineration or drying of wastewater sludges is limited to 3.2 kg/day/facility (EPA 1975a, 1975b). In addition, dumping wastes containing more than trace amounts of mercury is prohibited.

Recycling of mercury-containing compounds is an important method of disposal. Recycling (retorting) is a treatment for five categories of mercury wastes including: (D009) characteristic mercury; (K106) chlor-alkali waste; (P065) mercury fulminate; (P092) phenylmercuric acetate; and (U151) elemental mercury (see Table 7-1). From 1987 to 1991, annual production of mercury from old scrap averaged nearly 180 metric tons, equivalent to 16% of the average reported consumption during that period (Jasinski 1993). Virtually all mercury can be reclaimed from mercury cell chloralkali plants, electrical apparati, and control instruments when plants are dismantled or scrapped (Carrico 1985). Increased recycling would decrease the mercury load from waste sites and treatment plants. As environmental concerns increase with respect to the disposal of mercury, the recovery by recycling and industrial processes will become a more significant source of domestic supply (Carrico 1985).

Of the estimated 646,896 pounds of mercury reported in the Toxics Release Inventory (TRI) in 1991 to have been released to the environment, the largest percentage (96%, or 619,310 pounds) was transferred off-site from 51 industrial processing facilities, and another 314 pounds were transferred to publicly owned

treatment works (POTWs) (TRI91 1993) (see Section 5-2 for additional information). By comparison, in 1994, only 83,064 pounds of mercury (less than 14% of the total reported in 1991) were released to the environment; and of this amount, 81% (67,480 pounds) was transferred off-site from 29 large processing facilities (TRI94 1996) and an estimated 15 pounds of mercury were released to POTWs (TRI94 1996). Again, by comparison, in 1996, only 84,772 pounds of mercury (less than 14% of the total reported in 1991) were released to the environment and of this amount, 78% (66,573 pounds) was transferred off-site from 34 large processing facilities and an estimated 15 pounds of mercury were released to POTWs (TRI96 1998). Releases of mercury to each of these compartments—the total environment, POTWs, and the volume transferred off-site—decreased dramatically (approximately 90%) in only 5 years. The data listed in the TRI should be used with caution, because only certain types of facilities are required to report (EPA 1996d). This is not an exhaustive list. A facility is required to report information to the Toxics Release Inventory only if the facility is a general manufacturing or processing facility with 10 or more full-time employees that produces, imports, or processes 75,000 or more pounds of any TRI chemical or that uses more than 10,000 pounds of a TRI chemical in a calendar year. No additional information on trends in disposal volume or on specific methods of disposal was located.

In addition, unknown quantities of metallic mercury used in religious or ethnic ceremonies, rituals, and practices (see Sections 5.4.4, 5.6, and 5.7) may reach municipal landfill sites by being improperly disposed of in domestic garbage, or may reach POTWs by being improperly discarded into domestic toilets or sink drains (Johnson [in press]). A survey was conducted to determine the use patterns of elemental mercury in the Latin American and Caribbean communities in New York City (Johnson [in press]). In a survey of 203 adults, about 54% used elemental mercury in various religious and ethnic practices. Of these users, 64% disposed of the mercury in household garbage, 27% flushed the mercury down the toilet, and 9% disposed of the mercury outdoors. It is commonly thought that the high mercury load found in sewage and garbage in New York City comes from dental clinics; however, improper disposal of mercury by religious practitioners in the Latin American and Caribbean communities may also contribute to this load (Johnson [in press]).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Mercury occurs naturally as a mineral and is distributed throughout the environment by both natural and anthropogenic processes. The natural global bio-geochemical cycling of mercury is characterized by degassing of the element from soils and surface waters, followed by atmospheric transport, deposition of mercury back to land and surface water, and sorption of the compound to soil or sediment particulates. Mercury deposited on land and open water is in part revolatilized back into the atmosphere. This emission, deposition, and revolatilization creates difficulties in tracing the movement of mercury to its sources. Major anthropogenic sources of mercury releases to the environment include mining and smelting; industrial processes involving the use of mercury, including chlor-alkali production facilities; combustion of fossil fuels, primarily coal; production of cement; and medical and municipal waste incinerators and industrial/commercial boilers (EPA 1996b).

The element has three valence states and is found in the environment in the metallic form and in the form of various inorganic and organic complexes. The major features of the bio-geochemical cycle of mercury include degassing of mineral mercury from the lithosphere and hydrosphere, long-range transport in the atmosphere, wet and dry deposition to land and surface water, sorption to soil and sediment particulates, revolatilization from land and surface water, and bioaccumulation in both terrestrial and aquatic food chains.

Potential sources of general population exposure to mercury include inhalation of mercury vapors in ambient air, ingestion of drinking water and foodstuffs contaminated with mercury, and exposure to mercury through dental and medical treatments. Dietary intake is the most important source of nonoccupational exposure to mercury, with fish and other seafood products being the dominant source of mercury in the diet. Most of the mercury consumed in fish or other seafood is the highly absorbable methylmercury form. Intake of elemental mercury from dental amalgams is another major contributing source to the total mercury body burden in humans in the general population (WHO 1990, 1991).

Because the two major sources of mercury body burden include dietary intake and intake from dental amalgams, mercury is present at low concentrations in a variety of human tissues. Mercury has been detected in blood, urine, human milk, and hair in individuals in the general population. Inhalation of

mercury vapor in workplace atmospheres is the main route of occupational exposure to the compound. The most recent estimate (1983–1986) indicates that about 152,000 people, including over 50,000 women, are potentially exposed to mercury in workplace environments in the United States (RTECS 1998). Occupational exposure to mercury is highest in industries processing or using the element (e.g., chloralkali workers and individuals involved in the manufacturing of industrial instruments, thermometers, and fluorescent lights). Dentists and dental staff, house painters, chemists involved in the synthesis or analysis of environmental samples containing mercury, and individuals involved in disposal or recycling of mercury-contaminated wastes are also at risk of exposure.

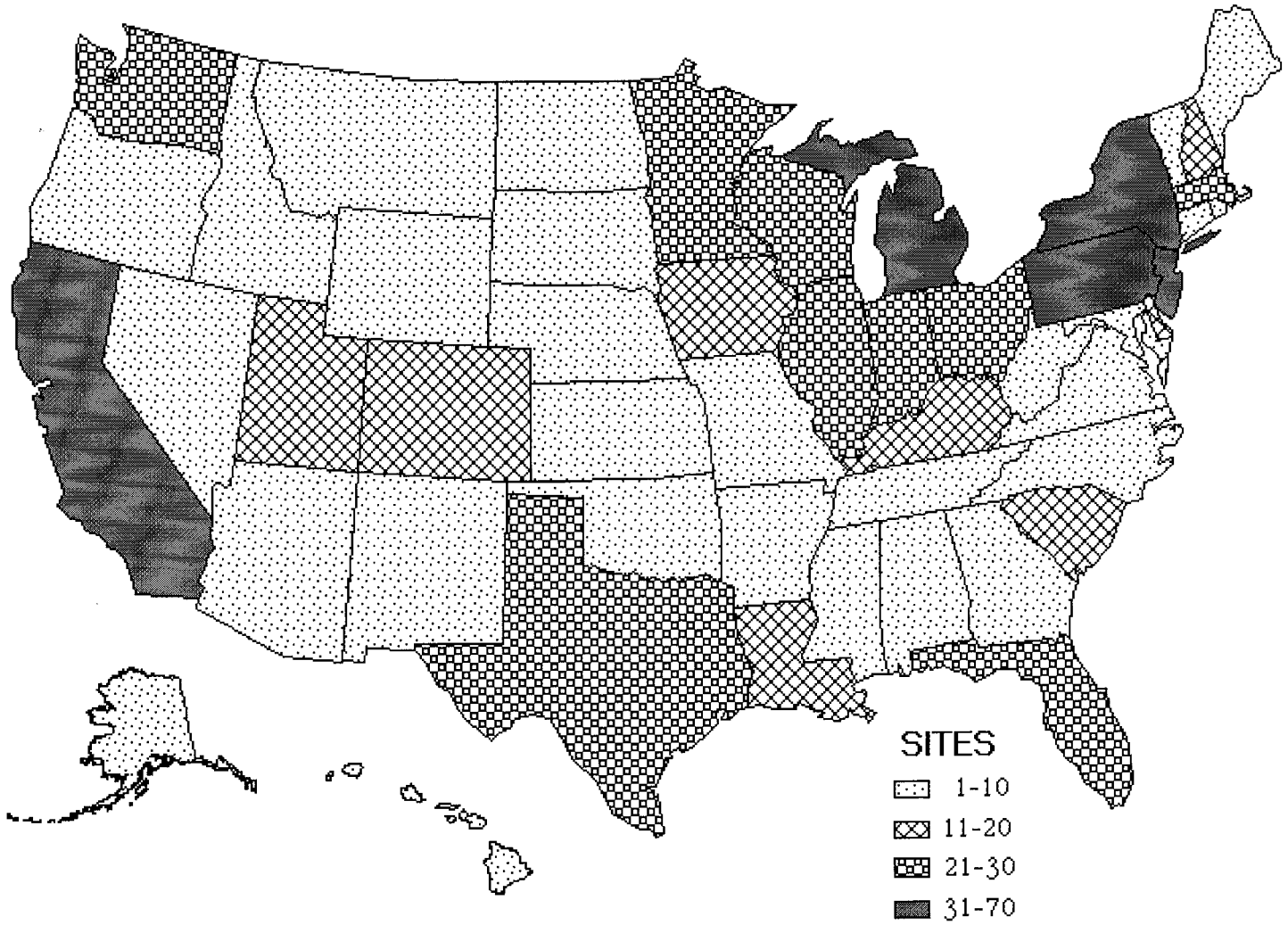
Members of the general public with potentially high exposures include individuals who live in proximity to former mercury mining or production sites, secondary production (recycling) facilities, municipal or medical incinerators, or coal-fired power plants. Other populations at risk of exposure include recreational and subsistence fishers who routinely consume meals of fish that may be contaminated; subsistence hunters who routinely consume the meat and organ tissues of marine mammals or other feral wildlife species; individuals with a large number of dental amalgams; pregnant women and nursing mothers (including their developing fetuses and breast-fed infants) who are exposed to mercury from dietary, medical, or occupational sources, or from mercury spills; individuals who use consumer products containing mercury (e.g., traditional or herbal remedies, or cosmetics, including skin lightening creams); and individuals living or working in buildings where mercury-containing latex paints were used, or where intentional (religious or ethnic use) or unintentional mercury spills have occurred.

Mercury (elemental) has been identified in 714 of the 1,467 hazardous waste sites on the NPL (HazDat 1998). The frequency of these sites can be seen in Figure 5-1. Of these sites, 705 are located in the contiguous United States, 6 are located in the Commonwealth of Puerto Rico (not shown), 2 are located in the U.S. Virgin Islands (not shown), and 1 is located in Guam (not shown). Mercuric acetate, mercuric chloride, mercurous chloride, and dimethylmercury have been identified in 2, 3, 1, and 2 sites, respectively, of the 1,467 hazardous waste sites on the NPL (HazDat 1998). The frequency of these sites can be seen in Figures 5-2 through 5-5. All of these latter sites are located in the contiguous United States.

5.2 RELEASES TO THE ENVIRONMENT

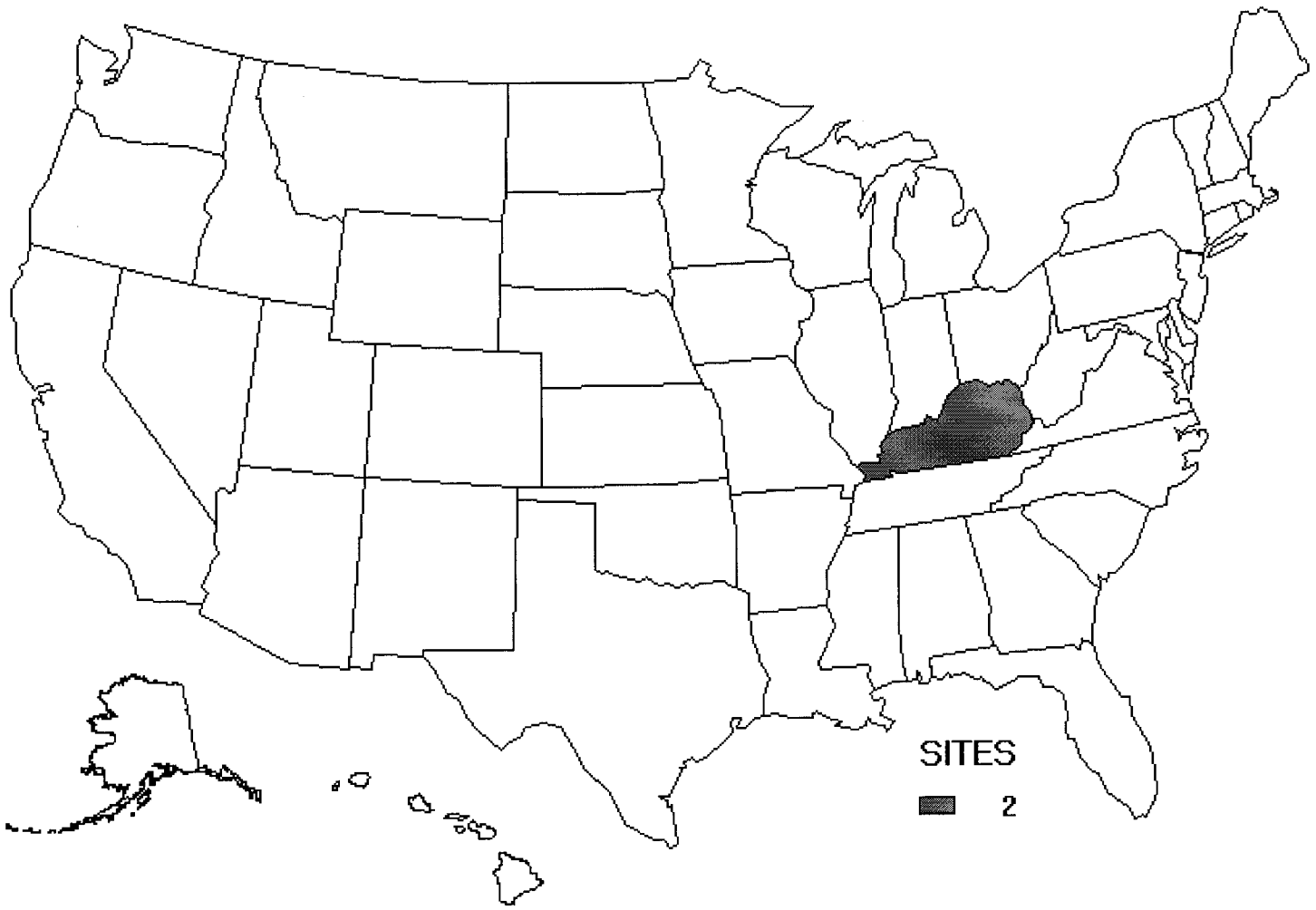
Mercury is released to the environment by both natural processes (e.g., volcanic activity and weathering of mercury-containing rocks) and anthropogenic sources. Anthropogenic releases are primarily to the

Figure 5-1. Frequency of NPL Sites with Mercury (Elemental) Contamination



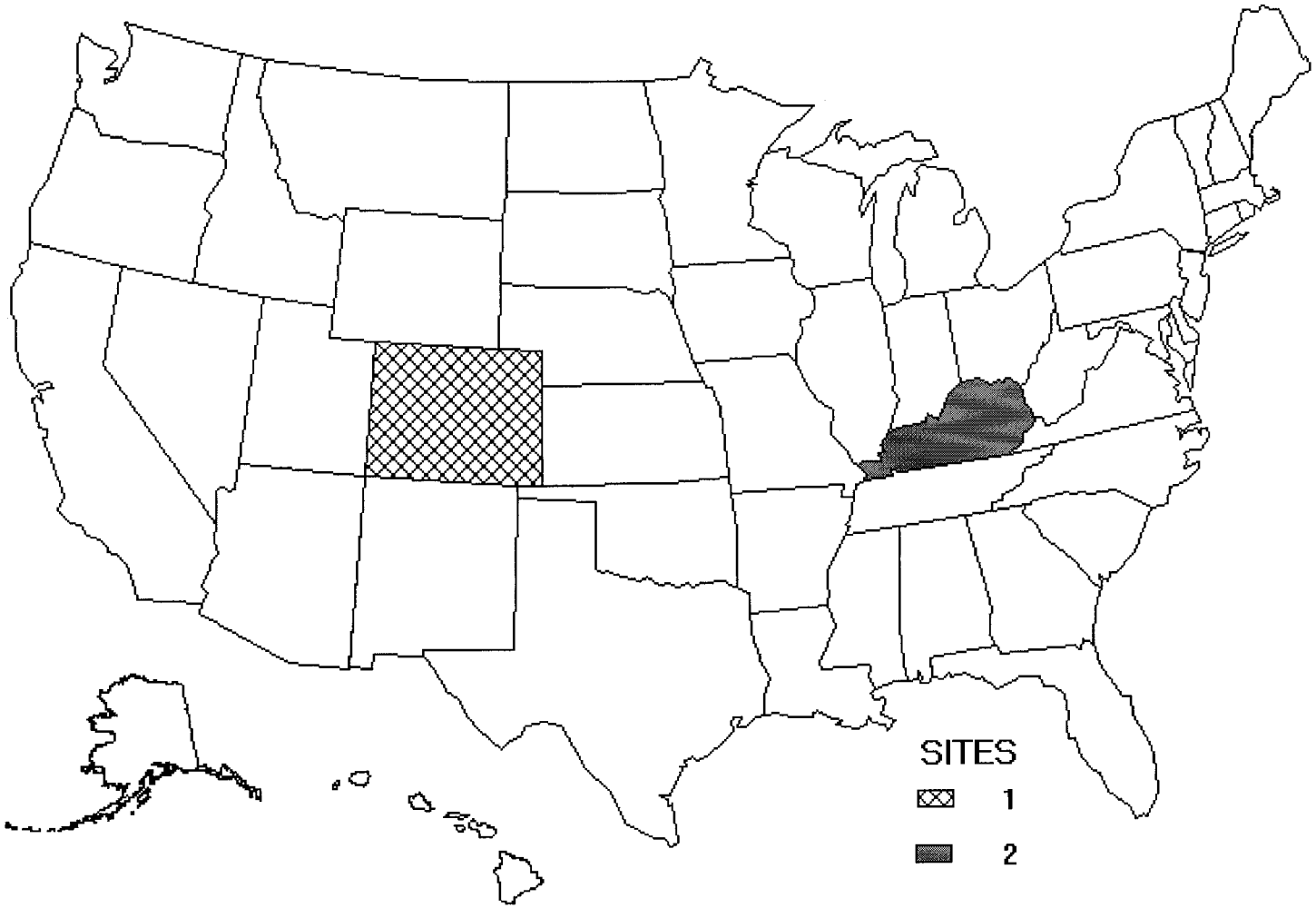
Derived from HazDat 1998

Figure 5-2. Frequency of NPL Sites with Mercuric Acetate Contamination



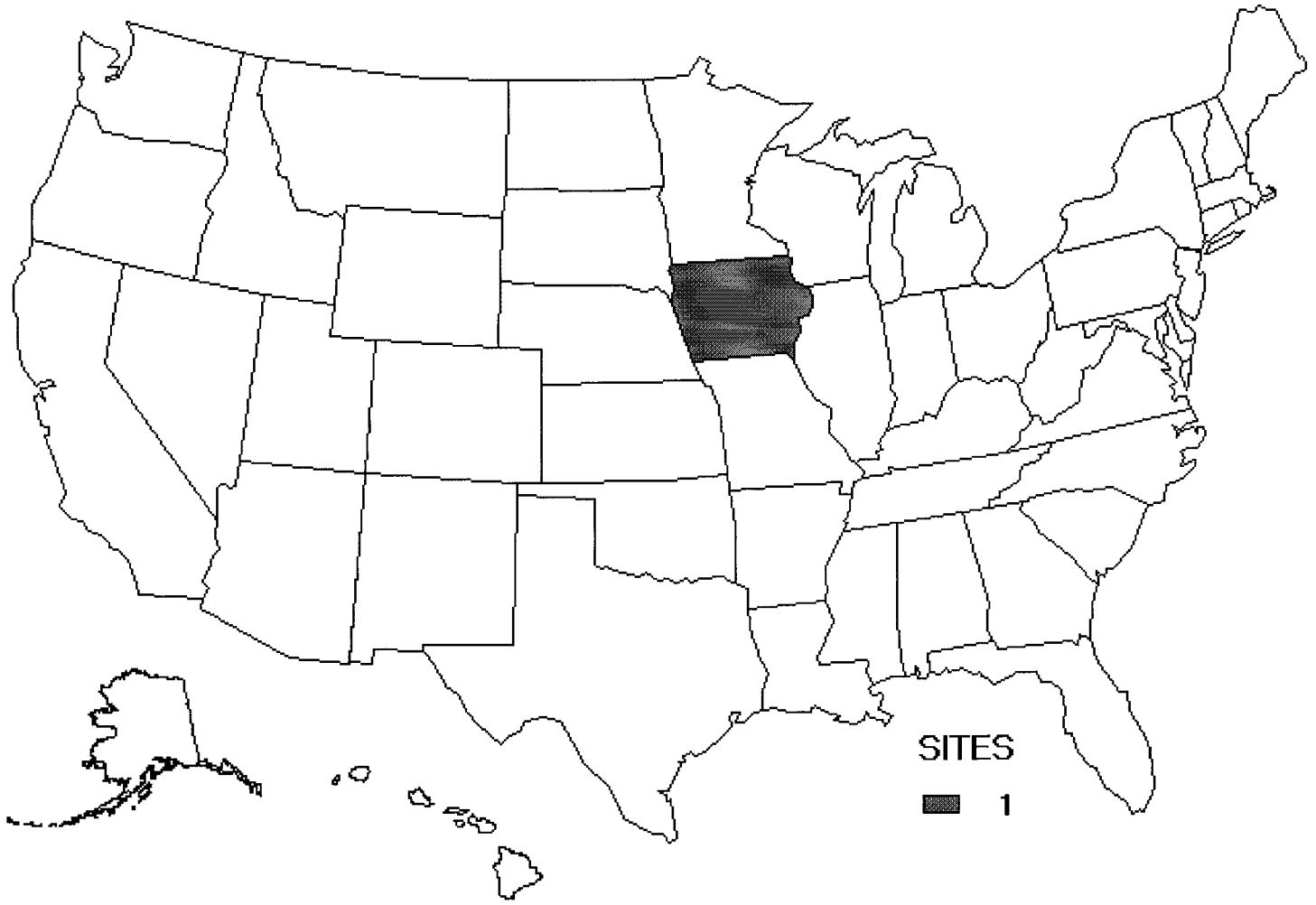
Derived from HazDat 1998

Figure 5-3. Frequency of NPL Sites with Mercuric Chloride Contamination



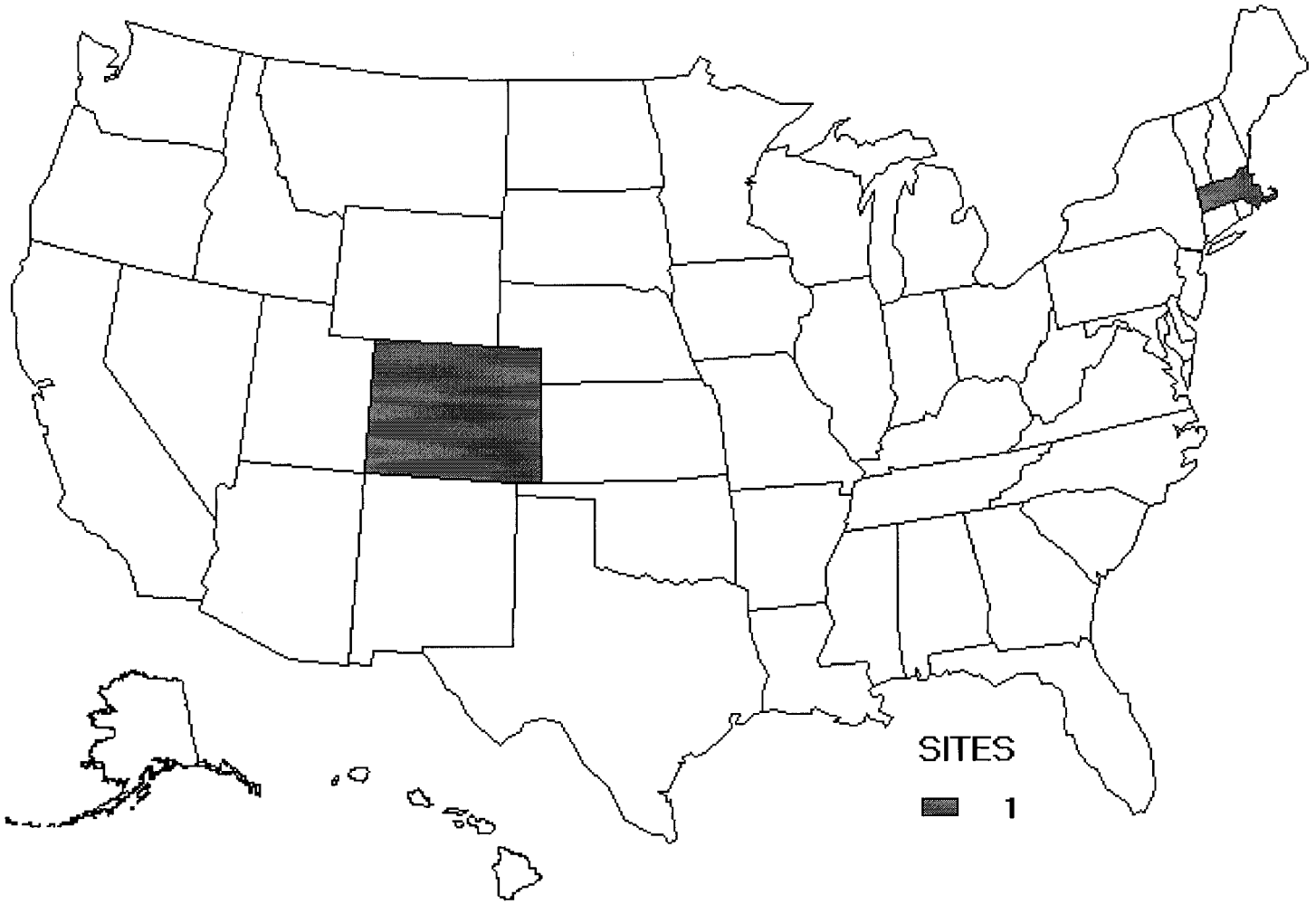
Derived from HazDat 1998

Figure 5-4. Frequency of NPL Sites with Mercurous Chloride Contamination



Derived from HazDat 1998

Figure 5-5. Frequency of NPL Sites with Dimethylmercury Contamination



Derived from HazDat 1998

atmosphere. According to the Toxic Chemical Release Inventory (TRI), in 1996, a total of 84,772 pounds of mercury were released to the environment (air, water, soil, underground injection, and off-site transfer) from 31 large processing facilities (TRI96 1998). Table 5-1 lists the amounts released from these facilities. The amounts of mercury released to the various environmental compartments in 1996, 1994, and 1991 are also compared in Table 5-2. It is noteworthy that the total environmental releases of mercury have decreased by about 90% from 1991 to 1996 from those production and processing facilities that are required to report their releases to TRI. The individual quantities of mercury released to land, publicly owned treatment works (POTWs), and via off-site waste transfer have decreased most substantially since 1991 by 90%, 95%, and 89% respectively. In contrast, releases to air, water, and underground injection have fluctuated over the past few years, but overall have remained relatively unchanged or declined slightly. The data listed in the TRI should be used with caution because only certain types of facilities are required to report (EPA 1996f). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the Toxics Release Inventory only if they employ 10 or more full-time employees; if their facility is classified under Standard Industrial Classification (SIC) codes 20 through 39; and if their facility produces, imports, or processes 25,000 or more pounds of any TRI chemical or otherwise uses more than 10,000 pounds of a TRI chemical in a calendar year (EPA 1996f). Nationwide mercury emissions from a variety of emission sources are discussed in detail in Sections 5.2.1 through 5.2.3.

5.2.1 Air

Mercury is a naturally occurring metal that is ubiquitous in the environment. Mercury is released to environmental media by both natural processes and anthropogenic sources. Mercury ore is found in all classes of rocks, including limestone, calcareous shales, sandstone, serpentine, chert, andesite, basalt, and rhyolite. The normal concentration of mercury in igneous and sedimentary rocks and minerals appears to be 10–50 ng/g (ppb) (Andersson 1979); however, the mineral cinnabar (mercuric sulfide) contains 86.2% mercury (Stokinger 1981). Currently, the average mercury level in the atmosphere is about 3 to 6 times higher than the estimated level in the preindustrial atmosphere (Mason et al. 1995). Results of several studies suggest increases in anthropogenic mercury emissions over time. Zillioux et al. (1993) used peat cores to estimate that present day deposition of mercury is 2 to 3 times greater than preindustrial levels. Lindqvist (1991c) estimated that sediment concentrations in Swedish lakes are 5 times higher than background levels from precolonial times. Travis and Blaylock (1992) reported that mercury levels in tree

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Mercury

			Reported amounts released in pounds per year [a]						
STATE [b]	CITY	FACILITY	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
AL	MUSCLE SHOALS	OCCIDENTAL CHEMICAL CORP.	1,069	24	0	0	0	539	1,632
DE	NEW CASTLE	OCCIDENTAL CHEMICAL CORP.	1,110	16	0	0	0	4,337	5,463
GA	AUGUSTA	OLIN CHLOR-ALKALI PRODS.	1,317	7	0	0	0	7,013	8,337
IA	MASON CITY	ALEXANDER MFG. CO.	1	0	0	0	5	0	6
IL	FREEPORT	MICRO SWITCH	4	0	0	0	0	2,500	2,504
IL	ROCKFORD	VALSPAR CORP.	5	0	0	0	5	760	770
IN	EDINBURGH	UNITED TECHS. AUTOMOTIVE INC.	5	0	0	0	0	2,250	2,255
IN	ELKHART	DURAKOOL INC.	5	0	0	0	0	0	5
IN	ELKHART	HERMASEAL CO.	5	0	0	0	0	0	5
KS	DE SOTO	KOCH SULFUR PRODS. CO.	0	0	0	0	0	5	5
KY	CALVERT CITY	BF GOODRICH CO.	1,200	250	0	0	0	2,000	3,450
KY	LOUISVILLE	DU PONT	0	0	0	0	0	1,063	1,063
LA	GEISMAR	BORDEN CHEMICALS & PLASTICS	0	17	0	9	0	13,121	13,147
LA	LAKE CHARLES	PPG IND. INC.	1,230	22	0	0	0	73	1,325
LA	PLAQUEMINE	DOW CHEMICAL CO.	20	0	0	0	0	0	20
LA	SAINT GABRIEL	PIONEER CHLOR ALKALI CO. INC.	1,204	23	0	0	0	8,752	9,979
ME	ORRINGTON	HOLTRACHEM MFG.	351	6	1	0	0	2,453	2,811
MI	JACKSON	ELM PLATING CO.	5	0	0	0	5	10	20
MI	ROMULUS	KERR CORP.	10	0	0	0	0	5,599	5,609
NC	RIEGELWOOD	HOLTRACHEM MFG. CO. L.L.C.	1,446	11	0	0	0	104	1,561
NY	ALBANY	MERCURY REFINING CO. INC.	255	5	0	0	0	520	780
OH	ASHTABULA	ASHTA CHEMICALS INC.	1,653	5	0	0	0	682	2,340
OK	TULSA	SINCLAIR OIL CORP.	0	20	2	0	0	0	22
PA	ALLENTOWN	ADVANCED ENVIRONMENTAL	0	0	0	0	0	255	255
PA	HELLERTOWN	BETHLEHEM APPARATUS CO. INC.	5	0	0	0	0	0	5
PA	MONACA	ZINC CORP. OF AMERICA	130	0	0	0	0	10,700	10,830
TN	CHARLESTON	OLIN CORP.	1,294	40	534	0	0	0	1,868
TX	DEER PARK	OCCIDENTAL CHEMICAL CORP.	1,040	6	0	0	0	3,343	4,389
WA	BELLINGHAM	GEORGIA-PACIFIC WEST INC.	1,460	45	0	0	0	205	1,710
WI	PORT EDWARDS	VULCAN MATERIALS CO.	1,143	4	0	0	0	98	1,245
WV	NEW MARTINSVILLE	PPG IND. INC.	1,130	40	0	0	0	191	1,361
		TOTALS	17,097	541	537	9	15	66,573	84,772

Source: TRI96 1998

[a] Data in TRI are maximum amounts released by each facility

[b] Post office state abbreviations used

[c] The sum of fugitive and stack releases are included in releases to air by a given facility

[d] The sum of all releases of the chemical to air, land, and water, and underground injection wells; and transfers off-site by a given facility

POTW = publicly owned treatment works

Table 5-2. Comparison of Environmental Releases of Mercury (pounds per year) from Facilities That Manufacture and Process Mercury Reported to the Toxics Release Inventory (TRI) in 1991, 1994, and 1996

Year	Air	Water	Land	Underground injection	POTW transfer	Off-site waste transfer	Total environmental releases
1991[a]	21,288	681	5,294	9	314	619,310	646,896
1994[b]	13,885	326	1,351	7	15	67,480	83,064
1996[c]	17,097	541	537	9	15	66,573	84,772

[a] Source: TRI91 1993
[b] Source: TRI94 1996
[c] Source: TRI96 1998

rings, as well as in soil and sediment cores, suggest that a four- to five-fold increase in mercury levels in air has occurred since the beginning of the industrial revolution.

A degree of uncertainty exists with respect to estimates of the relative contributions of natural and anthropogenic sources of mercury emissions to the environment reported in the scientific literature. Nriagu and Pacnya (1988) estimated anthropogenic emissions to be more than half of the total global emissions of 6,000 tons/year. Nriagu (1989) estimated mercury emissions from natural sources to be 2,500 tons/year. In contrast, WHO (1990, 1991) reported that the major source of atmospheric mercury is global degassing of mineral mercury from the lithosphere and hydrosphere at an estimated rate of 2,700–6,000 metric tons/year, which is approximately 1.3 to 3 times the rate of release from anthropogenic sources. Lindqvist (1991b) estimated world anthropogenic emissions at 4,500 tons with an additional 3,000 tons attributed to natural sources. Most recently, Pirrone et al. (1996) estimated world emissions of mercury at 2,200 metric tons/year and concluded that natural sources, industrial sources, and the recycling of anthropogenic mercury each contribute about one-third of the current mercury burden in the global atmosphere. A major source of the uncertainty is that emissions from terrestrial and marine systems include a “recycled” anthropogenic source component (WHO 1990).

Recent estimates of anthropogenic releases of mercury to the atmosphere range from 2,000–4,500 metric tons/year, mostly from the mining and smelting of mercury and other metal sulfide ores. An estimated 10,000 metric tons of mercury are mined each year, although there is considerable year-to-year variation (WHO 1990). Other anthropogenic sources include: industrial processes involving the use of mercury, including chloralkali manufacturing facilities; combustion of fossil fuels, primarily coal; production of cement; and medical and municipal waste incineration and commercial/ industrial boilers (Bache et al. 1991; EPA 1987f, 1996b; Lindberg 1984; Lindqvist 1991b; Nriagu and Pacyna 1988; WHO 1990, 1991). Stein et al. (1996) estimated that approximately 80% of the anthropogenic sources of mercury are emissions of elemental mercury to the air, primarily from fossil fuel combustion, mining, smelting, and from solid waste incineration. Another 15% of the anthropogenic emissions occur via direct application of fertilizers and fungicides and municipal solid waste (e.g., batteries and thermometers) to the land. Recently, Carpi et al. (1998) studied the contamination of sludge-amended soil with inorganic and methyl-mercury and the subsequent emission of this mercury contamination into the atmosphere. These authors reported the routine application of municipal sewage sludge to crop land significantly increased the concentration of both total mercury and methylmercury in surface soil from 80 to 6,1000 µ/kg (ppb) and 0.3 to 8.3 µ/kg (ppb), respectively. Both inorganic and methylmercury were transported from the

sludge/soil matrix to the environment by emission to the atmosphere. An additional 5% of mercury emissions occur via direct discharge of industrial effluent to bodies of water. Mercury emissions from coal-fired power plants are almost exclusively in the vapor phase (98%) (Germani and Zoller 1988). Brown et al. (1993) reported that 79–87% of mercury contained in coal was released with the flue gas at coal-fired power plants. These authors monitored emissions from plants using sub-bituminous C (low sulfur), lignite (medium sulfur), and bituminous (both low- and high-sulfur) coals. Anthropogenic emissions, mainly from combustion of fossil fuels, account for about 25% of mercury emissions to the atmosphere (WHO 1990). These mercury emissions eventually may be deposited on the surrounding soil, although soil concentrations have not been correlated with distance or direction from such plants (Sato and Sada 1992). Other potential emission sources include copper and zinc smelting operations, paint applications, waste oil combustion (EPA 1987f), geothermal energy plants (Baldi 1988), crematories (Nieschmidt and Kim 1997; WHO 1991), and incineration of agricultural wastes (Mariani et al. 1992). The incineration of medical waste has been found to release up to 12.3 mg/m^3 of mercury (Glasser et al. 1991). Medical wastes may release approximately 110 mercury mg/kg of uncontrolled emissions from medical waste incinerators, compared with 25.5 mercury mg/kg general municipal waste, indicating that medical equipment may be a significant source of atmospheric mercury. The use of scrubbers on the incinerators may remove up to 51% of the mercury emissions (Walker and Cooper 1992). Other potential emission sources of mercury emissions to the air include slag from metal production, fires at waste disposal sites, and diffuse emissions from other anthropogenic sources, such as dentistry and industrial activities. The anthropogenic mercury contributions are greater in the northern hemisphere than in the southern hemisphere, and are greatest in heavily industrialized areas.

Balogh and Liang (1995) conducted a 9-week sampling and analysis program to determine the fate of mercury entering a large municipal wastewater treatment plant. Mercury removal in primary treatment averaged 79%; and the average removal across the entire plant was 96%. Mercury loading on the secondary treatment (activated sludge) process was elevated to near plant influent levels due to recycling of the spent scrubber water from the sewage sludge incinerator control equipment. This internal recycling of the spent incinerator scrubber water resulted in elevated mercury loadings to the incinerator and reduced the mercury control efficiency to near zero. Measurements indicated that publicly owned treatment works (POTWs) can remove mercury from wastewater very effectively; however, approximately 95% of the mercury entering the plant was ultimately discharged to the atmosphere via sludge incineration emissions.

Bullock (1997) used the Regional Lagrangian Model of Air Pollution (RELMAP) to simulate the emission, transport, chemical transformation, and wet and dry deposition of elemental mercury gas, divalent mercury gas, and particulate mercury from various point and area source types to develop an atmospheric mercury emissions inventory by anthropogenic source type. The results of the RELMAP model are shown in Table 5-3. On a percentage basis, various combustion processes (medical waste incinerators, municipal waste incinerators, electric utility power production [fossil fuel burning] and non-utility power and heat generation) account for 83% of all anthropogenic emissions in the United States. Overall, of the emissions produced, 41% were associated with elemental mercury vapor (Hg^{o}), 41% with the mercuric form (Hg^{2+}), and 18% was mercury associated with particulates.

A more detailed estimate of national mercury emission rates for various categories of sources is shown in Table 5-4. As shown in this table, point sources of anthropogenic mercury emissions appear to represent the greatest contribution of mercury releases, with combustion sources representing 85% of all emissions.

According to the most recent Toxics Release Inventory (Table 5-1), in 1996, the estimated releases of 17,097 pounds of mercury to the air from 31 large processing facilities accounted for about 20% of annual environmental releases for this element (TRI96 1998). This is slightly more (13%) than the estimated 13,885 pounds that were released to the air in 1994 (TRI94 1996), but 35% less than the 21,288 pounds released to the air in 1991 (Table 5-2). The TRI data listed in Tables 5-1 and 5-2 should be used with some caution, since only certain types of facilities are required to report (EPA 1996f). This is not an exhaustive list.

Mercury has been identified in air samples collected at 25 of the 714 NPL hazardous waste sites where it has been detected in at least one environmental medium (HazDat 1998).

5.2.2 Water

Natural weathering of mercury-bearing minerals in igneous rocks is estimated to directly release about 800 metric tons of mercury per year to surface waters of the earth (Gavis and Ferguson 1972). Atmospheric deposition of elemental mercury from both natural and anthropogenic sources has been identified as an indirect source of mercury to surface waters (WHO 1991). Mercury associated with soils can be directly washed into surface waters during rain events. Surface runoff is an important mechanism for transporting mercury from soil into surface waters, particularly for soils with high humic content (Meili

Table 5-3. Atmospheric Mercury Emission Inventory for the United States by Anthropogenic Source Type[a]

Source type	Mg/yr^{-1}	% of total emissions	% mercury species		
			Hg^0	Hg^{2+}	Hg_p
Medical waste incineration	58.6	26	20	60	20
Municipal waste collection	49.8	22	20	60	2
Electric utility boilers (coal, gas, oil)	48.5	22	50	30	20
Non-utility power and heat generation	28.5	13	50	30	20
Non-ferrous metal smelting	8.7	4	85	10	5
Chloralkali factories	6.5	3	70	30	0
Other point sources	16.2	7	80	10	10
Area sources (e.g., dental amalgams, fluorescent lighting fixtures)	6.9	3	100	0	0
Total	223.7	100%	41%	41%	18%

[a] Emission rates are specified in units of megagrams per year ($Mg\ yr^{-1}$)

Hg^0 = elemental mercury vapor; Hg^{2+} = mercuric form; Hg_p = mercury associated with particulates

Source: Bullock 1997

Table 5-4. Estimates of U.S. Mercury Emission Rates by Category

Source of mercury	1990–1993 Mg/yr[a]	1990–1993 tons/yr[a]	% of total inventory
Area sources	**2.8**	**3.1**	**1.3**
Flourescent lamp breakage	1.4	1.5	0.6
General laboratory use	0.7	0.8	0.3
Dental preparations and use	0.7	0.8	0.3
Mobile sources	[b]	[b]	d
Paint use	[c]	[c]	e
Agricultural burning	[b]	[b]	d
Landfills	[b]	[b]	d
Point sources	**217.3**	**239.4**	**98.7**
Combustion sources	***186.9***	***205.9***	***84.9***
Medical Waste Incinerators[d]	58.8	64.7	26.7
Municipal Waste Combustors	50	55	22.7
Utility boilers	46.5	51.3	21.2
Coal	(46.3)[e]	(51.0)	(21.0)
Oil	(0.23)	(0.25)	(0.1)
Natural gas	(0.002)	(0.002)	(0.0)
Commercial/industrial boilers	26.3	29.0	12.0
Coal	(20.7)	(22.8)	(9.4)
Oil	(5.5)	(6.0)	(2.5)
Residential boilers	3.2	3.5	1.4
Coal	(0.5)	(0.6)	0.2
Oil	(2.7)	(3.0)	(1.2)
Sewage Sludge Incinerators	1.7	1.8	0.7
Crematories	0.4	0.4	0.2
Wood-fired boilers[h]	0.3	0.3	0.1
Hazardous waste combusters	[b]	[b]	[b]

Table 5-4. Estimates of U.S. Mercury Emission Rates by Category (continued)

Source of mercury	1990–1993 Mg/yr[a]	1990–1993 tons/yr[a]	% of total inventory
Manufacturing sources	***29.1***	***32***	***13.2***
Primary lead production	8.2	9.0	3.7
Secondary Hg production	6.7	7.4	3.1
Chlor-alkali production	5.9	6.5	2.7
Portland cement production	5.9	6.5	2.7
Primary copper production	0.6	0.7	0.3
Lime manufacturing	0.6	0.7	0.3
Electrical apparatus	0.42	0.46	0.2
Instruments	0.5	0.5	0.2
Carbon black production	0.23	0.25	0.1
Fluorescent lamp recycling	0.005	0.006	0.002
Batteries	0.02	0.02	0.0
Primary Hg production	[b]	[b]	[b]
Mercury compounds	[b]	[b]	[b]
Byproduct coke	[b]	[b]	[b]
Refineries	[b]	[b]	[b]
Miscellaneous sources	***1.3***	***1.4***	***0.6***
Geothermal power	1.3	1.4	0.6
Turf products	[c]	[c]	[c]
Pigments, oil, etc.	[c]	[c]	[c]
Total	**220.1**	**242.5**	**100.0**

[a] Numbers do not add exactly because of rounding.

[b] Insufficient information to estimate 1990 emissions.

[c] Mercury has been phased out of use.

[d] In the course of Medical Waste Incinerator rulemaking, with the receipt of new data, US EPA expects to revise the mercury emission estimate for Medical Waste lincinerators downward.

[e] Parentheses denote subtotal within a larger point source category.

[f] Includes boilers only; does not include residential wood combustion (wood stoves).

Source: EPA 1996b

1991). Mercury may also be released to surface waters in effluents from a number of industrial processes, including chloralkali production, mining operations and ore processing, metallurgy and electroplating, chemical manufacturing, ink manufacturing, pulp and paper mills, leather tanning, pharmaceutical production, and textile manufacture (Dean et al. 1972; EPA 1971c). Discharges from a regional wastewater treatment facility on the St. Louis River that received primarily municipal wastes contained 0.364 µg/L (ppb) of mercury, resulting in concentrations in the adjacent sediment of up to 5.07 µg/g (ppm) (Glass et al. 1990). Industrial effluents from a chemical manufacturing plant on the NPL (Stauffer Chemical's LeMoyne, Alabama site) contained more than 10 ppm of mercury; these effluents had contaminated an adjacent swamp and watershed with mercury concentrations in the sediments ranging from 4.3 to 316 ppm (Hayes and Rodenbeck 1992). Effluent monitoring data collected under the National Pollutant Discharge Elimination System (NPDES) Program were used to estimate pollutant loadings from effluent discharges to the San Francisco Bay Estuary between 1984 and 1987 (Davis et al. 1992). Of the 1,030 samples of industrial effluents monitored entering the San Francisco Estuary during this period, 39% were found to contain mercury (Davis et al. 1992). Although these authors did not specify the limits of detection for mercury and did not provide quantitative information on the concentrations detected, they did indicate that measurements for most of the priority pollutants including mercury were at or below the detection limit. This precluded quantitative assessment of spatial and temporal trends in calculating loadings to the estuary for all but four metals (Davis et al. 1992).

According to the most recent Toxics Release Inventory, in 1996, the estimated releases of 541 pounds of mercury to water from 31 large processing facilities accounted for about 0.64% of total environmental releases for this element (TRI96 1998). An addition 15 pounds of mercury were released indirectly to POTWs, and some of this volume ultimately may have been released to surface waters. This is approximately 215 pounds more mercury than was released to water directly or indirectly via POTWs in 1994 (TRI94 1996), but 445 pounds less than that released to water either directly (144 pounds) or indirectly via POTWs (301 pounds) in 1991 (TRI91 1993). The TRI data listed in Tables 5-1 and 5-2 should be used with some caution, since only certain types of facilities are required to report (EPA 1996f). This is not an exhaustive list.

Mercury has been identified in surface water, groundwater, and leachate samples collected at 197, 395, and 58 sites, respectively, of the 714 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998).

5.2.3 Soil

Atmospheric deposition of mercury from both natural and anthropogenic sources has been identified as an indirect source of mercury to soil and sediments (Sato and Sada 1992; WHO 1990, 1991). Mercury is released to cultivated soils through the direct application of inorganic and organic fertilizers (e.g., sewage sludge and compost), lime, and fungicides containing mercury (Andersson 1979). Recent interest in community recycling of sewage sludge and yard compost may result in increased releases of mercury from these wastes. Sewage sludge contained approximately 20 times more mercury than yard compost (2.90 ppm versus 0.15 ppm) (Lisk et al. 1992a); municipal solid waste contained the highest concentration (3.95 ppm) (Lisk et al. 1992b). Recently, Carpi et al. (1998) studied the contamination of sludge-amended soil with inorganic and methylmercury and the emission of this mercury contamination into the atmosphere. These authors reported the routine application of municipal sewage sludge to crop land significantly increased the concentration of both total mercury and methylmercury in surface soil from 80 to 6,1000 µg/kg (ppb) and 0.3–8.3 µg/kg (ppb), respectively. Both the inorganic and methylmercury were transported from the sludge/soil matrix to the environment by emission to the atmosphere.

Additional anthropogenic releases of mercury to soil are expected as a result of the disposal of industrial and domestic solid waste products (e.g., thermometers, electrical switches, and batteries) to landfills (see Table 5-5). Another source of mercury releases to soil is the disposal of municipal incinerator ash in landfills (Mumma et al. 1990). In 1987, nationwide concentrations of mercury present in the ash from municipal waste incineration ranged from 0.03 to 25 ppm (Mumma et al. 1990). Such releases may exhibit a seasonal variability. For example, fly ash collected prior to Christmas contained significantly less mercury (6.5 ppm) than ash collected after Christmas (45–58 ppm), possibly as a result of the increased use and disposal of batteries containing mercury in toys and other equipment during this season (Mumma et al. 1991). Emission sources include stack emissions, ashes collected at the stack, ashes from electrostatic precipitators, and in slags (Morselli et al. 1992). An analysis of mercury concentrations in soil, refuse combustibles, and bottom and fly ash from incinerators showed increasing concentrations of 0, 2, 4, and 100 mg/kg (ppm), respectively (Goldin et al. 1992).

According to the Toxics Release Inventory, in 1996, the estimated releases of 537 pounds of mercury to land from 31 large processing facilities accounted for about 0.63% of the total 1996 environmental releases for this element (TRI96 1998). In addition, an estimated 9 pounds of mercury (<0.01% of total environmental releases) were released via underground injection (see Table 5-1). This is approximately

Table 5-5. Estimated Discards of Mercury in Products in Municipal Solid Waste (in tons[a])

	Amount in tons[b]						
Products	1970	1975	1980	1985	1989	1995	2000
Batteries							
Alkaline	4.1	38.4	158.2	352.3	419.4	41.6	0.0
Mercuric oxide	301.9	287.8	266.8	235.2	196.6	131.5	98.5[c]
Others	4.8	4.7	4.5	4.5	5.2	3.5	0.0
Subtotal batteries	**310.8**	**330.9**	**429.5**	**592.0**	**621.2**	**176.6**	**98.5**
Electric lighting							
Fluorescent lamps	18.9	21.5	1.1	0.7	0.8	1.0	11.6[d]
High intensity lamps	0.2	0.3	23.2	27.9	26.0	14.7	1.2
Subtotal lighting	**19.1**	**21.8**	**24.3**	**28.6**	**26.7**	**15.7**	**12.6**
Paint residues	30.2	37.3	26.7	31.4	18.2	2.3	0.5
Fever thermometers	12.2	23.2	25.7	32.5	16.3	16.9	16.8
Thermostats	5.3	6.8	7.0	9.5	11.2	8.1	10.3
Pigments	32.3	27.5	23.0	25.2	10.0	3.0	1.5
Dental uses	9.3	9.7	7.1	6.2	4.0	2.9	2.3
Special paper coating	0.1	0.6	1.2	1.8	1.0	0.0	0.0
Mercury light switches	0.4	0.4	0.4	0.4	.04	1.9	1.9
Film pack batteries	2.1	2.3	2.6	2.8	0.0	0.0	0.0
Subtotal other sources	**91.8**	**107.8**	**83.7**	**109.8**	**61.1**	**35.1**	**33.3**
Total discards	**421.7**	**460.5**	**537.5**	**730.4**	**709.0**	**227.4**	**144.4**

[a] EPA (1992a) (except fluorescent lamps estimates)
[b] Discards before recovery, 1 ton equals 2,000 pounds
[c] The estimates for the years 1995 and 2000 do not reflect recent state, Federal, or battery manufacturers' efforts to reduce the mercury content of batteries. Since 1992, several states have restricted mercury use in batteries and/or banned the sale of mercuric oxide batteries. Federal legislation to restrict mercury use in batteries is pending. The battery industry has eliminated mercury as an intentional additive in alkaline batteries, except in button cells.
[d] The estimated contribution of mercury from fluorescent lamps disposal to MSW was calculated based on industry estimates of a 4% growth rate in sales in conjunction with a 53% decrease in mercury content between 1989–1995, and a further 34% decrease in mercury content by the year 2000 (to 15 mg mercury per 4-foot fluorescent lamp (National Electric Manufacturers Association (1995).

Source: EPA 1996b

57% of the mercury that was released to soil in 1994 (TRI94 1996) and is only 10% of the mercury released to soil in 1991 (see Table 5-2). The TRI data listed in Tables 5-1 and 5-2 should be used with some caution, since only certain types of facilities are required to report (EPA 1996f). This is not an exhaustive list.

Mercury has been identified in soil and sediment samples collected at 350 and 208 sites, respectively, of the 714 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998).

5.3 ENVIRONMENTAL FATE

The natural global bio-geochemical cycling of mercury is characterized by degassing of the element from soils and surface waters, followed by atmospheric transport, deposition of mercury back to land and surface waters, and sorption of the compound to soil or sediment particulates. Mercury deposited on land and open water is in part revolatilized back into the atmosphere. This emission, deposition, and revolatilization creates difficulties in tracing the movement of mercury to its sources (WHO 1990). Particulate-bound mercury can be converted to insoluble mercury sulfide and precipitated or bioconverted into more volatile or soluble forms that re-enter the atmosphere or are bioaccumulated in aquatic and terrestrial food chains (EPA 1984b).

5.3.1 Transport and Partitioning

Mercury has three valence states. The specific state and form in which the compound is found in an environmental medium is dependent upon a number of factors, including the redox potential and pH of the medium. The most reduced form is metallic or elemental mercury, which is a liquid at ambient temperatures, but readily vaporizes. Over 95% of the mercury found in the atmosphere is gaseous mercury (Hg^0), the form involved in long-range (global) transport of the element. Residence time in the atmosphere has been estimated to range from 6 days (Andren and Nriagu 1979) to 2 years (EPA 1984b). Approximately 5% of atmospheric mercury is associated with particulates, which have a shorter atmospheric residence time, are removed by dry or wet deposition, and may show a regional or local distribution pattern (Nater and Grigal 1992). Atmospheric inputs may be more significant in areas where other sources of contamination, such as contaminated rivers, are less important or nonexistent (Kelly et al. 1991). Although local sources are important, a 72-hour travel time trajectory for mercury indicates that some mercury found in rain may originate from sources up to 2,500 km (1,550 miles) away (Glass et al.

1991). Over the last 140 years, the atmospheric mercury concentrations have increased by a factor of 3.7, or approximately 2% per year (Swain et al. 1992).

Metallic mercury released in vapor form to the atmosphere can be transported long distances before it is converted to other forms of mercury, and wet and dry deposition processes return it to land and water surfaces. Dry deposition may account for approximately 70% of the total atmospheric deposition of mercury during the summer, although on an annual basis, wet and dry deposition may be of equal importance (Lindberg et al. 1991). Up to 22% of the annual input of mercury to Lake Erie is from dry deposition of mercury-containing atmospheric particles or from precipitation (Kelly et al. 1991). Wet deposition is the primary method of removal of mercury from the atmosphere (approximately 66%) (Fitzgerald et al. 1991; Lindqvist 1991c) and may account for virtually all of the mercury content in remote lakes that do not receive inputs from other sources (e.g., industrial effluents) (Hurley et al. 1991; Swain et al. 1992). Most inert mercury (Hg^{+2}) in precipitation is bound to aerosol particulates, which are relatively immobile when deposited on soil or water (Meili et al. 1991). Mercury is also present in the atmosphere to a limited extent in unidentified soluble forms associated with particulate matter. In addition to wet and dry deposition processes, mercury may also be removed from the atmosphere by sorption of the vapor form to soil or water surfaces (EPA 1984b).

In soils and surface waters, mercury can exist in the mercuric (Hg^{+2}) and mercurous (Hg^{+1}) states as a number of complex ions with varying water solubilities. Mercuric mercury, present as complexes and chelates with ligands, is probably the predominant form of mercury present in surface waters. The transport and partitioning of mercury in surface waters and soils is influenced by the particular form of the compound. More than 97% of the dissolved gaseous mercury found in water consists of elemental mercury (Vandal et al. 1991). Volatile forms (e.g., metallic mercury and dimethylmercury) are expected to evaporate to the atmosphere, whereas solid forms partition to particulates in the soil or water column and are transported downward in the water column to the sediments (Hurley et al. 1991). Vaporization of mercury from soils may be controlled by temperature, with emissions from contaminated soils being greater in warmer weather when soil microbial reduction of Hg^{+2} to the more volatile elemental mercury is greatest (Lindberg et al. 1991). Vapor-phase mercury volatilized from surface waters has been measured (Schroeder and Fanaki 1988); however, the dominant process controlling the distribution of mercury compounds in the environment appears to be the sorption of nonvolatile forms to soil and sediment particulates, with little resuspension from the sediments back into the water column (Bryan and Langston 1992). Cossa et al. (1988) found that 70% of the dissolved mercury in St. Lawrence River water was

associated with organic matter. The authors reported that the removal mechanism was flocculation of organic mercury colloids in freshwater. Methylmercury and other mercury fractions are strongly bound to organic matter in water and may be transported in runoff water from contaminated lakes to other surface waters and soils (Lee and Iverfeldt 1991). Small amounts (2–4 ng/L [ppt]) of mercury are able to move from contaminated groundwater into overlying lakes, with concentrations reaching a maximum near the sediment/water interface; however, since most of the mercury in the groundwater is derived from atmospheric sources, this low value indicates that most of the mercury deposited on soil (92–96% of the 10.3 µg/m^2/year of mercury deposited) is absorbed to the soil and does not leach down into the groundwater (Krabbenhoft and Babiarz 1992).

The sorption process has been found to be related to the organic matter content of the soil or sediment. Mercury is strongly sorbed to humic materials and sesquioxides in soil at a pH higher than 4 (Blume and Brummer 1991) and to the surface layer of peat (Lodenius and Autio 1989). Mercury has been shown to volatilize from the surface of more acidic soils (i.e., soil pH of less than 3.0) (Warren and Dudas 1992). Adsorption of mercury in soil is decreased with increasing pH and/or chloride ion concentrations (Schuster 1991). Mercury is sorbed to soil with high iron and aluminum content up to a maximum loading capacity of 15 g/kg (15,000 ppm) (Ahmad and Qureshi 1989). Inorganic mercury sorbed to particulate material is not readily desorbed. Thus, freshwater and marine sediments are important repositories for inorganic forms of the element, and leaching is a relatively insignificant transport process in soils. However, surface runoff is an important mechanism for moving mercury from soil to water, particularly for soils with high humic content (Meili 1991). Mobilization of sorbed mercury from particulates can occur through chemical or biological reduction to elemental mercury and bioconversion to volatile organic forms (Andersson 1979; Callahan et al. 1979; EPA 1984b). Metallic mercury may move through the top 3–4 cm of dry soil at atmospheric pressure; however, it is unlikely that further penetration would occur (Eichholz et al. 1988).

The volatilization and leaching of various forms of mercury (elemental, mercuric sulfide, mercuric oxide, and mercurous oxide) from soils or wastes was examined using the headspace method for volatilization and the Resource and Conservation Recovery Act (RCRA) leaching protocols for leaching through soil to determine if the leachates exceeded the RCRA limit of 200 µg/L (ppb) (Willett et al. 1992). With the exception of mercuric sulfide, the other forms of mercury increased in concentrations in the headspace vapor and in the leachate as the soil concentrations increased, although the elemental mercury concentrations never exceeded the RCRA limit, indicating that it was relatively unleachable. Mercuric sulfide also did not exceed the background level for the leachate and was consistently less than

0.001 mg/m^3 for the vapor concentrations, indicating that it was also nonleachable and did not readily volatilize. This study also showed that concentrations of mercury in leachate could not be correlated with the concentration of mercury in the soil or in the headspace vapors (Willett et al. 1992). Mercuric sulfide has been found to strongly adsorb to soil, and even with weathering, any mercury released from the mercuric sulfide is readsorbed by the soil (Harsh and Doner 1981).

The most common organic form of mercury, methylmercury, is soluble, mobile, and quickly enters the aquatic food chain. This form of mercury is accumulated to a greater extent in biological tissue than are inorganic forms of mercury (Riisgard and Hansen 1990). Methylmercury in surface waters is rapidly accumulated by aquatic organisms; concentrations in carnivorous fish (e.g., pike, shark, and swordfish) at the top of both freshwater and marine food chains are biomagnified on the order of 10,000–100,000 times the concentrations found in ambient waters (Callahan et al. 1979; EPA 1984b; WHO 1990, 1991). The range in experimentally determined bioconcentration factor (BCF) values is shown in Table 5-6. The bioaccumulation potential for methylmercury in fish is influenced by the pH of the water, with a greater bioaccumulation seen in waters with lower pH (Ponce and Bloom 1991). Mercury concentrations in fish have also been negatively correlated with other water quality factors, such as alkalinity and dissolved oxygen content (Wren 1992).

The biomagnification of methylmercury has been demonstrated by the elevated levels found in piscivorous fish compared with fish at lower levels of the food chain (Jackson 1991; Kohler et al. 1990; Porcella 1994; Watras and Bloom 1992). Biomagnification factors for methylmercury in the food webs of Lake Ontario were lowest for the transfer of methylmercury from mysids to amphipods (1.1), plankton to amphipods (1.8), and plankton to mysids (2.4); were intermediate for the transfer from mysids to fish (5.1) and amphipods to fish (6.5); and were highest for the transfer from plankton to fish (10.4) (Evans et al. 1991). (The biomagnification of methylmercury from water through several trophic levels is compared to the biomagnification of inorganic mercury in Table 5-7.) Watras and Bloom (1992) reported that biomagnification of methylmercury in Little Rock Lake seems to be a result of two processes: the higher affinity of inorganic mercury in lower trophic level organisms and the high affinity of methylmercury in fish. Fish appear to accumulate methylmercury from both food sources and the water column. However, Hall et al. (1997) found that food was the predominant source of mercury uptake in fish. The biological concentration factor (BCF) of methylmercury in fish in Little Rock Lake was three million (Porcella 1994). Mason et al. (1995) also compared bioaccumulation of inorganic mercury and methylmercury. These authors showed that passive uptake of the mercury complexes ($HgCl_2$ and CH_3HgCl) results in high

Table 5-6. Bioconcentration of Various Mercury Compounds by Freshwater and Saltwater Organisms

Species	Tissue	Chemical	Duration (days)	Bioconcentration factor[a]
Freshwater species				
		Mercury (II)		
Rainbow trout *Salmo gairdneri*	Whole body	Mercuric chloride	60	1,800
Fathead minnow *Pimephales promelas*	Whole body	Mercuric chloride	287	4,994[b]
		Organomercury compounds		
Rainbow trout *Salmo gairdneri*	Whole body	Methylmercuric chloride	60	11,000
Rainbow trout *Salmo gairdneri*	Whole body	Methylmercuric chloride	75	85,700
Brook trout *Salvelinus fontinalis*	Muscle	Methylmercuric chloride	273	11,000–33,000
Brook trout *Salvelinus fontinalis*	Whole body	Methylmercuric chloride	273	10,000–23,000
Brook trout *Salvelinus fontinalis*	Muscle and whole body	Methylmercuric chloride	756	12,000
Fathead minnow *Pimephales promelas*	Whole body	Methylmercuric chloride	336	44,130–81,670
Saltwater species				
		Mercury (II)		
Eastern oyster (adult) *Crassostrea virginica*	Soft parts	Mercuric chloride	74	10,000
American lobster (adult) *Homarus americanus*	Soft parts	Mercuric chloride	30	129
		Organomercury compounds		
Eastern oyster (adult) *Crassostrea virginica*	Soft parts	Methylmercuric chloride	74	40,000
Eastern oyster (adult) *Crassostrea virginica*	Soft parts	Phenylmercuric chloride	74	40,000

[a] Results are based on the concentration of mercury, not the concentration of the mercury compound to which the animal was exposed.
[b] From concentrations that caused adverse effects in a life-cycle test

Source: ASTER 1997

Table 5-7. Comparison of the Biomagnification of Methylmercury and Inorganic Mercury in a Freshwater Food Chain (Little Rock Lake)

Medium or trophic level	Methylmercury	Inorganic mercury	% Methylmercury
Water	1	10	10
Phytoplankton	10^5	$10^{5.7}$	15
Zooplankton	$10^{5.5}$	$10^{5.9}$	30
Fish	$10^{6.5}$	10^5	95

Source: Watras and Bloom 1992

concentrations of both the inorganic and methylated mercury in phytoplankton. However, differences in partitioning within phytoplankton cells between inorganic mercury (which is principally membrane-bound) and methylmercury (which accumulated in the cytoplasm) lead to a greater assimilation of methylmercury during zooplankton grazing.

Most of the discrimination between inorganic and methylmercury thus occurs during trophic transfer, while the major enrichment factor is between water and the phytoplankton. This also has been reported for the diatom *Thalassiosura weissflogii* in a marine food chain (Mason et al. 1996). Methylmercury was accumulated in the cell cytoplasm, and its assimilation by copepods was 4 times more efficient than the assimilation of inorganic mercury. Bioaccumulation has been demonstrated for predator fish in both freshwater and marine systems and in marine mammals (see Section 5.4.4). Bioaccumulation of methylmercury in aquatic food chains is of interest, because it is generally the most important source of nonoccupational human exposure to this compound (EPA 1984b; WHO 1990, 1991).

Aquatic macrophytes have been found to bioconcentrate methylmercury in almost direct proportion to the mercury concentration in the water (Ribeyre et al. 1991). Mortimer (1985) reported bioconcentration factors (BCFs) for several species of submerged aquatic plants exposed to inorganic mercury in laboratory aquaria of 3,300, 1.3, 0.9, and 1.3 for *Utricularia*, *Ceratophyllum*, *Najas*, and *Nitella*, respectively. The concentrations factor used by this author was based on µg g^{-1} dry weight in the plant/µg mL^{-1} water day^{-1}.

The potential for bioaccumulation in terrestrial food chains is demonstrated by the uptake of mercury by the edible mushroom *Pleurotus ostreatus*, grown on compost containing mercury at concentrations of up to 0.2 mg/kg (ppm). The bioaccumulation factors reported ranged from 65 to 140, indicating that there are potential risks to human health if these mushrooms are eaten in large quantities (Bressa et al. 1988). Elevated concentrations of mercury in 149 samples of mushrooms representing 11 different species were reported by Kalcac et al. (1991). These authors collected mushrooms within 6 km of a lead smelter in Czechoslovakia in operation since 1786. Mercury was accumulated by *Lepista nuda* and *Lepiota rhacodes* at 11.9 mg/kg (ppm) and 6.5 mg/kg (ppm) (dry weight), respectively. The mean concentration of other species ranged from 0.3 to 2.4 mg/kg (ppm). Concentrations of mercury in most of the mushroom species collected in that location were higher than in mushrooms collected in other parts of the country.

Data from higher plants indicate that virtually no mercury is taken up from the soil into the shoots of plants such as peas, although mercury concentrations in the roots may be significantly elevated and reflect the

mercury concentrations of the surrounding soil (Lindqvist 1991e). In a study by Granato et al. (1995), municipal solid waste sludge mercury concentrations from the Metropolitan Water Reclamation District of Greater Chicago were found to range from 1.1 to 8.5 mg/kg (ppm), with a mean concentration of 3.3 mg/kg (ppm). From 1971 to 1995, sludge applications were made to a Fulton County, Illinois sludge utilization site. About 80–100% of the mercury applied to the soils in sewage sludge since 1971 still resided in the top 15 cm of soil. These authors reported that sewage sludge applications did not increase plant tissue mercury concentrations in corn or wheat raised on the sludge utilization site.

Earthworms, *Lumbricus sp*., bioaccumulate mercury under laboratory and field conditions in amounts which are dependent on soil concentrations and exposure duration (Cocking et al. 1994). Maximum mercury tissue concentrations in laboratory cultures were only 20% of the 10–14.8 µg/g (ppm) (dry weight) observed in individual worms collected from contaminated soils (21 µg/g) on the South River flood plain at Waynesboro, Virginia. Bioconcentration occurred under field conditions in uncontaminated control soil (0.2 µg Hg/g); however, total tissue mercury concentrations (0.4–0.8 µg/g dry weight) were only 1–5% of those for earthworms collected on contaminated soils. Uptake by the earthworms appeared to be enhanced in slightly acidic soils (pH 5.9–6.0) in laboratory cultures. Soil and earthworm tissue mercury contents were positively correlated under both field and laboratory conditions. Predation of earthworms contaminated with mercury could pass the contamination to such predators as moles and ground feeding birds, such as robins (Cocking et al. 1994).

5.3.2 Transformation and Degradation

Mercury is transformed in the environment by biotic and abiotic oxidation and reduction, bioconversion of inorganic and organic forms, and photolysis of organomercurials. Inorganic mercury can be methylated by microorganisms indigenous to soils, fresh water, and salt water. This process is mediated by various microbial populations under both aerobic and anaerobic conditions. The most probable mechanism for this reaction involves the nonenzymatic methylation of mercuric mercury ions by methylcobalamine compounds produced as a result of bacterial synthesis. Mercury forms stable complexes with organic compounds. Monoalkyl mercury compounds (e.g., methylmercuric chloride) are relatively soluble; however, the solubility of methylmercury is decreased with increasing dissolved organic carbon content, indicating that it is bound by organic matter in water (Miskimmin 1991). Dialkyl mercury compounds (e.g., dimethyl-mercury) are relatively insoluble (Callahan et al. 1979; EPA 1984b). Dimethylmercury is volatile, although it makes up less than 3% of the dissolved gaseous mercury found in water (Andersson et al. 1990;

Vandal et al. 1991). The major pathways for transformation of mercury and various mercury compounds in air, water, and soil are shown in Figure 5-6.

5.3.2.1 Air

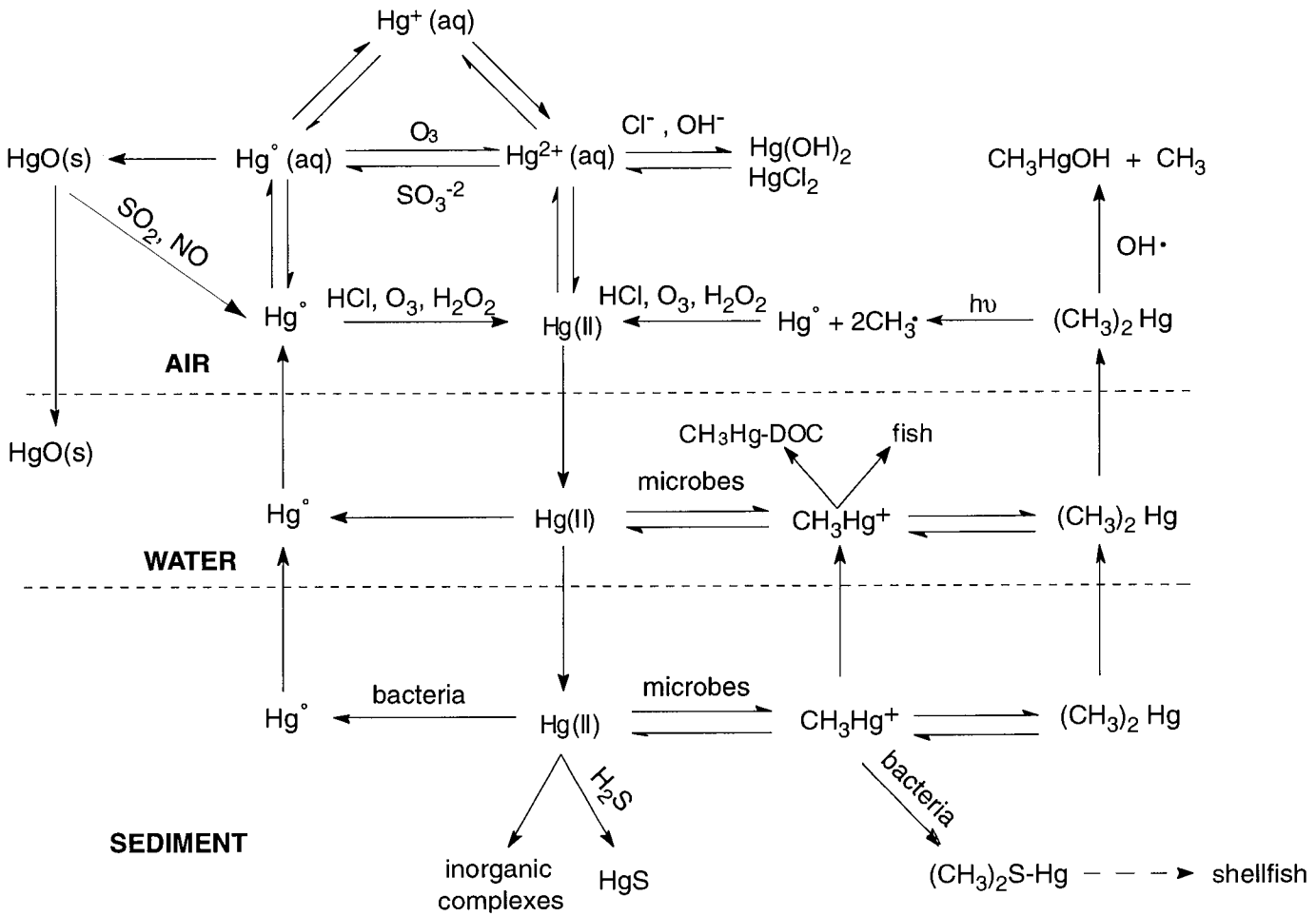
The primary form of atmospheric mercury, metallic mercury vapor (Hg^0), is oxidized by ozone to other forms (e.g., Hg^{+2}) and is removed from the atmosphere by precipitation (Brosset and Lord 1991). The oxidation/reduction of mercury with dissolved ozone, hydrogen peroxide, hypochlorite entities, or organoperoxy compounds or radicals may also occur in the atmosphere (Schroeder et al. 1991). The overall residence time of elemental mercury in the atmosphere has been estimated to be 6 days to 2 years, although in clouds, a fast oxidation reaction on the order of hours may occur between elemental mercury and ozone. Some mercury compounds, such as mercuric sulfide, are quite stable in the atmosphere as a result of their binding to particles in the aerosol phase (Lindqvist 1991b). Other mercury compounds, such as mercuric hydroxide ($Hg[OH]^2$), which may be found in the aqueous phase of the atmosphere (e.g., rain), are rapidly reduced to monovalent mercury in sunlight (Munthe and McElroy 1992). The main atmospheric transformation process for organomercurials appears to be photolysis (EPA 1984b; Johnson and Bramen 1974; Williston 1968).

5.3.2.2 Water

The most important transformation process in the environmental fate of mercury in surface waters is biotransformation. Photolysis of organomercurials may also occur in surface waters, but the significance of this process in relation to biotransformation is not clear (Callahan et al. 1979).

Any form of mercury entering surface waters can be microbially converted to methylmercuric ions, given favorable conditions. Sulfur-reducing bacteria are responsible for most of the mercury methylation in the environment (Gilmour and Henry 1991), with anaerobic conditions favoring their activity (Regnell and Tunlid 1991). Yeasts, such as *Candida albicans* and *Saccharomyces cerevisiae*, whose growth is favored by low pH conditions, are able to methylate mercury and are also able to reduce ionic mercury to elemental mercury (Yannai et al. 1991). Methyl cobalamine compounds produced by bacterial synthesis appear to be involved in the nonenzymatic methylation of inorganic mercury ions (Regnell and Tunlid 1991). The rate of methylmercury formation by this process is largely determined by the concentration of methyl cobalamine compounds, inorganic mercuric ions, and the oxygen concentration of the water, with the rate

Figure 5-6. Transformation of Mercury in Air, Water, and Sediment



Dashed lines represent the boundary between environmental compartments.

aq = associated with aqueous; DOC = dissolved organic carbon; s = solid

Source: Stem et al. 1996

increasing as the conditions become anaerobic. Volatile elemental mercury may be formed through the demethylation of methylmercury or the reduction of inorganic mercury, with anaerobic conditions again favoring the demethylation of the methylmercury (Barkay et al. 1989; Callahan et al. 1979; Regnell and Tunlid 1991). Increased dissolved organic carbon levels reduce methylation of mercury in the water column (Gilmour and Henry 1991), possibly as a result of the binding of free mercury ions to the dissolved organic carbon at low pH, thus reducing their availability for methylation, or the dissolved organic carbon may inhibit the methylating bacteria (Miskimmin et al. 1992). Alternatively, low pH favors the methylation of mercury in the water column, particularly in acid deposition lakes, while inhibiting its demethylation (Gilmour and Henry 1991). It has also been shown that the methylation rate is not affected by addition of sulfate in softwater lakes (Kerry et al. 1991).

At a pH of 4–9 and a normal sulfide concentration, mercury will form mercuric sulfide. This compound is relatively insoluble in aqueous solution (11×10^{-17} ppb), and therefore it will precipitate out and remove mercury ions from the water, reducing the availability of mercury to fish. Under acidic conditions, however, the activity of the sulfide ion decreases, thus inhibiting the formation of mercuric sulfide and favoring the formation of methylmercury (Bjornberg et al. 1988). Low pH and high mercury sediment concentrations favor the formation of methylmercury, which has greater bioavailability potential for aquatic organisms than inorganic mercury compounds. Methylmercury may be ingested by aquatic organisms lower in the food chain, such as yellow perch, which in turn are consumed by piscivorous fish higher on food chain (Cope et al. 1990; Wiener et al. 1990). Mercury cycling occurs in freshwater lakes, with the concentrations and speciation of the mercury being dependent on limnological features and water stratification. Surface waters may be saturated with volatile elemental mercury, whereas sediments are the primary source of the mercury in surface waters. During the summer months, surface concentrations of methyl and elemental mercury decline as a result of evaporation, although they remain relatively constant in deeper waters (Bloom and Effler 1990).

Abiotic reduction of inorganic mercury to metallic mercury in aqueous systems can also occur, particularly in the presence of soluble humic substances (i.e., acidic waters containing humic and fulvic acids). This reduction process is enhanced by light, occurs under both aerobic and anaerobic conditions, and is inhibited by competition from chloride ions (Allard and Arsenie 1991).

5.3.2.3 Sediment and Soil

Mercury compounds in soils may undergo the same chemical and biological transformations described for surface waters. Mercuric mercury usually forms various complexes with chloride and hydroxide ions in soils; the specific complexes formed depend on the pH, salt content, and composition of the soil solution. Formation and degradation of organic mercurials in soils appear to be mediated by the same types of microbial processes occurring in surface waters and may also occur through abiotic processes (Andersson 1979). Elevated levels of chloride ions reduce methylation of mercury in river sediments, sludge, and soil (Olson et al. 1991), although increased levels of organic carbon and sulfate ions increase methylation in sediments (Gilmour and Henry 1991). In freshwater and estuarine ecosystems, the presence of chloride ions (0.02 M) may accelerate the release of mercury from sediments (Wang et al. 1991).

In the late 1950s, unknown quantities of mercuric nitrate and elemental mercury were released into East Fork Poplar Creek from a government facility in Oak Ridge, Tennessee. Total mercury concentrations in the flood plain soil along the creek ranged from 0.5 to 3,000 ppm (Revis et al. 1989). An estimated 170,000 pounds of that mercury remained in floodplain soil of the creek (DOE 1994). The form of that mercury has been reported to be primarily mercuric sulfide (85–88%), with 6–9% present as elemental mercury (Revis et al. 1989, 1990). A very small amount was detected in the form of methylmercury (less than 0.02%). The reported presence of the mercuric sulfide suggests that the predominant biological reaction in soil for mercury is the reduction of Hg^{+2} to mercuric sulfide by sulfate-reducing bacteria under anaerobic conditions (Revis et al. 1989, 1990). Mercuric sulfide has very limited water solubility (4.5×10^{-24} mol/L), and thus, in the absence of other solvents, is likely to have limited mobility in soil. Aerobic microorganisms can solubilize Hg^{+2} from mercuric sulfide by oxidizing the sulfide through sulfite to sulfate, with the Hg^{+2} being reduced to elemental mercury (Wood 1974). However, examination of the weathering of mercuric sulfide indicated that mercuric sulfide does not undergo significant weathering when bound to riverwash soil with a pH of 6.8, although degradation may be increased in the presence of chloride and iron (Harsh and Doner 1981).

Mercury, frequently present in mine tailings, was toxic to bacteria isolated from a marsh treatment system used to treat municipal waste waters. The minimum concentration that inhibited the bacteria (as determined by intracellular ATP levels) was approximately 0.07±0.15 mg/L (ppm) (Desjardins et al. 1988).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to mercury and various mercury compounds depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of mercury in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of detection of current analytical methods even for determining total mercury. In reviewing data on mercury levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring mercury and various inorganic and organic mercury compounds in a variety of environmental media are discussed in Chapter 6.

5.4.1 Air

Indoor air mercury concentrations were determined in 37 houses in Ohio that had been painted with latex paint (Beusterien et al. 1991). Of the 37 homes studied, 21 homes had been painted with interior latex paint containing mercury a median of 86 days earlier, while the 16 control homes had not been recently painted with mercury-containing latex paints. Paint samples from the exposed homes contained a median concentration of 210 mg/L (ppm) (range, 120–610 mg/L). The median air mercury concentration (0.3 $\mu g/m^3$) was found to be significantly higher ($p<0.0001$) in the exposed homes (range, not detectable to 1.5 $\mu g/m^3$) than in the unexposed homes (range, not detectable to 0.3 $\mu g/m^3$). Among the exposed homes, there were 7 in which paint containing <200 mg/L had been applied. In these homes, the median air mercury concentration was 0.2 $\mu g/m^3$ (range, not detectable to 1 $\mu g/m^3$). Six exposed homes had air mercury concentrations >0.5 $\mu g/m^3$. The authors reported that elemental mercury was the form of mercury released to the air and that potentially hazardous mercury exposure could occur in homes recently painted with paint containing <200 mg Hg/L (Beusterien et al. 1991). In an indoor exposure study of families of workers at a chloralkali plant in Charleston, Tennessee, mercury levels in the air of the workers' homes averaged 0.92 $\mu g/m^3$ (ATSDR 1990).

Ambient air concentrations of mercury have been reported to average approximately 10–20 ng/m^3, with higher concentrations in industrialized areas (EPA 1980a). In 1990, metallic mercury concentrations in the gas and aerosol phases of the atmosphere in Sweden were 2–6 ng/m^3 and 0.01–0.1 ng/m^3, respectively (Brosset and Lord 1991). Higher levels (10–15 $\mu g/m^3$) have been detected near point emission sources, such as mercury mines, refineries, and agricultural fields treated with mercury fungicides. Atmospheric

concentrations of mercury over lakes in Wisconsin averaged 2.0 ng/m^3 (Wiener et al. 1990) and ranged from 6.3 ng/m^3 to 16.0 ng/m^3 above the water surface of the mercury-contaminated Wabigoon River in Ontario (Schroeder and Fanaki 1988). Mean vapor concentrations of mercury in air over a forested watershed (Walker Branch Watershed) in Tennessee were 5.5 ng/m^3 in 1988–1989, while particle-associated aerosol mercury concentrations were determined to be 0.03 ng/m^3, or approximately 0.5% of the total atmospheric mercury (Lindberg et al. 1991). Lindberg et al. (1994) measured mercury vapor at concentrations of 2–6 ng/m^3 and particulate mercury at 0.002–0.06 ng/m^3 at Walker Branch Watershed, Tennessee, from August 1991 to April 1992. Particulate mercury concentrations are greater in precipitation than in ambient air. In the St. Louis River estuary, mercury levels in precipitation averaged 22 ng/L (ppt), although ambient air levels averaged 3 ng/m^3 (Glass et al. 1990).

Total gaseous mercury was measured (1992–1993) as part of the Florida Atmospheric Mercury Study (FAMS) (Gill et al. 1995). Average total gaseous mercury concentrations for 3- to 6-day integrated samples ranged from 1.43 to 3.11 ng/m^3 (mean, 1.64 ng/m^3). In the same study, Dvonch et al. (1995) reported that the mean concentrations of total gaseous mercury measured at two inland Florida sites were significantly higher (3.3 and 2.8 ng/m^3) than measurements at an Atlantic coastal site (1.8 ng/m^3). The mean concentrations of particle phase mercury collected at the inland sites (51 and 49 pg/m^3) were 50% higher than those at the coastal site (34 pg/m^3). The mean mercury concentration in rain samples was 44 ng/L (ppt) (range, 14–130 ng/L). Guentzel et al. (1995) also reported results of the FAMS from 1992 to 1994. These authors found that the summer time wet season in south Florida accounted for 80–90% of the annual rainfall mercury deposition. Depositional rates in south Florida are 30 to almost 50% higher than those in central Florida. Particle phase measurements ranged from 2 to 18 pg/m^3 at all sites. Measurement of monomethylmercury in precipitation ranged from <0.005 to 0.020 ng/L (ppt).

Keeler et al. (1995) reported that particulate mercury may contribute a significant portion of the deposition of mercury to natural waters. Mercury can be associated with large particles (>2.5 µm) at concentrations similar to vapor phase mercury. Particulate phase mercury levels in rural areas of the Great Lakes and Vermont ranged from 1 to 86 pg/m^3, whereas particulate mercury levels in urban and industrial areas were in the range of 15–1,200 pg/m^3. Sweet and Vermette (1993) sampled airborne inhalable particulate matter in urban areas (southeast Chicago and East St. Louis) and at a rural site. Mean particulate phase mercury concentrations in particles (<2.5 µm and >2.5 µm) at the rural site were 0.3 ng/m^3 (range, <0.1–0.9 ng/m^3) and 0.2 ng/m^3 (range, <0.1–0.5 ng/m^3), respectively, as compared to 1.0 ng/m^3 (range, <0.1–0.7 ng/m^3) and

0.5 ng/m^3 (range, <0.1–1.5 ng/m^3), respectively, in Chicago and 0.7 ng/m^3 (range, <0.1–20 ng/m^3) and 0.5 ng/m^3 (range, <0.1–1.5 ng/m^3), respectively, in East St. Louis.

In an earlier study, Keeler et al. (1994) measured atmospheric mercury in the Great Lakes Basin. These authors reported that vapor phase mercury levels were four times higher in Chicago, Illinois, than in South Haven, Michigan, (8.7 ng/m^3 versus 2.0 ng/m^3). Furthermore, a diurnal pattern was observed in the vapor phase mercury levels measured at the Chicago site. The average concentration (ng/m^3) was 3.3 times greater for the daytime samples (8 AM to 2 PM) than for the night samples (8 PM to 8 AM), and the average concentration for the afternoon samples (2 PM to 8 PM) was 2.1 times greater than the night samples (average, 3.7 ng/m^3). Particulate phase mercury concentrations were also higher at the Chicago site than at the South Haven site (98 pg/m^3 versus 19 pg/m^3). Burke et al. (1995) reported that the concentration of mercury in vapor phase samples measured over Lake Champlain was consistent with other rural areas (mean, 2.0 ng/m^3; range, 1.2–4.2 ng/m^3), and the concentrations were consistent across all seasons. Particulate phase mercury concentrations averaged 11 pg/m^3, with the highest concentrations detected during the winter.

A monitoring program established at a facility at Oak Ridge National Laboratories found that the major sources of mercury release to the air were vaporization from soil, burning of coal for a steam plant, and fugitive exhaust from a former lithium isotope separation facility contaminated with mercury (Turner et al. 1992). When the monitoring program began in 1986, ambient air mercury vapor concentrations at the facility ranged from 0.011 to 0.108 µg/m^3. These values decreased to 0.006 to 0.071 µg/m^3 by 1990, while background levels near the facility remained at 0.006 µg/m^3. The decrease in mercury vapor concentrations occurred primarily as a result of an 80% reduction in coal burning at the steam plant; however, periods of drought and activities such as moving contaminated soil for construction were found to increase the atmospheric mercury concentrations on a transient basis (Turner et al. 1992). Turner and Bogle (1993) monitored ambient air for mercury around the same industrial complex site at Oak Ridge, Tennessee. Elemental mercury was used in large quantities at the nuclear weapons plant between 1950 and 1963 in a process similar to chloralkali production. Soil and water contamination had been found at the site. The results of weekly ambient monitoring for gaseous mercury from 1986 through 1990 showed that gaseous mercury levels were well below the National Emission Standard for Hazardous Air Pollutants (1.0 mg/m^3) with the exception of one station. Mean mercury levels at the control site ranged from 5 to 6 µg/m^3, while levels at the on-site stations were 6–11, 11–143, 68–174, 71–109, and 4–46 µg/m^3. Mean

particulate mercury levels were 0.00003 µg/m^3 at the control site, compared with mean concentrations at the on-site stations ranging from 0.00006 to 0.00024 µg/m^3 (Turner and Bogle 1993).

Mercury has been identified in air samples collected at 25 sites of the 714 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998).

5.4.2 Water

Concentrations of mercury in rainwater and fresh snow are generally below 200 ng/L (ppt) (EPA 1984b). Fitzgerald et al. (1991) measured total mercury in rainwater from May through August 1989 at Little Rock Lake, Wisconsin. The total mercury concentrations ranged from 3.2 to 15.2 ng/L (ppt). Mercury concentrations in precipitation collected in Minnesota during 1988 and 1989 averaged 18 ng/L (ppt) for an average annual mercury deposition of 15 µg/m^2 (Glass et al. 1991). Antarctic surface snow contained a mean mercury concentration of less than 1 pg/g (ppt) (Dick et al. 1990). In Ontario, Canada, mercury present in precipitation at an average concentration of 10 ng/L (ppt) accounted for more than half of the mercury inputs to surface waters compared with inputs from stream runoff, suggesting that atmospheric deposition is a significant source of mercury in surface waters (Mierle 1990). Lindberg et al. (1994) measured total mercury in rain collected at Walker Branch Watershed, Tennessee from August 1991 to April 1992. Rain concentrations of total mercury ranged from 7.57 ng/L (ppt) in February 1992 to 17.4 ng/L (ppt) in April 1992. Burke et al. (1995) reported that the average concentration of mercury in precipitation samples measured over Lake Champlain was 8.3 ng/L (ppt) for the sampling year, and the average amount of mercury deposited per precipitation event was 0.069 µg/m^2. The highest concentrations of mercury in precipitation samples occurred during spring and summer months. Guentzel et al. (1995) reported results of the Florida Atmospheric Monitoring Study from 1992 to 1994. These authors found that the summer time wet season in south Florida accounted for 80 to 90% of the annual rainfall mercury deposition. Depositional rates in south Florida are 30–50% higher than those in central Florida. Measurement of monomethylmercury in precipitation samples ranged from <0.005 to 0.020 ng/L (ppt).

The natural occurrence of mercury in the environment means that mercury is likely to occur in surface waters, even when anthropogenic sources of mercury are absent. Freshwaters without known sources of mercury contamination generally contain less than 5 ng/L (ppt) of total mercury in aerobic surface waters (Gilmour and Henry 1991). Mercury levels in water-borne particulates in the St. Louis River estuary ranged from 18 to 500 ng/L (ppt) (Glass et al. 1990). Water samples from lakes and rivers in the Ottawa,

Ontario, region of Canada had total mercury concentrations of 3.5–11.4 ng/L (ppt), with organic mercury constituting 22–37% of the total mercury (Schintu et al. 1989). Mercury was detected in water samples from Crab Orchard Lake, Illinois, at 70–281 ng/L (ppt) (Kohler et al. 1990). Total mercury concentrations in surface waters of California lakes and rivers ranged from 0.5 to 104.3 ng/L (ppt), with the dissolved particulate fraction being dominant (89%; 0.4–12 ng/L [ppt]) (Gill and Bruland 1990).

The baseline concentration of mercury in unpolluted marine waters has been estimated to be less than 2 ng/L (2 ppt) (Fowler 1990). In contrast, the New York Bight, an inshore coastal area near the industrialized areas of New York Harbor and northern New Jersey, contained dissolved mercury concentrations in the range of 10–90 ng/L (ppt) (Fowler 1990).

Near-surface groundwaters in remote areas of Wisconsin were found to contain approximately 2–4 ng/L (ppt) of mercury, of which only a maximum of 0.3 ng/L (ppt) was determined to be methylmercury, indicating that groundwater was not a source of methylmercury in the lake (Krabbenhoft and Babiarz 1992). Mercury was found at levels greater than 0.5 µg/L (ppb) in 15–30% of wells tested in some groundwater surveys (EPA 1985b). Drinking water is generally assumed to contain less than 0.025 µg/L (ppb) (EPA 1984b). A chemical monitoring study of California's public drinking water from groundwater sources was conducted by Storm (1994). This author reported that mercury was analyzed in 6,856 samples, with 225 positive detections and 27 exceedances of the maximum contaminant level (0.002 mg/L [200 ppb]). The mean mercury concentration was 6.5 ppb (median, 0.62 ppb; range, 0.21 to 300 ppb).

Mercury has been identified in surface water, groundwater, and leachate samples collected at 197, 395, and 58 sites, respectively, of the 714 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998).

5.4.3 Sediment and Soil

In a review of the mercury content of virgin and cultivated surface soils from a number of countries, it was found that the average concentrations ranged from 20 to 625 ng/g (0.020 to 0.625 ppm) (Andersson 1979). The highest concentrations were generally found in soils from urban locations and in organic, versus mineral, soils. The mercury content of most soils varies with depth, with the highest mercury concentrations generally found in the surface layers. Mercury was detected at soil concentrations ranging from 0.01 to 0.55 ppm in orchard soils in New York State (Merwin et al. 1994).

Granato et al. (1995) reported that municipal solid waste sludge mercury concentrations from the Metropolitan Water Reclamation District of Greater Chicago ranged from 1.1 to 8.5 mg/kg (ppm), with a mean concentration of 3.31 mg/kg (ppm). Sludge applications to a sludge utilization site in Fulton County, Illinois, from 1971 to 1995 significantly increased extractable soil mercury concentrations. In addition, 80–100% of the mercury applied to the soils in sewage sludge since 1971 still resided in the top 15 cm of soil.

Facemire et al. (1995) reported industrial contamination of soils and sediment in several states in the southeastern United States. The authors reported soil concentrations up to 141,000 ppm associated with contamination in northeastern Louisiana from mercury-charged manometers used to measure pressure and delivery from natural gas wells. In Tennessee, a maximum mercury concentration of 1,100 ppm (associated with previous operations of the Oak Ridge nuclear facility) was found in wetland soils adjacent to the East Fork Poplar Creek. A pharmaceutical company's effluents enriched sediments in a localized area of Puerto Rico to 88 ppm mercury (Facemire et al. 1995). Rule and Iwashchenko (1998) reported that mean soil mercury concentrations of 1.06 ppm were collected within 2 km of a former chlor-alkali plant in Saltsville, Virginia, and that these concentrations were 17 times higher than regional background soil samples (0.063 ppm). These authors further reported that soil organic content, topographic factors, wind patterns, and elevation were variables significantly related to mercury concentration as determined by regression analysis. Soil mercury levels decreasing with distance from the former plant were indicative of a point source distribution pattern. A made land soil type (Udorthent), which appears to be a by-product of the chlor-alkali manufacturing process, was found proximal to the former plant site and contained about 68 times (4.31 ppm) the regional background concentration.

The top 15 cm of sediments in Wisconsin lakes contained higher levels of mercury (0.09–0.24 µg/g [ppm]) than sediments at lower sediment levels (0.04–0.07 µg/g [ppm]). Because the lakes are not known to receive any direct deposition of mercury, it was postulated that the primary mercury source was atmospheric deposition (Rada et al. 1989). Mercury levels in surface sediments of the St. Louis River ranged from 18 to 500 ng/L (ppt) (Glass et al. 1990). Mercury was detected in sediment samples from Crab Orchard Lake in Illinois at concentrations greater than 60 µg/L (ppb) (Kohler et al. 1990). Surficial sediment samples from several sites along the Upper Connecting Channels of the Great Lakes in 1985 had mercury concentrations ranging from below the detection limit to 55.80 µg/g (ppm) (mean concentrations ranged from 0.05 to 1.61 µg/g [ppm] at four sites) (Nichols et al. 1991). Mercury concentrations were correlated with particle size fractions and organic matter content (Mudroch and Hill 1989). Surface

sediment samples from the Lake Roosevelt/Upper Columbia River in Washington State were found to contain up to 2.7 µg/g (ppm) mercury (Johnson et al. 1990). Mercury concentrations in sediments up to 28 cm in depth in lakes adjacent to coal-fired power plants near Houston, Texas ranged from 255 to 360 mg/kg (ppm) in the summer and from 190 to 279 mg/kg (ppm) in the winter (Wilson and Mitchell 1991).

Surface sediments taken from Canadian lakes receiving atmospheric input from smelters contained between 0.03 and 9.22 µg/g (ppm) mercury, with the highest values being found in lakes nearest the smelters. However, sediment concentrations were not correlated with mercury concentrations in fish from the lakes; the fish concentrations ranged from 0.003 to 0.88 µg/g (ppm), with the highest concentration found in fish from one of the least contaminated lakes (Harrison and Klaverkamp 1990).

Estuarine and coastal marine sediment samples analyzed for NOAA's National Status and Trends Program between 1984 and 1987 showed that 38 of 175 sites contained mercury concentrations in excess of 0.41 µg/g (ppm) (dry weight) (O'Connor and Ehler 1991). In addition, mercury sediment concentrations at 6 sites exceeded the NOAA ER-M concentration of 1.3 ppm (dry weight), which is the concentration determined to be equivalent to the median (50th percentile) for all sites monitored. These 6 sites included 5 sites in the Hudson River/Raritan Estuary, New York Bight, and Raritan Bay areas between New York and New Jersey (ranging from 1.6 to 3.3 ppm dry weight) and one site in the Oakland Estuary in California (2.3 ppm dry weight) (NOAA 1990). Sediments taken from coastal areas off British Columbia, Canada contained concentrations of mercury ranging from 0.05 µg/g to 0.20 µg/g (ppm), while mercury concentrations in fish from these waters were only slightly higher; bioconcentration factors ranged from less than 1 to 14 (Harding and Goyette 1989).

Mercury has been identified in soil and sediment samples collected at 350 and 208 sites, respectively, of the 714 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998).

5.4.4 Other Environmental Media

Foods. The U.S. Food and Drug Administration (FDA) conducted a Total Diet Study (April 1982 to April 1984) to determine dietary intakes of selected industrial chemicals (including mercury) from retail purchases of foods representative of the total diet of the U.S. population (Gunderson 1988). The data were collected as part of 8 food collections, termed “market baskets”, collected in regional metropolitan areas

during the 2-year study and involved individual analysis of 234 food items representing the diets of 8 different population groups. Mercury was detected in 129 adult foods; seafood, the major contributing food group, accounted for 77% (3.01 µg of the 3.9 µg of mercury) of the total mercury intake for 25–30 year old males (Gunderson 1988). Minyard and Roberts (1991) reported results of a survey conducted on food samples analyzed at 10 state food laboratories between 1988 and 1989. These laboratories conducted food regulatory programs and analyzed findings of pesticides and related chemical residues for 27,065 food samples. In 1988, these laboratories reported methylmercury residues in 13 (0.09%) of 13,980 samples, with 1 sample exceeding federal or state tolerances. Similarly, in 1989, methylmercury was detected in 25 (0.19%) of 13,085 samples, with 1 sample exceeding federal or state tolerances. A survey of 220 cans of tuna, conducted in 1991 by the FDA, found an average methylmercury content (expressed as mercury) of 0.17 ppm (range, <0.10–0.75 ppm) (Yess 1993). Levels of methylmercury were higher in solid white (0.26 ppm) and chunk white tuna (0.31 ppm) than in chunk light (0.10 ppm) or chunk tuna (0.10 ppm). Previously, the FDA had determined methylmercury concentrations in 42 samples of canned tuna between 1978 and 1990 (Yess 1993) to range from <0.01 to 0.67 ppm methylmercury (expressed as mercury), with an average concentration of 0.14 ppm. These earlier results are similar to those obtained in the 1991 survey (Yess 1993).

The use of fish meal as a food for poultry and other animals used for human consumption may result in increased mercury levels in these animals. In Germany, poultry and eggs were found to contain average mercury concentrations of 0.04 and 0.03 mg/kg (ppm), respectively. Cattle are able to demethylate mercury in the rumen and thus absorb less mercury; therefore, beef (meat) and cow's milk contained only 0.001–0.02 mg/kg (ppm) and 0.01 mg/kg (ppm) of mercury, respectively (Hapke 1991). A survey of raw foods in Germany in 1986 found that grains, potatoes, vegetables, and fruits contained average mercury concentrations of 0.005 to 0.05 mg/kg (ppm fresh weight); however, wild mushrooms contained up to 8.8 mg/kg (ppm) of mercury. Cocoa beans, tea leaves, and coffee beans contained average mercury concentrations of 0.005, 0.025, and 0.04 mg/kg (ppm), respectively. In all cases where the mercury content was high, selenium was also found in measurable, but lower, concentrations (Weigert 1991).

Pedersen et al. (1994) conducted a monitoring study to assess the levels of trace metals, including mercury, in table wine, fortified wine, beer, soft drinks, and various juices. These authors reported that in all samples tested, mercury concentrations were at or below the detection limit (6 µg/L [6 ppb]).

Fish and Shellfish. As part of the National Pesticide Monitoring Program (NPMP), the U.S. Fish and Wildlife Service collected freshwater fish during 1976–1977 from 98 monitoring stations nationwide and analyzed them for mercury and other heavy metals (May and McKinney 1981). As part of this program, duplicate composite samples of a bottom-dwelling species and several representative predatory species were collected. Bottom-dwelling species sampled included common carp, common sucker, and channel catfish or other catfish species. Predatory species sampled were rainbow, brown, brook or lake trout at cold water stations; largemouth bass or other sunfish family members, such as crappie or bluegill, at warm water stations; and walleye or other perch family members at cool water stations. May and McKinney (1981) reported that the mean concentration of mercury was 0.153 ppm (wet weight basis) in the 1972 NPMP survey and that the mean concentration declined significantly to 0.112 ppm (range, 0.01–0.84 ppm) in the 1976–1977 survey. This decline was presumably due to curtailed production, use, and emissions of mercury (Lowe et al. 1985). May and McKinney (1981) identified an arbitrary 85th percentile concentration of 0.19 ppm for mercury to identify monitoring stations having fish with higher than normal concentrations of mercury. Most of these stations were downstream of industrial sites (e.g., chloralkali operations, pulp and paper plants; or pre-1900 gold and silver mining operations), while others were located in areas with major mercury ore (cinnabar) deposits. In a follow-up NPMP study conducted from 1980–1981, Lowe et al. (1985) reported a geometric mean mercury concentration of 0.11 ppm (wet weight) (range, 0.01–1.10 ppm). These authors reported that the downward trend in mercury residues in fish reported by May and McKinney (1981) may have leveled off, since no significant difference in the geometric mean values was detected in the follow-up study conducted in 1984–1985 as part of the National Contaminant Biomonitoring Program (Lowe et al. 1985; Schmitt and Brumbaugh 1990). However, large variations in mercury uptake among the fish species sampled, as well as among size classes of fish within the same species, may mask actual trends.

From 1986 to 1989, the National Study of Chemical Residues in Fish (NSCRF) was conducted by the EPA to assess the concentrations of 60 toxic pollutants (including mercury) in the tissues of benthic and predatory gamefish nationwide (EPA 1992f). Benthic species were analyzed as whole-body samples, while game fish species were analyzed as fillet samples, and all concentrations were reported on a wet weight basis. Mercury was detected at 92% of the 374 sites surveyed nationwide at a mean concentration of 260 ng/g (0.26 ppm) (median concentration of 0.17 ppm and a maximum concentration of 1.8 ppm), and at 2% of the sites, measured mercury concentrations exceeded 1 ppm. Most of the higher mercury concentrations in fish were collected in the Northeast. Ten of the sites in the top 10th percentile for high mercury concentrations were near pulp and paper mills, four were near Superfund sites, and most of the

remaining sites were near industrial areas. However, the mercury sources could not be identified at all of these sites. Five sites were considered to represent background conditions and six U.S. Geological Survey (USGS) National Stream Quality Accounting Network (NASQAN) sites were also among the sites in the top 10th percentile (EPA 1992f).

A recent national survey conducted by the EPA solicited data on mercury concentrations in fish collected by the states as part of their fish contaminant monitoring programs (EPA 1997b). The EPA asked all states to submit mercury residue data collected from their fish sampling programs from 1990 through 1995 to assess whether there were geographic variations or trends in fish tissue concentrations of mercury. Thirty-nine states provided information on the levels of contamination in their fish. The study included the following: information on the tissue concentrations of mercury, including the number of fish sampled (by species); the mean mercury concentration; and the minimum, median, and maximum concentrations reported for each species by state. Residue information for the three most abundant species sampled in each state included such species as the largemouth and smallmouth bass; channel, flathead, and blue catfish; brown and yellow bullhead; rainbow and lake trout; carp; walleye; north pike; and white sucker. The highest mean mercury residue for an edible species was 1.4 ppm, reported by the state of Arizona; the highest maximum mercury concentrations were 7.0 ppm for bowfin in South Carolina, followed by 6.4 ppm for white sucker in Ohio and 5.7 ppm for bowfin in North Carolina. (Note: This EPA report is currently under review by the states; however, the final report should be available by December 1998).

A summary of the mean, minimum, and maximum tissue concentrations of mercury detected for two of the sampled species with the widest geographical distribution; the largemouth bass and the channel catfish are given in Tables 5-8 and 5-9. As Table 5-8 shows, the maximum mercury residues reported for the largemouth bass exceeded the FDA action level (1 ppm) in 15 of the 25 states that collected and analyzed tissue samples for this species. The highest maximum mercury concentration reported for this species was 4.36 ppm, reported by Florida. Table 5-9 shows the maximum mercury residue reported for another widely distributed species, the channel catfish. While the maximum mercury residues reported for this species are not consistently as high as those for the largemouth bass, maximum residues in channel catfish from 6 of the 20 reporting states still exceeded the FDA action level (1 ppm). The highest maximum value reported for the channel catfish was 2.57 ppm, reported by Arkansas. Consumption of large amounts of feral fish containing these high mercury residues exposes high-end fish consuming populations (those that consume >100 grams fish/day) to potentially greater risk of mercury exposure than members of the general population (see Sections 5.5 and 5.7).

Table 5-8. Mercury Concentrations (ppm) for Largemouth Bass Collected in Various States Throughout the United States (1990–1995)

State	Number of fish	Minimum	Mean	Maximum
Alabama	914	0.100	0.393	**1.630**
Arizona	35	0.700	**1.369**	**2.620**
Arkansas	1190	0.030	0.675	**3.170**
California	537	0.020	0.305	**1.800**
Delaware	14	0.060	0.101	0.200
District of Columbia	11	0.037	0.153	0.458
Florida	2008	0.020	0.642	**4.360**
Georgia	968	0.010	0.262	**1.650**
Illinois	305	0.010	0.018	0.880
Iowa	38	0.080	0.189	0.480
Kentucky	120	0.124	0.581	**1.460**
Louisiana	452	0.001	0.391	**1.883**
Mississippi	606	0.090	0.647	**2.630**
Nebraska	182	0.080	0.343	0.920
New Hampshire	35	0.210	0.573	**1.400**
New York	53	0.050	0.462	0.950
North Carolina	1569	0.020	0.532	**3.600**
Ohio	56	0.001	0.988	**1.400**
Oregon	140	0.030	0.332	0.980
Pennsylvania	139	0.090	0.560	**2.850**
South Carolina	505	0.190	0.992	**3.330**
Tennessee	64	0.100	0.255	0.830
Texas	58	0.030	0.190	0.460
Washington	20	0.024	0.137	0.350
Wisconsin	346	0.050	0.369	**1.500**

Tissue concentrations shown in **bold type** exceed the FDA action level of 1 ppm

Source: EPA 1997b

Table 5-9. Mercury Concentrations (ppm) for Channel Catfish Collected in Various States Throughout the United States (1990–1995)

State	Number of fish	Minimum	Mean	Maximum
Alabama	702	0.100	0.214	0.660
Arkansas	114	0.010	0.473	**2.570**
Delaware	19	0.020	0.050	0.133
District of Columbia	17	0.055	0.091	0.240
Georgia	658	0.010	0.081	**1.110**
Indiana	112	0.050	0.178	0.780
Iowa	323	0.030	0.104	0.410
Kansas	56	0.020	0.107	0.220
Louisiana	76	0.001	0.111	0.732
Maryland	157	0.006	0.029	0.179
Mississippi	157	0.040	0.272	**2.100**
Missouri	198	0.002	0.052	0.350
Nebraska	238	0.001	0.099	0.450
New Jersey	21	0.050	0.163	0.767
New Mexico	78	0.100	0.297	**1.800**
Oklahoma	171	0.100	0.186	0.540
South Carolina	42	0.250	0.345	**1.610**
Tennessee	138	0.100	0.173	0.650
Texas	44	0.030	0.148	0.830
West Virginia	65	0.030	0.139	**1.583**

Tissue concentrations shown in **bold type** exceed the FDA action level of 1 ppm

Source: EPA 1997b

Most recently, the Northeast states and Eastern Canadian provinces issued their own mercury study, including a comprehensive analysis of current mercury concentrations in a variety of fresh water sportfish species (NESCAUM 1998). This study involved a large number of fish sampling sites in each state, many of which were remote lake sites that did not receive point source discharges. Top level piscivores (i.e., predatory fish) such as walleye, chain pickerel, and large and smallmouth bass were typically found to exhibit some of the highest concentrations, with average tissue residues greater than 0.5 ppm and maximum residues exceeding 2 ppm. One largemouth bass sample was found to contain 8.94 ppm of mercury, while one smallmouth bass sampled contained 5.0 ppm. A summary of the mean and minimum–maximum (range) of mercury concentrations in 8 species of fish sampled is shown in Table 5-10. This study also identified a relationship between elevated mercury levels in fish and certain water quality parameters, including low pH, high conductivity, and elevated levels of dissolved organic carbon.

Lake trout taken from Lake Ontario between 1977 and 1988 did show a progressive decline in mercury contamination from 0.24 µg/g (ppm) in 1977 to 0.12 µg/g (ppm) in 1988 (Borgmann and Whittle 1991). Samples of zooplankton taken from an Illinois lake in 1986 contained approximately 10 ng/g (ppb) mercury; however, fish that fed on the zooplankton had whole body mercury concentrations ranging from 11.6 µg/kg (ppb) for inedible shad to 69 µg/kg (ppb) for edible largemouth bass, indicating bioaccumulation was occurring up the aquatic food chain. Older fish generally had higher mercury concentrations (Kohler et al. 1990). Mercury concentrations in crayfish taken from 13 Ontario lakes with no known mercury inputs ranged from 0.02 to 0.64 µg/g (ppm); the concentrations were positively correlated with organism weight and fish mercury concentrations (Allard and Stokes 1989). Brown trout taken from Lake Ontario contained between 0.18–0.21 µg/g (ppm) mercury in unskinned fillets and between 0.24–0.26 µg/g (ppm) mercury in skinned fillets, indicating that methylmercury is associated with the protein fraction of fish tissue (Gutenmann and Lisk 1991).

Methylmercury constitutes over 99% of the total mercury detected in fish muscle tissue, with no detection of inorganic or dimethylmercury (Grieb et al. 1990; Bloom 1992). Mercury levels were examined in aquatic organisms taken from the Calcasieu River/Lake Complex in Louisiana. The order of enrichment was as follows: shrimp (0.2 µg/g [ppm]) <mussel (0.3 µg/g [ppm]) <fish (0.4 µg/g [ppm]) = oyster (0.4 µg/g [ppm]) <zooplankton (1.4 µg/g [ppm]) (Ramelow et al. 1989). Average mercury concentrations for aquatic organisms collected from the Wabigoon/English/Winnipeg River system in Canada were as follows: 0.06–2.2 µg/g (ppm) for crayfish, 0.01–0.55 µg/g (ppm) for perch, and 0.04–1.2 µg/g (ppm) for pike. Methylmercury concentrations were found to increase with distance from the pollutant source,

Table 5-10. Combined Data on Mercury Concentrations in Selected Fish Species Sampled in the Northeast[a]

Species	Number of samples[b]	Mean Hg concentration	Minimum–maximum Hg[c] concentration range (ppm)
Largemouth bass	1,019	0.51	0–**8.94**
Smallmouth bass	738	0.53	0.08–**5.0**
Yellow perch	1,346	0.40	0–3.**15**
Eastern chain pickerel	157	0.63	0–**2.81**
Lake trout	877	0.32	0–**2.70**
Walleye[d]	257	0.77	0.10–**2.04**
Brown bullhead	421	0.20	0–**1.10**
Brook trout	200	0.26	0–0.98

[a] Northeastern states include ME, VT, NH, MA, RI, CT, NY, NJ.

[b] In some cases, states reported an average of values from a given location. Thus, the number of samples indicated may not represent the number of individual fish sampled.

[c] Maximum tissue concentrations shown in **bold type** exceed the FDA action level of 1 ppm

[d] Walleye data are from New York State only and may not be representative of walleye mercury concentrations in other parts of the Northeast.

Source: NESCAUM 1998

possibly as a result of the increased bioavailability of organic mercury produced by aquatic micro-organisms, whereas inorganic mercury was the predominant form at the source (Parks et al. 1991).

Typical mercury concentrations in large carnivorous freshwater fish (e.g., pike) and large marine fish (e.g., swordfish, shark, and tuna) have been found to exceed 1 µg/g (ppm) (EPA 1984b; Fairey et al. 1997; FDA 1998; Hellou et al. 1992; Hueter et al. 1995), with mercury content again being positively correlated with the age of the fish (Gutenmann et al. 1992; Hueter et al. 1995). Methylmercury concentrations in muscle tissue of 9 species of sharks were analyzed from 4 locations off Florida (Hueter et al. 1995). Muscle tissue methylmercury concentration averaged 0.88 µg/g (ppm) (wet weight) and ranged from 0.06 to 2.87 µg/g (ppm), with 33.1% of the samples exceeding the FDA action level (1 ppm). A positive correlation between methylmercury and shark body length (size) also was found, such that sharks larger than 200 cm in total length contained methylmercury concentrations >1 ppm. Sharks collected off the southern and southwestern coastal areas contained significantly higher concentrations than those caught in the northeast coastal region (Cape Canaveral and north).

Methylmercury concentrations were highest in the Caribbean reef shark (*Carcharhinus perezi*). The two most abundant shark species in the U.S. East Coast commercial shark fishery, sandbar *(C. plumbeus*) and blacktip (*C. limbatus*) sharks, are of special concern with respect to human health. Although the mean concentration of methylmercury in the sandbar shark (0.77 µg/g) was below the average for all sharks, sandbar shark tissues contained up to 2.87 ppm methylmercury, and 20.9% of the samples exceeded the FDA action level of 1 ppm. A total of 71.4% of the blacktip shark samples (mean, 1.3 µg/g) exceeded the FDA action level. The authors suggest that continued monitoring of methylmercury concentrations in various sharks species in the commercial marketplace is warranted. In a recent study of sportfish collected in San Francisco Bay, Fairey et al. (1997) reported that the highest concentrations of mercury were detected in leopard shark muscle tissue (1.26 ppm). Bluefin tuna caught in the Northwest Atlantic Ocean in 1990 contained mercury at a mean muscle concentration of 3.41 µg/g (ppm) dry weight (Hellou et al. 1992).

As part of the National Oceanic and Atmospheric Administration (NOAA) Status and Trends Program conducted from 1984 to 1987, mercury concentrations were analyzed in four marine bivalve species in U.S. coastal waters (NOAA 1987). Mercury concentrations in bivalve tissues ranged from 0.01 to 0.48 µg/g (ppm) dry weight in oysters (*Crassostrea virginica*), 0.28 to 0.41 µg/g (ppm) in the Hawaiian oyster (*Ostrea sandwichensis*), 0.05 to 0.47 µg/g (ppm) in the blue mussel (*Mytilus edulis*), and 0.04 to

0.26 µg/g (ppm) in the California mussel (*Mytilus californianus*). Oysters (*Crassostrea virginica*) collected around the Gulf of Mexico between 1986 and 1989 had mercury concentrations ranging from <0.01 to 0.72 µg/g [ppm] (mean, 0.127 µg/g [ppm]) (Presley et al. 1990). Oysters taken from the Mississippi Sound in 1986 generally did not contain mercury at levels exceeding the detection limit (0.02 µg/g [ppm]), although two samples had detectable mercury levels of 0.66 and 6.6 µg/g [ppm] (Lytle and Lytle 1990).

Mercury has been detected in fish samples collected at 56 of the 714 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998).

Marine mammals. Mercury concentrations have been analyzed in various tissues (i.e., muscle, liver, kidneys) from several species of marine mammals, including beluga whales, narwhal, white-toothed dolphins, pilot whales, ringed seals, harp seals, and walruses in the western and eastern Canadian Arctic (Wagemann et al. 1995). The mean mercury concentration (µg/g [ppm] dry weight) in liver tissue was highest in pilot whales (78 ppm), harp seals (36 ppm), Eastern Arctic ringed seals (29 ppm), narwhal (25 ppm), and Eastern Arctic beluga (22 ppm), with lesser amounts in Arctic walrus (5 ppm) and dolphins (4 ppm). Of the three tissues analyzed, mercury was most concentrated in the liver, with successively lower concentrations in the kidney and muscle tissue. This pattern prevails in most marine mammals. The concentration of total mercury is greater by a factor of 3 in the liver than in the kidney, but can be significantly higher in some species (see Table 5-11). Mean tissue residues in ringed seals from the western Arctic had significantly higher concentrations of mercury than those from the eastern Arctic. The authors reported higher mercury levels in sediment (68–243 ng/g [ppb] dry weight) and water (11–29 ng/L [ppt]) from the western Arctic, as compared to sediment (40–60 ng/g [ppb] dry weight) and water (3.7 ng/L [ppb]) from the eastern Arctic. These differences in sediment and water mercury levels may be responsible for some of the observed differences in mercury tissue concentrations in the seals.

Mercury tissue concentrations were detected in 17 adult and 8 fetal pilot whales from two stranding episodes off Cape Cod, Massachusetts (Meador et al. 1993). Total mercury occurred in high concentrations in both the liver and kidney, and liver concentrations were significantly correlated with the animal's length. Methylmercury, as a percentage of total mercury, varied inversely with total mercury, indicating that demethylation was occurring. Mean adult mercury concentrations in µg/g (ppm) dry weight in liver and kidneys were 176 ppm (range, 1.9–626 ppm dry weight) and 27.5 ppm (range, 6.8–49.7 ppm dry weight), respectively. Mean fetal mercury concentrations in µg/g (ppm) dry weight in liver and kidneys

Table 5-11. Total Mercury Concentrations in Tissues of Marine Mammals in Alaska and Canada

Species	Date collected	Muscle concentration (µg/g, wet weight)	Liver concentration (µg/g, wet weight)	Number	Source
Bearded seal		0.200±0.0150		7	Galster 1971
Bearded seal			1.910±1.200	4	Galster 1971
Pacific Alaska walrus		0.020±0.005		6	Galster 1971
Pacific Alaska walrus			0.490±0.100	7	Galster 1971
Polar bear	1972	0.040±0.014		12	Lentfer 1976
Polar bear	1972	0.040±0.260		4	Lentfer 1976
Polar bear	1972		4.800±1.460	9	Lentfer 1976
Polar bear	1972		3.920±1.280	16	Lentfer 1976
Beluga whale	1977	2.120±1.150		11	Muir et al. 1992
Beluga whale	1977		30.60±20.50	8	Muir et al. 1992
Ringed seal	1972	0.230±0.110		13	Smith and Armstrong 1975
Ringed seal	1972		1.000±1.160	13	Smith and Armstrong 1975
Ringed seal	1972–73	0.720±0.330		83	Smith and Armstrong 1975
Ringed seal	1972–73		27.50±30.10	83	Smith and Armstrong 1975
Ringed seal	1976	0.910±0.380		27	Smith and Armstrong 1975
Ringed seal	1976		16.10±13.80	27	Smith and Armstrong 1975
Ringed seal	1976	0.080±0.070		37	Smith and Armstrong 1975
Ringed seal	1976		0.320±0.800	36	Smith and Armstrong 1975
Ringed seal	1976	0.310±0.170		33	Smith and Armstrong 1975
Ringed seal	1976		3.760±3.420	33	Smith and Armstrong 1975
Bearded seal	1973	0.530±0.350		3	Smith and Armstrong 1975
Bearded seal	1973		143.0±170.0	6	Smith and Armstrong 1975
Bearded seal	1974	0.090±0.040		55	Smith and Armstrong 1975
Bearded seal	1974		26.20±26.10	56	Smith and Armstrong 1975

were 2.3 ppm (range, 0.9–5.4 ppm dry weight) and 1.9 ppm (range, 0.6–3.9 ppm dry weight), respectively. The mean methylmercury concentration in µg/g (ppm) dry weight in adult liver tissue was 8 ppm (range, 5.6–10 ppm). Aguilar and Borrell (1995) studied mercury tissue levels (1970 to 1988) in harbor porpoises in the eastern North Atlantic. These authors reported that in most tissues of harbor porpoises, the mercury was virtually all in the form of methylmercury; however, the fraction of organic mercury in the liver was much lower than in the rest of the body tissues. These authors found that for a given tissue, the concentrations detected were extremely variable between localities and years. Mercury concentrations in harbor porpoises ranged from 0.62 to 70 ppm in liver and from 0.66 to 22 ppm in muscle. The mean mercury concentration in liver for the eastern harbor porpoise population was 11.2 ppm. Mercury tissue levels progressively increased with the age of the animal; no significant differences were found between the sexes (Aguilar and Borrell 1995).

Plants. Although data on mercury distribution among freshwater vascular plant parts is lacking for unpolluted systems, Mortimer (1985) reported that total mercury in the roots of five species of freshwater vascular plants in the polluted Ottawa River was 10–40% higher than in the shoots. Speciation may be important in determining the patterns of mercury uptake, translocation, and excretion in macrophytes. Shoots of *Elodea densa* more readily accumulated methylmercury than inorganic mercury, and also excreted more inorganic mercury than methylmercury (Czuba and Mortimer 1980). Significant translocation of inorganic mercury from shoots to roots occurred in *E. densa* (Czuba and Mortimer 1980). In this species, methyl- and inorganic mercury moved in opposite directions, with methylmercury moving towards the young shoot apex, and inorganic mercury moving towards lower (older) parts of the shoot (Czuba and Mortimer 1980). Dolar et al. (1971) noted the same methylmercury pattern in the water milfoil (*Myriophyllum spicatum*). Using solution culture experiments, these authors showed that mercury accumulation was greater when plants were exposed to inorganic mercury ($HgCl_2$) than organic methylmercury (CH_3HgCl) and that mercury accumulation from the nutrient solution was rapid and approached maximum values in 2 hours. Organomercury compounds (methylmercury chloride, phenylmercuric acetate, phenylmercuric chloride, and phenylmercuric hydroxide) were more available than inorganic compounds (HgF_2 and $HgCl_{2)}$ from lake sediments. The various organomercury and inorganic mercury compounds were added to sediment at concentrations of 0, 46, 230, and 460 ppm prior to rooting water milfoil. After 20 days, concentration of mercury in the plant tissues exposure to 46, 230, and 460 ppm of the inorganic mercury compounds in the sediment ranged from 1.71 to 4.01, 4.81–6.03, and 6.61–10.2, respectively. In contrast, the concentrations of mercury in plant tissues exposed to 46, 230, and 460 ppm of the organic mercury compounds in the sediment ranged from 2.40 to 7.15 ppm, 36–84.5 ppm, and 114.6–243.1 ppm,

respectively. The control plants (no mercury compounds added to the sediments) contained 0.3 ppm mercury. It is clear from this experiment that organomercury compounds may accumulate significantly in the above-ground parts of some macrophytes. Mortimer (1985) found that although *E. densa* shoots had lower total mercury contents than roots, with 32% of the mercury in the shoots in the form of methylmercury, compared to only 10% in the roots.

Grasses sampled downwind of a municipal waste incinerator contained up to 0.20 µg/g (ppm) of mercury, with concentrations decreasing with increasing distance from the facility (Bache et al. 1991). Background mercury levels in vegetation were usually below 0.1 µg/g (ppm) dry weight (Lindqvist 1991e); however, mushrooms collected 1 km from a lead smelter in Czechoslovakia contained between 0.3 and 12 mg/kg (ppm) dry weight (Kalac et al. 1991).

Consumer and Medicinal Products. Various consumer and medicinal products contain mercury or mercury compounds (i.e., skin lightening creams and soaps, herbal remedies, laxatives, tattooing dyes, fingerpaints, artists paints, and make-up paints) (Barr et al. 1973; Dyall-Smith and Scurry 1990; Lauwerys et al. 1987; Rastogi 1992; Wendroff 1990).

Barr et al. (1973) reported elevated mercury levels in the blood of women using skin lightening creams, although the mercury compound and concentrations in the skin cream were not determined. More recently, Dyall-Smith and Scurry (1990) reported that one skin lightening cosmetic cream contained 17.5% mercuric ammonium chloride. Lauwerys et al. (1987) reported a case of mercury poisoning in a 3-month-old infant whose mother frequently used a skin lightening cream and soap containing inorganic mercury during her pregnancy and during the 1-month lactation period following birth. However, the mercury concentration and specific mercury compound in the cream and soap were not determined. Al-Saleh and Al-Doush (1997) analyzed the inorganic mercury content of 38 skin lightening creams in Saudi Arabian markets. The creams were manufactured in a variety countries, including India and Pakistan, other Arab countries, Thailand, Taiwan, Indonesia, England and Germany. Almost 50% of the creams tested exceeded the tolerance limit of 1 ppm. The mean concentration of mercury in the 38 creams was 994 ppm, with a range of 0–5,650 ppm. It is not known whether any of these products are available in the United States.

Metallic mercury was also the source of two cases of mercury poisoning caused by the dermal application of an over-the-counter anti-lice product (Bourgeois et al. 1986). The more severely poisoned individual applied 30 g of ointment containing 9 g of metallic mercury (300,000 ppm) to his entire body. Wands et al.

(1974) also reported the deaths of two individuals due to the excessive use of a laxative preparation containing mercurous chloride (calomel).

Metallic mercury has been used by Mexican American and Asian populations in traditional remedies for chronic stomach disorders (Espinoza et al. 1995; 1996; Geffner and Sandler 1980; Trotter 1985). Most recently, Perharic et al. (1994) reported cases of poisonings resulting from exposure to traditional remedies and food supplements reported to the National Poisons Unit in London, England. From 1989 to 1991, elemental mercury was implicated in several poisonings following exposure to traditional Asian medicines. In one case, the mercury concentration in the medicinal product taken orally was 540 mg/g (540,000 ppm). The mercury was in its elemental or metallic form. Espinoza et al. (1995, 1996) reported that while examining imported Chinese herbal balls for the presence of products from endangered species, the authors detected potentially toxic levels of arsenic and mercury in certain herbal ball preparations. Herbal balls are aromatic, malleable, earth-toned, roughly spherical, hand-rolled mixtures primarily composed of herbs and honey that are used to make medicinal teas. These herbal balls are used as a self-medication for a wide variety of conditions, including fever, rheumatism, apoplexy, and cataracts. Herbal balls similar to those analyzed are readily available in specialty markets throughout the United States. Mercury (probably mercury sulfide) was detected in 8 of the 9 herbal balls tested. The recommended adult dose for the herbal balls is two per day. Ingesting two herbal balls could theoretically provide a dose of up to 1,200 mg of mercury.

Samudralwar and Garg (1996) conducted trace metal analysis on a variety of plants used in Indian herbal remedies and other medicinal preparations. These authors reported mercury concentrations of 139, 180, 27, 12.5, 11.7, and <10 ppb for Bowen’s kale, Neem leaves, Gulvei leaves, Kanher bark, Vekhand root, and orange peel, respectively.

Hoet and Lison (1997) reported on an unusual non-occupational source of mercury exposure that resulted in a woman that used prescription nasal drops that contained 300 mg/L (ppm) borate phenylmercury. These authors reported that the woman, who had used the nasal drops over a long period of time, had high urinary levels of mercury (82 µg/g), but that blood levels were not abnormal (5.5 µg/L).

Mercuric sulfide, or cinnabar, was reported to be used in tattooing dyes to produce a red pigmentation (Bagley et al. 1987; Biro and Klein 1967). An analysis of finger paints and make-up paints manufactured in Europe showed that they all contained less than 1 ppm mercury (Rastogi 1992). Rastogi and Pritzi (1996)

conducted another study to assess the migration of several toxic metals from crayons, watercolor paints, and water-based paints. Migration of mercury from the art materials was determined by scraping flakes of the products into dichloromethane for 2 hours at 54E C. The degreased material was then placed in an aqueous HCl solution, shaken, and centrifuged. The supernatant was then filtered through a 0.45 µ membrane filter and was analyzed. These authors reported that the migration of mercury from these art supplies was 0.24–5.98 ppm for red, 0.26–3.63 ppm for blue, 0.20–4.79 ppm for yellow, 0.22–5.68 ppm for green, and 0.17–3.63 ppm for white paint. Migration of mercury from the product occurred in 57% of the samples tested. The migration limit set by European Standard EN71-3 for mercury is 60 ppm. This value was not exceeded in any of the art supplies tested. The authors, however, believe that children might be exposed not only to mercury, but to several other metals that also co-migrated from the paints.

Cigarettes. In a study conducted in West Germany, Pesch et al. (1992) analyzed mercury concentrations in 50 brands of cigarettes manufactured in 2 Western and 6 Eastern European countries. These authors reported that in 1987, the average mercury concentration detected in cigarettes was 0.098 µg/g (ppm) (dry weight) (range, 0.06 to 0.14 ppm dry weight). In 1991, the mean mercury concentrations for cigarettes were 0.034 µg/g (ppm) dry weight (range, 0.007–0.092 ppm dry weight) for Eastern Europe and 0.015 µg/g (ppm) dry weight (range, 0.006–0.037 ppm dry weight) for Western European countries. The authors attributed the decline in mercury content of cigarettes to environmental protection measures instituted in the intervening years (Pesch et al. 1992).

Religious and Ethnic Rituals, Ceremonies, and Practices. While some of medicinal and pharmaceutical uses of mercury compounds have been replaced in recent years, individuals in some ethnic or religious groups may still use mercury in various religious or ethnic rituals, practices, and ceremonies that can expose them to elevated mercury concentrations in room air. Metallic mercury has been used in Latin American and Caribbean communities as part of certain religious practices (e.g., Voodoo, Santeria, and Espiritismo), predominantly in domestic settings (Wendroff 1990). This use of mercury can contaminate a dwelling or automobile if the mercury is not completely removed from flooring, carpeting, and woodwork in an appropriate manner. Metallic mercury (sometimes under the name *azogue)* currently is sold in shops called botanicas which stock medicinal plants, traditional medicines, incense, candles, and perfumes. Botanicas typically dispense mercury in gelatin capsules or sometimes in small glass vials. Some religious practices involve sprinkling metallic mercury on the floor of the dwelling or of a car, mixing metallic mercury with soap and water to wash the floor, or placing it in an open container to rid the house of evil spirits. Other practices involve carrying a small amount of mercury in a vial on the person, or mixing

mercury in bath water or perfumed soaps, devotional candles, ammonia or camphor. Any of these practices can liberate mercury vapor into the room air, exposing the occupants to elevated levels of mercury vapors (ATSDR 1997; Wendroff 1990, 1991). In addition to the individuals that intentionally use mercury in their dwellings, the opportunity exists for nonusers to be inadvertently exposed when they visit the dwelling, or purchase or rent dwellings in which the former tenants used mercury for religious purposes. The issuance of cautionary notices and information by health departments to members of these user populations is appropriate.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Potential sources of general population exposure to mercury include inhalation of elemental mercury vapors in ambient air, ingestion of drinking water and foodstuffs contaminated with elemental mercury or various mercury compounds (i.e., methylmercury), and exposures to elemental mercury and various mercury compounds through dental and medical treatments (NIOSH 1973). EPA (1984b) reported that dietary intake is the most important source of nonoccupational human exposure to mercury, with fish and fish products being the dominant sources of methylmercury in the diet. This is consistent with an international study of heavy metals detected in foodstuffs from 12 different countries (Toro et al. 1994). These authors found that mercury concentrations of 0.15 mg/kg (ppm) for fish and shellfish were approximately 10–100 times greater than for the other foods tested, including cereals, potatoes, vegetables, fruits, meat, poultry, eggs, milk, and milk products. Another author also estimated mean mercury concentrations to be 100 times greater for fish than for foods other than fish ((0.4 µg/g vs. 0.004 µg/g [ppm]) (Fishbein 1991). Recent animal and human studies, however, have also shown that the uptake, distribution, and rate of excretion of elemental mercury from dental amalgams are also major contributing factors to mercury body burden in humans (Björkman et al. 1997; Lorscheider et al. 1995).

A summary of contributing sources of mercury to the body burden of humans is presented in Table 5-12. Because of the variability in fish consumption habits among U.S. consumers and the variability in the concentrations of methylmercury detected in various fish and shellfish species, exposures for individual members of the general population are difficult to measure. Similarly, because of the variability in the number of amalgam fillings in individual members of the general population and the high retention rate for elemental mercury, a wide range of potential exposures to elemental mercury can be shown for persons with dental amalgams. Dental amalgams, however, may represent the largest single non-occupational contributing source to total body burden of some mercury in people with large numbers of amalgam fillings.

Table 5-12. Estimated Average Daily Intake and Retention of Total Mercury and Mercury Compounds in the General Population

Source of exposure	Elemental mercury vapor	Inorganic mercury compounds	Methylmercury
Air	0.030 (0.024)	0.002 (0.001)	0.008 (0.0064)
Food			
Fish	0	0.600 (0.042)	2.4 (2.3)
Non-fish	0	3.6 (0.25)	0
Drinking water	0	0.050 (0.0035)	0
Dental amalgams	3.8–21 (3–17)	0	0
Total	3.9–21 (3–17)	4.3 (0.3)	2.41 (2.31)

Note: Values given are the estimated average daily intake (in µg/day) for adults in the general population who are not occupationally exposed to mercury; the figures in parentheses represent the estimated amount retained in the body of an adult.

Source: WHO 1990, 1991

Dietary Sources of Mercury. Galal-Gorchev (1993) analyzed dietary intakes of mercury from 14 countries, including the United States, between 1980 and 1988. This author reported that the contribution of fish to the total intake of mercury varied from a low of 20% in Belgium and the Netherlands to 35% in France, the United Kingdom, and the United States. The highest contribution of fish to mercury intake (85%) was reported for Finland. The author further pointed out (based on information from the Netherlands on levels of mercury contamination in a variety of foods) that although mercury was found at higher concentrations in fish (0.1 mg/kg [ppm]) than in other foods (0.01 mg/kg or less), higher consumption of cereals and meats render the contributions of these food groups to the total mercury intake about the same as that from fish. Therefore, the general assumption that fish is the main contributor to the intake of mercury may, at times, not be justified because of dietary habits of a given population (Galal-Gorchev 1993).

The FDA's Total Diet Study (April 1982–April 1984) estimated an average daily intake of mercury (total) based on measured levels and assumed trace amounts in foods to be representative of the "total diet" of the U.S. population (Gunderson 1988). Estimated daily exposures for mercury were 0.49 µg/day for infants ages 6–11 months, 1.3 µg/d for 2-year-old children, 2.9 µg/day for females ages 25–30, and 3.9 µg/day for males 25–30 years of age. Expressed on a per body weight basis, the intake for all age groups, except 2-year-old children, was approximately 50 ng/kg/day (Clarkson 1990; Gunderson 1988). For 2-year-old children, the intake was estimated to be approximately 100 ng/kg/day (assuming 50% of the fish intake was due to fish caught locally). More recently, MacIntosh et al. (1996) calculated average daily dietary exposure to mercury and 10 other contaminants for approximately 120,000 U.S. adults by combining data on annual diet, as measured by a food frequency questionnaire, with contaminant residue data for table-ready foods that were collected as part of the annual FDA Total Diet Study (1986–1991). The estimated mean dietary exposure (µg/day) for 78,882 adult females and 38,075 adult males in 1990 was 8.2 µg/day (range, 0.37–203.5 µg/day) for females and 8.6 µg/day (range, 0.22–165.7 µg/day) for males. Assuming a body weight of 65 kg for women and 70 kg for men, the daily intakes of mercury would be 126 ng/kg/day (range, 5.7–3,131 ng/kg/day) for women and 123 ng/kg/day (range, 3.1–2,367 ng/kg/day) for men respectively. These authors found that the coefficient of variation was 44% for mercury, indicating that the exposures to this chemical estimated for a given individual may be accurate to within approximately a factor of 2. Lack of data about the actual amount of food consumed accounted for 95% of the total uncertainty for mercury. Individual food items contributing most to the uncertainty of mercury measurements were canned tuna and other fish (MacIntosh et al. 1996).

The FDA currently has advice for consumers posted on the Internet that recommends that pregnant women and women of childbearing age, who may become pregnant, limit their consumption of shark and swordfish to no more that one meal per month (FDA 1998). This advice is given because methylmercury levels are much higher in these fish species than in the more commonly consumed species. Dietary practices immediately before pregnancy could also have a direct bearing on fetal exposure, particularly during pregnancy. The FDA states that nursing mothers who follow this advice, do not expose their infants to increased health risks from methylmercury (FDA 1998). The FDA further advises that persons other than pregnant women and women of child-bearing age limit their regular consumption of shark and swordfish (which typically contain methylmercury at approximately 1 ppm) to about 7 ounces per week (about one serving) to stay below the recommended maximum daily intake for methylmercury. For fish species with methylmercury levels averaging 0.5 ppm, regular consumption should be limited to 14 ounces (about 2 servings) per week. A summary of mercury concentrations in the top 10 types of fish consumed by the general U.S. population is presented in Table 5-13. There is a wide degree of variability in the amount of fish consumed in the diet by various subpopulations within the United States. Various ethnic groups, as well as recreational and subsistence fishers often eat larger amounts of fish than the general population and may routinely fish the same waterbodies (EPA 1995k). If these waterbodies are contaminated, these populations may consume a larger dose of mercury by virtue of the fact that they consume larger amounts of fish (from >30 g/day for recreational fishers to >100 g/day for subsistence fishers) with higher concentrations of mercury in their tissues than individuals in the general population that tend to consume smaller amounts (6.5 g/day) of supermarket-purchased fish that come from a variety of sources. Table 5-14 provides a summary of the amount of fish consumed daily by the general population, as compared to recreational and subsistence fishers, including some Native American tribal groups. Those individuals that consume greater than 100 g of fish per day are considered high-end consumers; they consume more than 10 times the amount of fish estimated to be consumed by members of the general population (6.5 g/day) (EPA 1995k).

Table 5-15 provides an summary of the estimated total number of persons in the U.S. population (excluding Alaska and Hawaii), the total female population of reproductive age (ages 15–44 years), and the total population of children (<15 years). Based on the percentage of people that reported eating fish during a 3-day dietary survey conducted from 1989 to 1991 as part of the Continuing Survey of Food Intake by Individuals (CSFII), the number of persons estimated to consume fish can be calculated. Using this method, more than 76 million people in the U.S. population eat fish; of these, more than 17 million females of reproductive age (15–44 years old) consume fish, and more than 13 million children (<15 years of age) eat

Table 5-13. Mercury Concentrations in the Top 10 Types of Fish Consumed by the U.S. Population

Fish	Mercury concentration (ppm)[a]	Comments
Tuna	0.206	Mercury content is the average of the mean concentrations in 3 tuna species: Albacore tuna (0.264 ppm) Skipjack tuna (0.136 ppm) Yellowfin tuna (0.218 ppm) The FDA measured the methylmercury concentration in 220 samples of canned tuna in 1991; the average amount of methylmercury measured was 0.17 µg/g and the range was <1–0.75 µg/g) (Yess 1993).
Shrimp	0.047	Mercury content is the average of the mean concentrations in 7 shrimp species: Royal red (0.074 ppm) White (0.054 ppm) Brown (0.048 ppm) Ocean (0.053 ppm) Pink (0.031 ppm) Pink northern (0.024 ppm) Alaska (sidestripe) (0.042 ppm)
Pollack	0.150	The Pesticide and Chemical Contaminant Data Base for the FDA (1991/1992) reports the methylmercury concentration in pollack in commerce as 0.04 ppm
Salmon	0.035	Mercury content is the average of the mean concentrations in 5 salmon species: Pink (0.019 ppm) Chum (0.030 ppm) Coho (0.038 ppm) Sockeye (0.027 ppm) Chinook (0.063 ppm)
Cod	0.121	Mercury content is the average of the mean concentrations in 2 cod species: Atlantic (0.114 ppm) Pacific (0.127 ppm)
Catfish	0.088 0.160	Two data sets were collected from U.S. freshwater sources: Bahnick et al (1994): channel, largemouth, rock, striped, and white Lowe et al. (1985): channel and flathead. Neither survey included farm-raised catfish, which is the type predominantly consumed in the U.S. Mercury content of farm-raised catfish may be significantly different from feral catfish.
	0.020	The Pesticide and Chemical Contaminant Data Base for USFDA (1991/1992) reports the methylmercury concentration in catfish as 0.02 ppm.
Clam	0.023	Mercury content is the average of the mean concentrations in 4 clam species: Hard (quahog) (0.034 ppm) Pacific littleneck (0 ppm) Soft (0.027 ppm) Geoduck (0.032 ppm)

Table 5-13. Mercury Concentrations in the Top 10 Types of Fish Consumed by the U.S. Population (continued)

Fish	Mercury concentration (ppm)[a]	Comments
Flounder (flatfish)	0.092	Mercury content is the average of the mean concentrations in 9 flounder species: Gulf (0.1487 ppm) Summer (0.127 ppm) Southern (0.078 ppm) Four-spot (0.090 ppm) Windowpane (0.151 ppm) Arrowtooth (0.020 ppm) Witch (0.083 ppm) Yellowtail (0.067 ppm) Winter (0.066 ppm)
Crab	0.117	Mercury content is the average of the mean concentrations in 5 crab species: Blue (0.140 ppm) Dungeness (0.183 ppm) King (0.070 ppm) Tanner *(C. opilio)* (0.088 ppm) Tanner *(C. bairdi)* (0.102 ppm)
Scallop	0.042	Mercury content is the average of the mean concentrations in 4 scallop species: Sea (smooth) (0.101 ppm) Atlantic bay (0.038 ppm) Calico (0.026 ppm) Pink (0.004 ppm)

[a] All concentrations determined on a wet weight basis

Source: EPA 1996e

Table 5-14. Fish Consumption Rates of Various Populations Including General Population and Recreational and Subsistence Fishers

Consumption rate (g/day)	Description	Population	Reference
170	95 %ile (adult)	Umatilla, Nez Perce, Yakima, and Warm Springs Tribes of Columbia River Basin Washington	CRITFC 1994
140	90 %ile (adult)	Subsistence fisher (default value)	EPA 1995k
109	Mean (adult)	Native Alaskans in 11 separate communities	Nobmann et al. 1992
63	95 %ile (adult)	Wisconsin anglers (10 counties) includes both recreationally and commercially caught fish	Fiore 1989
59	Mean (adult)	Umatilla, Nez Perce, Yakima, and Warm Springs Tribes of Columbia River Basin Washington	CRITFC 1994
37	95 %ile (adult)	Wisconsin anglers (10 counties) includes only recreationally caught fish	Fiore 1989
34	75 %ile (adult)	Wisconsin recreational anglers	Fiore 1989
30	Mean (adult)	Recreational fisher (default value)	EPA 1995k
28	Mean (adult)	New York anglers	Connelly 1990
26	Mean (adult)	Wisconsin anglers (10 counties) includes both recreationally and commercially caught fish	Fiore 1989
20	Mean (child 5 years and younger)	Umatilla, Nez Perce, Yakima, and Warm Springs Tribes of Columbia River Basin Washington	CRITFC 1994
12	Mean (adult)	Wisconsin anglers (10 counties) includes only recreationally caught fish	Fiore 1989
6.5	Mean (adults)	General U.S. population	EPA 1995k

Source: EPA 1996e

Table 5-15. Estimated U.S. Population Consuming Fish[a], Excluding Alaska and Hawaii

Population group	Estimated number of persons
Total U.S. population	247,052,000
Total female population ages 15–44 years	58,222,000
Total population of children aged <15 years	53,463,000
Percentage of respective group reporting fish consumption during the CSFII 3-day dietary survey period in 1989–1991[b]	
Total U.S. population	30.9%
Total female population ages 15–44 years	30.5%
Total population of children aged <15 years	24.9%
Number of persons predicted to consume fish based on percentage consuming fish in CSFII 3-day dietary survey period in 1989–1991	
Total U.S. population	76,273,000
Total female population ages 15–44 years	17,731,000
Total population of children aged <15 years	13,306,000
Number of persons in highest 5% of estimated population that consumes fish[c]	
Total U.S. population	3,814,000
Total female population ages 15–44 years	887,000
Total population of children aged <15 years	665,000
Estimated number of adult pregnant women in highest 5% of estimated population that consumes fish	
Number of females aged 15–44 years times percentage of women pregnant in given year	84,300

[a] Estimates based on the 1990 U.S. Census and the 1989-1991 Continuing Surveys of Food Intake by Individuals

[b] Numbers of persons rounded to 3 significant figures

[c] Persons who consumed an average 100 g or more of fish/day

Source: EPA 1996e

fish. In addition, estimates of the total number of persons in the high-end fish consumer group (subsistence fishers) have been calculated, as were estimates of the total number of adult women of reproductive age (15 to 44 years old) and children (<15 years old) in the high-end consumer group, i.e., those potentially at greatest risk of exposure (EPA 1996e). With respect to fish consumers, more than 3.8 million are high-end consumers (>100 grams of fish/day), and of these, it is estimated that more than 887,000 are women of reproductive age (15–44 years), and 665,000 are children (<15 years old). It was also estimated that of the fish consuming females of reproductive age, more than 84,000 are pregnant in any given year.

Fish is generally considered an excellent source of protein in the diet and the health benefit of fish consumption, including the reduction in the incidence of coronary heart disease, is well recognized (Salonen et al. 1995). However, Salonen et al. (1995) studied 1,833 eastern Finnish men ages 42–60 and related high dietary intake of freshwater fish containing mercury residues, as well as elevated hair content and urinary excretion of mercury, to a risk of acute myocardial infarction and death from coronary heart disease and cardiovascular disease. Men with the highest tertile of hair mercury had a 2-fold age-specific risk and a 2.9-fold adjusted risk of acute myocardial infarction and cardiovascular death, compared to men with lower mercury hair levels. Egeland and Middaugh (1997) and Clarkson et al. (1998) contend that the Seychelles population is a more appropriate sentinel population for fish consumers in the United States because: (1) the major source of methylmercury is from open ocean fish; (2) the mercury concentrations in hair are 10–20 times the average found in the United States; and (3) because the Seychellois consistently consume about 12 fish meals per week. These authors feels that the potential adverse effects of methylmercury in fish would be detected in the Seychelles Island population, long before such effects are observed in the United States. The Finnish study (Salonen et al. 1995), however, suggests that freshwater fish, low in selenium and omega-3 polyunsaturated fatty acids, may not protect against cardiovascular risks from methylmercury. The human health benefit/cost tradeoff between fish consumption and mercury exposure varies by species and mercury dose.

Dental Amalgams. Recent animal and human studies have also identified the uptake, distribution, and rate of excretion of elemental mercury from dental amalgams as another significant contributing source to mercury body burden in humans (Björkman et al. 1997; Lorscheider et al. 1995). A summary of contributing sources of mercury to the human body burden is presented in Table 5-12. Because of the wide range of potential exposures and the high retention rate for elemental mercury, dental amalgams potentially represent the largest single contributing source of mercury exposure in some individuals with large numbers (>8) of amalgam fillings.

Dental amalgams may contain 43–54% elemental mercury (DHHS 1993). A single amalgam filling with an average surface area of 0.4 cm^2 has been estimated to release as much as 15 µg mercury/day, primarily through mechanical wear and evaporation, but also through dissolution into saliva (Lorscheider et al. 1995). The rate of release is influenced by chewing, bruxism (grinding of teeth) food consumption, tooth brushing, and the intake of hot beverages (Weiner and Nylander 1995). For the average individual with eight occlusal amalgam fillings, 120 µg of mercury could be released daily into the mouth, and a portion of that swallowed or inhaled (Lorscheider et al. 1995). Experimental results regarding estimated daily dose of inhaled mercury vapor released from dental amalgam restorations are few and contradictory (Berglund 1990). More recently, Björkman et al. (1997) reported that approximately 80% of inhaled mercury from dental amalgams is absorbed (Björkman et al. 1997). Various laboratories have estimated the average daily absorption of amalgam mercury ranging from 1 to 27 µg, with levels for some individuals being as high as 100 µg/day (Björkman et al. 1997; Lorscheider et al. 1995; Weiner and Nylander 1995). Estimates of mean daily elemental mercury uptake from dental amalgams from these and earlier studies are summarized in Table 5-16. A report from the Committee to Coordinate Environmental Health and Related Programs (CCEHRP) of the Department of Health and Human Services determined that "measurement of mercury in blood among subjects with and without amalgam restorations . . . and subjects before and after amalgams were removed . . . provide the best estimates of daily intake from amalgam dental restorations. These values are in the range of 1–5 µg/day" (DHHS 1993). Another source indicates that the consensus average estimate is 10 µg amalgam Hg/day (range, 3–17 µg/day) (WHO 1991). However, Halbach (1994) examined the data from 14 independent studies and concluded that the probable mercury dose from amalgam is less than 10 µg/day. Most recently, Richardson (1995) computed a release rate per filled tooth surface as 0.73 µg/day-surface, with a standard deviation of 0.3 µg/day-surface and a “stimulation magnification factor” of 5.3, based on a weighted average enhancement of mercury vapor concentration following chewing, eating, or tooth brushing reported in three amalgam studies.

By comparison to the estimated daily absorbance of mercury from dental amalgams (range, 3–17 µg), the estimated daily absorbance from all forms of mercury from fish and seafood is 2.31 µg and from other foods, air, and water is 0.3 µg (WHO 1991). These other sources taken together only total 2.61 µg/day, in comparison to estimates of 3–17 µg/day for dental amalgams. Assuming a person has large numbers of amalgams, this source may account for 17 µg/day out of a total absorbance of 19.61 µg/day, or 87% of the absorbed mercury. In contrast, in individuals with only a few amalgams, mercury from this source may account for only 3 µg mercury/day out of a total absorbance of 5.61 µg/day, or 53% of absorbed mercury. Halbach et al. (1994) concluded that the sum of the mercury uptake from dental amalgam and dietary

Table 5-16. Estimates of Mean Daily Elemental Mercury Uptake from Dental Amalgam Restorations

Number of surfaces	Mercury (µg/day)	Reference
Not reported	27.0	Patterson et al. 1985
8–54	3.0	Langworth et al. 1988
13–48	1.7	Berglund 1990
1–16	19.8	Vimy and Lorscheider 1985
7	1.3	Snapp et al. 1989
8–54	3.0	Langworth et al. 1988
0–82	12.0	Skare and Engqvist 1994
		Clarkson et al. 1988[b]
Not reported	17.5	Svare et al. 1981
1–16	2.9	Vimy and Lorscheider 1985
0.2–4.2[a]	8.0	Abraham et al. 1984
Not reported	2.5	Patterson et al. 1985
		Mackert 1987[c]
1–16	1.24	Vimy and Lorscheider 1985
		Weiner and Nylander 1995[d]
1–75	≥27.0	Patterson et al. 1985
1–16	20.0	Vimy and Lorscheider 1985
1–16	1.2	Mackert 1987
Not reported	3–18	Clarkson et al. 1988
24–63	7–10	Aronsson et al. 1989
13–48	1.7	Berglund 1990
Not reported	3–17	WHO 1991
14 (avg)	≥1.3	Snapp et al. 1989
≥36	10–12	Jokstad et al. 1992

[a] Occlusal surface area in cm^2
[b] Clarkson's estimates based on the data from studies listed
[c] Mackert's estimate based on the data from the study listed
[d] Weiner and Nylander's estimate based on the data from the studies shown below

uptake is still below the dose corresponding to the acceptable daily intake (ADI) of mercury. The ADI of 40 µg total mercury, 30 µg of which are allowed for methylmercury, results in a total dose of approximately 30 µg after accounting for absorption (Halbach 1994; WHO 1976). WHO (1990) estimates a daily absorption of 2.61 µg from background exposure for persons without amalgam exposure.

In a recent study by Schweinsberg (1994), the author monitored mercury in blood, urine, and hair of subjects with amalgam fillings, in subjects who consumed fish, and in mercury-exposed workers. With respect to hair concentrations, the author reported a mean mercury level in hair of 560 µg/kg (ppb), 940 µg/kg, and 1,600 µg/kg in subjects that consumed the following mean amounts of fish per month: 120 g/month (range, 0–<400 g fish/month); 600 g/month (range, 400–<1,000 g/month); and 1,900 g/month (>1,000 g/month), respectively. Mercury concentrations in whole blood (µg/L) were 0.2–0.4 µg/L for individuals with no fish consumption and no dental amalgams, 1.047±0.797 µg/L for persons with no fish consumption and >6 dental amalgams, 2.56±2.123 µg/L for persons with fish consumption >990 g/month and no dental amalgams, and 2.852±2.363 µg/l for persons with fish consumption >990 g/month and >6 dental amalgams. Mercury concentrations in the urine of occupationally exposed thermometer factory workers were higher, by a factor of 100, than in the group with amalgam fillings. The author concluded that both amalgam fillings and the consumption of fish burden individuals with mercury in approximately the same order of magnitude.

In a more recent study of lactating women, Oskarsson et al. (1996) assessed the total and inorganic mercury content in breast milk and blood in relation to fish consumption and amalgam fillings. The total mercury concentrations (mean±standard deviation) in breast milk, blood, and hair samples collected 6 weeks after delivery from 30 Swedish women were 0.6±0.4 ng/g (ppb), 2.3±1.0 ng/g, and 0.28±0.16 µg/g, respectively. In milk, an average of 51% of total mercury was in the inorganic form, whereas in blood an average of only 26% was in the inorganic form. Total and inorganic mercury levels in blood and milk were correlated with the number of amalgam fillings. The concentrations of total mercury and organic mercury in blood and total mercury in hair were correlated with the estimated recent exposure to methylmercury via consumption of fish. There was no significant difference between the milk levels of mercury in any form and the estimated methylmercury intake. A significant correlation was found, however, between the levels of total mercury in blood and in milk, with milk levels being an average of 27% of the blood levels. There was also an association between inorganic mercury in blood and in milk; the average level of inorganic mercury in milk was 55% of the level of inorganic mercury in blood. No significant correlations were found between the levels of any form of mercury in milk and the levels of organic mercury in blood. The results indicated that

there was an efficient transfer of inorganic mercury from blood to milk and that, in the study population, mercury from amalgam fillings was the main source of mercury in breast milk. Exposure of the infant to mercury in breast milk was calculated to range up to 0.3 µg/kg/day, of which approximately one half was inorganic mercury. This exposure corresponds to approximately one-half the tolerable daily intake for adults recommended by the World Health Organization (WHO). The authors concluded that efforts should be made to decrease mercury burden in women of reproductive age.

Blood. (EPA 1996d). Because methylmercury freely distributes throughout the body, blood is a good indicator medium for estimating methylmercury exposure. However, because an individual's intake may fluctuate, blood levels may not reflect mercury intake over time (Sherlock and Quinn 1988; Sherlock et al. 1982). Recent reference values for total mercury levels in blood of non-exposed individuals in the general U.S. population are very limited. The mean concentration of mercury in whole blood based on a review of existing data from other countries, is 8 µg/L (ppb) (WHO 1990). Certain groups with high fish consumption may attain blood methylmercury levels of 200 µg/L (ppb), which is associated with a low (5%) risk of neurological damage to adults (WHO 1990).

Urine. Urine is a common indicator used to assess occupational mercury exposure (EPA 1996d). Urinary mercury is thought to indicate most closely the mercury levels present in the kidneys (Clarkson et al. 1988b). But while urinary mercury has been widely used to estimate occupational exposures, reference values for urinary mercury levels in non-exposed individuals in the general U.S. population are very limited. The mean concentration of urinary mercury, based on a review of existing data from other countries, is about 4 µg/L (ppb) (WHO 1990, 1991). For assessment of long-term inorganic mercury exposure, biological monitoring of the urinary mercury is normally used (Skare 1995). Several authors have related elevated urinary mercury levels to dental amalgams in individuals in the general population (Barregard et al. 1995; Skare 1995) and in dentists and dental personnel receiving occupational exposures (Akesson et al. 1991; Chien et al. 1996; WHO 1991).

Breast Milk. Recent reference values for mercury levels in breast milk in non-exposed individuals in the general U.S. population are very limited. The mean concentration of mercury in breast milk, based on a review of existing data from other countries, is 8 µg/L (ppb) (WHO 1990, 1991). Mean concentrations of mercury in breast milk samples from the United States and other countries are summarized in Table 5-17. Pitkin et al. (1976) reported a mean total mercury concentration of 0.93±0.23 ppb in a midwestern community in the United States. This mean value is only about one-third the mean value reported for Inuit

Table 5-17. Total Mercury Concentrations in Human Breast Milk

Population	Year	Number of samples (% positive)	Total Hg content in whole milk (ppb)[a]	Reference
Minamata, Japan (contaminated seafood)	1968	–	63	Fujita and Takabatake 1977
Iraq (contaminated grain)	1972	44	<200[b]	Bakir et al. 1973
Tokyo, Japan (urban population)	1974	34	3.6±2.2 (0.4–9.8)	Fujita and Takabatake 1977
Iowa, USA (general population without abnormal exposure)	1975	32 (44%)	0.9±0.23	Pitkin et al. 1976
Alaska, USA (coastal population) (interior population) (urban population)	1975	1155	7.6±2.7 3.2±0.8 3.3±0.5	Galster 1976
Madrid, Spain	1981	20 (100%)	9.5±5.5 (0.9-19)	Baluja et al. 1982
Sweden (15 women fish consumers)	1980s	NA	0.2–6.3	Skerfving 1988
Sweden (fish consumers with an average of 12 amalgam fillings)	1990s	30	0.6±0.4[c] (0.1–2.0)	Oskarsson et al. 1996
Faroe Islands (88 women who consumed pilot whale meat)	1990s	100	median 2.45 maximum 8.7	Grandjean et al. 1995

[a] Results are expressed as means ±S.D unless otherwise noted. Ranges are shown in parentheses.

[b] Of the total mercury, 40% was inorganic mercury; 60% was methylmercury

[c] Of the total mercury 51% was inorganic; 49% was organic mercury

women living in interior (3.2±0.8 ppb) or urban areas (3.3±0.5 ppb) of Alaska and less than one-seventh the mean value for coastal Alaskan Inuit women (7.6±2.7 ppb) known to consume seal meat and oil, as well as marine fish (Galster 1976). The latter breast milk total mercury level is comparable to the median (2.45 ppb) and maximum (8.7 ppb) values reported for women in the Faroe Islands that consume large amounts of fish and pilot whale meat (Grandjean et al. 1995a).

Levels of total mercury in breast milk have been monitored in several foreign countries over the past three decades. A mean breast milk mercury concentration of 3.6±2.2 ppb (range, non-detected to 9.8 ppb) was reported for an urban population in Tokyo, Japan (Fujita and Takabatake 1977). In a study of urban women residing in Madrid, Spain, the mean breast milk mercury concentration was 9.5±5.5 ppb (range, 0.9–19 ppb) (Baluja et al. 1982). These authors did not provide any information (i.e., whether females were fish consumers, the number of dental amalgams they had, or their occupations) that would explain the relatively high mercury levels. Skerfving (1988) reported mercury concentrations ranged from 0.2 to 6.3 ppb in breast milk of Swedish women that consumed fish; however, this author did not provide specific information on the fish consumption rate or the number of dental amalgams of the study population. Most recently, Oskarsson et al. (1996) reported a mean total breast milk concentration of 0.6±0.4 ppb (range, 0.1–2.0 ppb) for a group of Swedish women that consumed freshwater fish and had an average of 12 amalgam fillings. This was a smaller range in mercury concentrations than that reported by Skerfving (1988).

All of these general population breast milk mercury concentrations are in sharp contrast to those reported for samples collected from women in Minamata, Japan, where industrial effluents containing methylmercury caused widespread contamination of local seafood. Breast milk total mercury concentrations were on the order of 63 ppb in individuals who lived in the vicinity of Minamata, Japan and had consumed highly mercury-contaminated fish (Fujita and Takabatake 1977). Similarly, in Iraq, where consumption of bread made from seed grain treated with methylmercury as a fungicide caused a similar mercury poisoning outbreak, breast milk concentrations as high as 200 ppb were reported (Bakir et al. 1973). Breast milk containing total mercury levels of >4 ppb would exceed the safe level (2 µg methylmercury/day for an average 5-kg infant) (Wolff 1983). It is important to emphasize, however, that in general, the beneficial effects associated with breast feeding seem to override or at least compensate for any neurotoxic effects on milestone development that could be due to the presence of contaminants, such as mercury, in human milk (Egeland et al. 1997).

Hair. Scalp hair is another primary indicator used to assess methylmercury exposure, because the methylmercury is incorporated into the hair at the hair follicle in proportion to its content in the blood (EPA 1996d). The typical hair-to-blood ratio in humans has been estimated to be about 250:1 expressed as µg Hg/g hair to mg Hg/L blood, but some difficulties in measurements, inter-individual variation in body burden, differences in hair growth rates, and variations in fresh and saltwater fish intake have led to varying estimates (Birke et al. 1972; Skerfving 1974). Once incorporated into the hair strand, the methylmercury is stable and gives a longitudinal history of blood methylmercury levels (WHO 1990). Care must be exercised to ensure that the analysis of methylmercury levels in hair are not confounded by adsorption of mercury vapors or inorganic mercury onto the hair (Francis et al. 1982)

Recent reference values for mercury levels in hair from non-exposed individuals in the general U.S. population are very limited. A summary of mercury concentrations in hair from residents (adults, men, women, and children) of several U.S. communities is presented in Table 5-18. Most of the these studies, however, with the exception of Fleming et al. (1995) were conducted from 7 to 20 years ago. For populations studied in the United States, the range in mean hair concentrations was 0.47–3.8 ppm for adults (maximum value of 15.6 ppm) and 0.46–0.77 ppm for children (maximum value of 11.3 ppm). The mean concentration of mercury in hair based on a review of existing data from other countries is 2 µg/g (ppm) (WHO 1990), and the WHO advisory maximum tolerable level for hair is 6 ppm.

The concentration of total mercury in hair in the general population of Japan was determined by Nakagawa (1995). This author sampled hair from 365 healthy volunteers in Tokyo and the surrounding area from June 1992 to June 1993. The mean concentration of mercury in hair was higher in males (2.98 ppm, 81 individuals sampled) than in females (2.02 ppm, 284 individuals sampled). In both males and females, the mercury concentration in hair increased with age up to the mid-30s, then gradually declined. The authors also looked at dietary preferences and found the mean hair levels in males and females were highest in individuals that had a preference for fish (4.0 and 2.7 ppm, respectively), followed by those with a preference for fish and meat (2.88 and 2.00 ppm, respectively), a preference for meat (2.38 ppm and 1.96 ppm, respectively), and was lowest in those individuals that preferred a predominantly vegetarian diet (2.27 and 1.31 ppm, respectively). In an earlier study, the mercury content in human hair was studied in Japanese couples, with husbands having significantly higher mercury concentrations (4.01 ppm) than wives (1.99 ppm), possibly as a result of greater fish consumption among the men (Chen et al. 1990). This same pattern is also apparent for all but one of the U.S. populations (San Diego, California) studied by Airey (1983b). It is noteworthy that some of the highest mercury concentrations in hair measured in women

Table 5-18. Mercury Concentrations in Hair (µg Hg/g hair) from Residents of Various U.S. Communities

Population	Mean concentration (ppm)				Maximum concentration (ppm)				Reference
	Adults	Males	Females	Children	Adults	Males	Females	Children	
NY metropolitan area									Creason et al. 1978a
adults n=203	0.77				14.0				
children n=280				0.67				11.3	
4 NJ communities (Ridgewood, Fairlawn, Matawan, and Elizabeth)									Creason et al. 1978b may have to drop
adults n=117	0.78				5.6				
children n=204				0.77				4.4	
Birmingham AL and Charlotte NC									Creason et al. 1978c
adults n=282	0.47				7.5				may have to drop
children n=322				0.46				5.4	
U.S. unidentified community									Airey 1983b
males n=22		2.7				6.2			
females n=16			2.6				5.5		
adults n=24	2.1				5.6				
adults n=31	2.2				6.6				
adults n=24	2.9				7.9				
adults n=79	2.4				7.9				
LaJolla-San Diego CA									Airey 1983b
males n=13		2.4				6.2			
females n=13			2.7				5.5		
adults n=8	2.3				4.5				
adults n=17	2.9				6.6				
adults n=5	2.6				6.2				
adults n=30	2.7				6.6				
Maryland									Airey 1983b
adults n=11	1.8				3.8				
adults n=11	1.5				3.9				
adults n=11	2.3				4.5				
adults n=33	1.9				4.5				

Table 5-18. Mercury Concentrations in Hair (µg Hg/g hair) from Residents of Various U.S. Communities (continued)

Population	Mean concentration (ppm)				Maximum concentration (ppm)				Reference
	Adults	Males	Females	Children	Adults	Males	Females	Children	
Seattle WA									Airey 1983b
males n=9		3.3				5.6			
females n=3			2.2				4.1		
adults n=5	2.6				5.6				
adults n=3	1.5				2.1				
adults n=8	3.8				7.9				
adults n=16	3.0				7.9				
Nome AK females of child-bearing age n=80							15.2		Lasora and Citterman 1991
Seguim WA females of childbearing age n=7			0.70				1.5		Lasora and Citterman 1991
Florida Everglades adults that consumed local wildlife n=330	1.3				15.6				Fleming et al. 1995
Range	0.47–3.8	2.4–3.3	2.2–2.7	0.46–0.77	2.1–15.6	5.6–6.2	1.5–15.2	4.4–11.3	

Source: EPA 1996e

(15.2 ppm) were from Nome, Alaska where the population consumes large amounts of fish and marine mammals (Lasora and Citterman 1991) and from Florida (15.6 ppm), where measurements were made only in adults that consumed wildlife from the Everglades area, a region where high mercury levels in wildlife have been reported (Fleming et al. 1995). Most recently, Davidson et al. (1998) reported the results of the Seychelles Child Development Study at 66 months (5.5 years) post-parturition. These researchers reported that there were no adverse neurodevelopmental outcomes observed in mother-child pairs, with mean maternal and mean child hair total mercury concentrations of 6.8 ppm and 6.5 ppm, respectively, in the Seychelles Island study.

Oral Tissues. Mercury concentrations as high as 380 µg/g (ppm) have been found in oral tissues in contact with amalgam fillings. In individuals with more than six amalgam fillings, a mean value of 2.3 µg/g (ppm) was found in tissue without direct contact with amalgam fillings (Björkman et al. 1997). In some European countries, health authorities recommend that sensitive or susceptible individuals in higher risk groups (i.e., pregnant women and individuals with kidney disease) avoid treatment with dental amalgam (Björkman et al. 1997).

Occupational Exposure. Workplace environments presenting the largest potential sources of occupational exposure to mercury include chloralkali production facilities, cinnabar mining and processing operations, and industrial facilities involved in the manufacture and/or use of instruments containing liquid mercury (Stokinger 1981). According to NIOSH (1973), the principal route of occupational exposure to mercury is vapor phase inhalation from workplace atmospheres. Studies by Barregard et al. (1992) and by Langworth et al. (1992b) revealed increased total mercury levels in blood and urine of exposed chloralkali workers. These results are summarized in Table 5-19. Personal air sampling of workers in a mercury recycling plant in Germany showed mercury levels ranging from 115 to 454 µg/m^3 (Schaller et al. 1991).

Human tissues that are routinely monitored as evidence of exposure to mercury are urine, blood, and hair. Urine is most frequently monitored as an indicator of human body burden following chronic exposure to mercury vapor, particularly in occupational settings; approximately 95% of all urine samples contain less than 20 µg /L (ppb) (EPA 1984b). A comparison of mercury content in the urine of Swedish workers exposed to high levels of mercury, dentists, occupationally unexposed workers, and unexposed workers without dental amalgams gave values of 15, 1.7, 0.8, and 0.3 µmol/mol creatinine, respectively (corresponding mercury plasma levels were 35, 9.4, 5.3, and 2.8 nmol/L [7.19, 1.89, 1.06, and 0.56 ppt], respectively) (Molin et al. 1991). Blood and urine monitoring may be useful for groups of workers subject

Table 5-19. Total Mercury Levels in Exposed Workers and Controls

Number of subjects	Exposure group	Air ($\mu g/m^3$)	Blood (nmol/L)	Plasma (nmol/L)	Urine (nmol/mmol creatinine)	Serum (nmol/L)	Reference
26	Chloralkali workers	25–50	No data	48.0	16.0	No data	Barregard et al. 1991
26	Unexposed referents	No data	No data	7.5	1.3	No data	
89	Chloralkali workers	10–106	55	No data	14.3	45	Langworth et al. 1992b
75	Controls	No data	15	No data	1.1	4	

to chronic exposure to mercury, but the relative contribution of recent exposures to mercury levels in these media, in comparison to releases of mercury stored in tissues as a result of earlier exposures, is not well understood (EPA 1984b) (see Section 2.5).

Mercury exposure also may result from the transport of mercury to a workers' home on contaminated clothing and shoes (ATSDR 1990; Hudson et al. 1987; Zirschky 1990). Increased exposure to mercury has been reported in children of workers who are occupationally exposed (Hudson et al. 1987). The population of children at highest risk are those whose parents work in facilities that use mercury, but where no protective uniforms or footgear are used. The mercury is thought to be transferred to the workers' homes in their clothing and shoes. While prevention of employee-transported contamination to their homes is preferred, cleaning the homes of workers occupationally exposed to mercury is also effective in reducing exposure for family members (Zirschky 1990). In an exposure study of families of workers at a chloralkali plant in Charleston, Tennessee, mercury levels in the air of the workers' homes averaged 0.92 μg/m^3 (ATSDR 1990).

The use of fluorescent tube compactors by industrial facilities may also expose those operating the compactors and workers in adjacent areas to increased levels of mercury vapor if proper filters, scrubbing devices, and ventilation are not used (Kirschner et al. 1988).

Dentists and other dental professionals may have greater exposure to mercury as a result of preparing and applying dental amalgams (Ayyadurai and Krishnashamy 1988; Skare et al. 1990). Nylander et al. (1989) sampled pituitary gland tissue from autopsies of 8 dental staff and 27 control individuals in Sweden. These authors reported median mercury concentrations of 815 μg/kg (ppb) wet weight (range, 135–4,040 μg/kg) in pituitary tissue of dental staff (7 dentists and 1 dental assistant), as compared to a median of 23 μg/kg (wet weight) in 27 individuals from the general population. None of the dental staff had been working immediately prior to their deaths, and in several cases, more than a decade had passed since the cessation of their clinical work. The number of amalgams did not correlate to pituitary gland concentrations in the controls. However, if two of the controls with the highest mercury concentrations were excluded (there was some evidence that these individuals had received occupational exposures), then the correlation was significant ($p<0.01$). In another study, Nylander and Weiner (1991) also reported high mercury concentrations in the thyroid and pituitary glands, with a median of 1.1 μmol/kg (221 ppb) wet weight (range, 0.7–28 μmol/kg [140–5,617 ppb]) in the pituitary. the median mercury concentration in the pituitary of the controls was 0.11 μmol/kg (22 ppb) (range, 0.03–5.83 μmol/kg [6–1,170 ppb]).

Naleway et al. (1991) reported results of a screening study conducted in 1985 and 1986 by the American Dental Association to analyze urinary mercury concentrations in dentists and identify those individuals with elevated urinary mercury levels. In 1985, 1,042 U.S. dentists were screened, and a mean urinary mercury level of 5.8 µg/L (ppb) (maximum 84 µg/L) was reported. In 1986, 772 dentists screened had a mean urinary level of 7.6 µg/L (ppb) (maximum 115 µg/L). Their mean urinary mercury levels were substantially lower than pooled data (mean, 14.2 µg/L) from dentists participating in the screening program from 1975–1983 (Naleway et al. 1985). The authors noted a substantial decline, particularly during the last 5 years (1982–1986), which was attributed to better mercury hygiene and the reduced use of amalgam restorations. This study also evaluated responses from a questionnaire survey of 480 dentists. The results indicated that those dentists reporting skin contact with mercury amalgam had mean urinary mercury levels of 10.4 µg/L (ppb), compared to 6.3 µg/L (ppb) in dentists reporting no skin contact; this difference was found to be statistically significant. Similarly, the mean urinary mercury level in dentists reporting mercury spills in the office was 7.8 µg/L (ppb), compared to 6.0 µg/L (ppb) for those reporting no mercury spills. Again, the difference was significant. Additionally, the number of hours practiced per week was found to weakly correlate with urinary mercury concentrations (Naleway et al. 1991).

Painters are another group that may be occupationally exposed to mercury vapors from volatilization of mercury during application of paint containing phenylmercuric acetate. Hefflin et al. (1993) studied the extent of mercury exposure from the application of exterior latex paints. These authors compared the air and urinary mercury concentrations of 13 professional male painters with those of 29 men having other occupations (nonpainters). The painters applied 2 brands of exterior latex paint that contained mercury; the median concentration was 570 mg/L (ppm). The median air mercury concentration was higher for painters (1.0 µg/m^3; range, non-detectable to 4 µg/m^3) than for nonpainters (non-detected; range, not detected to 3 µg/m^3). The median urinary mercury concentration was nearly twice as high for painters (9.7 µg/L [ppb]; range, 5.9–20.4 µg/L) as for nonpainters (5.0 µg/L [ppb]); range, 2.6–11.6 µg/L [ppb]) (p=0.0001). The normal range of urinary mercury is <20 µg/L (ppb) (EPA 1984b). Among the professional painters, urinary mercury concentrations increased with the percentage of time spent applying the exterior paint. Tichenor and Guo (1991) also studied the amount of mercury emitted from latex paints containing mercury compounds. The concentrations of mercury in the 5 types of paint tested ranged from 93 ppm to 1,060 ppm. These authors also reported that from 12 to 57% of the mercury in the paint was emitted upon application as elemental mercury, with the highest emission rate within the first few hours after paint application.

Commercial artists and crafts people are another group that is also at risk of mercury exposure from a variety of professional arts and crafts materials and techniques (Grabo 1997). This author reported that mercury was a hazard to commercial artists using mercury-based pigments in airbrush painting, brush paintings, and in pastels via pigment in chalk dusts. The author concluded that occupational health professions should be aware of toxic nature of the materials used by artists, whether they are employed in industry, self-employed, or are hobbyists.

Chemists are another group at risk of occupational exposure as a result of activities involving the synthesis of mercury compounds or the analysis of environmental or biological samples containing mercury residues. Methylmercury compounds are still used in laboratory-based research, and so the possibility of occupational exposure remains. Junghans (1983) reviewed the toxicity of methylmercury compounds associated with occupational exposures attributable to laboratory use. Most recently, a poisoning incident was reported from a single acute exposure to dimethylmercury (Blayney et al. 1997). The analytical chemist involved was exposed to approximately 0.1–0.5 mL of dimethylmercury spilled on disposable platex gloves during a transfer procedure in a fume hood, while preparing a mercury nuclear magnetic resonance standard. Blood analyses 5 months after the exposure incident revealed a whole blood mercury concentration of 4,000 µg/L (ppb), which is 80 times the usual toxic threshold (50 µg/L) and 400 times the normal mercury blood range (<10 µg/L) (Blayney et al. 1997). These authors caution that highly resistant laminate gloves should be worn under a pair of long-cuffed unsupported neoprene, nitrile, or similar heavy duty gloves rather than latex or polyvinyl chloride (PVC) gloves. Another group of analytical chemists (Toribara et al. 1997) reported that during the calibration of a mass spectrometer, an operator used a pipette with a plastic tip to transfer dimethylmercury into a Pyrex glass vial equipped with a crimp top for a Teflon-lined silicone stopper in a fume hood. After transfer, the plastic tip was disposed of in a nearby wastebasket and, in a short time, the instrument (which can detect nanogram quantities of mercury) showed measurable quantities in the workplace air around the instrument and operator. Toribara et al. (1997) also cites three other historic incidents where laboratory staff and non-laboratory staff (secretaries) working in proximity to a dimethylmercury spill were poisoned. These authors caution colleagues about the hazards involved in shipping dimethylmercury, if the packaging and container is physically damaged during transport.

The National Occupational Exposure Survey (NOES) conducted by NIOSH from 1980 to 1983 estimated that 67,551 workers, including 21,153 women in 2,877 workplaces were potentially exposed to mercury in the workplace (NIOSH 1984b). Most of these workers were employed in the health services, business services, special trade contractor, and chemical and allied products industries as chemical technicians,

science technicians, registered nurses, and machine operators. These estimates were derived from observations of the actual use of mercury (97% of total estimate) and the use of trade-name products known to contain mercury (3%). It is unknown how many of the potentially exposed workers were actually exposed. Data from the NOES conducted by NIOSH from 1983 to 1986 was broken out by exposure to a variety of mercury compounds (RTECS 1998). Estimates of the total numbers of all workers and women workers potentially exposed are presented in Table 5-20. A total of 151,947 workers were potentially exposed to mercury or various mercury compounds; 33% (50,468) of these workers were women. Table 5-21 summarizes the calculated mercury absorption from air at various occupational exposure guideline concentrations.

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in Section 2.6, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, and breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

Significant health risks, including numerous neuropathological and neurobehavioral effects, are associated with prenatal exposure to methylmercury (Zelikoff et al. 1995). Fetuses and breast-fed infants may be exposed to higher than background concentrations of mercury via maternal consumption of large amounts of fish or marine mammals contaminated with mercury, via maternal exposure to mercury through dental amalgams, via maternal use of consumer products containing mercury or various mercury compounds, and via occupational exposure of the mother (Zelikoff et al. 1995). Fetuses can be exposed to mercury via exposures of their mothers either before or during pregnancy; nursing infants can be exposed via consumption of contaminated breast milk from mothers exposed via medical, domestic, or occupational

Table 5-20. Estimated Number of Workers Potentially Exposed to Mercury and Various Mercury Compounds in the Workplace

Mercury compounds	Number of workers	Number of female workers
Mercury (metallic)	71,933	23,826
Mercury chloride	45,492	18,717
Mercury acetate	6,063	2,770
Mercuric sulfide	98	--
Phenylmercuric acetate	28,347	5,150
Methylmercuric chloride	14	5

Source: RTECS 1998

Table 5-21. Calculated Mercury Absorption from Air

Route (source of exposure)	Guideline	Air concentration ($\mu g/m^3$)	Exposure (μg/week)	Exposure (μg/day)
Lung (work)[a]	OSHA PEL; NIOSH REL	50	3000	429
Lung (work)	WHO	25	1500	214
Lung (home)[b]	EPA RfC	0.03	33.6	4.8
Skin (work)[c]	OSHA PEL; NIOSH REL	50	52	7.4

[a] Work exposure assumes 8 hours per day, 5 days per week, ventilation rate of 15 m^3 and no other mercury exposure

[b] Home exposure to ambient air assumes 24 hours per day, 7 days per week, and ventilation rate 20 m^3/day

[c] Skin exposure excludes respiration exposure (Hursh et al. 1989)

exposures (see Section 5.7). Children can be exposed to various forms of mercury in a variety of ways, including playing with unsecured elemental mercury, inhalation of mercury vapors via the religious or ethnic practices of their parents or unintentional spills of elemental mercury, oral ingestion of herbal or ethnic remedies or mercury-containing consumer products, consumption of methylmercury-contaminated fish and wildlife, and dermal or oral exposure to contaminated soils and sediments.

Mercury concentrations have been measured in cord blood in one study in the United States with levels that suggest prenatal exposure. Pitkin et al. (1976) measured concentrations of total mercury in cord blood samples from 100 maternal cord blood pairs from a population in rural Iowa. The mean cord blood total mercury concentration was 1.24 ppb, while the mean of the paired maternal blood samples was 1.01 ppb. More recently, Wheatley and Paradis (1995a, 1995b) reported on the analysis of 2,405 cord blood samples collected from Canadian aboriginal peoples over the last 20 years. Of these cord blood samples, 523 (21.8%) were found to have total mercury levels greater than 20 ppb, with the highest cord blood sample containing 224 ppb. These latter samples were from populations that routinely consumed fish and marine mammal tissues. Grandjean et al. (1997b) measured cord blood samples from 894 Faroe Islands children whose mothers consumed large amounts of fish and pilot whale meat. The methylmercury exposure in the Faroe Island population is mainly from eating pilot whale meat. The geometric mean concentration of total mercury in these cord blood samples was 22.9 ppb.

Concentrations of mercury have also been measured in breast milk from several populations in the United States as well as other countries (see Table 5-17). Breast milk concentrations have been reported for two U.S. populations; one in rural Iowa (Pitkin et al. 1976) and the other from Alaska (Galster 1976). Pitkin et al. (1976) reported a total mean mercury concentration in breast milk of 0.9±0.23 ppb (range, 0.8–1.6 ppb). The mean total mercury concentrations in the Alaskan populations were 3.3± 0.5 ppb for the urban population, 3.2±0.8 ppb for the interior population, and 7.6±2.7 ppb for the coastal population that consumed fish and marine mammals.

Total mercury concentrations in breast milk from other countries and exposure scenarios were 3.6±2.2 ppb for an urban population in Tokyo, Japan (Fujita and Takabatake 1977), 0.6±0.4 ppb for Swedish women that were fish consumers with 12 dental amalgams (Oskarsson et al. 1996), 0.2–6.3 ppb (range) for Swedish women that consumed fish (Skerfving 1988), and 9.5±5.5 ppb for an urban population of women in Madrid, Spain (Baluja et al. 1982) (Table 5-17). Some of the highest levels were reported in fish eaters, and about 20% of the total mercury content of the milk was methylmercury. The median and maximum mercury

concentrations in breast milk from women in the Faroe Islands, a population that consumes large quantities of fish and marine mammal tissue, were 2.45 and 8.7 ppb, respectively (Grandjean et al. 1995a). Breast milk mercury concentrations reported by these authors were significantly associated with mercury concentrations in cord blood and with the frequency of pilot whale dinners during pregnancy. These are relatively low values in contrast to the values reported in Minamata, Japan, for women who ate contaminated seafood in the Minamata episode, which resulted in total mercury concentrations in breast milk of 63 ppb (Fujita and Takabatake 1977), and in Iraq, where consumption of homemade bread prepared from methylmercury-contaminated wheat occurred, resulted in breast milk concentrations of up to 200 ppb (about 60%) methylmercury (Amin-Zaki et al. 1976; Bakir et al. 1973).

Children can be exposed to mercury by many of the same pathways as adults as discussed in Sections 5.4.4., 5.5, and 5.7. Children can receive mercury exposures from oral or dermal contact with mercury-contaminated soils and sediments or mercury-contaminated objects. Exposure analysis of individuals living near an abandoned mercury-contaminated industrial site suggested that children were exposed primarily via soil ingestion (Nublein et al. 1995). Little experimental information on the bioavailability of mercury via oral or dermal exposure was found relative to mercury or mercury compounds sorbed to contaminated soils and sediments (De Rosa et al. 1996). Paustenbach et al. (1997) noted that, due to the presence of mercury at a number of major contaminated sites in the United States, the bioavailability of inorganic mercury following ingestion has emerged as an important public health issue. Although precise estimates are not available, *in vivo* and *in vitro* estimates of the bioavailability of different inorganic mercury species in different matrices suggest that the bioavailability of these mercury species in soil is likely to be significantly less (on the order of 3 to 10 fold), than the bioavailability of mercuric chloride, the mercury species used to derive the toxicity criteria for inorganic mercury (Paustenbach et al. 1997). These authors suggest that site specific estimates of bioavailability be conducted of various mercury compounds because bioavailability can vary significantly with soil type, soil aging, the presence of co-contaminants and other factors. Canady et al. (1997) concluded that the “100% bioavailability assumption” for mercury-contaminated soils is excessively conservative. These authors note that various mercury compounds have distinctly different bioavailability. For example, mercuric chloride has been reported to be approximately 20–25% bioavailable in adult animals (Nielsen and Andersen 1990; Schoof and Nielsen 1997). Methylmercury is thought to be nearly completely absorbed (Aberg et al. 1969; Miettinen et al. 1971; Rice 1989a, 1989b). Mercuric nitrate was reported to be only 15% bioavailable in humans (Rahola et al. 1973) and elemental mercury is thought to be very poorly absorbed, although experimental evidence is lacking for the latter. Recently, Barnett et al. (1997) reported that analysis of mercury contaminated soil from the flood

plain of East Fork Poplar Creek in Oak Ridge, Tennessee, revealed the presence of submicron, crystalline mercuric sulfide (HgS) in the form of metacinnabar. The HgS formed in place after the deposition and burial of mercury-contaminated soils. The formation of HgS is significant for remediation efforts at the site because the toxicity, leachability, and volatility of mercury in soils are dependent on the solid phase speciation. Because local hydrogeochemical conditions are not unique, the formation of HgS at this site has implications to other environments and contaminated sites as well.

Children may be exposed to mercury vapors when they play with metallic mercury. Metallic mercury is a heavy, shiny, silver liquid and when spilled, forms little balls or beads which fascinate children. Children come in contact with metallic mercury when they trespass in abandoned warehouses, closed factories, or hazardous waste sites (ATSDR 1997; George et al. 1996). Children also have taken metallic mercury from school chemistry and physics laboratories and abandoned warehouses (ATSDR 1997). Broken thermometers and other mercury-containing instruments or equipment (fluorescent light bulbs, barometers, blood pressure measurement equipment, and light switches) used in the home and in some children's sneakers that light up are other sources of metallic mercury. Muhlendahl (1990) reported a case of chronic mercury intoxication in three children who were exposed to vapors from a broken thermometer. The maximum urinary concentrations reported by this author (8 months after the broken thermometer incident) were 250.5 µg/L for a 33-month-old girl, 266.3 µg/L for a 20-month-old girl, and 137.4 ppm for the 7-year-old brother 2 days after each patient received chelation therapy with DMPS (2,3-dimercaptopropan-1-sulphonate). Sometimes children find containers of metallic mercury which were disposed of improperly (ATSDR 1997), or adults intentionally or unintentionally bring home metallic mercury from work (Ehrenberg et al. 1991; Wendroff 1990). Metallic mercury evaporates to a greater extent as the air temperature increases; when it is not stored in a closed container, children may be exposed to mercury vapors (ATSDR 1997; Wendroff 1991).

Metallic mercury is traditionally used in some religious rituals or remedies, including religions such as Santeria (a Cuban-based religion that worships both African deities and Catholic saints), voodoo (a Haitian-based set of beliefs and secret rites), Palo Mayombe (a secret form of ancestor worship practiced mainly in the Caribbean), or Espiritismo (a spiritual belief system native to Puerto Rico) (Wendroff 1990). If these rituals or spiritual remedies containing mercury are used in the home, children may be exposed and the house may be contaminated with mercury (ATSDR 1997; Johnson [in press]; Wendroff 1990, 1991; Zayas and Ozuah 1996). Metallic mercury is sold under the name "azogue" (pronounced ah-SEW-gay) in stores (sometimes called botanicas) which specialize in religious items and ethnic remedies (Johnson [in press];

Wendroff 1990; Zayas and Ozuah 1996). Azogue may be recommended by family members, spiritualists, card readers, and santeros. Typically, azogue is carried on one's person in a sealed pouch, or it is ritually sprinkled in the home or car. Some store owners suggest mixing azogue in bath water or perfume. Some people place azogue in devotional candles. Because metallic mercury evaporates into the air, there is a potential health risk from exposure to mercury vapors in a room where the mercury is sprinkled or spilled onto the floor, put in candles, or where open containers of metallic mercury are present (ATSDR 1997; Wendroff 1990, 1991). Young children spend a lot of time crawling on the floor and carpeting, so they may be subject to a higher risk of exposure, especially when mercury is sprinkled on the floors or carpets.

Very small amounts of metallic mercury (i.e., a few drops) may raise air concentrations of mercury to levels that could be harmful to health (ATSDR 1997). Metallic mercury and its vapors are extremely difficult to remove from clothes, furniture, carpet, floors, walls, and other such items. The mercury contamination can remain for months or years, and may pose a significant health risk for people continually exposed (ATSDR 1997; Johnson [in press]; Wendroff 1990, 1991).

Another potential source of children’s exposure to metallic mercury is breakage or improper disposal of a variety of household products, including thermostats, fluorescent light bulbs, barometers, glass thermometers, and some blood pressure machines that contain metallic mercury (ATSDR 1997). These devices do not pose a health threat when the mercury is properly contained within the device. Should the mercury be released, however, the potential for mercury vapors to contaminate the air increases. The appropriate method for cleaning up a spill of a small amount of mercury is to clean it up manually, *without using a vacuum cleaner*, which can cause the mercury to evaporate more rapidly into the air, creating a greater risk of exposure (ATSDR 1997; Schwartz et al. 1992; Votaw and Zey 1991). Votaw and Zey 1991 reported mean mercury concentrations in air samples collected in a dental office were 8.5 μ/m^3 when a vacuum cleaner was not in use and concentrations rose to 69 μ/m^3 when a vacuum cleaner was in use. Special techniques are often needed to prevent mercury vapor from being generated in the cleanup process (Votaw and Zey 1991). The first consideration is to remove children from the area of the spill. The beads of metallic mercury should be cleaned up by carefully rolling them onto a sheet of paper or by drawing them up into an eye dropper. After the mercury has been collected, it should be put in a plastic bag or airtight container. The piece of paper or eye dropper used to remove the mercury should also be bagged and disposed of properly, according to guidance provided by the local health department. After the mercury has been removed, the room should be ventilated to the outside and closed off to the rest of the house. Electric fans should be used for a minimum of one hour to speed the ventilation process. If larger quantities of

metallic mercury are found in a container, make sure the container is airtight and call the local health department for disposal instructions. If the container of mercury is open without a lid, a piece of plastic wrap can be used to seal the container. If the larger amount is spilled, leave the area immediately and contact the local health department or fire department. Members of the general public should seek professional guidance on proper disposal procedures of mercury (ATSDR 1997).

Metallic mercury vapors are very toxic and are virtually odorless. Inhalation of mercury-laden dust, vapor, or mist should be avoided. Metallic mercury not should not come in contact with eyes, skin, or clothing. If children are exposed directly to metallic mercury, the contaminated body area should be thoroughly washed, and contaminated clothing should be removed and disposed of in a sealed plastic bag (ATSDR 1997). ATSDR and EPA recommend very strongly against the use of any uncontained metallic (liquid) mercury in homes, automobiles, day care centers, schools, offices, and other public buildings. If a child has metallic mercury on his or her clothing, skin, or hair, the fire department should be advised and the child should be properly decontaminated (ATSDR 1997).

Some Chinese herbal remedies for stomach disorders contain mercury (probably as mercury sulfide). If these herbal remedies are made into teas and are given to children, they increase the risk of harmful effects (Espinoza et al. 1995, 1996). Some remedies are in the form of herbal balls, which are aromatic, malleable, earth-toned, roughly spherical, hand-rolled mixtures of primarily herbs and honey. These herbal balls are used as a self-medication for a wide variety of conditions, including fever, rheumatism, apoplexy, and cataracts. Herbal balls similar to those analyzed by Espinoza et al. (1995, 1996) are readily available in specialty markets throughout the United States. Ingesting two herbal balls (the recommended adult dose per day) could theoretically provide a dose of up to 1,200 mg mercury; even if the mercury is in the form of mercuric sulfide, a relatively less bioavailable form, there is an increased risk of mercury entering the body. If a pregnant woman or nursing mother uses mercury-containing herbal remedies, she may also pass the mercury to her unborn child or nursing infant via breast milk. Herbal remedies that contain mercury should be stored so that children can not reach them to prevent accidental poisoning.

Consumers should check the ingredients of any prescription or non-prescription medicine. Hoet and Lison (1997) recently reported an unusual non-occupational source of mercury exposure in a woman who used prescription nasal drops over a long period of time that contained 300 mg/L (ppm) borate phenylmercury. Prescription medicines that contain mercury should be stored out of children’s reach to avoid accidental poisoning.

Children may be exposed to mercury during play at home or in school when using art supplies that contain colors from mercury compounds. Rastogi and Pritzi (1996) reported the migration of several toxic metals including mercury from crayons and artist watercolor paints (see Section 5.4). Migration of mercury from these art supply products occurred in 57% of the samples tested. The authors believe that children might be exposed not only to mercury, but to several other metals that can migrate from the paints. Grabo (1997) also reported that artists may be exposed to mercury because it is a main component in airbrush and brush painting pigments as well as a component of pastel chalks. Artist supplies that contain mercury should be stored out of children's reach to avoid accidental poisoning.

Infants and developing fetuses may be exposed to methylmercury if their mothers consume certain methylmercury-contaminated fish, shellfish, or wildlife species from contaminated waters prior to their pregnancy, during their pregnancy, or while nursing. Older children also may be exposed to methylmercury by eating contaminated fish and wildlife species. Certain states, Native American tribes, and U.S. Territories have issued fish and wildlife advisories for mercury in fresh water, estuarine, and saltwater fish and in freshwater turtles (see Section 5.7).

In a study of lactating women, Oskarsson et al. (1996) assessed the total and inorganic mercury content in breast milk and blood in relation to fish consumption and amalgam fillings (see Section 5.5). In breast milk samples collected 6 weeks after delivery, about half of the total mercury was inorganic and half was methylmercury, whereas in blood samples only 26% was inorganic and 74% was methylmercury. Exposure of the infant to mercury from breast milk was calculated to range up to 0.3 µg/kg/day, of which approximately one-half was inorganic mercury. This exposure corresponds to approximately one-half the tolerable daily intake of total mercury for adults recommended by WHO. The authors concluded that efforts should be made to decrease total mercury burden in women of reproductive age (Oskarsson et al. 1996).

Two-year-old children seem to be different in their weight-adjusted intake of methylmercury as shown by the results of the FDA Total Diet Study. Expressed on a per weight basis, methylmercury intake for all age groups except 2-year-old children was approximately 50 ng/kg/day (Clarkson 1990; Gunderson 1988). For 2-year-old children, the intake was estimated to be approximately 100 ng/kg/day (assuming 50% of the fish intake was due to fish caught locally) or about twice as much methylmercury intake per body weight as for other age groups. For additional details, see Section 5.5, General Population and Occupational Exposure.

Parental exposure can result in subsequent exposure to the developing child or embryo. Anttila and Sallmen (1995) report some epidemiologic data suggesting that paternal exposure to mercury is associated with an increase in spontaneous abortions. These authors also report that maternal exposure to mercury has not been has not been associated with an increased risk of abortion. Lauwerys et al. (1987) reported a case of mercury poisoning in a 3-month-old infant whose mother frequently used a skin lightening cream and soap containing inorganic mercury during pregnancy and the 1-month lactation period following birth. Prenatal and early postnatal exposure of infants to mercury from maternal use of these products is a source of particular concern (Lauwerys et al. 1987).

Data from the National Occupational Exposure Survey (NOES) conducted by NIOSH from 1983 to 1986, provides information on exposure to a variety of mercury compounds, with estimates of the total numbers of workers and the total number of female workers potentially exposed. As presented in Table 5-19, an estimated 50,468 women (33% of workers) were potentially exposed to mercury and various mercury compounds in occupational settings during 1983–1986 (RTECS 1998). More current estimates are not available for the number of women occupationally exposed to mercury in the United States or the percentage of women of reproductive age that may become pregnant or may breast-feed their infants while continuing to work in these occupational settings.

Mercury exposure also may result from the transport of mercury to a workers' home on contaminated clothing and shoes (ATSDR 1990; Hudson et al. 1987; Zirschky 1990). Increased exposure to mercury has been reported in children of workers who are occupationally exposed to the compound (Hudson et al. 1987). Hudson et al. 1987 investigated the exposure to mercury of children of workers in a thermometer manufacturing plant. These investigators reported that the median mercury concentrations in the homes was 0.25 µg/m^3 (range, 0.02–10 µg/m^3), and the levels of mercury in the urine of the children averaged 25 µg/L (ppb), about five times higher than that reported for the controls. While measurements of clothing contamination were not made, the authors noted that elevated mercury concentrations were found in places where work clothes were located and in some washing machines. The children at the highest risk are those whose parents work in facilities that use mercury, but where no protective uniforms or footgear are used. The mercury from these settings is thought to be transferred to the workers' homes on their clothing and shoes. Danzinger and Possick (1973) reported that mercury particles became embedded in the clothing of workers at a scientific glassware plant, especially in knitted fabrics. In an exposure study of families of workers at a chloralkali plant in Charleston, Tennessee, mercury levels in the air of the workers' homes averaged 0.92 µg/m^3 (ATSDR 1990). Although protective clothing was used, work gloves, clothes, and

boots which were soaked with mercury were taken home, exposing family members. Cases of mine workers' homes being contaminated have also been reported, although the authors did not address the impact of this contamination on the health of the family members (West and Lim 1968). Although prevention of this kind of employee transport of mercury to homes is preferred, cleaning homes of workers occupationally exposed to mercury can be effective in reducing exposure for family members (Zirschky 1990).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to mercury (Section 5.5), there are several groups within the general population with potentially high exposures (i.e., higher than background levels) to metallic mercury and various mercury compounds. Historically, populations that have been exposed to higher-than-normal background levels of mercury in the air, water, soil, and/or food have included populations near industrial discharges (e.g., Minamata and Niigata, Japan) and those who inadvertently consumed methylmercury-contaminated food (e.g., grain in Iraq) (WHO 1990, 1991). People living in proximity to former mercury production facilities or mines, secondary mercury production (recycling) facilities, chloralkali facilities, municipal and medical waste incinerators, other mercury-disposal or recycling facilities, or the 714 current or former NPL hazardous waste sites where mercury has been detected (HazDat 1998) are at risk of receiving potentially higher-than-normal background levels of exposure.

Populations with potentially high exposure include recreational and subsistence fishers and hunters, Native American populations who routinely consume larger amounts of locally caught fish than the general population or who consume marine mammals in their diet. Other populations with potential for higher than average exposures are individuals with large numbers of dental amalgams, those who use various consumer products containing mercury (i.e., skin lightening creams and soaps, ethnic remedies, or fingerpaints and make-up paints containing mercury or mercury compounds), and those living or working in buildings recently painted with mercury-containing latex paints or buildings where mercury has been intentionally or unintentionally spilled.

Individuals Living Near Mercury Production, Use, and Disposal Sites. Individuals in the general population living in the vicinity of former primary production or mining sites or current secondary production sites, chloralkali plants, pulp and paper mills, coal-fired power plants, facilities where mercury is released (e.g., municipal waste or medical waste incinerators or other waste disposal facilities), or hazardous

waste sites may be exposed to mercury through several exposure pathways, including inhalation, dermal, and oral exposures. For example, numerous studies have reported increased levels of mercury in air, water, soil, plants, and fish in areas surrounding industrial facilities involved in production or use of mercury (Harnly et al. 1997; Lodenius and Tulisalo 1984; Shaw et al. 1986; Yamaguchi et al. 1971). Significant concentrations of mercury have been detected in sewer overflows and urban runoff (Murphy and Carleo 1977). Thus, general population exposure to mercury may be higher in both industrial and urban areas. Mercury has been detected in various environmental media (air, surface water, groundwater, soil, sediment, and fish and wildlife samples) collected at some of the 714 NPL sites where it has been detected in some environmental media (HazDat 1998). Populations living near hazardous waste sites may be at risk for exposure to high levels of mercury as a result of mercury contamination of surface waters, groundwater, soils, or fish. However, the available data are insufficient to allow for the characterization of the sizes of these populations or the intake levels of mercury to which they are exposed. In 1996, however, De Rosa et al. (1996) reported than in terms of populations at risk, an estimated 41 million people in the United States live within a 4-mile radius of at least one of the 1,134 NPL sites, and 3,300 people live within a 1-mile radius of an NPL site. These authors also reported that metallic mercury was ranked third on the top 10 priority list of hazardous substances found at these NPL sites.

Adults may receive higher mercury exposures from dermal contact if they work with mercury-contaminated soils. Mercury has been detected in soil and sediment at 350 and 208 sites, respectively, of the 714 NPL sites where it has been detected in some environmental media (HazDat 1998). No experimental information on dermal exposure related to the bioavailability of mercury or mercury compounds sorbed to soils was found. However, Hursh et al. (1989) conducted a study to determine the role of dermal exposure in the uptake of mercury vapor from air. These authors estimated that during an 8-hour day, a person would absorb through the skin only 2.6% of the mercury vapor retained by the lungs exposed to the same atmosphere. These authors also noted that half of the dermal uptake is lost through normal shedding of the stratum corneum. Therefore, dermal uptake of mercury adsorbed to soil is likely to be minor compared to other exposure pathways. Recent information from Harnly et al. (1997) showed that urine mercury levels in a Native American population living near an inactive mercury mine in Clear Lake, California were comparable to background levels, indicating that soil and dust exposures were not substantially elevated in the resident population near the inactive site. However, the mean blood methylmercury level in residents of this same community that consumed fish from Clear Lake was 15.6±8.8 µg/L (ppb), which was more than 7 times higher than the mean blood level in individuals that did not consume fish from the lake (2 ppb).

In addition, adults may receive potentially higher oral exposures from ingestion of mercury-contaminated soils from their unwashed hands while working in mercury-contaminated areas. Bioavailability is an integral factor in the estimation of the internal dose (or dose at the target tissue) of the chemical. Like dermal absorption, gastrointestinal absorption of various forms of mercury is highly variable (see Section 2.3.1). The more lipid soluble organic mercury compounds (e.g., methylmercury) are almost completely absorbed, while the extremely insoluble metallic mercury is poorly absorbed through the gut. The bioavailability of mercury from soil is likely to vary, since mercury binds tightly to soil, especially to soils with high organic content. Therefore, the mercury soil concentration alone may not be indicative of the potential for human health hazard from contaminated soils, and site-specific evaluation of the bioavailability of the various forms of mercury at the site is essential. However, unless toxicokinetic studies that use soil samples from the specific site are available, it is difficult to speculate on how much mercury will be bioavailable at any particular site. Adults may also receive higher doses from routine consumption of mercury-contaminated home grown fruits and vegetables (Nublein et al. 1995), and from consumption of fish from local waters receiving runoff or leachate from a waste site. Harnly et al. (1997) studied the impact of inorganic mercury in soil and dust and organic mercury in fish on a Native American population living near an inactive mercury mine near Clear Lake, California. These authors reported average methylmercury blood levels of 15.6±7 µg/L (ppb) in individuals that consumed fish from Clear Lake, which was higher than blood levels reported for individuals that did not consume fish (2 ppb). A significant correlation of methylmercury blood levels and fish consumption was observed. Mercury has been detected in fish collected at 56 of the 714 NPL sites where it has been detected in some environmental media (HazDat 1998). Adults may also receive higher mercury exposures from routine consumption of mercury-contaminated groundwater if this is the primary drinking water supply. Mercury has been detected in groundwater samples collected at 395 of the 714 NPL sites where mercury has been detected in some environmental media (HazDat 1998).

Individuals living near municipal and medical waste incinerators, power plants fired by fossil fuels (particularly coal fired plants), or hazardous waste sites may inhale vapors or particulates contaminated with mercury from ambient outdoor air. Lipfert et al. (1996) evaluated the health risks of methylmercury from burning coal using a Monte Carlo model to simulate a “baseline” and a “worst case” scenario in which a population of 5,000 fish eaters in the upper midwestern United States derived the freshwater fish portion of their diet from local waters near a large, hypothetical coal-fired power plant. The population was characterized by distributions of body mass, half-life of methylmercury, and the ratios of blood to body burden and hair to blood methylmercury. Each person’s diet consisted of varying amounts of tuna fish,

freshwater sportfish, and marine fish and shellfish, the methylmercury content of which were characterized by national distribution statistics, as were the consumption rates for marine fish. The consumption rates for freshwater fish were specific to the region. The fish portion size was linked to body mass by a variable correlation. Each meal was assumed to be an independent sample, so that as metabolic equilibrium was approached, each person's body burden of methylmercury tended to approach the value corresponding to the mean methylmercury intake for the population. Predictions of methylmercury levels in hair by this model compared well with an observed distribution in 1,437 women. Two neurological end points were examined: adult paresthesia as related to methylmercury body burden and congenital neurological effects as associated with average concentrations of methylmercury in maternal hair during pregnancy. In the baseline exposure scenario, the source of the mercury in fish was background atmospheric deposition. In the worst-case scenario, local mercury deposition and concentrations in fish were roughly doubled to represent additional deposition from the hypothetical power plant. For both scenarios, the 99th percentile of methylmercury body burden was more than an order of magnitude below the lowest level at which increased transient paresthesia in adults was experienced in an acute methylmercury poisoning incident in Iraq. The authors concluded that neurological risks to adults from methylmercury resulting from atmospheric deposition are negligible. Based on three epidemiological studies of congenital neurological risks, they found that fetal effects appeared to be more critical, and that there is a smaller margin of safety for pregnant consumers of freshwater sportfish. However, there is still a considerable margin of safety, and uncertainties in the relationships between maternal hair mercury and actual fetal exposures may have overstated the fetal risk (Lipfert et al. 1996).

Recreational and Subsistence Fishers. Methylmercury concentrations in sport fish can be at least an order of magnitude higher than in commercial fish purchased in a supermarket (see Section 5.4.4). Therefore, recreational and subsistence fishers, including some Native American peoples who consume locally caught fish from mercury-contaminated waterbodies or consume long-lived predatory oceanic species such as shark and swordfish, can be exposed to higher mercury concentrations than individuals who consume similar amounts of commercially marketed fish from a variety of sources (Ebert et al. 1996; EPA 1995k). The exposure to mercury will also be higher among people who regularly eat fish and other seafood products, compared to those who only occasionally or never eat fish or other seafood products. This increased exposure has been demonstrated by blood mercury levels several times higher in people who regularly eat fish, compared to those who occasionally or never eat fish (Buzina et al. 1989; Cappon and Smith 1982; Oskarsson et al. 1996; Phelps et al. 1980; Svensson et al. 1995). In addition, the consumption of certain species of fish (e.g., shark and swordfish) is likely to contribute disproportionately to the observed

methylmercury body burden. Because mercury is associated primarily with muscle tissue in the body of a fish, rather than with fatty deposits, trimming and skinning of mercury-contaminated fish does not reduce the mercury content of the fillet portion, as is the case for PCBs, dioxins, and other organochlorine pesticides (Armbuster et al. 1988; Gutenmann and Lisk 1991).

Several recent studies have documented higher fish consumption rates among subsistence fishers, some of which are Native American populations. In 1990, there were an estimated 1,959,234 Native Americans in the United States, including 1,878,285 American Indians, 57,152 Eskimos, and 23,797 Aleuts (Paisano 1998). Approximately 218,320 Native Americans were living on ten reservations and tribal lands, and these people accounted for half of all Native Americans living on reservations. Therefore, approximately 440,000 Native Americans live on reservations. The median family income in 1990 for Native Americans was $21,750, about 65% of the $35,225 median income of all U.S. families. In addition 27% of all Native Americans are living in poverty, compared with 10% of the general population. In a study of 11 Alaskan communities, Nobmann et al. (1992) reported an average daily fish consumption rate of 109 g/day. This average consumption rate for subsistence fishers is more than 16.8 times the mean fish consumption rate of 6.5 g/day estimated for the general population (EPA 1995k). A recent study of fish consumption patterns among the Umatilla, Nez Perce, Yakama, and Warm Springs tribes of the Columbia River Basin in Washington and Oregon (CRITFC 1994) found that adults in these tribes consume an average of 59 g/day and that the 95th percentile of fishers consume 170 g/day of fish. The mean consumption rate for the four tribes is more than nine times the mean fish consumption rate estimated for the general population (EPA 1995k). Furthermore, the consumption rate for Native American children (5 years and younger) from these four tribes was 20 g/day (a rate over 3 times that for adults in the general population) (see Section 5.6).

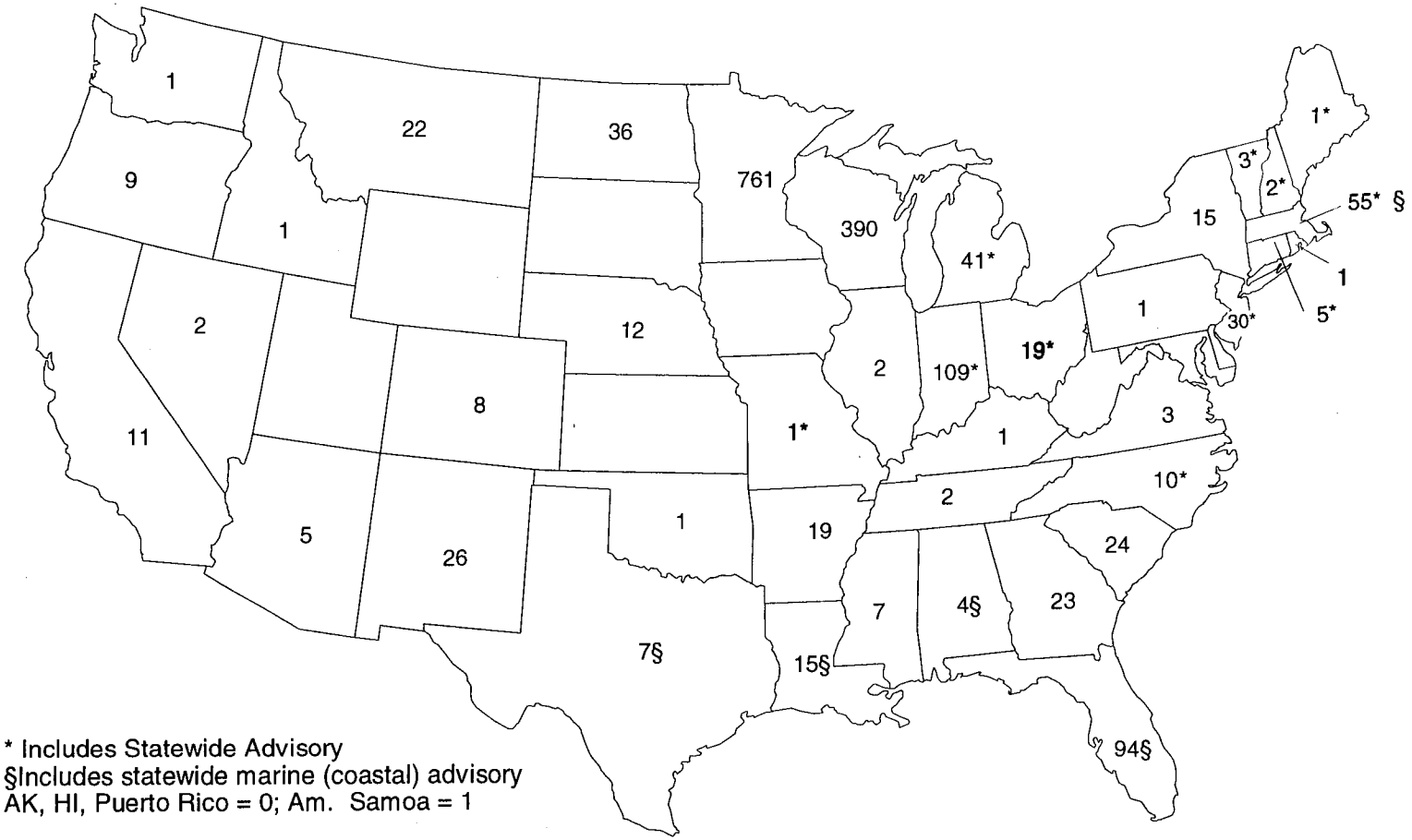
In order to reduce methylmercury exposure from consumption of mercury-contaminated fish and shellfish, consumption advisories are issued by states recommending that individuals restrict their consumption of specific fish and shellfish species from certain waterbodies where mercury concentrations in fish and shellfish tissues exceed the human health level of concern. This level of concern is set by individual state agencies, but several states use the FDA action level of 1 ppm to issue advisories recommending no consumption or restricting consumption of contaminated fish and shellfish from certain waterbody types (e.g., lakes and/or rivers). The FDA value was designed to protect consumers from the health risks associated with consumption of fish and shellfish that are shipped in interstate commerce and that are purchased in commercial markets. The FDA action level was not intended to be used as a criterion for the

protection of high-end fish consumers who routinely and repeatedly consume large quantities of fish from local bodies of water.

To address this concern, the EPA Office of Water issued guidance to states on sampling and analysis procedures to use in assessing the health risks from consuming locally caught fish and shellfish. The risk assessment method proposed by EPA was designed to assist states in developing fish consumption advisories for recreational and subsistence fishers, including pregnant women, nursing mothers, and children in these high-end consumption populations (EPA 1995k). Recreational and subsistence fishers consume larger quantities of fish and shellfish than the general population and frequently fish the same waterbodies routinely. Because of this, these populations are at greater risk of exposure to mercury and other chemical contaminants, if the waters they fish are contaminated. The EPA's Office of Water advises states to use a screening value of 0.6 ppm mercury (wet weight) in fillets for the general population as a criterion to evaluate their fishable waters (EPA 1995k). Currently, 1,782 advisories restricting the consumption of mercury-contaminated fish and shellfish are in effect in 41 states and one U.S. Territory (American Samoa) (EPA 1998b). The number of mercury advisories currently in effect in each state is shown in Figure 5-7. It should be noted that mercury is the chemical pollutant responsible in part for over 77% of the fish advisories issued in the United States (EPA 1998a). It is important to note that 11 states (Connecticut, Indiana, Maine, Massachusetts, Michigan, Missouri, New Hampshire, New Jersey, North Carolina, Ohio, and Vermont) currently have state-wide mercury advisories recommending that residents restrict consumption of locally caught freshwater fish. In addition, 5 states (Alabama, Florida, Louisiana, Massachusetts, and Texas) have issued statewide coastal mercury advisories for specific marine fish and shellfish species. In two states (Arizona and Minnesota), wildlife advisories recommending that residents restrict their consumption of freshwater turtles have been issued.

Subsistence Hunters. Native American populations, such as the Inuit of Alaska and other subsistence hunters (particularly those living in high latitude areas of the United States), may be exposed to mercury in wild game (e.g., seals, narwhal, walrus, and other game species or marine mammals). Mercury has been detected in liver, kidney, and muscle tissues of pilot whales, harp seals, narwhal, and walrus (Meador et al. 1993; Wagemann et al. 1995). Mean total mercury concentrations and methylmercury concentrations were highest in pilot whale liver tissue: 176 ppm (dry weight) and 8 ppm (dry weight), respectively. In fish, almost all of the mercury (>95%) body burden is methylmercury (Bloom 1992), but in marine mammals, the percentage of inorganic mercury is much higher, at least in liver tissue. For example, in Alaskan beluga whales, mean methylmercury levels were 0.788 ppm (μg/g wet weight), but mean total mercury levels were

Figure 5-7. Listing of Fish and Wildlife Consumption Advisories Issued for Mercury



* Includes Statewide Advisory
§Includes statewide marine (coastal) advisory
AK, HI, Puerto Rico = 0; Am. Samoa = 1

Source: EPA 1998

28 ppm (wet weight), in liver tissue (Becker et al. 1995). Similarly, in Alaskan ringed seal, mean methylmercury levels were 0.410 ppm (wet weight) and mean total mercury levels were 1.970 ppm (wet weight) in liver tissue. However, no information was available for methylmercury levels in muscle tissue from Alaskan mammals. An older report by Smith and Armstrong (1975) also examined total mercury and methylmercury levels in marine mammal livers eaten by native Inuit in the Northwest Territory of Canada. Smith and Armstrong (1975) reported total mercury concentrations of 143 and 26.2 ppm (wet weight) and mean methylmercury levels of 0.300 and 0.120 ppm (wet weight) in liver tissue of bearded seals sampled in 1973 and 1974, respectively. Smith and Armstrong (1975) also reported total mercury concentrations of 27.5 ppm (wet weight) (maximum, 184 ppm), and 0.72 ppm in liver and muscle tissue, respectively, and mean methylmercury levels of 0.96 and 0.83 ppm in liver and muscle tissue, respectively, of ringed seals sampled near Victoria Island in Canada's Northwest Territory. These authors also reported a mean total mercury concentration of 143 ppm and a mean methylmercury concentration of 0.30 ppm in liver tissue of bearded seals. The mean total mercury concentration in the muscle tissue of the bearded seals was 0.53 ppm (no methylmercury concentrations in muscle tissue were available for this species).

In Greenland, the percentage of total mercury that was methylmercury in seal muscle tissue was 57–86%; however, the concentration of total mercury was very low. Mercury concentrations in the blood of mothers and infants in Greenland were closely correlated with the amount of marine mammal meat the mothers consumed. Mercury concentrations in the blood of mothers eating primarily imported food ranged from 11.0 to 32.7 µg/L (ppb) and concentrations in the blood of their children ranged from 15.0 to 51.4 µg/L (ppb). In contrast, mercury concentrations in the blood of mothers who consumed primarily a local diet heavy in marine animals ranged from 16.4 to 44.6 µg/L (ppb) and concentrations in the blood of their children ranged from 27.5 to 140.0 µg/L (ppb) (Hansen 1991).

Native American populations that depend heavily on marine mammals are considered to be at higher risk than the general population. Wheatley and Paradis (1995a, 1995b) reported blood mercury levels in native peoples from 514 communities across Canada. Of these individuals, 23% had methylmercury blood levels >20 µg/L (the WHO assessment level), while 1.6% of these individuals had blood levels >100 µg/L (the WHO benchmark for at-risk populations). Native American populations in the western Arctic (Alaska) may be at similar risk as a result of their consumption of marine mammals, although no recent information on methylmercury concentrations in blood, hair or urine for these populations was located. In Alaskan Inuit women that consume marine mammal tissue, Galster (1976) reported higher total mercury levels in breast

milk of women living in coastal areas (7.6±2.7 ppb) than in breast milk of Inuit women living in the interior (3.2±0.8 ppb) or in urban areas (3.3±0.5 ppb). In addition, mercury red blood cell concentrations were also higher in Inuit women living in coastal areas (33.5±5.1 ppb), as compared to those living in the interior (22.6±3.0 ppb) or in urban areas (8.9±0.9 ppb). Higher mercury levels in coastal populations were attributed to higher consumption of seal meat and oil and marine fish (Galster 1976). By analogy to the Canadian populations of native peoples (Wheatley and Paradis 1995a, 1995b), it is anticipated that methylmercury concentrations in these tissues are likely to be higher among individuals who consume large quantities of marine mammal species with high concentrations of methylmercury (as well as inorganic mercury) in their tissues than among members of the general population. In a study of subsistence economies in the State of Alaska, Wolfe and Walker (1987) reported that total annual per capita harvest of wild game species (including land mammals, marine mammals, and fish) ranged from 10 to 1,498 pounds (median harvest of 252 pounds), compared to 222 pounds of meat, fish, and poultry (combined) consumed each year per individual in the western United States. The wild game harvest in 84% of the 98 Alaskan subsistence communities surveyed was at least half or greater than the 222 pounds consumed in the western United States. Because hunters often share wild game they harvest with other family members, the amount harvested may not represent the actual amount consumed (Egeland et al. 1998). The average daily per capita consumption was estimated to be 0.67 pounds of fish and 0.23 pounds of land mammals based on all 98 communities, and 0.2 pounds of marine mammals based on the 41 coastal communities surveyed. Marine mammals consumed in these communities included seal, walrus, and whales. Subsistence hunters and their families are a population at potentially higher risk of mercury exposure, if the wild game species they consume are contaminated with high concentrations of inorganic and methylmercury. Although the existence of larger amounts of mercury in subsistence diets does give cause for concern, the available Alaskan data do not support the conclusion that current exposures are a serious problem for Alaskan subsistence hunters (Egeland et al. 1998).

Individuals with Large Numbers of Dental Amalgams. Individuals with dental amalgams have greater exposure to elemental mercury than members of the general population that do not have dental amalgams. Richardson (1995) computed a release rate per filled tooth surface of 0.73 µg/day-surface, with a standard deviation of 0.3 µg/day-surface and a “stimulation magnification factor” of 5.3, based on a weighed average enhancement of mercury vapor concentration following chewing, eating, or tooth brushing

reported in three amalgam studies. Patterson et al. (1985) measured elemental mercury in exhaled breath, and levels of mercury ranging from 0.0001 to 62 ng/L (ppb) (mean, 0.0082 µg/L [ppb]) were detected in 167 persons with dental restorations, compared to 0.000008–0.0001 µg/L (ppb) (mean, 0.00006 µg/L [ppb]) in 5 persons with no amalgams; however, these values were measured after the people had brushed their teeth. Jokstad et al. 1992 reported that mercury urine concentrations increased with increasing number of amalgams. Individuals with 36 to 39 dental amalgams had mercury urine levels of 6 ppb compared to 1.2 ppb in individuals without amalgams. Mercury concentrations in whole blood were also higher in persons who ate no fish, but had >6 dental amalgam fillings (mean, 1.047±0.797 µg/L [ppb] as compared to persons who did not eat fish and had no dental amalgams (0.2±0.4 µg/L [ppb]) (Schweinberg 1994). Individuals who have large numbers of dental amalgams installed or replaced at one time are likely to exhibit transient elevated blood and urine mercury levels (PHS 1995).

Individuals Exposed to Consumer Products and Medicinal Products Containing Mercury. Individual who use various consumer products containing mercury (i.e., medicinal herbal remedies, skin lightening creams and soaps, laxatives, tattoo dyes, fingerpaints, and make-up paints) are also exposed to higher mercury levels than the general population (Barr et al. 1973; Dyall-Smith and Scurry 1990; Espinoza et al. 1995; Geffner and Sandler 1980; Lauwerys et al. 1987; Rastogi 1992; Wendroff 1990). Metallic mercury has been used by Mexican American and Asian populations in traditional remedies for a variety of medical conditions, including chronic stomach disorders. Several papers have been published related to the use of metallic mercury as a folk remedy (ATSDR 1992, 1997; Department of Health 1997; Geffner and Sandler 1980; Hartman 1995; Johnson [in press]; Trotter 1985; Wendroff 1990, 1991; Zayas and Ozuah 1996). Some Mexican-Americans believe that disorders of the alimentary tract may be caused by a bolus of food adhering to the stomach wall, a condition known as *empacho*. Geffner and Sandler (1980) reported cases of two young patients with acute gastroenteritis who received traditional remedies of oral administration of metallic mercury, presumably to dislodge the bolus. Both patients were successfully treated and released from the hospital after 2 and 10 days of treatment, respectively. Trotter (1985) reported that metallic mercury known as *azogue* is in common use in New Mexico and the bordering areas for treating this gastrointestinal condition, *empacho*. Metallic mercury was also implicated in two cases of mercury poisoning caused by the dermal application of an over-the-counter antilice product (Bourgeois et al. 1986). Wands et al. (1974) reported the deaths of two individuals due to the excessive use of a laxative

preparation containing mercurous chloride (calomel). Espinoza et al. (1995) reported that while examining imported Chinese herbal balls for the presence of products from endangered species, the authors detected potentially toxic levels of mercury and arsenic in certain herbal ball preparations. Herbal balls are aromatic, malleable, earth-toned, roughly spherical, hand-rolled mixtures of primarily herbs and honey. These herbal balls are used as a self-medication for a wide variety of conditions, including fever, rheumatism, apoplexy, and cataracts. Herbal balls similar to those analyzed are readily available in specialty markets throughout the United States. Mercury (probably mercury sulfide) was detected in 8 of the 9 herbal balls tested. The recommended adult dose for the herbal balls is two per day. Ingesting two herbal balls could theoretically provide a dose of up to 1,200 mg of mercury. Perharic et al. (1994) reported poisonings resulting from exposure to traditional remedies and food supplements reported to the National Poisons Unit in London, England. From 1989 to 1991, metallic mercury was implicated in several poisonings following exposure to Asian medicines. The issuance of informational notices by health departments cautioning members of these subpopulation about the toxic properties of mercury may be appropriate.

Mercuric sulfide, or cinnabar, was reported to be used in tattooing dyes to produce a red pigmentation (Bagley et al. 1987; Biro and Klein 1967). An analysis of finger paints and make-up paints manufactured in Europe showed that they all contained less than 1 ppm mercury (Rastogi 1992). The author did not discuss whether these products are available in the United States. While some of medicinal and pharmaceutical uses of mercury compounds have been replaced in recent years, individuals in some ethnic or religious groups may still use mercury in various traditional remedies, ceremonies, and rituals.

Individuals that Use Mercury in Religious Ceremonies and/or Ethnic Practices or Live in Dwellings where Intentional or Unintentional Elemental Mercury Spills have Occurred.

Metallic mercury has been used in Latin American and Caribbean communities as part of certain religious practices (e.g., Voodoo, Santeria, and Espiritismo) predominantly in domestic settings (Wendroff 1990). Metallic mercury is sold in shops called botanicas (sometimes under the name *azogue)* which stock medicinal plants, magical medicines, incense, candles, and perfumes. Botanicas typically dispense mercury in gelatin capsules or, sometimes, in small glass vials. Some practices involve sprinkling metallic mercury on the floor of the dwelling or of a car, mixing elemental mercury with soap and water to wash the floor, or placing it in an open container to rid the house of evil spirits. Other practices involve carrying a small amount of mercury in a vial on the person or mixing mercury in bath water or perfumed soaps, devotional

candles, ammonia, or camphor. Any of these practices can liberate mercury vapor into the room air exposing the occupants to unnecessarily elevated levels of mercury vapors (ATSDR 1997; Wendroff 1990, 1991). The issuance of cautionary notices by health departments to members of these user populations may be appropriate. While some medicinal and pharmaceutical uses of mercury compounds have been replaced in recent years, individuals in some religious and ethnic groups may still use mercury in various rituals. This use of mercury can contaminate the dwelling if the mercury is not removed from flooring, carpeting, and woodwork in an appropriate manner.

Individuals Living in Homes Where Mercury-containing Latex Paints Have Been Used. Prior to 1991, phenylmercuric compounds were used as biocides in 25–30% of interior and exterior latex paints; however, this use of mercury was voluntarily discontinued for interior paint in 1990 and for exterior paint in 1991 (Hefflin et al. 1993; Reese 1990). This use of phenylmercury resulted in the exposure of house painters and residents to elemental mercury vapors in homes where interior or exterior latex paint was applied. The concentration of mercury in interior paints was less than 200 ppm; however, the atmospheric concentrations of elemental mercury vapor were found to be as high as 200 µg/m^3 less than 6 hours after painting, 10 µg/m^3 at 24 hours, and 6 µg/m^3 after 1 month. Although the use of mercury biocides in latex paint has been discontinued, it is possible that people who use old latex paint in their homes will be exposed to mercury for a considerable time (Blondell and Knott 1993). Furthermore, although phenylmercury use in exterior latex paints was discontinued in 1991, paint companies were allowed to continue to produce and sell paint containing phenylmercury until the existing stocks of phenylmercury were exhausted. Paint produced after 1990 containing phenylmercury must be so labeled. Exterior latex paints may have contained phenylmercury at concentrations of up to 1,500 ppm, and their use has been shown to result in elevated mercury levels in painters (see Section 5.5) (Hefflin et al. 1993). However, each year many homeowners (66%) repaint their own homes, rather than employing professional painters; therefore, these individuals may also be exposed (Hefflin et al. 1993). In addition, consumers can mistakenly use exterior paints indoors, which may produce higher exposures to mercury than when the paints are used outdoors. Blondell and Knott (1993) estimated that approximately 13 million people could be exposed to mercury through painting, assuming the interior of houses were painted once every 5 years, that 78% of the interior paint used is latex, and that one-third of the interior latex paint contained mercury. These authors emphasize that key populations at risk include the painters, residents in the painted homes and children living in those homes.

5.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of mercury is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of mercury.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of metallic mercury and its inorganic and organic compounds have been well characterized to permit estimation of their environmental fate (Lewis 1993; Merck 1989; NFPA 1994; Osol 1980; Spencer and Voigt 1968; Verschueren 1983; Weast 1988; Weiss 1986). Most values are available for the log K_{ow}, log K_{oc}, Henry's law constant, vapor pressure, and solubility in water. Experimental data exist that allow characterization of the environmental fate of metallic mercury and inorganic and organic mercury compounds in a variety of environmental media.

Production, Import/Export, Use, Release, and Disposal. Information on mercury production, import/export, and use are well documented (Blayney et al. 1997; Drake 1981; EPA 1997a; Hefflin et al. 1993; IARC 1993; Jasinski 1993; Reese 1990; Reiber and Harris 1994; Toribara et al. 1997; USGS 1997).

Information on disposal methods and recycling of mercury and mercury containing wastes are available (Carrico 1985; DOI 1989; Jasinski 1993; TRI96 1998).

One area that requires additional study is the use of elemental mercury by members of specific religious or ethnic groups in their ceremonies, rituals, and practices so an assessment of the magnitude of these activities can be made. In addition, information on how mercury is used in these ceremonies and rituals, as well as the methods of mercury disposal used, would be helpful in assessing the potential pathways for human exposure and environmental releases.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1996, became available in May 1998. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Mercury released to the atmosphere may be transported long distances before being removed by wet or dry deposition. Residence time in the atmosphere has been estimated to range from 60–90 days to 0.3–2 years (EPA 1984b; Glass et al. 1991). Volatile forms of mercury released in water or soil can enter the atmosphere, but most mercury is adsorbed to soil and sediment (EPA 1984b; Meili et al. 1991). Sorbed mercury may be reduced to elemental mercury or bioconverted to volatile organic forms (EPA 1984b). The major transport and transformation processes involved in the environmental fate of mercury have been fairly well defined; the most important fate process for human exposure, bioaccumulation of methylmercury in aquatic food chains is also well defined (Callahan et al. 1979; EPA 1984b; Stein et al. 1996). Additional information on mercury transport and flux in waterbodies would be helpful.

Bioavailability from Environmental Media. Metallic mercury vapors in the air are readily absorbed through the lungs following inhalation exposure, while inorganic and organic mercury compounds are poorly absorbed via this route (Berlin et al. 1969). Gastrointestinal (GI) absorption of methylmercury is nearly complete, while GI absorption of inorganic mercury is low (typically <10%) (Clarkson 1989; Friberg and Nordberg 1973). Metallic mercury vapor can be absorbed following dermal exposure; however, dermal absorption of the vapor accounts for a much smaller percentage (2.6% of the total absorbed through the lungs) than absorption through the inhalation route (Hursh et al. 1989). Inorganic mercury salts and organomercury compounds can also be dermally absorbed to some extent (Blayney et al. 1997; Junghaus

1983; Schamberg et al. 1918; Toribara et al. 1997). Data are needed regarding the bioavailability of elemental, inorganic, and organic mercury forms from contaminated surface water, groundwater, soil, or plant material. Data are also needed regarding the bioavailability of mercuric chloride in air because of the possibility of inhalation of volatilized mercuric chloride near emission sources. Additional data on the bioavailability of elemental mercury, inorganic mercury compounds, and organic mercury compounds (specifically, methylmercury) in soil would also be useful in assessing the risks from dermal and oral exposures at mining, industrial, or hazardous waste sites.

Food Chain Bioaccumulation. Mercury is known to bioconcentrate in aquatic organisms and biomagnify in aquatic food chains (ASTER 1997; EPA 1984b; Jackson 1991; Kohler et al. 1990; Mason et al. 1995, 1996; Porcella 1994; Watras and Bloom 1992). While bioconcentration in the aquatic food chain is well studied, little is known about the bioaccumulation potential for terrestrial food chains, although it appears to be smaller than in aquatic systems (Lindqvist 1991a). Additional information on the potential for terrestrial food chain biomagnification would be useful in light of the binding of mercury to organic matter in soils and sediment. Information on foliar uptake of mercury and of plant/mercury chemistry is needed to determine whether plants convert elemental or divalent mercury into other forms of mercury that are more readily bioaccumulated and whether plants are able to emit these different forms to the air. Additional information is also needed to improve biotransfer factors for mercury from soil to plants to animals.

Exposure Levels in Environmental Media. Environmental monitoring data are available for mercury in ambient air, surface water, groundwater, drinking water, soils, sediments, and foodstuffs (EPA 1984b, 1985; Glass et al. 1990; Lindqvist 1994); however, additional monitoring data on mercury levels in all environmental media, particularly drinking water, would be helpful in determining current exposure levels. Estimates of human intake from inhalation of ambient air and ingestion of contaminated foods and drinking water are available (Burger et al. 1992), although the estimates may be based on specific intake scenarios (e.g., information is most extensive for fish and other seafood products). Better estimates of fish consumption rates for high-end consumers (subsistence fishers) and recreational fishers is needed, as is information on fish-specific consumption rates by these populations. Additional information on the levels of mercury in foods other than fish and seafood would be very useful in determining total dietary intakes. Additional research is needed to characterize mercury exposures via consumption of marine mammal species. Available data indicate that the ratio of methylmercury to total mercury varies within tissues, and that only a small portion of mercury is methylated in the marine mammal's liver. Also, other trace metal constituents of marine mammal tissues such as selenium, cadmium, and other metals may interact with and

influence the bioavailability of mercury. Additional studies are needed in order to understand why the relatively high concentrations of mercury measured in marine mammal tissues do not appear to result in elevation of hair mercury levels among Alaskan natives that consume marine mammal tissues.

Reliable monitoring data for the levels of mercury in contaminated media at hazardous waste sites are needed so that the information obtained on levels of mercury in the environment can be used in combination with the known body burden of mercury to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Mercury has been measured in human blood, hair, breast milk, urine, feces, and saliva (Bakir et al. 1973; EPA 1984b; Fujita and Takabatake 1977; Galster 1976; Oskarsson et al. 1996; Pitkin et al. 1976; Wheatley and Paradis 1995a, 1995b; WHO 1990). However, current information on mercury levels in blood, hair, breast milk, and urine of members of the general U.S. population are almost entirely lacking. Data are needed for the general population that measure the levels of mercury in blood, hair, breast milk, and urine derived from dietary exposures (such as fish consumption) versus mercury derived from dental amalgams in order to obtain additional information about the importance of each of these exposure pathways to resulting mercury body burden. Additional information on mercury levels in urine of persons with varying numbers of amalgam surfaces as well as in persons that have had amalgam fillings removed or replaced would be useful in evaluating mercury exposure form this source. Data are available for some Native American populations (Galster 1976) and several foreign populations that consume large amounts of locally caught fish and wildlife (Airey 1983b; Fleming et al. 1995; Lasora and Citterman 1991). The most common method of assessing human exposure in the workplace involves the measurement of mercury in urine (Baser and Marion 1990; Bell et al. 1973; Lindstedt et al. 1979; Roels et al. 1987; Rosenman et al. 1986). Urine mercury levels have been correlated with ambient air exposure levels, particularly to mercury vapor. A longitudinal epidemiological study that tracks individual exposure levels to metallic mercury vapors in occupational settings (chloralkali industry workers, fluorescent lightbulb manufacturers, or other mercury utilizing industries) on a daily basis and associated these exposure levels with weekly urine and blood samples for a period of 1–2 years is needed. Neurobehavioral testing should also be conducted of these workers at 6-month intervals. Workers new to these industries would make the best subjects since they could provide pre-exposure blood and urine levels as a point of reference. Information is available on populations living near former production sites or hazardous waste sites (Harnly et al. 1997; Nublein et al. 1995; Reif et al. 1993; Shaw et al. 1986). Additional information on the biological monitoring of populations living in the vicinity of hazardous waste

sites would be helpful in estimating exposure of these populations to mercury compounds. This information is useful for assessing the need to conduct health studies on these populations.

Exposures of Children. Children are exposed to mercury by a variety of exposure pathways depending on their age. The most important pathways appear to be via inhalation of metallic mercury vapors, intake of inorganic mercury associated with dental amalgams in children up to 18 years old, and ingestion of methylmercury in foods primarily fish and shellfish. These are the same important pathways of exposure for adults as well. Infants can also be exposed to mercury from mother's milk. More data are needed on the levels of mercury exposure in nursing women from inhalation of metallic mercury in occupational or domestic situations, including religious and ethnic uses (ATSDR 1997; Johnson [in press]; Wendroff 1990, 1991; Zayas and Ozuah 1996); from use of commercial or hobby arts and crafts (Grabo 1997; Rastogi and Pritzi 1996); from mercury-containing herbal remedies, cosmetics, and prescription drugs (Al-Saleh and Al-Doush 1997; Barr et al. 1973; Dyall-Smith and Scurry 1990; Espinoza 1995, 1996; Lauwerys et al. 1987; Perharic et al. 1994); and from consumption of mercury-contaminated fish and wildlife, including marine mammals (CRITFC 1994; Egeland et al. 1998; Oskarsson et al. 1996). Exposure and body burden studies especially related to consumption of freshwater fish in the U.S. populations are needed to determine exposure levels, particularly in the children of recreational and subsistence fishers. Individual members of freshwater sport fish species in the Northeastern United States have been found to have tissue concentrations as high as 8.94 ppm mercury, while some species have mean tissue concentrations as high as 0.77 ppm (NESCAUM 1998). Exposure and body burden studies are also needed in Alaskan populations of subsistence hunters that consume large amounts of marine mammal tissues. Existing data on levels of mercury in breast milk in Alaskan women (Galster 1976) are dated and may not reflect either current levels of mercury contamination in fish and wildlife or dietary habits of Inuit or other subsistence fishing/hunting populations.

A unique exposure pathway that has received little research attention is the exposure to children from religious and ethnic uses in homes and cars or in remedies containing metallic mercury (ATSDR 1997; Johnson [in press]; Wendroff 1990, 1991). In some religious practices of Latin American or Caribbean origin, there are traditional rituals or remedies that involve mercury. These include intentional sprinkling of liquid elemental mercury on the floor, burning candles made with mercury, using mercury in baths, adding it to perfume, or wearing small containers of mercury around the neck for good luck. There is an urgent need to obtain information on the levels of exposure from these practices to determine if children or adults are at risk. Mercury vapor concentrations may be much higher after use during the winter months when the heat is

turned on and the windows are closed, so data that reflect a variety of possible exposure scenarios are also needed.

Results of the Total Diet Study conducted by the FDA suggest that two-year-old children differ in their weight-adjusted intake of mercury, based on the assumption that 50% of the fish consumed were locally caught species (Clarkson 1990; Gunderson 1988). Additional information on weight adjusted intakes would be helpful for the general population, and particularly in determining the health risks for young children in Native American populations. Children in these populations may consume relatively large quantities of locally caught fish as part of their traditional ceremonial practices (CRITFC 1994) or may consume large quantities of marine mammal tissues (blubber, muscle, and organ meats) if they are in subsistence fishing or hunting populations.

One childhood-specific means of decreasing exposure scenarios for children is through better education of school age children and their parents on the health risks particularly of metallic mercury exposure from accidental spillage, intentional uses, or from improper industrial exposures.

Exposure Registries. New York State has instituted a Heavy Metals Registry that monitors occupational exposure to heavy metals, including mercury. Cases are reported when mercury exposure is equal to or exceeds 50 µg/L (ppb) in blood or 20 µg/L (ppb) in urine. Between 1982 and 1986, 1,000 cases of mercury exposure were reported and linked to 47 companies. Most exposures (494 cases) occurred in workers in the alkali and chlorine industry, where mercury is used as a cathode because exposure occurs when the cells are opened; the median blood mercury concentration was 76 µg/L (ppb) (maximum concentration 916 µg/L [ppb]). The second most frequent exposure category (213 cases) was the manufacture of industrial instruments, such as the manual assembly and fabrication of thermometers; median blood mercury concentration was 145 µg/L (ppb) and the maximum concentration was 889 µg/L (ppb) (Baser and Marion 1990).

This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.8.2 Ongoing Studies

A search of Federal Research in Progress (FEDRIP 1998) identified numerous research studies that are currently being conducted that may fill some of the data needs discussed in Section 5.8.1. Ongoing studies and long-term research concerning occupational or general population exposures to mercury and studies that address the issue of the religious and ethnic uses of elemental mercury are presented in Table 5-22.

Table 5-22. Ongoing Research Relevant to Human Exposure to Mercury

Investigator	Affiliation	Research description	Sponsor
Ford, TE	Harvard School of Public Health Boston, MA	Assessment of metal contamination and ecological implications	National Institute of Environmental Health Sciences
Myers, GJ	University of Rochester School of Medicine Rochester, NY	Child development following prenatal methylmercury exposure via fish diet	National Institute of Environmental Health Sciences
Clarkson, T	University of Rochester School of Medicine Rochester, NY	Health hazards of methylmercury	National Institute of Environmental Health Sciences
Pepper, IL	University of Arizona Tucson, AZ	Biodegradation within metal/organic contaminated soils	National Institute of Environmental Health Sciences
Fernando, Q	University of Arizona Tucson, AZ	Determination of toxic metal species with high energy ion beams	National Institute of Environmental Health Sciences
Schell, LM	State University of New York at Albany Rensselaer, NY	PCBs and well being of Mohawk children and youth--growth, development, cognition	National Institute of Environmental Health Sciences
Woods, JS	University of Washington Seattle, WA	Porphyrin profiles as biomarkers of trace metal exposure and toxicity	National Institute of Environmental Health Sciences
Janoff, EE	University of Washington Seattle, WA	Influence of dental amalgams on mercury and antibiotic resistant bacteria	National Institute of Dental Research
Owens, M	Sciences International Corporation McLean, VA	Dental amalgam study	National Institute of Dental Research
De Rouen, A	University of Washington Seattle, WA	Casa Pia study of dental amalgams in children	National Institute of Dental Research
Crawford, SL	New England Research Institutes, Inc. Watertown, MA	Health effects of dental amalgams in children	National Institute of Dental Research

Table 5-22. Ongoing Research on Environmental Exposure to Mercury (cont.)

Investigator	Affiliation	Research description	Sponsor
Echeverria, D	Battelle Centers Public Health Research and Evaluation Seattle, WA	Neurologic effects of metallic mercury exposure in dental personnel	National Institute of Dental Research
Factor-Litvak, P	Columbia University New York, NY	Dental amalgams and neuropsychological function	National Institute of Dental Research
Barkay, T	Environmental Protection Agency Gulf Breeze, FL	Bioremediation of mercury in aquatic systems	US Department of Energy, Environmental Restoration and Waste Management
Lindberg, SE	Oak Ridge National Laboratory Environmental Sciences Division. Oak Ridge, TN	Atmosphere canopy interactions	US Department of Energy, Energy Research
Miller, JR Douglas, J	Indiana University Indianapolis, IN	Collaborative research: Transport and fate of mercury within the Carson River Valley	National Science Foundation, Division of Earth Sciences
Warwick, JJ Lechler, P Douglas, J	University of Nevada Reno, NV	Collaborative research: Transport and fate of mercury within the Carson River Valley	National Science Foundation, Division of Earth Sciences
Mason, RP Baier, RW	University of Maryland Solomons, MD	Abiotic and biotic mechanisms for mercury reduction in marine waters	National Science Foundation, Division of Ocean Sciences
Mason, RP Baier, RW	University of Maryland Solomons, MD	Biogeochemical cycling and air-sea exchange of mercury in the south Atlantic	National Science Foundation, Division of Ocean Sciences
Fitzgerald, WF Baier, RW	University of Connecticut Marine Sciences Storrs, CT	Biogeochemical cycling and air-sea exchange of mercury in the equatorial and south Atlantic	National Science Foundation, Division of Ocean Sciences
Lyons, WB Cameron, M	University of Alabama Tuscaloosa, AL	Collaborative research: Mercury biogeochemistry in a semi-arid aquatic ecosystem: Processes controlling	National Science Foundation, Division of Earth Sciences

Table 5-22. Ongoing Research on Environmental Exposure to Mercury (cont.)

Investigator	Affiliation	Research description	Sponsor
Warwick, JJ Cameron, M	University of Nevada Reno, NV	Collaborative research: Mercury biogeochemistry in a semi-arid aquatic ecosystem: Processes controlling	National Science Foundation, Division of Earth Sciences
Hines, ME Cameron, M	University of New Hampshire Dept. of Biological Sciences Anchorage, AK	Collaborative research: Mercury biogeochemistry in a semi-arid aquatic ecosystem-Processes controlling	National Science Foundation, Division of Earth Sciences
Krabbenhoft, DP		Mercury accumulation, pathways, and processes	Department of Interior, US Geological Survey Water Resources Division.
Lent, RM		Chronology of mercury loading to Devils Lake, North Dakota, inferred from sediment core data	Department. of Interior, US Geological Survey Water Resources Division. North Dakota
Bianco, V Wendroff, A	Puerto Rican Family Institute, Queens, NY	Magico-religious mercury use in Hispanic communities	EPA/Office of Environmental Justice
Markowitz, M Ozuah, P	Montefiore Medical Center, Bronx, NY	Urinary levels of mercury in children exposed to mercury (background levels and from magico-religious exposures)	New York City Department of Health/ New York City Department of Mental Health
Moomey, M Hryhorczuk, D	Illinois Department of Public Health and Great Lakes Center for Occupational and Environmental Safety and Health	Identification of which ritual mercury uses result in the greatest exposure	EPA/Office of Environmental Justice

Source: FEDRIP 1998

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring mercury, its metabolites, and other biomarkers of exposure to and effects of mercury. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

The analysis of metals in biological and environmental samples is complicated by the different organic and inorganic forms of the metal that may be present. For mercury, this complication is usually overcome by reducing all the mercury in the sample to its elemental state prior to analysis; this solution is not appropriate when information about the individual mercury species is desired. Mercury has an additional problem of being relatively volatile and, therefore, easily lost during sample preparation and analysis. In spite of these complications, several methods have been developed for determining trace amounts of mercury in biological and environmental samples, even in complex media. Careful attention must be paid to inadvertent contamination of the sample with mercury, especially when determining trace concentrations. Labware (glass or Teflon) should be thoroughly cleaned and acid-leached before being used for trace-level analysis. It has been shown that final soaking of laboratory ware, particularly Teflon, in hot (70 EC) 1% HCL removes any traces of oxidizing compounds (e.g., chlorine) that may subsequently destroy methylmercury in solution (Horvat 1996). Appropriate method blanks must be included.

Attention must be paid also to sample preservation to avoid perturbing the distribution of mercury compounds in the sample (Horvat 1996). The preservation of aqueous samples is often accomplished using acidification. However, suspended matter must be removed prior to acidification and dimethylmercury and Hg(0) have to be removed or else conversion of these species into methylmercury and mercury(II) can occur (Horvat 1996). For solid matrices, the preservation method of choice is freezing (Bloom 1993). Freezing preserves all major mercury species indefinitely, although coagulation will occur for sediments thus making it difficult to obtain representative subsamples of the sediment for analysis. For most metals, such storage

issues would be solved by drying the samples first, but for mercury, especially methylmercury, there is a risk of losses from volatilization. Tissue samples may be freeze-dried without loss of methylmercury. Repeated freezing and thawing of wet, biological samples can also cause loss of methylmercury (Horvat and Byrne 1992) but such degradations are dependant on the matrix.

Numerous standard or certified reference materials exist for verifying the reliability of new or modified methods, especially for total mercury; standard reference materials for individual organomercury species can be more difficult to obtain. The existing methods for determining mercury in biological and environmental matrices are described more fully in the following sections.

6.1 BIOLOGICAL MATERIALS

Many researchers have attempted to determine mercury levels in the blood, urine, tissues, and hair of humans and animals. Most methods have used atomic absorption spectrometry (AAS), atomic fluorescence spectrometry (AFS), or neutron activation analysis (NAA). In addition, methods based on mass spectrometry (MS), spectrophotometry, and anodic stripping voltametry (ASV) have also been tested. Of the available methods, cold vapor (CV) AAS is the most widely used. In most methods, mercury in the sample is reduced to the elemental state. Some methods require predigestion of the sample prior to reduction. At all phases of sample preparation and analysis, the possibility of contamination from mercury found naturally in the environment must be considered. Rigorous standards to prevent mercury contamination must be followed. Table 6-1 presents details of selected methods used to determine mercury in biological samples. Methods have been developed for the analysis of mercury in breath samples. These are based on AAS with either flameless (NIOSH 1994) or cold vapor release of the sample to the detection chamber (Rathje et al. 1974). Flameless AAS is the NIOSH-recommended method of determining levels of mercury in expired air (NIOSH 1994). No other current methods for analyzing breath were located.

In recent years, increasing attention has been paid to human exposure to mercury via dental amalgams (Skare 1995). Exposure results from elemental mercury vapor released from amalgams that is either inhaled directly or swallowed after dissolution in saliva. A Jerome 511 Gold Film Mercury Vapor Analyzer (Arizona Instrument Corp., Jerome, AZ) has been used to measure mercury vapor released from amalgam during routine dental procedures (Engle et al. 1992) or at other times to establish baseline exposure data (Halbach 1995). Accuracy and precision data were not reported. Although the detection limit for this method was not reported, mercury concentrations at μg concentrations are detectable. A similar instrument

Table 6-1. Analytical Methods for Determining Mercury in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Breath	Personal sampler (collection of an aliquot of air); analysis of sample at 253.7 nm.	AAS (flameless)	1 ng/sample	No data	NIOSH 1984 (method 6000)
Breath	Fasten a hopcalite sampling tube to a temple of the worker's safety glasses; draw air through the sampler.	CVAAS	No data	No data	Rathje et al. 1974
Human whole blood	Treatment of sample with dilute hydrochloric acid; addition of a pH buffer and a complexing agent (diethyldithiocarbamate); extraction of mercury species into toluene	ETAAS	2 µg/dm^3	>94%	Emteborg et al. 1992
Blood	Cleavage of both organic and inorganic mercury from blood protein thiol groups using hydrochloric acid, extraction of mercury species into toluene as their diethyldithiocarbamate (DDTC) complexes; addition of Grignard reagent to toluene phase to form butyl derivatives of the mercury species	GC/MPD	0.4 µg/L	>100%	Bulska et al. 1992
Blood and erythrocytes (inorganic, total)	Digestion of sample with H_2SO_4 (mixture of nitric and perchloric for total) overnight, reduction with $SnCl_2$, purging onto gold wire to form amalgam (preconcentration) followed by thermal release of elemental mercury.	CVAAS	0.06 ng/g (0.06 ppb) for total; 0.04 ng/g for inorganic.	75–114%	Bergdahl et al. 1995
Blood and urine	Dilution of sample in ammonia buffer; reduction with sodium borohydride	ICPAES	0.5 µg/L	100	Buneaux et al. 1992
Blood and urine	Total mercury: precipitation-extraction with 50% volume/volume hydrochloric acid containing EDTA and cysteine; centrifugation; filtration through screening column. Methyl mercury: extraction of the methyl mercury into benzene or toluene; back extract into aqueous cysteine solution	ICP-MS	0.2 µg/L	91.6–110.2	Kalamegham and Ash 1992
Blood, plasma, urine (total)	Digestion of blood and plasma samples overnight in a mixture of nitric acid and perchloric acid	CVAAS	5 nmol/L	93.4–103	Vesterberg 1991
Blood, urine, tissues (inorganic)	Dilution of blood or urine sample with water; homogenization of tissue samples with water; reduction of mercury with $SnCl_2$ followed by purging to detector	CVAAS	≈6 µg/L	77–110	Friese et al. 1990

Table 6-1. Analytical Methods for Determining Mercury in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood, breast milk (total, inorganic)	Digestion of sample with nitric/perchloric acid overnight for total, and with H_2SO_4 overnight for inorganic; reduction and purging	CVAAS	0.1 ng/g (blood); 0.04 ng/g (milk)	97%	Oskarsson et al. 1996
Blood (total)	Irradiation of sample followed by treatment with permanganate, sulfuric acid, distilled water, ammonia, and hydroxylamine hydrochloride; treatment with ion exchange.	NAA	0.3 ng/mL	100%	Fung et al. 1995
Serum, bovine liver (total)	Digestion of sample with HNO_3 and heat in closed container in microwave oven; reduction with $SnCl_2$ and TBP; purging to gold-coated sand adsorber to preconcentrate (amalgamation); thermally desorb to detector	CVAAS	0.84 ng/g	93–111	Vermeir et al. 1989
Urine (total)	Digestion with $HNO_3/HClO_3$ and heat; evaporation; addition of NH_4Cl/ammonium solution; dilution with water	ASV	NR	100–105	Liu et al. 1990
Urine (total)	Addition of HCl to sample followed by bromate/bromide solution and equilibration for 15 minutes; decomposition of excess bromine by addition of hydroxylamine hydrochloride.	AFS	1 ng/L	95-98% (methyl mercury, phenyl mercury)	Corns et al. 1994
Urine, tissue, hair (total)	Digestion of sample with HNO_3 in closed vessel in microwave; cooling and dilution with water; reduction with $SnCl_2$; purging to detector	AFS	0.9 ng/L	94–102	Vermeir et al. 1991a, 1991b
Blood, urine, hair, fish (total, methyl Hg)	Total: digestion of sample with nitric, perchloric, and sulfuric acids; Methyl mercury in hair: digestion with HCl and extraction into benzene. Methyl mercury in blood, fish, and urine: digestion with KOH and extraction into dithizone solution, cleaned up via extractions.	Total: CVAAS, methyl mercury: GC/ECD	0.5 ng	No data	Akagi et al. 1995

Table 6-1. Analytical Methods for Determining Mercury in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Tissue, hair	Washing of hair sample with acetone and water; homogenization of hair or tissue sample in micro dismembrator; irradiation; addition of carriers; digestion with concentrated HNO_3/ H_2SO_4 solution and heat in a closed Teflon bomb; extraction of digest with $CHCl_3$ to remove bromide ion, extraction of aqueous phase with Zn-$(DDC)_2$/$CHCl_3$; counting of ^{197}Hg in organic phase	NAA	0.36 ng/g (tissue) 3.6 ng/g (hair)	85–110	Zhuang et al. 1989
Liver tissue (methyl mercury)	Extraction of sample with toluene; concentration of methylmercury in aqueous phase; mixing with bacterial cells and incubation in microreaction vessel; injection of headspace gas containing methane	GC/FID	15 ng	NR	Baldi and Filippelli 1991
Hair	Washing of samples with acetone and water; digestion with HNO_3 and heat; oxidation with permanganate solution and heat; cooling and addition of hydroxylamine hydrochloride; reduction of mercury with $SnCl_2$; purging to detector	CVAAS	NR	100–101	Pineau et al. 1990
Wrist and temporal areas	None	XRF	20 µg/g	No data	Bloch and Shapiro 1986

AAS = atomic absorption spectrometry; AFS = atomic fluorescence spectrometry; ASV = anodic stripping voltametry; $CHCl_3$ = trichloromethane; CVAAS = cold vapor atomic absorption spectrometry; ECD = electron capture detection; ETAAS = electrothermal atomic absorption spectrometry; FID = flame ionization detector; GC = gas chromatography; $HClO_3$ = perchlorous acid; Hg = mercury; HNO_3 = nitric acid; H_2SO_4 = sulfuric acid; ICPAES = inductively coupled plasma atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry; MPD = microwave-induced plasma emission; NAA = neutron-activation analysis; NH_4Cl = ammonium chloride; NR = not reported; $SnCl_2$ = tin(II) chloride; TBP = tri-*n*-butyl-phosphate; XRF = X-ray fluorescence; Zn-$(DCC)_2$ = zinc diethyldithiocarbamate

(Jerome 431X Mercury Vapor Analyzer) was used by Chien et al. (1996) to measure elemental mercury vapor released from dental amalgams in the oral cavity and was reported to have a sensitivity of 0.003 mg/m^3. Absorbed mercury can be measured using blood and urine measurements as described below.

CVAAS is the primary method that is used to determine mercury in blood and serum (Friese et al. 1990; Ngim et al. 1988; Vermeir et al. 1988, 1989; Vesterberg 1991). Using CVAAS, concentrations in the sub- to low-ppb can be reliably measured. Both direct reduction of sample (Friese et al. 1990; Ngim et al. 1988) and predigestion followed by reduction (Oskarsson et al. 1996; Vermeir et al. 1988, 1989) produced good accuracy and precision. However, with predigestion techniques, best results were obtained on samples that were heated in a closed teflon container in a microwave oven and preconcentrated on gold-coated sand (Vermeir et al. 1989). A complimentary method to CVAAS for total mercury determination in blood is electrothermal atomic absorption (ETAAS) (Emteborg et al. 1992). Recoveries are excellent and sensitivity is 2 µg/dm^3. GC/microwave-induced plasma atomic emission detection (MPD) can also be used to measure both organic and inorganic mercury in blood samples (Bulska et al. 1992). Sensitivity is in the sub-ppb range, and recovery is excellent (100%).

Methylmercury and inorganic mercury were extracted from human whole blood samples, as their diethyldithiocarbamate complexes, into toluene and butylated them by using a Grignard Reagent (Bulska et al. 1992). The mercury species were then detected by a microwave-induced plasma atomic emission spectrometric system (GC/MPD). The absolute detection limit was calculated to be 1 pg of mercury in either the methylmercury or inorganic mercury form. This corresponds to a detection limit of about 0.4 µg/L. The method is reproducible. Methods for inorganic mercury and organic mercury (mostly methylmercury) have been reported for blood, urine, hair, and breast milk (Akagi et al. 1995; Bergdahl et al. 1995; Oskarsson et al. 1996). Total mercury is typically determined using CVAAS after complete conversion of all mercury to the volatile elemental form using harsh (nitric acid/perchloric acid, bromate/bromide) digestions followed by reduction of ionic mercury to the elemental form. Inorganic mercury can be determined after milder digestions (HCl, sulfuric acid) and reduction. The organic form is determined by the difference between total and inorganic. Sub-ng/g (ppb) detection limits are routine. Methylmercury is also determined using GC with electron capture detection (ECD) (Akagi et al. 1995).

There is evidence to suggest that urinary mercury levels are good measures of exposure to inorganic mercury in the environment (Ikingura and Akagi 1996). The primary method used to analyze urine for mercury is CVAAS (Akagi et al. 1995; Friese et al. 1990; Ngim et al. 1988; Oskarsson et al. 1996; Ping

and Dasgupta 1989, 1990; Vesterberg 1991). Methods using AFS (Corns et al. 1994; Vermeir et al. 1991a, 1991b), ASV (Liu et al. 1990), and isotope-dilution spark source (IDSS) MS have also been developed. CVAAS is sensitive (low-ppt), reliable (recovery is >76% and precision is generally <10% relative standard deviation [RSD]), and may be used on either digested or undigested samples (Friese et al. 1990; Ngim et al. 1988; Ping and Dasgupta 1989, 1990). Improved sensitivity (sub-ppt), accuracy (>90% recovery), and precision (7% RSD or better) were obtained with AFS when samples were digested in a closed container in a microwave (Vermeir et al. 1991a, 1991b). Good results have also been achieved with ASV (Liu et al. 1990) and IDSSMS (Moody and Paulsen 1988). The precision of these methods is especially high (<5% RSD), and recoveries with ASV are >90%. Both these methods require predigestion of the sample. As an alternative to CVAAS, total mercury determination in blood and urine can be performed by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) or ICP-mass spectrometry (Buneaux et al. 1992; Kalamegham and Ash 1992). These methods are sensitive, with detection limits in the sub-ppb range. Recoveries (>90%) and precision (<17% coefficient of variation [CV]) are good.

AAS-based methods and NAA have been used to measure mercury in tissues. The AAS methods differ in the way the sample is released for detection. CVAAS is the best-defined of the AAS techniques. Mercury concentrations in the sub- to low-ppb have been reliably determined in tissue samples (Friese et al. 1990; Vermeir et al. 1988, 1989). Best results were obtained when the sample was digested in a closed container in a microwave oven, and the vaporized mercury was preconcentrated on gold-coated sand (Vermeir et al. 1989). Flameless AAS, which uses an electric furnace to atomize the mercury, has yielded high recoveries, but no data are available on the sensitivity or precision of the technique (Ichinose and Miyazawa 1989). Separative column atomizer AAS (SCA-AAS) introduces the mercury to the detector by running the sample through a heat-activated charcoal column (Yanagisawa et al. 1989). Little sample preparation is required, but high background interference is a problem with this method. Good results were reported for tissue samples with sub-ppm mercury concentrations (from control rats), but decreased accuracy and precision occurred in samples containing higher levels (from dosed rats). AFS offers a good alternative to CVAAS. Sensitivity was in the sub-ppt range, and recovery and precision were excellent (Vermeir et al. 1991a, 1991b). In addition, sample preparation is relatively simple and rapid. NAA permits determination of mercury in tissue samples at the sub- to low-ppb level, but erratic accuracy and precision make the method less reliable (Taskaev et al. 1988; Zhuang et al. 1989). An extraction method using zinc diethyldithiocarbamate produced good results with NAA (Zhuang et al. 1989). GC equipped with a flame ionization detector (FID) has also been used to detect methylmercury in tissues at ng levels (Baldi and Filippelli 1991). Recovery and precision data were not reported.

Studies have indicated that the mercury concentration in the hair correlates well with dietary mercury exposure (Inasmasu et al. 1986; Wilhelm and Idel 1996). Methylmercury is the primary dietary mercury contaminant and is present in large amounts in seafood (Ikingura and Akagi 1996). Most of the mercury measured in hair is methylmercury; hair is a good matrix for assessing exposure to methylmercury (Wilhelm and Idel 1996). Hair analysis has been conducted using CVAAS, AFS, and NAA (Grandjean et al. 1992; Ngim et al. 1988; Pineau et al. 1990; Suo et al. 1992; Suzuki et al. 1992; Taskaev et al. 1988; Vermeir et al. 1991a, 1991b; Zhuang et al. 1989). Segmental hair analysis is commonly used as a means of determining an historical record of exposure or uptake of mercury (Grandjean et al. 1992; Suzuki et al. 1992). The method involves cutting the hair strands into smaller segments, usually 1 cm each, and analyzing each segment separately. Detection limits for hair using CVAAS were not reported but are expected to be similar to those for tissue (sub- to low-ppb). The sensitivity of NAA is similar to that of CVAAS, but variable recoveries and precision make NAA less reliable. Good results were reported for one NAA method (Zhuang et al. 1989). Results from studies using AFS suggest this method may be the most sensitive and reliable technique (Suo et al. 1992; Vermeir et al. 1991a, 1991b). A detection limit in the sub-ppt range was obtained, and precision and accuracy were both excellent.

An X-ray fluorescence (XRF) technique has been used to measure mercury in the wrist and temporal areas of dentists exposed to various heavy metals in the work place (Bloch and Shapiro 1986). This technique allows simultaneous evaluation of the tissue burden of a number of different metals. Bone levels may be more closely related to long-term exposure than levels in blood, urine, and hair. The detection limit for XRF is in the low ppm.

A method for detecting methylmercury in biological samples by its enzymatic conversion to methane is an alternative biological technique for methylmercury or other organomercurial analyses (Baldi and Filippelli 1991). *Pseudomonas putida* strain FB1, a broad spectrum mercury-resistant strain, is able to enzymatically convert methylmercury to Hg^0 and methane either in whole cell or in cell-free extracts. GC/FID was used to determine methane produced by the biological derivatization of methylmercury. The detection limit was 15 ng of methylmercury extracted from 1 g of biological tissue. The coefficient of variation was 1.9%. Chemical interferences are negligible in the enzymatic determination of methyl-mercury. The specificity of this determination places the method among the most reliable ones. Recovery was not reported.

6.2 ENVIRONMENTAL SAMPLES

Mercury levels have been determined in numerous environmental matrices, including air, water (surface water, drinking water, groundwater, sea water, and industrial effluents), soils and sediments, fish and shellfish, foods, pharmaceuticals, and pesticides. The sample preparation varies with the complexity of the matrix, but most complex samples require decomposition of the matrix and reduction of the mercury to its elemental form. As described Section 6.1 for biological samples, special sample preparation methods need to be employed if inorganic and organic mercury are to be determined separately, or if the individual species of the organic mercury fraction are to be determined. More detailed information on selected methods in various environmental samples is given in Table 6-2.

Both CVAAS and CVAFS have been used to monitor air and suspended particulates in air for mercury (Baeyens and Leermakers 1989; Bloom and Fitzgerald 1988; Friese et al. 1990; NIOSH 1994; Paudyn and Van Loon 1986; Sengar et al. 1990; Stockwell et al. 1991; Temmerman et al. 1990). Both methods are sensitive, accurate, and precise, although slightly greater sensitivity was reported with AFS (low ppt) than with AAS (mid ppt); AFS is becoming a more common method of analysis (Horvat 1996). When AAS or AFS was combined with gas chromatography (GC), the different mercury species (inorganic mercury, dimethylmercury, diethylmercury, and methylmercury chloride) present in the air could be separated (Bloom and Fitzgerald 1988; Paudyn and Van Loon 1986). A colorimetric method, based on the formation of a colored complex formed in the presence of mercury, has been used as a quick and simple field test that can detect mercury present at the mid-ppb level (Cherian and Gupta 1990).

Numerous methods, including CVAAS, ASV, inductively coupled plasma (ICP) MS, ICP atomic emission spectrometry (AES), microwave-induced plasma (MIP) AES, NAA, GC/AFS, high-performance liquid chromatography (HPLC)/UV, HPLC/ECD, and spectrophotometry, have been used to determine mercury levels in aqueous media. Mercury has been measured in drinking water, surface water, groundwater, snow, waste water effluents, and sea water. Of the available methods, CVAAS is the method of choice (Baxter and Frech 1989, 1990; Birnie 1988; Eaton et al. 1995; Goto et al. 1988; Lee et al. 1989; Mateo et al. 1988; Munaf et al. 1991; Paudyn and Van Loon 1986; Ping and Dasgupta 1989; Robinson and Schuman 1989; Schintu et al. 1989; Shkinev et al. 1989) and the method recommended by EPA and AOAC (AOAC 1984; Beckert et al. 1990; EPA 1994f, 1994g). This method is very sensitive for mercury in water (sub- to low-ppt) and has been proven to be reliable. Water samples generally do not require digestion, but mercury in the samples is usually reduced to the elemental state and preconcentrated prior to analysis. When combined

Table 6-2. Analytical Methods for Determining Mercury in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (elemental)	Drawing of air through Hopcalite sorbent tube, dissolution of sorbent with HNO_3 then HCl, dilution, addition of stannous chloride	CVAAS	3 µg/m^3	100 (4.6% RSD at 0.9 µg)	NIOSH 1994 (Method 6009)
Air (methyl mercury)	Passage of air through a Tenax column, thermal desportion.	GC/AAS	0.1 ng/m^3 (methyl mercury)	No data	Paudyn and Van Loon 1986
Air (elemental mercury)	Preconcentration of mercury in sample by collection onto gold-coated sand absorber; thermal desorption and collection onto second absorber; desorb to detector	CVAFS	<1 ng/m^3	105–111	Temmerman et al. 1990
Air (methyl, dimethyl mercury)	Preconcentration of sample onto graphitized carbon substrate; separation by cryogenic gas chromatography	GC/CVAFS	0.3 pg (mercury, dimethyl mercury); 0.4 pg (diethyl mercury); 2 pg (methyl mercury chloride)	91–105	Bloom and Fitzgerald 1988
Air	Collection of sample onto gold-coated quartz wool; thermal desorption	CVAAS	0.08 ng	97–101	Friese et al. 1990
Water (total)	Addition of H_2SO_4/HNO_3 and $KMNO_4$, equilibrate, addition of $K_2S_2O_8$ and heating; addition of hydroxylamine, reduction to elemental mercury using stannous chloride, purging of sample	CVAAS	<1 µg/L (1 ppb)	79–92 (9–23% RSD)	Eaton et al. 1995 (Standard Method 3112B/3500B)
Water	Addition of permanganate and sulfuric acid and heating; addition of $K_2S_2O_8$ and hydroxylamine; extraction with dithizone	Spectro-photometry at 492 nm	2 µg/L (2 ppb)	95 at 250 µg/L	Eaton et al. 1995 (Standard Method 3500C)
Water (inorganic mercury)	Reduction of sample with $SnCl_2$ in HNO_3; purging of mercury to detector	CVAAS	0.1 ng/L	99	Lee et al. 1989
Water, sea water (inorganic)	Reduction of mercury in sample with $SnCl_2$; preconcentration onto platinum-lined graphite tube	GFAAS	<2 ng/L	94–102	Baxter and French 1989

Table 6-2. Analytical Methods for Determining Mercury in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water, waste water	Oxidation of organic Hg to inorganic Hg by $KMnO_4$, $K_2S_2O_8$ and heat; reduction to elemental state with stannous ion	AAS (flameless)	No data	No data	AOAC 1984 (methods 32.095 to 33.099)
Water (total)	Digestion of sample with HNO_3/H_2SO_4 plus permanganate and persulfate solutions; reduction with hydroxylamine; purging to detector	CVAAS	0.1 mg/L	101–112	Beckert et al. 1990; EPA 1994f (method 7470a)
Water and snow	Extraction of organic mercury immediately after sampling; addition of organic mercury standards; addition of KB and a benzene/ toluene mixture; isolation and volume reduction of organic layer	GC/AAS	4 ng (dimethyl mercury); 5 ng (ethyl mercury)	No data	Paudyn and Van Loon 1986
Drinking water	Collection of sample in quartz ampoule and evaporation followed by irradiation; precipitation of Hg as sulfide; isolation of precipitate and dissolution in aqua regia; counting of ^{203}Hg	NAA	45 µg/L	95–107	Itawi et al. 1990
Water (total)	Digestion with $HNO_3/HClO_4$ and heat; volume reduction; addition of NH_4Cl/ ammonium solution; dilution with water	ASV	No data	100–105	Liu et al. 1990
Surface water	Acidification of sample with HNO_3; addition of ^{199}Hg; oxidization with potassium permanganate solution; reduction with sodium borohydride; purging to plasma	ICP/IDMS	ng/L	86–98	Haraldsson et al. 1989
Drinking water	Direct injection	DIN-ICPMS PN-ICPMS	30–40 ng/L	No data	Powell et al. 1992
Drinking water and groundwater	Separation of mercury species in sample on HPLC column using buffered methanol as eluent	HPLC/ECD	≈1.8 µg/L	77–104	Evans and McKee 1988

Table 6-2. Analytical Methods for Determining Mercury in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water, sea water	Reduction of sample with $SnCl_2$ in H_2SO_4; oxidation with $KMnO_4$; addition of Cd(IV), sodium arsenite, iodide, and H_2SO_4 to thermometric cell; inject sample	Kinetic thermometry	≈2 µg/L	No data	Mateo et al. 1988
Waste water (total)	Digestion of sample with HNO_3/H_2O_2 and heat; cooling and adjustment of pH to 6; equilibration with polyacrylamidoxime; stripping of Hg from resin by equilibration with HNO_3; filtration	ICP/AES	1.15 µg/L	96–98	Mahanti 1990
Waste water	Addition of HNO_3 to sample and evaporation; redissolution in water (pH should be ≈2); separation on ion chromatography column using $TPPS_4$/PAR/NaCl/$Na_2B_4O_7$-NaOH as post-column derivatization agent	Spectro-photometry	50 µg/L	No data	Yan et al. 1989
Industrial effluents	Concentration of sample by heating; digestion with concentrated H_2SO_4; dilution; addition of sodium salicylate to aqueous sample; adjustment of pH to 5.5–5.8; extraction with triphenylphosphine oxide solution; for high levels of Hg (mg), back-extraction with acetate buffer and analysis; for low levels of Hg (µg), addition of sodium hydrogen carbonate buffer and PAN; isolation of organic layer; dilution with toluene and analysis	Spectro-photometry	No data	99–119	Raman and Shinde 1990
Soil (total)	None	XRF	10 µg/g	No data	Grupp et al. 1989
Soil (total)	Digestion of sample with HCl/HNO_3 with heat in closed Teflon vessel in microwave; dilution; reduction with $SnCl_2$ and hydroxylammonium chloride in H_2SO_4; purging to detector	CVAAS	No data	90–110	Van Delft and Vos 1988

Table 6-2. Analytical Methods for Determining Mercury in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil, sediment, sludge (total)	Digestion of sample with aqua regia and permanganate in steam bath or with HNO_3/H_2SO_4 and permanganate in autoclave; reduction with hydroxylamine; purging to detector	CVAAS	0.1 mg/L	84–101	Beckert et al. 1990; EPA 1994g (method 7471a)
Soil, sediment (methyl Hg, phenyl Hg)	SFE of spiked sample using CO_2methanol containing diethylammonium diethyldithio-carbamate; dilution with octane, addition of pentylMgBr to form pentyl derivatives, addition of H_2SO_4, extraction of organic phase with water, treatment with anhydrous magnesium sulfate	GC/AED	2.5 ng/mL in extract	106 (methyl) 6.3% RSD; 59 (phenyl) 12% RSD)	Liu et al. 1994
Sediment, mussel (total)	Digestion of sample with concentrated acid; evaporation; redissolution in HNO_3 and dilution with water; reduction of sample with $SnCl_2$ in HNO_3; purging to detector	CVAAS	0.1 ng/L	111 (sediment); 60 (mussel)	Lee et al. 1989
Sediment (total)	Digestion of sample with HCl/HNO_3 and heat in Teflon bomb; oxidation with potassium permanganate solution; reduction with sodium borohydride; purging to plasma	ICP/MS	≈2 ng/g	96	Haraldsson et al. 1989
Solid samples (total)	Introduction of a slurry of sample in nitric acid into FIA system using on-line microwave digestion, mix with tin(II) chloride to form elemental mercury	CV-AFS	0.09 ng/g	84–108 (2.9–4% RSD)	Morales-Rubio et al. 1995
Fish (methyl mercury)	Homogenization of sample; extraction with HCl/KBr/ $CuSO_4$/toluene solution; centrifugation; mixing of organic phase with cysteine and centrifugation; mixing of aqueous phase with HCl/KBr/ $CuSO_4$/toluene solution; centrifugation; drying of organic phase over anhydrous Na_2SO_4	GC/ECD	50 ng/g (methyl mercury)	89–111	Ahmed et al. 1988

Table 6-2. Analytical Methods for Determining Mercury in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish	Drying of visceral parts of fish in oven; digestion of sample with concentrated H_2SO_4; dilution and filtration of digest; addition of sodium salicylate to aqueous sample; adjustment of pH to 5.5–5.8; extraction with triphenylphosphine oxide solution; for high levels of Hg (mg), back-extraction with acetate buffer and analysis; for low levels of Hg (µg), addition sodium hydrogen carbonate buffer and PAN; isolation of organic layer; dilution with toluene and analysis	Spectro-photometry	No data	99–119	Raman and Shinde 1990
Fish and plant materials	Preparation of sample condensate; dilution with HNO_3; addition of Ag and co-precipi-tatation of Ag and Hg with H_2S; preparation of sample electrode	IDSSMS	0.1 µg/g	95	Moody and Paulsen 1988
Fish and shell fish (methyl mercury)	Homogenization of sample; removal of organics by washing with acetone and benzene; addition of HCl to release protein-bound methyl mercury and extraction into benzene; analysis for methyl mercury chloride	GC/ECD	No data	No data	AOAC 1984 (methods 25.146–25.157)
Fish (total)	Digestion of samples with nitric acid in a microwave acid digestion bomb, reduction to elemental mercury	CVAAS	0.195 ng/mL	>95	Navarro et al. 1992
Fish muscle (total)	Digestion of sample with H_2SO_4-HNO_3	AAS (flameless)	No data	No data	AOAC 1984 (methods 25.134–25.137)
Oyster tissue, milk powder, wheat flour (total)	Digestion of sample with HNO_3 and heat in closed container in microwave over; reduction with $SnCl_2$ and TBP; purging of mercury to gold-coated sand absorber to preconcentrate; desorption to detector	CVAAS	0.84 ng/g	93–111	Vermeir et al. 1989

Table 6-2. Analytical Methods for Determining Mercury in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Wheat flour, citrus leaves, pine needles (total)	Digestion of sample using $K_2Cr_2O_7$ and H_2SO_4, heating and dilution	CVAAS	6 ng/g	91–108	Landi et al. 1990
Milk powder, oyster tissue (total)	Digestion of sample with HNO_3 in closed vessel in microwave; dilution with water; reduction with $SnCl_2$; purging to detector	AFS	0.9 ng/L	94–102	Vermeir et al. 1991a, 1991b
Food (total)	Digestion of 5 g of sample with HNO_3-$HClO_4$	AAS (flameless)	No data	No data	AOAC 1984 (methods 25.131–25.133)
Food (total)	Digestion of sample with HNO_3 and H_2SO_4 under reflux; isolation of mercury by dithizone extraction	Colorimetric dithizone method	No data	No data	AOAC 1984 (methods 25.138–25.145)
Wine (total)	Digestion of sample with concentrated HNO_3 and chromic acid; addition of hydroxylamine chlorhydrate to cold flask; transferring to mercury/hydride generator; addition of $SnCl_2$ in H_2SO_4 to reduce; purging to detector	AAS (flameless)	6 µg/L	95–107	Cacho and Castells 1989
Pharmaceuticals	Extraction of mercury with *N*-phenylcinnamo-hydroxamic acid; measurement of absorbance at 390 nm	Spectrophoto-metry	No data	No data	Agrawal and Desai 1985
Pharmaceuticals	Removal of lipids from greasy or soapy samples with diethyl ether; digestion of sample with $KMnO_4/HNO_3$; removal of excess permanganate with sodium oxalate; adjustment of pH to alkaline with ammonium chloride/ ammonia buffer and H_2O_2 ; filtration; heating and dilution; titration of mercury with 4,4'-dihydroxybenzophenone	Spectro-photometry	2 µg/L	95–111	Marquez et al. 1988

Table 6-2. Analytical Methods for Determining Mercury in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Cigarettes	Digestion by heating with concentrated H_2SO_4; dilutition and filtration of digest; addition of sodium salicylate to sample; adjustment of pH to 5.5–5.8; extraction with triphenylphosphine oxide solution; for high mercury (mg), back-extraction with acetate buffer and analysis; for low mercury (µg), addition of sodium hydrogen carbonate buffer and PAN; isolation of organic layer; dilution with toluene	Spectro-photometry	No data	99–119	Raman and Shinde 1990

AAS = atomic absorption spectrometry; AED = atomic emission detection; AES = atomic emission spectrometry; AFS = atomic fluorescence spectrometry; Ag = silver; ASV = anodic stripping voltammetry; Cd = cadmium; $CuSO_4$ = copper sulfate; CVAAS = cold vapor atomic absorption spectrometry; CVAFS = cold-vapor atomic fluorescence spectrometry; DIN-ICPMS = direct injection nebulizer inductively coupled plasma mass spectrometry; ECD = electron capture detection or electrochemical detector; GC = gas chromatography; GFAAS = graphite furnace atomic absorption spectrometry; HCl = hydrochloric acid; $HClO_3$ = perchlorous acid; $HClO_4$ = perchloric acid; Hg = mercury; HNO_3 = nitric acid; HPLC = high-performance liquid chromatography; H_2O_2 = hydrogen peroxide; H_2S = hydrogen sulfide; H_2SO_4 = sulfuric acid; ICP = inductively coupled plasma; IDMS = isotope-dilution mass spectrometry; IDSSMS = isotope-dilution spark-source mass spectrometry; KB = potassium boride; KBr = potassium bromide; $K_2Cr_2O_7$ = potassium chromate; $KMnO_4$ = potassium permanganate; $K_2S_2O_8$ = potassium sulfhydrate; MS = mass spectrometry; NAA = neutron-activation analysis; $Na_2B_4O_7$ = sodium borohydrate; NaOH = sodium hydroxide; Na_2SO_4 = sodium sulfate; NaCl = sodium chloride; NH_4Cl = ammonium chloride; PAN = 1-(2-pyridylazo)-2-naphthol; PAR = 4-(2-pyridylazo)resorcinol; PN-ICPMS = pneumatic nebulizer inductively coupled plasma mass spectrometry; $SnCl_2$ = tin(II) chloride; TBP = tri-*n*-butyl-phosphate; $TPPS_4$ = meso-tetra(4-sulfonatophenyl)porphyrin; XRF = x-ray fluorescence

with GC, CVAAS has been used to separate and determine individual mercury species in aqueous samples (Paudyn and Van Loon 1986). Spectrophotometry has often been used to determine mercury in aqueous matrices (Abbas et al. 1989; Ajmal et al. 1989; Eaton et al. 1995; Raman and Shinde 1990; Singh et al. 1989). Sample preparation methods vary and have included separation by thin-layer chromatography (TLC) (Ajmal et al. 1989) or column chromatography (Yan et al. 1989), selective extraction (Abbas et al. 1989), and ligand formation (Raman and Shinde 1990; Singh et al. 1989). While recoveries were good, spectrophotometry is not as sensitive a technique as CVAAS. Tests of additional methods, including ASV (Liu et al. 1990), ICP/MS (Haraldsson et al. 1989), NAA (Itawi et al. 1990), AES-based techniques (Kitagawa and Nishimoto 1989; Mahanti 1990; Nakahara et al. 1988), HPLC-based techniques (Evans and McKee 1988; Shofstahl and Hardy 1990), and graphite-furnace (GF) AAS (LeBihan and Cabon 1990) indicate that these methods may also be useful for determining mercury in water samples. One of the most promising methods is GC/AFS, which has the advantages of increased sensitivity and precision compared to CVAAS and can also be used to isolate individual mercury species (Bloom 1989). A colorimetric assay has also been developed that is useful for rapid preliminary screening of field samples (Cherian and Gupta 1990).

CVAAS is the most commonly used technique for determining the mercury concentration of sediments, soils, and sludge (Bandyopadhyay and Das 1989; Beckert et al. 1990; EPA 1994g; Van Delft and Vos 1988). As with other matrices, it is sensitive, reliable, and requires little sample preparation beyond digestion of the matrix and reduction of the mercury to its elemental form. It is the method recommended by EPA for solid matrices (Beckert et al. 1990; EPA 1994g). A method based on CVAFS that uses flow injection analysis with on-line microwave digestion for the determination of total mercury has been described recently (Morales-Rubio et al. 1995). Good sensitivity (90 ppt) and precision (4% RSD) was demonstrated. Gas chromatography in conjunction with atomic emission detection (GC/AED) has been used to determine organomercury species in soils and sediments (Liu et al. 1994). Direct current ASV (DCASV) has been tested for use in determining mercury levels in river sediment (Lexa and Stulik 1989). The accuracy and sensitivity of this method are good, but it is less precise than CVAAS. A field method using XRF has been developed to monitor soil contamination (Grupp et al. 1989). This method is rapid and portable, but its high detection limit (low-ppm) makes it useful only for on-site screening.

Methods have been developed for the determination of mercury in fish, shellfish, foods, food sources, and pharmaceuticals. AAS, usually with cold vapor generation (CVAAS), is one of the primary methods used to measure mercury in these complex matrices (Carrillo et al. 1986; Friese et al. 1990; Landi et al. 1990;

Navarro et al. 1992; Odukoya 1990; Vermeir et al. 1988, 1989), because of its sensitivity and reliability. Although the sensitivity (sub- to low-ppb), accuracy, and precision are not as good as with less complex gaseous and aqueous media, it is still one of the best methods available for analysis of mercury in any matrix. Flameless AAS without cold vapor generation has also produced good results when used to determine ppb levels of mercury in wine (Cacho and Castells 1989) and fish (Filippelli 1987); it is also one of the methods recommended by AOAC for fish and food (AOAC 1984). When combined with high resolution GC (HRGC), the individual organic mercury species in fish could be determined (Jiang et al. 1989). Sub-ppt levels of mercury in powdered milk and oyster tissue were reliably determined using AFS (Vermeir et al. 1991a, 1991b). NAA was used to measure mercury levels in copepod homogenate and tomato leaves, but the sensitivity (mid- to low-ppb) and reliability were not as good as that of CVAAS or AFS (Taskaev et al. 1988; Zhuang et al. 1989). Several other methods, including IDSSMS (Moody and Paulsen 1988), HPLC/ICP/MS (Bushee 1988), square-wave voltametry (ASV) (Mannino et al. 1990), ASV (Golimowski and Gustavsson 1983), MIP/AES (Natajaran 1988), GC/ECD (Ahmed et al. 1988; AOAC 1984), and spectrophotometry (Agrawal and Desai 1985; Marquez et al. 1988) have also been used to analyze fish, plant material, and pharmaceuticals for mercury. HPLC/ICP/MS has the additional advantage of permitting separation and quantitation of individual mercury species (Bushee 1988). An AOAC-recommended colorimetric method is available for screening food samples (AOAC 1984).

Several other environmental matrices have been analyzed for mercury content. These include coal fly ash (Horvat and Lupsina 1991; Lexa and Stulik 1989), coal dust (Wankhade and Garg 1989), minerals (Bichler 1991), pesticides (Sharma and Singh 1989), gasoline (Costanzo and Barry 1988), and oily waste (Campbell and Kanert 1992). The methods used include CVAAS, DCASV, NAA, spectrophotometry, and GC/alternating current plasma detection (ACPD). The data on each method for each matrix were insufficient for making comparisons.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of mercury is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of mercury.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. There are reliable methods for detecting and quantifying elemental mercury in human breath, blood, urine, milk, tissues, hair, and bones. The method of choice is CVAAS (Akagi et al. 1995; Friese et al. 1990; Pineau et al. 1990; Ping and Dasgupta 1989, 1990; Rathje et al. 1974; Vermeir et al. 1988, 1989; Vesterberg 1991). Other methods that have produced good results include ETAAS (Emteborg et al. 1992), AFS (Corns et al. 1994; Vermeir et al. 1991a, 1991b; Suo et al. 1992), flameless AAS (NIOSH 1994), IDSSMS (Moody and Paulsen 1988), XRF (Bloch and Shapiro 1986), NAA (Fung et al. 1995; Zhuang et al. 1989), GC/MPD (Bulska et al. 1992), ICP-AES (Buneaux et al. 1992), and ICP-MS (Kalamegham and Ash 1992). Using these methods, mercury levels at µg to pg concentrations are detectable. This makes them useful for measuring background and higher levels (Ikingura and Agaki 1996). Many of the methods can also distinguish between organic and inorganic mercury. No further methods for analysis of elemental mercury in biological fluids and tissues are needed. Additional research will be needed to validate the determination of individual mercury species (i.e., methylmercury, phenyl mercury, mercury acetate, etc.) in matrices determined to be important. Methods exist for the separation and detection of these species, but few standard reference materials exist for comparative studies.

Biochemical indicators of possible renal dysfunction (increased urinary NAG levels, and elevated porphyrins) have been associated with increased urinary levels of mercury (Rosenman et al. 1986; Wada et al. 1969; Woods 1996). Functional indicators of adverse neurological effects (reduced nerve conduction velocity, prolonged nerve latency, increased tremor frequency, increased reaction time, reduced hand-eye coordination, and performance on memory and verbal intelligence tests) have also been correlated with increased urinary levels of mercury (Levine et al. 1982; Piikivi et al. 1984; Smith et al. 1970, 1983; Verberk et al. 1986; Vroom and Greer 1972; Williamson et al. 1982). Decreased nerve conduction velocity has been correlated with increased tissue levels of mercury (Shapiro et al. 1982). These biomarkers are not specific for mercury and may be induced by exposure to other metals and chemicals or to disease conditions. Other

nonspecific indicators of possible mercury exposure (insomnia, emotional instability, paresthesia, and abnormal EEG) that have been observed in exposed individuals cannot be quantified, but an increased incidence in specific populations may be correlated with increased urinary levels of mercury in the population (Davis et al. 1974; Jaffe et al. 1983; McFarland and Reigel 1978). The existing analytical methods that have been discussed for exposure can reliably measure the levels in blood, urine, and tissue at which these effects occur. Standard methods exist to measure the effects that can be quantified. No further methods need to be developed.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. There are analytical methods to detect and measure elemental and organic mercury in air, water, sediment, soil, sludge, foods, plant materials, and other environmental matrices. The methods used include CVAAS (the most commonly used and recommended method) (AOAC 1984; Baxter and Frech 1989; Eaton et al. 1995; EPA 1994f, 1994g; Munaf et al. 1991; Navarro et al. 1992; Paudyn and Van Loon 1986; Ping and Dasgupta 1989), AFS (Bloom 1989; Bloom and Fitzgerald 1988; Morales-Rubio et al. 1995; Vermeir et al. 1991a, 1991b), IDSSMS (Moody and Paulsen 1988), flameless AAS (Cacho and Castells 1989; Filippelli 1987; NIOSH 1994), and several other methods. Several of the methods have been proven reliable and are sensitive enough to measure background levels. Methods also exist to determine individual mercury species (Bloom and Fitzgerald 1988; Liu et al. 1994; Paudyn and Van Loon 1986). No further methods are needed for mercury analysis in environmental samples. Additional work would be required to validate methods for individual organomercury species in particular matrices.

6.3.2 Ongoing Studies

Ongoing studies concerning the detection and measurement of mercury in biological or environmental samples identified through a search of Federal Research in Progress (FEDRIP 1998) are shown in Table 6-3.

Table 6-3. Research on New Methods for the Detection of Mercury

Investigator	Sponsor	Research
RJ Schlager ADA Technologies Englewood, CA	USDoE, Energy Research	Developing a continuous emission monitor for total and organic mercury in stack gases
PC Efthimion EEI Pluckemin, NJ	EPA	Developing a continuous emission monitor for flue gas based on plasma emission using a microwave-powered source
CW Brown Brooks Rand, Ltd. Seattle, WA	DoE	Developing a monitor for methyl mercury based on luminescence
D Mcallister Biode, Inc. Cape Elizabeth, ME	DoE	Developing a simple sensor for use in waste, surface, and groundwater using a shear horizontal acoustic plate mode (SHAPM) sensor, a form of piezoelectric sensor
LG Piper Physical Sciences, Inc., Andover, MA	DoE	Developing a sensor for mercury in exhaust stack effluents from coal burning power plants based on the fluoerescence of merucry excited by active nitrogen
JCMay	FDA	Developing methods for the determination of mercury and trace metals in injectable products based on high performance liquid chromatography in conjunction with ICP-MS

Source: FEDRIP 1998

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding mercury and mercury compounds in air, water, and other media are summarized in Table 7-1. Unless otherwise indicated, the listings in the table refer to mercury.

An MRL of 0.0002 mg/m^3 has been derived for chronic-duration inhalation exposure (365 days or more) to metallic mercury vapor in a group of 26 mercury-exposed workers from three industries exposed to low levels of mercury for an average of 15.3 years (range, 1–41 years) (Fawer et al. 1983).

An MRL of 0.007 mg mercury/kg/day has been derived for acute-duration oral exposure (14 days or less) to inorganic mercury based on a NOAEL of 0.93 mg mercury/kg for renal effects (increased absolute and relative kidney weights) in rats exposed to gavage doses of mercuric chloride for 14 days (NTP 1993).

An MRL of 0.002 mg mercury/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to inorganic mercury based on a NOAEL of 0.23 mg mercury/kg for renal effects (increased absolute and relative kidney weights) in rats (Dieter et al. 1992; NTP 1993).

An MRL of 0.0003 mg mercury/kg/day has been derived for chronic-duration (365 days or more) oral exposure to methylmercury, based on neurodevelopmental outcomes in a study by Davidson et al. (1998) of children exposed *in utero* to methylmercury from maternal fish ingestion.

EPA has derived an oral RfD of 8×10^{-5} mg/kg/day (0.08 µg/kg/day) for phenylmercuric acetate as mercury (IRIS 1997). The RfD is based on a LOAEL of 0.5 ppm mercury or 0.042 mg/kg/day phenyl mercuric acetate for detectable kidney damage in female rats after 2 years (Fitzhugh et al. 1950). EPA has derived an oral RfD of 3×10^{-4} mg/kg/day (0.3 µg/kg/day) for mercuric chloride. The RfD is based on LOAELs of 0.226, 0.317, and 0.633 mg/kg/day of mercuric chloride. Although no one study was found adequate for deriving an oral RfD, EPA's mercury workgroup derived an oral RfD of high confidence using the weight of evidence from three studies (Andres 1984; Bernaudin et al.; Druet et al. 1978) which used Brown-Norway rats, and an intensive review and discussion of the entire inorganic mercury data base (IRIS 1997). EPA has derived an oral RfD of 1×10^{-4} mg/kg/day (0.1 µg/kg/day) for methylmercury based on developmental neurological abnormalities in human infants (IRIS 1997). EPA has not derived an RfD value for elemental mercury. The EPA inhalation reference concentration (RfC) for elemental mercury is $3x10^{-4}$ mg/m^3

(0.3 µg/m^3). The RfC is based on a LOAEL of 0.025 ppm for human occupational exposure studies. Critical effects seen during these studies included hand tremors, increases in memory disturbances, and slight subjective and objective evidence of autonomic dysfunction (IRIS 1997). No RfC was reported for other mercury compounds.

The American Conference of Governmental Industrial Hygienists (ACGIH) and the EPA have determined that inorganic forms of mercury, including metallic mercury, are not classifiable as to their human carcinogenicity. These agencies have assigned mercury and its inorganic compounds the weight-of-evidence classifications of A4 and D, respectively (ACGIH 1996; IRIS 1997). Mercuric chloride and methylmercury have been assigned EPA's weight-of evidence classification of C, which indicates that they are possible human carcinogens (IRIS 1997).

OSHA requires employers of workers who could be occupationally exposed to mercury to institute engineering controls and work practices which ensure that during any part of the workday, mercury concentrations do not exceed the ceiling value of 1 mg/10 m^3 (0.1 mg/m^3) (OSHA 1974).

Mercuric cyanide, mercuric nitrate, mercuric sulfate, mercuric thiocyanate, mercurous nitrate, mercury, and mercury fulminate have been designated as hazardous substances pursuant to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (EPA 1995i). Mercuric acetate, mercuric chloride, and mercuric oxide are mercury compounds that have been individually designated as extremely hazardous substances under Section 313 of Title III of the Superfund Amendments and Reauthorization Act (SARA) of 1986 (EPA 1995j). Phenylmercury acetate is consider both a hazardous substance and an extremely hazardous substances. The statutory sources designating mercury and regulated mercury compounds as CERCLA hazardous substances are section 307(a) of the Clean Water Act (CWA), section 112 of the Clean Air Act (CAA), and section 3001 of the Resource Conservation and Recovery Act (RCRA) (EPA 1995i). The owner and operator of facilities using these substance on their sites are required to immediately report releases to any environmental media, if the amount released exceeds the established "reportable quantity" (EPA 1995i). The statutory and final reportable quantities for mercury and regulated mercury compounds as established by Section 102 of CERCLA are given in Table 7-1 (EPA 1995i). Although mercury compounds are listed generically as CERCLA hazardous substances no reportable quantity has been established for them as a broad class (EPA 1995i). Title III of SARA is also known as "The Emergency Planning and Community Right-to-Know Act (EPCRA) of 1986." As chemicals subject to the emergency planning and release reporting requirements of EPCRA, owners and operators of

facilities that have mercuric acetate, mercuric chloride, and mercuric oxide on their sites in amounts exceeding the "threshold planning quantity" established for these substances must develop a program that addresses implementing emergency response plans and for notifying the public of accidental releases (EPA 1987a, 1995j). When extremely hazardous substances are formulated as a solids they are subject to either of two threshold planning quantities (EPA 1995j). If the solid exits in powdered form and has a particle size less than 100 microns, it is subject to the lower number. If the solid does not meet this criteria, it is subject to the higher number. The threshold planning quantities for mercuric acetate, mercuric chloride, mercuric oxide, and phenylmercury acetate are given in Table 7-1. It is important to note that reportable quantities for these compounds are the same as their threshold planning quantities.

The EPA regulates mercury under the Clean Air Act (CAA) and has designated it as a hazardous air pollutant (HAP). Emission standards for release of mercury to the atmosphere have been promulgated for mercury cell chloralkali plants, mercury ore processing facilities, major stationary sources, and municipal waste combustors (EPA 1975a, 1975b, 1995a, 1996b).

In accordance with the authority of the Safe Drinking Water Act (SDWA), EPA has established a safe drinking water standard for mercury at 2 µg/L (FSTRAC 1995). Under the Clean Water Act (CWA) EPA provides criterion concentrations for mercury as a priority toxic pollutant (EPA 1992).

Mercury is regulated as a "priority pollutant" in accordance with the Clean Water Act (CWA). The CWA establishes the basic structure for regulating the discharge of pollutants to waterways and is designed to ensure that all waters are sufficiently clean to protect public health and/or the environment. However, if waters and their sediments become contaminated from sources such as atmospheric deposition and discharges from industrial, municipal, or agricultural operations, toxic substances could concentrate in the tissue of fish and wildlife.

Advisories have been developed and issued to warn people about the health risks of consuming methylmercury-contaminated fish, shellfish, or wildlife and provide guidance as to the amount of fish or wildlife that can be safely consumed by each group (adults, pregnant women, nursing mothers, and young children). Each state, Native American tribe, or U.S. Territory establishes its own criteria for issuing fish and wildlife advisories. A fish or wildlife advisory will specify which waters (lake, rivers, estuaries, or coastal areas) or hunting areas have restrictions. The advisory provides information on the species and size range of the fish or wildlife of concern. The advisory may completely ban eating fish, shellfish, or

freshwater turtles, or it may recommend consumption limits (numbers of fish meals per specified time period) considered to be safe to eat. For example, an advisory may recommend that a person eat a certain type of fish no more than once a month. Advisories may specify the tissues of the fish or wildlife that can be safely eaten or proper preparation and cooking practices to help decrease exposure to methylmercury. The fish or wildlife advisory is typically more restrictive to protect pregnant women, nursing mothers, and young children. To reduce children's exposure to methylmercury, state advisory recommendations for fish consumption limits (meals per week or meals per month) should be strictly observed. Published information in the form of brochures on fish and wildlife advisories is available from State Public Health Departments, Natural Resources Departments, or Fish and Game Departments. Signs may be posted in certain fishing and hunting areas frequently used by recreational fishers and hunters to warn them about specific contamination problems (EPA 1995 Fish Sampling analysis and Guidance Document).

Currently, 1,782 advisories are in effect in 41 states and one U.S. Territory (American Samoa) restricting the consumption of mercury-contaminated fish, shellfish, or wildlife (freshwater turtles) (EPA 1998a). Methylmercury is the chemical pollutant responsible, in part, for over 77% of fish advisories issued in the United States (EPA 1998b). Eleven states (Connecticut, Indiana, Maine, Massachusetts, Michigan, Missouri, New Hampshire, New Jersey, North Carolina, Ohio, and Vermont) currently have state-wide mercury advisories recommending that all residents restrict consumption of locally caught freshwater fish. In addition, 5 states (Alabama, Florida, Louisiana, Massachusetts, and Texas) have issued statewide coastal mercury advisories for specific marine fish or shellfish species. In two states (Arizona and Minnesota), wildlife advisories have been issued recommending that residents restrict their consumption of freshwater turtles (EPA 1998a, 1998b).

The FDA currently has advice for consumers (posted on the Internet) recommending that pregnant women, and women of childbearing age who may become pregnant, limit their consumption of shark and swordfish to no more that one meal per month (FDA 1998). Methylmercury levels are much higher in these fish species than in the more commonly consumed species. The FDA advisory covers women of childbearing age who might become pregnant because dietary practices immediately before the pregnancy may have a direct bearing on fetal exposure during pregnancy. The FDA states that nursing mothers who follow this advice, will not expose their infants to increased health risks from methylmercury (FDA 1998). The FDA consumer advice hotline telephone number is **1-800-332-4010** and the FDA Web site is **www.FDA.gov**.

7. REGULATIONS AND ADVISORIES

The Food and Drug Administration (FDA) regulates the use of mercury compounds in the cosmetics industry. The FDA regulations on the use of mercury compounds in cosmetics state that "because of the known hazards of mercury, its questionable efficacy as a skin-bleaching agent, and the availability of effective and less toxic non-mercurial preservatives, there is no justification for the use of mercury in skin-bleaching preparations or its use as a preservative in cosmetics, with the exception of eye-area cosmetics" (FDA 1974). The use of mercury compounds as cosmetic ingredients has primarily been limited to their use as preservatives in eye area cosmetics for which no other effective and safe non-mercurial preservative is available. In other preparations they must contain no more than trace amounts of mercury that are unavoidable under the conditions of good manufacturing practices (FDA 1974). The mercurial concentration in these other preparations must measure less than 1 ppm or 0.0001% mercury metal (FDA 1974).

The FDA has also established an action level of 1 ppm for methylmercury in fish (FDA 1994, 1996). Because of reports that swordfish, shark and other large predatory fish may contain methylmercury levels which exceed the FDA 1 ppm limit, the agency’s advice to consumers warns pregnant women and women of childbearing age to limit their consumption of shark and swordfish to no more than one meal a month (FDA 1996). For others, the agency recommends that regular consumption of fish species with methylmercury levels around 1 ppm be limited to approximately 7 ounces per week; for fish with levels averaging 0.5 ppm, the limit is about 14 ounces per week (FDA 1996). The consumption advice is considered unnecessary for the top 10 species of fish that make up approximately 80% of the seafood market (FDA 1996). Canned tuna, shrimp, pollock, salmon, cod, catfish, clams, flatfish, crabs, and scallops are the top 10 species of fish consumed (FDA 1996). Since methylmercury levels in these species are usually less than 0.2 ppm and because few people eat more than the suggested weekly limit of 2.2 pounds (1 kilogram) for this contamination level, consumption limits are considered unnecessary (FDA 1996).

On May 28, 1998, the Consumer Product Safety Commission (CPSC) issued a guidance statement recommending that manufacturers of liquid-filled consumer products eliminate the use of hazardous chemicals in the liquid portion of their products (CPSC 1998). The guidance statement was issued as an effort to reduce the risk of exposing young children to hazardous chemicals contained in the liquid. The hazardous chemicals found in the liquid include mercury, ethylene glycol, diethylene glycol, methanol, methylene chloride, petroleum distillates, toluene, and xylene. Children’s products identified by the Commission as containing these hazardous chemicals include rolling balls, maze toys, bubble watches, and necklaces. Paperweights, keychains, liquid timers, and pens were household items identified as containing

mercury or other hazardous chemicals (CPSC 1998). In addition to the recommendation that manufacturers eliminate the use of hazardous chemicals in these products, the Commission also recommends that importers, distributors, and retailers who purchase a liquid-filled product for resale, obtain from the manufacturer assurances that their product does not contain hazardous liquid chemicals. Although the guidance is not a rule, it focuses on certain obligations authorized by the Federal Hazardous Substance Act (FHSA). Under the FHSA toys or other articles that contain an accessible and harmful amount of hazardous chemical and are intended for use by children are banned (CPSC 1998). Articles that are not intended for use by children, but create a risk of injury because they contain hazardous chemicals, require precautionary labeling under the FHSA (CPSC 1998).

In 1995, the CPSC assisted in facilitating the recall of necklaces bearing small vials or glass balls containing metal mercury (CPSC 1995). Although the vials and glass balls posed no immediate health threat, the recall noted that exposure to mercury vapor could cause long term health problems, especially for small children and pregnant women, if the vials or balls were broken (CPSC 1995).

Table 7-1. Regulations and Guidelines Applicable to Mercury

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
WHO	Drinking-water guideline values for health-related organics (applies to all forms of mercury)	0.001 mg/L	WHO 1984
	Permissible tolerable weekly intake	5 µg/kg total 3.3 µg/kg CH_3Hg	WHO 1976
NATIONAL			
Regulations: a. Air:			
OSHA	Air Contaminants permissible exposure limit (PEL) 8-hr. time weighted average (TWA)	0.1 mg/m^3	29 CFR 1910.1000 OSHA 1974[a]
EPA/OAR	Hazardous Air Pollutants	Yes	CAA Amendment Title III, Section 112 (b) U.S. Congress 1990
	Prevention of Significant Deterioration of Air Quality–pollutant emissions rate defined as significant	0.1 tons per year	40 CFR 51.166 EPA 1996h
	pollutant emission rate-exemption of major stationary source	< 0.25 µg/m^3 (24-hour average)	
	Standards of Performance for New Stationary Sources–emissions limits for municipal waste combustors	0.080 mg/m^3 or 15% of the potential mercury emission concentration corrected to 7% oxygen	40 CFR 60, Subpart Cb EPA 1995a
	standards of performance for municipal waste combustors	Yes	40 CFR 60, Subpart Eb EPA 1995b
	National Emission Standards for Hazardous Air Pollutants (NESHAPs)–list of pollutants and applicability	Yes	40 CFR 61.01 EPA 1971a
	standard for mercury ore processing facilities and mercury cell chlor-alkali plants (mercury)	< 2300 g per 24-hour period	40 CFR 61, Subpart E EPA 1975c
	standard for sludge incineration plants, sludge drying plants, or a combination of these that process wastewater treatment plant sludges (mercury)	< 3200 g per 24-hour period	

Table 7-1. Regulations and Guidelines Applicable to Mercury (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	National Emission Standards for Hazardous Air Pollutants for Source Categories-Regulations Governing Extension for Early Reductions of Hazardous Air Pollutants–list of high-risk pollutants	Yes	40 CFR 63, Subpart D EPA 1994a
b. Water			
EPA-ODW	National Primary Drinking Water Regulations		
	Maximum Contaminant Level (MCL) for inorganic compounds	0.002 mg/L	40 CFR 141, Subpart F EPA 1992b
	BAT for inorganic compounds	coagulation/ filtration[e,f], granular activated charcoal, lime softening[e,f], reverse osmosis[e]	
	Hazardous Waste Injection Restrictions–waste specific prohibitions; California list wastes	Yes	40 CFR 148.12 EPA 1988
EPA-OW	Designation of Hazardous Substances- List of hazardous substances, Table 116.4 (mercuric cyanide, mercuric nitrate, mercuric sulfate, mercuric thiocyanate, mercurous nitrate)	Yes	40 CFR 116.4 EPA 1978a
	Determination of Reportable Quantities for Hazardous Substances-RQ Pursuant to Section 311 CWA–mercuric cyanide	1 pound (0.45 kg)	40 CFR 117.3 EPA 1995c
	mercuric nitrate, mercuric sulfate, mercuric thiocyanate, mercurous nitrate	10 pounds (4.54 kg)	
	EPA Permit Programs: National Pollution Discharge Elimination System (NPDES)–other toxic pollutant (metals and cyanide) and total phenols	Yes	40 CFR 122, App. D EPA 1983
	Criteria and Standards for the NPDES-Instructions for Form 2C, Application for Permit to Discharge Wastewater (mercuric cyanide, mercuric nitrate, mercuric sulfate, mercuric thiocyanate, mercurous nitrate)	Yes	40 CFR 125 EPA 1984a

Table 7-1. Regulations and Guidelines Applicable to Mercury (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	Toxics Criteria for those States Not Complying with CWA Section 303(c)(2)(B)-criterion concentration for priority toxic pollutants	Maximum[b] (µg/L)	Continous[c] (µg/L)	40 CFR 131.36 EPA 1992a
	freshwater	2.10	0.012[d]	
	saltwater	1.80	0.025	
	human health consumption of:			
	water and organisms	0.14[e]		
	organisms only	0.15[e]		
	Water Quality Guidance for the Great Lakes Systems-protection of aquatic life in ambient water	Maximum[b] (µg/L)	Continous[c] (µg/L)	40 CFR 132 EPA 1995d
	acute water quality criteria for mercury (II) total recoverable	1.694 µg/L	NA	
	chronic water quality criteria for mercury (II) total recoverable	NA	0.908 µg/L	
	water quality criteria for protection of human health (HNV for mercury including methylmercury) drinking water and non-drinking water	1.8×10^{-3} µg/L		
	water quality criteria for protection of human health (mercury including methylmercury)	1.3×10^{-3} µg/L		
	pollutants that are bioaccumulative chemicals of concern	mercury		
	Standards for the Control of Residual Radioactive Materials from Inactive Uranium Processing Sites–maximum concentration of constituents for groundwater (mercury)	0.002 µg/L		40 CFR 192.04 EPA 1995e
	Criteria for the Evaluation of Permit Applications for Ocean Dumping of Materials–constituents prohibited as other than trace contaminants	Yes		40 CFR 227.6 EPA 1978b
c. Food:				
FDA	Action Level for Poisonous or Deleterious Substances in Human Food and Animal Feed			FDA 1994 and FDA 1998
	fish, shellfish, crustaceans, other aquatic animals (fresh, frozen or processed)	1 ppm		
	wheat-pink kernels only; an average of 10 or more pink kernels per 500 grams	1 ppm		
	Bottled water	0.002 µg/L		21 CFR 165.110 FDA 1995

Table 7-1. Regulations and Guidelines Applicable to Mercury (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
d. Other:			
EPA-OERR	List of Hazardous Substances and Reportable Quantities (RQ)	Statutory / Final (pounds)	40 CFR 302.4 EPA 1995i
	mercury	1 / 1	
	mercuric cyanide	1 / 1	
	mercuric nitrate	10 / 10	
	mercuric sulfate	10 / 10	
	mercuric thiocyanate	10 / 10	
	mercurous nitrate	10 / 10	
	mercury fulminate	1 / 10	
	phenylmercury acetate	1 / 100	
EPA-OSW	Criteria for Classification of solid Waste Disposal Facilities and Practices	Yes	40 CFR 257, App I EPA 1991a
	Criteria for Municipal Solid Waste Landfills–MCLs	0.002 µg/L	40 CFR 258.40 and App. II
	list of hazardous constituent	Yes	EPA 1991b
	Identification and Listing of Hazardous Waste–definition of a Hazardous Waste	Yes	40 CFR 261.3 EPA 1992c
	generic exclusion levels for K061 and K062 wastes for nonwastewater HTMR residues	0.009 mg/L (maximum for single composite sample-TCLP)	
	toxicity characteristic–maximum concentration	0.2 mg/L	40 CFR 261.24 EPA 1993a
	hazardous waste from specific sources	K071 K106	40 CFR 261.32 EPA 1992d
	discarded commercial chemical products, off-specification, container residues, and spills	Yes	40 CFR 261.33 EPA 1994b
	mercury	U151	
	mercury fulminate	P065	
	phenylmercuric acetate	P092	
	basis for listing hazardous wastes	K071 K106	40 CFR 261, App. VII EPA 1995g
	hazardous constituents-		40 CFR 261, App. VIII
	mercury	U151	EPA 1994c
	mercury fulminate	P065	
	phenylmercury acetate	P092	
	Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities–Releases from Solid Waste Management Units	Yes	40 CFR 264.94 EPA 1995f
	concentration limits for groundwater protection	0.002 µg/L	
	ground-water monitoring list	yes	40 CFR 264, App. IX EPA 1995h

Table 7-1. Regulations and Guidelines Applicable to Mercury (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Interim Status Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities–thermal treatment, incinerators, and land treatment	Yes	40 CFR 265 EPA 1991c
	Standards for Management of Specific Hazardous Wastes Facilities–hazardous waste burned in boilers and industrial furnaces	Yes	40 CFR 266.100 EPA 1991d
	reference air concentration	0.3 µg/m^3	40 CFR 266 App. IV EPA 1991d
	health-based limits for exclusion of waste-derived residues	2x10^{-1}	40 CFR 266 App. VII EPA 1993b
	mercury bearing waste that may be processed in exempt mercury recover units	Yes	40 CFR 266 App. XIII EPA 1994d
	methods Manual for Compliance with BIF Regulations	Yes	40 CFR 266, App. IX EPA 1991e
	Land Disposal Restrictions– treatment Standards	WW NWW (technology code or mg/L TCLP)	40 CFR 268.40 EPA 1997d
	D009	0.20 IMERC, RMERC, AMLGM, 0.20	
	F039	0.15 0.025	
	K001	NA 0.025	
	K071	NA 0.20	
	K084	0.15 0.25 or 0.25	
	K101	0.15 NA	
	K102	0.15 NA	
	K106 (≥260 mg/kg total mercury)	0.15 RMERC, 0.20, 0.025	
	P065 (mercury fulminate)	0.15 IMERC, RMERC, 0.2, 0.025	
	P092 (phenylmercuric acetate)	0.15 IMERC, RMERC, 0.20, 0.025	
	U151	0.15 RMERC, AMLGM, 0.20, 0.025	
	Treatment Standards Expressed as Specified Technologies	AMLGM, IMERC, and RMERC,	40 CFR 268.42 EPA 1994e

Table 7-1. Regulations and Guidelines Applicable to Mercury (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Treatment Standards for Hazardous Debris	Yes	40 CFR 268.45 EPA 1992e
	Emergency Planning and Notification-Extremely Hazardous Substances and Their Threshold Planning Quantities		40 CFR 355, App. A EPA 1995j
	mercuric acetate	500/10,000 pounds	
	mercuric chloride	500/10,000 pounds	
	mercuric oxide	500/10,000 pounds	
	phenylmercury acetate	500/10,000 pounds	
	Emergency Planning and Notification-Extremely Hazardous Substances and Their Reportable Quantities		
	mercuric acetate	500 pounds	
	mercuric chloride	500 pounds	
	mercuric oxide	500 pounds	
	phenylmercury acetate	100 pounds	
	Toxic Chemical Release Reporting: Community Right-to-Know--Specific Chemical Listing-Chemicals and Chemical Categories	Yes	40 CFR 372.65 EPA 1987a
FDA	Cosmetics-use of mercury compounds	Yes	21 CFR 700.13 FDA 1974
	eye area cosmetics (mercury calculated as the metal)	< 65 ppm	
NRC	Standards for Protection Against Radiation	Yes	10 CFR 20 DOE 1993
	Rules of General Applicability to Domestic Licensing of Byproduct Material	Yes	10 CFR 30 DOE 1994a
	Domestic Licensing of Source Material	Yes	10 CFR 40 DOE 1994b
	Packaging and Transport of Radioactive Material	Yes	10 CFR 71 DOE 1996a
	Export and Import of Nuclear Equipment and Material	Yes	10 CFR 110 DOE 1996b
Guidelines a: Air:			
ACGIH	STEL/Ceiling-alkyl compounds	0.3 mg/m^3	ACGIH 1996
	TWA-alkyl compounds	0.01 mg/m^3	
	aryl compounds	0.1 mg/m^3	
	inorganic forms including metallic mercury	0.025 mg/m^3	
NIOSH	Recommended Exposure Limit for Occupation Exposure (8-hr TWA)-aryl or inorganic mercury as mercury	0.1 mg/m^3 ceiling (skin)	NIOSH 1992
	mercury (organo) alkyl compounds as mercury	0.01 mg/m^3 TWA 0.03 mg/m^3 STEL (skin)	
	mercury vapor as mercury	0.05 mg/m^3 TWA	

Table 7-1. Regulations and Guidelines Applicable to Mercury (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
b. Water:			
EPA-ODW	National Primary Drinking Water Regulations–MCLGs for inorganic compounds	0.002 mg/L	40 CFR 141, Subpart F EPA 1992b
	Lifetime Health Advisory (adult)-inorganic mercury (final)	0.002 mg/L	EPA 1996g
	Longer-term Health Advisory (adult)-inorganic mercury (final)	0.002 mg/L	
	Drinking Water Equivalent Level	0.002 mg/L	
	Ambient Water Quality Criteria for Human Health–mercury and phenylmercuric acetate		IRIS 1997 IRIS 1997
	water and fish	1.44×10^{-1} µg/L	
	fish only	1.46×10^{-1} µg/L	
	Ambient Water Quality Criteria for Aquatic Organisms–mercury and phenylmercuric acetate as mercury	Marine Freshwater (µg/L)	IRIS 1997 IRIS 1997
	acute(1- hour average)	2.1 2.4	
	chronic (4-day average)	2.5×10^{-2} 1.2×10^{-2}	
c. Food			
FDA	Consumption of shark or swordfish by pregnant or childbearing age women	No more than one meal a month	FDA 1998
	Regular consumption of fish species with methylmercury levels around 1 ppm	7 ounces per week	
	Fish with levels averaging 0.5 ppm	14 ounces per week	
d. Other:			
ACGIH	Cancer Ranking-metallic mercury	A4[g]	ACGIH 1996
EPA	Cancer Classification		IRIS 1997
	elemental (metallic) mercury	D[h]	
	methyl mercury	C[i]	
	mercuric chloride	C[i]	
CPSC	Notice of Availability of Guidance Document on Hazardous Liquid Chemicals in Children's Products	Yes	63 FR 29182 CPSC 1998
EPA	RfC (elemental mercury)	3×10^{-4} mg/m^3 (0.3 µg/m^3)	IRIS 1997
	RfD (mercuric chloride)	3×10^{-4} mg/kg/day (0.3 µg/kg/day)	
	RfD (methyl mercury)	1×10^{-4} mg/kg/day (0.1 µg/kg/day)	
	RfD (phenylmercuric acetate)	8×10^{-5} mg/kg/day (0.08 µg/kg/day)	

Table 7-1. Regulations and Guidelines Applicable to Mercury (continued)

Agency	Description	Information	References
STATE			
Regulations and Guidelines:			
a. Air:	Average Acceptable Ambient Air Concentrations-Mercury		NATICH 1992
AZ	1 hour	1.5 $\mu g/m^3$	
	24 hours	$4.0x10^{-1}$ $\mu g/m^3$	
(phenylmercuric acetate)	1 hour	$2.5x10^{-1}$ $\mu g/m^3$	
	24 hours	$7.9x10^{-2}$ $\mu g/m^3$	
CT	8 hours	1.0 $\mu g/m^3$	
	8 hours	2.0 $\mu g/m^3$	
FL-FtLdle	8 hours	$5.0x10^{-4}$ mg/m^3	
FL-Pinella	8 hours	$1.0x10^{-1}$ $\mu g/m^3$	
	24 hours	$2.4x10^{-2}$ $\mu g/m^3$	
(phenylmercuric acetate)	Annual	$7.5x10^{-1}$ $\mu g/m^3$	
FL-Tampa	8 hours	$5.0x10^{-4}$ mg/m^3	
IN	8 hours	$5.0x10^{-2}$ $\mu g/m^3$	
KS	Annual	$2.4x10^{-2}$ $\mu g/m^3$	
LA	8 hours	1.19 $\mu g/m^3$	
MT	24 hours	$8.0x10^{-2}$ $\mu g/m^3$	
	Annual	$1.0x10^{-2}$ $\mu g/m^3$	
NC	15 minutes	$6.0x10^{-4}$ mg/m^3	
NC-Forco	24 hours	$6.0x10^{-4}$ mg/m^3	
ND	8 hours	$5.0x10^{-4}$ mg/m^3	
NV	Not Indicated	$2.0x10^{-3}$ mg/m^3	
NY	1 year	$1.67x10^{-1}$ $\mu g/m^3$	
OK	24 hours	$5.0x10^{-1}$ $\mu g/m^3$	
(phenylmercuric acetate)	24 hours	$5.0x10^{-1}$ $\mu g/m^3$	
PA-Phil	1 year	$2.4x10^{-1}$ $\mu g/m^3$	
	Annual	$2.4x10^{-1}$ $\mu g/m^3$	
SC	24 hours	$2.5x10^{-1}$ $\mu g/m^3$	
TX	30 minutes	$5.0x10^{-1}$ $\mu g/m^3$	
	Annual	$5.0x10^{-2}$ $\mu g/m^3$	
VA	24 hours	$1.7x10^{4}$ $\mu g/m^3$	
	24 hours	$8.3x10^{1}$ $\mu g/m^3$	
	24 hours	1.7 $\mu g/m^3$	
VT	Annual	$1.2x10^{-1}$ $\mu g/m^3$	
WA-SWEST	Annual	$3.0x10^{-1}$ $\mu g/m^3$	
b. Water	Water Quality Criteria: Human Health		FSTRAC 1995
AL	Drinking water (standard)	2 µg/L	
AZ	Drinking water (standard)	2 µg/L	

Table 7-1. Regulations and Guidelines Applicable to Mercury (continued)

Agency	Description	Information		References
STATE (cont.)				
ME	Drinking water (guideline)	2 µg/L		
MN	Drinking water (guideline)	2 µg/L		
c. Other				
	Fish and Wildlife Consumption Advisories	Number of Advisories Issued for 1997		EPA 1998a
		Fish	Wildlife	
AL[j]	Freshwater; Marine (statewide)	4		EPA 1998a EPA 1998b
AS	Marine	1		EPA 1998a
AZ	Freshwater	2	3 (turtles)	
AR	Freshwater	19		
CA	Freshwater; Estuarine	11		
CO	Freshwater	8		
CT[k]	Freshwater (statewide)	5		EPA 1998a EPA 1998b
FL[j]	Freshwater;Estuarine;Marine (statewide)	96		
GA	Freshwater; Estuarine	23		EPA 1998a
ID[k]	Freshwater	1		EPA 1998a EPA 1998b
IL	Freshwater	2		EPA 1998a
IN	Freshwater (statewide)	109		EPA 1998a EPA 1998b
KY	Freshwater	1		EPA 1998a
LA[j]	Freshwater; Marine (statewide)	15		
MA[j,k]	Freshwater (statewide); Marine (statewide)	55		
ME[k]	Freshwater (statewide)	1		
MI[k]	Freshwater (statewide)	41		
MN	Freshwater	755	6 (turtles)	EPA 1998a
MO[k]	Freshwater (statewide)	1		EPA 1998a EPA 1998b
MS	Freshwater	7		EPA 1998a
MT	Freshwater	22		
NC[k]	Freshwater (statewide)	10		EPA 1998a EPA 1998b
ND	Freshwater	36		EPA 1998a
NE	Freshwater	12		
NH[k]	Freshwater (statewide)	2		EPA 1998a EPA 1998b
NJ[k]	Freshwater (statewide)	30		
NM	Freshwater	26		EPA 1998a
NY	Freshwater	15		
NV	Freshwater	2		EPA 1998a

Table 7-1. Regulations and Guidelines Applicable to Mercury (continued)

Agency	Description	Information	References
STATE (cont.)			
OH[k]	Freshwater (statewide)	19	EPA 1998a EPA 1998b
OK	Freshwater	1	EPA 1998a
OR	Freshwater	9	
PA	Freshwater	1	
RI	Freshwater	1	
SC	Freshwater	24	
TN	Freshwater	2	
TX[j]	Freshwater; Estuarine; Marine (statewide)	7	EPA 1998a EPA 1998b
VT[k]	Freshwater (statewide)	3	
VA	Freshwater	3	EPA 1998a
WA	Estuarine	1	
WI	Freshwater	390	

[a] A U.S. Court of Appeals rescinded the 1989 PELs promulgated by OSHA. Only PELs in place prior to the 1989 rule are currently allowed (58 FR 35338, June 30, 1993).
[b] Criteria maximum concentration (CMC) is the highest concentration of a pollutant to which aquatic life can be exposed for a short period of time (l-hour average) without deleterious effects and is not to be exceeded more than once every three years.
[c] Criteria continuous concentration (CCC) is the highest concentration of a pollutant to which aquatic life can be exposed for a short period of time (4 days) without deleterious effects and is not to be exceeded more than once every three years.
[d] If the CCC for total mercury exceeds 0.012 µg/L more than once in a 3-year period in the ambient water, the edible portion of aquatic species of concern must be analyzed to determine whether the concentration of methyl mercury exceeds the FDA action level of 1.0 mg/kg.
[e] BAT only if influent mercury concentration is less than 10 µg/L.
[f] BAT for systems with less than 500 service connections.
[g] A4 means that the substance in not classifiable as a human carcinogen. There are inadequate data on which to classify the substance for humans and/or animals.
[h] Cancer classification D means that the substance is not classifiable as to its carcinogenicity. There is inadequate or no human and animal evidence of carcinogenicity.
[i] Cancer classification C means that the substance is a possible human carcinogen.
[j] States issuing coastal for mercury in specific marine fish and shellfish species.
[k] State issuing state-wide advisories for mercury recommending that all residents restrict consumption of locally-caught freshwater fish.

AMLGM = Amalgamation of Liquid, Elemental Mercury Contaminated with Radioactive Materials; BAT = Best Available Technology; BIF = Boilers and Industrial Furnaces; CAA = Clean Air Act; CWA = Clean Water Act; CPSC = Consumer Product Safety Commission; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FSTRAC = Federal State Toxicology and Regulatory Alliance committee; HAP = Hazardous Air Pollutants; HNV = Human Noncancer Value; HTMR = High Temperature Metals Recovery; IARC = International Agency for Research on Cancer; IMERC = Incineration of Wastes containing Organics and Mercury;MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NAS = National Academy of Sciences; NESHAP= National Emission Standards for Hazardous Air Pollutants; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollution Discharge Elimination System; NRC = Nuclear Regulatory Commission; NWW = Nonwastewaters; OAR - Office of Air and Radiation; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; PEL = Permissible Exposure Limit; RfD = Reference Dose; RMERC = Retorting or Roasting of Mercury RQ = Reportable Quantities; SOCMI = Synthetic Organic Chemicals Manufacturing Industry; STEL = Short-term exposure Limit; TCLP = Toxicity Characteristic Leaching Procedure; TLV= Threshold Limit Value; TWA = Time-weighted Average; WHO = World Health Organization; WW = Wastewaters

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9. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—is usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—is a statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—the quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and in utero death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—a specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—a measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunological Effects—are functional changes in the immune response.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL) —An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio—a means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—a phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40 hour workweek.

Pesticide—general classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—is a set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—is a type of physiologically based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information 4such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study--a type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—the possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Mercury (metallic, vapor)
CAS Number: 7439-97-6
Date: June 15, 2001
Profile Status: Final Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 21
Species: Human

Minimal Risk Level: 0.0002 [ ] mg/kg/day [X] mg/m^3

Reference: Fawer RF, de Ribaupierre Y, Guillemin MP, et al. 1983. Measurement of hand tremor induced by industrial exposure to metallic mercury. British Journal of Industrial Medicine 40:204-208.

Experimental design. Hand tremors were measured in 26 male workers exposed to metallic mercury and 25 control males working in the same facilities, but not exposed to mercury. Workers had been exposed to mercury through the manufacture of fluorescent tubes, chloralkali, or acetaldehyde. Mercury-exposed workers had a duration of exposure of 15.3±2.6 years, blood mercury of 41.3±3.5 micromoles Hg/L, and urinary mercury of 11.3±1.2 micromoles Hg/mole of creatinine. The mean mercury level measured using personal air monitors was 0.026±0.004 mg/m^3 (3 subjects were exposed to greater than 0.05 mg/m^3). Hand tremors were measured in the subjects using an accelerometer attached to the dorsum of the hand both at rest and while holding 1,250 grams. The highest peak frequency of the acceleration was determined.

Effects noted in study and corresponding doses: The highest peak frequency of the tremor was greater in exposed men than in controls. The highest peak frequency corresponded significantly to duration of exposure and age. Comparison of tremors using an index of the entire spectrum of the tremor showed no differences between exposed men and controls at rest, but the changes observed between rest and load were higher in the exposed men. These changes correlated with the duration of exposure and biological indices of exposure (blood and mercury levels), but not with age.

Dose and end point used for MRL derivation: 0.026 mg/m^3; increased frequency of tremors.

[ ] NOAEL [X] LOAEL

Uncertainty and Modifying Factors used in MRL derivation: 30

[ ] 1 [X] 3 [ ] 10 (for use of a minimal LOAEL)
[X] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so explain: No.

Was a conversion used from intermittent to continuous exposure?
If so, explain: Yes. To estimate an equivalent continuous exposure concentration, the average concentration assumed for the 8 hour/day exposures was multiplied by 8/24 and 5/7 (0.026 mg/m^3 x 8/24 hours/day x 5/7 days/week = 0.0062 mg/m^3). Uncertainty factors of 10 for variability in sensitivity to mercury within the human population and 3 for use of a minimal effect LOAEL in MRL derivation were then applied to the calculated 0.0062 mg/m^3 value, yielding a chronic inhalation MRL of 0.2 $\mu g/m^3$. It should be noted that this MRL, although based upon an adult working population, is considered also to be sufficiently protective of neurodevelopmental effects in developing embryos/fetuses and children, the most sensitive subgroups for metallic mercury toxicity.

$LOAEL_{(ADJ)}$ = 0.026 mg/m^3 x (8 hr/24 hr) x (5 days/7 days)
= 0.0062 mg/m^3

MRL = $LOAEL_{(ADJ)}$ ÷ UF = 0.0062 mg/m^3 ÷ 30 = 0.0002 mg/m^3

If an inhalation study in animals, list the conversion factors used in determining human equivalent concentration (HEC): No.

Additional studies or pertinent information which lend support to this MRL: Inhaled metallic mercury is quickly absorbed through the lungs into the blood. Its biologic half-life in humans is approximately 60 days, with the half-life varying with the physiological compartment (e.g., 21 days in the head, versus 64 days in the kidneys; Cherian et al. 1978). Since the duration of exposure does influence the level of mercury in the body, the exposure level reported in the Fawer et al. (1983) occupational study was extrapolated from an 8-hour/day, 40-hour/workweek exposure to a level equivalent to a continuous 24 hour/day, 7 days/week exposure as might be encountered near a hazardous waste site containing metallic mercury.

The ability of long-term, low level exposure to metallic mercury to produce a degradation in neurological performance was also demonstrated in other studies. One such study (Ngim et al. 1992) attributed adverse neurological effects to a lower average level of exposure than did the Fawer et al. (1983) study; however, this study was not used in deriving a chronic inhalation MRL due to uncertainties concerning the study protocol, including methodological and reporting deficiencies. In the Ngim et al. (1992) study, dentists with an average of 5.5 years of exposure to low levels of metallic mercury were reported to have demonstrated impaired performance on several neurobehavioral tests. Exposure levels measured at the time of the study ranged from 0.0007 to 0.042 mg/m^3, with an average of 0.014 mg/m^3. Mean blood mercury levels among the dentists ranged from 0.6 to 57 µg/L, with a geometric mean of 9.8 µg/L. The performance of the dentists on finger tapping (motor speed measure), trail making (visual scanning measure), digit symbol (measure of visuomotor coordination and concentration), digit span, logical memory delayed recall (measure of visual memory), and Bender-Gestalt time (measures visuomotor coordination) were significantly poorer than controls. The exposed dentists also showed higher aggression than did controls. Furthermore, within the group of exposed dentists, significant differences were reported to have been observed between a subgroup with high mercury exposure compared to a subgroup with lower exposure. These exposure severity subgroups were not compared to controls, and average exposure levels for the subgroups were not reported. The design and reporting of this study limit its usefulness in deriving an MRL for metallic mercury. The exposure status of the subjects was known to the investigator during testing, mercury levels were not reported for controls, and methods used to correct for confounders (especially the common use in this population of traditional medicines containing mercury) were not reported. It was also unclear whether the results for the mercury exposure group were inordinately influenced or skewed by the individual dentists with the highest exposures and/or blood levels. These confounding factors precluded the use of the Ngim et al. (1992) study for the derivation of an MRL, but the study does provide support for both the premise that

low-dose chronic exposure to metallic mercury can result in adverse health sequelae and the chronic inhalation MRL that is based upon the Fawer et al. (1983) study of occupationally exposed individuals.

Other occupational studies further support the ability of metallic mercury to induce neurologic deficits. Several studies have reported significant effects on tremor or cognitive skills among groups exposed occupationally to comparable or slightly higher (up to 0.076 mg/m^3) levels (Ehrenberg et al. 1991; Piikivi et al. 1984; Roels et al. 1982). Difficulty with heel-to-toe gait was observed in thermometer plant workers subjected to mean personal breathing zone air concentrations of 0.076 mg/m^3 (range of 0.026–0.27 mg/m^3 (Ehrenberg et al. 1991).

Tremors have also been reported in occupationally exposed workers with urinary mercury concentrations of 50–100 µg/g creatinine, and blood levels of 10–20 µg/L (Roels et al. 1982). By comparison, blood mercury levels in the Fawer et al. (1983) study averaged 41.3 and 16.6 µmol Hg/L for the exposed and control groups, respectively. Urinary mercury levels for the exposed workers in the Fawer et al. (1983) study averaged 11.3 µmol Hg/mol creatinine (about 20 µg/g creatinine), compared with 3.4 µmol/mol creatinine in the controls. In another study (Piikivi et al. 1984), decreases in performance on tests that measured intelligence (similarities) and memory (digit span and visual reproduction) were observed in chloralkali workers exposed for an average of 16.9 years (range, 10–37 years) to low levels of mercury when compared to an age-matched control group. In this study, significant differences from controls were observed on these tests among 16 workers with blood levels ranging from 75 to 344 nmol/L and urine levels ranging from 280 (about 56 µg/L) to 663 nmol/L. Abnormal nerve conduction velocities have also been observed in chloralkali plant workers at a mean urine concentration of 450 µg/L (Levine et al.1982). These workers also experienced weakness, paresthesias, and muscle cramps. Prolongation of brainstem auditory evoked potentials was observed in workers with urinary mercury levels of 325 µg/g creatinine (Discalzi et al. 1993). Prolonged somatosensory evoked potentials were found in 28 subjects exposed to airborne mercury concentrations of 20–96 mg/m^3 (Langauer-Lewowicka and Kazibutowska 1989).

Agency Contact (Chemical Manager): John Risher

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Mercury inorganic
CAS Number: 7439-97-6
Date: June 15, 2001
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 7
Species: Rat

Minimal Risk Level: 0.007 [X] mg/kg/day [ ] mg/m^3

Reference: NTP. 1993. NTP technical report on the toxicology and carcinogenesis studies of mercuric chloride (CAS no. 7487-94-7) in F344/N rats and $B6C3F_1$ mice (gavage studies). NTP TR408.

Experimental design: Fischer 344 rats (5/sex/group) were administered 0, 0.93, 1.9, 3.7, 7.4, or 14.8 mg Hg/kg/day as mercuric chloride once daily for 14 days, excluding weekends. The mercuric chloride was administered in deionized water via gavage. Body weights were measured and a complete necropsy was performed. Organ weights were obtained for the brain, heart, kidney, liver, lung, and thymus.

Effects noted in study and corresponding doses: The relative and absolute kidney weights were significantly increased for males exposed to at least 1.9 mg Hg/kg/day and for females exposed to at least 3.7 mg Hg/kg/day. An increased incidence of renal tubular necrosis (graded minimal in severity) was observed in 3 of 5 males and 1 of 5 females at the 3.7 mg Hg/kg/day dose level. At 7.4 mg Hg/kg/day, 5/5 males and 3/5 females had minimal-to-mild effects, and at 14.8 mg Hg/kg/day all animals exhibited mild-to-moderate effects.

Dose and end point used for MRL derivation: 0.93 mg Hg/kg/day; no renal effects.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation: 100

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so explain: No.

Was a conversion used from intermittent to continuous exposure?
If so, explain: Yes. To estimate an equivalent continuous exposure concentration, the average concentration was multiplied by 5 days/7 days.

$NOAEL_{(ADJ)}$ = 0.93 mg/kg/day x (5 days/7 days)
= 0.66 mg/kg/day

MRL = $NOAEL_{(ADJ)}$ ÷ UF = 0.66 mg/kg/day ÷ 100 = 0.007 mg/kg/day

If an inhalation study in animals, list the conversion factors used in determining human equivalent concentration (HEC): None.

Additional studies or pertinent information which lend support to this MRL: Several other studies examining the effects of oral exposure to inorganic mercury salts have also shown renal toxicity in humans as a result of acute oral exposures. Kidney effects (i.e., heavy albuminuria, hypoalbuminemia, edema, and hypercholesterolemia) have been reported after therapeutic administration of inorganic mercury (Kazantzis et al. 1962). Acute renal failure has been observed in a number of case studies in which mercuric chloride has been ingested (Afonso and deAlvarez 1960; Murphy et al. 1979; Samuels et al. 1982). Autopsy of a 35-year-old man who ingested a lethal dose of mercuric chloride and exhibited acute renal failure showed pale and swollen kidneys (Murphy et al. 1979). A case study reported acute renal failure characterized by oliguria, proteinuria, hematuria, and granular casts in a woman who ingested 30 mg mercury/kg as mercuric chloride (Afonso and deAlvarez 1960). Another case study reported a dramatic increase in urinary protein secretion by a patient who ingested a single dose of 15.8 mg mercury/kg as mercuric chloride (assuming a body weight of 70 kg) (Pesce et al. 1977). The authors of the report surmised that the increased excretion of both albumin and β_2-microglobulin were indicative of mercury-induced tubular and glomerular pathology. Acute renal failure that persisted for 10 days was also observed in a 19-month-old child who ingested an unknown amount of powdered mercuric chloride (Samuels et al. 1982). Decreased urine was also observed in a 22-year-old who attempted suicide by ingesting approximately 20 mg mercury/kg (Chugh et al. 1978).

Agency Contact (Chemical Manager): John Risher

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Mercury (inorganic)
CAS number(s): 7439-97-6
Date: June 15, 2001
Profile status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 17
Species: Rat

Minimal Risk Level: 0.002 [X] mg/kg/day [ ] ppm

Reference: NTP. 1993. NTP technical report on the toxicology and carcinogenesis studies of mercuric chloride (CAS no. 7487-94-7) in F344/N rats and B6C3F$_1$ mice (gavage studies). NTP TR408.

Experimental design: Fischer 344 rats (10/sex/group) were administered 0, 0.23, 0.46, 0.93, 1.9, or 3.7 mg Hg/kg/day as mercuric chloride in deionized water by oral gavage once daily 5 days per week for 26 weeks. Body weights were recorded weekly. Surviving animals were sacrificed and necropsied. Organ weights were determined for the brain, heart, liver, lung, kidney, thymus, and testes. Histopathological examinations were performed.

Effects noted in study and corresponding doses: The relative and absolute kidney weights were significantly increased for dosed males and for females exposed to at least 0.46 mg/kg/day. At the two low-dose groups and the control group, minimal nephropathy was observed in nearly all the males. At 0.93 mg/kg/day level, renal tubule necrosis became more severe (moderate) and was statistically significant and remained at this severity at the higher dose groups. The female rats had a significant increased incidence at the high dose only, and severity was minimal. Nephropathy was characterized by foci of tubular regeneration, thickened tubular basement membrane, and scattered dilated tubules containing hyaline casts. Macroscopic changes included granular kidneys in dosed males. After 4 months of exposure, urinary levels of alkaline phosphatase, aspartate aminotransferase, lactate dehydrogenase, and gamma-glutamyl transferase were significantly elevated in both sexes at 3.7 mg Hg/kg/day, but at 6 months control levels had increased such that enzyme levels in males were no longer statistically significant and only levels of alkaline phosphatase and gamma-glutamyl transferase were significantly elevated in females.

Dose end point used for MRL derivation: 0.23 mg Hg/kg/day; no renal effects
[X] NOAEL [ ]LOAEL

Uncertainty and modifying factors used in MRL derivation: 100

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so explain: No conversion factor used.

Was a conversion used from intermittent to continuous exposure?

If so, explain: Yes. The dose was adjusted for a continuous exposure by multiplying the NOAEL (0.23 mg/kg/day) by a conversion factor of 5/7:

$NOAEL_{(ADJ)}$ = 0.23 mg/kg/day x (5 days/7 days)
= 0.16 mg/kg/day

MRL = $NOAEL_{(ADJ)}$ ÷ UF = 0.16 mg/kg/day ÷ 100 = 0.002 mg/kg/day

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Additional studies or pertinent information that lend support to this MRL: Renal toxicity has been observed in other intermediate-duration oral studies on rats and mice exposed to inorganic mercury (Carmignani et al. 1992; Jonker et al. 1993a; NTP 1993), as well as case reports on humans ingesting inorganic mercury for acute and chronic durations (Afonso and deAlvarez 1960; Davis et al. 1974; Kang-Yum and Oransky 1992; Nielsen et al. 1991; Pesce et al. 1977).

Agency Contact (Chemical Manager): John Risher

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Methylmercury
CAS Number: 22967-92-6
Date: June 15, 2001
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 88
Species: Human

Minimal Risk Level: 0.0003 [X] mg/kg/day [ ] mg/m^3

Reference: Davidson et al. 1998. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: Outcomes at 66 months of age in the Seychelles Child Development Study. JAMA 280(8):701-707.

Experimental design. This MRL is based on the results of the Seychelles Child Development Study (SCDS), a series of evaluations on a population in the Seychelles Islands. The chronic oral MRL for methylmercury is based upon the Seychelles Child Development Study (SCDS), in which over 700 mother-infant pairs have, to date, been followed and tested from parturition through 66 months of age (Davidson et al. 1998). The SCDS was conducted as a double-blind study and used maternal hair mercury as the index of fetal exposure. Enrollees were recruited by the head nurse/hospital midwife by asking the mothers if they wished to participate in the study when they arrived at the hospital for delivery. The first 779 who did not decline participation became the mothers in the study cohort. Of the initial 779 mothers enrolled in the study at parturition, 740 remained at the predetermined child testing age of 6.5 months, 738 remained in the 19-month cohort, 736 remained at 29 months, and 711 remained for the 66-month neurobehavioral and developmental examinations.

The Seychellois were chosen as a study population for a number of reasons. (1) All fish contain some level of methylmercury (Davidson et al. 1998); and the Seychellois regularly consume a large quantity and variety of ocean fish, with 12 fish meals per week representing a typical methylmercury exposure. (2) The median total mercury concentration in 350 fish sampled from 25 species consumed by the Seychellois was <1 ppm (range, 0.004–0.75 ppm), comparable to that consumed by the U.S. population; thus, the methyl-mercury levels in the Seychellois population are 10–20 times those in the United States, not because they consume more highly contaminated fish than do Americans, but rather because they consume more fish than the U.S. population. (3) The Seychelles represent a relatively pristine environment, with no local industry for pollution, and are situated more than 1,000 miles from any continent or large population center. (4) The population is highly literate, cooperative, and has minimal immigration and emigration. (5) The Seychellois constitute a generally healthy population, with low maternal alcohol consumption and tobacco use (<2%). (6) In the 66-month study cohort, the mean maternal hair level of total mercury during pregnancy was 6.8 ppm (range, 0.5–26.7 ppm).

Effects noted in study and corresponding doses: The results of the 66-month testing in the SCDS revealed no evidence of adverse effects attributable to chronic ingestion of low levels of methylmercury in fish (Davidson et al. 1998). In this study, developing fetuses were exposed *in utero* through maternal fish ingestion before and during pregnancy (Davidson et al. 1998). Neonates continued to be exposed to maternal mercury during breastfeeding (i.e., some mercury is secreted in breast milk), and methylmercury

exposure from the regular diet continued after the gradual post-weaning shift to a fish diet. In the 66-month study cohort, the mean maternal hair level of total mercury during pregnancy was 6.8 ppm (range, 0.5–26.7 ppm; n = 711), and the mean child hair level at the 66-month testing interval was 6.5 ppm (range, 0.9–25.8 ppm; n = 708). The 66-month test battery, which was designed to test multiple developmental domains, included as primary measures the following: (1) General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities (to estimate cognitive ability); (2) the Preschool Language Scale (PLS) total score (to measure both expressive and receptive language ability); (3) the Letter and Word Recognition and (4) Applied Problems subtests of the Woodcock-Johnson (W-J) Tests of Achievement (to measure reading and arithmetic achievement); (5) the Bender-Gestalt test (to measure visual-spatial ability); and (6) the total T score from the Child Behavior Checklist (CBCL) (to measure the child's social and adaptive behavior). Serum sampling revealed no detectable levels of PCBs (detection limit = 0.2 ng/mL).

None of the tests indicated an adverse effect of methylmercury exposure. In contrast, four of the six measures showed better scores in the highest MeHg-exposed groups, compared with lower exposure groups for both prenatal and postnatal exposure (the four test were the (1) General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities (to estimate cognitive ability); (2) the Preschool Language Scale (PLS) total score (to measure both expressive and receptive language ability); (3) the Letter and Word Recognition and (4) Applied Problems subtests of the Woodcock-Johnson (W-J) Tests of Achievement (to measure reading and arithmetic achievement). While the positive outcomes are not considered to indicate any beneficial effect of methylmercury on neurological development or behavior, they might be more appropriately attributed to the beneficial effects of omega-3 fatty acids or other constituents present in fish tissue, since the methylmercury levels in hair are known to correlate closely with fish intake. The slight decreases in the subjectively reported activity level of boys reported in the 29-month observations were not seen during the 66-month tests. The mean maternal hair level of 15.3 ppm in the group with the highest exposure in the 66-month test cohort is, therefore, considered a NOAEL for SCDS, and is used by ATSDR as the basis for derivation of a chronic oral MRL for methylmercury. A related study (Myers et al. 1997) by the same team of researchers from the University of Rochester examined the Seychellois children for attainment of the same developmental milestones reported to have been delayed in the Iraqi poisoning incident in the early 1970s (Cox et al. 1989) and found no such delays in the Seychellois children exposed in utero. Since the children had been exposed *in utero*, they represent the most sensitive subpopulation.

Sensitivity of Neurobehavioral Measures /Reliability of Tests Used in Critical Study

The neurobehavioral test battery used in the 66-month Seychelles study was designed to assess multiple developmental domains (Davidson et al. 1998). The tests were considered to be sufficiently sensitive and accurate to detect neurotoxicity in the presence of a number of confounding factors. On-site test administration reliability was assessed by an independent scorer, and mean interclass correlations for interscorer reliability were 0.96–0.97 (Davidson et al. 1998). The sample size was determined to be sufficient to detect a 5.7 point difference on any test with a mean (SD) of 100 (16) between low (0–3 ppm) and high >12 ppm) hair mercury concentration groups for a 2-sided test (A = 0.05 at 80% power).

Converting blood concentration to daily intake.

The concentration of mercury in the blood may be converted to a daily intake by using the following equation from WHO (1990):

$$C = \frac{f(d}{b(V} \cdot \frac{A_D(A_B(d}{b(V}$$

Where:

C	=	concentration in blood
f	=	fraction of the daily intake taken up by the blood
d	=	daily dietary intake
b	=	elimination constant
A_D	=	percent of mercury intake in diet that is absorbed
A_B	=	percent of the absorbed amount that enters the blood
V	=	volume of blood in the body

Hair to Blood Concentration Ratio.

The hair:blood concentration ratio for total mercury is frequently cited as 250. However, a precise basis for this particular value is unclear. Ratios reported in the literature range from 140 to 370, a difference of more than a factor of 2.5 (see Table 2-9). Differences in the location of hair sampled (head versus chest, distance of sample from head or skin) may contribute to differences in observed ratios between studies. For example, as much as a 3-fold seasonal variation in mercury levels was observed in average hair levels for a group of individuals with moderate-to-high fish consumption rates, with yearly highs occurring in the fall and early winter (Phelps et al. 1980; Suzuki et al. 1992). Thus, it is important to obtain hair samples as close to the follicle as possible to obtain an estimate of recent blood levels. Large errors (the direction of which depends on whether samples were taken while blood levels were falling or rising) could result if hair samples are not taken close to the scalp. Several studies did not report the distance to the scalp for the hair samples taken. The high slope reported by Tsubaki (1971a) may have reflected the fact that mercury levels were declining at the time of sampling (Berglund et al. 1971), so the hair levels may reflect earlier, higher blood levels. Hair taken from different parts of the body also may yield different ratios. In 26 subjects with moderate-to-high fish consumption, axillary hair (i.e., from the armpit area) was found to contain an average of 23% less mercury than head hair (Skerfving et al. 1974).

Phelps et al. (1980) obtained multiple blood samples and sequentially analyzed lengths of hair from 339 individuals in Northwestern Ontario. The large sample size and the attention to sampling and analysis with regard to the hair:blood relationship make this study the most appropriate to use for estimating the mercury blood levels of the Seychellois women during pregnancy. The actual ratio Phelps et al. (1980) observed between the total mercury concentration in hair taken close to the scalp and simultaneous blood sampling for this group was 296. To estimate the actual ratio, the authors assumed that blood and hair samples were taken following complete cessation of methylmercury intake. They also assumed a half-life of methylmercury in blood of 52 days and a lag of 4 weeks for appearance of the relevant level in hair at the scalp. Based on these assumptions, they calculated that if the actual hair:blood ratio were 200, they would have observed a ratio of 290 (i.e., essentially equivalent to the observed value of 296). Based on these and other considerations, Phelps et al. (1980) state that the actual ratio is "probably higher than 200, but less than the observed value of 296." As the authors point out, two-thirds of the study population were sampled

during the falling phase of the seasonal variation and one-third or less in the rising phase. This fact would tend to result in a lower observed ratio; therefore, the actual average value is likely to be >200. Phelps et al. (1980) also provide estimates assuming a 2-week lag for the appearance of the relevant level of mercury in the centimeter of hair nearest the scalp. For a 2-week lag time, an actual ratio of 250 would have resulted in an observed ratio of 301 (again, essentially identical to the observed value of 296). A study of ingestion of a large dose of mercuric chloride in one individual suggests that the lag time is longer than 2 weeks (Suzuki et al. 1992). Hair samples were taken at 41 and 95 days following ingestion of the mercuric chloride. In the 41-day hair sample, a large mercury peak occurred in the centimeter of hair closest to the scalp, with no elevation in mercury in the second centimeter of hair. Head hair grows at a rate of about 1.1 cm a month (Al-Shahristani and Shihab 1974; Cox et al. 1989). If emergence had occurred so that the elevation in mercury could be measured in the first centimeter of hair by 2 weeks after exposure, then by day 41 after exposure the peak should have moved into the second centimeter of hair, at least enough to raise the mercury level slightly in the second centimeter. Because no elevation was seen in the second centimeter of hair at 41 days, it would appear that emergence occurred at a lag of >2 weeks. In the hair sample taken at 95 days, the leading edge of the mercury peak occurred in the third centimeter of hair.

Based on the data presented in Phelps et al. (1980) and the lag time indicated in the individual studied by Suzuki et al. (1992), the actual average value is likely to be somewhere between 200 and 250. Because the data do not allow a more accurate determination of an average ratio, the value 250 is acceptable for the purpose of estimating average blood levels in the Seychellois population. Using 250 rather than a lower number results in a lower MRL. It should be noted that a wide range in hair:blood ratios has been reported for individuals in various studies: 137–342 in Soria et al. (1992), 171–270 in Phelps et al. (1980), and 137–585 in Birke et al. (1972). Therefore, this ratio (250) should not be used as the sole basis for determining levels of exposure and potential effect for individuals.

Calculation of dietary intake from blood concentration.

Fraction of mercury in diet that is absorbed (A_D). Radiolabeled methyl-mercuric nitrate was administered in water to three healthy volunteers (Aberg et al. 1969). The uptake was >95%. Miettinen et al. (1971) incubated fish liver homogenate with radiolabeled $MeHgNO_3$ to yield a methylmercury proteinate. The proteinate was then fed to fish that were killed after a week, cooked, and fed to volunteers after confirmation of the methylmercury in the fish. Mean uptake exceeded 94%. For the derivation of an MRL, an absorption factor of 0.95 is used.

Fraction of the absorbed dose that is found in the blood (A_B). The value 0.05 has been used for this parameter in the past (Berglund et al. 1971; WHO 1990). Three studies report observations of the fraction of the absorbed methylmercury dose distributed to blood volume in humans. Kershaw et al. (1980) report an average fraction of 0.059 of the absorbed dose in the total blood volume, based on a study of 5 adult male subjects who ingested methylmercury-contaminated tuna. In a group of 9 male and 6 female volunteers who had received ^{203}Hg-methylmercury in fish, approximately 10% of the total body burden was present in 1 L of blood in the first few days after exposure, dropping to approximately 5% over the first 100 days (Miettinen et al. 1971). In another study, an average value of 1.14% for the percentage of absorbed dose in 1 kg of blood was derived from subjects who consumed a known amount of methylmercury in fish over a period of 3 months (Sherlock et al. 1984). Average daily intake for the 4 groups observed in the study ranged from 43 to 233 µg/day. The authors report a dose-related effect on the estimated percentage of the absorbed dose in 1 kg of blood, with 1.26% of the absorbed dose in 1 kg of blood at an average daily intake of 43 µg/day and 1.03% of the absorbed dose in 1 kg of blood at an average daily intake of 233 µg/day. The average for all subjects in the study was 1.14%. When individual values for distribution to one kilogram of blood reported in the study are converted into the percentage of the absorbed

dose in the total blood volume (assuming that blood is 7% of body weight [Best 1961] and using body weights reported for individuals in the study), the average value for A_B for all individuals is 0.056 (0.057 using the values for percentage in 1 kg normalized for body weight as reported in the study). The average value for A_B for 6 women as reported in Sherlock et al. (1984) is 0.048 (0.047 using values normalized for body weight). The average for 14 men is 0.059 (0.061 using values normalized for body weight).

The average values for A_B for all studies ranged from 0.047 to 0.061 (the values for women and men reported in Sherlock et al. [1984]). The data suggest that the average value of A_B for women may be lower than that for men, and they further suggest that 0.05 may be appropriate for modeling intake in a group of women (Sherlock et al. 1984). Based on these studies, the best estimate of A_B based on the available data is 0.05. Use of a higher value (i.e., 0.06 instead of 0.05) for this parameter would result in a lower MR, but the sensitive populations are pregnant women and developing fetuses, making the 0.5 value more appropriate for the Seychelles study population.

Elimination constant (b). Reported clearance half-times for methylmercury from blood or hair range from 48 to 65 days (Table 2-5). The average elimination constant based on the 6 studies listed in Table 2.5 is 0.014. The average of the individual values for *b* reported for 20 volunteers ingesting from 42 to 233 µg Hg/day in fish for 3 months (Sherlock et al. 1984) is also 0.014. Use of the value 0.014 for this parameter, rather than 0.01 (as used by WHO 1990), results in a higher MRL.

Volume of blood in body (V), and body weight. Blood volume is assumed to be 7% of body weight, with an increase to about 9% during pregnancy (Best 1961). Data for the body weight of the Seychelles Islands women were not found. Assuming an average body weight of 60 kg for women, the blood volume is 4.2 L (60 kg x 0.07 L/kg).

Calculation of Exposure Dose

The concentration of mercury in hair is assumed to be 250 times the concentration in blood. Using the mean total mercury level of 15.3 ppm in maternal hair taken at parturition to represent a NOAEL in the 66-month Seychelles testing (Davidson et al. 1998), the corresponding methylmercury concentration in blood would be: 1/250 x 15.3 µg/g x 1 mg/1,000 µg x 1,000 g/L = 0.061 mg/L.

Calculation of Daily Intake from Blood Concentration

$$C = \frac{f(d}{b(V} \cdot \frac{A_D(A_B(d}{b(V}$$

Using the above equation to relate the concentration in blood (C, in µg/L) to daily intake (d, in µg/day): where C = (percent of ingested dose absorbed through the GI tract x percent of that dose absorbed into the blood x the daily amount ingested) divided by (elimination constant x blood volume in a 60 kg female)

that is,

C = (0.95 x 0.05 x d)/(0.014 x 4.2)
C = 0.81 d
0.061 mg/L = 0.81 d
d = 0.075 mg/day

Using the assumed body weight of 60 kg for women, the estimated dose that would result in a hair level of 15.3 ppm is 0.075/60 kg = 0.0013 mg/kg/day. Therefore, the NOAEL derived from the highest exposure group (n = 95) at 66 months is 0.0013 mg/kg/day.

Dose and end point used for MRL derivation: 0.0013 mg/kg/day NOAEL

[X] NOAEL [ ] LOAEL

Uncertainty and Modifying Factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a minimal LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [X] 3 [ ] 10 (for human pharmacokinetic and pharmacodynamic variability)
[X] 1.5 [ ] 3 [ ] 10 (Modifying factor to account for domain-specific findings in Faroe study)

Consideration of Uncertainty

The standard/traditional areas of uncertainty addressed in any duration-specific MRL are: (1) interspecies variability (i.e., cross-species extrapolation of a NOAEL or LOAEL); (2) intra-human variability (i.e., differences in susceptibility to a substance or effect within the human population); (3) use of an LOAEL for MRL derivation when an NOAEL for the critical effect is not available; and (4) extrapolation from subchronic to chronic duration. In addition, a modifying factor may also be used when special circumstances exist that may contribute to, or introduce, uncertainty into the calculated health guidance value (MRL) in an area not typically covered by the traditional uncertainty factor approach.

The NOAEL of 15.3 ppm mercury in maternal hair from Davidson et al. (1998) used as the starting point for MRL derivation was based upon an unusually large study cohort of the population considered most sensitive to the neurodevelopmental effects of methylmercury, i.e., pregnant women and their developing fetuses. The negative results of this study are strongly supported by the BMD NOAEL range of 13 to 21 ppm calculated for the New Zealand cohort of 237 mother-child pairs (Crump et al. 1998). Consequently, much of the uncertainty normally present in the MRL derivation process does not exist in the case of methylmercury. Nonetheless, in view of the nature of the most susceptible group (developing fetuses) and some questions raised in the vast human data base for this chemical, an aggregate value of 4.5 was employed.

This value (4.5) was based upon three separate components, two of which are interrelated and the other independent. For the Seychelles data, a value of 1.5 was used to address the variability in hair-to-blood ratios among women and fetuses in the U.S. population, as determined by pharmacokinetic modeling of actual data by Clewell et al. (1998); a second value of 1.5 was applied to address the remainder of any inter-individual variability (i.e., pharmacodynamics) in the U.S. population. A third, and independent, factor of 1.5 was employed to account for the possibility that the domain-specific tests, as employed extensively in the Faroe Islands, but not the Seychelles (which used primarily neurobehavioral tests of global function) might be able to detect very subtle neurological effects not tested for in the 66-month Seychelles cohort.

The World Health Organization (WHO, 1993, 1996) has defined the -kinetic and -dynamic components of intrahuman variability as being equal contributors to, and collectively constituting the total of, human variability. In order to ensure a conservative approach, these two interdependent components were added to give a composite uncertainty factor of three (i.e., 1.5 + 1.5 = 3) to account for the full range of variability attributable to mercury in the Seychelles study. A modifying factor of 1.5 was also used to account for the

possibility of domain-specific effects, as were seen in the Faroe study, being attributable to mercury. Since these effects were considered to be entirely separate or "independent" events, this modifying factor of 1.5 was multiplied by the uncertainty factor of 3.0 (for uncertainty attributable solely to the Seychelles study) to yield an aggregate uncertainty of 4.5 for chronic oral exposure to methylmercury.

While domain-specific tests from the Seychelles were reviewed at the North Carolina meeting in November 1998 and the results failed to demonstrate effects, the tests do not represent the full range of domain-specific tests that were administered in the Faroe Islands. For these reasons, and based on our consultation with our Board of Scientific Counselors about concerns for "missing" data sets (i.e., in relation to the Executive Order of children's health and the agency's efforts to protect the health of children, including the developing fetus), ATSDR determined that an additional factor of 1.5 should be used since the full range of domain-specific neuropsychological test results from the Seychelles are not yet available. When these results become available and if they fail to show domain-specific effects, this additional factor of 1.5 would no longer be needed. At that time ATSDR will re-evaluate its MRL, as well as all other relevant data, in compliance with the agency's mandates and authorities.

Therefore, in the calculation of the chronic oral MRL for methylmercury, the NOAEL of 0.0013 mg/kg/day from the 66-month study (Davidson et al. 1998) is divided by 4.5, giving a chronic oral MRL for methylmercury of 0.0003 mg/kg/day [0.0013 mg/kg/day / 4.5 (UF) = 0.0003 mg/kg/day].

<u>If an inhalation study in animals, list the conversion factors used in determining human equivalent concentration (HEC)</u>: Not applicable.

<u>Additional studies or pertinent information which lend support to this MRL</u>:

Crump et al. (1998) conducted benchmark dose (BMD) calculations and additional regression analyses of data collected in a study in which a series of scholastic and psychological tests were administered to children whose mothers had been exposed to methylmercury during pregnancy. Hair samples were collected from 10,970 new mothers in New Zealand in 1977 and 1978. High hair mercury levels were considered to be those over 6 ppm, which was the hair level predicted to result at steady state from consumption of mercury at the WHO/FAO Provisional Tolerable Weekly Intake of 0.3 mg total mercury/week and 0.2 mg methylmercury/week. By this criterion, 73 of approximately 1,000 mothers who had consumed fish more than three times/week during pregnancy were determined to have high hair mercury levels. In 1985, when the children were 6 to 7 years of age, 61 children (1 set of twins) of the 73 mothers in the high hair mercury group were located, and constituted the high exposure group, which was matched with three control groups (one with 3-6 ppm maternal hair mercury levels, one with 0-3 ppm whose mothers had been high fish consumers, and one with 0-3 ppm whose mothers had not been high fish consumers). The entire study cohort consisted of 237 children. A battery of 26 psychological and scholastic tests were administered to the children at school during the year 1985. Mothers were interviewed at the time of test administration to obtain additional data on social and environmental factors. In the high exposure group of children, one boy's mother had a hair mercury level of 86 ppm, which was more than four times higher than the next highest hair mercury level of 20 ppm. BMDs (10% response rate) calculated from five tests ranged from 32 to 73 ppm, when the 86 ppm mother's child was included. This corresponded to a BMDL range of 17 to 24 ppm. Although none of the 86 ppm child's test scores was an outlier according to the definition used in the analyses, his scores were significantly influential in the analyses. When this child was omitted from the analyses, BMDs ranged from 13 to 21, with corresponding BMDLs of 7.4 to 10 ppm.

Developing fetuses in the SCDS were exposed through maternal fish ingestion before and during pregnancy. Each child was evaluated at 19 months and again at 29 months (±2 weeks) for infant intelligence (Bayley

Scales of Infant Development [BSID] Mental and Psychomotor Scales), with a modified version of the BSID Infant Behavior Record to measure adaptive behaviors at 29 months (Davidson et al. 1995b). Testing was performed by a team of Seychellois nurses extensively trained in administration of the BSID. Maternal hair concentrations, measured in hair segments that corresponded to pregnancy, ranged from 0.5 to 26.7 ppm, with a median exposure of 5.9 ppm for the entire study group. The mean BSID Mental Scale Indices determined at both 19 and 29 months were found to be comparable to the mean performance of U.S. children. The BSID Psychomotor Scale Indices at both measurement intervals were two standard deviation units above U.S. norms, but were still consistent with previous findings of motor precocity in children reared in African countries. The study found no effect that could be attributed to mercury on the BSID scores obtained at either the 19- or 29-month measurement/testing interval. The 29-month cohort represented 94% of the 779 mother-infant pairs initially enrolled in the study, and approximately 50% of all live births in the Seychelles in 1989.

The only observation in the 29-month testing that might be attributable to prenatal mercury exposure was a slight decrease in the activity level in boys (but not girls) as determined by the Bayley Infant Behavior Record (subjective observation). Whereas this decrease was significant in males ($p = 0.0004$), it was not statistically significant in females ($p = 0.87$). When the subjective activity scores for male and female children were evaluated collectively, no statistically significant or remarkable decrease in activity was apparent outside the >12 ppm maternal hair concentration group. The affect on activity level in boys is not considered an adverse effect by the authors of the study.

Grandjean et al. (1997b, 1998) reported another epidemiological study of methylmercury exposure for a population in the Faroe Islands. Although the Faroese are a fishing culture, the major source of methylmercury exposure for this population is pilot whale meat, which is intermittently consumed as part of the cultural tradition . The initial study cohort consisted of 1,022 singleton births occurring in a 21-month window during 1986-1987. At approximately 7 years of age, neurobehavioral testing was conducted on 917 of the remaining cohort members. No abnormalities attributable to mercury were found during clinical examinations or neurophysiological testing. A neuropsychological test battery was also conducted, which included the following: Finger Tapping; Hand-Eye Coordination; reaction time on a Continuous Performance Test; Wechsler Intelligence Scale for Children - Revised Digit Spans, Similarities, and Block Designs; Bender Visual Motor Gestalt Test; Boston Naming Test; and California Verbal Learning Test (Children). Neuropsychological tests emphasized motor coordination, perceptual-motor performance, and visual acuity. Pattern reversal visual evoked potentials (VEP) with binocular full-field stimulation, brain stem auditory evoked potentials (BAEP), postural sway, and the coefficient of variation for R-R inter-peak intervals (CVRR) on the electrocardiogram were all measured. The neuropsychological testing indicated mercury-related dysfunction in the domains of language, attention, memory, and visuospatial and motor function (to a lesser extent), which the authors considered to remain after the children of women with maternal hair mercury concentrations above 10 µg/g (10 ppm) were excluded. While this study represents a significant contribution to the human database for methylmercury exposure and effects, a number of potentially influential factors not fully considered as possible covariates somewhat cloud the interpretation of the results.

These differences between the neuropsychological effects observed in the Faroe Island cohort and the absence of effects reported in the Seychelles Island cohort might result from a variety of factors. The Faroe Island children were older (7–8 years versus 5.5 in the SCDS). Some of the measurement instruments (i.e., the neuropsychological test administered) were also different. Since the first neuropsychological testing in the Faroe study was not conducted until 7 years of age, it is not known whether the observed effects might have been apparent at an earlier age. Ongoing and planned future testing of the Seychelles population will provide additional information on the progression of any observed effects. Further examination of the

Seychelles population using the neuropsychological test that showed positive results in the Faroe Islands population will also allow a more direct comparison of results.

The diet in the two studies was also considerably different. The majority of the mercury exposure to the Faroe Island population came from whale meat (estimated at about 3 ppm in muscle tissue) with a relatively small portion coming from fish. Some of the mercury in whale meat is in the form of inorganic mercury. In the Seychelles study, all of the mercury came from fish as methylmercury with concentrations of around 0.3 ppm. Whale meat blubber is widely consumed in the Faroe Islands and also contains polychlorinated biphenyls (PCBs). Grandjean et al. (1995b) estimated a daily intake of 200 µg of PCB. This value can be compared to the Tolerable Daily Intake of PCBs established by the FDA, of 60–70 µg/day for an adult. Further statistical analysis of the possible influence of PCBs on the observed study results needs to be conducted (see the discussion below on Peer Panel 1Review of Key Studies for additional comments).

The primary biomarker used to estimate mercury exposure was also different between the two studies. The Faroe Island analysis used cord blood, and the Seychelles study used maternal hair level. The use of mercury in cord blood has the advantage of being a more direct measure of exposure to the fetus, but the levels at term may not reflect exposures at earlier developmental stages. While Grandjean et al. (1997) did report maternal hair mercury levels, the mean hair level for the interquartile range of 2.6–7.7 ppm was reported only as a geometric average (4.27 ppm). In contrast, the Seychellois study reported only an arithmetic mean level for the entire study population (6.8 ppm). While both are valid measures, a direct comparison of "average" values for the two studies is not possible without further statistical analysis of both data sets.

In the case of the Faroe study, there were no data presented in the peer-reviewed publications to address variability of food/whale meat or blubber intake among the Faroe Islanders, making it difficult to evaluate the possibility of peak intake levels during critical development phases. Consumption data was reported only as <1 pilot whale meat meal/month and 1-2 fish meals per week. In contrast, the Seychelles dietary habits provide a relatively stable intake, and a high degree of correlation was found between mean hair levels in samples covering each trimester versus levels in samples for the entire pregnancy (Cernichiari et al. 1995a). Cernichiari et al. (1995b) also report a good correlation between levels of total mercury in neonatal brain and levels in the corresponding maternal hair. While the contribution of continued mercury exposure through breast feeding or post-weaning diet was not fully addressed in the Seychellois study reports (Davidson 1995, 1998), that is not considered a significant drawback with the study, since no effects on neurobahavioral/neuropsychological testing were seen at any maternal hair level. In the Faroese assessment of latent neuropsychological effects from an *in utero* exposure to mercury, however, the role of continuing postnatal exposure to mercury either from breast milk or from ingestion of methylmercury-containing foods (e.g., pilot whale meat) is less clear. Specifically, it is not known what proportion, if any, of the neuropsychological effects reported in the Faroe Island population could be attributed to seven years of postnatal exposure to methylmercury in food. The variability and magnitude of this postnatal exposure should, therefore, be further evaluated.

Peer Panel Review of Key Studies

In addition to the traditional peer review process that precedes publication in most scientific journals, the studies considered by ATSDR for use in estimating a chronic oral MRL for methylmercury underwent two stringent reviews by recognized experts in the environmental health field.

On July 20 and 21, 1998, ATSDR assembled a panel of 18 experts from the scientific and medical communities to review current issues and the relevant literature on mercury and its compounds, including

methylmercury (ATSDR 1999). Several members of each of the respective research teams that conducted the Iraqi, Seychelles, Faroe, and Madeira studies were included among the expert panelists, and provided extensive overviews of their studies. The presentations were followed by an open, wide- ranging scientific discussion of the merits and interpretations of the currently available studies. Topics of significant discussion included the relative merits of the respective study populations, exposure regimens, sensitivity of neurobehavioral measures, and determination of an uncertainty factor. While it was unanimously agreed that the Seychelles and Faroe studies were both excellent studies that provided a significant contribution to the human database for methylmercury exposure and effects, a number of factors that could have contributed to the study results, but were not considered as possible statistical covariates, were discussed. In the case of the Faroe study, the consumption of whale blubber, which is known to be contaminated with PCBs, DDT, and possibly other organochlorines, introduces a potentially significant influence on the study results. Weihe et al. (1996) reported that the PCB and DDT concentrations in blubber of pilot whales taken in Faroese waters are about 30 ppm and 20 ppm, respectively. In contrast, the Seychellois population does not eat marine mammals at all. In addition, the Faroe study did not address other possible statistical covariates, such as the dietary and nutritional status of the study population and the use of tobacco during pregnancy, further complicating the interpretation of the neuropsychological test results.

On November 18–20, 1998, a workshop on Scientific Issues Relevant to the Assessment of Health Effects from Exposure to Methylmercury was conducted in Raleigh, North Carolina. Jointly sponsored by the U.S. Department of Health and Human Services, the National Institute of Environmental Health Sciences (NIEHS), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the U.S. Environmental Protection Agency (EPA), the National Oceanic and Atmospheric Administration (NOAA), the Office of Science and Technology Policy (OSTP), the Office of Management and Budget (OMB), and ATSDR, the purpose of this workshop was to discuss and evaluate the major epidemiologic studies that associated methylmercury exposure and the results of an array of developmental measures in children. These studies monitored and evaluated exposed populations in Iraq, the Seychelles Islands, the Faroe Islands, and the Amazon River Basin. A number of animal studies were also considered in support of a human health risk assessment. Presentation of these studies by the research team that conducted the study was followed by an expert panel evaluation that examined each study, taking into consideration the exposure data, experimental design and statistical analysis, potential confounders and variables, and neurobehavioral endpoints evaluated. A fifth panel evaluated the results of relevant animal studies. Significant issues that were discussed included the use of umbilical cord blood mercury levels vs. hair mercury concentrations as an index of methylmercury exposure during pregnancy, the patterns of exposure, the dietary/health status of study populations, other potentially relevant exposures, other confounding influences, and the adjustments made for statistical covariates. All five panels at this workshop commended the efforts of the investigators and respective staffs of the Seychelles and Faroe studies for conducting highly sophisticated investigations under difficult conditions. However, specific findings of several of the panels raise issues that, at present, preclude the Faroe data from consideration as a starting point for MRL derivation.

In their addressal of the potential influence of concurrent PCB exposure on the Faroe results, the Confounders and Variables (Epidemiology) panel indicated that with respect to four of the pre-natal outcomes (related primarily to verbal and memory performance), when PCBs were included in the model, only one of these outcomes is specifically related to mercury exposure. Concerning this matter, the panel wrote that "... the most likely explanation is that both (mercury and PCBs)... affect these three outcomes, but their relative contributions cannot be determined given their concurrence in this population." The Neurobehavioral Endpoints Panel also looked at this issue, and noted that "PCB exposure might act as an effect modifier, increasing the susceptibility to MeHg."; however, this panel further indicated that it did not believe that the effects seen in the Faroe Islands were due to uncontrolled confounding by PCBs. A third

panel that addressed the issue of concurrent PCB exposures, the Statistics/Design Panel, noted that only 3 of 208 PCB congeners were measured in the Faroe study, and stated that it "seems likely that mercury was measured more accurately than the biologically relevant PCB exposure. Consequently even if the neurological effects seen in this study were caused entirely by PCBs, it is possible that mercury would still be more highly correlated with these effects than PCBs." The Statistics/Design Panel also said that "the best method to deal with this problem would be to study a population where exposure to PCBs is not an issue." This statement points directly to the Seychelles study as the study most appropriate for MRL derivation.

Another issue raised at Raleigh workshop concerned the taking of hair samples for determining pre-natal exposure. In the Seychelles, hair samples were collected 6 months post-partum, and segments corresponding to pregnancy were selected for analysis. In the case of the Faroese, hair samples were taken at the scalp. Regarding that, the Confounders and Variables (Epidemiology) panel stated that "Given the time it takes the Hg to be excreted into the hair, we can assume that samples collected at parturition do not cover the last 6 weeks of gestation, during which critically important neuronal proliferation and differentiation is taking place."

Regarding both the Seychelles and Faroe studies, the Neurobehavioral Endpoints Panel found "no specific neurobehavioral signature injury from MeHg" in the data from either study (Seychelles or Faroe). The same panel also noted that episodic exposure in the Faroe Islands (1–2 fish meals/week and <1 pilot whale meal/month) "may reduce the likelihood of detecting a consistent 'neurobehavioral signature injury' specific to MeHg and may account for different observations in children with the same average exposure."

Based upon the discussions at the Raleigh workshop and the individual panel findings, as well as the aforementioned Atlanta expert panel review, ATSDR has determined the Seychellois study to represent the most appropriate and reliable data base currently available for calculation of a chronic oral MRL from a population exposed only to methylmercury by a relevant route of exposure for the overall U.S. population.

[It should be emphasized that the Seychelles study and the Faroe study represent credible scientific contributions by widely respected research teams. Similarly, both studies extend our knowledge base well beyond that provided by the Iraqi study and make significant contributions to our understanding of the effects of low-level exposure to methylmercury by an exposure route and vehicle (i.e., food) relevant to U.S. populations. The continuing monitoring and evaluation of the Seychellois and Faroese populations with more comparable neurobehavioral indices should help strengthen our understanding of the effects of low level chronic methylmercury exposure and should reduce the uncertainty regarding the public health implications of exposure.]

Other epidemiology studies were also considered by the workshop panels. Lebel et al. (1997) evaluated a fish-eating populations in the Amazon River Basin with a neurofunctional test battery and clinical manifestations of nervous system dysfunction in relation to hair mercury concentrations. The villagers examined live along the Tapajos River, a tributary of the Amazon. The study population consisted of 91 adult inhabitants 15-31 years of age. Hair mercury levels were below 50 µg/g (ppm). Clinical examinations were essentially normal, although persons displaying disorganized movements on an alternating movement task and those with restricted visual fields generally had higher hair mercury levels. Near visual contrast, sensitivity, and manual dexterity (adjusted for age) were found to decrease significantly with increasing mercury levels, while a tendency for muscular fatigue and decreasing strength were observed in women. The authors suggested that dose-dependent nervous system alterations might be associated with hair mercury levels below 50 ppm. This study, however, also had a number of potentially confounding factors. The impact of parasitic and other diseases endemic to the study area is of primary

concern in the interpretation of the Lebel et al. (1997) results. In addition, the overall nutritional status of the study population was not known or reported, and the use of neuroactive drugs (from local herbs, plants, roots, or mushrooms) was not considered as a potential confounder or covariate. The previous mercury exposure history of the study cohort was also unclear. This is of particular importance because gold mining procedures that use metallic mercury have been commonly practiced along the Amazon Basin for decades. Finally, the endpoints of the Lebel et al. (1977) study evaluated adult toxicity and not effects in the developing fetus or the newborn (i.e., the most sensitive human population).

The panel also reviewed the Iraqi study. Cox et al. (1989) and WHO (1990) reported delayed onset of walking in offspring in Iraqi children whose mothers were exposed to methylmercury through the consumption of seed grain treated with methylmercury as a fungicide (Al-Mufti et al. 1976; Bakir et al. 1973; Cox et al. 1989; Marsh et al. 1981, 1987). Exposure to methylmercury from other sources (e.g., fish or meat) was probably very low or nonexistent (Al-Mufti et al. 1976). It is likely that the children were exposed both prenatally through the placenta and postnatally through the mother's milk. A maternal exposure level of 0.0012 mg/kg/day, corresponding to the hair level of 14 ppm, was estimated using a simple, one-compartment pharmacokinetic model.

Myers et al. (1997) evaluated the population of the SCDS for developmental milestones similar to those determined in Iraq. As part of this ongoing study, cohort children were evaluated at 6.5, 19, 29, and 66 months of age. At 19 months care-givers were asked at what age the child walked (n=720 out of 738) and talked (n=680). Prenatal mercury exposure was determined by atomic absorption analysis of maternal hair segments corresponding to hair growth during the pregnancy. The median mercury level in maternal hair for the cohort in this analysis was 5.8 ppm, with a range of 0.5–26.7 ppm. The mean age (in months) at walking was 10.7 (SD=1.9) for females and 10.6 (SD=2.0) for males. The mean age for talking (in months) was 10.5 (SD=2.6) for females, and 11.0 (SD=2.9) for males. After adjusting for covariates and statistical outliers, no association was found between the age at which Seychellois children walked or talked and prenatal exposure to mercury. The ages for achievement of the developmental milestones were normal for walking and talking in the Seychellois toddlers following prenatal exposure to methylmercury from a maternal fish diet. The 5.8 ppm NOAEL of this study is considerably below the one estimated from the dose-response analysis of the data for the Iraqi methylmercury poisonings (10 ppm).

Clarkson (1995) raised some interesting issues concerning whether is it reasonable to apply health effects data based on an acute exposure to methylmercury fungicide eaten in homemade bread (in the 1971–1972 Iraq incident) to fish-eating populations having chronic exposure to much lower concentrations of methyl-mercury. Clarkson (1995) addressed two specific issues. The first regards the body's "defense mechanisms" that serve to mitigate the potential damage from mercury. One such mechanism in the case of methylmercury involves an enterohepatic cycling process in which methylmercury from dietary sources absorbed through the intestine is carried to the liver, where substantial quantities are secreted back into the bile and returned to the intestinal tract. During the residence time in the gut, microflora break the carbon-mercury bond, converting methylmercury into inorganic mercury, which in turn is poorly absorbed and is excreted in the feces. This creates an effective detoxification pathway for low-dose dietary exposures to methylmercury, but probably not for acute, high-dose exposures, such as occurred in Iraq. Secondly, the transport of methylmercury into brain tissue is inhibited by the presence of many amino acids, including leucine, methionine, and phenylalanine. Thus, it is possible that the rising plasma concentrations of amino acids from ingestion of fish protein may serve to depress the uptake of methylmercury by the brain.

While both of these issues need further laboratory/clinical investigation, they do raise appropriate questions concerning the relevance of the relatively short-term (i.e., about six weeks), high-level contaminated grain exposure scenario encountered in Iraq to the dietary methylmercury exposure scenarios encountered in many

fish-eating populations (e.g., the Seychelles Islanders, Faroe Islanders, Peruvian villagers, and Inuit native people of Greenland). This position is supported by Cicmanec (1996), who reviewed data from the Iraqi study, as well as data from studies of fish-consuming populations in the Faroe Islands, Seychelles Islands, and Peruvian fishing villages. Cicmanec concluded that the Iraqi population does not represent a sensitive subpopulation within a perinatal group; rather, the relative lower threshold identified in that study was the result of confounders. Crump et al. (1995) reanalyzed the dose-response data from the Cox et al. (1989) report of the Iraqi incident and found the results to be potentially skewed by inadequacies in the study design and data-collection methods. Shortcomings or potentially confounding factors include: (1) the retrospective recall of developmental milestones by mothers and other family members; (2) the lack of precision in the determination of birth and other milestone dates; (3) and the possible biasing of the dose-response analysis by variation in symptom reporting and infant sex composition in the two study subcohorts. Crump et al. (1995) noted that perhaps the most serious limitation of the Iraqi study is the inability to assess the potential effects of low-level chronic-duration exposure to methylmercury, as these particular data are based on very high intake levels over a relatively brief period of time.

No increase in the frequency of neurodevelopmental abnormalities in early childhood was observed in a cohort of 131 infant-mother pairs in Mancora, Peru (Marsh et al. 1995b). The mean concentration of mercury in maternal hair was determined to be 8.3 ppm (range, 1.2–30 ppm), and the source of the mercury was believed to be from consumption of marine fish. Similarly, a study of 583 Faroe Island infants for the first 12 months after birth found no decrease in the age of attainment of sitting, creeping (crawling), and standing developmental milestones (Grandjean et al. 1995a). The age at which a child reached a particular developmental milestone was not only not found to be associated with prenatal mercury exposure, but infants that reached a milestone early were found to have significantly higher mercury concentrations in their hair at 12 months of age. It was also found that early milestone attainment was clearly associated with breast-feeding, which was in turn related to higher infant hair mercury levels. The authors (Grandjean et al. 1995a) concluded that the beneficial effects associated with breast-feeding seemed to overrule, or to compensate for, any neurotoxic effects on milestone development that could be due to the presence of contaminants (e.g., mercury) in human milk.

Additional studies have shown developmental toxicity after oral exposure of humans and animals to organic mercury compounds (Amin-Zaki et al. 1974; Bakir et al. 1973; Bornhausen et al. 1980; Cagiano et al. 1990; Elsner 1991; Engleson and Herner 1952; Fowler and Woods 1977; Guidetti et al. 1992; Harada 1978; Hughes and Annau 1976; Ilback et al. 1991; Inouye and Kajiwara 1988; Khera and Tabacova 1973; Lindstrom et al. 1991; McKeown-Eyssen et al. 1983; Nolen et al. 1972; Olson and Boush 1975; Rice 1992; Rice and Gilbert 1990; Snyder and Seelinger 1976; Stoltenburg-Didinger and Markwort 1990).

The accumulation of mercury is greater in larger fish and in fish higher in the food chain. The tendency for increased mercury concentration with increasing fish body weight is particularly noticeable in carnivorous fish species. Malm et al. (1995) analyzed mercury concentrations in 16 species of carnivorous fish from the Tapajos River basin in Brazil and hair samples from local populations who regularly ate such fish. Mercury levels in the fish averaged 0.55 ppm (range, 0.04–3.77 ppm), and the mercury levels in the hair of the affected fish-eating populations averaged approximately 25 ppm. In one population that consumed higher quantities of large carnivorous fish at the end of the local rainy season, 8 of 29 persons evaluated had hair mercury levels above 40 ppm, and one individual had a hair mercury concentration of 151 ppm. Some villages along the river can have per capita daily fish consumption rates around 200 g or more, which would greatly impact the human body burden and hair levels of mercury in such populations.

Alternative Derivations of the MRL

To ensure a health guidance value based upon the best use of the Seychelles study data (widely considered the most relevant data available), ATSDR evaluated alternate MRL derivation methods for methylmercury.

One such method was a physiologically based pharmacokinetic approach using the mean total mercury level of 6.8 ppm in maternal hair for the entire Seychellois study cohort. Using the same formula as in the previous MRL calculation,

C = (0.95 x 0.05 x d) / (0.014 x 4.2)
C = 0.81 d
(1/250 x 6.8) = 0.027
0.027 mg/L = 0.81 d
d = 0.034 mg/day
0.034 mg/day / 60 kg = 0.0006 mg/kg/day

In consideration of uncertainty factors for this MRL approach, multiple factors also apply. In this case, the mean value of 6.8 ppm for the NOAEL is for the entire study cohort at 66 months (n = 711). An uncertainty factor of 1.5 was used to account for the pharmacokinetically based variability of hair-to-blood ratios (95% confidence level) in pregnant women and fetuses in the U.S. population (Clewell et al. 1998, 1999). The extremely large size of the study population (n=711), in combination with an uncertainty factor of 1.5, is considered adequate to encompass the full range of pharmacokinetic and pharmacodynamic variability within the human population. An independent modifying factor of 1.5 was also used to take into consideration the positive results of the domain-specific tests administered in the Faroe study (Grandjean et al. 1997, 1998). The uncertainty factor of 1.5, multiplied by the modifying factor of 1.5, yields a total aggregate value of 2.25. Applying the factor of 2.25 to the daily intake calculated from the 6.8 ppm NOAEL yields a chronic oral MRL value of 0.0003 mg/kg/day for methylmercury (0.0006 mg/kg/day divided by 2.25 = 0.0003 mg/kg/day).

A third approach to deriving a health guidance value is the use of bench mark dose (BMD) modeling. Clewell et al. (1998) used a benchmark dose analysis to determine a reference dose (RfD, a health guidance value used by the Environmental Protection Agency and, in some ways, the equivalent of ATSDR's chronic oral MRL). Clewell et al. (1998) used the data from the 29-month test in the Seychellois population (Davidson et al. 1995b) for their analysis (i.e., the 66-month study had not been published at the time of their benchmark dose analysis). The BMD is calculated by fitting a mathematical dose-response model to dose-response data. The bench mark dose level (BMDL) is a lower statistical confidence bound on the BMD and replaces the NOAEL in the calculation of a health guidance value. The BMD approach has been proposed as superior to the use of "average" or "grouped" exposure estimates when dose-response information is available, as is the case for the Seychelles study. Clewell et al. (1998) note that the Faroe Islands study reported by Grandjean et al. (1997b) could not be used for dose-response modeling due to inadequate reporting of the data and the confounding influence of co-exposure to PCBs.

For the 29-month Seychelles data, Clewell et al. (1998) used the 95% lower bound on the 10% benchmark dose level (BMDL), which represents a conservative estimate of the traditional NOAEL. The benchmark dose modeling over the entire range of neurological endpoints reported by Davidson et al. (1995b) yielded a lowest $BMDL_{10}$ of 21 ppm methylmercury in maternal hair. This $BMDL_{10}$ was then converted to an expected distribution of daily ingestion rates across a population of U.S. women of child-bearing age by using a Monte Carlo analysis with a physiologically based pharmacokinetic (PBPK) model of methylmercury developed by Gearhart et al. (1995). This analysis addresses the impact of interindividual

pharmacokinetic variability on the relationship between ingestion rate and hair concentration for methyl-mercury. The resulting distribution had a geometric mean value of 0.00160 mg/kg/day (S.D. 0.00133). The 1st, 5th, and 10th percentiles of that distribution were 0.00086, 0.00104, and 0.00115 mg/kg/day, respectively. Clewell et al. (1998) suggested that the 5th percentile of 0.00104 mg/kg/day provides a scientifically based, conservative basis that incorporates the pharmacokinetic variability across the U.S. population of child-bearing women and that no other uncertainty factor for interindividual variability would be needed. To the benchmark-estimated NOAEL of 21 ppm derived from the Seychelles 29-month data, Clewell et al. (1998) applied an uncertainty factor of 3 to account for data base limitations. (Note: The 66-month Seychelles data was not yet published at the time; hence the reliance on the 29-month Seychelles data for the benchmark analysis.) Consequently, Clewell et al. (1998) concluded that using a NOAEL of 7 ppm (21 ppm / 3 (UF) provides additional protection against the possibility that effects could occur at lower concentrations in some populations. Based upon this reasoning, they recommended a health guidance value (i.e., an RfD) of 0.0004 mg/kg/day. If a modifying factor of 1.5 is used to further address the domain-specific findings in the Faroe study, a final MRL of 0.3 µg/kg/day results.

The above benchmark analysis of 29-month data from the Seychelles Child Development Study strongly supports the MRL of 0.0003 mg/kg/day calculated by ATSDR in this profile. Similarly, addressing the Seychellois 66-month data from the perspective of using the mean value (15.3 ppm) of the highest exposure group in the study, a method prescribed in ATSDR's published guidance for MRL development (Chou et al. 1998), also results in an identical MRL. ATSDR therefore has high confidence that this level is protective of the health of all potentially exposed human populations.

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APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 6

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					9		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

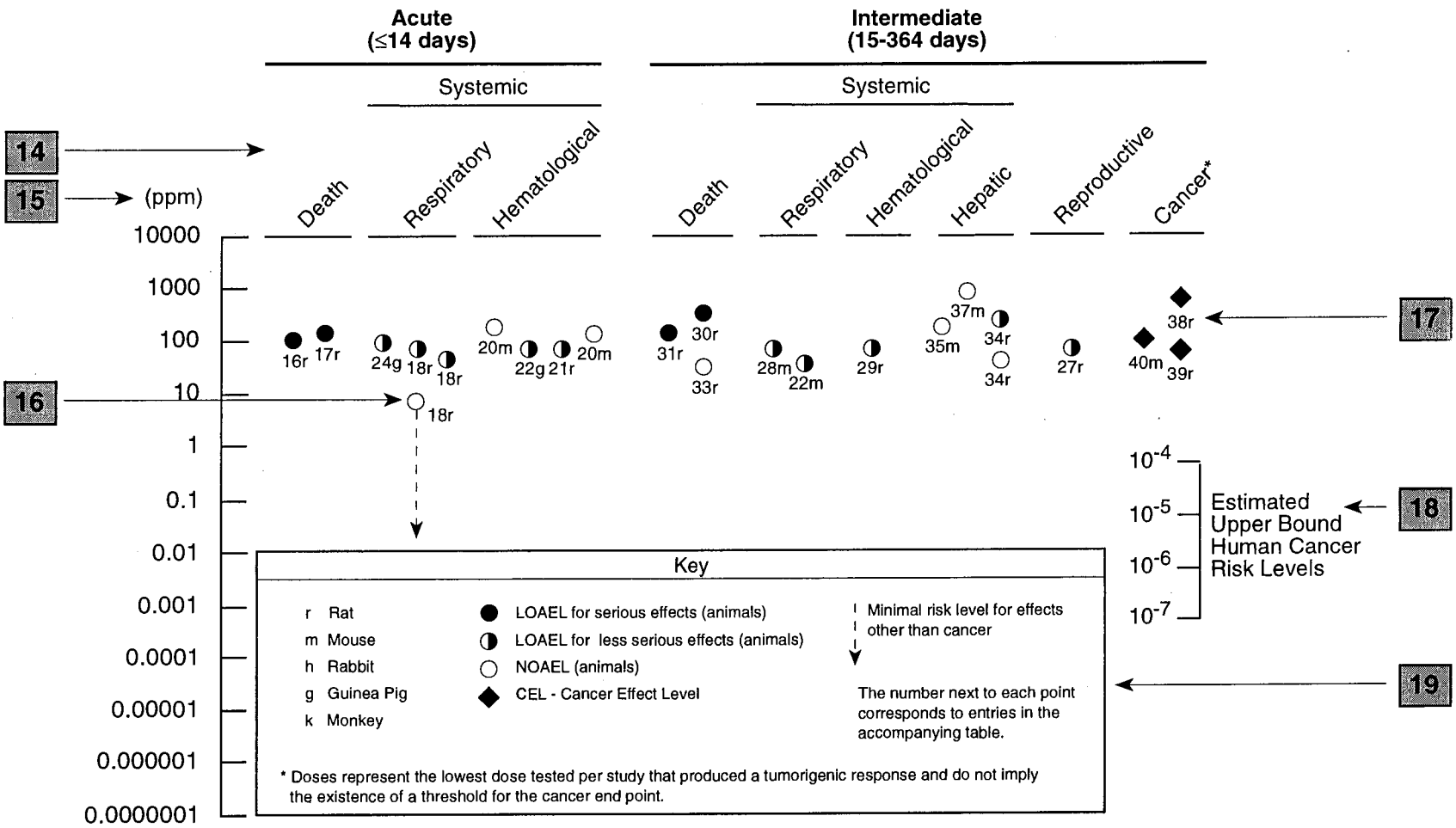
[a] The number corresponds to entries in Figure 2-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level

ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level

MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA

PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short-term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	greater than
$\geq$	greater than or equal to
=	equal to

<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

TOXICOLOGICAL PROFILE FOR

POLYCYCLIC AROMATIC HYDROCARBONS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

August 1995

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Polycyclic Aromatic Hydrocarbons was released in December 1990. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, that describes in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protect public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicologic information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on February 28, 1994 (59 FR 9486). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); and October 17, 1991 (56 FR 52166); and October 28, 1992 (57 FR 48801).

Foreword

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects our assessment of all relevant toxicologic testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

David Satcher, M.D., Ph.D.
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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. The Green Border review assures consistency with ATSDR policy.

2. Health Effects Review. The Healths Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for the PAHs. The panel consisted of the following members:

1. Dr. Gail Charnley, Consultant in Toxicology, Arlington, Virginia;

2. Dr. Edmond LaVoie, Professor, Rutgers University College of Pharmacy, Piscataway, New Jersey; and

3. Dr. Alexander Wood, Distinguished Research Leader and Director, Department of Oncology, Hoffmann-LaRoche, Inc., Nutley, New Jersey.

These experts collectively have knowledge of the polycyclic aromatic hydrocarbons' physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about polycyclic aromatic hydrocarbons (PAHs) and to emphasize the human health effects that may result from exposure to them. The Environmental Protection Agency (EPA) has identified 1,408 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. PAHs have been found in at least 600 of the sites on the NPL. However, the number of NPL sites evaluated for PAHs is not known. As EPA evaluates more sites, the number of sites at which PAHs are found may increase. This information is important because exposure to PAHs may cause harmful health effects and because these sites are potential or actual sources of human exposure to PAHs.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to substances such as PAHs, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

1.1 WHAT ARE POLYCYCLIC AROMATIC HYDROCARBONS?

PAHs are a group of chemicals that are formed during the incomplete burning of coal, oil, gas, wood, garbage, or other organic substances, such as tobacco and charbroiled meat. There are more than 100 different PAHs. PAHs generally occur as complex mixtures (for example, as part of combustion products such as soot), not as single compounds. PAHs usually occur

naturally, but they can be manufactured as individual compounds for research purposes; however, not as the mixtures found in combustion products. As pure chemicals, PAHs generally exist as colorless, white, or pale yellow-green solids. They can have a faint, pleasant odor. A few PAHs are used in medicines and to make dyes, plastics, and pesticides. Others are contained in asphalt used in road construction. They can also be found in substances such as crude oil, coal, coal tar pitch, creosote, and roofing tar. They are found throughout the environment in the air, water, and soil. They can occur in the air, either attached to dust particles or as solids in soil or sediment.

Although the health effects of individual PAHs are not exactly alike, the following 17 PAHs are considered as a group in this profile:

- acenaphthene
- acenaphthylene
- anthracene
- benz[a]anthracene
- benzo[a]pyrene
- benzo[e]pyrene
- benzo[b]fluoranthene
- benzo[g,h,i]perylene
- benzo[j]fluoranthene
- benzo[k]fluoranthene
- chrysene
- dibenz[a,h]anthracene
- fluoranthene
- fluorene
- indeno[1,2,3-c,d]pyrene
- phenanthrene
- pyrene

These 17 PAHs were chosen to be included in this profile because (1) more information is available on these than on the others; (2) they are suspected to be more harmful than some of the others, and they exhibit harmful effects that are representative of the PAHs; (3) there is a greater chance that you will be exposed to these PAHs than to the others; and (4) of all the PAHs analyzed, these were the PAHs identified at the highest concentrations at NPL hazardous waste sites.

More information can be found on the chemical and physical properties of PAHs in Chapter 3 and on their use and disposal in Chapter 4.

1.2 WHAT HAPPENS TO POLYCYCLIC AROMATIC HYDROCARBONS WHEN THEY ENTER THE ENVIRONMENT?

PAHs enter the environment mostly as releases to air from volcanoes, forest fires, residential wood burning, and exhaust from automobiles and trucks. They can also enter surface water through discharges from industrial plants and waste water treatment plants, and they can be released to soils at hazardous waste sites if they escape from storage containers. The movement of PAHs in the environment depends on properties such as how easily they dissolve in water, and how easily they evaporate into the air. PAHs in general do not easily dissolve in water. They are present in air as vapors or stuck to the surfaces of small solid particles. They can travel long distances before they return to earth in rainfall or particle settling. Some PAHs evaporate into the atmosphere from surface waters, but most stick to solid particles and settle to the bottoms of rivers or lakes. In soils, PAHs are most likely to stick tightly to particles. Some PAHs evaporate from surface soils to air. Certain PAHs in soils also contaminate underground water. The PAH content of plants and animals living on the land or in water can be many times higher than the content of PAHs in soil or water. PAHs can break down to longer-lasting products by reacting with sunlight and other chemicals in the air, generally over a period of days to weeks. Breakdown in soil and water generally takes weeks to months and is caused primarily by the actions of microorganisms. For more information on what happens to PAHs in the environment see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO POLYCYCLIC AROMATIC HYDROCARBONS?

PAHs are present throughout the environment, and you may be exposed to these substances at home, outside, or at the workplace. Typically, you will not be exposed to an individual PAH, but to a mixture of PAHs.

1. PUBLIC HEALTH STATEMENT

In the environment, you are most likely to be exposed to PAH vapors or PAHs that are attached to dust and other particles in the air. Sources include cigarette smoke, vehicle exhausts, asphalt roads, coal, coal tar, wildfires, agricultural burning, residential wood burning, municipal and industrial waste incineration, and hazardous waste sites. Background levels of some representative PAHs in the air are reported to be 0.02-1.2 nanograms per cubic meter (ng/m^3; a nanogram is one-millionth of a milligram) in rural areas and 0.15-19.3 ng/m^3 in urban areas. You may be exposed to PAHs in soil near areas where coal, wood, gasoline, or other products have been burned. You may be exposed to PAHs in the soil at or near hazardous waste sites, such as former manufactured-gas factory sites and wood-preserving facilities. PAHs have been found in some drinking water supplies in the United States. Background levels of PAHs in drinking water range from 4 to 24 nanograms per liter (ng/L; a liter is slightly more than a quart).

In the home, PAHs are present in tobacco smoke, smoke from wood fires, creosote-treated wood products, cereals, grains, flour, bread, vegetables, fruits, meat, processed or pickled foods, and contaminated cow's milk or human breast milk. Food grown in contaminated soil or air may also contain PAHs. Cooking meat or other food at high temperatures, which happens during grilling or charring, increases the amount of PAHs in the food. The level of PAHs in the typical U.S. diet is less than 2 parts of total PAHs per billion parts of food (ppb), or less than 2 micrograms per kilogram of food (µg/kg; a microgram is one-thousandth of a milligram).

The primary sources of exposure to PAHs for most of the U.S. population are inhalation of the compounds in tobacco smoke, wood smoke, and ambient air, and consumption of PAHs in foods. For some people, the primary exposure to PAHs occurs in the workplace. PAHs have been found in coal tar production plants, coking plants, bitumen and asphalt production plants, coal-gasification sites, smoke houses, aluminum production plants, coal tarring facilities, and municipal trash incinerators. Workers may be exposed to PAHs by inhaling engine exhaust and by using products that contain PAHs in a variety of industries such as mining, oil refining, metalworking, chemical production, transportation, and the electrical industry. PAHs have also been found in other facilities where petroleum, petroleum products, or coal are used

or where wood, cellulose, corn, or oil are burned. People living near waste sites containing PAHs may be exposed through contact with contaminated air, water, and soil. For more information on human exposure to PAHs, see Chapter 5.

1.4 HOW CAN POLYCYCLIC AROMATIC HYDROCARBONS ENTER AND LEAVE MY BODY?

PAHs can enter your body through your lungs when you breathe air that contains them (usually stuck to particles or dust). Cigarette smoke, wood smoke, coal smoke, and smoke from many industrial sites may contain PAHs. People living near hazardous waste sites can also be exposed by breathing air containing PAHs. However, it is not known how rapidly or completely your lungs absorb PAHs. Drinking water and swallowing food, soil, or dust particles that contain PAHs are other routes for these chemicals to enter your body, but absorption is generally slow when PAHs are swallowed. Under normal conditions of environmental exposure, PAHs could enter your body if your skin comes into contact with soil that contains high levels of PAHs (this could occur near a hazardous waste site) or with used crankcase oil or other products (such as creosote) that contain PAHs. The rate at which PAHs enter your body by eating, drinking, or through the skin can be influenced by the presence of other compounds that you may be exposed to at the same time with PAHs. PAHs can enter all the tissues of your body that contain fat. They tend to be stored mostly in your kidneys, liver, and fat. Smaller amounts are stored in your spleen, adrenal glands, and ovaries. PAHs are changed by all tissues in the body into many different substances. Some of these substances are more harmful and some are less harmful than the original PAHs. Results from animal studies show that PAHs do not tend to be stored in your body for a long time. Most PAHs that enter the body leave within a few days, primarily in the feces and urine. More information on how PAHs enter and leave your body can be found in Chapters 2 and 6.

1.5 HOW CAN POLYCYCLIC AROMATIC HYDROCARBONS AFFECT MY HEALTH?

PAHs can be harmful to your health under some circumstances. Several of the PAHs, including benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno [1,2,3-c,d]pyrene, have caused tumors in laboratory animals when they breathed these substances in the air, when they ate them, or when they had long periods of skin contact with them. Studies of people show that individuals exposed by breathing or skin contact for long periods to mixtures that contain PAHs and other compounds can also develop cancer.

Mice fed high levels of benzo[a]pyrene during pregnancy had difficulty reproducing and so did their offspring. The offspring of pregnant mice fed benzo[a]pyrene also showed other harmful effects, such as birth defects and decreased body weight. Similar effects could occur in people, but we have no information to show that these effects do occur.

Studies in animals have also shown that PAHs can cause harmful effects on skin, body fluids, and the body's system for fighting disease after both short- and long-term exposure. These effects have not been reported in people.

The Department of Health and Human Services (DHHS) has determined that benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene are known animal carcinogens. The International Agency for Research on Cancer (IARC) has determined the following: benz[a]anthracene and benzo[a]pyrene are probably carcinogenic to humans; benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-c,d]pyrene are possibly carcinogenic to humans; and anthracene, benzo[g,h,i]perylene, benzo[e]pyrene, chrysene, fluoranthene, fluorene, phenanthrene, and pyrene are not classifiable as to their carcinogenicity to humans. EPA has determined that benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene are probable human carcinogens and that acenaphthylene, anthracene,

benzo[g,h,i]perylene, fluoranthene, fluorene, phenanthrene, and pyrene are not classifiable as to human carcinogenicity. Acenaphthene has not been classified for carcinogenic effects by the DHHS, IARC, or EPA. More information on the health effects associated with exposure to PAHs can be found in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO POLYCYCLIC AROMATIC HYDROCARBONS?

In your body, PAHs are changed into chemicals that can attach to substances within the body. The presence of PAHs attached to these substances can then be measured in body tissues or blood after exposure to PAHs. PAHs or their metabolites can also be measured in urine, blood, or body tissues. Although these tests can show that you have been exposed to PAHs, these tests cannot be used to predict whether any health effects will occur or to determine the extent or source of your exposure to the PAHs. It is not known how effective or informative the tests are after exposure is discontinued. These tests to identify PAHs or their products are not routinely available at a doctor’s office because special equipment is required to detect these chemicals. More information on tests used to determine the presence of PAHs in your body is presented in Chapters 2 and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has set regulations to protect people from the possible health effects of eating, drinking, or breathing PAHs. EPA has suggested that taking into your body each day the following amounts of individual PAHs is not likely to cause any harmful health effects: 0.3 milligrams (mg) of anthracene, 0.06 mg of acenaphthene, 0.04 mg of fluoranthene, 0.04 mg of fluorene, and 0.03 mg of pyrene per kilogram (kg) of your body weight (one kilogram is equal to 2.2 pounds). Actual exposure for most of the United States population occurs from active or passive inhalation of the compounds in tobacco smoke, wood smoke, and contaminated air, and from eating the compounds in foods. Skin contact

with contaminated water, soot, tar, and soil may also occur. Estimates for total exposure in the United States population have been listed as 3 mg/day.

From what is currently known about benzo[a]pyrene, the federal government has developed regulatory standards and guidelines to protect people from the potential health effects of PAHs in drinking water. EPA has provided estimates of levels of total cancer-causing PAHs in lakes and streams associated with a risk of human cancer development. If the following amounts of individual PAHs are released to the environment within a 24-hour period, EPA must be notified: 1 pound of benzo[b]fluoranthene, benzo[a]pyrene, or dibenz[a,h]anthracene; 10 pounds of benz[a]anthracene; 100 pounds of acenaphthene, chrysene, fluoranthene, or indeno[1,2,3-c,d]pyrene; or 5,000 pounds of acenaphthylene, anthracene, benzo[k]fluoranthene, benzo[g,h,i]perylene, fluorene, phenanthrene, or pyrene.

PAHs are generally not produced commercially in the United States except as research chemicals. However, PAHs are found in coal, coal tar, and in the creosote oils, oil mists, and pitches formed from the distillation of coal tars. The National Institute for Occupational Safety and Health (NIOSH) concluded that occupational exposure to coal products can increase the risk of lung and skin cancer in workers. NIOSH established a recommended occupational exposure limit, time-weighted average (REL-TWA) for coal tar products of 0.1 milligram of PAHs per cubic meter of air (0.1 mg/m^3) for a 10-hour workday, within a 40-hour workweek. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends an occupational exposure limit for coal tar products of 0.2 mg/m^3 for an 8-hour workday, within a 40-hour workweek. The Occupational Safety and Health Administration (OSHA) has established a legally enforceable limit of 0.2 mg/m^3 averaged over an 8-hour exposure period.

Mineral oil mists have been given an IARC classification of 1 (sufficient evidence of carcinogenicity). The OSHA Permissible Exposure Limit (PEL) for mineral oil mist is 5 mg/m^3 averaged over an 8-hour exposure period. NIOSH has concurred with this limit, and has established a recommended occupational exposure limit (REL-TWA) for mineral oil mists

of 5 mg/m^3 for a 10-hour work day, 40-hour work week, with a 10 mg/m^3 Short Term Exposure Limit (STEL).

More information on rules and standards for exposure to PAHs can be found in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of polycyclic aromatic hydrocarbons (PAHs). It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt

at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of PAHs are indicated in Tables 2-1, 2-2, and 2-3 and Figures 2-l and 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for PAHs. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions,

asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

PAHs are a group of chemicals that are formed during the incomplete burning of coal, oil, gas, wood, garbage, or other organic substances, such as tobacco and charbroiled meat. PAHs can either be synthetic or occur naturally. Most of these chemicals as individual compounds (i.e., not as part of a combustion product) have no known use except for research purposes. A few PAHs are used in medicines and to make dyes, plastics, and pesticides. Others are contained in asphalt used in road construction. They are found throughout the environment in the air, water, and soil. There are more than 100 different PAH compounds and the health effects of the individual PAHs are not exactly alike.

Fifty-four PAHs have been identified at one or more NPL hazardous waste sites. These 54 are acenaphthene, acenaphthylene, 2-acetoaminofluorene, anthracene, 9, 10-anthracenedione, benz[a]anthracene, benzo[a]pyrene, benzo[e]pyrene, benzo[a]fluoranthene, benzo[b]fluoranthene, benzo[b]fluorene, benzofluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]fluoranthene, benzoperylene, benzo[g,h,i]perylene, benzophenanthrene, benzopyrene, benzothiophene, benzo[b]thiophene, chrysene, 4H-cyclopenta[d,e,f]phenanthrene, dibenz[a,j]anthracene, dibenz[a,h]anthracene, 7,12-dimethylbenz[a]anthracene, 2,7-dimethylbenzo[b]thiophene, 1,4-dimethoxyanthracene, dimethyl phenanthrene, 2,5dimethyl phenanthrene, dodecachlorodecahydrotrim, fluoranthene, fluorene, indeno[1,2,3-c,d] pyrene, 12-methylbenz[a]anthracene, methyl anthracene, 9-methylanthracene, 3-methylcholanthrene, methylfluorene, methylphenanthrene, 2-methylphenanthrene, 1-methylphenanthrene, 4-methylphenanthrene, methylpyrene, phenanthrene, phenanthridine, phenanthroline, pyrene, perylene, 6,7-tetrahydropyrene, tetramethylphenanthrene, 3,4,5,6-tetramethylphenanthrene, and trimethylphenanthrene.

However, only 17 PAHs are discussed in this profile. These 17 PAHs are:

- acenaphthene
- acenaphthylene
- anthracene

- benz[a]anthracene
- benzo[a]pyrene
- benzo[e]pyrene
- benzo[b]fluoranthene
- benzo[j]fluoranthene
- benzo[g,h,i]perylene
- benzo[k]fluoranthene
- chrysene
- dibenz[a,h]anthracene
- fluoranthene
- fluorene
- indeno[l,2,3-c,d]pyrene
- phenanthrene
- pyrene

These 17 PAHs were selected using the following four criteria:

(1) toxicity
(2) potential for human exposure
(3) frequency of occurrence at NPL hazardous waste sites
(4) extent of information available.

The 17 PAHs were combined into one profile to avoid repetition across multiple profiles on the individual PAHs since these chemicals often occur together in the environment and many have similar toxicological effects, environmental fate, etc. Instances in which it is known that the various PAHs differ with regard to toxicological effects or environmental fate will be pointed out. For example, PAHs can be classified as “alternant” (e.g., benzo[a]pyrene, benz]a]anthracene, chrysene, dibenz[a,h]anthracene) or “nonalternant” (e.g., fluoranthene, benzo[k]fluoranthene, benzol[j]fluoranthene, indeno[1,2,3-c,d]pyrene). This distinction is based on the electron density associated with the molecule. Altemant PAHs have an equally distributed electron density, whereas nonalternant PAHs behave almost as if they were two different molecules because of an uneven distribution of electron density from one portion of the molecule to another. The toxicological significance of this difference is that alternant and nonalternant PAHs appear to behave differently, for example, with regard to how they are metabolized to ultimate carcinogens (see Section 2.3.3, Metabolism).

Reliable health-based and environmental information exists on only a few of the 17 PAHs discussed in this profile, and the potential health effects of the other less well-studied PAHs must be inferred from this information. By combining all 17 PAHs in one profile, these comparisons and inferences can

easily be made. Although a large toxicity database exists on complex mixtures that contain PAHs (such as crude oils, various high boiling point distillates, complex petroleum products, coal tars, creosote, and the products of coal liquification processes), these data generally have not been used in this profile. It is difficult to ascertain the toxicity of the component PAHs in these mixtures because of the potential interactions that could occur and the presence of other toxic substances in the mixtures. Furthermore, ATSDR has developed a profile on one of these complex mixtures, creosote, and the reader is referred to this profile for information on this complex mixture (ATSDR 1994). However, most of the available information on the health effects of PAHs in humans must be inferred from studies that reported the effects of exposure to complex mixtures that contain PAHs. Several epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke oven emissions, roofing-tar emissions, and cigarette smoke. Each of these mixtures contains benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene as well as other potentially carcinogenic PAHs and other carcinogenic and potentially carcinogenic chemicals, tumor promoters, initiators, and co-carcinogens such as nitrosamines, coal tar pitch, and creosote. It is thus impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens. Despite these limitations, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs such as benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene to cause cancer in humans. For this reason, and also because of the lack of data on the effects of individual PAHs in humans, such information has been included in this profile on PAHs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to any of the 17 PAHs discussed in this profile. However, a dose-related decrease in survival was noted in hamsters after 60 weeks of inhalation exposure to 46.5 mg/m^3 benzo[a]pyrene for 109 weeks (Thyssen et al. 1981). The authors attributed this reduced survival in part to toxic and carcinogenic effects induced by this PAH (e.g., tumors in the pharynx and larynx that could have inhibited food intake).

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, dermal, or ocular effects in humans or animals following inhalation exposure to any of the 17 PAHs discussed in this profile. The systemic effects observed after inhalation exposure are discussed below.

The highest NOAELs for respiratory and renal effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. Only one study was located regarding respiratory effects in humans following inhalation exposure to PAHs, specifically, benzo[a]pyrene. The respiratory health of 667 workers in a rubber factory was investigated (Gupta et al. 1993). Respiratory health was evaluated and examined for correlations to length of employment at the factory. In addition, total suspended particulate matter and benzo[a]pyrene concentrations were monitored in various parts of the factory and examined for possible correlation with the respiratory health of the workers in the same area of the factory. Statistically significant decrements in ventilatory function occurred following prolonged exposure as assessed by duration of employment. When different sections of the factory were considered, workers in the compounding section were the most affected, which was associated with the highest exposure to particulate matter and benzo[a]pyrene. Workers in the compounding section exhibited radiographic abnormalities including patch opacities, prominent bronchiovascular markings, and pleural effusions. Other symptoms included bloody vomit, breathing problems, chest pains, chest irritation, throat irritation, and cough. Workers in other areas of the plant exposed to lower levels of particulate matter and benzo[a]pyrene were similarly affected although to a lesser degree and in fewer numbers (Gupta et al. 1993). No attempt was made to separate the effects of exposure to benzo[a]pyrene and particulate matter, or to identify possible simultaneous exposure to other toxic chemicals.

Groups of 40 Fischer-344/Crl rats/sex were exposed nose-only to an aerosol of benzo[a]pyrene (7.7 mg/m^3) 2 hours/day, 5 days/week, for 4 weeks (Wolff et al. 1989a). Nasal and left lung sections were examined histopathologically. No treatment-related lesions were noted in the lungs or nasal cavities of the animals exposed to benzo[a]pyrene. Although this was a well-conducted inhalation toxicity study, it is not appropriate for use in risk assessment because only one concentration was

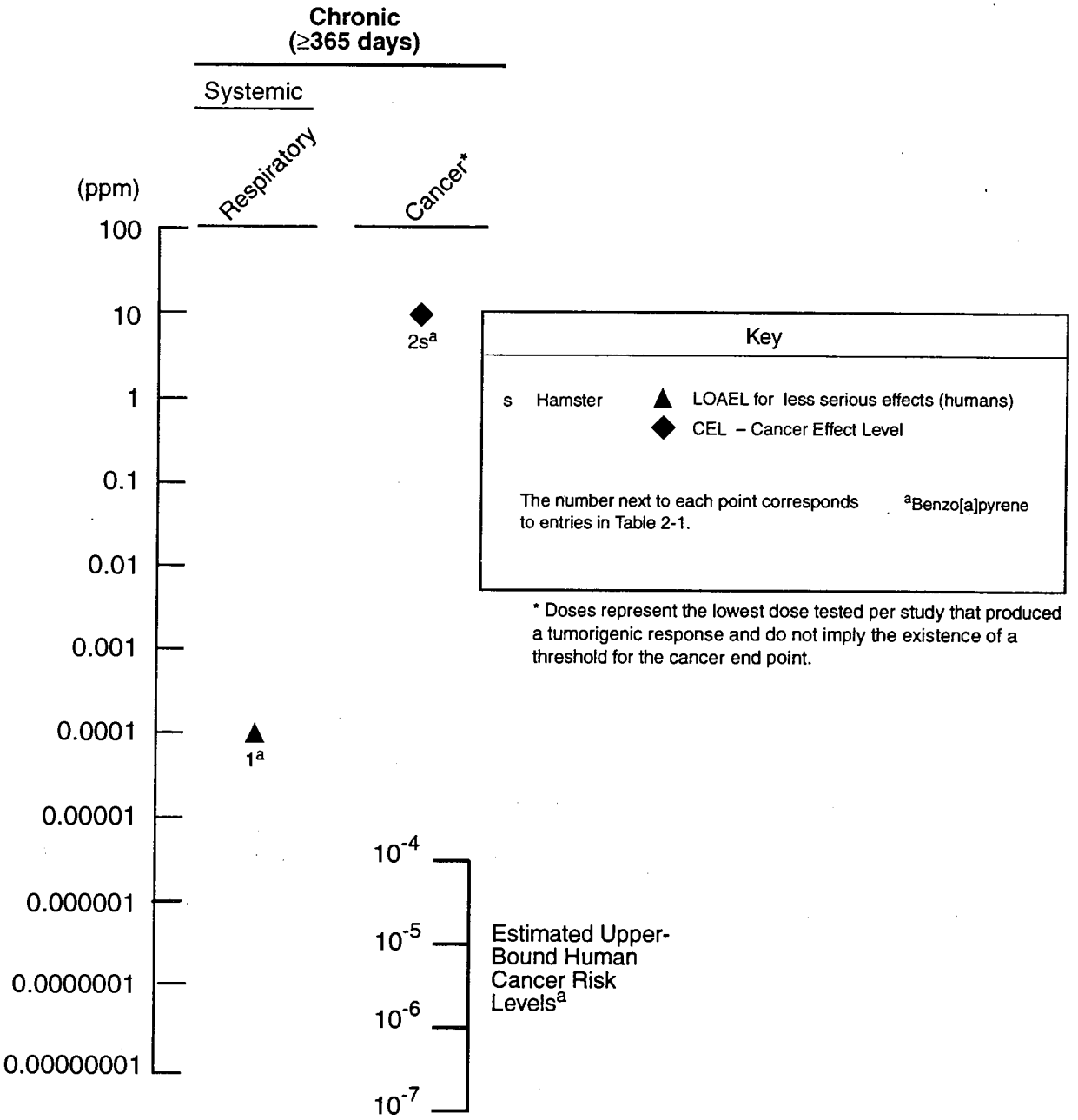
TABLE 2-1. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference
CHRONIC EXPOSURE							
Systemic							
1	Human	6 mo - >6 yr	Resp			0.0001 NS (reduced lung function, abnormal chest x-ray, cough, bloody vomit, throat and chest irritation.	Gupta et al. 1993 benzo[a]pyrene
Cancer							
2	Hamster (Syrian golden)	109 wk 7 d/wk 3-4.5 hr/d				9.5 M (CEL: 34.6% increase in respiratory tract tumors; neoplasms of the upper digestive tract in 26.9%)	Thyssen et al. 1981 benzo[a]pyrene

[a]The number corresponds to entries in Figure 2-1.

CEL = cancer effect level; d = day(s); hr = hour; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons – Inhalation



studied (thereby precluding the assessment of a dose-response relationship); no adverse treatment-related effects were observed; and the only parts of the respiratory tract examined histopathologically were the lungs and nose.

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to any of the 17 PAHs discussed in this profile.

Groups of 40 Fischer-344/Crl rats/sex were exposed nose-only to an aerosol of benzo[a]pyrene 2 hours/day, 5 days/week, for 4 weeks (Wolff et al. 1989a). Kidney sections were examined histopathologically. No treatment-related lesions were noted in the kidneys of the animals exposed to benzo[a]pyrene.

2.2.1.3 Immunological and Lymphoreticular Effects

Humoral immunity was monitored in male iron foundry workers in Poland (Szczeklik et al. 1994). Coke oven workers (199) were compared to cold-rolling mill workers (76). The groups were similar with respect to age, length of employment, and smoking habits. The results showed that coke oven workers, exposed to high concentrations of atmospheric PAHs, including fluoranthene, perylene, pyrene, benzo[a]pyrene, chrysene, benz[a]anthracene, dibenz[a,h]anthracene, and benzo[g,h,i]perylene, had reduced levels of serum immunoglobins. The workers most exposed to PAHs worked at the topside area of the coke ovens. Benzo[a]pyrene exposure was used as a reference point. Coke oven workers, exposed to 0.0002-0.50 mg/m^3 benzo[a]pyrene, were compared to cold-rolling mill workers, whose exposure to benzo[a]pyrene was 3-5 orders of magnitude less. Average length of employment was 15 years. IgG, IgA, IgM, and IgE concentrations were measured. Coke oven workers exhibited a marked depression of mean serum IgG and IgA, compared to mill workers. IgM tended to decrease, whereas IgE tended to increase in the coke oven workers. The biological significance of this finding is unclear and is not addressed by the authors. However, the authors suggest that serum immunoglobulin levels may be a useful biomarker for PAH exposure. The authors note, however, that the coke oven workers were exposed to higher levels of sulfur dioxide and carbon monoxide than were the cold-rolling mill workers, and they suggest that this additional exposure may have potentiated the effects of the PAH exposure. The potential contribution of the smoking habits of the subjects was not investigated.

No studies were located regarding the following effects in humans or animals following inhalation exposure to any of the 17 PAHs discussed in this profile:

2.2.1.4 Neurological Effects

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Becher et al. (1984) evaluated urine and blood samples from 15 aluminum plant workers (average age, 29 years; average years employed, 3.8) exposed to an estimated total PAH concentration of 1 mg per 8-hour work shift. The main PAH components identified by air sampling and also detected in the urine samples included phenanthrene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[e]pyrene, and benzo[a]pyrene. Results of the cytogenetic analysis of peripheral lymphocytes of the exposed workers indicated that the frequency of sister chromatid exchange was not influenced by the presence of large amounts of PAHs. These findings were reported to be consistent with the negligible increase in lung cancer found in epidemiological studies of aluminum workers. The investigators, therefore, questioned the relevance of PAH air monitoring as a measure of the occupational hazards associated with PAH exposure. Alternatively, it is possible that there are no occupational hazards associated with PAH exposure at these levels. Similar results were obtained with iron factory workers (length of employment: 2-46 years) exposed to 0.0005-0.00 mg/m^3 benzo[a]pyrene (Perera et al. 1993), who exhibited an increased rate of mutations in peripheral lymphocytes that were not correlated with PAH exposure. These authors suggest that both biomonitoring and personal monitoring may be necessary to evaluate exposure.

The high lung cancer rate in Xuan Wei, China, is associated with smokey coal use in unvented homes, but not with wood or smokeless coal use (Mumford et al. 1993). Smoky coal combustion emits higher PAH concentrations than wood combustion. This study evaluated PAH-DNA adducts in placentas, and in peripheral and cord white blood cells (WBC) from Xuan Wei women burning smoky coal or wood and from Beijing women using natural gas. Exposures were based on benzo[a]pyrene concentrations determined by personal monitors. Women in Xuan Wei burning smoky coal without a chimney were

exposed to 0.383 mg/m^3 benzo[a]pyrene, those burning smoky coal with chimneys were exposed to 0.184 mg/m^3, and women burning wood or using natural gas (Beijing) had no detectable exposure to benzo[a]pyrene. Positive results (detection of PAH-DNA adducts) were found in 58, 47, and 5% of the placentas from Xuan Wei women burning smoky coal without a chimney, with a chimney, and Beijing women using natural gas, respectively. Positive results were found in 46, 6.5, 56, and 25% of placentas from Xuan Wei women who lived in houses without and with chimneys, Xuan Wei women burning wood, and Beijing controls, respectively. Peripheral WBC samples were positive in 7 of 9, 8 of 9, and 3 of 9 for the Xuan Wei women who lived in houses without and with chimneys and Beijing women, respectively. No dose-response relationship was observed between the air benzo[a]pyrene concentrations and DNA adduct levels or percentage of detectable samples. However, using the fluorescent color assay, there was a significant association between DNA adduct detection in the placenta and cooking methods. Moreover, individual comparisons of the data revealed a significant difference between both smokey coal groups (chimney, no chimney) and natural gas cooking. The results of this study suggest that DNA adducts can be used as a biomarker to assess human exposure to combustion emissions.

Thirty-four workers in an electrode paste plant were monitored for response to exposure (Ovrebo et al. 1994). Exposure to benzo[a]pyrene was 0.9 μg/m^3; exposure to pyrene was 3.5μg/m^3. 1-Hydroxypyrene was measured in the urine, and PAH-DNA adducts were measured in white blood cells to demonstrate their relationship to the exposure. Results from these workers were compared to two reference control groups: research and development (R&D) workers and nickel refinery workers. Mean values of PAH-DNA adducts in the white blood cells from randomly selected participants in the three groups were only marginally different, with the exception of two smokers in the electrode plant, who had the highest levels. Mean PAH-DNA adduct levels were 10.9 adducts per 108 nucleotides for the electrode workers, 10.8 adducts per 10^8 nucleotides for the R&D personnel, and 10.0 adducts per 10^8 nucleotides for nickel plant workers not occupationally exposed to PAHs. No correlation was found between PAH-DNA adducts and 1-hydroxypyrene in the urine.

In an ongoing comprehensive evaluation of biological markers, workers in or near an iron foundry with varying exposures to PAHs were examined for response to exposure (Santella et al. 1993). Exposure to benzo[a]pyrene, determined by personal monitors, was 2-60 ng/m^3, which are the lowest levels yet analyzed in foundry workers. 1-Hydroxypyrene was measured in the urine, and PAH-DNA adducts were measured in white blood cells to demonstrate their relationship to the exposure.

Cigarette smoking, but not age or charbroiled food, influenced the level of 1-hydroxypyrene but not PAH-DNA adducts. When workers were classified into three categories of exposure (low, <.0005 mg/m^3; medium, 0.0005-0.0012 mg/m^3; high, >0.0012 mg/m^3), PAH-DNA adducts showed an increasing trend, with exposure from 5.2 to 6.2-9.6 adducts per 10^8 nucleotides in the low-, medium, and high-exposure groups, respectively. However, the three exposure groups did not differ significantly from each other, and no independent control group was used.

In order to evaluate the correlation between peripheral blood leukocyte DNA adducts as an indicator of exposure to PAHs and the airborne contamination of PAH at the workplaces, a survey of 69 coke oven workers was carried out (Assennato et al. 1993). In each workplace, total PAH and specific (benz[a]anthracene, benzo[a]pyrene, chrysene) PAH airborne concentrations were measured. Job titles included supervisor, door maintenance, machine operator, gas regulators, temperature operators, and top side workers. For the workplaces evaluated, the range of airborne concentrations (μg/m^3) for benz[a]anthracene, benzo[a]pyrene, and chrysene, respectively, were: supervisor (0.41, 0.29, 0.32), door maintenance (4.26-14.79, 2.31-6.37, 2.34-6.53), machine operator (0.11-33.19, 0.08-13.17, 0.03-12.63), gas regulators (0.21-2.10, 0.12-1.61, 0.13-1.60), temperature operators (1.77-10.07, 1.37-5.03, 0.98-4.78), and top side workers (0.45-3.40, 0.47-4.73, 0.23-2.42). Mean values (fmol/μg DNA) for PAH-DNA adducts in leukocytes by job title were: supervisor (0.059), door maintenance (0.174) machine operator (0.065), gas regulators (0.081), and temperature operators (0.071). Levels of exposure were correlated with PAH-DNA adduct formation. However, the differences were not statistically significant. The major limitations of the study included no record of length of exposure, no independent control group, no reporting of expected background levels of adducts, and no estimation of the length of time individual workers were exposed to particular levels of the PAHs. Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans following inhalation exposure to any of the 17 PAHs discussed in this profile. However, epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke oven emissions (Lloyd 1971; Mazumdar et al. 1975; Redmond et al. 1976), roofing-tar emissions (Hammond et al. 1976), and cigarette smoke (Maclure and MacMahon 1980; Wynder and Hoffmann 1967). Each of these mixtures contains benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene as well as other

potentially carcinogenic PAHs and other carcinogenic and potentially carcinogenic chemicals, tumor promoters, initiators, and co-carcinogens such as nitrosamines, coal tar pitch, and creosote. It is thus impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens. Furthermore, the levels of individual or total PAHs were not quantified in any of these reports. Despite these limitations, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs such as benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene to cause cancer in humans.

Several inhalation studies for animals given benzo[a]pyrene were located. Shulte et al. (1993) found a significant increase in all lung tumors and a dose-dependent increase in malignant lung tumors for mice exposed to PAH-enriched exhausts containing 0.05 or 0.09 mg/m^3 benzo[a]pyrene. The chronic study of Thyssen et al. (1981) provides clear-cut evidence of a dose-response relationship between inhaled benzo[a]pyrene particles (99% of the benzo[a]pyrene particles were between 0.2 and 0.54 microns in diameter) and respiratory tract tumorigenesis. Respiratory tract tumors were induced in the nasal cavity, pharynx, larynx, and trachea in a dose-related manner in hamsters exposed to 9.5 mg/m^3 or 46.5 mg/m^3 for 109 weeks. No lung tumors were found, and the reason for the absence of lung tumors is not known. Furthermore, the particle sizes were reported to be within the respirable range (0.2-0.5 microns in diameter). Tumors were also observed following exposure to 46.5 mg/m^3 in the esophagus and forestomach (presumably as a consequence of mucocilliary particle clearance) (Thyssen et al. 1981). These tumor types consisted of papillomas, papillary polyps, and squamous cell carcinomas.

The CEL from the Thyssen et al. (1981) study is recorded in Table 2-1 and plotted in Figure 2-l.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to any of the 17 PAHs discussed in this profile.

Oral exposure to 120 mg/kg/day benzo[a]pyrene has resulted in decreased survival time in two strains of mice (DBA/2N and AKR/N) whose hepatic aryl hydrocarbon hydroxylase (AHH) activity is not induced by PAHs ("nonresponsive" mice) (Robinson et al. 1975). AHH is a microsomal enzyme believed to be responsible for the metabolism of benzo[a]pyrene. All of the mice in the treatment group died, with at least half the deaths occurring within 15 days of dosing. Only three mice in the control group died. Death appeared to be caused by bone marrow depression (aplastic anemia, pancytopenia), leading to hemorrhage or infection. In contrast, only 6 of 90 (7%) mice with inducible AHH activity ("responsive" mice) similarly exposed to benzo[a]pyrene died over the same period of time. The authors concluded that the decreased survival in the nonresponsive mice was associated with a single gene difference encoding aromatic hydrocarbon responsiveness and was dependent on route of exposure. Benzo[a]pyrene was not as rapidly metabolized by the liver and excreted following oral administration in nonresponsive mice as in responsive mice. Therefore, more benzo[a]pyrene was available to reach the target tissue (i.e., bone marrow) in the nonresponsive mice, resulting in bone marrow depression and death.

A LOAEL for death for intermediate-duration exposure in mice is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, hematological, musculoskeletal, hepatic, dermal, or ocular effects in humans following oral exposure to any of the 17 PAHs discussed in this profile. The systemic effects observed in humans or animals after oral exposure are discussed below.

The highest NOAEL values and all LOAEL values from each reliable study for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of respiratory distress were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, and 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Systemic						
1	Rat (Wistar/Af/Ha n/Mol/ Kuo)	4 d 1 x/d (G)	Gastro	150 M			Nouslainen et al. 1984 benz[a]anthracene
			Hepatic	150 M			
			Renal	150 M			
2	Rat (Wistar/Af/Ha n/Mol/ Kuo)	4 d 1 x/d (G)	Gastro	150 M			Nouslainen et al. 1984 benzo[a]pyrene
			Hepatic	150 M			
			Renal	150 M			
	Reproductive						
3	Mouse (CD-1)	10 d Gd 7-16 (G)		40 F		160 F (reduced pregnancy)	Mackenzie and Angevine 1981 benzo[a]pyrene
	Developmental						
4	Mouse (B6AKF1, AKR/J)	8 d Gd 2-10 (F)				120 F (fetal resorption in Ahd/Ahd)	Legraverend et al. 1984 benzo[a]pyrene
5	Mouse (CD-1)	10 d Gd 7-16 (G)		10 F		40 F (reduced pup weight at 20 days)	Mackenzie and Angevine 1981 benzo[a]pyrene
	Cancer						
6	Mouse (CFW Swiss)	1-7 d ad lib (F)		13.3		33.3 (CEL: gastric neoplasms)	Neal and Rigdon 1967 benzo[a]pyrene

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	INTERMEDIATE EXPOSURE						
	Systemic						
7	Mouse (CD-1)	13 wk 1 x/d (GO)	Resp	700			EPA 1989c acenaphthene
			Cardio	700			
			Gastro	700			
			Hemato	700			
			Musc/skel	700			
			Hepatic		175[b]	(increased relative liver weight)	
			Renal	700			
			Endocr	700			
			Dermal	700			
			Ocular	700			
			Bd Wt	700			
8	Mouse (CD-1)	13 wk 1 x/d (GO)	Resp	1000			EPA 1989d anthracene
			Cardio	1000			
			Gastro	1000			
			Hemato	1000			
			Musc/skel	1000			
			Hepatic	1000[c]			
			Renal	1000			
			Endocr	1000			
			Dermal	1000			
			Ocular	1000			
			Bd Wt	1000			

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
9	Mouse (DBA/2,ARR/N); (C57B1/b, C3H/HeN, BALB/cAnN)	6 mo (F)	Hemato			120 (aplastic anemia)	Robinson et al. 1975 benzo[a]pyrene
			Hepatic		120 (increased liver weight)		
10	Mouse (CD-1)	13 wk 1 x/d (GO)	Resp	500			EPA 1988e fluoranthene
			Cardio	500			
			Gastro	500			
			Hemato	125 F 500 M	250 F (decrease in packed cell volume)		
			Musc/skel	500			
			Hepatic		125[d] M (increased relative liver weight)		
				125 F	250 F (increased relative liver weight; centrilobular pigmentation, increased enzymes)		
			Renal	250 M 125 F	500 M (renal tubular 250 F regeneration; interstitial lymphocytic infiltrates and/or fibrosis)		
			Endocr	500			
			Dermal	500			
			Ocular	500			
			Bd Wt	500			

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
11	Mouse (CD-1)	13 wk 1 x/d (GO)	Resp	500			EPA 1989e fluorene
			Cardio	500			
			Gastro	500			
			Hemato	125	250 (decreased PCV and MCHC in males; decreased RBC, PCV, MCH, and MCHC in females)		
			Musc/skel	500			
			Hepatic		125[e] (increased relative liver weight)		
			Renal	250 M 500 F	500 M (increased absolute and relative kidney weight)		
			Endocr	500			
			Dermal	500			
			Ocular	500			
			Bd Wt	500 M 250 F	500 F (increased body weight)		
	Immunological/Lymphoreticular						
12	Mouse (CD-1)	13 wk 1 x/d (GO)		700			EPA 1989c acenaphthene
13	Mouse (CD-1)	13 wk 1 x/d (GO)		1000			EPA 1989d anthracene
14	Mouse (CD-1)	13 wk 1 x/d (GO)		500 F	500 M (increased serum globulin values)		EPA 1988e fluoranthene

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
15	Mouse (CD-1)	13 wk 1 x/d (GO)		125	250 M (increased spleen weight)		EPA 1989e fluorene
	Neurological						
16	Mouse (CD-1)	13 wk 1 x/d (GO)		700			EPA 1989e acenaphthene
17	Mouse (CD-1)	13 wk 1 x/d (GO)		1000			EPA 1989d anthracene
18	Mouse (CD-1)	13 wk 1 x/d (GO)		500			EPA 1988 fluoranthene
19	Mouse (CD-1)	13 wk 1 x /d (GO)		500			EPA 1989e fluorene
	Reproductive						
20	Mouse (CD-1)	13 wk 1 x/d (GO)		700 M 350 F	700 F (decreased ovary weights correlated with increased incidence and degree of inactivity of the ovary and uterus)		EPA 1989c acenaphthene
21	Mouse (CD-1)	13 wk 1 x/d (GO)		1000			EPA 1989d anthracene

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference
22	Mouse (White Swiss)	19-29 d ad lib (F)		133.3 F				Rigdon and Neal 1965 benzo[a]pyrene
23	Mouse (CD-1)	13 wk 1 x/d (GO)		500				EPA 1988 fluoranthene
24	Mouse (CD-1)	13 wk 1 x/d (GO)		500				EPA 1989e fluorene
	Cancer							
25	Mouse (CFW Swiss)	30-197 d ad lib (F)		1.3		2.6	(CEL: gastric tumor)	Neal and Rigdon 1967 benzo[a]pyrene
26	Mouse (Swiss)	23-238 d ad lib (F)				33.3	(CEL: papillomas; squamous cell carcinomas)	Rigdon and Neal 1966 benzo[a]pyrene

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
27	Mouse (Swiss)	80-140 d ad lib (F)					33.3	(CEL: tumors of the forestomach in 69/108)	Rigdon and Neal 1969 benzo[a]pyrene

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.6 mg/kg/day for acenaphthene; dose divided by an uncertainty factor of 300 (3 for use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability)

[c]Used to derive an intermediate-duration oral MRL of 10 mg/kg/day for anthracene; dose obtained by dividing the NOAEL value by 100 (10 for extrapolation from animals to humans and 10 for human variability)

[d]Used to derive an intermediate-duration oral MRL of 0.4 mg/kg/day for fluoranthene; dose divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans and 10 for human variability)

[e]Used to derive an intermediate-duration oral MRL of 0.4 mg/kg/day for fluorene; dose divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans and 10 for human variability)

ad lib = ad libitum; BaP = benzo(a)pyrene; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day(s); (GO) = gavage (oil); Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; M = male; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; PCV = packed cell volume; RBC = red blood cells; Resp = respiratory; TPA = tetradecanoyl phorbol acetate; wk = week(s); x = time(s)

Figure 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons – Oral

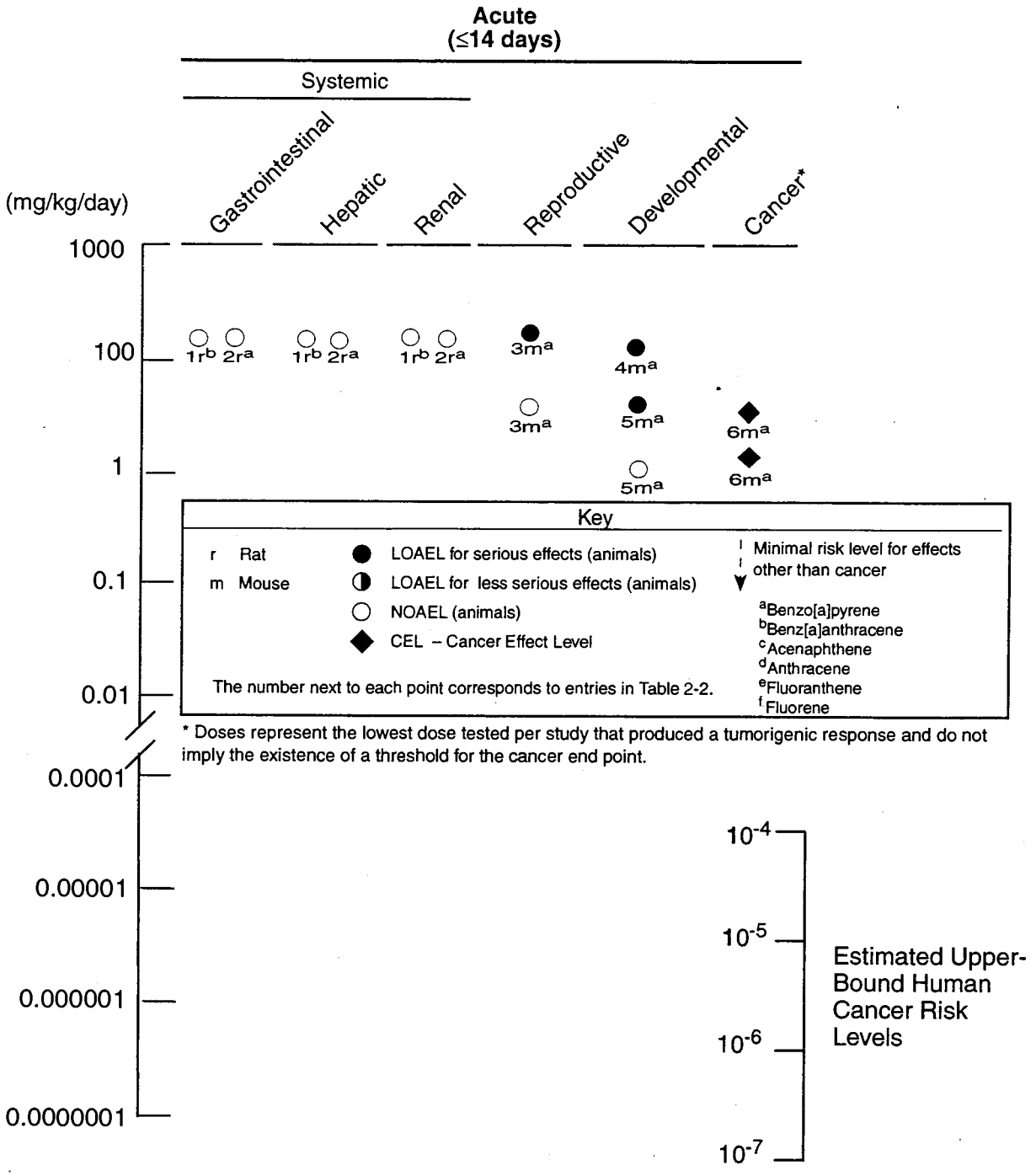


Figure 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons – Oral (continued)

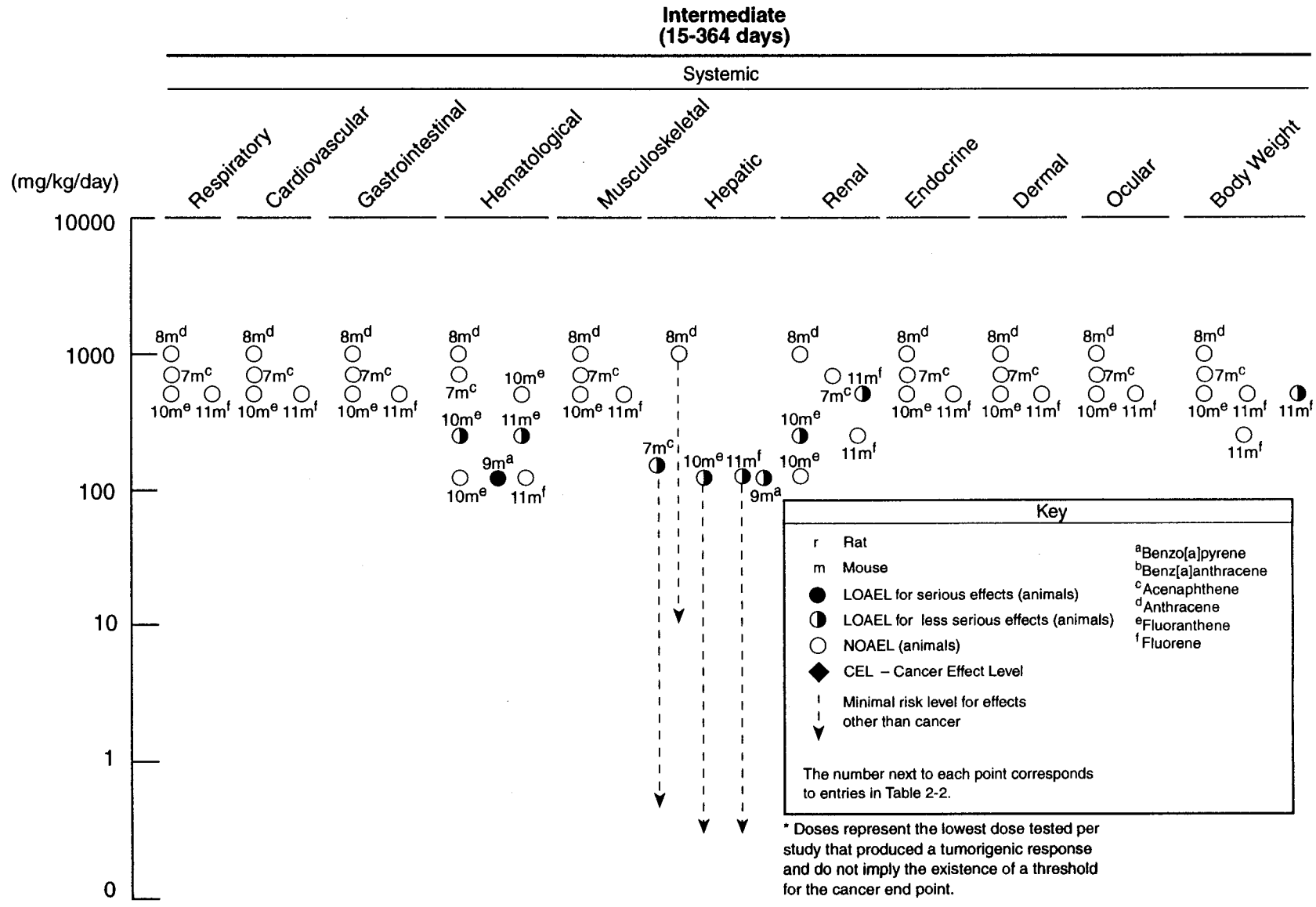
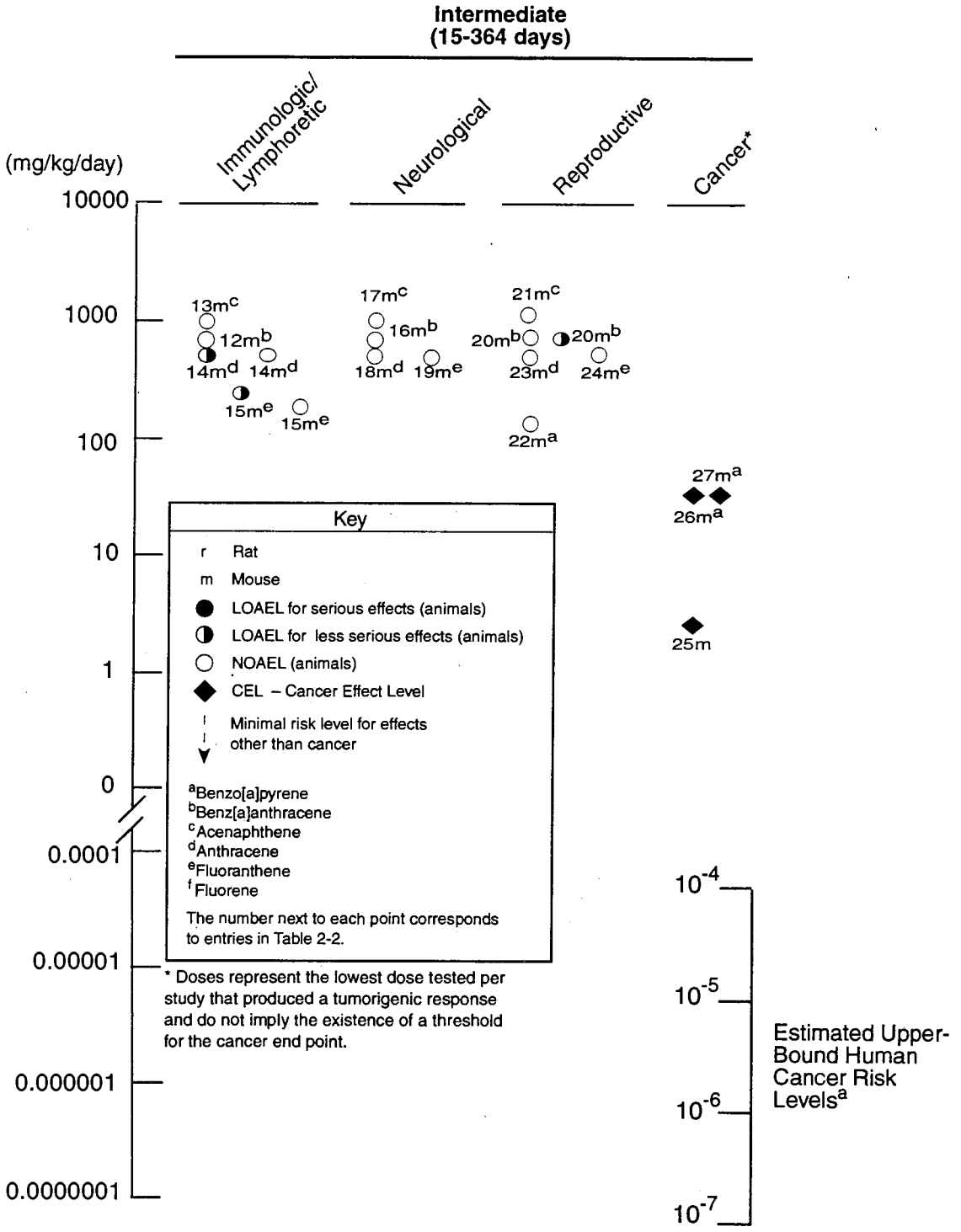


Figure 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons – Oral (continued)



Cardiovascular Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of cardiovascular distress were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, and 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Gastrointestinal Effects. Minimal information is available on the gastrointestinal effects of human oral exposure to PAHs. In one study, humans that consumed anthracene-containing laxatives (the anthracene concentration was not specified) for prolonged periods of time were found to have an increased incidence of melanosis of the colon and rectum (i.e., unusual deposits of black pigments in the colon and rectum) compared to patients who did not consume anthracene laxatives. However, no definitive conclusions can be drawn from these results because of study limitations that include possible misclassification of patients with respect to the level of anthracene laxative use over 30 years and no accounting for other factors involved in the pathogenesis of melanosis (Badiali et al. 1985).

Enzyme alterations in the mucosa of the gastrointestinal tract have been observed in animals acutely exposed to anthracene, benz[a]anthracene, benzo[a]pyrene, or phenanthrene. In rats, acute intragastric administration of 50 or 150 mg/kg/day benz[a]anthracene or benzo[a]pyrene, respectively, for 4 days resulted in suppression of carboxylesterase activity in the intestinal mucosa (reduction of activity by 30% and 44%, respectively); rats exposed to 100 mg/kg/day of anthracene or phenanthrene exhibited carboxylesterase activity that was increased by 13% and 30%, respectively (Nousiainen et al. 1984). Enzyme alteration in the absence of other signs of gastrointestinal toxicity is not considered an adverse health effect, but it may precede the onset of more serious effects. Based on this very limited information, it would appear that acute ingestion of anthracene, benz[a]anthracene, benzo[a]pyrene, or phenanthrene at these doses may not adversely affect the gastrointestinal tract of animals; however, exposed animals exhibited biochemical changes and it is possible that more serious effects could occur at high doses.

Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No adverse effects on the gastrointestinal system were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Hematological Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No hematological effects were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene (EPA 1989d). Administration of 250 mg/kg/day fluoranthene by gavage for 13 weeks to mice resulted in decreased packed cell volume in females, but not in males, given doses up to 500 mg/kg/day (EPA 1988e). Both male and female mice exposed to 250 mg/kg/day fluorene exhibited hematologic effects, including decreased packed cell volume and hemoglobin content (EPA 1989e).

Adverse hematopoietic effects (e.g., aplastic anemia, pancytopenia) that ultimately led to death were reported in the Ah-nonresponsive strains of mice, DBA/2N and AKR/N, following oral exposure to 120 mg benzo[a]pyrene/kg/day for 180 days. Death was attributed to hemorrhage or infection that resulted from pancytopenia (Robinson et al. 1975). Similar results were obtained by Legraverend et al. (1983). The Ah gene encodes a cytosolic receptor (Ah receptor) that regulates the induction of the cytochrome P-450 enzymes. Differences in this gene locus determine whether the Ah receptor will be “high-affinity” (i.e., will allow for the induction of the cytochrome P-450 enzymes [more specifically, AHH] and is found in responsive mice) or “low-affinity” (i.e., does not allow for the induction of the AHH and is found in nonresponsive mice). Mice with a high-affinity Ah receptor (i.e., responsive mice) were administered 120 mg/kg/day benzo[a]pyrene in the diet for 3 weeks and exhibited no myelotoxicity. However, all nonresponsive mice that were treated according to the same regimen died from myelotoxic effects within 3 weeks (Legraverend et al. 1983). These results support the results of Robinson et al. (1975).

Musculoskeletal Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of musculoskeletal effects were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Hepatic Effects. The induction of foci of altered hepatocytes is often seen in rats and mice that also develop liver tumors. These foci have altered enzyme activities and higher rates of cell proliferation than normal hepatocytes. A l-day intragastric administration of 200 mg/kg of benzo[a]pyrene or dibenz[a,h]anthracene, or of 180 mg/kg benz[a]anthracene to rats was followed by a

diet containing 2-acetylaminofluorene (2-AAF) and carbon tetrachloride induced gamma-GT foci (Tsuda and Farber 1980). Partially hepatectomized rats and sham hepatectomized rats were used, to provide proliferating and non-proliferating hepatocytes, respectively. Partially hepatectomized rats were more responsive to treatment than the sham-operated animals. For partially hepatectomized rats, benzo[a]pyrene was a more potent foci inducer than either benz[a]anthracene or dibenz[a,h]anthracene. Increased relative liver weight was seen in male mice and increased absolute and relative liver weight was seen in female mice given 175 mg/kg/day acenaphthene daily by gavage for 13 weeks; these effects were unaccompanied by other hepatic effects (EPA 1989c). Increased absolute and relative liver weight correlated with hepatocellular hypertrophy was seen in male and female mice given 350 mg/kg/day acenaphthene daily by gavage for 13 weeks (EPA 1989c). Increased serum cholesterol was also seen in females receiving 350 mg/kg/day acenaphthene (EPA 1989c). Increased liver weight and dose-related centrilobular pigmentation accompanied by an increase in liver enzymes were observed in both male and female mice receiving 250 mg/kg/day fluoranthene by gavage for 13 weeks (EPA 1988e). Male mice exposed to 125 mg/kg/day fluoranthene exhibited a slight increase in centrilobular pigmentation, and an increase in relative liver weight (EPA 1988e). Increased relative liver weight was observed in all treated groups, whereas increased absolute and relative liver weight was observed in the mid- and high-dose animals receiving 0, 125, 250, and 500 mg/kg/day fluorene for 13 weeks (EPA 1989e). However, there were no accompanying histopathological changes. No statistically significant effects of treatment were reported after 13-week administration of 1,000 mg/kg/day anthracene (EPA 1989d)

The ability to induce aldehyde dehydrogenase (ADH) in animals has been correlated with carcinogenic potency. Rats that were intragastrically administered 100 mg/kg/day of benzo[a]pyrene, benz[a]anthracene, anthracene, chrysene, or phenanthrene for 4 days exhibited cytosolic ADH induction (Torronen et al. 1981). However, benzo[a]pyrene and benz[a]anthracene were much more effective than phenanthrene, chrysene, or anthracene. Exposure to benzo[a]pyrene and benz[a]anthracene also increased the relative liver weights by 27% and 19%, respectively (Torronen et al. 1981). The authors concluded that anthracene, phenanthrene, and chrysene, which have been characterized as either noncarcinogens or equivocal carcinogens (see Section 2.2.2.8), are poor ADH inducers (Torronen et al. 1981).

The induction of carboxylesterase activity has also been observed in animals exposed to PAHs (Nousiainen et al. 1984). Benzo[a]pyrene, benz[a]anthracene, and chrysene were moderate inducers of

hepatic carboxylesterase activity in rats that were intragastrically administered 50, 100, and 150 mg/kg/day (100 mg/kg/day for chrysene), respectively, for 4 days. However, rats administered 100 mg/kg/day anthracene or phenanthrene did not exhibit induction of hepatic carboxylesterase activity. Induction of hepatic microsomal enzymes generally results in enhanced biotransformation of other xenobiotics (to either more or less toxic forms).

Increases in liver weight following partial hepatectomy have also been examined following acute oral exposure to various PAHs. Partially hepatectomized rats were fed diets containing various PAHs for 10 days. Administration of 51.4 mg/kg/day acenaphthene or 180 mg/kg/day fluorene resulted in statistically significant increases in liver weight compared to controls, which may have indicated an effect on regeneration, although rates of cell proliferation were not determined. Administration of 15.4 mg/kg/day acenaphthene, 51.4 mg/kg/day benzo[a]pyrene, or 51.4 mg/kg/day pyrene, anthracene, or phenanthracene had no effect. Diets containing 51.4 mg/kg/day acenaphthene or dibenz[a,h]anthracene, 180 mg/kg/day anthracene or phenanthracene, or 437 mg/kg/day pyrene produced no increase in the liver-to-body-weight ratio. Rats that were fed a diet containing 514 mg/kg/day chrysene exhibited equivocal results: in one trial, a significant increase in liver weight gain was noted, while in another trial, no increase in. liver-to-body-weight ratio was observed (Gershbein 1975). Thus, both suspected carcinogenic and noncarcinogenic PAHs can affect liver weights, although much higher doses are required for noncarcinogenic PAHs. The livers of rats administered single doses of ,fluorene by gavage in dimethyl sulfoxide (DMSO) were evaluated for the promotion of growth (i.e., cell proliferation as determined by organ weight and mitotic index) (Danz et al. 1991). The authors claimed that liver weight was increased in a dose-dependent manner to 20% over control values, and that the mitotic index of the hepatocytes was increased by 6-fold after 48 hours. However, the organ weight data were not presented, and the mitotic index data presented graphically in the text do not indicate a 6-fold increase over controls.

Ah-responsive strains of mice (C57BL/6, C3H/HeN, BALB/cAnN) that were orally administered 120 mg benzo[a]pyrene/kg/day in their diet for 180 days exhibited a 13% increase in relative liver weights (Robinson et al. 1975).

The hepatic effects observed in animals following oral exposure to PAHs are generally not considered serious. However, the enzyme alterations, gamma-GT foci induction, liver regeneration, and increased liver weight may precede the onset of more serious hepatic effects.

Renal Effects. The kidney microsomal carboxylesterase activity of rats was moderately induced by 50-150 mg/kg of benzo[a]pyrene following 4 days of intragastric administration; however, rats administered 100 mg/kg/day of anthracene or phenanthrene and 50-150 mg/kg benz[a]anthracene did not exhibit increased activity. The authors conclude that anthracene, phenanthrene, and benz[a]anthracene are not inducers of kidney carboxylesterase activity (Nousiainen et al. 1984). Enzyme induction is considered an adverse effect when observed concurrently with more serious effects such as impaired renal function and/or histopathological changes of the kidney.

Increasing dietary doses of pyrene ranging from 1,000 mg/kg food (127 mg/kg/day) up to 25,000 mg/kg food (917 mg/kg/day) for a mean dose of 426.6 mg/kg/day over a 25-day study produced dilation of the renal tubules in an unspecified number of mice. This effect was not observed until the highest dose was administered (Rigdon and Giannukos 1964). The limitations of this study (e.g., doses changed throughout exposure period and no statistical analyses performed) render these results of questionable toxicological significance.

Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of renal toxicity were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene (EPA 1989d). Increased absolute and relative kidney weight was observed in males, but not females receiving 500 mg/kg/day fluorene for 13 weeks (EPA 1989e). Renal tubular regeneration, and interstitial lymphocytic infiltrates and/or fibrosis were observed after 13-week oral administration of fluoranthene to female mice at 250 mg/kg/day, and male mice at 500 mg/kg/day (EPA 1988e).

Endocrine Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of endocrine imbalance were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Dermal Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of derrnal effects were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings

were reported after 13-week administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Ocular Effects. Male and female mice were exposed to 0, 17.5, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of ocular toxicity were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Body Weight Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No adverse effects on body weight were seen during life or upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, and 500 mg/kg/day fluoranthene (EPA 1988e, 1989d). After administration of 500 mg/kg/day fluorene for 13 weeks; however, female mice exhibited increased body weight, although male mice showed no effect at the same dose level (EPA 1989e).

Other Systemic Effects. The number of thymic glucocorticoid receptors in 6-week-old rats treated once with 2 mg/kg benzo[a]pyrene was measured (Csaba et al. 1991). It is assumed that administration was by oral gavage, but this was never explicitly stated. The number of these receptors was decreased by 40% in females and unaffected in males relative to the vehicle control animals. The statistical significance of these effects was not indicated, nor was the functional consequences of a decrease in receptor number assessed by examination of functional parameters.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following oral exposure to any of the 17 PAHs discussed in this profile.

A single gavage dose of 150 mg/kg fluorene to male Sprague-Dawley rats had no effect on thymus or spleen weight (Danz and Brauer 1988). Little useful information can be obtained from this study as only one dose was tested (thereby precluding assessment of the validity of the negative response) and no tests of immune function were evaluated. Male and female mice exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks showed no effect of treatment on splenic weight

or histopathology (EPA 1989c). Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, and 500 mg/kg/day fluoranthene (EPA 1988e, 1989d). After administration of 2.50 mg/kg/day fluorene for 13 weeks, however, increased absolute and relative spleen weight was seen in both sexes (EPA 1989e).

Lee and Strickland (1993) looked for antibodies specific to PAH-DNA adducts in the serum of BALB/c mice treated orally twice per week for 8 weeks with 0.5 or 5 mg/kg benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, chrysene, dibenz[a,h]anthracene, or fluoranthene. Increased antibody response was noted in animals treated with the low dose of benz[a]anthracene and benzo[b]fluoranthene, but not any of the other PAHs.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to any of the 17 PAHs discussed in this profile.

Male and female mice exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks showed no effect of treatment on behavior, or histopathologic effects on nerve or brain samples (EPA 1989c). Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, and 500 mg/kg/day fluoranthene (EPA 1988e, 1989d). After administration of 500 mg/kg/day fluorene for 13 weeks, however, increased brain weight was observed in females, but not in males (EPA 1989e). No histopathologic changes were observed.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to the PAHs discussed in this profile. Three animal studies were located that evaluated the reproductive effects of benzo[a]pyrene in animals. The results of two oral studies in mice (Mackenzie and Angevine 1981; Rigdon and Neal 1965) and one in rats (Rigdon and Rennels 1964) indicate that benzo[a]pyrene induces reproductive toxicity in animals. The incidence and severity of these effects depends on the strain, method of administration, and dose levels used. In one study, benzo[a]pyrene administered by gavage to pregnant CD-l mice decreased the percentage of pregnant females that reached parturition and produced a high incidence of sterility in the progeny (Mackenzie and Angevine 1981). In

contrast, benzo[a]pyrene administered in the diet caused no adverse effects on fertility of Swiss mice (Rigdon and Neal 1965) but reduced the incidence of pregnancy in female rats (Rigdon and Rennels 1964). Based on these studies, the LOAEL for benzo[a]pyrene-induced reproductive toxicity in parental mice was 160 mg/kg/day, and the LOAEL for these effects in the progeny of exposed animals was 10 mg/kg/day (Mackenzie and Angevine 1981). Because only the parental doses are quantifiable, these are the only data presented in Table 2-2.

When CD-l mice were administered benzo[a]pyrene by gavage daily for 10 days during gestation, there was a significant reduction in the percentage of pregnant females to reach parturition at 160 mg/kg/day, the highest dose tested (Mackenzie and Angevine 1981). When F_1 progeny were bred with untreated animals, the fertility index decreased significantly in all treatment groups. At 10 mg/kg/day, the lowest dose tested, the reduced fertility noted was associated with significant alterations in gonadal morphology and germ cell development. The treatment at higher doses resulted in total sterility. Contrary to these results, no adverse effects on reproduction were observed in Swiss mice fed benzo[a]pyrene in the diet at ≤133 mg/kg/day over varying time spans during mating, gestation, and parturition (Rigdon and Neal 1965). The apparent discrepancy in the results of the two studies may be attributable to the method of benzo[a]pyrene administration and metabolic differences in the two strains of mice used.

Dietary administration of benzo[a]pyrene for 28 days revealed no treatment-related effects on the estrous cycle of female rats. These rats experienced no significant adverse effects on their fertility when bred to untreated male rats (Rigdon and Rennels 1964). In another series of experiments, when benzo[a]pyrene-fed male and female rats were bred, only two of seven females became pregnant (as compared to 3 of 6 controls); the offspring of one rat were stillborn while those of others were resorbed (Rigdon and Rennels 1964). Although the data suggest that benzo[a]pyrene may induce reproductive toxicity in rats, they are inconclusive because of the use of a single dose level, small number of animals, and inadequate reporting of data.

Male mice exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks showed no effect of treatment on reproductive organ weight or histology (EPA 1989c). Female mice, however, exhibited decreased ovary weights correlated with an increase of inactivity of the ovary and uterus (EPA 1989c). No adverse effects on reproductive organs were reported after 13-week

administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene to male and female mice (EPA 1988e, 1989d, 1989e).

The available information from animal studies suggests that benzo[a]pyrene may have the potential to produce adverse reproductive effects in exposed humans. The highest NOAEL and all LOAEL values from each reliable study for reproductive effects following acute- and intermediate-duration exposures are reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to PAHs. Three animal studies were reviewed that assessed developmental effects of benzo[a]pyrene in inbred strains of rats and mice. The data from these studies indicate that prenatal exposure to benzo[a]pyrene produced reduced mean pup weight during postnatal development and caused a high incidence of sterility in the F_1 progeny of mice (Mackenzie and Angevine 1981). Using Ah-responsive and Ah-nonresponsive strains of mice, the increased incidences of stillboms, resorptions, and malformations observed correlated with the maternal and/or embryonal genotype (Legraverend et al. 1984). In another study, negative results were obtained when benzo[a]pyrene was administered to Swiss (responsive) mice (Rigdon and Neal 1965).

Benzo[a]pyrene was administered by gavage to pregnant CD-l mice during gestation at doses of 10, 40, and 160 mg/kg/day. The viability of litters at parturition was significantly reduced in the highest dose group (Mackenzie and Angevine 1981). The mean pup weight was significantly reduced in all treatment groups by 42 days of age. The F_1 progeny that were exposed prenatally to benzo[a]pyrene (10, 40, and 160 mg/kg/day) were bred with untreated animals and further studied for postnatal development and reproductive function. The F_1 progeny from the 10-mg/kg/day group experienced decreased fertility with associated alterations in gonadal morphology and germ-cell development. Because only the parental doses are quantifiable, these are the only data presented in Table 2-2. Therefore, the LOAEL of 10 mg/kg/day noted in the F_1 progeny discussed above is not presented in Table 2-2. Higher doses produced total sterility. This study provides good evidence for the occurrence of developmental effects following *in utero* exposure to benzo[a]pyrene.

The effect of genetic differences in metabolism of orally administered benzo[a]pyrene on *in utero* toxicity and teratogenicity was evaluated in mice that either metabolize benzo[a]pyrene readily (Ah-responsive) or not (Ah-nonresponsive) (Legraverend et al. 1984). Pregnant mice, either B6AKFl (Ah-responsive) or AKR/J (Ah-nonresponsive), were fasted prior to a diet containing 120 mg/kg/day benzo[a]pyrene on days 2-10 of gestation. The mice were killed on day 18 of gestation. On day 16 of gestation, intraperitoneal injections of napthoflavone were administered to distinguish between fetuses with different Ah-genotypes (Ahb/Ahd and Ahd/Ahd). Oral administration of benzo[a]pyrene to the pregnant AKR/J mice (non-responsive) caused more stillbirths, decreased weight gain, resorptions, and birth defects among Ahd/Ahd (Ah-nonresponsive) than among Ahb/Ahd (Ah-responsive) embryos. However, no differences in *in utero* toxicity or teratogenicity were observed in Ah-genetically different embryos (Ahd/Ahd and Ahb/Ahd) of B6AKFl mothers (responsive). The authors concluded that differences in *in utero* toxicity and teratogenicity are specific to the route of administration and can be attributed to "first pass" liver metabolism occurring with oral dosing. They also concluded that *in utero* toxicity and teratogenicity are directly related to the maternal and/or embryonal genotype controlled by the Ah-locus; that is, both maternal metabolism as well as target organ metabolism (embryo/fetus) were important in determining susceptibility to developmental toxicity. Specifically, metabolism by a responsive mother reduces *in utero* toxic effects in the fetus. Similarly, responsive fetuses in the uterus of a non-responsive mother show fewer *in utero* toxic effects. Non-responsive fetuses in the uterus of a non-responsive mother show the highest incidence of *in utero* toxic effects. Although the study emphasizes the importance of administrative route in benzo[a]pyrene metabolism and resulting toxicity, it had the following limitations: 1) only one dose was evaluated; 2) no quantitative comparisons between treated groups and corresponding control animals were presented for any of the reported *in utero* toxicity or teratogenic effects; 3) small sample size; 4) purity of benzo[a]pyrene was not specified.

In another study, negative results were obtained when the potential developmental effects of benzo[a]pyrene were studied in mice (Rigdon and Neal 1965). Dietary administration of this chemical to mice at concentrations equivalent to 33.3, 66.7, or 133.3 mg/kg/day at various times before and after mating elicited no adverse effects on the developing embryos. Maternal weight gain was reduced in the mice administered the higher levels of benzo[a]pyrene, but this effect was reversed when the animals were changed to the control ration. Limitations of this study that preclude its inclusion in Table 2-2 consist of the use of an inconsistent protocol, varying number of animals, and varying time of gestation exposure.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in mice for acute-duration exposure is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following oral exposure to any of the 17 PAHs discussed in this profile.

Pregnant *Erythrocebus patas* monkeys were treated once on gestation day (Gd) 50, 100, or 150 (term = 160 days) with 5-50 mg/kg benzo[a]pyrene (Lu et al. 1993). Fetuses were removed by Cesarean section l-50 days after treatment and fetal organs, placentae, and maternal livers were assayed for DNA adducts. Benzo[a]pyrene-DNA adducts were high in fetal organs, placentae, and maternal livers in all three trimesters of gestation. Adduct levels were higher in mid-gestation compared to early or late gestation. dG-N2-BPDE was the major adduct detected. The adduct levels in fetal tissues increased with benzo[a]pyrene dose, but at a much lower rate that placentae or maternal livers. Preference in binding to DNA of various fetal tissues was more apparent in early gestation compared to late gestation, and at lower doses compared to higher doses. During early gestation and at lower doses, benzo[a]pyrene produced a similar level of DNA binding in fetal lung, liver, maternal liver, and placenta. Individual fetal organ adduct levels correlated significantly with placental adduct levels, indicating placental and/or maternal contribution to adduct formation in fetuses. Evidence of fetal contribution to adduct formation was also found. DNA adduct levels in fetal skin were lowest of all fetal organs tested and less affected by gestational stage at time of treatment. In contrast, DNA adduct levels in fetal liver exhibited distinct gestation stage specificity with higher adduct, levels attained during mid-gestation compared to other stages of gestation. Adduct levels decreased at a much faster rate during the first 10-15 days compared to 15-50 days after treatment. However, 10% of the DNA adducts persisted 50 days after treatment in all organs studied. Together, the results suggest that placental adduction accurately indicates fetal exposure.

Male B6C3F_1 mice were fed 0, 0.325, 0.1825, 1.625, 3.25, or 6.5 mg/kg/day benzo[a]pyrene for 21 days (Culp and Beland 1994). Animals were killed and the liver, lung, and forestomach DNA extracted and analyzed for benzo[a]pyrene-DNA adducts. The major adduct, dG-N2-BPDE, was quantified. Adduct levels in liver and lung increased in a linear manner. Adduct levels in the forestomach appeared to plateau at the highest dose. At doses below the highest, adduct levels were in

the order of forestomach > liver > lung, with the values of average slopes being 3.0 + 0.59, 2.1 + 0.17, 1.3 + 0.37 fmol adduct/mg DNA/μg benzo[a]pyrene/day, respectively. At these doses, the lung and the forestomach were not significantly different. At the high dose, liver > forestomach > lung, and each tissue was significantly different from the other.

DNA binding of coal tar components in male mice was investigated following the ingestion of coal tar obtained from a manufactured coal plant (Weyand et al. 1991). One of four different samples (A-D) of coal tar or a mixture of four equal portions of the four samples was administered in a gel diet which contained 0.25% coal tar. The coal tar contained phenanthrene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, indeno[1,2,3-c,d]pyrene, and benzo[g,h,i]perylene, among other PAHs. In addition, a diet containing benzo[a]pyrene at the same level as the 0.25% diet prepared with Sample C was administered; animals consuming this diet ingested 0.01-0.02 mg benzo[a]pyrene per day. The diets were administered for 15 days. Chemical-DNA adduct formation was evaluated in animals following 14 days of treatment. Chemical-DNA adduct formation was also evaluated in animals maintained on a 0.1, 0.2, 0.5, and 1.0% coal tar diet prepared with one of the coal tar samples (C). Chemical-DNA adduct formation in animals dosed with 0.l-1.0% Sample C indicated a dose-related effect in lung DNA adduct formation, but no dose-related effect was observed for forestomach tissue. In addition, overall adduct levels in lung tissue were considerably higher than forestomach levels for animals on the 0.5 or 1% diet. In contrast, adduct levels were highest in the forestomach of animals on diets lower in coal tar content (0.1 or 0.2%). Chemical-DNA adducts of coal tar components evaluated for Samples A-D and the mixture of the four coal tar samples at 0.25% in the diet administered for 15 days indicated adducts in the lung, liver, and spleen of all animals. Adduct patterns were similar, but quantitative differences were observed between coal tar samples and tissue sites. The highest adduct levels were detected in lung DNA. Adduct formation in animals fed the benzo[a]pyrene diet, could not account for the differences in the adduct levels observed in animals given the mixtures. Also, adduct formation in animals fed the coal tar mixtures correlated with benzo[a]pyrene content in the coal tar, indicating the adducts arose from a variety of PAHs in the coal tar mixtures. The levels of 1-hydroxypyrene in the urine of these animals correlated with the pyrene content of these coal tars.

The DNA binding of manufactured gas plant residue (MGP) components in male B6C3Fl mice was investigated following oral administration (Weyand and Wu 1994). Male mice were fed a gel diet containing manufactured gas plant (MGP) residue (coal tar) at 0.3% for 28 days, or the corresponding

control diet. Two mixtures of MGP residue were used: Mix of 3 combining equal amounts of samples from three different MGP plant sites, and Mix of 7 combining equal amounts of samples from seven different MGP plant sites, including those used in the Mix of 3. The mixtures contained pyrene, benz[a]anthracene, chrysene, benzo[b]fluorene, benzo[k]fluorene, benzo[a]pyrene, indeno[l,2,3-cd] pyrene, dibenz[a,h]anthracene, benzo[g,h,i]perylene. Data was presented in terms of pyrene consumed. Animals were sacrificed on the twenty-ninth day and lung and forestomach were excised and DNA isolated. Chemical-DNA adduct formation was evaluated. Ingestion of the adulterated diets resulted in a relatively low level of DNA adducts in the forestomach in comparison with the lung (one-tenth the level). PAH-DNA adduct levels in the lung of mice maintained on the Mix of 3 (1.4 mg/kg/day pyrene) were two times greater than the level induced by the Mix of 7 (1.2 mg/kg/day pyrene) suggesting that the composition of the MGP residue may have influence PAH absorption or DNA adduct formation.

Oral exposure to a total dose of 10 mg/kg benzo[a]pyrene produced gene mutations in the mouse coat color spot test (Davidson and Dawson 1976, 1977). Dose-related increases in the frequency of micronuclei were seen in bone marrow cells harvested from MS/Ae and CD-l male mice (four mice/strain/dose) 48 hours after administration of a single oral dose of benzo[a]pyrene ranging from 62.5 to 500 mg/kg (Awogi and Sato 1989). Although the response appeared to be stronger in the MS/Ae strain, the reduction in polychromatic erythrocytes, indicative of target cell toxicity at all levels in the CD-1 strain, limited the comparative evaluation of strain specificity.

In another study, a dose of benzo[a]pyrene (150 mg/kg) known to induce a clastogenic response was orally administered to groups of five adult males and females, pregnant females, and fetal ICR mice. An increased incidence of micronuclei in bone marrow cells harvested from the various groups of adult animals and also in the livers of the fetuses was observed (Harper et al. 1989). Genetic damage was most severe in the fetuses. The approximately 7-fold increase in micronuclei in fetal livers as compared to maternal bone marrow suggests that the transplacentally-induced genotoxicity was probably associated with the immature detoxification processes of fetal liver as compared to adult bone marrow. It would, nevertheless, appear that the fetus may be at an increased risk.

Data showing that orally administered benzo[a]pyrene induces micronuclei were confirmed in subsequent studies (Shimada et al. 1990, 1992) using rats (Sprague-Dawley) and mice (CD-l and BDF_1), different dosing regimes (single, double, or triple doses), and different target cells (bone

marrow and peripheral blood reticulocytes). A single oral gavage dose of 63 mg/kg benzo[a]pyrene significantly ($p<0.0l$) increased the yield of chromosomes with abnormal morphology in bone marrow cells collected from hybrid $lC3F_1$ male mice (Adler and Ingwersen 1989).

There is conflicting evidence that the genetic damage induced by benzo[a]pyrene is partially controlled by the expression of structural genes for benzo[a]pyrene-specific cytochromes P-450. In one study, two inbred strains of mice differing in AHH inducibility (AHH-inducible strain C57BL/6 and AHH-noninducible strain DBA/2) received two consecutive daily doses of either 10 or 100 mg/kg of the test material (Wielgosz et al. 1991). Animals were sacrificed 5 days postexposure, and bone marrow and spleen cells were examined for sister chromatid exchange and DNA adducts. Results showed a marked increase in sister chromatid exchange induction and the formation of DNA adducts in bone marrow and spleen cells recovered from the DBA/2 mice (AHH-noninducible) in both dose groups compared to the C57BL/6 (AHH-inducible) mice. However, no clear correlation between AHH inducibility and the positive clastogenic response induced by 150 mg/kg benzo[a]pyrene was found in adult male and female mice with genetically determined differences in AHH induction (Adler et al. 1989). Similarly, the transplacental exposure of 11-day-old homozygous and hybrid embryos (dams received a single oral gavage dose of 150 mg/kg and embryos were sampled 15 hours after treatment) to benzo[a]pyrene showed that the clastogenic response was independent of genetic constitution.

In contrast to the relatively uniform evidence that benzo[a]pyrene is a genotoxin in whole animals, the test material failed to induce unscheduled DNA synthesis (UDS) in the parenchymal liver cells of Brown Norway rats exposed by oral gavage to 12.5 mg/mL (Mullaart et al. 1989). There was, however, a clear increase in single-strand DNA breaks in cells from the two major centers of metabolism (the parenchymal liver and intestinal cells) of the treated animals that was not apparent in the nonparenchymal liver cells.

Significant ($p<0.05$), but marginal, increases in the frequency of abnormal sperm were found in CD-l mice (8-12/group) exposed via oral gavage to benzo[a]pyrene doses ranging from 360 to 432 mg/kg (Salamone et al. 1988). The effect, however, was not clearly dose related, and the wide variation in the background frequency rendered the data inconclusive. Comparable doses produced no adverse effects in $B6C3F_1$ mice. Similarly, the evaluation of pyrene (241-844 mg/kg) in this study yielded uniformly negative results.

Orally administered fluoranthene (400 and 750 mg/kg) did not increase the sister chromatid exchange frequency in mice (Palitti et al. 1986). Gene mutations were not produced in bacteria or yeast in a host-mediated assay in which anthracene, benzo[a]pyrene, chrysene, or fluoranthene were administered to mice by gavage; positive results were produced in bacteria in the same test system in which mice were exposed to benz[a]anthracene and injected intraperitoneally with the bacteria (Simmon et al. 1979). Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to the 17 PAHs discussed in this profile. The animal studies discussed in this section are presented first by exposure duration (acute, intermediate, and chronic), and within each duration category the information on individual PAHs is discussed in alphabetical order. PAHs for which no information was available for specified exposure durations were omitted.

Acute-Duration Exposure. Mice acutely administered 1.5 mg/day benz[a]anthracene by oral gavage two times over 3 days exhibited increased incidences of hepatomas and pulmonary adenomas (80% and 85%, respectively) as compared to control incidences (10% and 30% for hepatomas and pulmonary adenomas, respectively) after 568 days of observation (Klein] 1963). No malignant tumors were observed in this study.

Mice fed benzo[a]pyrene in the diet at a concentration equivalent to 33.3 mg/kg/day exhibited forestomach neoplasms following 2 or more days of consumption. However, a lower concentration of benzo[a]pyrene (equivalent to 13.3 mg/kg/day) administered for up to 7 days did not produce forestomach tumors (Neal and Rigdon 1967) (see Table 2-2). Hamsters have also been observed to develop papillomas and carcinomas of the alimentary tract in response to gavage or dietary exposure to benzo[a]pyrene (Chu and Malmgren 1965). A 77% mammary tumor incidence was observed 90 weeks after a single oral dose of 50 mg benzo[a]pyrene (100 mg/kg) was administered to rats, as compared to a 30% incidence in untreated animals (McCormick et al. 1981).

A single dose of 0.05 mg/kg dibenz[a,h]anthracene in polyethylene glycol (PEG)-400 failed to induce tumors in male Swiss mice after 30 weeks. However, forestomach papillomas were found in 10% of mice administered a single dose of 0.05 mg/kg dibenz[a,h]anthracene followed by 30 weekly doses of

PEG alone, and in 21% of the mice when the dibenz[a,h]anthracene dose was followed by 30 weekly doses of PEG plus 3% croton oil (Berenblum and Haran 1955). Treatment with croton oil alone yielded a 14-16% tumor incidence. These results suggest that the carcinogenic activities of croton oil and dibenz[a,h]anthracene are additive in the mouse forestomach.

Intermediate-Duration Exposure. One intermediate-duration study was located that evaluated the carcinogenic potential of acenaphthene. Male and female mice exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks showed no evidence of tumorigenesis at necropsy (EPA 1989c).

Similarly, only one intermediate-duration study was located that evaluated the carcinogenic potential of anthracene. Male and female mice exposed to 0, 250, 500, 1,000 mg/kg/day anthracene by gavage for 13 weeks showed no evidence of tumorigenesis at necropsy (EPA 1989d).

One intermediate-duration study was located that evaluated the carcinogenic potential of benz[a]anthracene. Mice that received intermittent gavage doses of 1.5 mg/kg/day benz[a]anthracene for 5 weeks (Klein 1963). Mice were sacrificed at a median age of 437 or 547 days. The treated mice killed at 437 days exhibited a 95% incidence of pulmonary adenomas at an average of 3 per lung and a 46% incidence of hepatomas, with an average of 2.1 per tumor-bearer. Forestomach papillomas were found in 5% of the mice. Control animals killed after 441 days exhibited a 10% incidence of pulmonary adenomas. Treated mice sacrificed after 547 days exhibited a 95% pulmonary adenoma incidence, as was observed in the group sacrificed earlier, but an increased hepatoma incidence of 100%. Control animals sacrificed after 600 days had 30 and 10% incidences of pulmonary adenomas and hepatomas, respectively. This study was not adequately reported; it did not include complete histopathology, adequate treatment durations, large enough sample sizes, or statistical analysis. Although this study is inconclusive because of methodological limitations, it does provide some qualitative evidence for the potential carcinogenicity of benz[a]anthracene by the oral route.

Intragastric doses of 67-100 mg/kg benzo[a]pyrene have been shown to elicit pulmonary adenomas and forestomach papillomas in mice (Sparnins et al. 1986; Wattenberg and Leong 1970). Intermittent gavage exposure of mice to 67-100 mg/kg benzo[a]pyrene resulted in increased forestomach (100%) and pulmonary tumor incidences relative to controls at 30 weeks of age (Sparnins et al. 1986;

Wattenberg and Leong 1970). The study by Wattenberg and Leong (1970) involved gavage administration of approximately 1.0 mg of benzo[a]pyrene once a week for 8 weeks.

The incidence of forestomach tumors (papillomas and carcinomas) in mice was related to the duration of oral exposure to benzo[a]pyrene following intermediate-duration administration of dietary benzo[a]pyrene at various doses up to 250 ppm (33.3 mg/kg/day) for 30-197 days (Neal and Rigdon 1967, see Table 2-2). The tumor incidence also increased with increasing dose. In the same study, mice fed 250 ppm (33 mg/kg/day) for periods of 1-7 days exhibited increased forestomach tumor incidences following 2 or more days of benzo[a]pyrene exposure (total dose of 2 mg), while mice fed 10 ppm (13.3 mg/kg/day) for 110 days (total dose of 4.48 mg) did not develop tumors. The authors suggest that these findings provide evidence that there are no cumulative carcinogenic effects of benzo[a]pyrene or its metabolites in mice. These data suggest that differences in susceptibility may be strongly influenced by the age of the mice at the time that they were initially exposed. This study provides the best dose-response information available for the oral route of exposure despite the irregular protocol employed, although the relevance of forestomach tumors in rodents to human cancer is the subject of some controversy because humans lack a forestomach.

An association between dietary benzo[a]pyrene and the development of leukemia and tumors of the forestomach and lung has been observed in mice. Tumor incidence was related to both dose and length of exposure (except in the case of leukemia). Mice administered dietary doses of up to 1,000 ppm (up to 133 mg/kg/day) for intermediate lengths of time (23-238 days) exhibited an increased incidence of forestomach tumors (papillomas and carcinomas) (Rigdon and Neal 1966, 1969) (see Table 2-2). Mice administered 250 ppm (33.3 mg/kg/day) benzo[a]pyrene developed papillomas or carcinomas of the forestomach (64%) and all the mice in the 1,000-ppm (133 mg/kg/day) group exhibited forestomach tumors after 86 days of benzo[a]pyrene consumption. A similar relationship was observed for the incidence of lung tumors: mice fed 250 ppm (33.3 mg/kg/day) benzo[a]pyrene exhibited an increased lung adenoma incidence. The occurrence of leukemia was related to the ingestion of 250 ppm (33.3 mg/kg/day) benzo[a]pyrene; 37% of the treated mice developed leukemias (Rigdon and Neal 1969) (see Table 2-2). The lack of consistent protocol in these experiments and the short exposure duration and observation periods preclude the assessment of a dose-response relationship. Furthermore, because tumors were reported as combined papillomas and carcinomas, no distinction between these benign and malignant tumors can be made.

Mammary tumors have also been observed following intermediate-duration exposure to benzo[a]pyrene in rats. Eight weekly oral doses of 6.25 mg benzo[a]pyrene (12.5 mg/kg) administered to rats resulted in a 67% increase in the incidence of mammary tumors in female rats after 90 weeks of observation (McCormick et al. 1981). A 30% incidence of these tumors was observed in the control animals.

Two intermediate-duration studies investigated the carcinogenicity of dibenz[a,h]anthracene in animals following oral exposure. Mammary carcinomas were observed in 5% of the female BALB/c mice dosed with 0.5% dibenz[a,h]anthracene after 15 weeks of dosing; however, no control group was included (Biancifiori and Caschera 1962). In the other study, male and female rats were administered an emulsion of aqueous olive oil and dibenz[a,h]anthracene in place of their drinking water for up to 200 days (Snell and Stewart 1963). Pulmonary adenomatosis, alveologenic carcinoma, mammary carcinoma, and hemangioendotheliomas were observed in the treated rats. These tumors were not observed in the control animals. However, extensive dehydration and emaciation occurred because the animals did not tolerate the vehicle well, which lead to early death and the need to periodically remove the animals from the treatment vehicle. Neither of these studies was adequately reported: they did not perform appropriate histopathologic evaluations, treatment or study durations were inadequate, and the sample size was inadequate. Despite these methodological limitations, these studies do provide some evidence of dibenz[a,h]anthracene's carcinogenicity by the oral route.

One intermediate-duration study was located that evaluated the carcinogenic potential of fluoranthene. Male and female mice exposed to 0, 125, 250, or 500 mg/kg/day fluoranthene by gavage for 13 weeks showed no evidence of tumorigenesis at necropsy (EPA 1988e).

Similarly, only one intermediate-duration study was located that evaluated the carcinogenic potential of fluorene. Male and female mice exposed to 0, 125, 250, or 500 mg/kg/day fluorene by gavage for 13 weeks showed no evidence of tumorigenesis at necropsy (EPA 1989e).

Chronic-Duration Exposure. Benzo[a]pyrene was administered in the diet of 32 Sprague-Dawley rats/sex/group either every 9th day or 5 times/week at a dose of 0.15 mg/kg until the animals were either moribund or dead (Brune et al. 1981). An untreated control group consisted of 32 animals/sex. There was no treatment-related effect on survival and no treatment-related increase in tumors at any one site. However, a statistically significant increase in the proportion of animals with tumors of the forestomach, esophagus, and larynx combined was noted among animals receiving treatment

5 times/week (the combined incidence of animals with these tumors was 3/64, 10/64, and 3/64 in the controls, the group fed benzo[a]pyrene 5 times/week, and the group fed benzo[a]pyrene every 9th day). In the same study, groups of 32 Sprague-Dawley rats/sex were administered 0.15 mg/kg benzo[a]pyrene by gavage in a 1.5% caffeine solution either every 9th day (Group 3), every 3rd day (Group 2), or 5 times/week (Group 1) until the animals were moribund or dead, resulting in average annual doses of 6, 18, or 39 mg/kg, respectively. Survival was adversely affected only in Group 3 (mean survival.time = 87 weeks versus 102 weeks in the controls). Treatment with benzo[a]pyrene significantly increased the proportion of animals with tumors of the forestomach, esophagus, and larynx (the combined tumor incidence was 3/64, 6/64, 13/64, 2664, and 14/64 for the untreated controls, the gavage controls, and Groups 3, 2, and 1, respectively).

Summary. These results indicate that benz[a]anthracene, benzo[a]pyrene, dibenz[a,h]anthracene, and possibly other PAHs are carcinogenic to rodents following oral exposure at high doses.

All reliable CELs in mice for acute- and intermediate-duration exposure are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to the 17 PAHs discussed in this profile.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or ocular effects in humans or animals after dermal exposure to any of the 17 PAHs discussed in this profile. Other systemic effects observed after dermal exposure are discussed below.

The highest NOAEL values and all LOAEL values from each reliable study for each species and duration category are recorded in Table 2-3.

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL			Reference
				Less Serious		Serious	
ACUTE EXPOSURE							
Systemic							
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal	0.05 M mg/c m2				Iwata et al. 1981 anthracene
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal	0.001 M mg/c m2	0.005 M mg/cm 2	(induction of melanocytes)	0.025 M (substantial melanocytes)	Iwata et al. 1981 benzo[a]pyrene
Mouse (C34/HeN)	5 d 2 x/5d	Dermal		120 mg F	(contact hypersensitivity)		Klemme et al. 1987 benzo[a]pyrene
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal		0.0125 M mg/cm 2	(slight increase melanocytes)		Iwata et al. 1981 chrysene
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal	0.05 M mg/c m2				Iwata et al. 1981 fluoranthene
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal	0.05 M mg/c m2				Iwata et al. 1981 fluorene
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal	0.05 M mg/c m2				Iwata et al. 1981 pyrene
Immunological/Lymphoreticular							
Mouse (C34/HeN)	5 d 2 x/5d			120 F	(contact hypersensitivity)		Klemme et al. 1987 benzo[a]pyrene

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
Cancer						
Mouse (CD-1)	20 d 10 x				10.1µg F [CEL: 35% (7/20) tumor incidence]	Weyand et al. 1993b benzo[b]fluoranthene
INTERMEDIATE EXPOSURE						
Immunological/Lymphoreticular						
Gn pig (Hartley)	2-3 wk 2 x			0.001% F (slight contact sensitivity)	1.0% F (contact sensitivity)	Old et al. 1963 benzo[a]pyrene
Cancer						
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M (CEL: 1/13 (8%) had a papilloma with coadministration of 0.0005 mg BaP)	Warshawshy et al. 1993 anthracene
Mouse (CD-1)	1 d 1 x/d, then 25 wk 3 d/wk (TPA)		0.09 F mg/kg		0.57 F mg/kg (CEL: 36% skin tumor incidence)	Levin et al. 1984 benz[a]anthracene
Mouse (SENCAR)	once then 23 wk 2 d/wk (TPA)				0.2 mg F (CEL: 6 papillomas/mouse)	Cavalieri et al. 1988b benzo[a]pyrene
Mouse (Swiss)	20 wk 2 x/wk 1 x/d				0.025 F mg (CEL: tumors in 90%)	Cavalieri et al. 1988b benzo[a]pyrene

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL			Reference
				Less Serious	Serious		
Mouse (Crl:CD-1)	20 d every other day				0.01 mg F	(CEL: 35% developed skin tumors)	LaVoie et al. 1993a benzo[b]fluoranthene
Mouse (CD-1)	20 d every other day				0.006 mg F	(CEL: 5% developed skin tumors)	LaVoie et al. 1993b benzo[j]fluoranthene
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M	(CEL: 1/15 (7%) had a papilloma from chrysene alone; 3/13 (23%) having papillomas or malignancies with coadministration of 0.0005 mg BaP)	Warshawshy et al. 1993 chrysene
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M	(CEL: 1/12 (8%) had papillomas with coadministration of 0.0005 mg BaP)	Warshawsky et al. 1993 fluoranthene
Mouse (CD-1)	20 d 1 x/2d, then 22 wks (TPA)				100 mg F	(CEL: 80% incidnece of tumors)	Rice et al. 1985a indeno(1,2,3-c,d)pyr
Mouse (Swiss)	12 mo 3 x/wk		50 F		100 µg F	(CEL: 6/20 had papillomas, 3/20 had carcinomas)	indeno(1,2,3-cd)pyre

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL			Reference
				Less Serious	Serious		
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M	(CEL: 3/13 (23%) had a tumor (papillomas and malignant) from the mixture alone; 8/17 (47%) with coadministration of 0.0005 mg BaP)	Warshawsky et al. 1993 mix
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M	(CEL: 1/12 (8%) had papillomas from phenanthrene alone; 1/17 (6%) had a malignant tumor with coadministration of 0.0005 mg BaP)	Warshawsky et al. 1993 phenanthrene
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M	(CEL: 1/13 (8%) had a papillomas from pyrene alone)	Warshawsky et al. 1993 pyrene
CHRONIC EXPOSURE							
Cancer							
Mouse (NMRI)	17-22 mo 2 d/wk 1 x/d				2 mg F	(CEL: 45% developed skin tumors)	Habs et al. 1984 benzo[a]pyrene
Mouse (C3H/HrJ)	99 wk 2 d/wk 1 x/d				12.5 µg M	(CEL: malignant tumors in 47/50)	Warshawsky and Barkley 1987 benzo[a]pyrene
Mouse (Swiss)	lifetime 3 d/wk 1 x/d				0.01% F	(CEL: papillomas in 5%)	Wynder and Hoffmann 1959b benzo[b]fluoranthene

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Mouse (NMRI)	19-20 mo 2 d/wk 1 x/d				15 µg F (CEL: skin carcinomas in 1/20)	Habs et al. 1984 mix

BaP = benzo(a)pyrene; CEL = cancer effect level; d = day(s); F = female; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; TPA = tetradecanoyl phorbol acetate; wk = week(s); x = time(s)

Dermal Effects. Mixtures of carcinogenic PAHs cause skin disorders in humans and animals; however, specific effects in humans of individual PAHs, except for benzo[a]pyrene, have not been reported. Mixtures of PAHs are also used to treat some skin disorders in humans. From these patients comes much of the data describing dermal effects of PAH exposure.

Regressive verrucae (i.e., warts) was reported following up to 120 dermal applications of 1% benzo[a]pyrene in benzene to human skin over 4 months (Cottini and Mazzone 1939). Although reversible and apparently benign, the changes were thought to represent neoplastic proliferation.

Adverse dermal effects have been noted in humans following intermediate-duration dermal exposure to benzo[a]pyrene in patients with the preexisting dermal conditions of pemphigus vulgaris (acute or chronic disease characterized by occurrence of successive crops of blisters) and xeroderma pigmentosum (a rare disease of the skin marked by disseminated pigment discolorations, ulcers, and cutaneous and muscular atrophy) (Cottini and Mazzone 1939). A 1% benzo[a]pyrene solution topically applied to patients with pemphigus resulted in local bullous eruptions characteristic of the disease. Patients with xeroderma pigmentosum exposed to 1% benzo[a]pyrene slightly longer than the pemphigus patients exhibited only pigmentary and slight verrucous effects. Similarly treated patients with preexisting active skin lesions due to squamous cell cancer showed a general improvement and/or retardation of the lesion. The severity of abnormal skin lesions appeared to be related to age; those in the lowest age range exhibited fewer and less-severe effects than those in the mid-range groups. No such age relationship of effects involving those patients with normal or preexisting skin lesions was noted.

Adverse dermal effects have also been ohserved in animals following both acute- and intermediate-duration dermal exposure to various PAHs. For example, acute topical application of benzo[a]pyrene, benz[a]anthracene, or dibenz[a,h]anthracene applied to the shaved backs of Swiss mice were all reported to suppress sebaceous glands (Bock and Mund 1958). However, controls were not employed; therefore, it is not possible to determine if the effects seen were due to the solvent and/or the application procedures.

Benzo[a]pyrene was applied once weekly to the skin of female ICR/Harlan mice (43-50/group) at doses of 16, 32, or 64 μg per application for 29 weeks (Albert et al. 1991b). Cell cycle kinetics and

morphometrics were evaluated. Evidence of epidermal cytotoxicity and death followed by regeneration was seen in animals administered 64 μg benzo[a]pyrene beginning the first weeks of exposure and later in the lower dose groups. This evidence included dose-related epidermal thickening and vertical nuclei stacking, increased mitotic labeling (2-4-fold with increasing dose), increased incidence of pyknotic and dark cells, and a pronounced inflammatory response in the dermis. The increase in cell proliferation was accompanied by only a minor increase in the size of the epidermal cell population, indicating that the proliferation was a regenerative response.

An acute (96-hour) dermal application of anthracene to the backs of hairless mice followed by ultraviolet radiation exposure for 40 minutes resulted in enhanced dermal inflammation compared to mice exposed exclusively to ultraviolet radiation. However, this effect was reversed within 48 hours (Forbes et al. 1976). Anthracene thus potentiates the skin damage elicited by sunlight exposure and may be considered a photosensitizer in hairless mice.

In animals, dermal application of 1% benzo[a]pyrene to the skin of hairless mice resulted in epidermal cell growth alterations (Elgjo 1968). Increases were observed in mitotic rates, mitotic counts, and mitotic duration and the author suggested that these were indicative of a regenerative reaction. However, concurrent controls were not utilized. The authors concluded that the alterations in the kinetics of epidermal cell growth produced by benzo[a]pyrene were more sustained than after application of croton oil. The study is limited for drawing conclusions concerning the dermal toxicity of benzo[a]pyrene because experimental data were compared with historical controls only, no acetone control was evaluated, and the statistical significance of the increased values was not determined.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following dermal exposure to the 17 PAHs discussed in this profile.

Benzo[a]pyrene can elicit an immune response when applied dermally to the skin of animals. In mice, acute application of 120 μg benzo[a]pyrene elicited an allergic contact hypersensitivity in C3H mice that was antigen specific (Klemme et al. 1987). Slight contact hypersensitivity was also observed in guinea pigs following two dermal applications of 0.001% benzo[a]pyrene given over a period of 2-3 weeks. This response was more severe at a dose of 1.0% benzo[a]pyrene (Old et al. 1963).

In addition to eliciting a contact hypersensitivity response, benzo[a]pyrene has been shown to suppress this response to other sensitizers. The effects of dermally applied benzo[a]pyrene (alone or following dermal pretreatment with the prostaglandin synthetase inhibitor, indomethacin) on contact hypersensitivity (cell-mediated immunity), and production of antibodies to dinitrophenol (DNP) (humoral immunity) were studied in male BALB/c mice treated for 6 weeks to 6 months (Andrews et al. 1991a). A group of mice treated with acetone served as controls. Benzo[a]pyrene alone caused a significant reduction ($p<0.01$) in the contact hypersensitivity response to dinitrofluorobenzene (DNFB) as measured by increases in ear thickness when compared to the vehicle controls. However, indomethacin pretreatment prevented the benzo[a]pyrene-induced contact hypersensitivity response. Benzo[a]pyrene also reduced antibody titres to DNP in treated mice. This suppressive effect on humoral immune function was not restored by pretreatment with indomethacin. These findings led the authors to conclude that the mechanism of benzo[a]pyrene-induced suppression of cell-mediated immunity involved prostaglandins, whereas benzo[a]pyrene-induced suppression of humoral immunity operated via a mechanism independent of prostaglandins. In a subsequent experiment, the effects of dermally applied benzo[a]pyrene (alone or following subcutaneous implantation of the prostaglandin synthetase inhibitor, indomethacin) on Langerhans cells and on skin prostaglandin (PGE_2) levels were studied in male BALB/c mice treated for 3 weeks (Andrews et al. 1991b). Langerhans cells are antigen-presenting cells involved in cell-mediated immunity in skin. A group of mice treated with indomethacin served as controls. Benzo[a]pyrene alone caused a significant increase in the number of skin Langerhans cells, but reduced the percentage of Langerhans cells with dendritic morphology. Skin PGE_2 levels were also significantly increased by benzo[a]pyrene. Indomethacin attenuated the increase in Langerhans cell number and the changes in their morphology, and increased PGE_2 levels, such that all of these parameters were similar to those measured in the control animals. Based on these results, the authors suggested that benzo[a]pyrene induces increases in skin PGE_2 that in turn alter Langerhans cell number and morphology such that the cell-mediated immune response to skin antigens is suppressed.

An earlier study also demonstrated that benzo[a]pyrene affects epidermal Langerhans cells and dermal immunological responses. Female BALB/c mice were administered dermal applications on the dorsal skin of 0.5% benzo[a]pyrene in acetone twice weekly for up to 6 months (Ruby et al. 1989). Animals treated with acetone served as controls. The density, area, perimeter, and morphology of epidermal Langerhans cells were evaluated, along with the contact hypersensitivity response to DNFB. Benzo[a]pyrene treatment caused an increase in the number of epidermal Langerhans cells (as

determined by Ia antigens and B-glucuronidase) from week 2 to week 5 of treatment and after weeks 10 and 18. The area and perimeter of these cells were unaffected by benzo[a]pyrene treatment, but the morphology was altered in that the dendrites appeared shortened. The contact hypersensitivity response to DNFB was significantly reduced in the benzo[a]pyrene-treated mice from 4 to 24 weeks of treatment. The authors propose that benzo[a]pyrene alters Langerhans cell number and morphology such that the cell-mediated immune response to skin antigens is suppressed. Skin tumors appeared in 20% of the benzo[a]pyrene-treated mice after 18 weeks of treatment, and 35% of the mice had l-3 tumors after 24 weeks of treatment. The tumors were squamous papillomas (58%) and squamous cell carcinomas (42%). The changes in Langerhans cell number, distribution, and morphology coincided with the onset of tumors and other nonneoplastic skin lesions that were observed (epidermal hyperplasia and cellular atypia).

All reliable LOAELs from each reliable study for immunological effects for each species and duration category are recorded in Table 2-3.

No studies were located regarding the following health effects in humans or animals following dermal exposure to the 17 PAHs discussed in this profile:

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following dermal exposure to the 17 PAHs discussed in this profile. A single topical application of benzo[a]pyrene (0.5-500 μg/mouse) or chrysene (50-1,000 μg/mouse) to groups of HRA/Skh hairless mice (four mice/dose/group) resulted in significantly increased frequencies of micronucleated keratinocytes (He and Baker 1991). In the same study, micronuclei were not induced in the mouse skin cells following application of 2.5-2,500 μg/pyrene per mouse. Male SENCAR mice receiving two topical applications of 20 μg benzo[a]pyrene at 72-hour intervals exhibited increased DNA adduct formation in both epidermal and

lung tissue (Mukhtar et al. 1986). Following a single topical application, 100 μg benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-c,d]pyrene were reported to bind to DNA in CD-l mouse skin (Weyand et al. 1987). The relative extent of binding was benzo[b]fluoranthene > benzo[j]fluoranthene > benzo[k]fluoranthene > indeno[1,2,3-c,d]pyrene. Covalent binding of chemicals to DNA can result in strand breaks and DNA damage, ultimately leading to mutations.

Benzo[a]pyrene (62.5 or 500 μg) was applied once to the shaved backs of male C57BL/6 mice (Bjelogrlic et al. 1994). Mice were killed at different time intervals after the treatment. DNA was isolated from the skin, purified, and analyzed for benzo[a]pyrene-7,8-diol-9,10-epoxide-DNA adducts. Skin was also evaluated for monoclonal antibody binding to mouse p53 protein, which has been shown to increase in response to DNA damage. Alterations in p53 are the most frequently observed mutations in human cancer. Benzo[a]pyrene-7,8-diol-9,10-epoxide-DNA adducts reached their maximum concentration 24 hours after the treatment, and decreased sharply within 1 week, regardless of the dose. An increase in p53 protein was seen only after treatment with 500 μg benzo[a]pyrene.

Benzo[j]fluoranthene, benzo[j]fluoranthene-4,5-diol, and benzo[j]fluoranthene-9,10-diol were applied to the shaved backs of CD-l mice and the DNA adducts were isolated and separated using multidimensional thin-layer chromatography (TLC) and reverse-phase high performance liquid chromatography (HPLC) (Weyand et al. 1993a). The highest level of adducts was observed with benzohlfluoranthene-4,5-diol, which resulted in the formation of 383 pmol of DNA adducts/mg DNA. This level of DNA modification was more than 2 orders of magnitude greater than that observed with benzo[j]fluoranthene. In contrast, the major DNA adducts detected with benzo[j]fluoranthene-9,10-diol had chromatographic properties distinctly different than the adducts formed from either benzo[j]fluoranthene or B[j]F-4,5-diol. The adducts of the diols corresponded to DNA adducts produced *in vitro* from the respective diolepoxides. In a companion study, benzo[b]fluoranthene, benzo[b]fluoranthene-9,10 diol, 6-hydroxy-benzo[b]fluoranthene-9,10-diol, or 5-hydroxybenzo[b]fluoranthene-9,10-diol were applied to the shaved backs of CD-1 mice and the DNA adducts were isolated and separated using multidimensional TLC and reverse-phase HPLC (Weyand et al. 1993b). Benzo[b]fluoranthene formed one major adduct and 4 minor adducts. The DNA adducts formed from 5-hydroxybenzo[b]fluoranthene-9, l0 diol had identical retention to the major and one of the minor adducts of benzo[b]fluoranthene. These two adducts accounted for 58% of the modified nucleotides produced by benzo[b]fluoranthene application to mouse skin.

The DNA binding of manufactured gas plant residue (MGP) components in male B6C3Fl mice was investigated following topical administration (Weyand and Wu 1994). For topical exposure, male mice were treated with 10 mg MGP residue in 200 μL acetone, and sacrificed 24 hours later. Two mixtures of MGP residue were used: Mix of 3 combining equal amounts of samples from three different MGP plant sites, and Mix of 7 combining equal amounts of samples from seven different MGP plant sites, including those used in the Mix of 3. The mixtures contained pyrene, benz[a]anthracene, chrysene, benzo[b]fluorene, benzo[k]fluorene, benzo[a]pyrene, indeno[l,2,3-cd]pyrene, dibenz[a,h]anthracene, benzo[g,h,i]perylene. Data were presented in terms of pyrene. Animals were sacrificed 24 hours after treatment, and skin and lung were excised and DNA isolated. Chemical-DNA adduct formation was evaluated. Topical application MGP residue in acetone resulted in similar levels of DNA adduct in the skin for both the Mix of 3 and the Mix of 7. The total level of adducts detected in the lung after topical administration was identical to the response after dietary exposure, i.e., the Mix of 3 (1.4 mg/kg/day pyrene) produced adduct levels that were two times greater than the levels induced by the Mix of 7 (1.2 mg/kg/day pyrene). Other genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located that gave evidence of a direct association between human dermal exposure to individual PAHs and cancer induction. However, reports of skin tumors among individuals exposed to mixtures containing PAHs lend some qualitative support to their potential for carcinogenicity in humans. The earliest of these is the report by Pott (1775) of scrotal cancer among chimney sweeps. More recently, skin cancer among those dermally exposed to shale oils has been reported (Purde and Etlin 1980). However, these reports provide only qualitative suggestions pertaining to the human carcinogenic potential of all of the 17 PAHs discussed in this profile, or at least the compounds found in chimneys and shale oils, such as benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, benz[a]anthracene, and benzo[b]fluoranthene. Limitations in these reports include no quantification of exposure to individual PAHs and concurrent exposure to other putative carcinogens in the mixtures.

It has been suggested that an increase in the number of skin melanocytes correlates with the sebaceous gland suppression index, and that the short-term melanocyte-activation test is useful for the detection of skin carcinogens and promoters. Some chemical carcinogens have been shown to induce melanogenesis in melanoblasts in the skin. Anthracene, benzo[a]pyrene, chrysene, fluoranthene,

fluorene, and pyrene were examined for their ability to induce melanocyte activation by topical application to the backs of mice for 1 or 2 consecutive days. Benzo[a]pyrene, an animal skin carcinogen, was a potent melanocyte inducer at doses of 20-100 μg/mouse (0.005-0.025 mg/cm^2) as demonstrated by an increase of up to 19 times over controls in the number of dopa-positive cells, whereas no effects were seen at 4 μg/mouse (0.001 mg/cm^2). Chrysene, a weak skin carcinogen (in animals), increased the number of dopa-positive cells to four times that of controls following an application of 50 μg/mouse (0.0125 mg/cm^2), while larger doses did not cause further increases in the numbers of these cells. Other PAHs such as anthracene, fluoranthene, fluorene, and pyrene (PAHs that are considered to be noncarcinogenic) produced no increases in the number of active melanocytes when applied at a dose of 200 μg/mouse (0.05 mg/cm^2) (Iwata et al. 1981).

Complete Carcinogenesis Studies. Studies in laboratory animals have demonstrated the ability of benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, and indeno[l,2,3-c,d]pyrene to induce skin tumors (i.e., they are complete carcinogens) following intermediate dermal exposure. Anthracene, fluoranthene, fluorene, phenanthrene, and pyrene do not act as complete carcinogens. The data supporting these conclusions are discussed below by chemical. Only those studies considered adequate and reliable with respect to study design and adequacy of reporting are presented in Table 2-3.

Anthracene. Skin painting experiments were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al. 1993). Anthracene dissolved in toluene was applied to shaved skin twice weekly for six months at a dose of 0.05 mg. Tumor incidence was determined at the end of the study. For anthracene, administration alone produced tumors in 0 of 14 animals. With coadministration of 0.05 mg benzo[a]pyrene, 1 of 13 (8%) had a papilloma, with a mean latency period of 85 weeks. Anthracene was negative as a complete carcinogen following chronic dermal exposure (Habs et al. 1980). Swiss mice receiving 10% anthracene in acetone topically applied to their backs three times a week throughout their lifetime did not develop any skin tumors after 20 months (Wynder and Hoffmann 1959a).

Benz[a]anthracene. Benz[a]anthracene has been shown to cause skin tumors in mice following intermediate-duration dermal application. Graded concentrations of benz[a]anthracene in toluene or *n*-dodecane applied to the backs of mice for 50 weeks resulted in dose-related increases in tumor incidence (Bingham and Falk 1969). This response was enhanced when *n*-dodecane was the solvent

compared with toluene. Malignant tumors were observed at dose levels of about 0.02% benz[a]anthracene (0.15 mg/kg/day) and above when toluene was the solvent; however, when n-dodecane was the solvent, tumors were observed.at much lower concentrations of 0.0002% benz[a]anthracene (0.0015 mg/kg/day). The dose-response relationship reported in this study is extremely shallow (sublinear) over two orders of magnitude. A possible explanation for this is that the tumorigenic potency of certain PAHs is tempered by their cytotoxicity. Thus, the cytotoxic effects to epithelial cells may self-limit their potency as tumorigens. No solvent controls were included for comparison (Bingham and Falk 1969).

Intermediate-duration topical application of benz[a]anthracene to the backs of mice for 30 weeks resulted in a slightly elevated (2.6%) (but not statistically significant) skin tumor incidence. No definitive conclusions can be drawn from this study since only one dose was employed and no statistical analysis was performed.

Benzo[b]fluoranthene. A dose-response relationship for the dermal carcinogenicity of benzo[b]fluoranthene has been demonstrated over a one order-of-magnitude dose range in Swiss mice receiving (0.0l-0.5%) benzo[b]fluoranthene throughout their lifetime. Survival was also dose related. Although this study was designed as a long-term (chronic) bioassay, malignant tumors (90% carcinomas) appeared as early as 4 months in the high-dose group. Papillomas and carcinomas (65% and 85%, respectively) also appeared after 5 months in the mid-dose group. As a result, this study provides evidence that benzo[b]fluoranthene is carcinogenic following intermediate-duration exposure. The lowest dose at which benzo[b]fluoranthene elicited malignant tumors was 0.l%, which is approximately equal to a dose of 2.9 mg/kg received three times weekly, or an average daily dose of 1.2 mg/kg (Wynder and Hoffmann 1959b, see Table 2-3). In another chronic dermal study, benzo[b]fluoranthene produced a significant carcinogenic response of approximately one-third the potency of benzo[a]pyrene. The lowest dose at which tumors appeared was 3.4 μg benzo[b]fluoranthene; however, no distinction was made between papillomas and carcinomas (Habs et al. 1980).

Benzo[j]fluoranthene. Benzofilfluoranthene (0.1% or 0.5%) applied to the skin of female Swiss mice thrice weekly for life induced skin papillomas in 70% and 95% of the animals, respectively, and skin carcinomas in 105% and 95% of the animals, respectively, after 9 months of treatment (Wynder and Hoffmann 1959b).

No statistically significant increase in the incidence of skin tumors was noted in female NMRI mice dermally administered 3.4, 5.6, or 9.2 μg benzo[j]fluoranthene in acetone twice weekly for life (Habs et al. 1980). A total of 4 benzo[j]fluoranthene-treated mice developed skin tumors (application site sarcoma, papillomas, and a carcinoma).

Benzo[k]fluoranthene. Chronic dermal application of benzo[k]fluoranthene to Swiss mice resulted in no tumors, but skin papillomas were observed in 10% of animals when the concentration of benzo[k]fluoranthene was increased. Statistical analyses were not performed (Wynder and Hoffmann 1959b). In another study, no significant increase in tumor incidence was observed in NMRI mice painted with up to 9.2 μg of benzo[k]fluoranthene twice a week for a lifetime; no effect on mortality was noted (Habs et al. 1980).

Benzo[a]pyrene. Benzo[a]pyrene is a potent experimental skin carcinogen, and it is often used as a positive control in bioassays of other agents. Mixtures of PAHs that include benzo[a]pyrene such as coal tar were shown to be dermal carcinogens in animals as early as 1918 (Yamagiwa and Ichikawa 1918). In its role as a positive control, benzo[a]pyrene is usually administered at a single dose level, and thus quantitative evaluation of dose-response relationships is not possible.

Intermediate (19-20 weeks) topical application of a benzo[a]pyrene solution to the backs of mice resulted in a dose-related development of skin papillomas and squamous cell carcinomas (Cavalieri et al. 1988b, see Table 2-3; Shubik and Porta 1957). Benzo[a]pyrene was applied once weekly to the skin of female ICR/Harlan mice (43-50/group) at doses of 16, 32, or 64 μg for 29 weeks (Albert et al. 1991ba). Cell kinetics, morphometrics, and tumor formation were evaluated. Skin tumors were first apparent 12-14 weeks after the start of exposure in the 32- and 64-μg groups and after 18 weeks in the 16-μg group. The overwhelming majority of these tumors were benign. The average time of progression from benign papillomas to malignant carcinomas was 8.1 ± 4.5 weeks. Because there was good correspondence between the dose-response patterns for epidermal damage and the occurrence of skin tumors, and because tumors that initially appear as benign can be the result of tumor promoting agents that increase cell proliferation rates, the authors proposed that the tumors seen after benzo[a]pyrene treatment were the result of promotion related to benzo[a]pyrene-induced tissue damage. However, benign tumors can be formed as a result of genetic damage as well. Because benzo[a]pyrene causes genetic damage in addition to increased rates of cell proliferation, it is likely that genetic damage also played a role. Following a similar protocol in mice (once weekly dermal

applications of benzo[a]pyrene in acetone at doses of 16, 32, and 64 μg/mouse for 34 weeks), tumor development was reported to be best described by a dose-squared response. Quantitative data for tumor incidence were not presented (Albert et al. 1991b).

Carcinogenicity experiments on mouse skin were conducted with groups of 20 female CD-l mice. Benzo[a]pyrene (0.05 mg) dissolved in 50 mL toluene was applied to shaved skin of mice twice weekly for 6 months (Warshawsky et al. 1993). Tumor incidence was determined at the end of the study. Benzo[a]pyrene produced no tumors.

In mice, the tumorigenic dose of benzo[a]pyrene is influenced by the solvent used for delivery. Graded concentrations of benzo[a]pyrene dissolved in decalin or a solution of n-dodecane and decalin were topically administered to the backs of mice for 50 weeks (Bingham and Falk 1969). Use of the n-dodecane and decalin solvent mixture significantly enhanced the potency of benzo[a]pyrene at lower doses in comparison with decalin alone. Malignant tumors appeared in 21% of the animals at 0.00002% (0.0054 mg/kg/day) benzo[a]pyrene in dodecane and decalin solvent. In contrast, a 42% skin tumor incidence was not observed until 0.02% (4.8 mg/kg/day) benzo[a]pyrene in decalin alone was applied. The method of application was not specified, sample sizes were small and no decalin solvent controls were included; however, decalin is not considered to be carcinogenic. In this same study, intermediate (50 weeks) dermal application of benzo[a]pyrene dissolved in the co-carcinogens 1-dodecanol or 1-phenyldodecane produced skin tumors in animals exposed to 0.05% benzo[a]pyrene in either solvent. The tumor incidence varied depending on the solvent concentration; however, the latency period was reduced only when 1-dodecanol was the solvent (Bingham and Falk 1969).

Mice receiving 0.00l-0.01% of benzo[a]pyrene dermally applied to their backs throughout their lifetimes exhibited a dose-response relationship for skin tumors (Wynder and Hoffmann 1959a). A dose of 0.001% benzo[a]pyrene produced skin carcinoma and papilloma incidences of 4% and 45%, respectively. In another study conducted by Wynder and Hoffmann (1959b), higher concentrations of benzo[a]pyrene produced an 85% incidence of combined papillomas and carcinomas. These studies had a number of weaknesses, including no statistical treatment and no solvent control group. Dose quantification is difficult because of the method of application (Wynder and Hoffmann 1959a, 1959b). NMRI mice topically administered 2 μg benzo[a]pyrene throughout their lifetime also developed skin papillomas and carcinomas (45%) (Habs et al. 1984, see Table 2-3). CH3 mice administered a higher dose of 12.5 μg benzo[a]pyrene for 99 weeks exhibited malignant skin tumors (94%) (Warshawsky

and Barkley 1987, see Table 2-3). Increasing malignant carcinoma incidences in these dermal application studies can be correlated to increasing benzo[a]pyrene concentrations.

In mice, the tumorigenic dose of benzo[a]pyrene is dependent on the strain. For example, Habs et al. (1980) tested 1.7-4.6 μg benzo[a]pyrene (0.016-0.04 mg/kg/day) in order to determine its dose-response relationship as a carcinogen when topically applied to the backs of NMRI mice throughout their lifetimes. A clear-cut dose-response relationship was seen for benzo[a]pyrene and the induction of tumors. The lowest dose at which skin tumors appeared was 1.7 μg (0.016 mg/kg/day). This strain of NMRI mice also has a high (70%) background incidence rate of systemic tumors, so an evaluation of the effects of benzo[a]pyrene on any organ other than the site of administration was not possible:

Chrysene. Skin painting experiments with intermediate (6 months) dermal exposure with chrysene were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al. 1993). Chrysene (0.05 mg) dissolved in toluene was applied to shaved skin twice weekly for 6 months. Tumor incidence was determined at the end of the study. For chrysene, administration alone produced papillomas in 1 of 15 animals (7%), with a mean latency period of 81 weeks. With coadministration of 0.0005 mg benzo[a]pyrene, 3 of 13 (23%) had tumors (papillomas and malignant), with a mean latency period of 70 weeks.

Chrysene has elicited skin tumors in mice following chronic (68-82 weeks) dermal exposure. Topical application of a chrysene solution in *n*-dodecane/decalin to the skin of mice produced a significant increase in the carcinogenic potency of chrysene compared with the use of decalin alone; 26% and 63% of mice exhibited papillomas and carcinomas, respectively, at 49 weeks (Horton and Christian 1974). Because only one dose level was employed, no dose-response relationship can be inferred, and no solvent control was included. However, in other experiments decalin and *n*-dodecane have been shown to be noncarcinogenic in mice (Bingham and Falk 1969). An average dose of 1.2 mg/kg/day is the lowest dose of chrysene that has been found to elicit malignant tumors in laboratory animals.

In another chronic study, a higher concentration of chrysene applied dermally to the backs of Swiss mice for a lifetime also resulted in increased papilloma and carcinoma incidences (48% and 42%, respectively) compared to controls (Wynder and Hoffmann 1959a). Since only one dose was employed, no dose-response information can be inferred from this study.

Dibenz[a,h]anthracene: Dibenz[a,h]anthracene has also demonstrated a dose-response relationship for skin tumors over a two-orders-of-magnitude dose range following chronic exposure. Swiss mice received concentrations of 0.00l-0.1% dibenz[a,h]anthracene applied to their backs throughout their lifetimes and exhibited dose-related papilloma and carcinoma incidences at the site of application at the two lowest doses. A decreased tumor rate at the highest dose tested probably reflects dibenz[a,h]anthracene's toxicity and the resulting decreased survival observed. The lowest concentration at which dibenz[a,h]anthracene elicited tumors was 0.001% (40% incidence of papillomas and 40% incidence of carcinomas), which is approximately equal to a dose of 0.029 mg/kg (0.012 mg/kg/day) (Wynder and Hoffmann 1959a). In another chronic derrnal study of dibenz[a,h]anthracene, a dose-related increase in skin carcinoma formation was observed, as well as decreased survival time and tumor latency period (Van Duuren et al. 1967).

Groups of 50 female NMRI mice received dermal applications of dibenz[a,h]anthracene in acetone (total doses = 0, 136, 448, or 1,358 nmol) three times a week for a total of 112 weeks (Platt et al. 1990). Papillomas were observed in 6%, 8%, and 32% of the treated animals, respectively.

Fluoranthene. Skin painting experiments with intermediate-duration (6 months) dermal exposure were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al. 1993). Fluoranthene was dissolved in toluene and applied to shaved skin twice weekly for 6 months. Tumor incidence was determined at the end of the study. For fluoranthene, administration alone produced tumors in 0 of 15 animals. With coadministration of 0.0005 mg benzo[a]pyrene, 1 of 12 (8%) had papillomas, with a mean latency period of 95 weeks.

Chronic dermal application of up to 1% fluoranthene to the backs of mice did not induce skin tumors following a lifetime of application (Hoffmann et al. 1972; Horton and Christian 1974; Wynder and Hoffmann 1959a).

Fluorene. Fluorene has been reported to be negative as a complete carcinogen (dose not specified) (Kennaway 1924). This information was obtained from an old, secondary source and therefore, its reliability is not known.

Indeno[l,2,3-c,d]pyrene. Indeno[1,2,3-c,d]pyrene was applied to the skin of female Swiss mice three times weekly for 12 months in concentrations of 0.5% (500 μg/application), 0.l%, 0.05%, and 0.01%

(20 mice per group) using acetone as the solvent. A tumor dose-response with 7 papilloma-bearing mice and 5 carcinoma-bearing mice for 0.5%, 6 papilloma-bearing and 3 carcinoma-bearing mice for 0.l%, and no skin tumors for 0.05% and 0.01% solutions was observed (Hoffmann and Wynder 1966). Chronic dermal application of indeno[1,2,3-c,d]pyrene in dioxane to mice did not produce an increased incidence of skin tumors. Similarly, chronic topical application of up to 9.2 μg of indeno[l,2,3-c,d]pyrene in acetone to the backs of mice for a lifetime resulted in no tumor induction (Habs et al. 1980).

Phenanthrene. Phenanthrene tested negative as a complete carcinogen in a mouse study inadequately reported in an old secondary source (Kennaway 1924). Skin painting experiments with intermediate-duration (6 months) dermal exposure were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al. 1993). Phenanthrene dissolved in toluene was applied to shaved skin twice weekly for 6 months. Tumor incidence was determined at the end of the study. For phenanthrene, administration alone produced papillomas in 1 of 12 animals (8%), with a mean latency period of 100 weeks. With coadministration of 0.0005 mg benzo[a]pyrene, 1 of 17 (6%) had malignant tumors, with a mean latency period of 53 weeks.

Pyrene. Skin painting experiments with intermediate-duration (6 months) exposure were conducted on groups of 20 male C3H/HeJ mice. Pyrene dissolved in toluene was applied to shaved skin twice weekly for 6 months. Tumor incidence was determined at the end of the study. For pyrene, administration alone produced papillomas in 1 of 13 animals (8%), with a mean latency period of 96 weeks. With coadministration of 0.0005 mg benzo[a]pyrene, 0 of 13 animals had tumors.

Mice chronically administered a 10% pyrene solution throughout their lifetimes did not develop skin tumors (Wynder and Hoffmann 1959a). However, prolonged dermal exposure of mice to 0.5% pyrene in decalin/n-dodecane solvent produced a slightly elevated (15%) skin carcinoma incidence; the level of statistical significance was not provided (Horton and Christian 1974).

Mixtures. Chronic dermal exposure of NMRI mice to a tar condensate that contained several PAHs (pyrene, fluoranthene, chrysene, benz[a]anthracene, benzo[a]pyrene, indeno[1,2,3-c,d]pyrene, benzo[g,h,i]perylene) in addition to other compounds produced a carcinogenic effect as evidenced by an increase in the incidence of skin papillomas and carcinomas (Habs et al. 1984). Because of the

presence of other compounds in the tar condensate, the carcinogenic effect cannot be definitely attributed to the PAHs present in the mixture.

Skin painting experiments of a mixture of anthracene, chrysene, fluoranthene, phenanthrene, and pyrene were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al. 1993). Compounds dissolved in toluene were applied to shaved skin twice weekly for 6 months. Tumor incidence was determined at the end of the study. Treatment included solutions of a mixture of the five noncarcinogenic PAHs at 0.05 mg, or the same compounds in solution with 0.0005 mg benzo[a]pyrene, a dose known to be noncarcinogenic in a similar study design. For the mixture of the 5 PAHs at 0.05 mg each, administration alone produced papillomas and malignant tumors in 3 of 13 animals (23%), with a mean latency period of 73 weeks. With coadministration of benzo[a]pyrene, 8 of 17 (47%) had tumors (papillomas and malignant), with a mean latency period of 66 weeks.

Initiation-Promotion Studies. Carcinogenesis has been demonstrated to be a multistage process in the cells of certain animal tissues, including skin, lung, liver, and bladder. This process is believed to occur in human tumorigenesis as well. The PAHs have been studied extensively for their ability to act as tumor initiators and/or promoters. Following is a brief discussion, by chemical, of the results of the initiation-promotion studies performed with 13 of the 17 PAHs discussed in this profile. Only those studies considered adequate and reliable are presented in Table 2-3.

The difficulty inherent in extrapolating initiation-promotion experiments to human exposure precludes their being used as the basis for human cancer effect levels. Since PAHs occur in complex mixtures of chemicals that may include tumor promoters, their activity as initiating agents is noteworthy. Thus, it is possible that humans dermally exposed to PAHs that are initiating agents, concomitantly with other chemicals that may be active as tumor promoters (including other PAHs) found at nearby hazardous waste sites, may have an increased risk of skin cancer.

Anthracene. Anthracene has been found to be inactive as an initiating agent under a dermal initiation/promotion protocol using tetradecanoyl phorbol acetate (TPA) as the promoter (LaVoie et al. 1983a).

Benz[a]anthracene. Benz[a]anthracene has been observed to be a tumor initiator in an intermediate-duration dermal study. CD-l mice topically administered 2.5 µmol (0.57 mg) benz[a]anthracene

followed by promotion with TPA (for 25 weeks) exhibited an increased skin tumor incidence (36%) as compared to controls (Levin et al. 1984, see Table 2-3).

Benzo[a]pyrene. Benzo[a]pyrene is active as a tumor initiator using initiation/promotion protocols. Topical application of a single initiating dose of benzo[a]pyrene to the backs of mice followed by promotion with TPA or croton oil resulted in an 80-92% incidence of skin papillomas (Cavalieri et al. 1988b, see Table 2-3). Ten doses of benzo[a]pyrene (0.1 mg/dose) topically applied to the backs of Swiss mice followed by promotion with croton oil (for 20 weeks) also resulted in the development of skin tumors (Hoffmann et al. 1972).

In a dermal initiation/promotion assay, groups of 24 female SENCAR mice were administered a single dermal application of benzo[a]pyrene at doses ranging from 4 to 300 nmol (initiating dose), followed 7 days later by twice weekly applications of the promoter TPA, for a total of 24 weeks. Benzo[a]pyrene was active as a skin tumor initiator; the number of tumors per tumor bearing mouse, the percentage of tumor bearing mice, and the number of tumors per mouse were all significantly greater than in acetone controls and increased in a dose-related manner at doses ≥20 nmol (Cavalieri et al. 1991).

In a similar experiment, 24 8-week-old female SENCAR mice were treated dermally with 0.0002 mg (1 nmol) of benzo[a]pyrene in acetone on a shaved portion of dorsal skin (Higginbotham et al. 1993). One week later, tumor promotion was begun with TPA twice weekly for 27 weeks. The number of skin tumors was charted weekly and the mice were killed after experimental weeks. Complete necropsies were performed and tissues were fixed in formalin. Benzo[a]pyrene-treated mice had no skin tumors.

Benzo[e]pyrene. Benzo[e]pyrene is inactive as a skin tumor initiator in mouse skin (Slaga et al. 1980a).

Benzo[b]fluoranthene. The ability of benzo[b]fluoranthene to initiate skin tumor formation has been demonstrated using a standard initiation/promotion protocol with either croton oil or phorbol myristate acetate as a tumor promoter (Amin et al. 1985a; LaVoie et al. 1982). In another study, dermal applications of initiation doses of benzo[b]fluoranthene (10-100 μg) followed by TPA (for 20 weeks)

to the backs of CD-l mice elicited a dose-related skin tumor incidence, predominantly consisting of squamous cell papillomas (LaVoie et al. 1982).

In a dermal initiation/promotion assay, groups of 20 female CD-l mice were administered 10 dermal applications of benzo[b]fluoranthene at total doses of 0, 1, and 4 umol (initiating dose), followed 10 days later by thrice weekly applications of the promoter TPA for a total of 20 weeks (Weyand et al. 1991). Benzo[b]fluoranthene was active as a skin tumor initiator; the number of tumors per tumor-bearing mouse (8.5) and the percentage of tumor-bearing mice (100%) were significantly greater than in acetone controls and were increased in a dose-related manner.

Tumor initiation experiments were conducted with groups of 20 female CD-1 mice. Benzo[b]fluoranthene was applied to the shaved backs of the mice every other day using a total of 10 subdoses (Weyand et al. 1993b). Total doses were 10.1, 30.3, and 100.9 μg in acetone. Negative control mice were treated with acetone. Ten days after the last dose, promotion was begun by applying 2.5 μg TPA thrice weekly for 20 weeks. Tumors were counted weekly. Benzo[b]fluoranthene produced a 35%, 90%, and 95% incidence of tumor-bearing mice with 0.45, 3.70, and 8.65 tumors per mouse for the low, mid and high doses, respectively. No distinction was made between papillomas and carcinomas (Weyand et al. 1993b). Groups of 20 female Crl:CD-1 mice were dermally exposed to a total of 0, 0.01, 0.03, or 0.1 mg of benzo[b]fluoranthene in acetone applied every other day for 20 days in 10 subdoses (LaVoie et al. 1993a). Negative control mice were treated with acetone only. Ten days after the last application of acetone or hydrocarbon, tumor promotion was begun by applying 2.5 μg TPA in acetone three times weekly for 20 weeks. Tumor incidence was recorded after 20 weeks of promotion. The study was repeated for the 0.03 and 0.1 mg doses. Of the mice receiving 0.01 mg benzo[b]fluoranthene, 35% had developed tumors, with an average of 0.45 tumors/mouse. For the 0.03 mg dose, 70-90% of the mice developed tumors with an average of 1.4-3.7 tumors per mouse, whereas the 0.1 mg dose caused 95% of the mice to develop and average of 7.1-8.6 tumors. Of the animals treated with acetone only, 5-15% developed skin tumors. In this study, tumors were not identified as papillomas or carcinomas.

Benzo[j]fluoranthene. Benzo[j]fluoranthene has also been demonstrated to be a tumor initiator in mice, although it is not as potent as benzo[b]fluoranthene. Benzo[j]fluoranthene, however, is more potent than benzo[k]fluoranthene. Mice receiving initiating doses of benzo[j]fluoranthene (30-1,000 μg) followed by TPA promotion exhibited a dose-related increase in tumor incidence

(LaVoie et al. 1982, 1993a; Weyand et al. 1992). Groups of 20 female Crl:CD-1 mice were dermally exposed to a total of 0, 0.006, 0.012, 0.025, or 0.25 mg of benzojjlfluoranthene in acetone applied every other day for 20 days in 10 subdoses (LaVoie et al. 1993b). Negative control mice were treated with acetone only. Ten days after the last application of acetone or hydrocarbon, tumor promotion was begun by applying 2.5 μg TPA in acetone three times weekly for 20 weeks. Tumor incidence was recorded after 20 weeks of promotion. Five percent of the mice receiving 0.006 mg benzo[j]fluoranthene had developed tumors, with an average of 0.4 tumors per mouse. For the 0.012 mg dose, 10% of the mice developed tumors with an average of 0.4 tumors per mouse; 0.025 mg PAH caused 45% of the mice to develop tumors at an average of 0.65 tumors per mouse, whereas the 0.25 mg dose caused 95% of the mice to develop an average of 8.7 tumors. The control animals developed no tumors.

Benzo[k]fluoranthene. Benzo[k]fluoranthene has also been demonstrated to be a tumor initiator in mice, although it too, is not as potent as benzo[b]fluoranthene. Mice receiving initiating doses of benzo[k]fluoranthene (30-1,000 μg) followed by TPA promotion exhibited a dose-related increase in ‘tumor incidence (LaVoie et al. 1982).

Benzo[g,h,i]perylene. Benzo[g,h,i]perylene has been shown to be inactive as an initiating agent when applied at a total dose of 0.25 mg/animal and negative as a complete carcinogen when a 1% solution was applied thrice weekly for 12 months (IARC 1983).

Chrysene. Chrysene is a tumor initiator in classic initiation/promotion bioassays on mouse skin using croton oil or phorbol myristate acetate as promoting agents (Slaga et al. 1980a; Wood et al. 1979a). Initiating doses of chrysene followed by promotion with TPA or croton resin induced a dose-related papilloma incidence in mice (Slaga et al. 1980a; Wood et al. 1979a).

Dibenz[a,h]anthracene. Dibenz[a,h]anthracene has also demonstrated tumor-initiating activity using a standard initiation/promotion protocol (Slaga et al. 1980a). Dibenz[a,h]anthracene has been reported to initiate skin development in a dose-response relationship at doses as low as 0.028 μg followed by promotion with TPA (for 25 weeks) (Buening et al. 1979a).

In a dermal initiation/promotion assay, groups of 50 female NMRI mice were administered a single dermal application of dibenz[a,h]anthracene at doses of 0, 300, or 600 nmol (initiating dose) followed

7 days later by twice weekly applications of the promoter, TPA, for a total of 24 weeks (Platt et al. 1990). Dibenz[a,h]anthracene was active as a skin tumor initiator only at the highest dose tested; 93% of the animals administered 600 nmol dibenz[a,h]anthracene developed skin tumors by 24 weeks.

Fluoranthene. Fluoranthene did not exhibit initiating activity in Swiss mice topically administered 10 doses followed by promotion with croton oil (for 20 weeks) (Hoffmann et al. 1972).

Indeno[l,2,3-c,d]pyrene. A pronounced dose-response relationship has been exhibited by indeno[l,2,3-c,d]pyrene in an initiation-promotion bioassay when TPA was employed as the promoting agent, although it was not as potent an initiator as benzo[b]fluoranthene (Rice et al. 1985a). In another study, 2.83 tumors/mouse were noted after a total initiating dose of 1.0 mg indeno[1,2,3-c,d]pyrene and promotion with TPA for 20 weeks (Rice et al. 1986).

The skin tumor initiating activity of indeno[1,2,3-c,d]pyrene and several of its metabolites generated *in* viva in mouse skin was tested in female Crl:CD/l mice (Rice et al. 1986). Initiating doses of indeno[1,2,3-c,d]pyrene or the metabolites were applied every other day to the shaved skin of groups of 25 mice for a total of 10 doses, which was followed 10 days later by thrice weekly applications of the tumor promotor, TPA, for 20 weeks. None of the metabolites were as active in inducing skin tumors as the parent compound (2.83 tumors/mouse as compared to 0.48-1.68 tumors/mouse at 20 weeks). These findings led the authors to conclude that the principal ultimate mutagenic metabolite, indeno[l,2,3-c,d]pyrene-1,2-oxide, is not the ultimate carcinogenic metabolite of indeno[l,2,3-c,d]pyrene.

Phenanthrene. Phenanthrene was ineffective as an initiator in various mouse strains (LaVoie et al. 1981b; Salaman and Roe 1956; Wood et al. 1979a). CD-1 mice topically administered a single dose of 10 μmol phenanthrene followed by a promoter were observed to have a papilloma incidence 2-4 times that of background; however, the incidences were not statistically significant in comparison to controls because of the small number of animals tested and the high spontaneous tumor incidence (Wood et al. 1979a).

Pyrene. Pyrene has been shown to be inactive as an initiating agent (Salaman and Roe 1956; Van Duuren and Goldschmidt 1976).

Mixtures. Co-administration of pyrene and benzo[a]pyrene to the backs of ICR/Ha mice has produced an enhancement of benzo[a]pyrene tumorigenicity (Van Duuren and Goldschmidt 1976). There is evidence that benzo[g,h,i]perylene is a co-carcinogen with benzo[a]pyrene when both are applied simultaneously to the skin of Swiss mice (Van Duuren et al. 1973). Dermal pretreatment with 100 μg pyrene substantially enhanced benzo[a]pyrene tumor initiation in CD-1 mice, while 100 μg fluoranthene produced a marginal enhancement (Slaga et al. 1979).

2.3 TOXICOKINETICS

Occupational studies provide evidence that inhaled PAHs are absorbed by humans. Animal studies also show that pulmonary absorption of benzo[a]pyrene occurs and may be influenced by carrier particles and solubility of the vehicle; however, the extent of absorption is not known. Absorption of benzo[a]pyrene following ingestion is low in humans, while oral absorption in animals varies among the PAH compounds depending on the lipophilicity. Oral absorption increases with more lipophilic compounds or in the presence of oils in the gastrointestinal tract. Percutaneous absorption of PAHs appears to be rapid for both humans and animals, but the extent of absorption is variable among these compounds and may be affected by the vehicle used for administration. Therefore, absorption of PAHs following inhalation, oral, or dermal exposure may be affected by vehicle of administration.

There was no information available on the distribution of PAHs in humans. PAHs appear to be widely distributed in tissues of animals following oral and inhalation exposure; peak tissue concentrations occurred earlier with higher exposure levels. Placental transfer of PAHs appears to be limited, and therefore, fetal levels are not as high as maternal levels.

Metabolism of PAHs occurs in all tissues and involves several possible pathways. Metabolism of PAHs has been studied extensively *in vitro* and *in vivo.* The metabolism products include epoxide intermediates, dihydrodiols, phenols, quinones, and their various combinations. The phenols, quinones, and dihydrodiols can all be conjugated to glucuronides and sulfate esters; the quinones also form glutathione conjugates.

Quantitative data on the excretion of PAHs in humans are lacking. In general, feces is the major elimination route of PAHs in animals following inhalation exposure. Excretion of benzo[a]pyrene appears to be high following low-level exposure in rats but low in dogs and monkeys. PAHs are

eliminated to a large extent within 2 days following low- and high-level oral exposure in rats. Following dermal exposure, elimination of PAHs occurs rapidly in the urine and feces of guinea pigs and rats.

Absorption of inhaled PAHs appears to occur through the mucous lining of bronchi, while ingested PAHs are taken up by the gastrointestinal tract in fat-soluble compounds. Percutaneous absorption is through passive diffusion. The mechanism of action of most PAHs involves covalent binding to DNA by PAH metabolites. The bay region diol epoxide intermediates of PAHs are currently considered to be the ultimate carcinogen for alternant PAHs. Once the reactive bay region epoxide is formed, it may covalently bind to DNA and other cellular macromolecules and presumably initiate mutagenesis and carcinogenesis.

2.3.1 Absorption

2.3.1.l Inhalation Exposure

Absorption of PAHs in humans following inhalation exposure can be inferred from the presence of urinary metabolites of PAHs in workers exposed to these compounds in an aluminum plant (Becher and Bjorseth 1983). The high concentration of PAHs in the occupational setting did not correspond to the amount of PAHs deposited, metabolized, and excreted in the urine in this study. The authors suggested that PAHs adsorbed to airborne particulate matter may not be bioavailable and that the dose-uptake relationship may not be linear over the entire PAH concentration range.

Twelve workers from a coke plant participated in an intensive skin monitoring program combined with personal air sampling and biological monitoring during 5 consecutive 8-hour shifts (Van Rooij et al. 1993b). The mean concentration of total pyrene in the breathing zone air of the 12 workers ranged from 0.1 to 5.4 μg/m^3. The mean respiratory uptake of pyrene varied between 0.5 and 32.2 μg/day. Based on the estimates of the dermal and respiratory pyrene uptake, it is concluded that an average of 75% of the total absorbed amount of pyrene enters the body through the skin. The total excreted amount of urinary 1-hydroxypyrene as a result of exposure to PAHs during the five consecutive work shifts varied between 36 and 239 nmol. Analysis indicated that dermal absorption was most important in contributing to 1-hydroxypyrene excretion. Of the total dose absorbed by both routes combined,

13-49% is excreted as 1-hydroxypyrene. Variation in excretion is influenced by smoking habits, and consumption of alcohol (see Section 2.3.1.3).

Eleven healthy male smokers and 11 male smokers with lung cancer between the ages of 30-60 years, with a smoking history of 15-25 cigarettes per day for over 10 years were involved in a study (Likhachev et al. 1993). Urinary excretion of benzo[a]pyrene-7,8-diol and 3-hydroxybenzo[a]pyrene was determined. Both benzo[a]pyrene metabolites were detected in the urine, but quantities of 3-hydroxybenzo[a]pyrene were very low. The level of benzo[a]pyrene-7,8-diol in the urine varied considerably both in healthy smokers and smokers with lung cancer. However, the average value of this metabolite in the urine of healthy smokers was significantly higher than in the urine of lung cancer patients who smoked (1.06 mg/kg/day versus 0.56 mg/kg/day).

Animal studies on inhalation absorption of PAHs are limited to benzo[a]pyrene exposure. Rapid absorption was evident following inhalation exposure of low and high levels of benzo[a]pyrene to rats. Acute and intermediate-duration exposure to 4.8 mg/m^3 [^{14}C]-benzo[a]pyrene by nose-only inhalation in rats resulted in elevated levels of radioactivity in tissues and excreta within 3 hours of exposure (Wolff et al. 1989c). High levels of radioactivity were detected in the gastrointestinal tract, which may be due to biliary excretion or mucocilliary clearance of benzo[a]pyrene from the upper respiratory tract. Intratracheal administration of 0.001 mg/kg [^{3}H]-benzo[a]pyrene to rats also resulted in rapid absorption through the lungs. Radioactivity in the liver reached a maximum of 21% of the administered dose within 10 minutes of instillation (Weyand and Bevan 1986, 1988). Presence of radioactivity in other tissues and the bile was also indicative of its absorption in rats. Similar results were also seen in guinea pigs and hamsters following intratracheal exposure to benzo[a]pyrene (Weyand and Bevan 1986, 1987b, 1988).

Pregnant Wistar rats were exposed head-only to 200, 350, 500, 650, or 800 mg/m^3 of [^{14}C]-benzo[a]pyrene aerosol for 95 minutes on gestational day 17 (Withey et al. 1993a). Animals were killed immediately or 6 hours postexposure. Concentration of benzo[a]pyrene and metabolites in maternal blood sampled immediately after exposure were elevated 10-fold over the 4-fold increase in dose. At 6 hours postdosing, the increase was still approximately 10-fold, although the actual concentrations were 2-7-fold less than at 0 hours. Concentrations of benzo[a]pyrene and metabolites in fetal blood sampled immediately after exposure were elevated 5-fold over the 4-fold increase in exposure concentrations. Fetal tissues sampled 6 hours post-dosing had a 9-fold increase in

benzo[a]pyrene and metabolite concentration over the dose range, due to lower concentration in the 200-650 mg/m^3 dose groups at 6 hours compared to 0 hours. Fetal concentrations were 2-10-fold less than maternal concentrations. Benzo[a]pyrene concentrations in blood, lung, liver, and fetal tissues were significantly decreased from 0 to 6 hours postexposure while levels in fat tissue increased. For benzo[a]pyrene sampled immediately postdosing, lung > blood > liver > kidney > fat > fetus. For total metabolites sampled immediately postdosing, lung > blood > liver > kidney > fetus > fat. For benzo[a]pyrene sampled 6 hours postdosing, fat > lung > kidney > liver > blood > fetus. For total metabolites sampled 6 hours postdosing, lung = fat > kidney > liver = blood > fetus.

Twenty male Fisher 344 DuCrj rats were divided into two groups and exposed to diesel exhaust containing 0.151 mg/m^3 pyrene or HEPA-filtered air for 8 weeks, 5 days/week, 7 hours/day (Kanoh et al. 1993). At 2, 4, and 8 weeks during the exposure, the rats from each group were put into a metabolic cage and their urine was collected for 24 hours. Urinary levels of 1-hydroxypyrene in the rats of the exposure group increased remarkably over those of the control group, reaching 2.4 times as much by the end of the 2nd week, and 5.6 times by the 4th and 8th weeks.

Inhalation absorption of benzo[a]pyrene may be affected by the size of particles on which benzo[a]pyrene is adsorbed. The elimination of benzo[a]pyrene from the lungs was studied following intratracheal administration of pure benzo[a]pyrene crystals or benzo[a]pyrene coated on carbon particles in two size ranges (0.5-1.0 μm and 15-30 μm) (Creasia et al. 1976). Fifty percent of the pure benzo[a]pyrene crystals was cleared from the lungs within 1.5 hours and >95% cleared within 24 hours, while only 50% of the benzo[a]pyrene adsorbed to the small carbon particles cleared within 36 hours. Elution of benzo[a]pyrene was even slower with the larger particle size (approximately 4-5 days). These results indicate that the bioavailability of benzo[a]pyrene is altered by the particle size of the carrier. The initial lung deposition of [^{3}H]-benzo[a]pyrene adsorbed onto gallium oxide (Ga_2O_3) particles was 4.9 μg of which 3.1% remained after 30 minutes (Sun et al. 1982). A control study, conducted without the Ga_2O_3 particles at a concentration of 1 mg/m^3, found that 8.2 μg was inhaled, of which 0.9% remained in lungs after 30 minutes. The excretion of hydrocarbon was monitored for over 2 weeks at which time nearly all the initial lung burden was recovered in the excreta, indicating complete absorption of the instilled hydrocarbon. Significant differences in the clearance of benzo[a]pyrene coated with Ga_2O_3 and pure benzo[a]pyrene suggested that a substantial amount of benzo[a]pyrene/Ga_2O_3 particles was removed from the lungs by mucocilliary clearance and subsequent ingestion.

The above results corroborate findings in an *in vitro* experiment by Gerde and Scholander (1989) who developed a model of the bronchial lining layer. These investigators concluded that the release rate of PAHs from carrier particles is the rate-determining step in the transport of PAHs from these particles to the bronchial epithelium.

The absorption of benzo[a]pyrene may also be affected by the solubility of the vehicle used in administration. Approximately 70% of benzo[a]pyrene administered with triethylene glycol was excreted 6 hours following intratracheal instillation (Bevan and Ulman 1991). Excretion rates of benzo[a]pyrene were only 58.4% and 56.2% with ethyl laurate and tricaprylin, respectively, within a 6-hour period. The small volume of benzo[a]pyrene instilled is probably deposited in the bronchial region which allows more water-soluble materials (triethylene glycol) to pass the mucous layer lining than water-insoluble compounds (ethyl laurate and tricaprylin) (Bevan and Ulman 1991).

Nasal instillation of [^{3}H]-benzo[a]pyrene (0.13 mg/kg) to hamsters resulted in the metabolism of [^{3}H]-benzo[a]pyrene in the nasal cavity (Dahl et al. 1985). A large fraction of the metabolites was recovered from the epithelial surface, indicating that benzo[a]pyrene was first absorbed in the mucosa, metabolized, and returned to the mucus. Monkeys and dogs received nasal instillation of [^{14}C]-benzo[a]pyrene at doses of 0.16-0.21 mg/kg (Petridou-Fischer et al. 1988). Radiolabeled metabolites were detected in the nasal cavity, but little or no activity was detected in the blood and excreta of either species during the 48 hours after exposure. These results indicate that absorption of benzo[a]pyrene and/or its metabolites was poor or very slow following nasal instillation in monkeys and dogs.

2.3.1.2 Oral Exposure

There is evidence suggesting that benzopyrene is orally absorbed in humans (Buckley and Lioy 1992; Hecht et al. 1979). Following ingestion of diets containing very low levels of benzo[a]pyrene, the metabolite, 1-hydroxypyrene, was detected in the urine (Buckley and Lioy 1992). No quantitative data on the excretion of the benzo[a]pyrene were provided. The concentration of benzo[a]pyrene in human feces was examined in eight volunteers who ingested broiled meat that contained approximately 9 µg of benzo[a]pyrene (Hecht et al. 1979). The feces of these individuals did not contain detectable levels of benzo[a]pyrene (<0.1 µg/person), which is similar to what was seen following consumption of

control meat that contained undetectable amounts of benzo[a]pyrene by these same volunteers, suggesting that most of the ingested benzo[a]pyrene was absorbed.

Oral absorption of benzo[a]pyrene in rats is incomplete and may be influenced by the presence of oils and fat in the gastrointestinal tract. Oral absorption of benzo[a]pyrene was estimated to be 40%, with a bioavailability of 7.8-11.5%, in Sprague-Dawley rats infused intraduodenally to a total dose of approximately 0.0005 mg/kg for 90 minutes (Foth et al. 1988a). Nearly 80% of a gavage dose of 0.0527 mg/kg [^{14}C]benzo[a]pyrene in peanut oil was detected in the excreta of rats 48 hours after exposure; however, some of the recovered radioactivity may never have been absorbed by the alimentary tract of the rats, but may have passed into the excreta in the peanut oil (Hecht et al. 1979). Radioactivity found in the liver, lungs, kidneys, and testis following a low dose of [^{3}H]-benzo[a]pyrene to Sprague-Dawley rats provides supporting evidence of oral absorption (Yamazaki and Kakiuchi 1989; Yamazaki et al. 1987). The extent of oral absorption in rats is enhanced when benzo[a]pyrene is solubilized in a vehicle (triolein, soybean oils, high-fat diet) that is readily absorbed following low- and high-dose levels (Kawamura et al. 1988; O'Neill et al. 1991).

Oral absorption of benzo[a]pyrene was estimated to be 38-58% following dietary or gavage exposure to high levels in rats (Chang 1943). Anthracene was absorbed to a slightly higher extent (53-74%) than benzo[a]pyrene in rats while phenanthracene was poorly absorbed (4-7%) (Chang 1943). However, the data were limited because an inadequate number of rats was used and study details were lacking.

In general, the oral absorption of chrysene, dibenzanthracene, and pyrene was high following exposure to high doses in rats (Chang 1943; Grimmer et al. 1988; Withey et al. 1991). Following dietary or gavage administration of chrysene in rats, 64-87% of the dose was excreted in the feces (Chang 1943). Recovery of chrysene in excreta of Wistar rats was 74% four days after a single gavage dose of 22 mg/kg chrysene in corn oil (Grimmer et al. 1988). Administration of dibenz[a,h]anthracene in the diet (250 mg) or by stomach tube (200 mg) resulted in more than 90% of the dose being excreted in the feces of white rats (Chang 1943). As with chrysene, absorption of dibenz[a,h]anthracene could not be quantified. Male Wistar rats administered 2-15 mg/kg of [^{14}C]-pyrene recovered 68-92% of the dose in the excreta by 6 days postexposure (Withey et al. 1991). Bioavailability of pyrene and its metabolites was 65-84% over a period of 8 hours following administration.

Blood levels of fluoranthene, pyrene, and benz[a]anthracene after oral administration were examined in rats (Lipniak and Brandys 1993). Fluoranthene, pyrene, or benz[a]anthracene in Tween 80/isotonic saline, was administered orally to rats at a dose of 20 mg/kg. Blood levels after administration indicated that peak concentrations of the three compounds were reached at 1-2 hours after administration. The peak concentration of fluoranthene (≈30 mg/cm^3) was twice as high as that of pyrene, and 5 times higher than benz[a]anthracene.

The effect of diet matrix (gel or powder) on urinary excretion of 1-hydroxypyrene and hydrocarbon binding to DNA was investigated in mice (Wu et al. 1994). Female mice were fed a gel or powder diet containing manufactured gas plant (MGP) residue (coal tar) at 0.1% or 0.3% for 15 days, or the corresponding control diet. Two mixtures of MGP residue were used: Mix of 3 combining equal amounts of samples from three different MGP plant sites, and Mix of 7 combining equal amounts of samples from seven different MGP plant sites, including those used in the Mix of 3. The mixtures contained pyrene, benz[a]anthracene, chrysene, benzo[b]fluorene, benzo[k]fluorene, benzo[a]pyrene, indeno[1,2,3-cd]pyrene, dibenz[a,h]anthracene, benzo[g,h,i]perylene. Data were presented in terms of pyrene consumed and 1-hydroxypyrene excreted. Urine was collected on the first, seventh, and fourteenth day of diet administration. 1-Hydroxypyrene levels in the urine were determined using HPLC and fluorescence. Diet matrix had little effect on the bioavailability of the PAHs.

The intestinal absorption of PAHs is highly dependent on the presence of bile (Rahman et al. 1986). To study the role of bile in the intestinal absorption of PAHs, conscious rats with bile duct and duodenal catheters were given [^{3}H]-benzo[a]pyrene, phenanthrene, anthracene, 2,6-dimethylnaphthalene (DMN), and 7,12-dimethylbenz[a]anthracene (DMBA) with or without exogenous bile. The efficiency of PAH absorption was estimated from the cumulative recovery of radioactivity in the bile and urine over 24 hours. The efficiencies of absorption without bile (as a percentage of absorption with bile) were benzo[a]pyrene, 22.9%; phenanthrene, 96.7%; anthracene, 70.8%; DMN, 91.6%; DMBA, 43.4%. Absorption of the four- or five-membered rings (DMBA and benzo[a]pyrene) was strongly dependent on the presence of bile in the intestinal lumen. The absorption of the tricyclic PAHs (phenanthrene and anthracene) differed with respect to their dependency on bile for efficient absorption. This difference correlated with a difference in water solubility, with anthracene being 18 times less water-soluble than phenanthrene. Those products with low water solubility are dependent on the creation of an intermediate phase of the products of lipolysis and bile salts (Rahman et al. 1986). These reactions occur during the normal process of lipid digestion and absorption in the intestine.

2.3.1.3 Dermal Exposure

Application of 2% crude coal tar to the skin of humans for 8-hour periods on 2 consecutive days yielded evidence of PAH absorption (Storer et al. 1984). Phenanthrene, anthracene, pyrene, and fluoranthene were detected in the blood, but benzo[a]pyrene (which is present in coal tar) was not detected. This difference was attributed to differences in percutaneous absorption, rapid tissue deposition after absorption, or metabolic conjugation with rapid urine excretion. In another study, coal tar ointment was applied to skin of volunteers at various sites (Van Rooij et al. 1993a). The surface disappearance of PAH and the excretion of urinary 1-hydroxy-pyrene were used as parameters for dermal absorption. Surface disappearance measurements showed low but significant differences in dermal PAH absorption between anatomical sites: shoulder > forehead, forearm, groin > ankle, hand (palmar site). An *in vitro* study using human skin revealed that the extent of permeation across viable human skin after 24 hours was estimated to be 3% of the total applied radioactivity from [^{14}C]-benzo[a]pyrene (10 µg/cm^2) (Kao et al. 1985). Using human cadaver skin, it was shown that 23.7±9.7% of the applied benzo[a]pyrene penetrated into the skin (Wester et al. 1990). These results suggest that substantial metabolism and/or binding of benzo[a]pyrene takes place in viable human skin which limits the amount of PAH available to penetrate the skin into the systemic circulation.

Twelve workers from a coke plant participated in an intensive skin monitoring program combined with personal air sampling and biological monitoring during 5 consecutive 8-hour shifts (Van Rooij et al. 1993b). Measurements on exposure pads at six skin sites (jaw/neck, shoulder, upper arm, wrist, groin, ankle) showed that mean total skin contamination of the 12 workers ranged between 21 and 166 µg pyrene per day. The dermal uptake of pyrene ranged between 4 and 34 µg/day, which was about 20% of the pyrene contamination on the skin. The mean concentration of total pyrene in the breathing zone air of the 12 workers ranged from 0.1 to 5.4 µg/m^3. The mean respiratory uptake of pyrene varied between 0.5 and 32.2 µg/day. Based on the estimates of the dermal and respiratory pyrene uptake, it is concluded that an average of 75% of the total absorbed amount of pyrene enters the body through the skin. The total excreted amount of urinary 1-hydroxy-pyrene as a result of exposure to PAHs during the 5 consecutive work shifts varied between 36 and 239 nmol. Analysis indicated that dermal absorption was most important in contributing to 1-hydroxy-pyrene excretion. Of the total dose absorbed by both routes combined, 13-49% is excreted as 1-hydroxy-pyrene. Variation in excretion is influenced by smoking habits, and consumption of alcohol.

Percutaneous absorption of [^{14}C]-benzo[a]pyrene in mice, rats, monkeys, and guinea pigs is rapid and high (Ng et al. 1992; Sanders et al. 1986; Wester et al. 1990; Yang et al. 1989). A single dose of 7 µg/cm^2 [^{14}C]-benzo[a]pyrene in acetone was applied to a 4-cm^2 area of the dorsal skin of female hairless guinea pigs for 24 hours (Ng et al. 1992). Approximately 73% of the administered dose was absorbed dermally by 7 days postexposure; most of the dose was absorbed by day 3. The skin wash at 24 hours of exposure contained about 10.6% of dose (Ng et al. 1992). *In vitro* absorption of benzo[a]pyrene through guinea pig skin demonstrated similar results; 67% absorption in a 24-hour exposure (Ng et al. 1992). Seven days after exposure to 125 µg/cm^2 benzo[a]pyrene, 80% of the total recovered radioactivity was eliminated in the feces of mice (Sanders et al. 1986). The site of application still retained 7% of the recovered radioactivity after 7 days. However, the area of application was not covered to prevent animals from licking the test material which may have lead to ingestion of benzo[a]pyrene.

Groups of 12 male Wistar rats were dosed with 2, 6, or 15 mg/kg of [^{14}C]-pyrene applied to 4 cm^2 of a shaved area of the mid-back (Withey et al. 1993b). Three animals in each dose group were killed at 1,2,4, and 6 days postdosing, and the brain, lungs, heart, liver, spleen, kidneys, testes, muscle, and perirenal fat were removed and analyzed for pyrene and [^{14}C]-pyrene equivalents. Blood, urine, and feces, as well as the skin from the application site were also analyzed. The rate of uptake from the skin was rapid (t1/2 = 0.5-0.8 d) relative to rate processes for the other organs, and about 50% of the applied dose was excreted over the 6 days of the study. Levels of pyrene were highest in the liver, kidneys, and fat. Levels of metabolites were also high in the lung.

Dermal absorption of benzo[a]pyrene in rats and monkeys may be affected by the vehicle of administration (Wester et al. 1990; Yang et al. 1989). Following application of 10 ppm benzo[a]pyrene on the skin of rhesus monkeys, an average absorption of 51 ± 22% was reported with acetone vehicle and 13.2 ± .4% with soil; however, absorption data were based on radioactivity recovered in urine only, and not in feces (Wester et al. 1990). The great variation in the absorption with the acetone vehicle limits these results. This may be related, in part, to the dependence on monitoring radioactivity recovered in urine only as opposed to monitoring radioactivity recovered in urine and feces. Disappearance of the applied dose from the application site was 40% at 24 hours following administration (Wester et al. 1990). Sprague-Dawley rats absorbed 4-5 times more of a 1 ppm dose of benzo[a]pyrene when it was applied dermally alone, compared to a soil-sorbed crude oil mixture (Yang et al. 1989). The greater lipophilicity of the crude oil alone probably increased the

rate of dermal uptake of the test material, since the authors determined that absorption was dependent on the monolayer of soil in contact with the skin, which is comparable to the contact between the skin and oil. Therefore, the soil binding of the PAHs may have slowed absorption. However, no quantitative data were available.

Female Sprague-Dawley rats were exposed dermally to [^{3}H]-benzo[a]pyrene (1 ppm) containing petroleum crude oil alone or in fortified soil matrix for 4 days (Yang et al. 1989). Recovery of radioactivity was 35.3% of the dose applied in oil, as follows: urine (5.3% of dose), feces (27.5%), and tissues (2.5%) 96 hours after beginning of exposure. Recovery was 9.2% of applied dose with benzo[a]pyrene from petroleum crude-fortified soil; recoveries in urine, feces, and tissues were 1.9%, 5.8%, and 1.5%, respectively, at 96 hours. Benzo[a]pyrene (10 ppm) with acetone vehicle or in soil was applied to a 12 cm^{2} area of abdominal skin of female rhesus monkeys for 24 hours (Wester et al. 1990). Urine contained 5l ± 22% of the dose with acetone vehicle and 13.2 ± 3.4% with soil.

The percutaneous absorption of [^{14}C]-anthracene (9.3 µg/cm^{2}) was 52.3% in rats, estimated from radioactivity in urine, feces, and tissues over a 6-day period (Yang et al. 1986). Over time, the permeation of anthracene significantly decreased suggesting that anthracene was dermally absorbed in a dose-dependent manner. Diffusion of anthracene through the skin (stratum corneum) depended on the amount of anthracene on the skin's surface.

When 6.25 µg/cm^{2} [^{14}C]-phenanthrene and pyrene was applied to guinea pigs, dermal absorption was 80% and 94%, respectively (Ng et al. 1991, 1992). *In vitro* absorption of phenanthrene and pyrene in guinea pig skin was about 79-89% and 70%, respectively (Ng et al. 1991, 1992).

Monitoring the removal of compounds from the epidermis is indicative of measuring the compound's dermal absorption. The disappearance of radiolabeled benzo[a]pyrene and its metabolites from the epidermis was monophasic, following first order kinetics with a half-life of approximately 2 hours (Melikian et al. 1987). Recovery of the radiolabel was 99-100% throughout the period of the experiment (8 hours), indicating that volatilization of benzo[a]pyrene from the skin was not a confounding factor (Melikan et al. 1987). In contrast, removal of one of its metabolites, 7,8-dihydroxy-9,10-epoxy-7,8,9,l0-tetrahydrobenzo[a]pyrene (anti-BPDE), from the epidermis was biphasic. The second, slower phase of removal suggested that the stratum comeum, the outermost layer of skin which consists of several layers of inactive, keratinized cells surrounded by extracellular

lipids, may act as a reservoir that can retain and slowly release topically applied lipophilic substances such as benzo[a]pyrene but is penetrated rapidly by more polar compounds such as anti-BPDE.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of PAHs in humans following inhalation exposure. In general, tissue distribution of benzo[a]pyrene following inhalation exposure is qualitatively similar for different species (Bevan and Weyand 1988; Weyand and Bevan 1986, 1987a, 1988; Wolff et al. 1989c). Highest radioactivity was distributed to the cecum, small intestine, trachea, kidneys, and stomach in rats following a 3-hour or 4-week inhalation exposure to 4.8 mg/m^3 [^{14}C]-benzo[a]pyrene (Wolff et al. 1989c). The lungs and liver of rats contained 2.7% and 4.6% of the recovered dose 6 hours after intratracheal administration of 0.001 mg/kg [^{3}H]-benzo[a]pyrene (Bevan and Weyand 1988). [^{3}H]-Benzo[a]pyrene intratracheally administered to rats demonstrated that the highest fractions were distributed to the lung, liver, kidney, gastrointestinal tract, and carcass (Weyand and Bevan 1986, 1987a, 1988). The concentration of benzo[a]pyrene and its metabolites in the intestine increased with time, suggesting the occurrence of biliary excretion and enterohepatic recirculation. Tissue distribution of radioactivity was qualitatively similar in guinea pigs and hamsters (Weyand and Bevan 1987b). Mice that received 2.5 mg/kg benzo[a]pyrene intratracheally also experienced a similar tissue distribution, but Schnizlein et al. (1987) noted that as the lung burden of benzo[a]pyrene diminished, radioactivity continued to increase in the lung-associated lymph nodes for 6 days. This accumulation may eventually affect humoral immunity.

The distribution pattern of benzo[a]pyrene was not significantly affected following aerosol exposure with or without Ga_2O_3 particles (Sun et al. 1982). However, significant differences in the levels of benzo[a]pyrene delivered to the different tissues did exist. Maximum levels were achieved in the liver, esophagus, small intestine, and blood at 30 minutes following exposure. At 12 hours, maximum levels were seen in the lower gastrointestinal tract. Higher tissue levels of hydrocarbon resulted from absorption of benzo[a]pyrene-Ga_2O_3 particles. Inhaled benzo[a]pyrene adsorbed on insoluble Ga_2O_3 particles was cleared predominantly by mucocilliary transport and ingestion. This latter mechanism of

absorption led to the increased levels and longer retention times of benzo[a]pyrene in the stomach, liver, and kidneys (Sun et al. 1982).

Pregnant Wistar rats inhaled head-only high levels of [^{14}C]-pyrene aerosol on gestational day 17 (Withey et al. 1992). Concentrations of pyrene and metabolites in maternal and fetal blood were elevated 8-fold with a fourfold increase in exposure concentrations. However, pyrene levels in fetal blood were about 10 times lower than maternal blood immediately after exposure. In general, radioactivity increased in fat but decreased in blood, lungs, and liver tissues from 0 to 6 hours postexposure. There was only a small increase in the concentration of radioactivity in fetuses over the whole exposure range compared to maternal levels, suggesting placental transfer of pyrene and its metabolites are limited or that metabolism in fetal tissues is limited.

In a similar study, pregnant Wistar rats were exposed head-only to 200, 350, 500, 650, or 800 mg/m^3 of [^{14}C]-benzo[a]pyrene aerosol for 95 minutes on gestational day 17 (Withey et al. 1993a). Animals were killed immediately or 6 hours postexposure. Concentration of benzo[a]pyrene and metabolites in maternal blood sampled immediately after exposure were elevated 10-fold over the 4-fold increase in dose. At 6 hours postdosing, the increase was still approximately 10-fold, although the actual concentrations were 2-7-fold less than at 0 hours. Concentrations of benzo[a]pyrene and metabolites in fetal blood sampled immediately after exposure were elevated 5-fold over the 4-fold increase in exposure concentrations. Fetal tissues sampled 6 hours post-dosing had a 9-fold increase in benzo[a]pyrene and metabolite concentration over the dose range, due to lower concentration in the 200-650 mg/m^3 dose groups at 6 hours compared to 0 hours. Fetal concentrations were 2-10-fold less than maternal concentrations. Benzo[a]pyrene concentrations in blood, lung, liver, and fetal tissues were significantly decreased from 0 to 6 hours postexposure while levels in fat tissue increased. For benzo[a]pyrene sampled immediately postdosing, lung > blood > liver > kidney > fat > fetus. For total metabolites sampled immediately postdosing, lung > blood > liver > kidney > fetus > fat. For benzo[a]pyrene sampled 6 hours postdosing, fat > lung > kidney > liver > blood > fetus. For total metabolites sampled 6 hours postdosing, lung = fat > kidney > liver = blood > fetus.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of PAHs in humans following oral exposure.

Tissue levels of benzo[a]pyrene in Sprague-Dawley rats were highest 2-8 days after initial exposure to multiple doses of 0.0005 mg [^{3}H]-benzo[a]pyrene (Yamazaki and Kakiuchi 1989). The highest radioactivities were found in the kidney and testis. [^{3}H]-Benzo[a]pyrene distributed to the protein fractions of the liver, lung, and kidney (Yamazaki et al. 1987). The radioactivity in the protein fractions of these tissues increased gradually over time. In contrast, the radioactivity in the lipid fractions of these tissues accounted for 70% of the administered dose at 3 hours but decreased rapidly with time. The nucleic acid fraction maintained approximately 10% of the total radioactivity throughout the experiment. The increase in protein binding of radioactivity associated with benzo[a]pyrene and its metabolites, and the persistence of the radioactivity associated with the protein fractions, suggests that protein binding may allow benzo[a]pyrene and its metabolites to accumulate in certain tissues, thus increasing the likelihood of cytotoxicity, mutagenicity, or carcinogenicity of benzo[a]pyrene and its metabolites in these organs. In addition, these organs have low metabolic activity while the liver has a high detoxification potential and can facilitate the excretion of these toxic products (Yamazaki et al. 1987).

Single oral doses of 12 mg/kg [^{14}C]-benzo[a]pyrene were administered by gavage to pregnant NMRI:Han mice on gestational days 11, 12, 13, or 18 (Neubert and Tapken 1988). Distribution of radioactivity was measured at 6, 24, and 48 hours after exposure. Maternal and embryo levels were highest with exposure on gestational day 11. The difference in radioactivity between maternal and embryo liver tissues increased when exposure occurred at later gestation. In another experiment, mice were exposed to 24 mg/kg benzo[a]pyrene for 3 consecutive days during early (gestational days 9-l1) or late gestation (days 15-17) (Neubert and Tapken 1988). Maternal tissue levels were not much different from those observed following the administration of single doses. After multiple dose administration, elimination appeared to be faster in maternal tissues, but slower in embryonic tissues. Placental levels were always higher than those in embryonic tissue. Results suggest that benzo[a]pyrene does not cross the placental barrier readily and, therefore, that levels in embryonic tissues of mice never reach levels found in maternal tissues.

In general, orally absorbed benz[a]anthracene, chrysene, and pyrene were rapidly and widely distributed in the rat (Bartosek et al. 1984; Withey et al. 1991). Maximum concentrations of benz[a]anthracene and chrysene in perfused tissues, like the liver, blood, and brain, were achieved within l-2 hours after administration of high doses (76 and 152 mg/kg) (Bartosek et al. 1984). Maximum levels in lesser perfused tissues, like adipose and mammary tissue, were reached in

3-4 hours. In male Wistar rats receiving a gavage dose of 2-15 mg/kg of [^{14}C]-pyrene, the fat had the highest tissue levels of radioactivity, followed by kidney, liver, and lungs (Withey et al. 1991).

Orally absorbed dibenz[a,h]anthracene in rats was also widely distributed to several tissues (Daniel et al. 1967). However, maximum tissue concentrations were not reached until 10 hours after administration. Highest tissue concentrations were in the liver and kidneys, followed by adrenal glands, ovaries, blood, and fat. Soon after administration, large quantities of dibenz[a,h]anthracene were found in the liver and kidneys. The elimination rate from these organs was rapid. At 3-4 days after administration, dibenz[a,h]anthracene was distributed only in the adrenal glands, ovaries, and fat.

The permeability of the placenta to dimethylbenz[a]anthracene, benzo[a]pyrene, and 3-methylcholanthrene (MC) was compared by Shendrikova and Aleksandrov (1974). Pregnant rats received the PAH orally in sunflower oil at a dose of 200 mg/kg on the 21st day of pregnancy. Within 30 minutes after administration of dimethylbenz[a]anthracene, trace amount of the compound could be detected in the fetus. Maximum levels (1.53-1.6 µg/g) were reached 2-3 hours after administration. Only trace amounts were detected in the fetus at 5 hours after administration. Concentration profiles in the liver and placenta were similar to those seen in the fetus. Benzo[a]pyrene was detected in the fetus at 2.77 µg/g. MC was only present in trace amounts. Concentration differences in the fetus among the various PAHs appeared to be highly dependent on the gastrointestinal absorption of the compound. The difference in fetal concentration of the PAHs did not reflect their ability to permeate the placenta.

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of PAHs in humans following dermal exposure. Evidence regarding the distribution of PAHs in animals following dermal exposure is limited. Although PAHs can readily penetrate the skin, there are few data on distribution to tissues. In one published study on this subject, only 1.3% of an applied dose of [^{14}C]-anthracene (9.3 µg/cm^2) was detected in tissues, primarily liver and kidneys, of rats 6 days after administration (Yang et al. 1986). Groups of 12 male Wistar rats were dosed with 2, 6, or 15 mg/kg of [^{14}C]-pyrene applied to 4 cm^2 of a shaved area of the mid back (Withey et al. 1993b). Three animals in each dose group were killed at

1, 2, 4, and 6 days postdosing, and the brain, lungs, heart, liver, spleen, kidneys, testes, muscle, and perirenal fat were removed and analyzed for pyrene and [^{14}C]-pyrene equivalents. Blood, urine, feces, as well as the skin from the application site were also analyzed. The rate of uptake from the skin was rapid (t1/2 = 0.5-0.8 d) relative to rate processes for the other organs, and about 50% of the applied dose was excreted over the 6 days of the study. Levels of pyrene were highest in the liver, kidneys, and fat. Levels of metabolites were also high in the lung.

2.3.3 Metabolism

The lipophilicity of PAHs enables them to readily penetrate cellular membranes and remain in the body indefinitely. However, the metabolism of PAHs renders them more water-soluble and more excretable. Metabolism of PAHs occurs in all tissues. The metabolic process involves several possible pathways with varying degrees of enzyme activities. The activities and affinities of the enzymes in a given tissue determine which metabolic route will prevail.

The metabolism of PAHs has been studied extensively *in vitro* and *in vivo.* The most commonly used system is the rat liver microsomal fraction, although other species are also used. Cells and cultured tissues from human and other animals have also significantly contributed to the elucidation of the PAH metabolic scheme.

The structural similarity of PAHs contributes to the similarities that exist in their biotransformation. Benzo[a]pyrene metabolism has been extensively reviewed and will be used as a model for PAH metabolism. In the many microsomal, cell, and cultured tissue preparations that have been examined, the metabolic profiles are qualitatively similar. However, there are differences in the relative levels and rates of formation of specific metabolites among tissues and cell preparations used from various animal species and strains. These differences are susceptible to change as a result of pretreatment of the animals with either inducers or inhibitors of particular enzymes. Furthermore, it is known that the metabolism of alternant PAHs (such as benzo[a]pyrene, benz[a]anthracene, chrysene, and dibenz[a,h]anthracene) differs from nonalternant PAHs (such as benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, and indeno[1,2,3-c,d]pyrene) (see Section 2.2). Therefore, the metabolism of benzo[b]fluoranthene will also be discussed as a model for nonalternant PAH metabolism.

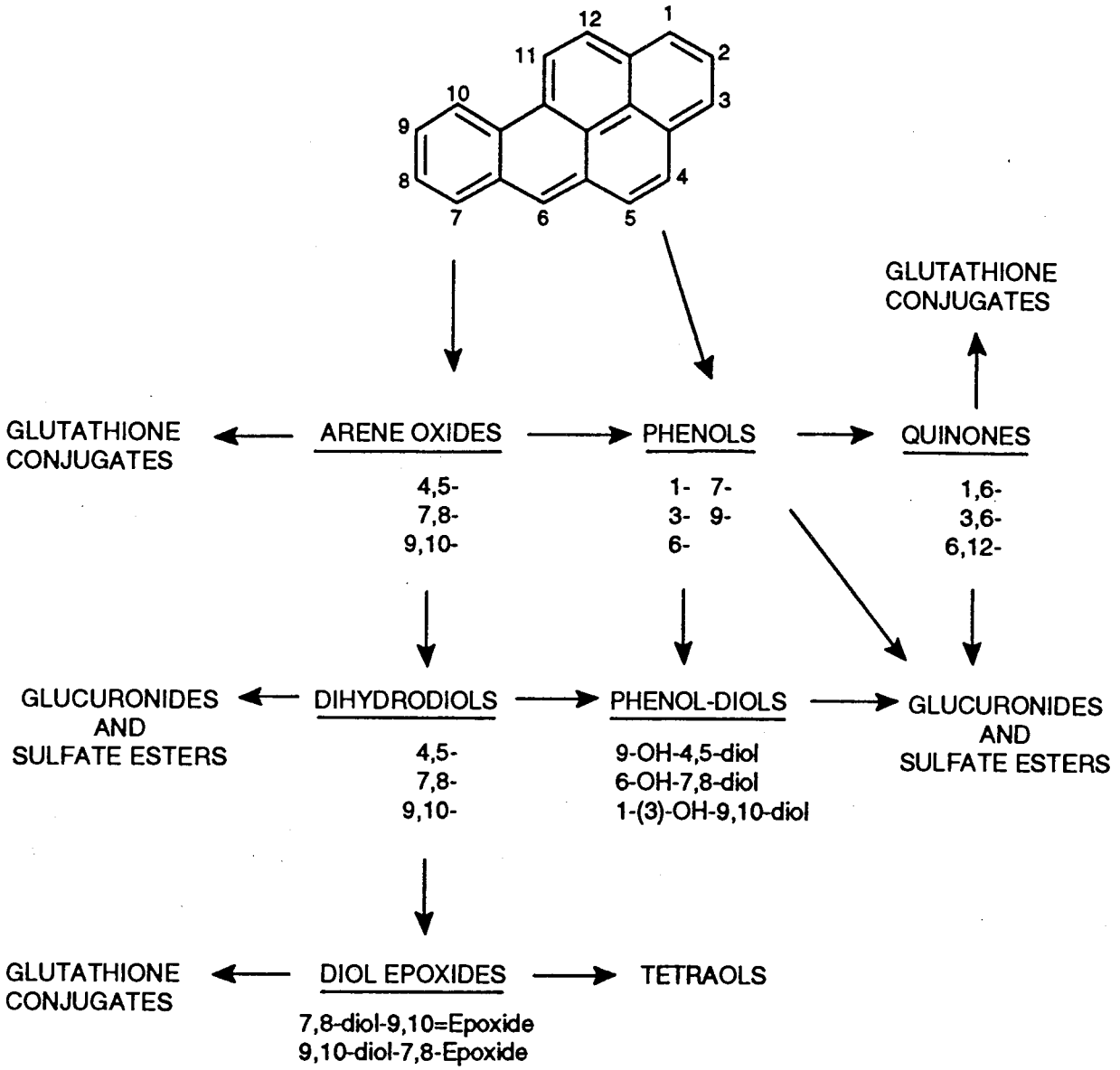
The metabolism of benzo[a]pyrene is summarized in Figure 2-3. Benzo[a]pyrene is metabolized initially by the microsomal cytochrome P-450 systems to several arene oxides. Once formed, these arene oxides may rearrange spontaneously to phenols, undergo hydration to the corresponding trans-dihydrodiols in a reaction catalyzed by microsomal epoxide hydrolase, or react covalently with glutathione, either spontaneously or in a reaction catalyzed by cytosolic glutathione-S-transferases (IARC 1983). Phenols may also be formed by the P-450 system by direct oxygen insertion, although unequivocal proof for this mechanism is lacking. 6-Hydroxybenzo[a]pyrene is further oxidized either spontaneously or metabolically to the 1,6-, 3,6-, or 6,12-quinones. This phenol is also a presumed intermediate in the oxidation of benzo[a]pyrene to the three quinones catalyzed by prostaglandin endoperoxide synthetase (Panthanickal and Marnett 1981). Evidence exists for the further oxidative metabolism to two additional phenols. 3-Hydroxybenzopyrene is metabolized to the 3,6-quinone and 9-hydroxy-benzo[a]pyrene is further oxidized to the K-region 4,5-oxide, which is hydrated to the corresponding 4,5-dihydrodiol (4,5,9-triol). The phenols, quinones, and dihydrodiols can all be conjugated to glucuronides and sulfate esters; the quinones also form glutathione conjugates (Agarwal et al. 1991; IARC 1983).

In addition to being conjugated, the dihydrodiols undergo further oxidative metabolism. The cytochrome P-450 system metabolizes benzo[a]pyrene-4,5-dihydrodiol to a number of uncharacterized metabolites, while the 9,10-dihydrodiol is metabolized predominantly to its l- and/or 3-phenol derivative with only minor quantities of a 9,10-diol-7,8-epoxide being formed. In contrast to the 9,10-diol, benzopyrene-7,8-diol is metabolized to a 7,8-dihydrodiol-9,10-epoxide, and phenol-diol formation is a relatively minor pathway. The diol epoxides can be conjugated with glutathione either spontaneously or by a glutathione-S-transferase catalyzed reaction. They may also hydrolyze spontaneously to tetrols (Hall and Grover 1988).

The route by which PAHs and other xenobiotics enter the body may determine their fate and organ specificity. For example, an inhaled compound may bypass the first-pass effect of the liver and reach peripheral tissues in concentrations higher than one would see after oral exposures. Enzyme activities among tissues are variable.

Benzo[a]pyrene was metabolized *in vitro* by human bronchial epithelial and lung tissue to the 9,10-dihydrodiol, 7,8-dihydrodiol, and small quantities of the 4,5-dihydrodiol and 3-hydroxybenzo[a]pyrene, all of which are extractable into ethyl acetate (Autrup et al. 1978; Cohen et

FIGURE 2-3. Proposed Metabolic Scheme for Benzo(a)pyrene.



al. 1976; Kiefer et al. 1988). These metabolites also conjugated with glutathione and sulfates, but none conjugated with glucuronide. The rate of formation of the dihydrodiols was greater in the bronchial epithelium than in the lung (Autrup et al. 1978; Cohen et al. 1976). This may render some areas of the respiratory tract more sensitive to the effects of carcinogens. One principal difference seen in human lung was the generation of a major ethyl acetate-soluble metabolite that was identified as the sulfate conjugate of 3-hydroxybenzo[a]pyrene, benzo[a]pyrene-3-yl-hydrogen sulfate. This sulfate is very lipid soluble and, thus, would not be readily excreted in the urine (Cohen et al. 1976). Activation of benzo[a]pyrene has also been detected in human fetal esophageal cell culture (Chakradeo et al. 1993).

Intratracheal instillation of benzo[a]pyrene to rats resulted in quinones constituting the highest concentration of metabolites in the lung and the liver within 5 minutes after instillation (Weyand and Bevan 1986, 1988). An *in vitro* study with rat lung demonstrated that the lung tissue has a high capacity to form quinones originating from oxidation at the six position of benzo[a]pyrene to form quinones and subsequently to water-soluble products. Ozone exposure resulted in an increase in the metabolism of benzo[a]pyrene metabolites with the greatest increase observed in the formation of metabolites generated by oxidation at the six position. The proposed retention of quinones following ozone exposure might lead to cytotoxicity associated with superoxide-anion generation by quinone-quinol redox-cycling. However, the high levels of benzo[a]pyrene used in this *in vitro* study may not relate to what occurs *in vivo*. Metabolism of benzo[a]pyrene at carbon six was higher at a lower dose than at the higher dose. Therefore, quinone production and detoxification may represent a major pathway of lung PAH detoxification *in vivo* (Basett et al. 1988).

Approximately 50% of the benzo[a]pyrene that was intratracheally instilled in hamsters was metabolized in the nose (Dahl et al. 1985). The metabolite produced in the hamster nose included tetrols, the 4,5-, 7,8-, and 9,10-dihydrodiol, quinones, and 3-and 9-hydroxybenzo[a]pyrene. Similar metabolites were detected in nasal and lung tissues of rats inhaling benzo[a]pyrene (Wolff et al. 1989b). The prevalence of quinone production was not seen in hamsters as it was in rats (Dahl et al. 1985; Weyand and Bevan 1987a, 1988). In monkeys and dogs, dihydrodiols, phenols, quinones, and tetrols were identified in the nasal mucus following nasal instillation of benzo[a]pyrene (Petridou-Fischer et al. 1988). *In vitro* metabolism of benzo[a]pyrene in the ethmoid turbinates of dogs resulted in a prevalence of phenols (Bond et al. 1988). However, small quantities of .quinones and dihydrodiols were also identified.

Rat lung microsomes facilitated the dissociation of small amounts of benzo[a]pyrene from diesel particles, but only a small fraction of the amount dissociated was metabolized (Leung et al. 1988). The ability to dissociate benzo[a]pyrene was related to the lipid content of the microsomal fraction. Microsomes are able to enhance the slow dissociation of a small amount of benzo[a]pyrene from diesel particles in a form that can be metabolized. Free benzo[a]pyrene was principally and extensively metabolized to the 9,10-dihydrodiol.

A human hepatoma cell line (HepG2) has high benzo[a]pyrene-metabolizing activity and converts benzo[a]pyrene to metabolites (Diamond et al. 1980). When [^{3}H]-benzo[a]pyrene was added to the incubate, a large fraction of the radioactivity was not extractable into chloroform. The extractable fraction contained 9,10-dihydrodiols, 7,8-dihydrodiols, quinones, 3-hydroxybenzo[a]pyrene, and the unchanged parent compound. The cell lysate also consisted of the same metabolites, but the proportions of 3-hydroxybenzo[a]pyrene and the parent compound were much higher than in the medium. Conversely, the proportion of water-soluble metabolites in the cell lysate was lower than in the medium. Treatment of the medium and cell lysate with β-glucuronidase converted only 5-7% of the water-soluble metabolites to chloroform-extractable material. Aryl sulfatase had no effect on radioactivity. These results suggested that this human liver tumor cell line does not extensively utilize the phenol detoxification pathway (Diamond et al. 1980).

Metabolism of benzo[a]pyrene in the primary culture of human hepatocytes primarily resulted in the formation of 3-hydroxybenzo[a]pyrene, 4,5-dihydrodiol, 9,10-dihydrodiol, and 7,8-dihydrodiol (Monteith et al. 1987). As the dose of benzo[a]pyrene increased, the amount of metabolites increased linearly. Binding to DNA was associated with the amount of unconjugated 7,8-dihydrodiol. DNA binding was linear up to a benzo[a]pyrene concentration of 100 μmol. At this concentration, binding increased 64-844 times over the extent of binding at 10 umol. As the concentration of benzo[a]pyrene increased, the ratio of dihydrodiol/phenolic metabolites also increased. Although the capacity to form dihydrodiols was not saturated at 100 umol benzo[a]pyrene, there was a change in the relative proportion of the dihydrodiol metabolites formed as the dose of benzo[a]pyrene increased. As benzo[a]pyrene concentration increased, the 9,10-dihydrodiol was the more prevalent metabolite, but levels of 7,8-dihydrodiol also increased (Monteith et al. 1987).

Epoxide hydrolase is a microsomal enzyme that converts alkene and arene oxides to dihydrodiols. Appreciable enzyme activity was observed in human livers. Comparison of epoxide hydrolase

activities with various substrates revealed that the human liver has a single epoxide hydrolase with broad substrate specificity (Kapitulnik et al. 1977). Epoxide hydrolase activity is also present in other tissues and increases the likelihood for carcinogenic effects in these organs. Ethyl acetate extracts of human and rat bladder cultures contained 9,10-dihydrodiol, 7,8-dihydrodiol, and 3-hydroxybenzo[a]pyrene. Covalent binding of [^{3}H]-benzo[a]pyrene with DNA occurring in both human and rat bladder cultures suggested that benzo[a]pyrene-7,8-diol-9, 10-epoxide is generated. The urothelium of the bladder clearly has the ability to generate the ultimate carcinogen (Moore et al. 1982).

Hepatic microsomes from rats induced with 3-methylcholanthrene convert benzo[a]pyrene to benzo[a]pyrene-7,8-diol-9,10-epoxide (BPDE) 10 times faster than untreated microsomes. The rate-limiting step in BPDE formation is the competition for P-450 between benzo[a]pyrene and the 7,8-dihydrodiol. Formation of BPDE is directly correlated with the 3-methylcholanthrene inducible form(s) of P-450 (Keller et al. 1987). Formation of the proximate carcinogen, 7,8-dihydrodiol, is stereoselective. Rabbit hepatic microsomes generated more of the 7R,8R enantiomer with an optical purity of >90% (Hall and Grover 1987). The major stereoisomer formed by rat liver microsomes is (+)-diol-epoxide-2 (R,S,S,R absolute conformation) (Jerina et al. 1976, 1980). This metabolite is highly tumorigenic (Levin et al. 1982) and gives rise to the major adduct formed upon reaction with DNA. The adduct is a diol epoxide-deoxyguanosine formed by alkylation at the exocyclic nitrogen (N-2) of deoxyguanosine. This diol epoxide-deoxyguanosine has been isolated from several animal species (Autrup and Seremet 1986; Horton et al. 1985) and human tissue preparations (Harris et al. 1979).

Studies using rat liver microsomes have shown that hydroxy metabolites of benzo[a]pyrene undergo glucuronidation (Mackenzie et al. 1993). Assays with three different DNA-expressed glucuronidases from human liver indicate preferential glucuronidation for the 2- and 5-hydroxy, 4- and 11-hydroxy, or l-, 2-, and 8-hydroxy derivatives of benzo[a]pyrene. There are differences in preferential activities for the glucuronidation of various benzo[a]pyrene metaboiites among the various DNA-expressed glucuronidases from human liver, with some glucuronidases being relatively or totally inactive toward this class of compounds (Jin et al. 1993). The results of this study suggest that the relative content of particular types of glucuronidases in a cell or tissue may be important for determining the extent to which a particular carcinogen is deactivated.

Several xenobiotics can induce enzymes to influence the rat liver microsomal metabolite profiles of various PAHs. For example, AHH, the cytochrome P-450 isoenzyme believed to be primarily responsible for the metabolism of benzo[a]pyrene and other PAHs, is subject to induction by PAHs. Treatment of pregnant and lactating rats with a single intraperitoneal dose of Aroclor 1245 increased the metabolism of benzo[a]pyrene by liver microsomes from pregnant and fetal rats 9-fold and 2-fold, respectively, and 2-fold in lactating rats (Borlakoglu et al. 1993). The pretreatment enhanced the formation of all metabolites, but the ratio of the 7,8-diol (the proximate carcinogen) was increased 3-fold in lactating rats and 5-fold in pregnant rats. Similar results were observed in rabbit lung microsomes (Ueng and Alvares 1993). Cigarette smoke exposure has been shown to increase PAH metabolism in human placental tissue (Sanyal et al. 1993), and in rat liver microsomes (Kawamoto et al. 1993). In studying benz[a]anthracene metabolism, some xenobiotics were found to be weak or moderate inducers, but even less efficient ones altered the benz[a]anthracene profile significantly. Thiophenes equally enhanced oxidation at the 5,6- and the 8,9-positions. Benzacridines favored K-region oxidation (5,6-oxidation) (Jacob et al. 1983b). Indeno[1,2,3-c,d]pyrene stimulated the bay region oxidation (3,4-oxidation) of benz[a]anthracene (Jacob et al. 1985). Similar xenobiotic effects were observed with chrysene as a substrate (Jacob et al. 1987). While some enzyme activities are being enhanced, alternate enzymatic pathways may be suppressed (Jacob et al. 1983a).

Rat liver microsomes also catalyzed benzo[a]pyrene metabolism in cumene hydroperoxide (CHP)-dependent reactions which ultimately produced 3-hydroxybenzo[a]pyrene and benzo[a]pyrene-quinones (Cavalieri et al. 1987). At low CHP concentrations, 3-hydroxybenzo[a]pyrene was the major metabolite. As CHP concentrations increased, levels of quinones increased and levels of 3-hydroxybenzo[a]pyrene decreased. This effect of varying CHP levels was reversed by preincubating with pyrene. Pyrene inhibited quinone production and increased 3-hydroxybenzo[a]pyrene production. Pretreatment with other PAHs like naphthalene, phenanthrene, and benz[a]anthracene nonspecifically inhibited the overall metabolism. The binding of benzo[a]pyrene to microsomal proteins correlated with quinone formation. This suggested that a reactive intermediate was a common precursor. The effects of pyrene on benzo[a]pyrene metabolism indicated that two distinct microsomal binding sites were responsible for the formation of 3-hydroxybenzo[a]pyrene and benzo[a]pyrene-quinone (Cavalieri et al. 1987).

Rat mammary epithelial cells (RMEC) have been shown to activate PAHs (Christou et al. 1987). Cytochrome-P-450 in RMEC is responsible for the monooxygenation of DMBA. Prior exposure’of

cultured cells to benz[a]anthracene induced DMBA metabolism. The metabolite profile following benz[a]anthracene-induction was significantly different from the profile obtained with purified P-450c, the predominant PAH-inducible enzyme in rat liver. The bay region 3,4-dihydrodiol, which was not formed with P-450c, was clearly detectable in RMEC. Low epoxide hydrolase activity in the benz[a]anthracene-induced RMEC limited the formation of all other DMBA dihydrodiols. The DMBA monooxygenase activity of benz[a]anfhracene-induced RMEC was inhibited by a-naphthaflavone. The study concluded that DMBA metabolism by RMEC depended on the induction of P-450c and at least one additional form of P-450 that is sensitive to α-naphthaflavone (Christou et al. 1987).

As expected from results of other studies, the perfused rat lung can release high quantities of benzo[a]pyrene metabolites and conjugates into the perfusate (Molliere et al. 1987). Addition of a liver to this perfusion system up gradient from the lungs reduces the concentration of parent compound and free metabolites to less than 20% of that seen in the liver's absence. The liver provides a protective effect on the lung to inhibit covalent binding of benzo[a]pyrene metabolites to pulmonary macromolecules.

The effects of various factors that can modify the hepatic clearance of PAHs, specifically benz[a]anthracene and chrysene, were studied by Fiume et al. (1983). The hepatic clearance and rate constants of these PAHs were significantly reduced in the perfused livers of fasted rats relative to those of fed rats. This reduction was attributed to a decrease in aryl hydrocarbon hydroxylase activity. Fasting also accelerated the depletion of cytochrome P-450 and other microsomal enzymes. In contrast, pretreatment of the rats with these PAHs resulted in increased clearance of both hydrocarbons from the perfusion medium when compared to control rats.

It was also noted by Fiume et al. (1983) that the livers of male rats demonstrated a significantly higher hepatic clearance of benz[a]anthracene than female rats, perhaps suggesting a sexual difference with aryl hydrocarbon hydroxylase activity. Similar findings regarding sexual differences in the metabolism of chrysene by rat livers were also reported by Jacob et al. (1985, 1987). Furthermore, Fiume et al. (1983) demonstrated that age can play a role in PAH metabolism. The hepatic clearance of PAHs in older rats (2 years) was significantly less than the hepatic clearance in younger rats (8 weeks). However, activation of benzo[a]pyrene to mutagenic derivatives, as measured by the *Salmonella typhimurium* test, with hepatic microsomes from male rats from 3 weeks to 18 months of age showed no age-dependent changes (Hilali et al. 1993).

A proposed metabolic scheme for the metabolism of the nonaltemant PAH, benzo[b]fluoranthene is presented in Figure 2-4. Nonalternant PAHs, in contrast to several alternant PAHs, do not appear to exert their genotoxic effect primarily through the metabolic formation of simple dihydrodiol epoxides. In the case of benzo[b]fluoranthene, there is evidence to suggest that metabolism to the dihydrodiol precursor to its bay-region dihydrodiol does occur. Rather than this metabolite being converted to its dihydrodiol epoxide; however, it appears to be extensively converted to its 5-hydroxy derivative. It is the further metabolism of this phenolic dihydrodiol to 5, 9, 10-trihydroxy- 11,12-epoxy-9,10,11,12-tetra-hydrobenzo[b]fluoranthene that has been linked to the genotoxic activity of benzo[b]fluoranthene in mouse skin (Weyand et al. 1993b). In the case of benzo[j]fluoranthene, two potentially genotoxic metabolites have been identified. These are the trans-4,5- and 9,10-dihydrodiols of benzo[j]fluoranthene. It is the conversion of trans-4,5-dihydro-4,5-dihydroxybenzo[j]fluoranthene to anti-4,5-dihydroxy-5,6a-epoxy-4,5,6,6a-tetrahydrobenzo[j]fluoranthene that is principally associated with DNA adduct formation in mouse skin (LaVoie et al. 1993b; Weyand et al. 1993a). Benzo[k]fluoranthene in rat microsomes was shown to result in the formation of 8,9-dihydrodiol. This dihydrodiol can form a dihydrodiol epoxide that is not within a bay region. This may represent an activation pathway of benzo[k]fluoranthene that may be associated, in part, with its genotoxic activity. In the case of nonalternant PAHs, reactive metabolites, that deviate from classical bay region dihydrodiol epoxides, have been linked to their tumorigenic activity.

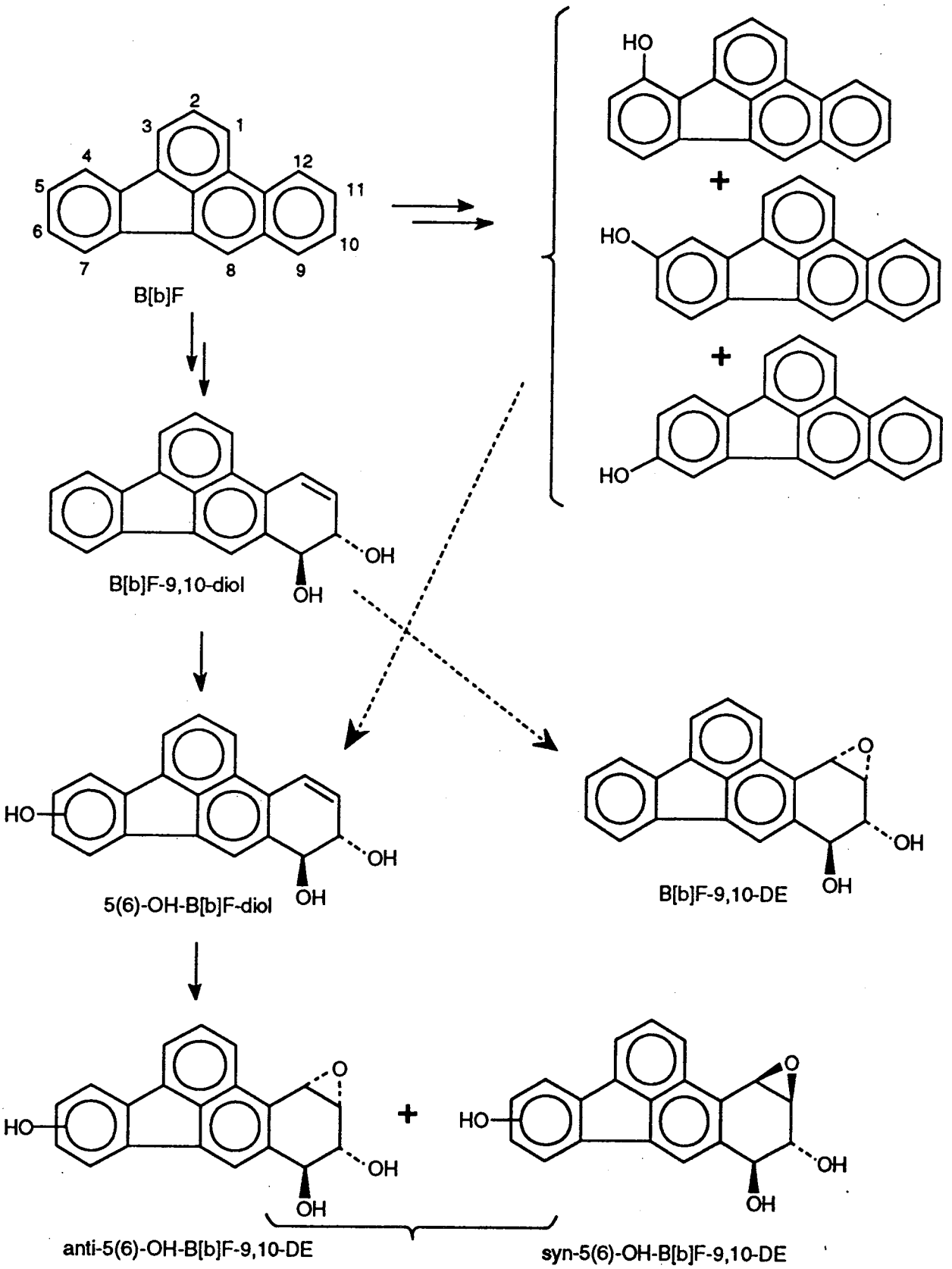
2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Urinary metabolites of PAHs were detected in workers exposed to these compounds in an aluminum plant (Becher and Bjorseth 1983). The ambient levels of PAHs in the workplace (indicated by the authors to exceed 95 mg/m^3, although these data were not presented) did not correspond to the amount of PAHs deposited, metabolized, and excreted in the urine in this study. No quantitative inhalation data were available in humans regarding the excretion of PAHs.

Thirty-four workers in an electrode paste plant were monitored for response to exposure (Ovrebo et al. 1994). Exposure to benzo[a]pyrene was 0.9 µg/m^3; exposure to pyrene was 3.5 µg/m^3. 1-Hydroxypyrene was measured in the urine. Results from these workers were compared to two reference control groups, research and development workers and nickel refinery workers.

FIGURE 2-4. Proposed Metabolic Scheme for Benzo(b)fluoranthene.



Measurements of PAH levels were collected by personal sampling and at two stationary sites. PAH aerosols were collected on filters during the mixing of hot coal tar with carbon. The value of PAHs on the filters varied from 4.3 to 84.6 µg/m^3, with a mean of 14.4 µg/m^3. The PAH particulates were assayed for 8 of 11 PAHs classified as carcinogenic, including benz[a]anthracene, benz[g,h,i]perylene, benzo[a]pyrene, benzo[e]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, chrysene, fluoranthene, and indeno[1,2,3-c,d]pyrene, and presented relative to the marker compound, pyrene. Content of these compounds ranged from 30 to 150% of the pyrene content on the filters, which was 1.6 µg/m^3. For example, the benzo[a]pyrene level was 0.8 µg/m^3. Urine analysis indicated a mean urinary value of 1-hydroxypyrene among electrode paste plant workers of 6.98 umol/mol creatinine, compared to 0.08 µmol/mol creatinine for the R&D workers, and 0.14 µmol/mol creatinine for the industrial worker group. Smokers had higher levels of 1-hydroxypyrene compared to non-smokers in all groups. The urinary 1-hydroxypyrene level in the electrode plant workers correlated inversely with age. No correlation was found between frequency of use of a protective mask and the urinary 1-hydroxypyrene concentration.

In an ongoing comprehensive evaluation of biological markers, workers in or near an iron foundry with varying exposures to PAHs were analyzed for response to exposure (Santella et al. 1993). Exposure to benzo[a]pyrene, determined by personal monitors, was 2-60 ng/m^3. 1-Hydroxypyrene was measured in the urine. Cigarette smoking, but not age or charbroiled food, influenced the level of 1-hydroxypyrene. When workers were classified into three categories (low, <.0005 mg/m^3; medium, 0.0005-0.0012 mg/m^3; high, >0.0012 mg/m^3), mean 1-hydroxypyrene levels were 2.7, 1.8, and 3.6 µmol/mol creatinine, respectively. There was a significant difference between the groups after controlling for smoking exposure, but there was no consistent trend. The authors indicate that this study evaluates biological markers of exposure at PAH levels that are very low, compared to other studies.

Workers employed in a graphite electrode producing plant (n=16) and a coke oven (n=33) were compared to a control population of maintenance workers in a blast furnace (n=54) (Van Hummelen et al. 1993). The concentration of PAHs in the environment was measured by personal air samplers, the concentration of hydroxypyrene in urine was measured, and smoking habits were evaluated. The mean age of the workers was 40, and did not differ significantly between the three plants. The proportion of smokers was not different among the three groups. The mean exposure for workers in the graphite electrode producing plant was 11.33 µg/m^3 (0.011 mg/m^3) and was correlated with a urinary

hydroxypyrene concentration of 3.18 µg/g creatinine prior to the shift and 6.25 µg/g creatinine after the shift. For the coke oven workers, airborne PAHs were measured at 23.7 µg/m^3 but this was not illustrative of true exposure, since there were a few very high exposures in the sample: 90.10 µg/m^3 for 7 workers compared to 5.57 µg/m^3 for 26 workers. In accordance with the predominantly low exposure, the urinary hydroxypyrene levels were 0.51 µg/g creatinine before the shift and 0.75 µg/g creatinine after the shift.

The excretion of benzo[a]pyrene following low-level inhalation exposure is rapid and high in rats (Bevan and Weyand 1988; Weyand and Bevan 1986; Wolff et al. 1989c); however, elimination is low in dogs and monkeys (Petridou-Fischer et al. 1988). After nose-only inhalation of 4.8 mg/m^3 [^{14}C]-benzo[a]pyrene for a single exposure or daily for 4 weeks, excretion of radioactivity in the feces of Fischer-344 rats was approximately 96% of the administered concentration (Wolff et al. 1989c). The excretion half-lives in feces and urine were 22 and 28 hours, respectively.

2.3.4.2 Oral Exposure

Five volunteers (21-41 years of age) ingested specially prepared diets high in PAHs, specifically benzo[a]pyrene (from grilled beef), for 2-3 days for an intake of approximately 0.007-0.02 mg/day (Buckley and Lioy 1992). A 100-250-fold increase in ingested benzo[a]pyrene in the high-PAH diet corresponded to a 6-12-fold increase in the elimination of 1-hydroxypyrene. However, benzo[a]pyrene and its other metabolites (not specified) were not measured in excreta, which prevented determination of the total excretion (and an estimate of oral absorption).

Male Sprague-Dawley rats received a low dose of [^{3}H]-benzo[a]pyrene (suspended in 10% ethanolsoybean oil) daily for 3, 5, or 7 days (Yamazaki and Kakiuchi 1989). Highest radioactivity was excreted 2-8 days after first exposure. Polar and phenol metabolites represented approximately 60% and 20% of the radioactivity detected in urine, respectively. The conjugated form accounted for 80% of these urinary metabolites. Only small amounts of unmetabolized benzo[a]pyrene were detected in the urine. Excretion into the feces was not studied.

Male Wistar rats eliminated a large amount of a single gavage dose of 0.22 mg/kg chrysene by 2 days postexposure (Grimmer et al. 1988). The unchanged parent compound represented 0.17% and 13.09% in the urine and feces, respectively. The recovery of the dose in excreta was 74% of dose after 4 days

of which about 61% was represented by hydroxychrysene compounds. The metabolite pattern was similar for urine and feces. The major metabolites identified were 1- and 3-hydroxychrysene, with about 100 times higher amounts in the feces (33.1% and 17.87%, respectively, of administered dose) than urine (0.79% and 0.35%, respectively). Approximately 79% of a large chrysene dose (1,217-2,717 mg/kg in the diet) was eliminated in the feces of rats; however, levels in the urine were not measured (Chang 1943). As the dose of chrysene in the diet increased, the percentage of excreted hydrocarbon also increased.

Male Wistar rats were given single oral doses of 2, 4, 6, 9, or 1.5 mg/kg of [^{14}C]-pyrene (Withey et al. 1991). Recovery of the dose in excreta was 82% for the two low-dose groups and 50-63% for the other groups 2 days postexposure. The urine and feces contained 34-45% and 21-50% of the dose, respectively, at 4 days postexposure. Recovery of radioactivity in the bile was approximately 10% of the dose after 6 hours.

2.3.4.3 Dermal Exposure

No studies were located regarding the excretion of PAHs in humans following dermal exposure to single PAHs. Excretion patterns of 1-hydroxypyrene in urine were studied in two psoriatic patients, each treated daily with coal tar pitch covering over 50% of their skin for 3 weeks (Hansen et al. 1993). The coal tar contained 1.43 mg/g pyrene. After 1 week of treatment, the urinary concentration of 1-hydroxypyrene increased approximately 100 times. However, the concentration after 3 weeks of treatment was decreased to that observed before treatment was initiated. The authors speculate that the healing of the psoriatic lesions may have rendered the skin less permeable to the PAHs after 3 weeks of treatment and healing.

The urinary excretion of 1-hydroxypyrene was evaluated in 65 automotive repair workers (automobile or diesel truck repair) whose skin was exposed to used mineral oils, and compared to values from non-professionally exposed control males on control diets (Granella and Clonfero 1993). Smoking exposure was equivalent in both groups. Pyrene concentrations were determined in the oily material taken from cloths used to clean various types of engines. Values of urinary 1-hydroxypyrene were determined on Friday at the end of the working week, and again on Monday morning prior to work. Smoking and PAH-rich diets were considered confounding factors. At both the beginning and the end of the working week, the values of urinary 1-hydroxypyrene were slightly higher in exposed subjects

(0.178 + 0.150 and 0.194 + 0.135 µmol creatinine on Monday and Friday, respectively) than in controls ((0.124 + 0.090 µmol/mol creatinine on Monday and Friday, respectively). The urinary 1-hydroxypyrene values were higher in both smoking and non-smoking subjects than controls. The highest values were found in urinary samples of smokers exposed to used mineral oils (0.259 + 0.090 µmol/mol creatinine). In non-smoking workers, post-shift 1-hydroxypyrene values were 0.154 + 0.105 µmol/mol creatinine, compared to 0.083 + 0.042 µmol/mol creatinine for the non-smoking controls. In automobile repair workers, there was no significant difference in the levels of 1-hydroxypyrene at the beginning and end of the work week. Tobacco smoking had more influence on the levels of 1-hydroxypyrene than did occupational exposure in this group. The influence of PAHs in the diet was only detectable when the subjects returned to work after the weekend. No explanation was given for this finding. This data suggests that exposure to PAHs through dermal contact with used engine oil is low.

The elimination of benzo[a]pyrene was rapid and high in mice and guinea pigs following low- and high-level dermal exposure (Ng et al. 1992; Sanders et al. 1986). The percentages of recovered radioactivity in urine and feces were 24.5%, 46.9%, and 25% for Swiss Webster mice dermally exposed to benzo[a]pyrene at 1.25, 12.5, and 125 µg/cm^2, respectively, for 7 days (Sanders et al. 1986). The feces in the high-dose animals had 35%, 58%, and 80% of the total recovered radioactivity after 24 hours, 48 hours, and 7 days, respectively. The amount of radioactivity excreted in urine was about 10% of amount excreted in feces. A elimination half-life of about 30 hours was estimated for benzo[a]pyrene. The data are limited because the exposed area of skin was not reportedly covered or collars were not employed to prevent ingestion of test compound by the animal. In guinea pigs, 73% of the dose was excreted 7 days after low-level (0.28 mg) exposure to benzo[a]pyrene (Ng et al. 1992).

The excretion of dermally absorbed phenanthrene and pyrene was rapid in guinea pigs (Ng et al. 1991, 1992). The presence of [^{14}C]-activity in the urine and feces of rats that received [^{14}C]-anthracene applied to the skin provides evidence of its absorption (Yang et al. 1986). Six days after administration of 9.3 µg/cm^2, the amounts detected in the urine and feces were 29.1% and 21.9% of the dose, respectively.

2.3.4.4 Other Routes of Exposure

No studies were located regarding excretion of PAHs in humans following other routes of exposure.

Three female Beagle dogs were given a bolus of aerosolized crystals of 7.7 mg/kg benzo[a]pyrene or 2.8 mg/kg phenanthrene in a single breath by intratracheal instillation (Gerde et al. 1993a). The blood borne clearance of the PAHs was monitored by repeatedly sampling blood through catheters in the ascending aorta and the right atrium of the dog. Half of the benzo[a]pyrene cleared within 2.4 minutes. Half of the phenanthrene cleared in 1.0 minute. Compared to clearance of phenanthrene, a less lipophilic PAH, the data indicate that the clearance of benzo[a]pyrene was limited by diffusion through the alveolar septa, while clearance of the moderately lipophilic phenanthrene was limited mostly by the rate of perfusion of the blood. The results indicate that inhaled PAHs of sufficient lipophilicity to limit diffusion through cells have a greater potential for toxicity to the lung than less lipophilic PAHs. Because of the thicker epithelia, bronchi should be at greater risk than the alveoli for PAH-induced toxicity exerted at the port of entry. Clearance of PAHs from the respiratory tract follows a biphasic pattern, with a rapid clearance of most of the PAH followed by a slow clearance of a small fraction. Previously published models predict that the rapid phase represents clearance through the thin epithelial barriers in the alveoli, the slow clearance is through the thicker epithelium of the airways, and the rate of clearance from either region will be slowed if the PAH has a high degree of lipophilicity. This study sought to validate model predictions for rates of alveolar clearance of PAHs of different lipophilicities. In a companion study, 3 female Beagle dogs were given doses of 0.00091 g/kg benzo[a]pyrene instilled on the surface of the conducting airways (Gerde et al. 1993b). Sequential lavage of the mucous-retained materials followed the instillations. Benzo[a]pyrene was retained within the mucous lining layer sufficiently to be transported with the mucocilliary escalator. Fractions of benzo[a]pyrene penetrating to the bronchial epithelium had a clearance half-time in the range of 1.4 hours. This long retention indicates a diffusion-limited uptake of benzo[a]pyrene by the airways. Physiological models have predicted that the lipophilicity of solutes such as PAHs will delay clearance from the respiratory tract. This clearance consists of a delayed penetration of the mucous lining layer, allowing mucocilliary clearance, followed by a slow penetration of PAHs through walls of the conducting airways.

Excretion of radioactivity in the urine of rats following intratracheal instillation only accounted for 2.2% of the administered benzo[a]pyrene at 6 hours (Bevan and Weyand 1988; Weyand and Bevan

1986). Amounts of radiolabel in the blood were also very small. However, levels could still be determined in order to derive toxicokinetic parameters. The data obtained by Weyand and Bevan (1986) fit best to a three-compartment model whereby the half-lives for the three phases were 4.3, 31.5, and 277 minutes.

Results obtained by Weyand and Bevan (1986, 1988) revealed that a large fraction of the administered dose was excreted in the bile of rats, therefore suggesting that fecal elimination is the major excretion route. After 6 hours, 53% of the 0.001 mg/kg dose was excreted into the intestine and intestinal contents of rats that were without a bile duct cannula, while cannulated rats excreted 74% in the bile over the same period (Weyand and Bevan 1986). These results indicate the occurrence of enterohepatic recirculation. Metabolites excreted in the bile included thioether conjugates (62.5%), glucuronide conjugates (22.8%), sulfate conjugates (7.4%), and free benzo[a]pyrene (9.8%) (Weyand and Bevan 1988). Radioactivity detected in the gastrointestinal tract of rats following pulmonary exposure to benzo[a]pyrene also suggests that biliary excretion occurs (Weyand and Bevan 1987a; Wolff et al. 1989c). The percentage of benzo[a]pyrene excretion into bile declined as intratracheal doses increased from 0.00016 to 0.35 mg in rats and guinea pigs (Weyand and Bevan 1987b). However, the biliary excretion of benzo[a]pyrene in hamsters remained the same after administration of either dose.

Female Wistar rats received low doses of chrysene (0.002 and 0.004 mg/kg) intratracheally (Grimmer et al. 1988). The major metabolite in the excreta was 1-hydroxychrysene. Hydroxychrysene compounds represented 31.26-48.9% of dose in the feces and about 3% in the urine. The unmetabolized parent compound was 17-19% of the administered dose in feces and only l-2% in urine.

Less than 10% of instilled radioactivity was excreted in the urine and feces of dogs and monkeys 48 hours after intratracheal administration of [^{3}H]-benzo[a]pyrene into the nostril (Petridou-Fischer et al. 1988).

Nineteen outbred male rats were dosed intraperitoneally once with 200 mg/kg benzo[a]pyrene in sunflower oil (Likhachev et al. 1993). Concentrations of benzo[a]pyrene-7,8-diol, a marker metabolite of bioactivation of benzo[a]pyrene, and 3-hydroxy-benzo[a]pyrene, a marker metabolite of deactivation, were measured daily in the urine and feces for 15 days. Levels of these metabolites were

correlated with tumor latency. Another group of- 10 rats was dosed intraperitoneally once with 15 mg/kg benzo[a]pyrene in sunflower oil and urine was collected for 3 days. Five rats were killed on day 3 and the other 5 were killed on day 8. Liver DNA concentrations of benzo[a]pyrene-7,8,9,10-tetrols were determined in animals killed on day 8. Considerable individual variation was observed in the levels of daily and total excretion of benzo[a]pyrene-7,8-diol and 3-hydroxy-benzo[a]pyrene in rats receiving 200 mg/kg benzo[a]pyrene. Both metabolites were excreted primarily in the feces. More than half of the total metabolites excreted were detected during the first five days, and peak concentrations were observed on the second day after benzo[a]pyrene administration. Peritoneal malignant fibrous histiocytomas developed in 10 of the 16 survivors at 15 days. Levels of urinary benzo[a]pyrene-7,8-diol correlated positively with tumor latency. In the animals exposed to 15 mg/kg benzo[a]pyrene, a high correlation was found between excretion of benzo[a]pyrene-7,8-diol and benzo[a]pyrene-DNA adducts in the liver.

[^{14}C]-Benzo[a]pyrene was administered to male germfree rats (Yang et al. 1994). Urine was collected 24 hours before and every 24 hours for 7 days after administration. Urinary metabolites, consisting of 9% of the administered radioactivity, were fractionated by lipophilic ion exchange chromatography, and characterized by reversed-phase HPLC, ultraviolet spectrometry, and gas chromatography/mass spectrometry. About 90% of the administered dose was excreted within 7 days; 80% in the feces and 9% in the urine. About 90% of the radioactivity in the urine was recovered in the methanol eluate. In this eluate, more than 80% of the urinary metabolites were conjugated, while neutral metabolites constituted 13-18%. The neutral metabolites consisted of 7,8,9,10-tetrols (trace), trans-11,12-dihydrodiol (major), trans-7,8-dihydrodiol (trace), three isomer trihydroxy-benzo[a]pyrenes (major), carboxylic methyl ester derivatives of benzo[a]pyrene quinones, and trioxo-benzo[a]pyrenes (major). Most of the urinary radioactivity was excreted within 72 hours of dosing, with a peak excretion of 24-48 hours. A similar time course was observed for excretion in feces (data not shown).

Six hours after intravenous administration of 0.08 mg/kg [^{14}C]-benzo[a]pyrene to rabbits, 30% and 12% of the dose was excreted in the bile and urine, respectively (Chipman et al. 1982). Excretion of activity into the bile was biphasic over a period of 30 hours with apparent half-lives of 0.27 and 4.623 hours for the rapid and slow phases, respectively. Treatment of the bile and urine with β-glucuronidase and aryl sulfatase increased the amount of activity in the bile and urine that was extractable into ethyl acetate indicating the presence of glucuronide and sulfate conjugates.

Intraduodenal administration of the bile resulted in 21% and 14% of the intraduodenal dose being excreted into the bile and urine, respectively. Since biliary metabolites undergo enterohepatic recirculation, the half-life for ^{14}C-activity is expected to be longer in animals without biliary fistulae (Chipman et al. 1982).

The overall elimination of [^{3}H]-benzo[a]pyrene following intravenous administration (0.001 mg/kg) best fits a triexponential model, as after inhalation exposure (Weyand and Bevan 1986). The half-lives for the three phases were 1.5, 22.4, and 178 minutes. These parameters were very similar to those derived from intratracheal instillation.

2.3.5 Mechanisms of Action

PAHs are absorbed through the lungs by transport across the mucus layer lining the bronchi (Bevan and Ulman 1991). In general, PAHs are lipophilic compounds that can cross the lungs through passive diffusion and partitioning into lipids and water of cells (Gerde et al. 1991, 1993a, 1993b). The rapid, blood-bound redistribution of hydrocarbons at low blood concentrations from lungs to other organs indicates that diffusion is the rate-determining step (Gerde et al. 1991). The absorption rates vary among the PAHs, probably depending on the octanol/water partition coefficient. Essentially all of gastrically instilled benzo[a]pyrene is absorbed via uptake of fat-soluble compounds (Busbee et al. 1990). Oral absorption of benzo[a]pyrene is enhanced by some oils (such as corn oil) in the gastrointestinal tract (Kawamura et al. 1988). The mechanism of dermal absorption of PAHs is most likely passive diffusion through the stratum comeum (Yang et al. 1986).

PAHs and their metabolites are distributed to tissues by transport through the blood. Therefore, PAHs reach more-perfused tissues rapidly following exposure and are eliminated more slowly from less-perfused tissues (Bartosek et al. 1984). A large fraction of orally absorbed benzo[a]pyrene is believedto be transported by lipoproteins from the gastrointestinal tract to the blood via the thoracic duct lymph flow (Busbee et al. 1990).

The carcinogenic mechanism of action of altemant PAHs is fairly well elucidated, but it is not as well described for nonaltemant PAHs. Furthermore, it is not known exactly how PAHs affect rapidly proliferating tissues. PAHs express their carcinogenic activity through biotransformation to chemically reactive intermediates that then covalently bind to cellular macromolecules (i.e., DNA) leading to

mutation and tumor initiation. The products of PAH metabolism include epoxide intermediates, dihydrodiols, phenols, quinones, and their various combinations. The bay region (e.g., the sterically hindered, cup-shaped area between carbons 10 and 11 of benzo[a]pyrene or 1 and 12 of benz[a]anthracene) diol epoxide intermediates of PAHs are considered to be the ultimate carcinogen for alternant PAHs (Jerina et al. 1980). These diol epoxides are easily converted into carbonium ions (carbocations) which are alkylating agents and thus mutagens and initiators of carcinogenesis. Therefore, the carcinogenic and toxic potential of PAHs relies on their metabolites. However, several of the tumorigenic PAHs (i.e., the nonaltemant PAHs) discussed in this profile do not have a bay region, or have been shown not to be similarly activated via a simple bay region epoxide (e.g., Amin et al. 1985a, 1985b). This observation has important implications regarding the expression of carcinogenicity for the nonalternant PAHs. If these chemicals are activated to carcinogens via a mechanism that differs from alternant PAHs, then they may also differ with respect to tumor site and species specificity.

A prerequisite for conversion of PAHs into these active bay region diol epoxides is the presence of cytochrome P-450 and associated enzymes.responsible for this conversion. These enzymes can be found primarily in the liver, but they are also present in the lung, intestinal mucosa, and other tissues. Thus, factors such as distribution to the target tissue(s), solubility, and intracellular localization proximate to these enzymes figure prominently in the expression of a PAH's carcinogenicity. In fact, in order to assess whether there was any correlation between carcinogenic potency and the ability to induce P-450 isoenzymes, several indices of P-450 isoenzyme activity (*O*-demethylation of ethoxyresorufin, metabolic activation of 2-amino-6-methyldipyrido [1,2-α:3',2'd]imadazol [Glu-P-I] to mutagens, and immunological detection of polyclonal antibodies against purified rat P-450 I) were measured in microsomal preparations incubated with benzo[a]pyrene and benzo[e]pyrene (Ayrton et al. 1990). While both PAHs increased several parameters of P-450-I activity, benzo[a]pyrene was markedly more potent than benzo[e]pyrene. Based on these results, the authors concluded that the carcinogenic potency of the PAHs tested could be predicted by the degree to which they induced these enzymes.

Changes in the cytochrome P-450 system can affect the carcinogenicity of the PAHs. This system is susceptible to induction by the PAHs themselves as well as other chemicals commonly found in the environment. The degree and specificity (i.e., which enzymes are affected) of induction depend on the tissue and species and strain. The induction of one enzyme particularly important to the metabolism

of PAHs, AHH, is also known to be under genetic control (see discussions in Section 2.2.2 on responsive versus nonresponsive mouse strains). Given the heterogeneity of human genotypes, it is likely that certain human subpopulations exist that are more susceptible to AHH induction and thus more susceptible to the induction of cancer (see Section 2.7).

Once the reactive bay region epoxide is formed, it may covalently bind to DNA and other cellular macromolecules and presumably initiate mutagenesis and carcinogenesis. Indeed, the level of DNA-adduct formation has been found to correlate with tumor induction activity for a number of PAHs in newborn rat liver and lung (Weyand and LaVoie 1988) and in mouse skin (Albert et al. 1991b; Alexandrov and Rojas-Moreno 1990). Furthermore, no benzo[a]pyrene-DNA-adducts were found in rat skin, which is known to be resistant to PAH-induced skin tumor formation (Alexandrov and Rojas-Moreno 1990). The types of adducts formed in various tissues may dictate target organ susceptibility to PAH-induced carcinogenicity. Various metabolites of benzo[a]pyrene were administered to rats intraperitoneally and DNA adducts from lung, liver, and lymphocytes were measured (Ross et al. 1991). The only metabolites that led to DNA binding were 2-, 9-, and 12-hydroxybenzo[a]pyrene and the truns-7,8-dihydrodiol of benzo[a]pyrene. The authors suggested that different DNA adducts resulting from the *in vivo* metabolism of benzo[a]pyrene in different tissues may be related to tissue specificity of benzo[a]pyrene-induced carcinogenicity.

Although the bulk of this work on PAH-induced carcinogenicity has been done in animal models and animal *in vitro* systems, work in human *in vitro* systems indicates that these same mechanisms of activation may be involved in humans. For example, induction of AHH and formation of the reactive intermediate, benzo[a]pyrene 7,8-dihydrodiol, has been observed in the epithelial tissue from human hair follicles (Merk et al. 1987). All the steps necessary for cellular transformation and cancer induction were demonstrated in cultured human skin fibroblasts: inducible AHH activity, altered cellular proliferation kinetics, and DNA damage (Milo et al. 1978). Thus, humans are likely to be susceptible to tumor induction by PAHs by these mechanisms.

Carcinogenic PAHs have been suggested to have an effect on immune function (Luster and Rosenthal 1993; Saboori and Newcombe 1992), thereby allowing the induction of carcinogenesis, while noncarcinogenic PAHs do not affect immune function (see Section 2.4). The effects of dermally applied benzo[a]pyrene alone or following dermal pretreatment with the prostaglandin synthetase inhibitor, indomethacin, on contact hypersensitivity (cell-mediated immunity), production of antibodies

to DNP (humoral immunity), and the induction of skin tumors was studied in male BALBc mice treated for 6 weeks to 6 months (Andrews et al. 1991b). A group of mice treated with acetone served as controls. Skin tumors were observed in the mice treated with benzo[a]pyrene beginning at week 18 of treatment. Pretreatment with indomethacin significantly increased (by 21%) the latency of tumor induction by benzo[a]pyrene and significantly reduced (by 46%) the weight of benzo[a]pyrene-induced skin tumors. Based on these findings, the authors suggested that benzo[a]pyrene-induced skin carcinogenesis may be mediated by a mechanism that involves prostaglandin suppression of cellular immunity. Undoubtedly, several other factors yet to be determined are involved in the ultimate expression of PAH-induced toxicity and carcinogenicity.

2.4 RELEVANCE TO PUBLIC HEALTH

PAHs occur ubiquitously in the environment from both synthetic and natural sources. PAHs occur in the atmosphere most commonly in the products of incomplete combustion. These products include fossil fuels; cigarette smoke; industrial processes (such as coke production and refinement of crude oil); and exhaust emissions from gasoline engines, oil-fired heating, and burnt coals. PAHs are present in groundwater, surface water, drinking water, waste water, and sludge. They are found in foods, particularly charbroiled, broiled, or pickled food items, and refined fats and oils. Individuals living in the vicinity of hazardous waste sites where PAHs have been detected at levels above background may experience exposure to these chemicals via inhalation of contaminated air or ingestion of contaminated food, soil, or water.

Evidence exists to indicate that certain PAHs are carcinogenic in humans and animals. The evidence in humans comes primarily from occupational studies of workers who were exposed to mixtures containing PAHs as a result of their involvement in such processes as coke production, roofing, oil refining, or coal gasification (e.g., coal tar, coke oven emissions, soot, shale, and crude oil). Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lungs and skin following inhalation and dermal exposure, respectively. Some ingestion of PAHs is probably due to swallowing of particulates containing PAHs subsequent to mucocilliary clearance from the lung. Certain PAHs have also been shown to induce cancer in animals. The site of tumor induction is influenced by route of administration: stomach tumors are observed following ingestion, lung tumors following inhalation, and skin tumors following dermal exposure, although tumors can form at other locations (e.g., lung tumors after dermal exposure).

Noncancer adverse health effects associated with PAH exposure have been observed in animals but generally not in humans (with the exception of adverse hematological and dermal effects). Animal studies demonstrate that PAHs tend to affect proliferating tissues such as bone marrow, lymphoid organs, gonads, and intestinal epithelium.

Minimal Risk Levels (MRLs) for Polycyclic Aromatic Hydrocarbons

Inhalation MRLS

No inhalation MRLs have been derived for PAHs because no adequate dose-response data that identify threshold levels for noncancer health effects are available in humans or animals for any duration of exposure.

Oral MRL.s

No acute, or chronic oral MRLs were derived for PAHs because there are no adequate human or animal dose-response data available that identify threshold levels for appropriate noncancer health effects. Serious reproductive and developmental effects in animals associated with acute oral exposure to PAHs have been reported. These are not appropriate end points for the derivation of an MRL. Noncancer effects noted in longer term oral toxicity studies in animals include increased liver weight (generally not considered to be adverse) and aplastic anemia (a serious effect), neither of which is an appropriate end point for the derivation of an MRL. Intermediate-duration oral MRLs were derived for acenaphthene, anthracene, fluoranthene, and fluorene.

Acenaphthene

- An MRL of 0.6 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to acenaphthene.

The MRL was based on a minimal LOAEL of 175 mg/kg/day for liver weight (EPA 1989c). Four groups of CD-l mice (20/sex/group) were gavaged daily with 0, 175, 350, or 700 mg/kg/day acenaphthene for 90 days. The toxicological evaluations of this study included body weight changes, food consumption, mortality, clinical pathological evaluations (including hematology and clinical

chemistry), organ weights and histopathological evaluations of target organs. The results of this study indicated no treatment-related effects on survival, clinical signs, body weight changes, total food intake, and ophthalmological alterations. Liver weight changes accompanied by microscopic alterations (cellular hypertrophy) were noted in both the mid- and high-dose groups, and seemed to be dose-dependent. Additionally, high-dose males and mid- and high-dose females showed significant increases in cholesterol levels. Increased relative liver weights in males, and increased absolute and relative liver weight in females, without accompanying microscopic alterations or increased cholesterol levels were also observed at the low dose; in light of the effects seen at higher doses, this change was considered to be a minimum LOAEL. There was no NOAEL. The MRL was obtained by dividing the LOAEL value by 300 (3 for a minimum LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and rounding to one significant figure.

MRLs for acute-duration and chronic-duration have not been derived because suitable NOAEL and LOAEL values have not been identified in the available literature.

Fluoranthene.

- An MRL of 0.4 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to fluoranthene.

The MRL was based on a minimal LOAEL of 125 mg/kg/day for increased relative liver weight in male mice (EPA 1988e). Four groups of CD-1 mice (20/sex/group) were gavaged daily with 0, 125, 250, or 500 mg/kg/day fluoranthene for 90 days. The toxicological evaluations of this study included body weight changes, food consumption, mortality, clinical pathological evaluations (including hematology and clinical chemistry), organ weights, and histopathological evaluations of target organs. The results of this study indicated no treatment-related effects on survival, clinical signs, body weight changes, total food intake, or ophthalmological alterations. All treated mice exhibited nephropathy, increased salivation, and increased liver enzyme levels in a dose-dependent manner. However, these effects were either not significant, not dose-related, or not considered adverse at 125 mg/kg/day. Mice exposed to 500 mg/kg/day had increased food consumption throughout the study. Mice exposed to 250 mg/kg/day had statistically increased SGPT values and increased liver weight. Compound-related microscopic liver lesions (indicated by pigmentation) were observed in 65 and 87% of the mid- and high-dose mice, respectively. Male mice exposed to 125 mg/kg/day had increased relative liver

weight. The LOAEL is 125 mg/kg/day, based on-relative liver weight in males. There was no NOAEL. The MRL was obtained by dividing the LOAEL value by 300 (3 for a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and rounding to one significant figure.

Fluorene.

- An MRL of 0.4 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to fluorene.

The MRL was based on a minimal LOAEL of 125 mg/kg/day for relative liver weight (EPA 1989e). Four groups of CD-l mice (20/sex/group) were gavaged daily with 0, 125, 250, or 500 mg/kg/day fluorene for 90 days. The toxicological evaluations of this study included body weight changes, food consumption, mortality, clinical pathological evaluations (including hematology and clinical chemistry), organ weights and histopathological evaluations of target organs. The results of this study indicated no treatment-related effects on survival, body weight changes, total food intake, or ophthalmological alterations. All treated male mice exhibited increased salivation, hypoactivity, and urine-wet abdomens. A significant decrease in red blood cell count and packed cell volume was observed in females treated with 250 mg/kg/day and in males and females at 500 me/kg/day. Decreased hemoglobin concentration was also observed in the high-dose group. A dose-related increase in relative liver weight was observed in all treated mice, and in absolute liver weight at >250 mg/kg/day. A significant increase in absolute and relative spleen and kidney weight was observed at 250 mg/kg/day.. Increases in absolute and relative liver and spleen weights at the high dose were accompanied by histopathological increases in hemosiderin in the spleen and in the Kupffer cells of the liver. The LOAEL is 125 mg/kg/day based on increased relative liver weight. There was no NOAEL. The MRL was obtained by dividing the LOAEL value by 300 (3 for a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and rounding to one significant figure.

Anthracene.

- An MRL of 10 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to anthracene.

The MRL was based on a NOAEL of 1,000 mg/kg/day for liver effects (EPA 1989d). The objective of this study was to evaluate the toxicity of anthracene in a subchronic toxicity study. Four groups of male and female CD-1 mice (20/sex/group) were placed on study, and were dosed with 0, 250, 500, and 1,000 mg/kg/day fluorene in corn oil by gavage for 13 weeks. The mice were observed twice daily for clinical signs. Body weights and food consumption were reported weekly. Hematologic and serum chemistry evaluations were completed at final sacrifice. At final sacrifice, gross post-mortem examinations were completed, organ weights were taken, and histological examinations were subsequently done on the tissues collected from all organ systems. No treatment-related finding were noted in survival, clinical signs, mean body weights, food consumption, and ophthalmological examinations, hematology, clinical chemistry, organ weights , gross pathology, and histopathology. In summary, anthracene produced no discemable effects. This study was conducted under the same laboratory conditions as the 90-day study of acenaphthene (EPA 1989c), and under similar laboratory conditions as the 90-day studies of fluoranthene (EPA 1988e) and fluorene (EPA 1989e), from which intermediate-duration MRLs were derived, based on liver effects. In these studies (EPA 1988e, 1989c, 1989e), many other treatment-related and dose-related effects were observed, including renal, hematological, and splenic, that lent support to the derivation of the MRL for each compound. Thus, although no toxic effects were noted even at the highest dose tested in the study cited for anthracene (EPA 1989d), this free-standing NOAEL has considerable credibility, based on the assumption that toxic effects would have been observed if present, as was seen for the other compounds using the same study design. The NOAEL is 1,000 mg/kg/day based on the absence of liver effects, and any other effects in the organ systems studied. The NOAEL was the highest dose used in the study. The MRL was obtained by dividing the NOAEL value by 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Dermal MRLs

No acute-, intermediate-, or chronic-duration MRLs were derived for the 17 PAHs because of the lack of appropriate methodology for the development of dermal MRLs.

Death. There have been no reports of death in humans following exposure to any of the PAHs. However, benzo[a]pyrene is fatal to mice following ingestion, and aeath in animals has been reported following parenteral exposure to a number of PAHs. The intraperitoneal LD_{50} values in mice for pyrene, anthracene, and benzo[a]pyrene are 514, >430, and 232 mg/kg, respectively (Salamone 1981).

Reduced survival time in “Ah-responsive” mice (those capable of producing increased levels of cytochrome P-450 enzymes) was observed following a single intraperitoneal dose of 500 mg/kg benzo[a]pyrene (Robinson et al. 1975). In contrast, oral exposure to 120 mg/kg/day benzo[a]pyrene results in reduced survival of “Ah-nonresponsive” mice (those whose P-450 enzymes are not induced by PAHs).

While the results in animal studies indicate that exposure to high doses of PAHs is lethal, the majority of the data are from parenteral exposure. This route is not applicable to exposure routes humans may expect to encounter, so the relevance of these findings to public health is not known. Parenteral administration bypasses the first-pass effect in the liver that occurs following oral exposure (PAHs may be expected to be ultimately biotransformed to inactive metabolites more quickly in the liver than in other tissues). However, because death has been observed in animals following oral exposure as well, it can be assumed that acute exposure to high enough doses of the PAHs can be lethal.

Systemic Effects.

Respiratory Effects. Adverse noncancer respiratory effects, including bloody vomit, breathing problems, chest pains, chest and throat irritation, and abnormalities in chest X-rays have been reported in humans exposed to PAHs and respirable particles in a rubber factory (Gupta et al. 1993). Inhalation is a significant route of exposure to PAHs in humans. *In vitro* studies using human lung tumor cells demonstrate that the benzo[a]pyrene-induced cytotoxicity (as measured by protein incorporation or cloning efficiency) observed was most likely due to formation of such reactive products as the 7,8-diol 9,10-epoxide metabolite of benzo[a]pyrene (Kiefer et al. 1988). Thus, human lung cells are capable of metabolizing PAHs to reactive intermediates. This implies that inhalation exposure to PAHs could result in toxicity in the respiratory tract.

Adverse effects on the respiratory tissue of laboratory animals have also been observed. The effects of benzo[e]pyrene, pyrene, anthracene, benz[a]anthracene, and benzo[a]pyrene on respiratory mucosa were studied in tracheal explants in rats (Topping et al. 1978). The PAHs were incorporated into beeswax pellets that were placed into tracheal grafts that had been transplanted subcutaneously into the subscapular region of isogenic host rats and the pellets remained in place for 4 weeks. Approximately 50-60% of the test substance was delivered to the tracheal tissue by the end of 4 weeks, in most instances. Benzo[e]pyrene induced only mild changes that included slight hyperplasia of the tracheal

epithelium. A more long-lasting epithelial hyperplasia was observed with pyrene, anthracene, and benz[a]anthracene, and tracheas implanted with pyrene also exhibited a more severe mucocilliary hyperplasia. In addition, undifferentiated epithelium and small areas of squamous metaplasia were also seen with these PAHs, effects that persisted at least 8 weeks after exposure. Severe and long-lasting hyperplasia and transitional hyperplasia as well as metaplasia were seen in tracheas exposed to benzo[a]pyrene, and after 8 weeks, 75% of the epithelium was still abnormal. Acute inflammation (edema and/or granulocyte infiltration), subacute inflammation (mononuclear infiltration and an increase in fibroblasts), and fibrosis and hyalinization in the second half of the experiment were seen with all PAHs. The authors concluded that all of the PAHs tested induced pathological changes in the respiratory mucosa of the transplanted tracheas. The effects were different for the noncarcinogenic PAHs (benzo[e]pyrene, pyrene, anthracene, benz[a]anthracene), as compared to the carcinogenic PAH (benzo[a]pyrene); the former induced changes that were short-lived while the latter produced more severe, long-lasting (metaplastic) changes.

Cultured fetal hamster tracheal explants were exposed to two concentrations each of benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[e]pyrene, and pyrene *in vitro* for 4 days, and the effects of these PAHs on the respiratory epithelium were evaluated by scanning electron microscopy (Richter-Reichhelm and Althoff 1986). Exposure to benzo[e]pyrene and pyrene, as well as the lower concentrations of benz[a]anthracene and benzo[b]fluoranthene, resulted in effects similar to those seen in the DMSO controls: up to a 10% incidence of focally slight inhibition of epithelial differentiation and/or metaplasia. When the concentrations of all of the PAHs except benzo[e]pyrene and pyrene were doubled, the frequency of these lesions increased to 50-l00%, and the incidence of dysplasia (including hyperplasia) 1 was also observed to occur in a dose-related manner in explants exposed to benz[a]anthracene, benzo[b]fluoranthene, and benzo[k]fluoranthene. These lesions were not seen in the cultures exposed to benzo[e]pyrene, pyrene, or DMSO. The authors note that these effects on respiratory epithelium seen *in vitro* are similar to the preneoplastic changes seen *in vivo* following exposure to PAHs, and thus, this system may serve as a good screen for assessing risk to the respiratory tract.

These observations, coupled with the fact that the respiratory system appears to be a target for PAH-induced cancer in humans, suggest that the respiratory system may be a target organ for PAH-induced noncancer adverse effects in humans as well.

Cardiovascular Effects. PAHs are contained in cigarette smoke, and smoking is a well-established risk factor in the development of atherosclerosis. Arterial smooth muscle cell proliferation, collagen synthesis, lipid accumulation, and cellular necrosis are all involved in the pathogenesis of the atherosclerotic plaque. *In vitro* studies conducted using bovine, rabbit, and human smooth muscle cells from arteries demonstrated that benzopyrene affects some of the aforementioned processes. Cell proliferation was not affected by benzo[a]pyrene, but a decrease in collagen secretion and an increase in cellular toxicity were noted in both the animal and human cell cultures (Stavenow and Pessah-Rasmussen 1988).

Male White Leghorn chickens (six/group) were given weekly intramuscular injections of benzo[a]pyrene, benzo[e]pyrene, anthracene, and dibenz[a,h]anthracene for 16 weeks prior to removal of the abdominal aorta to investigate the effects of benzo[a]pyrene on the development of arteriosclerotic plaques (Penn and Snyder 1988). Animals injected with DMSO (the vehicle) served as controls. Microscopic plaques were found in the aortas of all treated and control animals. However, the plaque volume index (PVI), which is a measure of both plaque cross-sectional area and plaque length, was nine times larger in the benzo[a]pyrene animals than the controls. Benzo[e]pyrene and dibenz[a,h]anthracene also caused an increase in plaque volume as compared to controls. However, the plaque sizes in the animals treated with anthracene were no different than controls. Therefore, the authors concluded that benzo[a]pyrene, benzo[e]pyrene, and dibenz[a,h]anthracene “promoted” the development of preexisting atherosclerotic plaques in male chickens as opposed to initiating the development of new plaques. The ability to promote plaque development was not correlated with the mutagenicity or carcinogenicity of the PAH tested. Similarly, administration of benzo[a]pyrene or benzo[e]pyrene into atherosclerosis-susceptible or atherosclerosis-resistant pigeons for 3-5 months of treatment indicated that benzo[a]pyrene, but not benzo[e]pyrene, enhanced the formation of arterial lesions in female, but not male, birds (Hough et al. 1993). Female pigeons were also infertile, and showed ovarian abnormalities.

These results, therefore, suggest that PAHs may contribute to the pathogenesis of atherosclerosis in humans. This is a particularly relevant health risk for those individuals who are exposed to high levels of PAHs in the environment and who also smoke cigarettes.

Gastrointestinal Effects. Anthracene has been associated with gastrointestinal toxicity in humans. Humans that consumed laxatives that contained anthracene (anthracene concentration not specified) for

prolonged periods were found to have an increased incidence (73.4%) of melanosis of the colon and rectum as compared to those who did not consume anthracene-containing laxatives (26.6%) (Badiali et al. 1985). The authors suggested that the melanosis observed may be attributed to the consumption of anthracene laxatives and not to intestinal stasis. This study is severely limited because of confounding factors such as the existence of other predisposing factors for melanosis and lack of follow-up.

Several PAHs discussed in this profile have been shown to alter enzyme activity in the intestinal mucosa of animals following oral administration, which could conceivably lead to increased production of reactive intermediates and tissue injury. Given the selectivity of PAHs for rapidly proliferating tissues such as gastrointestinal mucosa and the results discussed above, exposure to PAHs (particularly oral) by humans could lead to adverse gastrointestinal effects.

Hematological Effects. Adverse hematological effects have been observed in animals following exposure to PAHs. For example, administration of a single intraperitoneal dose of benzo[a]pyrene to mice resulted in a small spleen, marked cellular depletion, prominent hemosiderosis, and follicles with large lymphocytes. These pathological lesions were associated with death (Shubik and Porta 1957). Death due to adverse hematological effects (e.g., aplastic anemia and pancytopenia resulting in hemorrhage) has also been observed in mice following intermediate-duration oral exposure to benzo[a]pyrene (Robinson et al. 1975). Fluoranthene and fluorene administered by gavage to male and female mice for 13 weeks caused hematological effects including decreased packed cell volume and decreased hemoglobin content (EPA 1988e, 1989e). In addition, it has been shown that benzo[a]pyrene is toxic to cultured bone marrow cells when applied directly (Legraverend et al. 1983)

PAHs appear to affect other blood elements, as well. The influence of several PAHs on calcium ionophore-induced activation of isolated rabbit platelets was studied (Yamazaki et al. 1990). The activation of the platelets was assessed by measuring thromboxane B_2 synthesis in response to stimulation by the calcium ionophore, A-23 187. The authors reported that thromboxane B_2 synthesis was inhibited by incubation of the stimulated platelets with benz[a]anthracene, chrysene, benzo[a]pyrene, and benzo[g,h,i]perylene, and stimulated by incubation with anthracene and pyrene. However, no statistical analysis was performed on these data, and the changes reported are generally within ±10% of control values. In addition, the effects of the PAHs on thromboxane B_2 synthesis are bidirectional, and in many instances, the same compound induced both inhibition and stimulation at different concentrations.

As discussed above, PAHs tend to exert their adverse effects on rapidly proliferating tissues, such as the bone marrow blood forming elements. It is likely that PAH-induced toxicity in this tissue is due to a specific attack on DNA of cells in the S or synthetic phase of mitosis (EPA 1988a).

Although the human data available on PAH-induced hematological toxicity are flawed by confounding factors, they, together with the animal data and the propensity for PAHs to attack rapidly proliferating tissues, indicate that humans exposed to PAHs may be at risk for developing hematological toxicity.

Hepatic Effects. No adverse hepatic effects have been reported in humans following exposure to PAHs. However, hepatic effects have been observed in animals following acute oral, intraperitoneal, or subcutaneous administration of various PAHs. These effects include the induction of preneoplastic hepatocytes, known as y-glutamyl transpeptidase foci, induction of carboxylesterase and aldehyde dehydrogenase activity, an increase in liver weight, and stimulation of hepatic regeneration (an indication of a proliferative effect) (Danz et al. 1991; Gershbein 1975; Kemena et al. 1988; Robinson et al. 1975; Shubik and Porta 1957; Torronen et al. 1981; Tsuda and Farber 1980). These hepatic changes are not considered serious adverse effects, but their incidence and severity have been shown to correlate with the carcinogenic potency of particular PAHs. Thus, monitoring of liver function and tissue integrity may prove useful in the evaluation of PAH exposure.

More serious effects indicative of hepatic injury have been observed in animals. For example, an acute intraperitoneal injection of phenanthrene to rats resulted in liver congestion with a distinct lobular pattern, and an increase in serum aspartate aminotransferase, gamma-GT, and creatinine (Yoshikawa et al. 1987). Similarly, a single intraperitoneal injection of pyrene resulted in minimal swelling of the liver but no significant alterations in serum chemistry. Longer-term administration of PAHs has also been reported to result in adverse hepatic effects in animals. For example, increased absolute and relative liver weight correlated with hepatocellular hypertrophy was seen in male and female mice given 350 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). Increased liver weight and dose-related centrilobular pigmentation accompanied by an increase in liver enzymes was observed in both male and female mice receiving 250 mg/kg/day fluoranthene by gavage for 13 weeks (EPA 1988e).

Renal Effects. Adverse renal effects associated with PAHs have not been reported in humans. A single injection of anthracene or fluorene had no adverse effect on the kidneys of mice (Shubik and

Porta 1957). Dilated tubules were observed in the kidneys of mice administered pyrene in the diet for 25 days (Rigdon and Giannukos 1964); the toxicological significance of this effect is not known. Renal tubular regeneration, and interstitial lymphocytic infiltrates and/or fibrosis were observed after 13-week oral administration of fluoranthene to female mice at 250 mg/kg/day, and to male mice at 500 mg/kg/day (EPA 1988e). Given the lack of renal toxicity in humans and the limited value of the observations made in animals, the risk to humans for renal toxicity following exposure to PAHs is not known.

Endocrine Effects. There is suggestive evidence that PAHs may adversely affect endocrine function as well. The number of thymic glucocorticoid receptors in 6-week-old rats treated once with 2 mg/kg benzo[a]pyrene was measured (Csaba et al. 1991). It is assumed that the route of exposure was by oral gavage, but this was never explicitly stated. The number of these receptors was decreased by 40% in females and was unaffected in males relative to the vehicle control animals. The statistical significance of these effects was not indicated, nor was the adversity of a decrease in receptor number assessed by examination of functional parameters.

Dermal Effects. The skin is susceptible to PAH-induced toxicity in both humans and animals. Regressive verrucae were reported following intermediate-duration application of benzo[a]pyrene to human skin (Cottini and Mazzone 1939). Although reversible and apparently benign, these changes were thought to represent neoplastic proliferation. Benzo[a]pyrene application also apparently exacerbated skin lesions in patients with pre-existing skin conditions (pemphigus vulgaris and xeroderma pigmentosum) (Cottini and Mazzone 1939). Workers exposed to substances that contain PAHs (e.g., coal tar) experienced chronic dermatitis and hyperkeratosis (EPA 1988a). Coal tar preparations containing PAHs are used in the therapeutic treatment of some skin disorders. Adverse reactions have been noted in these patients, also.

Adverse dermatological effects have also been noted in animals in conjunction with acute and intermediate-duration dermal exposure to PAHs. These effects include destruction of sebaceous glands, skin ulcerations, hyperplasia, and hyperkeratosis (Bock and Mund 1958), and alterations in epidermal cell growth (Albert et al. 1991b; Elgjo 1968).

The observation that PAHs adversely affected the skin in both humans and animals is not surprising. The skin undergoes rapid cell turnover and is thus a likely target for PAH attack on DNA synthesis.

Given the information discussed above, the ubiquitous nature of PAHs in the environment, and the susceptibility of the skin to PAH-induced toxicity, adverse skin effects may occur in individuals exposed to these chemicals by the dermal route.

Immunological and Lymphoreticular Effects. Humoral immunity was depressed in male iron foundry workers exposed to benzo[a]pyrene (Szczeklik et al. 1994). IgG, and IgA were depressed in those workers exposed to high levels. There are reports in the literature concerning the immunotoxicity of PAHs following dermal and parenteral exposure in animals. The carcinogenic PAHs as a group have an immunosuppressive effect. There are limited data that suggest that the degree of immunosuppression correlates with the carcinogenic potency. For example, using spleen cell cultures from C3H/Anf mice, suppression of humoral immunity (as measured by the plaque-forming cell [PFC] response to sheep red blood cells) and cell-mediated immunity (as measured by the one-way mixed lymphocyte response) were observed following incubation with 10^{-5}-10^{-7} mol benzo[a]pyrene (Urso et al. 1986). There was no loss in cell viability at these concentrations. These immunological responses were unaffected by treatment with equivalent concentrations of benzo[e]pyrene. These findings led the authors to speculate that carcinogenic PAHs alter immune function, thereby allowing the induction of carcinogenesis while noncarcinogenic PAHs do not affect immune function. In addition, benzo[a]pyrene, but not benzo[e]pyrene, in the presence of S9 metabolic activation mix, has been shown to inhibit interferon induction by viruses by 60-70% in cultured LLC-MK_2 cells (Hahon and Booth 1986).

Benzo[a]pyrene has been shown to markedly inhibit the immune system, especially T-cell dependent antibody production by lymphocytes exposed either *in vivo* or *in vitro* (Blanton et al. 1986; Lyte and Bick 1985; White and Holsapple 1984). These effects are generally seen at high dose relative to those that can induce cancer in animals.

The effects of benzo[a]pyrene on several parameters of cell-mediated immune function in isolated and T-cell enriched mononuclear cell populations from three strains of mice (C57, C3H, and DBA) given a single intraperitoneal injection of 10-50 mg/kg benzo[a]pyrene or benzo[e]pyrene following stimulation with phytohemagglutinin (PHA) were studied (Wojdani and Alfred 1984). Neither benzo[a]pyrene nor benzo[e]pyrene had an inhibitory effect on lymphocyte blastogenesis induced by PHA; blastogenesis was slightly stimulated at 2.5 and 10 mg/kg of either PAH. Dose-related suppression of cell-mediated cytotoxicity of allosensitized lymphocytes was observed in all strains of

mice treated with benzo[a]pyrene, but no effect on this parameter was observed following treatment with benzo[e]pyrene. The percentage and adherence of macrophages from benzo[a]pyrene-treated mice were increased. The authors suggest that benzo[a]pyrene, but not benzo[e]pyrene, causes alterations in cell-mediated immune function that could compromise the animal's immune function allowing the development of PAH-induced tumors. A major limitation of this study was the lack of statistical analysis, thereby making it difficult to determine the validity of the changes seen. As mentioned previously, relatively high doses of benzo[a]pyrene were employed in these studies.

Benzo[a]pyrene-induced immune suppression was reported in male $B6C3F_1$ mice (Lyte and Bick 1985) and in the offspring of C3H/Anf mice treated intraperitoneally with benzo[a]pyrene (Urso and Gengozian 1980). Cell-mediated and humoral immune function of the liver, thymus, and spleen were evaluated in both maternal animals and the offspring of C3H mice administered one intraperitoneal dose of benzo[a]pyrene (150 mg/kg) during "mid-pregnancy" (Urso et al. 1992). The offspring were evaluated at 1 week and 18 months of age. Suppression of these various aspects of the immune system was observed in both the mothers and the offspring at these relatively high doses. However, the study lacked sufficient detail to adequately assess either the protocol or the results.

Groups of four $B6C3F_l$ female mice were administered single injections of 0, 50, or 200 mg/kg benzo[a]pyrene in corn oil to study the correlation between DNA adduct formation (as measured by ^{32}P-postlabelling analysis) and the suppression of polyclonal immune responses (^{3}H-TdR incorporation following stimulation by *Escherichia coli* lipopolysaccharide [LPS] and concanavalin A [Con A] and IgM secretion) and decreased cell viability in splenic lymphocytes harvested from the treated mice (Ginsberg et al. 1989). Spleen weight was significantly decreased (18%, $p<0.05$) at 50 mg/kg. The polyclonal response to LPS and Con A was suppressed by 30-45%, and this suppression was statistically significant at 200 mg/kg. IgM secretion was also significantly depressed (42%) at 200 mg/kg. These immunosuppressive effects were accompanied by high levels of benzo[a]pyrene/DNA adducts. The authors speculated that the immunosuppressive effects of benzo[a]pyrene were due to a cytotoxic mechanism (as supported by *in vitro* experiments) that in turn resulted partially from the genotoxic effects of benzo[a]pyrene (i.e., the formation of benzo[a]pyrene/DNA adducts).

Benzo[a]pyrene exerts its inhibitory effects on antibody production through alterations on the normal functioning of macrophages, T cells, and B cells (Blanton et al. 1988; Zhao et al. 1990). In contrast,

benzo[a]pyrene has no effect on most cellular immune responses before the appearance of tumors (Dean et al. 1983b), although benzo[a]pyrene exposure does inhibit IL-2-dependent proliferation (Myers et al. 1988).

Benzo[a]pyrene may also induce autoimmune responses. Groups of eight female Sprague-Dawley rats were administered a single subcutaneous injection of 2 mg benzo[a]pyrene or benzo[e]pyrene (11.1 mg/kg) in sesame oil in the right thigh (Faiderbe et al. 1992). The animals were observed for up to 150 days and blood samples were taken at regular intervals to measure anti-phosphatidylinositol (PtdIns) antibodies. Serum levels of anti-PtdIns in animals treated with benzo[a]pyrene exceeded those of the oil-injected controls after day 10, and the difference became statistically significant ($p<0.05$) after day 40. The levels reached a peak at day 60 after which time they reached a plateau. The anti-PtdIns were of the IgG type and specific to phosphatidylinositol. Malignant sarcomas developed at the injection site in the animals treated with benzo[a]pyrene within 100-120 days. Serum levels of anti-PtdIns in animals treated with benzo[e]pyrene did not differ from those of the oil-injected controls. No malignant sarcomas developed at the injection site in 100% of the animals administered benzo[e]pyrene within 100-120 days. The authors speculated that constant stimulation of lymphocytes reactive for PtdIns by an endogenous antigen, of which PtdIns could be a part, was responsible for the increased serum levels of anti-PtdIns. The authors suggested that PtdIns metabolism is altered in rapidly proliferating malignant cells (the neoplasia being stimulated by benzo[a]pyrene), resulting in the synthesis of the PtdIns-containing antigen. The lack of an autoimmune response to benzo[e]pyrene was due to the fact that benzo[e]pyrene was not carcinogenic; there was no neoplastic transformation occurring that could result in the production of PtdIns-containing antigens such as was seen with benzo[a]pyrene. Therefore, this study provides evidence that benzo[a]pyrene-induced neoplasia may cause an alteration in the metabolism of endogenous substances, resulting in the production of autoimmune antibodies to those substances.

The immunotoxic effects of benzo[a]pyrene have been noted *in vitro* as well (e.g., Ladies et al. 1991), and these studies provide some insight into the mechanism of action of benzo[a]pyrene-induced immunological effects. Splenic lymphocytes from $B6C3F_1$ mice were incubated with various concentrations of benzo[a]pyrene for either 2 hours or the entire culture period (Ginsberg et al. 1989). A dose- and duration-related decrease in splenic lymphocyte viability (as measured by ^{3}H-TdR incorporation) and immune response (as measured by IgM secretion) was observed in the absence of S9 activation. Addition of S9 enhanced this effect after acute-duration exposure. However, there was

very little formation of benzo[a]pyrene/DNA adducts at benzo[a]pyrene concentrations of l-200 μmol in the splenic lymphocytes; this lack of effect was accompanied by a very low level of benzo[a]pyrene metabolism to DNA-adducting metabolites. Benzo[a]pyrene/DNA adducts were measured in liver and lung; however, in the *in vivo* experiment. This led the authors to suggest that benzo[a]pyrene-induced immunotoxicity as expressed by splenic lymphocytes was the result of a cytotoxic effect that was mediated, in part, by a genotoxic mechanism involving the formation of benzo[a]pyrene/DNA adducts remote from the spleen and a direct cytotoxic effect not requiring activation of benzo[a]pyrene to the reactive intermediate.

Incubation of human lymphocytes with 0.1-01.0 μg/mL benzo[a]pyrene resulted in a suppression of lymphokine-activated killer cell (LAK) activity against tumor targets after 3 and 7 days (Lindemann and Park 1989). LAK DNA synthesis was also inhibited after 3 or 7 days of incubation with benzo[a]pyrene. However, benzo[a]pyrene had no effect on LAK binding with tumor targets, and benzo[a]pyrene did not interfere with the cytotoxic effect of natural killer cells added to the incubation medium. Based on these results, the authors concluded that benzo[a]pyrene interferes with the development of the immunological defense killer cells.

Benzo[a]pyrene has also been shown to affect immune responses to viral infection. Benzo[a]pyrene can reversibly inhibit the induction of viral interferon in 32 different mammalian cell lines but only in the presence of S9 metabolic activation (Hahon and Booth 1988). This inhibition must occur at an early level and not affect viral interferon interactions because the activity of exogenous interferon was unaffected. In addition, influenza virus multiplication was also inhibited by activated benzo[a]pyrene. Benzo[e]pyrene had no effect on interferon induction. The authors suggest that benzo[a]pyrene's inhibition of interferon induction may be an early step in compromising the host's immune function, thereby allowing the induction of carcinogenesis.

There is evidence to suggest that PAHs may alter the levels of brain neurotransmitters, which in turn affects the function of the immune system. The levels of two catecholamines, dopamine and norepinephrine, were determined in discrete brain areas in mice in which fibrosarcomas had been induced following a single subcutaneous injection of benzo[a]pyrene (Dasgupta and Lahiri 1992). Both dopamine and norepinephrine levels were significantly decreased in some brain regions (e.g., the corpus striatum and the hypothalamus), and these decreases were evident in both early and late tumor development. The authors state that since immunological function is compromised during

carcinogenesis and certain alterations in brain catecholamines impair immune function, the mechanism by which carcinogens such as benzo[a]pyrene cause immunosuppression and subsequent carcinogenesis may be via depression of brain catecholamines.

Very little information is available on the immunological effects of other PAHs. Mice treated with high doses of dibenz[a,h]anthracene exhibited a reduced serum antibody level in response to antigenic challenge by comparison to controls (Malmgren et al. 1952). The immunosuppressive effects of dibenz[a,h]anthracene were studied in AHH-inducible mice (C57BL/6) and AHH-noninducible mice (DBA/2N) by intraperitoneal and oral administration (Lubet et al. 1984). Immunosuppression occurred in both strains and was more pronounced in the C57BL/6 mice than in the DBA/2N mice, following intraperitoneal administration. However, the DBA/2N mice were more susceptible to immunosuppression following oral administration. These results suggest that PAHs are rapidly metabolized and excreted following oral administration in AHH-inducible mice, whereas in AHH-noninducible mice, the PAHs are absorbed and distributed to target organs. Based on these results, the authors concluded that AHH inducibility plays an important role in the immunosuppressive activity of PAHs.

B-cell lymphopoiesis in mouse bone marrow has been shown to be inhibited by incubation with fluoranthene *in vitro* at concentrations of ≥5 µg/mL (25 µmol). This effect on B-cell precursors may be mediated in part by a stimulation of programmed cell death; as demonstrated by the increase in DNA fragmentation induced by fluoranthene 15-17 hours after addition to the incubation medium. Furthermore, fluoranthene-induced DNA fragmentation always preceded fluoranthene-induced B-cell precursor death. Another mechanism for fluoranthene-induced inhibition of B-cell lymphopoiesis may be alterations in cell growth rates (fluoranthene was shown to slow the rate of B-cell precursor growth at concentrations <5 µg/mL) and/or altered cell survival (Hinoshita et al. 1992).

The lymphoid system, because of its rapidly proliferating tissues, is susceptible to PAH-induced toxicity. The mechanism of action for this effect is most likely inhibition of DNA synthesis. No adverse effects on this system associated with PAH exposure have been reported in humans, but several accounts of lymphoid toxicity in animals are available. A single intraperitoneal injection of benzo[a]pyrene to mice resulted in a small spleen with marked cellular depletion, prominent and edematous trabeculae, and large lymphocytes. These lesions resulted in death (Shubik and Porta 1957). The Shubik and Porta (1957) study was severely limited by the following: the benzo[a]pyrene

was only partly in solution, only one dose was employed, there was a small sample size, the purity of benzo[a]pyrene was not specified, only one sex was tested, and the presence of benzo[a]pyrene in the peritoneal cavity indicates inadequate absorption. No other similar studies were found in the literature.

Even though these effects have not been noted in humans, and the data in animals are contained in only one study, the rapidly proliferating nature of this tissue suggest that humans exposed to PAHs may be a risk for the development of adverse effects on the lymphoid system.

Given the high potential for exposure to PAHs in the vicinity of hazardous waste sites, the evidence from animal studies, and the heterogeneity of human genotypes with regard to enzyme induction capabilities, it would be prudent to consider that PAHs may pose an immunotoxic risk to humans living in areas surrounding hazardous waste sites.

Neurological Effects. No information is available on the short- or long-term neurotoxic effects of exposure to PAHs in humans and animals. Acute-, intermediate-, or chronic-duration studies conducted in animals do not indicate that any of the PAHs tested showed evidence of neurotoxicity, although these tests were not designed to detect subtle neurological changes.

However, there is evidence to suggest that PAHs may alter the levels of brain neurotransmitters. The levels of two catecholamines, dopamine and norepinephrine, were determined in discreet brain areas in mice in which fibrosarcomas had been induced following a single subcutaneous injection of benzo[a]pyrene (Dasgupta and Lahiri 1992). The mice were divided into two groups: early tumor development and late tumor development 3-4 months after administration of the benzo[a]pyrene. Both dopamine and norepinephrine levels were significantly decreased in some brain regions (e.g., the corpus striatum and the hypothalamus), and these decreases were evident in both early and late tumor development. The authors state that because immunological function is compromised during carcinogenesis and because certain alterations in brain catecholamines impair immune function, the mechanism by which carcinogens such as benzo[a]pyrene cause immunosuppression and subsequent carcinogenesis may be via depression of brain catecholamines.

Reproductive Effects. In both prospective and retrospective studies, a decrease in fecundity was observed in women who were exposed prenatally to cigarette smoke (i.e., their mothers smoked when pregnant) (Weinberg et al. 1989; Wilcox et al. 1989). This association was apparent even after

adjustment for age, frequency of intercourse, current smoking status, age at menarche, childhood exposure to cigarette smoking, educational level, reproductive history, body weight, and consumption of alcohol and caffeine. On the other hand, an increase in fecundity was observed in a retrospective study of women who were exposed to cigarette smoke in early childhood. These apparently opposite effects may be partially explained by the fact that when a woman smokes during pregnancy, her fetus is exposed to the components of the cigarette smoke that cross the placenta as well as changes in fetal and placental oxygenation and metabolism that are secondary to changes in maternal metabolism resulting from smoking. However, childhood exposure involves direct inhalation of cigarette smoke. The authors could offer no explanation as to why fecundity should be *increased* as a result of childhood exposure to cigarette smoke (Weinberg et al. 1989; Wilcox et al. 1989).

The testes and ovaries contain rapidly proliferating cells and therefore should be considered susceptible to damage by PAHs. The reproductive toxicity data in animals for the PAHs are limited. The available animal studies exclusively discuss the reproductive effects of benzo[a]pyrene. Adverse effects such as decreased fertility and total sterility in F_1 progeny of CD-1 mice (Mackenzie and Angevine 1981) and decreased incidence of pregnant female rats at parturition (Rigdon and Rennels 1964) were reported following oral exposure to benzo[a]pyrene. However, no adverse reproductive effects were observed in Swiss mice fed benzo[a]pyrene in their diet (Rigdon and Neal 1965). The metabolic differences and method of benzo[a]pyrene administration could account for the differential response to benzo[a]pyrene induced toxicity in these studies. A single intraperitoneal injection of benzo[a]pyrene to female C57BL/6N mice decreased the number of corpora lutea (Swartz and Mattison 1985). The, antiestrogenic effects causing decreased uterine weights in pseudopregnant Sprague-Dawley rats were reported following daily subcutaneous injections of benzo[a]pyrene during days 6-11 of pseudopregnancy (Bui et al. 1986). Similar treatment to pregnant rats during gestation caused resorptions, reduced percentage of viable litters, and decreased uterine weights (Bui et al. 1986; Cervello et al. 1992). Female mice exhibited decreased ovary weights after 13 weeks oral exposure to 700 mg/kg/day acenaphthene (EPA 1989c). The studies conducted on the reproductive effects of benzo[a]pyrene via parenteral routes are briefly discussed below.

Single intraperitoneal injection of benzo[a]pyrene to female C57BL/6N mice at doses as high as 500 mg/kg body weight produced a dose- and time-dependent decrease in the number of corpora lutea (Swartz and Mattison 1985). The NOAEL in this study was 1 mg/kg/day. Groups of 20 C57BL/6N mice were given single intraperitoneal injections of 0-500 mg/kg benzo[a]pyrene (Miller et al. 1992)

and were killed at various intervals after injection. Total ovarian volume, total corpora lutea volume, and total number of corpora lutea per ovary were significantly reduced by doses of benzo[a]pyrene >5 mg/kg in a dose-related manner. These effects resolved in a dose- and time-dependent fashion, so that after 4 weeks, most changes were only evident in the animals treated with the 100 or 500 mg/kg benzo[a]pyrene. Individual corpora lutea volume actually increased in the treated animals, indicating that compensatory hypertrophy was probably occurring. The authors concluded that based on these findings and previous findings, benzo[a]pyrene impairs corpora lutea formation by destroying follicles. In another study, DBA/2N (D2), C57BL/6N (B6), and (DBA/2N x C57BL/6N)F_1 (F_1) mice (7-8/group) were injected with 10 µg of either benzo[a]pyrene or one of three different metabolites of benzo[a]pyrene ([+]7,8-oxide, [-]7,8-dihydrodiol, or [+]-diol-epoxide-2) into the right ovary (Mattison et al. 1989). The left ovary served as a control, and an additional control group injected with the vehicle (DMSO) also served as controls. Ovarian volume, wet weight, and small, growing, and large follicle number were measured in both the treated and contralateral control ovaries. Benzo[a]pyrene and one or more of its'metabolites caused decreases in the treated ovarian weight, the ovarian volume, and the small, growing, and large follicles in one or more strains. In most instances, the contralateral untreated ovary exhibited a compensatory response; ovarian weight and volume increased as compared to the DMSO controls. This study shows that benzo[a]pyrene and some of its metabolites are toxic to the ovaries of mice, and that the ovary is capable of metabolizing benzo[a]pyrene into reactive metabolites. Similarly, administration of benzo[a]pyrene or benzo[e]pyrene into atherosclerosis-susceptible or atherosclerosis-resistant pigeons for 3-5 months of treatment indicated that benzo[a]pyrene, but not benzo[e]pyrene, rendered female pigeons infertile, with ovarian abnormalities (Hough et al. 1993). Cumulatively, these results demonstrate the sensitivity of integrated hypothalamic-pituitary-ovarian function to adverse effects of benzo[a]pyrene.

Daily subcutaneous injection of benzo[a]pyrene beginning on day 6 of gestation for 6 days as opposed to 3 days significantly increased the number of resorptions, and decreased the fetal survival and uterine weights in Sprague-Dawley rats (Bui et al. 1986). In pseudopregnant (i.e., condition occurring following sterile matings in which anatomical and physiological changes occur similar to those of pregnancy) rats, similar benzo[a]pyrene treatment during days 6-l1 of pseudopregnancy significantly decreased the cyclic nucleotide levels and uterine weights suggesting an antiestrogenic effect (Bui et al. 1986). Use of a single dosage level precluded the assessment of dose response in these studies.

Pregnant Sprague-Dawley rats were administered subcutaneous injections of benzo[a]pyrene (in DMSO and corn oil) or the vehicle alone on gestation days 7, 9, 11, 13, and 15 (Cervello et al. 1992). The animals were sacrificed on gestation day 16. There were no maternal deaths or signs of maternal toxicity. However, the number of fetuses per litter and number of live fetuses per litter were significantly decreased in the animals treated with benzo[a]pyrene, and the number of resorptions was significantly increased. In addition, uterine weight, and whole uterine gravid weight were significantly decreased and increased, respectively. These results demonstrate the reproductive toxicity of benzo[a]pyrene, but a dose-response relationship could not be established because only one dose was tested.

These results suggest that the potential for adverse reproductive effects may be increased in humans exposed to benzo[a]pyrene in the workplace or at hazardous waste sites.

Developmental Effects. The developmental toxicity data for PAHs are mostly limited to *in utero* exposure of pregnant animals to benzo[a]pyrene via various routes of exposure. The placental transfer of benzo[a]pyrene has been shown in mice following oral and intravenous exposure of dams (Shendrikova and Aleksandrov 1974) and in rats after intratracheal administration (Srivastava et al. 1986). The available data from oral studies in animals indicate that exposure of pregnant dams to benzo[a]pyrene produced resorptions and malformations in fetuses (Legraverend et al. 1984) and sterility in F_1 mouse progeny (Mackenzie and Angevine 1981). Investigations by Legraverend et al. (1984) suggest that benzo[a]pyrene metabolites generated in the fetus rather than in the maternal tissues are responsible for these adverse effects. Also, the genetic differences observed in this study using the oral route were contrary to those induced by intraperitoneal administration of benzo[a]pyrene (Hoshino et al. 1981; Shum et al. 1979), thus emphasizing the importance of route of administration in benzo[a]pyrene metabolism and resulting toxicity.

The developmental effects of benzo[a]pyrene have also been investigated in animals using the parenteral route of administration. Intraperitoneal injection of benzo[a]pyrene to pregnant mice produced stillbirths, resorptions and malformations at a greater incidence in Ah-responsive mice than in Ah-nonresponsive mice (Shum et al. 1979); testicular changes including atrophy of seminiferous tubules with lack of spermatids and spermatozoa; interstitial cell tumors (Payne 1958); immunosuppression (Urso and Gengozian 1980); and tumor induction (Bulay and Wattenberg 1971; Soyka 1980). Adverse effects observed following subcutaneous injection of benzo[a]pyrene include

increased fetal resorptio'ns in rats (Wolfe and Bryan 1939) and lung tumor induction in mice (Nikonova 1977). Decreased fetal survival (Wolfe and Bryan 1939) and lung tumor development (Rossi et al. 1983) were reported in Swiss mice following direct intra-embryonal injection of benzo[a]pyrene.

Results of *in vitro* studies suggest that benzo[a]pyrene may affect a number of enzyme and hormone activities in the human placenta. The effects of benzo[a]pyrene on the binding of epidermal growth factor (EGF) and receptor autophosphorylation were studied in human placental cell cultures from early and late gestation placentas (Guyda et al. 1990). In a subsequent study, the effects of benzo[a]pyrene on the uptake of aminoisobutyric acid (AIB) by early and late gestational human placental cells was also studied (Guyda 1991). Benzo[a]pyrene decreased binding of EGF (37-60%) to the early gestation placental cells, but not the late gestation placental cells. The decrease in binding was due to a decrease in the number of high-affinity EGF binding sites. This effect was specific for EGF receptor sites and not due to a nonspecific effect of benzo[a]pyrene on the membranes because benzo[a]pyrene had no effect on the binding of ^{125}I-labeled insulin and insulin-like growth factors. The authors concluded that the effects of benzo[a]pyrene on EGF binding were specific and related to gestational age. Benzo[a]pyrene stimulated AIB uptake by both early and late gestational cells and enhanced EGF-stimulated AIB uptake in spite of a decrease in the number of EGF receptors. The implications of these finding are that benzo[a]pyrene could alter EGF-induced secretion of human chorionic gonadotrophin and human placental lactogen secretion as well as metabolic functions, thereby affecting the regulation of cell growth and differentiation in human placentas.

The activity of quinone reductase, a major protective enzyme, was increased 2-3-fold in first trimester human placental extracts *in vitro* when incubated for 6 hours with benz[a]anthracene, dibenz[a,h]anthracene, and chrysene at a concentration of 50 µmol (Avigdor et al. 1992). Based on these results, it can be postulated that the early placenta is capable of metabolizing certain toxic xenobiotics such as PAH quinone metabolites to inactive intermediates thereby protecting the developing embryo.

Benzo[a]pyrene (50 µmol) has been shown to stimulate human gonadotropin release by first trimester human placental explants *in vitro* (Bamea and Shurtz-Swirski 1992). This stimulation was evident following static exposure for 24 hours and also in cultures that were superfused, meaning the benzo[a]pyrene had a delayed effect and did not need to be present for this effect to be expressed.

The implication of these findings is that benzo[a]pyrene can alter human placental endocrine function early in pregnancy.

Results of animal and *in vitro* studies suggest that benzo[a]pyrene may produce adverse effects in the offspring of women exposed during pregnancy. Furthermore, the results of genetic studies conducted via oral and intraperitoneal routes emphasize the importance of route of administration in benzo[a]pyrene metabolism and resulting toxicity and the severity of the effect may vary depending upon the genotype of the individual exposed (see Section 2.7, Populations That Are Unusually Susceptible). Based on these observations, it is therefore prudent to consider that the genetically heterogeneous human population may show variation in response to *in utero* exposure to benzo[a]pyrene.

Other PAHs such as anthracene, benzanthracene, chrysene, and dibenz[a,h]anthracene have also been tested for developmental effects via parenteral routes. Of these compounds, dibenz[a,h]anthracene produced fetolethal effects in rats (Wolfe and Bryan 1939), while chrysene produced liver tumors in the mouse progeny (Buening et al. 1979a; Grover et al. 1975)

Genotoxic Effects. As the results presented in Tables 2-4 and 2-5 indicate, benzo[a]pyrene has been thoroughly studied in genetic toxicology test systems. It induces genetic damage in prokaryotes, eukaryotes, and mammalian cells *in vitro* and produces a wide range of genotoxic effects (gene mutations in somatic cells, chromosome damage in germinal and somatic cells, DNA adduct formation, UDS, sister chromatid exchange, and neoplastic cell transformation). In cultured human cells, benzo[a]pyrene binds to DNA and causes gene mutations, chromosome aberrations, sister chromatid exchange, and UDS.

The results of *in vivo* studies indicate that many of the same types of adverse effects observed *in vitro* were seen in mice, rats, and hamsters exposed to benzo[a]pyrene via the oral, dermal, or intraperitoneal routes. The available data also indicate that benzo[a]pyrene is genotoxic in both somatic and germinal cells of intact animals (Table 2-4). The only study that was found regarding genotoxic effects in humans following exposure to benzo[a]pyrene reported no correlation between aluminum plant workers' exposure to PAHs, including benzo[a]pyrene, and sister chromatid exchange frequency (Becher et al. 1984). The findings from assays using human cells as the target, in

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo*

Species (test system)	End point		Results	Reference
	ANTHRACENE			
Mammalian systems:				
Chinese hamster/bone marrow	Chromosome aberrations	–		Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Sister chromatid exchange		–	Roszinsky-Kocher et al. 1979
Mouse/bone marrow	Micronuclei		–	Salamone et al. 1981
Mouse	Sperm abnormalities	–		Topham 1980
Host-mediated systems:				
Salmonella typhimurium/mouse host-mediated	Gene mutation		(+)[a]	Simmon et al. 1979
Saccharomyces cerevisiae/mouse host-mediated	Gene mutation	–		Simmon et al. 1979
Chinese hamster V79 cells/mouse host-mediated	Sister chromatid exchange	–		Sirianni and Huang 1978
	BENZ(*a*)ANTHRACENE			
Mammalian systems:				
Chinese hamster/bone marrow	Chromosome aberrations	–		Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Sister chromatid exchange		+	Roszinsky-Kocher et al. 1979
Insect systems:				
Drosophila melanogaster/sex-linked recessives	Gene mutation		–	Zijlstra and Vogel 1984
D. melanogaster/somatic mutation	Gene mutation	–		Fahmy and Fahmy 1980
Host-mediated systems:				
S. typhimurium/mouse host-mediated	Gene mutation		+	Simmon et al. 1979
S. cerevisiae/mouse host-mediated	Gene mutation	–		Simmon et al. 1979
	BENZO(*b*)FLUORANTHENE			
Mammalian systems:				
Chinese hamster/bone marrow	Chromosome aberrations	–		Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Sister chromatid exchange		–	Roszinsky-Kocher et al. 1979
Mouse skin	DNA binding		+	Weyand et al. 1987, 1992a

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Rat/lung, liver, peripheral blood lymphocytes	DNA binding	+	Ross et al. 1992
Rat peripheral blood lymphocytes	Sister chromatid exchange	+	Ross et al. 1992
New born mice/lung, liver	DNA binding	+	Weyand et al. 1993b
	BENZO(*j*)FLUORANTHENE		
Mammalian systems:			
Mouse skin	DNA binding	+	La Voie et al. 1991a; Weyand et al. 1987, 1993a
	BENZO(*k*)FLUORANTHENE		
Mammalian systems:			
Mouse skin	DNA binding	+	Weyand et al. 1987
	BENZO(*g,h,i*)PERYLENE		
Host-mediated systems:			
Hamster embryos/transplacental exposure	Transformation	–	Quarles et al. 1979
	BENZO(*a*)PYRENE		
Mammalian systems:			
Mouse/dominant lethals	Gene mutation	+	Epstein 1968; Generoso et al. 1982; Russell 1977
Mouse/spot test	Gene mutation	+	Davidson and Dawson 1976, 1977
Rat hepatocytes/unscheduled DNA synthesis	DNA damage	–	Miralis et al. 1982
Rat hepatocytes/unscheduled DNA synthesis	DNA damage	–	Mullaart et al. 1989
Mouse germ cells/unscheduled DNA synthesis	DNA damage	–	Sega 1979
Mouse skin/lung	DNA binding	+	Mukhtar et al. 1986
Mouse skin	DNA binding	+	Morse et al. 1985; Rice et al. 1984; Weyand and Bevan 1987a

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Mouse/bone marrow	DNA binding	+	Wielgosz et al. 1991
Mouse/spleen cells	DNA binding	+	Wielgosz et al.1991
Rat liver parenchymal cells	DNA single strand breaks	+	Mullaart et al. 1989
Rat liver nonparenchymal cells	DNA single strand breaks	–	Mullaart et al. 1989
Rat intestinal cells	DNA single strand breaks	+	Mullaart et al. 1989
Mouse/bone marrow	Chromosome aberrations	+	Adler and Ingwersen 1989
Mouse/bone marrow	Chromosome aberrations	+	Adler et al. 1989
Mouse/embryos	Chromosome aberrations	+	Adler et al. 1989
Chinese hamster/bone marrow	Chromosome aberrations	+	Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Chromosome aberrations	(+)	Bayer 1978
Mouse/heritable translocation	Chromosome aberrations	–	Generoso et al. 1982
Mouse/bone marrow	Chromosome aberrations	+	Wielgosz et al. 1991
Mouse/spleen cells	Chromosome aberrations	+	Wielgosz et al. 1991
Chinese hamster/bone marrow	Sister chromatid exchange	+	Bayer 1978; Roszinsky-Kocher et al. 1979
Mouse/bone marrow	Micronuclei	+	Salamone et al. 1981
Mouse/bone marrow	Micronuclei	–	Bruce and Heddle 1979
Mouse/fetal liver	Micronuclei	+	Harper et al. 1989
Mouse/bone marrow	Micronuclei	+	Harper et al. 1989
Mouse/bone marrow	Micronuclei	+	Awogi and Sato 1989
Mouse/keratinocytes	Micronuclei	+	He and Baker 1991
Mouse/bone marrow	Micronuclei	+	Shimada et al. 1990

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Mouse/peripheral blood reticulocytes	Micronuclei	+	Shimada et al. 1992
Rat/peripheral blood reticulocytes	Micronuclei	+	Shimada et al. 1992
Chinese hamster/bone marrow	Micronuclei	–	Bayer 1978
Mouse	Sperm abnormalities	+	Bruce and Heddle 1979; Topham 1980
Mouse	Sperm abnormalities	(+)	Salamone et al. 1988
Mouse	Sperm abnormalities	+	Salamone and Logan 1988
Mouse/bone marrow	Micronuclei	+	Balansky et al. 1994
Mouse/bone marrow	Micronuclei	+	Koratkar et al. 1993
Mouse papilloma cells	Gene mutation	+	Colapietro et al. 1993
Human lung	DNA damage	+	Weston et al. 1993a
Mouse papilloma cells	Gene mutation	+	DiGiovanni et al. 1993
Insect systems:			
D. melanogaster/sex-linked recessive	Gene mutation	(+)	Vogel et al. 1983
D. melanogaster/sex-linked recessive	Gene mutation	–	Valencia and Houtchens 1981; Zijlstra and Vogel 1984
D. melanogaster/somatic mutation	Gene mutation	+	Fahmy and Fahmy 1980
D. melanogaster	Chromosome aberration	(+)	Vogel et al. 1983
Host-mediated systems:			
S. typhimurium/mouse host-mediated	Gene mutation	–	Glatt et al. 1985; Simmon et al. 1979
S. cerevisiae/mouse host-mediated	Gene mutation	–	Simmon et al. 1979
Chinese hamster V79/mouse host-mediated	Sister chromatid exchange	+	Sirianni and Huang 1978
Hamster embryos/transplacental exposure	Transformation	+	Quarles et al. 1979

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo* (continued)

Species (test system)	End point	Results	Reference
	BENZO(*e*)PYRENE		
Mammalian systems:			
Chinese hamster/bone marrow	Sister chromatid exchange	(+)	Roszinsky-Kocher et al. 1979
	CHRYSENE		
Mammalian systems:			
Chinese hamster/bone marrow	Chromosome aberrations	–	Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Sister chromatid exchange	+	Roszinsky-Kocher et al. 1979
Host-mediated systems:			
S. typhimurium/mouse host-mediated	Gene mutation	–	Simmon et al. 1979
S. cerevisiae/mouse host-mediated	Gene mutation	–	Simmon et al. 1979
	DIBENZ(*a,h*)ANTHRACENE		
Mammalian systems:			
Chinese hamster/bone marrow	Chromosome aberrations	–	Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Sister chromatid exchange	+	Roszinsky-Kocher et al. 1979
	FLUORANTHENE		
Mammalian systems:			
Mouse/bone marrow	Sister chromatid exchange	–	Palitti et al. 1986
	INDENO(1,2,3-*c,d*)PYRENE		
Mammalian systems:			
Mouse skin	DNA binding	+	Weyand et al. 1987
	PHENANTHRENE		
Mammalian systems:			
Chinese hamster/bone marrow	Chromosome aberrations	–	Bayer 1978; Roszinsky-Kocher et al. 1979

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Chinese hamster/bone marrow	Sister chromatid exchange	(+)	Bayer 1978; Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Micronuclei	–	Bayer 1978
Host-mediated systems: *S. typhimurium*/mouse host-mediated	Gene mutation	–	Simmon et al. 1979
S. cerevisiae/mouse host-mediated	Gene mutation	–	Simmon et al. 1979
Hamster embryos/transplacental exposure	Transformation	–	Quarles et al. 1979
	PYRENE		
Mammalian systems: Mouse/bone marrow	Micronuclei	–	Salamone et al. 1981
Mouse	Sperm abnormalities	–	Salamone et al. 1988
Mouse	Sperm abnormalities	–	Salamone and Logan 1988
Insect systems: *D. melanogaster*/sex-linked recessive	Gene mutation	–	Valencia and Houtchens 1981
Host-mediated systems Chinese hamster V79/mouse host-mediated	Sister chromatid exchange	–	Sirianni and Huang 1978

[a]A positive result was obtained in one experiment; this result was not reproduced in the same laboratory or in a second laboratory.

DNA = deoxyribonucleic acid; – = negative result; + = positive result; (+) = weakly positive result

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
		ACENAPHTHENE		
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	No data	Pahlman and Pelkonen 1987
Escherichia coli SOS chromotest	Gene mutation	–	No data	Mersch-Sundermann et al. 1992b
		ACENAPHTHYLENE		
Prokaryotic organisms:				
S. typhimurium	Gene mutation	–	No data	Bos et al. 1988
		ANTHRACENE		
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Sakai et al. 1985
S. typhimurium	Gene mutation	+	No data	Carver et al. 1986
S. typhimurium	Gene mutation	–	–	LaVoie et al. 1983b; 1985; Rosenkranz and Poirier 1979; Simmon 1979a
S. typhimurium	Gene mutation	–	No data	Bos et al. 1988; LaVoie et al. 1979; Pahlman and Pelkonen 1987
Escherichia coli/Pol A	DNA damage	–	–	Rosenkranz and Poirier 1979
E. coli WP2-WP100/rec-assay	DNA damage	–	No data	Mamber et al. 1983
E. coli/differential killing	DNA damage	–	–	Tweats 1981
E. coli SOS chromotest	DNA damage	–	No data	Mersch-Sundermann et al. 1992b
E. coli SOS chromotest	DNA damage	–	–	Mersch-Sundermann et al. 1992a
Eukaryotic organisms:				
Fungi: *Saccharomyces cerevisiae D3*	Miotic recombination	–	–	Simmon 1979b
S. cerevisiae D4-RDII	Gene conversion	No data	–	Siebert et al. 1981

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Mammalian cells:				
Fischer rat embryo cells	Gene mutation	No data	–	Mishra et al. 1978
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	(+)	No data	Amacher and Turner 1980
Mouse lymphoma L5178/TK$^{+/-}$	Gene mutation	–	No data	Amacher et al. 1980
Human lymphoblasts TK6	Gene mutation	–	No data	Barfknecht et al. 1982
Human epithelial cells EUE	Gene mutation	No data	–	Rochhi et al. 1980
HeLa cells/unscheduled DNA synthesis	DNA damage	–	–	Martin et al. 1978
Human skin fibroblasts	DNA damage	No data	–	Milo et al. 1978
Rat liver cells RL1	Chromosome aberrations	No data	–	Dean 1981
Rat liver cells ARL18	Sister chromatid exchange	No data	–	Tong et al. 1981
Hamster BHK21 clone 13	Transformation	–	No data	Greb et al. 1980
Syrian hamster embryo cells	Transformation	No data	–	Dunkel et al. 1981
Mouse C3H/10T1/2 clone 8	Transformation	No data	–	Dunkel et al. 1981
Mouse Balb/3T3 cells	Transformation	No data	–	Lubet et al. 1983b; Peterson et al. 1981
Fischer rat embryo cells	Transformation	No data	–	Mishra et al. 1978
Fischer rat embryo cells/leukemia virus transformation	Transformation	No data	–	Dunkel et al. 1981
	BENZ[a]ANTHRACENE			
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Norpoth et al. 1984; Simmon 1979a

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
S. typhimurium	Gene mutation	+	No data	Bos et al. 1988; Carver et al. 1986; Coombs et al. 1976; Hermann 1981; Pahlman and Pelkonen 1987
S. typhimurium	Gene mutation	+[a]	No data	Phillipson and Ioannides 1989
S. typhimurium	Gene mutation	–[b]	No data	Phillipson and Ioannides 1989
S. typhimurium	Gene mutation	–	–	Rosenkranz and Poirier 1979
E. coli/Pol A	DNA damage	–	–	Rosenkranz and Poirier 1979
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann 1992a
Eukaryotic organisms: Fungi: *S. cerevisiae* D3	Mitotic recombination	–	–	Simon 1979b
Mammalian cells:				
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	+	No data	Amacher et al. 1980
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	+	–	Amacher and Turner 1980; Amacher and Paillet 1982
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	–	–	Amacher and Paillet 1983
Chinese hamster V79	Gene mutation	–	–	Huberman 1975
Chinese hamster V79	Gene mutation	–	No data	Huberman 1975
Human lymphoblasts TK6	Gene mutation	+	No data	Barfknecht et al. 1982
Human epithelial cells EUE	Gene mutation	No data	–	Rochhi et al. 1980
Human keratinocytes	Gene mutation	No data	–	Allen-Hoffmann and Rheinwald 1984
HeLa cells/unshceduled DNA synthesis	DNA damage	+	No data	Martin et al. 1978

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Rat liver cells ARL18	Sister chromatid exchange	No data	(+)	Tong et al. 1981
Hamster BHK21 clone 13	Transformation	+	No data	Greb et al. 1980
Hamster embryo cells	Transformation	No data	(+)	DiPaolo et al. 1969, 1971
Hamster embryo cells	Transformation	–	No data	Grover et al. 1971
Syrian hamster embryo cells	Transformation	No data	+	Dunkel et al. 1981
Syrian hamster lung cells FSHL	Transformation	No data	+	Emura et al. 1980
Mouse ventral prostate C3H clone G23	Transformation	No data	–	Grover et al. 1971; Marquardt et al. 1972
Mouse Balb/3T3 cells	Transformation	No data	(+)	Dunkel et al. 1981
Fischer rat embryo cells/leukemia virus transformation	Transformation	No data	+	Dunkel et al. 1981
	BENZO[b]FLUORANTHENE			
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	Amin et al. 1984; Hermann 1981; LaVoie et al. 1979
S. typhimurium	Gene mutation	–	No data	Mossanda et al. 1979
S. typhimurium/fluctuation test	Gene mutation	–	No data	Mossanda et al. 1979
E. coli PQ37 SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992b
Mammalian cells:				
Chinese hamster V79	Gene mutation	–	–	Huberman 1975
Hamster BHK21 clone 13	Transformation	+	No data	Greb et al. 1980
Syrian hamster lung cells FSHL	Transformation	No data	+	Emura et al. 1980

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
BENZO[j]FLUORANTHENE				
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	LaVoie et al. 1979
S. typhimurium/fluctuation test	DNA binding	+	No data	Marshall et al. 1992; Weyand et al. 1992
S. typhimurium/fluctuation test	Gene mutation	+	+	Marshall et al. 1993
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
BENZO[k]FLUORANTHENE				
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	Amin et al. 1985b; LaVoie et al. 1979; LaVoie et al. 1980; Weyand et al. 1988
Mammalian cells:				
Syrian hamster lung cells FSHL	Transformation	No data	–	Emura et al. 1980
BENZO[g,h,i]PERYLENE				
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Andrews et al. 1978; Sakai et al. 1985
S. typhimurium	Gene mutation	+	No data	Carver et al. 1986; LaVoie et al. 1979; Mossanda et al. 1979
S. typhimurium/fluctuation test	Gene mutation	(+)	No data	Mossanda et al. 1979
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
BENZO[a]PYRENE				

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Glatt et al. 1987; Grolier et al. 1989; Prasanna et al. 1987; Rosenkranz and Poirier 1979; Sakai et al. 1985; Simmon 1979a
S. typhimurium	Gene mutation	+	No data	Alfheim and Randahl 1984; Alzieu et al. 1987; Ampy et al. 1988; Andrews et al. 1989; Antignac et al. 1990; Bos et al. 1988; Bruce and Heddle 1979; Carver et al. 1986; Hermann 1981; LaVoie et al. 1979; Lee and Lin 1988; Marino 1987; Norpoth et al. 1984; Pahlman and Pelkonen 1987
S. typhimurium	Gene mutation	+	No data	Phillipson and Ioannides 1989a
S. typhimurium	Gene mutation	–	No data	Gao et al. 1991
S. typhimurium	Gene mutation	–	No data	Phillipson and Ioannides 1989b
S. typhimurium TM677	Gene mutation	+	–	Rastetter et al. 1982
S. typhimurium TM677	Gene mutation	+	No data	Babson et al. 1986
S. typhimurium	Gene mutation	+	No data	Balansky et al. 1994
E. coli WP2-WP100/rec-assay	DNA damage	+	No data	Mamber et al. 1983
E. coli/PoLA		+	–	Rosenkranz and Poirier 1979
E. coli/differential killing	DNA damage	+	–	Tweats 1981
E. coli/SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992b
Eukaryotic organisms:				
Fungi: *S. cerevisiae* D3	Mitotic recombination	–	–	Simmon 1979b
S. cerevisiae D4-RDII	Mitotic recombination	No data	–	Siebert et al. 1981

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Animal systems:				
Chinese hamster V79	Gene mutation	+	No data	Arce et al. 1987; Diamond et al. 1980; Huberman 1975
Chinese hamster V79	Gene mutation	+	–	Huberman 1975
Chinese hamster CHO	Gene mutation	+	(+)	Gupta and Singh 1982
Fischer rat embryo cells/OUA®	Gene mutation	No data	+	Mishra et al. 1978
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	+	–	Amacher and Paillet 1983; Clive et al. 1979
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	+	No data	Amacher et al. 1980; Amacher and Turner 1980; Arce et al. 1987
Mouse lymphoma L5178Y/HGPRT	Gene mutation	(+)	No data	Clive et al. 1979
Human lymphoblasts AHH	Gene mutation	No data	+	Crespi et al. 1985
Human lymphoblasts TK6	Gene mutation	(+)	No data	Crespi et al. 1985
Human lymphoblasts	Gene mutation	+	No data	Danheiser 1989
Human epithelial cells EUE	Gene mutation	No data	+	Barfknecht et al. 1982; Rocchi et al. 1980
Human fibroblasts HSC172	Gene mutation	+	–	Gupta and Goldstein 1981
Human keratinocytes	Gene mutation	No data	+	Allen-Hoffmann and Rheinwald 1984
Rat hepatocytes/DNA repair	DNA damage	No data	+	Williams et al. 1982
Rat tracheal epithelial cells	DNA damage	No data	+	Cosma and Marchock 1988; Cosma et al. 1988
Mouse C3H/10T1/2 clone 8	DNA damage	No data	(+)	Lubet et al. 1983b
HeLa cells/unscheduled DNA synthesis	DNA damage	+	NR	Martin et al. 1978
Human skin fibroblasts	DNA damage	No data	+	Milo et al. 1978
Human mammary cells	DNA damage	No data	+	Leadon et al. 1988

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Human fibroblasts/unscheduled DNA synthesis	DNA damage	+	No data	Agrelo and Amos 1981
Human fibroblasts WI-38/unscheduled DNA synthesis	DNA damage	+	–	Robinson and Mitchell 1981
Human lymphocyte	DNA damage	No data	+	Wienke et al. 1990
Calf thymus DNA	DNA binding	+	No data	Cavalieri et al. 1988a
Chick embryo fibroblasts	DNA binding	No data	+	Liotti et al. 1988
Chick embryo hepatocytes	DNA binding	No data	+	Liotti et al. 1988
Chinese hamster V79	DNA binding	No data	No data	Arce et al. 1987
Mouse lymphoma L5178Y/TK$^{+/-}$	DNA binding	+	No data	Arce et al. 1987
Mouse C3H/10T1/2	DNA binding	+	No data	Arce et al. 1987
Syrian hamster embryo SHE	DNA binding	No data	+	Arce et al. 1987
Rat bladder epithelial cells	DNA binding	No data	+	Moore et al. 1982
Rat mammary epithelial cells	DNA binding	No data	+	Moore et al. 1987
Human liver HepG2 cells	DNA binding	No data	+	Diamond et al. 1980
Human mammary cells	DNA binding	No data	+	Leadon et al. 1988; Moore et al. 1987
Human bladder cells	DNA binding	No data	+	Moore et al. 1982
Human endometrial cells	DNA binding	No data	+	Dorman et al. 1981
Human bronchus cells	DNA binding	No data	+	Harris et al. 1984
Human colon cells	DNA binding	No data	+	Harris et al. 1984
Human lymphocytes	DNA binding	No data	+	Pavanello and Levis 1992

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Chinese hamster V79-4	Chromosome aberrations	–	–	Popescu et al. 1977
Chinese hamster CHL	Chromosome aberrations	+	–	Matsuoka et al. 1979
Mouse lymphoma L5178Y/TK$^{+/-}$	Chromosome aberrations	+	No data	Arce et al. 1987
Rat liver cells RL1	Chromosome aberrations	No data	+	Dean 1981
Human fibroblasts WI-38	Chromosome aberrations	+	–	Weinstein et al. 1977
Chinese hamster V79	Sister chromatid exchange	+	No data	Arce et al. 1987; Mane et al. 1990
Chinese hamster V79	Sister chromatid exchange	+	–	Popescu et al. 1977; Wojciechowski et al. 1981
Chinese hamster bone marrow	Sister chromatid exchange	No data	+	Roszinsky-Kocher et al. 1979
Chinese hamster Don-6	Sister chromatid exchange	No data	+	Abe et al. 1983b
Chinese hamster CHO	Sister chromatid exchange	+	–	Husgafvel-Pursiainen et al. 1986
Rat pleural mesothelial cells	Sister chromatid exchange	No data	+	Achard et al. 1987
Rat liver cells ARL18	Sister chromatid exchange	No data	+	Tong et al. 1981
Rat hepatoma Reuber H4-II-E	Sister chromatid exchange	No data	+	Dean et al. 1983a
Rat esophageal tumor R1	Sister chromatid exchange	No data	+	Abe et al. 1983b
Rat ascites hepatoma AH66-B	Sister chromatid exchange	No data	+	Abe et al. 1983b
Human fibroblasts TIG-II	Sister chromatid exchange	+	(+)	Huh et al. 1982
Human hepatoma C-HC-4	Sister chromatid exchange	No data	+	Abe et al. 1983a, 1983b
Human hepatoma C-HC-20	Sister chromatid exchange	No data	+	Abe et al. 1983a, 1983b
Human lymphocyte	Sister chromatid exchange	+	–	Lo Jacono et al. 1992
Human lymphocyte	Sister chromatid exchange	No data	+	Wienke et al. 1990

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Golden hamster embryo cells	Transformation	+	No data	Mager et al. 1977
Hamster BHK21 clone 13	Transformation	+	–	Greb et al. 1980
Hamster embryo cells/SA7 virus transformation	Transformation	No data	+	Casto et al. 1977
Syrian hamster embryo cells	Transformation	No data	+	DiPaolo et al. 1969, 1971; Dunkel et al. 1981
Syrian hamster embryo cells/focus assay	Transformation	No data	+	Casto et al. 1977
Syrian hamster lung FSHL	Transformation	No data	+	Emura et al. 1980, 1987
Syrian hamster SHE/SA7 virus transformation	Transformation	No data	+	Arce et al. 1987
Mouse C3H/10T1/2	Transformation	No data	+	Arce et al. 1987; Lubet et al. 1983b; Peterson et al. 1981
Mouse Balb/3T3	Transformation	No data	+	Dunkel et al. 1981
Mouse Balb/3T3 clone A31-1-1	Transformation	No data	+	Little and Vetroys 1988
Fischer rat embryo cells	Transformation	No data	+	Mishra et al. 1978
Rat embryo cells/SA7 virus transformation	Transformation	No data	+	DiPaolo and Casto 1976
Fischer rat embryo cells/leukemia virus transformation	Transformation	No data	+	Dunkel et al. 1981
Human breast cancer cells	Gene expression	+	No data	Moore et al. 1994
Human breast epithelial cells	Transformation	No data	+	Calaf et al. 1993
Rat heptocyte	Sister chromatid exchange	+	No data	Kulka et al. 1993
Chinese hamster cells	Sister chromatid exchange	No data	+	Kulka et al. 1993

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Mouse Balb/c-3T3 cells	Transformation	No data	+	Matthews 1994
Hamster tracheal cells	DNA damage	No data	+	Roggeband et al. 1994
Rat tracheal cells	DNA damage	No data	+	Roggeband et all. 1994
	BENZO[e]PYRENE			
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	Andrews et al. 1978
S. typhimurium	Gene mutation	(+)	No data	Wood et al. 1979b
S. typhimurium	Gene mutation	+[c]	No data	Wood et al. 1979b
S. typhimurium	Gene mutation	+	No data	LaVoie et al. 1979b
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
E. coli SOS chromotest	DNA damage	(+)	–	Mersch-Sundermann et al. 1992a
Mammalian cells:				
Chinese hamster V79 ovary cells	Sister chromatid exchange	–	No data	Mane et al. 1990
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Sakai et al. 1985
S. typhimurium	Gene mutation	+	No data	Bos et al. 1988; Carver et al. 1986; Hermann 1981; LaVoie et al. 1979; Pahlman and Pelkonen 1987
S. typhimurium	Gene mutation	(+)	No data	Wood et al. 1977
S. typhimurium	Gene mutation	–	–	Rosenkranz and Poirier 1979; Simmon 1979a
E. coli/PolA	DNA damage	–	–	Rosenkranz and Poirier 1979
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Eukaryotic organisms:				
Fungi:				
S. cerevisiae D3	Mitotic recombination	–	–	Simmon 1979b
S. cerevisiae D4-RDII	Mitotic recombination	No data	–	Siebert et al. 1981
Mammalian cells:				
Chinese hamster V79	Gene mutation	–	No data	Huberman 1975
Human lymphoblasts TK6	Gene mutation	+	No data	Barfknecht et al. 1982
Human ephithelial cells EUE	Gene mutation	No data	–	Rocchi et al. 1980
Hamster BHK21 clone 13	Tranformation	+	No data	Greb et al. 1980
Mouse ventral prostrate C3H clone G23	Transformation	No data	–	Marquardt et al. 1972
	DIBENZ[a,h]ANTHRACENE			
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	Andrews et al. 1978; Carver et al. 1986; Hermann 1981; Lecoq et al. 1991b; Pahlman and Pelkonen 1987; Wood et al. 1978
S. typhimurium	Gene mutation	–[a,b]	No data	Phillipson and Ioannides 1989
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
Eukaryotic organisms:				
Fungi:				
Neurospora crassa	Gene mutation	No data	+	Barrat and Tatam 1958
S. cerevisiae D4-RDII	Mitotic recombination	No data	–	Siebert et al. 1981
Mammalian cells:				
Chinese hamster V79	Gene mutation	(+)	No data	Huberman 1975
Human epithelial cells EUE	Gene mutation	No data	(+)	Rocchi et al. 1980

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
HeLa cells/unscheduled DNA synthesis	DNA damage	+	NR	Martin et al. 1978
Human bronchus cells	DNA binding	No data	+	Harris et al. 1984
Hamster embryo cells	Transformation	–	No data	Grover et al. 1971
Hamster embryo cells/SA7 virus transformation	Transformation	No data	+	Casto 1973; Casto et al. 1977
Syrian hamster embryo cells	Transformation	No data	+	DiPaolo et al. 1969
Syrian hamster embryo cells/focus assay	Transformation	No data	+	Casto et al. 1977
Hamster BHK21 clone 13	Transformation	+	–	Greb et al. 1980
Mouse ventral prostate C3H clone G23	Transformation	No data	–	Marquardt et al. 1972
Mouse C3H/10T$^{1/2}$ clone 8	Transformation	No data	(+)	Lubet et al. 1983b
Rat embryo cells/SA7 virus transformation	Transformation	No data	+	DiPaolo and Casto 1976
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	Bos et al. 1988; Carver et al. 1986; Hermann 1981; LaVoie et al. 1979
S. typhimurium	Gene mutation	(+)	No data	Bos et al. 1987
S. typhimurium	Gene mutation	–	No data	Mossanda et al. 1979
S. typhimurium/fluctuation test	Gene mutation	+	No data	Mossanda et al. 1979
S. typhimurium/fluctuation test	Gene mutation	+	–	Bhatia et al. 1987
S. typhimurium/taped plate assay	Gene mutation	+	–	Bos et al. 1987
S. typhimurium TM 677	Gene mutation	+	–	Rastetter et al. 1982

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
S. typhimurium TM 677	Gene mutation	+	No data	Babson et al. 1986
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
Mammalian cells:				
Human lymphoblasts AHH1	Gene mutation	No data	–	Crespi et al. 1985
Human lymphoblasts TK6	Gene mutation	+	No data	Barfknecht et al. 1982
Chinese hamster CHO-1	Sister chromatid exchange	+	–	Palitti et al. 1986
Prokaryotic organisms:				
S. typhimurium	Gene mutation	–	–	Sakai et al. 1985
S. typhimurium	Gene mutation	–	No data	Bos et al. 1988; Hermann 1981; LaVoie et al. 1979; Pahlman and Pelkonen 1987
E. coli WP2-WP100/rec-assay	DNA damage	–	No data	Mamber et al. 1983
E. coli SOS chromotest	DNA damage	–	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	–	No data	Mersch-Sundermann et al. 1992b
Mammalian cells:				
Chinese hamster lung cell	Chromosome abberrations	+	–	Matsuoka et al. 1991
IDENO[1,2,3-c,d]PYRENE				
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Rice et al. 1985b
S. typhimurium	Gene mutation	+	No data	LaVoie et al. 1979
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Mammalian cells:				
Syrian hamster lung cells FSHL	Transformation	No data	+	Emura et al. 1980
		PHENANTHRENE		
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Sakai et al. 1985
S. typhimurium	Gene mutation	+	No data	Carver et al. 1986; Oesch et al. 1981
S. typhimurium	Gene mutation	(+)	No data	Bos et al. 1988
S. typhimurium	Gene mutation	–	–	LaVoie et al. 1981b; Rosenkranz and Poirier 1979; Simmon 1979a
S. typhimurium	Gene mutation	–	No data	Hermann 1981; LaVoie et al. 1979; Pahlman and Pelkonen 1987
E. coli/PolA	DNA damage	–	–	Rosenkranz and Poirier 1979
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
Eukaryotic organisms:				
Fungi: *S. cerevisiae* D3	Mitotic recombination	–	–	Simmon 1979b
S. cerevisiae D4-RDII	Mitotic recombination	No data	–	Siebert et al. 1981
Mammalian cells:				
Fischer rat embryo cells	Gene mutation	No data	–	Mishra et al. 1978
Chinese hamster V79	Gene mutation	–	No data	Huberman 1975
Human lymphoblasts TK6	Gene mutation	(+)	No data	Barfknecht et al. 1982
Human skin fibroblasts	DNA damage	No data	–	Milo et al. 1978
Chinese hamster V79-4	Chromosome aberrations	–	–	Popescu et al. 1977

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Chinese hamster Don	Chromosome aberrations	No data	–	Abe and Sasaki 1977
Chinese hamster CHL	Chromosome aberrations	No data	–	Ishidate and Odashima 1977
Chinese hamster CHL	Chromosome aberrations	–	–	Matsuoka et al. 1979
Chinese hamster V79-4	Sister chromatid exchange	–	–	Popescu et al. 1977
Chinese hamster Don	Sister chromatid exchange	No data	–	Abe and Sasaki 1977
Syrian hamster embryo cells	Transformation	No data	–	DiPaolo et al. 1969; Dunkel et al. 1981
Hamster BHK21 clone 13	Transformation	–	No data	Greb et al. 1980
Hamster embryo cells/SA7 virus transformation	Transformation	No data	–	Casto et al. 1977
Mouse ventral prostate C3H clone G23	Transformation	No data	–	Marquardt et al. 1972
Mouse C3H/10T$^{1/2}$	Transformation	No data	–	Lubet et al. 1983b; Peterson et al. 1981
Mouse Balb/3T3 cells	Transformation	No data	–	Dunkel et al. 1981
Fischer rat embryo cells	Transformation	No data	–	Mishra et al. 1978
Fischer rat embryo cells/leukemia virus transformation	Transformation	No data	–	Dunkel et al. 1981
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Sakai et al. 1985
S. typhimurium	Gene mutation	+	No data	Bos et al. 1988
S. typhimurium	Gene mutation	–	No data	Carver et al. 1986; Hermann 1981; LaVoie et al. 1979
S. typhimurium/fluctuation test	Gene mutation	+	+	Bhatia et al. 1987
S. typhimurium/taped plate	Gene mutation	+	No data	Bos et al. 1988
E. coli WP2-WP100/rec-assay	DNA damage	–	No data	Mamber et al. 1983

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
E. coli/differential killing	DNA damage	–	–	Tweats 1981
E. coli/SOS chromotest	DNA damage	–	–	Mersch-Sundermann et al. 1992a
E. coli/SOS chromotest	DNA damage	–	No data	Mersch-Sundermann et al. 1992b
Mammalian cells:				
Fisher rat embryo cells	Gene mutation	No data	+	Mishra et al. 1978
Chinese hamster V79	Gene mutation	–	–	Huberman 1975
Chinese hamster V79	Gene mutation	–	No data	Huberman 1975
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	–	No data	Amacher et al. 1980
Human lymphoblasts TK6	Gene mutation	–	No data	Barfknecht et al. 1982
HeLa cells/unscheduled DNA synthesis	DNA damage	–	–	Martin et al. 1978
Rat hepatocytes/DNA repair	DNA damage	No data	–	Williams et al. 1982
Human skin fibroblasts	DNA damage	No data	–	Milo et al. 1978
Human skin fibroblasts	DNA damage	–	No data	Agrelo and Amos 1981
Human fibroblasts WI-38 unscheduled DNA synthesis	DNA damage	+	–	Robinson and Mitchell 1981
Chinese hamster V79-4	Chromosome aberrations	+	–	Popescu et al. 1977
Human fibroblasts WI-38	Chromosome aberrations	–	–	Weinstein et al. 1977
Rat liver cells RL1	Chromosome aberrations	No data	–	Dean 1981
Chinese hamster V79-4	Sister chromatid exchange	–	–	Popescu et al. 1977
Rat liver cells ARL18	Sister chromatid exchange	No data	–	Tong et al. 1981
Syrian hamster embryo cells	Transformation	No data	–	DiPaolo et al. 1969
Fischer rat embryo cells	Transformation	No data	–	Mishra et al. 1978

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Hamster embryo cells/SA7 virus transformation	Transformation	No data	–	Casto et al. 1977
		Chrysene		
Prokaryotic organisms: *S. typhimurium*	Gene mutation	+	No data	Glatt et al. 1993
S. typhimurium	Gene mutation	+	No data	Cheung et al. 1993

[a]Noninduced hamster S9
[b]Noninduced mouse, rat, pig and human S9
[c]Synthetically prepared diol epoxide was strongly mutagenic

AHH = aromatic hydrocarbon hydroxylase; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; FSHL = female sex hormone lutenizing; NR = Not reported; PAHs = polycyclic hydrocarbons; SOS = DNA repair assay; – = negative result; + = positive result; (+) = weakly positive result

conjunction with the data from whole animal experiments, suggest that benzo[a]pyrene would probably have similar deleterious effects on human genetic material.

Because the genotoxic activity of benzo[a]pyrene is well established, it is frequently used as a positive control to demonstrate the sensitivity of various test systems to detect the genotoxic action of unknown compounds. It also serves as the model compound for PAHs, and the available information on the formation of metabolites and structure of benzo[a]pyrene can theoretically be used to predict potential genotoxicity/carcinogenicity of other PAHs that have not been as extensively studied.

Benzo[a]pyrene is generally considered to be biologically inert but can be metabolized by enzyme systems into at least 27 identified metabolites; however, only a few of these metabolites are reactive species that can damage DNA (De Bruin 1976). Benzo[a]pyrene 7,8-diol-9,10-epoxide is thought to be the ultimate mutagenic/carcinogenic metabolite. The primary metabolic pathway leading to the formation of the genotoxic/carcinogenic diol epoxides is assumed to be cytochrome P-450-dependent mixed-function oxidases (MFO), which in the case of PAHs are called AHHs. AHH is an ubiquitous enzyme system and has been found in a variety of tissues including liver, lung, and gastrointestinal tract of rats, mice, hamsters, and monkeys. AHH has also been detected in human liver, lung, placenta, lymphocytes, monocytes, and alveolar macrophages (Singer and Grunberger 1983). The evidence indicating that a variety of human tissues including human lymphocytes (GAO 1991; Wiencke et al. 1990), human lymphoblasts (Danheiser et al. 1989), and human mammary epithelial cells (Mane et al. 1990) can serve as a source of exogenous metabolic activation tends to support the role of AHH systems in initiating the conversion of benzo[a]pyrene to genotoxic forms. However, human erythrocytes, which do not contain an effective cytochrome P-450 system, were more efficient than induced rat liver fractions in converting benzo[a]pyrene to a genotoxin as indicated by higher sister chromatid exchange and micronuclei frequencies observed in human lymphocytes co-cultivated with human erythrocytes (Lo Jacono et al. 1992). The findings, while unconfirmed, suggest that enzymatic systems other than AHH may yield reactive intermediates. Similar evidence that uninduced lung, kidney, or spleen from Sprague-Dawley rats or BALB/c mice did not convert benzo[a]pyrene to a mutagen in *S. typhimurium* was reported by Ampy et al. (1988) who concluded that these tissues may, therefore, not be at risk from exposure. Superficially, the data from the studies conducted by Phillipson and Ioannides (1989) (indicating that neither benzo[a]pyrene nor benz[a]anthracene were mutagenic in *S. typhimurium* TA100 in the presence of noninduced hepatic fractions from rats, mice, pigs, or humans) would tend to support the data reported by Lo Jacono et al. (1992) and Ampy et al.

(1988) (suggesting either that other enzyme systems are involved in the bioactivation of these compounds or that certain tissues are not at risk). However, it is important to note, as pointed out by Phillipson and Ioannides (1989), that the level of P-450 isoenzyme proteins in unexposed animals is relatively low. Support for this statement was provided by the data demonstrating that uninduced hamster liver fractions, which contain high cytochrome P-448 levels, converted both benzo[a]pyrene and benz[a]anthracene to mutagens. By inference, it can reasonably be assumed that repeated exposures are required to induce the requisite enzyme systems to metabolize these promutagens to ultimate mutagenic/carcinogenic forms. It can further be assumed that the tissues of any species, including humans, that contain the appropriate inducible enzyme system are at risk.

The function of other enzyme systems in the biotransformation of benzo[a]pyrene should not be ruled out. However, the evidence that cytochrome P-448 plays a major role in this process was further substantiated by the observation that rat liver enzymes induced by PAHs such as 3-MC or dibenz[a,h]anthracene were more efficient in metabolizing benzo[a]pyrene, dibenz[a,h]anthracene, and benz[a]anthracene to mutagenic metabolites for *S. typhimurium* than was phenobarbital (Teranishi et al. 1975). This finding is consistent with the well-documented observation that various inducing agents such as phenobarbital and 3-MC cause the preferential synthesis of specific forms of cytochrome P-450. In the case of 3-MC, cytochrome P-448 is the principal form of induced cytochrome (Singer and Grunberger 1983).

Epoxidation is thought to be the major pathway for benzo[a]pyrene metabolism pertinent to macromolecular interaction. The metabolic attack consists of the cytochrome P-450/P-448-dependent MFO system converting the benzo[a]pyrene molecule into an epoxide; the epoxide is acted upon by epoxide hydrolase to form a dihydrodiol, and a second cytochrome MFO reaction gives rise to the ultimate mutagenic/carcinogenic form, benzo[a]pyrene 7,8-diol-9,10-epoxide. One of the unique structural features of the diol epoxide is that it appears to form in the area of the PAH molecule referred to as the bay region (i.e., a deep-pocketed area formed when a single benzo ring is joined to the remainder of the multiple ring system to form a phenanthrene nucleus). The location of the bay region(s) for the various PAHs in this profile is depicted in Chapter 3 (Table 3-l).

An additional feature of bay region diol epoxides is the ease of carbonium ion formation, which renders the PAH molecule highly reactive and susceptible to attack by nucleophiles (Jerina 1980; Singer and Grunberger 1983). The carbonium ion is more likely to form in structures where the

epoxide is part of the bay region of a saturated terminal angular ring than in an area where the diol epoxide is not associated with a bay region. Further enhancement of bay region epoxides can occur by the formation of an intramolecular hydrogen bond between the oxygen molecule of the epoxide and an associated hydroxyl group. These metabolites are also more resistant to enzymatic detoxification by epoxide hydrolase and glutathione transferase. The increased reactivity conferred by intramolecular hydrogen bonding and the decreased rate of further metabolism favor the interaction with DNA.

Analysis of the bay region diol epoxides and their contribution to the DNA binding, genotoxicity, and carcinogenicity of various PAHs has provided the basis for the bay region hypothesis (Wood et al. 1979a). For example, DNA adducts formed with non-bay region diol epoxides of benzo[a]pyrene have low mutagenic potential (MacLeod et al. 1994). The hypothesis further predicts that structures with more reactive bay regions would probably be more genotoxic and more carcinogenic. The body of evidence on the mutagenic and tumorigenic activity of the PAHs that form bay region diol epoxides (benzo[a]pyrene, benz[a]anthracene, chrysene, dibenz[a,h]anthracene; benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-c,d]pyrene) supports this hypothesis.

Based on these considerations, the available genetic toxicology results from studies conducted with the other PAHs in this profile are discussed relative to the bay region hypothesis. It is cautioned, however, that while the use of structural relationships to predict potentially reactive compounds is a powerful tool, it is not infallible, nor does it replace *in vitro* or *in vivo* testing. The formation of bay region epoxides is not an absolute requirement for carcinogenic activity because several PAHs that cannot form bay region epoxides are known to be carcinogens. It can, nevertheless, serve as a warning system to alert regulatory agencies to a potential health hazard and to enable investigators to establish priority lists for testing PAHs.

There is no convincing evidence that the PAHs lacking a bay region structure (acenaphthene, acenaphthylene, and fluorene) are genotoxic; the results for acenaphthene and acenaphthylene are consistently negative. The induction of chromosome aberrations only, at a single dose in Chinese hamster lung cells exposed to fluorene (Matsuoka et al. 1991), is not sufficient to conclude that fluorene is a clastogen. However, none of these compounds have been extensively studied in *in vitro* assays, and they have not been tested *in vivo.*

The majority of the data for anthracene and pyrene were negative. Although isolated positive results were obtained, particularly in microbial systems, neither compound produced consistent genotoxic effects in mammalian cells *in vitro*, and both were negative in the limited *in vivo* studies that have been performed.

The results obtained with fluoranthene, the remaining PAH without a bay region configuration, illustrate the need to apply the bay region hypothesis judiciously. There is ample evidence indicating that fluoranthene induced gene mutations in bacteria and human lymphoblasts and sister chromatid exchange in Chinese hamster ovary cells. Based on the evidence of a powerful response in the *Escherichia coli* PQ37 SOS DNA repair assay (SOS chromotest), Mersch-Sundermann et al. (1992a) predicted that fluoranthene has a relatively high probability of being genotoxic (80%). However, fluoranthene did not induce sister chromatid exchanges in mouse bone marrow cells (Palitti et al. 1986). The work of Busby et al. (1984) in newborn mice, suggests that fluoranthene should be classified as a carcinogen.

The occurrence of a bay region structure on the phenanthrene molecule suggests that this compound is genotoxic. However, the overall findings from the genetic toxicology studies do not support such a prediction. Similarly, the reported observation that the intraperitoneal injection of phenanthrene resulted in sister chromatid exchange induction in Chinese hamster bone marrow cells was not convincing (Bayer 1979; Roszinsky-Kocher et al. 1979). In both studies, the sister chromatid exchange increase over background was less than 1.5 fold and comparable doses did not cause chromosome aberrations. As stated earlier, the occurrence of a bay region on the molecule in conjunction with the reactivity of the bay region appear to be the determinants of genotoxic/carcinogenic activity. It is, therefore, probable that the bay region on phenanthrene is not very reactive, which would account for the lack of genotoxicity and for the low carcinogenicity index (<2) assigned to this compound (Arcos et al. 1968). Similarly, quantum mechanical calculations indicate a low probability of carbonation formation for the bay region diol epoxide of phenanthrene (Jerina 1980).

The lack of genotoxicity for phenanthrene is thought to be related to the metabolism of this substance to its 9,10-dihydrodiol. However, specific methylated phenanthrenes, which direct the metabolic fate of this tricyclic hydrocarbon towards the formation of a classical bay region dihydrodiol epoxide, have exhibited significant genotoxicity (LaVoie et al. 1983a). It was demonstrated that the presence of a

methyl group at or adjacent to the K-region of phenanthrene can inhibit the formation of the 9,10-dihydrodiol and produce powerful mutagens in *Salmonella.* Additionally, the presence of a halogen at the K-region site produced similar results, which further support the association between inhibition of 9,10-dihydrodiol formation and mutagenic potency of substituted phenanthrenes. The study authors concluded that derivatives of phenanthrene that can inhibit metabolism at this site have a greater probability of exerting genotoxic effects. Additionally, methylated derivatives of phenanthrene may act as tumor initiators, as shown on mouse skin (LaVoie et al. 1981b).

The weight of evidence from the *in vitro* and *in vivo* studies conducted with benz[a]anthracene, dibenz[a,h]anthracene, and chrysene indicates that these three agents are genotoxic and that they exert their genotoxic effects through the binding of bay region diol epoxides to cellular DNA. Similarly, there is a substantive body of evidence that confirms the hypothesis implicating the formation of bay region diol epoxides as the major mechanism of action for both the genotoxicity and carcinogenicity induced by these PAHs (Cheung et al. 1993; Fuchs et al. 1993a, 1993b; Glatt et al. 1993; Lecoq et al. 1989, 1991a; Wood 1979). It is also of note that these three compounds, as well as benzo[a]pyrene, induced neoplastic cell transformation in at least one cell line (see Table 2-5).

Both benzo[b]fluoranthene and indeno[1,2,3-c,d]pyrene are known to exhibit mutagenic activity in *S. typhimurium* TA100 in the presence of rat liver homogenate (Amin et al. 1984; Hermann 1981; LaVoie et al. 1979; Rice et al. 1985b). Both of these agents were positive for *in vitro* cell transformation (Emura et al. 1980; Greb et al. 1980) and were shown to bind to mouse skin DNA *in vivo* (Hughes et al. 1993; Weyand 1989; Weyand et al. 1987). In addition, benzo[b]fluoranthene formed DNA adducts in the lungs and livers of adult rats (Ross et al. 1992) and newborn mice (Weyand et al. 1993b) and formed DNA adducts as well as induced sister chromatid exchange in peripheral blood lymphocytes of treated rats (Ross et al. 1992). These data are consistent with reports on the tumorigenic activity of these PAHs in rodents and their potential to act as carcinogens in humans.

Studies on the mutagenic activity of benzofilfluoranthene and benzo[k]fluoranthene have also indicated that these nonalternant PAHs are mutagenic in *S. typhimurium* TAl00 (Amin et al. 1985b; LaVoie et al. 1979, 1980a; Weyand et al. 1988, 1992). There is also evidence that application of either of these PAHs to mouse skin results in DNA adduct formation (Hughes et al. 1993; LaVoie et al. 1991a, 1991b; Weyand et al. 1987, 1993a). The relative extent of binding to mouse skin DNA (i.e.,

benzo[j]fluoranthene > benzo[k]fluoranthene) parallels the relative tumorigenic potency of these hydrocarbons on mouse skin (i.e., benzo[j]fluoranthene is more potent than benzo[k]fluoranthene as a tumor initiator) (LaVoie et al. 1982).

Benzo[g,h,i]perylene has been reported to be mutagenic in *S. typhimurium* and to cause DNA damage in *E. coli.* Benzo[g,h,i]perylene has been shown to be responsible for the formation of DNA adducts isolated after topical application of pharmaceutical grade coal tar to the skin of mice (Hughes et al. 1993). However, the few studies that were found were insufficient to draw meaningful conclusions.

The final compound in this group, benzo[e]pyrene, contains two equivalent bay regions. *In vivo,* benzo[e]pyrene induced a marginal increase in sister chromatid exchanges but did not cause structural chromosome aberrations in bone marrow cells harvested from Chinese hamsters receiving two daily intraperitoneal doses of 450 mg/kg (Roszinsky-Kocher et al. 1979). Similarly, sister chromatid exchange frequencies were not increased in V-79 cells co-cultivated with rat mammary epithelial cells as the source of exogenous metabolic activation (Mane et al. 1990). Benzo[e]pyrene was, however, reported to be weakly mutagenic in *S. typhimurium* (Andrews et al. 1978) and weakly genotoxic in the *E. coli* SOS chromotest (Mersch-Sundermann et al. 1992a, 1992b).

The weak genotoxicity and the very weak carcinogenicity of benzo[e]pyrene appear to contradict the bay region diol epoxide hypothesis. Quantum mechanical analysis of the ringed structure strongly suggests the likelihood of carbonium ion formation and an associated chemical reactivity equivalent to the bay region diol epoxide of dibenz[a,h]anthracene (Wood et al. 1979a). Similarly, synthetically prepared bay region tetrahydro-epoxides of benzo[e]pyrene were found to be highly mutagenic in bacteria and mammalian cells, suggesting that bay region diol epoxide(s), if formed, would also be mutagenic. However, the parent compound was not metabolized to a reactive state by Aroclor 1254 S9 or by purified cytochrome P-450 derived from rat livers induced with Aroclor 1254. From these results, Wood et al. (1979a) concluded that the lack of mutagenicity for benzo[e]pyrene may be associated with the failure of the cytochrome P-450-dependent monooxygenase system to catalyze the critical oxidations necessary to form the bay region diol. Specifically, there was very little formation of the bay region 9,10-dihydrodiol and low conversion of authentic 9,10-dihydrodiol to the bay region diol epoxide. Subsequent studies with authentic bay region diol epoxides of benzo[e]pyrene showed that they had relatively low mutagenic and tumorigenic activity as a result of the diaxial conformation of the diol. The diaxial conformation of the 9,10-dihydrodiol also provides an explanation for the low

formation of the bay region diol epoxide since metabolism is shifted away from the adjacent isolated double bond (Chang et al. 1981; Wood et al. 1980). Since structural-activity analysis suggests that the bay region diol epoxides would have biological activity, Wood et al. (1979a) caution that extrapolation of these findings to *in vivo* metabolic events in species other than rats should be approached with caution. It is conceivable that benzo[e]pyrene would be genotoxic in species capable of carrying out the appropriate enzymatic steps.

In summary, several general conclusions can be reached for the unsubstituted PAHs evaluated in this profile. The formation of diol epoxides that covalently bind to DNA appears to be the primary mechanism of action for both genotoxicity and carcinogenicity of several of the unsubstituted PAHs that are genotoxins (benzo[a]pyrene, benz[a]anthracene, dibenz[a,h]anthracene, chrysene, benzo[b]fluoranthene, benzo[j]fluoranthene). There was insufficient evidence to draw meaningful conclusions regarding the genotoxic potential of benzo[g,h,i]perylene, although some evidence does exist.

With regard to the unsubstituted PAHs that either lack a bay region configuration (acenaphthene, acenaphthylene, anthracene, fluorene, and pyrene) or appear to have a weakly reactive bay region (phenanthrene), there is no compelling evidence to suggest that they interact with or damage DNA. The five PAHs that appear to be exceptions to the bay region diol epoxide hypothesis are fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, and indeno[1,2,3-cd]pyrene (no bay region), and benzo[e]pyrene (two bay regions). The evidence does suggest, however, that fluoranthene possesses genotoxic properties while benzo[e]pyrene is either weakly mutagenic or nonmutagenic.

Cancer. Evidence exists to indicate that mixtures of PAHs are carcinogenic in humans. The evidence in humans comes primarily from occupational studies of workers exposed to mixtures containing PAHs as a result of their involvement in such processes as coke production, roofing, oil refining, or coal gasification (e.g., coal tar, roofing tar, soot, coke oven emissions, soot, crude oil) (Hammond et al. 1976; Lloyd 1971; Maclure and MacMahon 1980; Mazumdar et al. 1975; Redmond et al. 1976; Wynder and Hoffmann 1967). PAHs, however, have not been clearly identified as the causative agent. Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lung and skin following inhalation and dermal exposure, respectively. Some ingestion of PAHs is likely because of swallowing of particles containing PAHs subsequent to mucocilliary clearance of these particulates from the lung.

Certain PAHs are carcinogenic to animals by the oral route (e.g., benz[a]anthracene, benzo[a]pyrene, and dibenz[a,h]anthracene) (Berenblum and Haran 1955; Chu and Malmgren 1965; Klein 1963; McCormick et al. 1981; Neal and Rigdon 1967; Rigdon and Neal 1966; Snell and Stewart 1963; Spamins et al. 1986; Wattenberg and Leong 1970). The results of dermal studies indicate that benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[l,2,3-c,d]pyrene are tumorigenic in mice following dermal exposure (Albert et al. 1991b; Cavalieri 1988b; Habs et al. 1984; Levin et al. 1984; Warshawsky and Barkley 1987; Wilson and Holland 1988; Wynder and Hoffmann 1959b). The sensitivity of mouse skin to PAH tumorigenesis forms the basis for the extensive studies performed using dermal administration. This tumorigenicity can be enhanced or modified with concomitant exposure to more than one PAH, long straight-chain hydrocarbons (i.e., dodecane), or similar organic compounds commonly found at hazardous waste sites. Thus, humans exposed to PAHs in combination with these substances could be at risk for developing skin cancer.

For many of the carcinogenic PAHs discussed in this profile, it appears that the site of tumor induction is influenced by the route of administration and site of absorption, i.e., forestomach tumors are observed following ingestion, lung tumors following inhalation, and skin tumors following dermal exposure. However, the observations (discussed below) that (1) mammary tumors are induced following intravenous injection in Sprague-Dawley rats, (2) the susceptibility to tumor development on the skin after dermal application is not similar in rats and mice, and (3) oral cavity tumors are not observed when benzo[a]pyrene is administered in the diet, suggest that the point of first contact may not always be the site of PAH-induced tumors. The results of carcinogenicity studies conducted with the 17 PAHs discussed in this profile by parenteral routes of exposure are summarized in Table 2-6.

TABLE 2-6. Summary of Carcinogenicity Studies with Polycyclic Aromatic Hydrocarbons Using Parenteral Routes of Exposure

Chemical	Species	Route	Duration	Result/Site	Reference
Anthracene	Rat	Lung implantation	1 dose, 55-week observation	–	Stanton et al. 1972
	Newborn mouse	Subcutaneous	Single dose	–/lung	Platt et al. 1990
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
Benz[a]anthracene	Mouse	Subcutaneous	10 weeks	+/injection site	Boyland and Sims 1967
		Intramuscular	No data	+/fibrosarcomas, hemangioendotheliomas	Klein 1952
	Newborn mouse	Intraperitoneal	3 days	+/lung	Levin et al. 1984
	Hamster	Intratracheal	30 weeks	–	Sellakumar and Shubik 1974
Benzo[a]pyrene	Mouse	Subcutaneous	Single dose	+/injection site sarcomas	Pfeiffer 1977
	Newborn mouse	Intraperitoneal	Single dose	+/liver	LeVoie et al. 1987
	Newborn mouse	Intraperitoneal	No data	+/lung	Busby et al. 1984
	Rat	Intramammary	Single dose	+/mammary gland	Cavalieri et al. 1988b, 1988c
	Mouse	Intravaginal	5 months	+/cervix	Naslund et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
	Hamster	Intratracheal	Chronic	–	Kunstler 1983
	Rat	Tracheal implant	Intermediate	+/tracheal	Nettesheim et al. 1977
	Rat	Intrapulmonary	Single dose	+/lung	Iwagawa et al. 1989
	Newborn mouse	Subcutaneous	15 days	+/lung	Busby et al. 1989
	Rat	Intramammary	Single dose	+/mammary gland	Cavalieri et al. 1991
	Mouse	*In utero*	2 days	+/lung	Turusov et al. 1990
	Rat	Tracheal explant	Single dose	+/lung	Topping et al. 1981
	Rat	Intrapulmonary	Single dose	+/lung	Wenzel-Hartung et al. 1990
	Mouse	Intraperitoneal	Single dose	+/lung	Mass et all. 1993
	Hamster	Silastic implant	170 d	+/lung	Hammond and Benfield 1993
	Hamster	Intratracheal	1 time, for 6 weeks	+/lung	Kimizuka et al. 1993
Benzo[b]fluoranthene	Newborn mouse	Intraperitoneal	Single dose	+/liver	LaVoie et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
	Hamster	Intratracheal	30 weeks	–	Sellakumar and Shubik 1974
Benzo[e]pyrene	Rat	Tracheal explant	Single dose	–/trachea	Topping et al. 1981
	Rat	Intrapulmonary	Single dose	–/lung	Deutsch-Wenzel et al. 1983
Benzo[j]fluoranthene	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
Benzo[g,h,i]perylene	Mouse	Subcutaneous	Single dose	–	IARC 1983
	Rat	Intrapulmonary	Single dose	+	Deutsch-Wenzel et al. 1983
Benzo[k]fluoranthene	Newborn mouse	Intraperitoneal	Single dose	–	LaVoie et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983

TABLE 2-6. Summary of Carcinogenicity Studies with Polycyclic Aromatic Hydrocarbons Using Parenteral Routes of Exposure (continued)

Chemical	Species	Route	Duration	Result/Site	Reference
Anthracene	Rat	Lung implantation	1 dose, 55-week observation	–	Stanton et al. 1972
Chrysene	Newborn mouse	Intraperitoneal	No data	–	Buening et al. 1979a
	Newborn mouse	Intraperitoneal	Single dose, 70-week, week observation	+/liver	Grover et al. 1975
	Mouse	Subcutaneous	10 weeks	+/injection site tumors	Boyland and Sims 1967
	Rat	Intrapulmonary	Single dose	+/lung	Wenzel-Hartung et al. 1990
Dibenz[a,h]anthracene	Newborn mouse	Intraperitoneal	No data	+/lung	Buening et al. 1979b
	Mouse	Subcutaneous	10 weeks	+/injection site tumors	Boyland and Sims 1967
	Hamster	Intratracheal	30 weeks	–	Sellakumar and Shubik 1974
	Newborn mouse	Subcutaneous	Single dose	+/lung	Platt et al. 1990
	Newborn mouse	Subcutaneous	Single dose	+/injection site sarcoma	O'Gara et al. 1965
	Rat	Intrapulmonary	Single dose	+/lung	Wenzel-Hartung et al. 1990
Fluoranthene	Mouse	Intraperitoneal	15 days	+/lung	Busby et al. 1984
	Mouse	Intraperitoneal	3 doses in 15 days, 9-month observation	+/lung	Wang and Busby 1993
Fluorene	Mouse	Subcutaneous	Single dose	–	Roe 1962; Shear and Luter 1941; Steiner 1955
Ideno[1,2,3-c,d]pyrene	Newborn mouse	Intraperitoneal	Single dose	–	LaVoie et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
Phenanthrene	Newborn mouse	Intraperitoneal	No data	–	Buening et al. 1979a
	Rat	Intrapulmonary	Single dose	–/lung	Wenzel-Hartung et al. 1990
Pyrene	Hamster	Intratracheal	30 weeks	–	Sellakumar and Shubik 1974
	Newborn mouse	Subcutaneous	Single dose	–/lung	Busby et al. 1989

+ = increased incidence of tumors; – = no increase in tumor incidence

EPA has performed weight-of-evidence evaluations of several of the PAHs discussed in this profile. The carcinogenicity classifications currently verified by EPA's Carcinogenicity Risk Assessment Verification Endeavor Work Group (EPA 1994) are listed below:

PAH	EPA Classification
Acenaphthylene	D (not classifiable as to human carcinogenicity)
Anthracene	D
Benz[a]anthracene	B2 (probable human carcinogen)
Benzo[b]fluoranthene	B2
Benzo[k]fluoranthene	B2
Benzo[g,h,i]perylene	D
Benzo[a]pyrene	B2
Chrysene	B2
Dibenz[a,h]anthracene	B2
Fluoranthene	D
Fluorene	D
Indeno[1,2,3-c,d]pyrene	B2
Phenanthrene	D
Pyrene	D

A quantitative cancer risk estimate (i.e., cancer potency factor) has thus far been developed for benzo[a]pyrene only (EPA 1992). This cancer potency factor (q_1^*) is 7.3 per (mg/kg)/day and is based on the geometric mean of risk estimates calculated from the Neal and Rigdon (1967) and Brune et al. (1981) studies.

EPA and others have developed a relative potency estimate approach for the PAHs (EPA 1993a; Nisbet and LaGoy 1992). By using this approach, the cancer potency of the other carcinogenic PAHs can be estimated based on their relative potency to benzo[a]pyrene. Following are the toxicity equivalence factors (based on carcinogenicity) calculated for PAHs discussed in this profile considered by the authors of one of these approaches to be of most concern at hazardous waste sites (Nisbet and LaGoy 1992):

Compound	Toxicity Equivalency Factor (TEF)
Dibenz[a,h]anthracene	5
Benzo[a]pyrene	1
Benz[a]anthracene	0.1
Benzo[b]fluoranthene	0.1
Benzo[k]fluoranthene	0.1
Indeno[1,2,3-c,d]pyrene	0.1
Anthracene	0.01
Benzo[g,h,i]perylene	0.01
Chrysene	0.01
Acenaphthene	0.001
Acenaphthylene	0.001
Fluoranthene	0.001
Fluorene	0.001
Phenanthrene	0.001
Pyrene	0.001

EPA (1993) has derived the following relative potency estimates based on mouse skin carcinogenesis:

Compound	Relative Potency[a]
Benzo[a]pyrene	1.0
Benz[a]anthracene	0.145
Benzo[b]fluoranthene	0.167
Benzo[k]fluoranthene	0.020
Chrysene	0.0044
Dibenz[a,h]anthracene	1.11
Indeno[1,2,3-c,d]pyrene	0.055[b]

[a]Model was $P(d)=1-\exp[-a(1+bd)^2]$ for all but indeno[1,2,3-c,d]pyrene

[b]Simple mean of relative potencies (0.021 and 0.089); the latter derived using the one-hit model

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to PAHs are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by PAHs are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism’s ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed

dose, a decrease in the biologically effective dose;or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Polycyclic Aromatic Hydrocarbons

PAHs and their metabolites can be measured in the urine of exposed individuals. In workers exposed to PAHs and dermatology patients treated with coal tar, the PAH metabolite 1-hydroxypyrene has been detected in the urine at concentrations of 0-40 µg/g creatinine or 290 ng/g creatinine, respectively (Jongeneelen et al. 1985). The amount of 1-hydroxypyrene detected in urine samples taken during the weekend was less than that detected during the weekdays, when the exposure was presumably higher than on the weekends. No correlation was found between occupational exposure levels and urine levels, so it is not known whether urinary metabolites could be detected following exposure to low levels of PAHs (as might be expected to occur in individuals living in the vicinity of hazardous waste sites). The presence of 1-hydroxypyrene in urine has also been demonstrated in workers exposed to PAHs in several different environments (creosote-impregnating plant, road workers laying asphalt, and workers exposed to diesel exhaust fumes) (Jongeneelen et al. 1988). In another study, the levels of urinary 1-hydroxypyrene significantly correlated with the environmental levels of pyrene and benzo[a]pyrene in coke plants, steel plants, and several Chinese cities where coal burning occurs (Zhao et al. 1990). The usefulness of monitoring urinary 1-hydroxypyrene concentration by liquid chromatography in occupationally exposed individuals as a biomarker for exposure to environmental PAHs was assessed. Postshift 1-hydroxypyrene urinary levels were significantly increased over preshift 1-hydroxypyrene levels in exposed workers as compared to nonexposed controls (the net mean change was 17-fold higher in the exposed workers as opposed to the nonexposed controls), and smoking status did not affect this result. In addition, in this work setting (an aluminum production plant), environmental levels of pyrene were strongly correlated with the environmental levels of total PAHs, indicating that pyrene is an appropriate environmental PAH marker in this situation. Thus, 1-Hydroxypyrene levels in urine may be used as a biomarker of exposure to PAHs in certain situations (Tolos et al. 1990). Additional studies have evaluated the usefulness of determining PAH or metabolite levels in human urine as a measure of exposure in industrial and environmental exposure settings (Granella and Clonfero 1993; Hansen et al. 1993; Herikstad et al. 1993; Kanoh et al. 1993; Likhachev et al. 1993; Ovrebo et al. 1994; Santella et al. 1993; Strickland et al. 1994; Van Hummelen et al. 1993; Van Rooij et al. 1993a, 1993b; Viau et al. 1993). Based on these results, the identification

of PAH metabolites in the urine could serve as a method of biological monitoring of exposed workers, and possibly individuals living in the vicinity of hazardous waste sites where PAHs have been detected although it would be very difficult to distinguish exposures resulting from hazardous waste sites form those resulting from normal human activities.

Autopsies performed on cancer-free patients found PAH levels of 1l-2,700 ppt in fat samples. Several PAHs were detected, including anthracene, pyrene, benzo[e]pyrene, benzo[k]fluoranthene, benzo[a]pyrene, and benzo[g,h,i]perylene, with pyrene being detected in the highest concentrations (Obana et al. 1981). A similar study done on livers from cancer-free patients found levels of 6-500 ppt of all of the same PAHs except benzo[e]pyrene, which was not detected in the liver. As in the fat samples studies, pyrene appeared in the highest concentrations in the liver, but the overall levels were less than in fat (Obana et al. 1981). However, because of the ubiquitous nature of PAHs in the environment, detection of PAH metabolites in the body tissues or fluids is not specific for exposure to PAHs from hazardous waste sites. In addition, it is impossible to determine from these biological media whether exposure was to high or low levels of PAHs or if the exposure duration was acute, intermediate, or chronic. Benzo[a]pyrene and 1-nitropyrene were determined in excised lung samples from Chinese and Japanese cancer patients (Tokiwa et al. 1993). Exposure to the two marker compounds was from burning coal (Chinese, benzo[a]pyrene) or oil (Japanese, 1-nitropyrene). Compound levels in the lung correlated with individual exposure history. Using a large sample population, total PAH levels in lung tissue has also been shown to correlate to cancer incidence (Seto et al. 1993).

PAHs form DNA adducts that can be measured in body tissues or blood in both humans and laboratory animals following exposure to PAHs or mixtures containing PAHs (e.g., Assennato et al. 1993; Bjelogrlic et al. 1994; Chou et al. 1993; Culp and Beland 1994; Day et al. 1990; Fuchs et al. 1993a, 1993b; Garg et al. 1993; Garner et al. 1988; Gallagher et al. 1993; Herberg et al. 1990; Hughes and Phillips 1990; Hughes et al. 1993; Jones et al. 1993; Khanduja and Majid 1993; Lee et al. 1993; Lewtas et al. 1993; Likhachev et al. 1993; Lu et al. 1993; Mass et al. 1993; Mumford et al. 1993; Newman et al. 1988, 1990; Nowak et al. 1992; Oueslati et al. 1992; Roggeband et al. 1994; Ross et al. 1990, 1991; Shamshuddin and Gan 1988; Van Schooten et al. 1991, 1992; Weston et al. 1988, 1993a; Weyand et al. 1993a, 1993b). PAHs also form adducts with other cellular macromolecules, such as hemoglobin, globin, and other large serum proteins (e.g., Bechtold et al. 1991; Sherson et al. 1990; Weston et al. 1988). Again, these PAH-DNA and PAH-protein adducts are not specific for any

particular source of PAHs, and the adducts measured could have been from exposure to other sources of PAHs, such as complex mixtures that contain PAHs (e.g., crude oils, various high-boiling point distillates, complex petroleum products, coal tars, creosote, and the products of coal liquification processes), as well as vehicle exhausts, wild fires, agricultural burning, tobacco smoke, smoke from home heating of wood, cereals, grains, flour, bread, vegetables, fruits, meat, processed or pickled foods, beverages, and grilled meats. It is impossible to determine from these adducts whether exposure was to high or low levels of PAHs or if the exposure duration was short or long.

In another study, an evaluation of mutations in peripheral lymphocytes was conducted in workers in or near an iron foundry; data were examined for correlations to benzo[a]pyrene exposure determined by personal monitors. Exposure levels for benzo[a]pyrene were 2-60 ng/m^3, which are the lowest levels yet analyzed in foundry workers. Mutations at the hypoxanthine guanine phosphoribosyl transferase (HPRT) and glycophorin A (GPA) loci, which are measures of molecular effects in lymphocytes and erythrocytes, respectively, were assessed to demonstrate their relationship to external exposure at these low levels. The rate of mutation was also compared to PAH-DNA adducts in the blood (Santella et al. 1993). Workers were classified into three exposure categories, low (<5), medium (5-12), and high (>12). HPRT mutant frequencies for these groups were 1.04, 1.13, and 1 .82x10^{-6} cells, respectively, and demonstrated an upward trend that was marginally significant. In contrast, HPRT mutations were highly correlated with PAH-DNA adducts (Santella et al. 1993). GPA variants were not correlated with PAH exposure. These results support the use of both biomonitoring and personal environmental monitoring in the determination of exposure.

Three methods were evaluated for their usefulness as biomarkers of exposure to benzo[a]pyrene in Wistar rats administered a single dose of l-200 mg/kg (Willems et al. 1991). These three methods were mutagenicity observed in urine and fecal extracts, chromosome aberrations and sister chromatid exchanges in peripheral blood lymphocytes, and DNA adduct formation in peripheral blood lymphocytes and liver. Mutagens were measured in urine and feces at levels of 10 and 1 mg/kg, respectively. DNA adduct formation (measured by ^{32}P-postlabelling) could be detected at doses of ≥10 mg in lymphocytes and ≥100 mg in liver, and the levels were twice as high in the lymphocytes as in the liver. Only a slight increase in sister chromatid exchanges and no enhanced frequency of chromosomal aberrations were seen. These results indicate that mutagenicity observed in excreta and DNA adducts in lymphocytes are both useful biomarkers of exposure in the rat, with mutagenic activity in feces being the more sensitive.

The ability of phenanthrene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, indeno[l,2,3-c,d]pyrene, and dibenz[a]anthracene to bind to mouse hemoglobin and serum proteins after tail vein injection was investigated (Singh and Weyand 1994). Urinary excretion of these compounds was also investigated. A direct correlation between urinary excretion and hydrocarbon molecular weight was observed. Binding to both globin and serum proteins was detectable, with binding to serum proteins 10-fold higher than to globin. These results provide an assessment of the potential usefulness of various PAHs as biomarkers of exposure to complex mixtures.

2.5.2 Biomarkers Used to Characterize Effects Caused by Polycyclic Aromatic Hydrocarbons

The available genotoxicity data indicate that several of the 17 PAHs discussed in this profile are genotoxic in both nonmammalian and mammalian systems and are indirect mutagens (i.e., requiring the presence of an exogenous mammalian metabolic system). There were no tests reported for humans exposed to benzo[a]pyrene (the most widely tested PAH) *in vivo*, but several types of cultured human tissue cells demonstrated positive results for benzo[a]pyrene-induced genotoxicity (as evidenced by the induction of chromosomal aberrations, sister chromatid exchange) and binding of benzo[a]pyrene to DNA. The measurement of DNA adduct formation as well as the induction of sister chromatid exchange in human lymphocytes has been proposed as a biomarker of benzo[a]pyrene-induced effects for human monitoring programs (Wiencke et al. 1990). It is probable, however, that the analysis of DNA adducts would be the more sensitive diagnostic tool since hundreds of benzo[a]pyrene-DNA adducts per nucleus would be required to yield a detectable increase in the sister chromatid exchange frequency for an exposed population. Although these results are exclusively from *in vitro* tests and the limited genotoxicity tests conducted on urine obtained from humans exposed to creosote (a complex mixture containing PAHs) have been negative, the genotoxic effects observed in human tissue cells, particularly DNA adduct formation, may serve as a biomarker of effects for at least one of the PAHs, benzo[a]pyrene. It would not be possible to identify the source.of the benzo[a]pyrene, however.

PAHs have been shown to cause noncancer adverse effects on rapidly proliferating tissues such as the hematopoietic system, the lymphoid system, and the skin in both humans and animals. The skin is susceptible to PAH-induced toxicity in both humans and animals. Regressive verrucae were reported following intermediate-duration application of benzo[a]pyrene to human skin (Cottini and Mazzone

1939). Although reversible and apparently benign, these changes were thought to represent neoplastic proliferation. Benzo[a]pyrene application also apparently exacerbated skin lesions in patients with pre-existing skin conditions (pemphigus vulgaris and xeroderma pigmentosum) (Cottini and Mazzone 1939). Workers exposed to substances that contain PAHs (e.g., coal tar) experienced chronic dermatitis and hyperkeratosis (EPA 1988a). However, none of these end points is specific to PAHs, and all can be seen with other agents. No other biomarkers of effect (specific or otherwise) have been identified following exposure to PAHs.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990). Additional information can be found in a series of reports on biomarkers issued by the National Research Council (NRC 1989, 1992).

2.6 INTERACTIONS WITH OTHER SUBSTANCES

Because humans are usually exposed to PAHs in complex mixtures rather than to individual PAHs, it is important to understand the potential interactions between the PAHs and other components of the mixture. Interactions may occur among chemicals in a mixture prior to exposure, or may occur after exposure as a result of differing effects of the mixture components on the body. Synergistic and/or antagonistic interactions with regard to the development of health effects, particularly carcinogenesis, may occur.

The extent of human exposures to PAH mixtures in occupational settings is generally not known in quantitative terms. However, exposures to complex chemical mixtures that include PAHs, such as use of tobacco products and exposure to roofing tar emissions, coke oven emissions, coal tar, and shale oils, have been associated with adverse health effects in humans. The biological consequences of human exposure to complex mixtures of PAHs depend on the interaction of the various strongly carcinogenic, weakly carcinogenic, or noncarcinogenic PAHs. For example, there is evidence to suggest that PAHs in cigarette smoke require other components in the smoke in order to exert their tumorigenic effect (Akin et al. 1976).

The interaction between noncarcinogenic and carcinogenic PAHs has been extensively examined in animals. Noncarcinogenic PAHs exhibit co-carcinogenic potential and tumor-initiating and promoting

activity when applied with benzo[a]pyrene to the skin of mice. Simultaneous administration of weakly carcinogenic or noncarcinogenic PAHs including benzo[e]pyrene, benzo[g,h,i]perylene, fluoranthene, or pyrene significantly elevated the benzo[a]pyrene-induced tumor incidence. Benzo[e]pyrene, fluoranthene, and pyrene were more potent co-carcinogens than benzo[g,h,i]perylene (Van, Duuren and Goldschmidt 1976; Van Duuren et al. 1973). Benzo[e]pyrene, fluoranthene, and pyrene have also demonstrated weak tumor-promoting activity following initiation with benzo[a]pyrene, and these compounds increased benzo[a]pyrene-DNA adduct formation (Di Giovanni et al. 1982; Lau and Baird 1992; Rice et al. 1984, 1988; Slaga et al. 1979; Smolarek et al. 1987; Van Duuren and Goldschmidt 1976; Van Duuren et al. 1973).

Interactions between selected noncarcinogenic PAHs and carcinogenic benzo[a]pyrene have also been documented to reduce the carcinogenic potential of benzo[a]pyrene in animals. Benzo[a]fluoranthene, benzo[k]fluoranthene, chrysene, perylene, and a mixture of anthracene, phenanthracene, and pyrene significantly inhibited benzo[a]pyrene-induced injection-site sarcomas. However, other PAHs including anthracene, benzo[g,h,i]perylene, fluorene, and indeno[1,2,3-c,d]pyrene had no antagonistic effects (Falk et al. 1964). Coexposure of tracheal explants to benzo[e]pyrene and benzo[a]pyrene resulted in an increased incidence of tracheal epithelial sarcomas over that seen with either PAH alone (Topping et al. 1981). Phenanthrene administration with benzo[a]pyrene decreased the DNA adduct formation in mice (Rice et al. 1984).

There is evidence to suggest that benz[a]anthracene may serve as an anticarcinogen when administered with benzo[a]pyrene. Coadministration of benz[a]anthracene and benzo[a]pyrene decreased benzo[a]pyrene metabolism, benzo[a]pyrene-DNA adduct formation, and reduced the mutagenic activity of benzo[a]pyrene on hamster embryo cells. It has been postulated that the antimutagenic effect of benz[a]anthracene results from competition with benzo[a]pyrene for MFO enzymes, rather than the induction of detoxifying enzymes (Smolarek et al. 1986).

The synergistic effect of individual PAHs on the mutagenicity of benzo[a]pyrene has also been demonstrated. Anthracene and benzo[e]pyrene enhanced the mutagenicity of benzo[a]pyrene, the maximal increase being obtained with anthracene. Benzo[e]pyrene (at a ratio of 2:l) had no effect on benzo[a]pyrene-induced mutation frequencies in V79 cells, but at a ratio of 15:1, benzo[e]pyrene inhibited the benzo[a]pyrene-induced mutations by approximately 10-fold. Benzo[e]pyrene inhibited the metabolism of benzo[a]pyrene by cultured hamster embryo only at high doses, but at both low and

high doses, the proportion of metabolites formed was altered by benzo[e]pyrene (Baird et al. 1984). The percentage of water-soluble metabolites was decreased, whereas the percentage of diols was increased. The authors postulated that benzo[e]pyrene alters the activity of other PAHs by inhibiting the conversion of the proximate carcinogenic diol of a particular PAH to a diol epoxide.

Benzo[a]pyrene and dibenz[a,h]anthracene in combination with 10 noncarcinogenic PAHs were less potent tumor-inducers than was dibenz[a,h]anthracene alone or in combination with benzo[a]pyrene. The noncarcinogenic or weakly carcinogenic PAHs include benzo[e]pyrene, phenanthrene, anthracene, pyrene, fluoranthene, chrysene, perylene, benzo[g,h,i]pyrene, and coronene. Dose-response relationships for tumor incidences were observed for benzo[a]pyrene and dibenz[a,h]anthracene either alone or in combination with the 10 noncarcinogenic PAHs; however, no treatment-related sarcoma incidences were observed for any of the 10 noncarcinogenic PAHs (Pfeiffer 1977).

Phenanthrene, a noncarcinogenic PAH, demonstrated a dose-related inhibition of dibenz[a,h]anthracene-induced carcinogenicity in mice. Phenanthrene significantly reduced the incidence of injection-site sarcomas elicited by dibenz[a,h]anthracene, especially at low doses. However, when triethylene glycol was the vehicle administered in combination with phenanthrene and dibenz[a,h]anthracene, a substantial increase (50%) in the rate of tumor induction was observed (Falk et al. 1964).

Several experiments have shown that most PAH mixtures are considerably less potent than individual PAHs. Various combustion emissions and benzo[a]pyrene have been examined for carcinogenic potency and tumor initiation activity on mouse skin. In all cases, PAH mixtures were much less potent than benzo[a]pyrene. The authors calculated relative potency estimates that ranged from 0.007 for coke oven emissions extract to less than 0.002 for diesel engine exhaust extract, using papillomas per mouse per milligram of the mixture as the end point (Slaga et al. 1980b). Another study demonstrated that the relative tumorigenicities, as compared to benzo[a]pyrene, of automobile exhaust .condensate (AEC), diesel emission condensate, and a representative mixture of carcinogenic PAHs were 0.0053, 0.00011, and 0.36, respectively, following chronic application to mouse skin (Misfeld 1980). AEC has also exhibited an antagonistic influence on benzo[a]pyrene carcinogenicity when subcutaneously administered to mice; this effect was particularly augmented at higher benzo[a]pyrene concentrations (Pott et al. 1977).

Carcinogenic and noncarcinogenic PAHs, comprising a quantitative fraction of automobile exhaust gas condensate, were selected for carcinogenicity testing via dermal exposure of female NMRI mice. The purpose was to identify interactions between mixtures of the carcinogenic and noncarcinogenic PAHs (Schmahl et al. 1977). The carcinogenic PAHs were benzo[a]pyrene, dibenz[a,h]anthracene, benz[a]anthracene, benzo[b]fluoranthene; and the noncarcinogenic PAHs were phenanthrene, anthracene, fluoranthene, pyrene, chrysene, benzo[e]pyrene, and benzo[g,h,i]perylene. Treatment was carried out twice a week, for the natural lifetime of the animals. Although the carcinogenic action observed could be attributed almost entirely to the action of the carcinogenic PAHs, in relatively small doses, addition of the noncarcinogenic PAHs did not inhibit carcinogenesis, but had an additive effect.

Predicting the toxicity of a complex mixture on the basis of one of several of its components may be misleading, because the interactions among the components may modify toxicity. Since PAHs require metabolic activation by monoxygenases to elicit carcinogenic effects, any alteration in these metabolic pathways will influence the observed toxicity. There are two primary mechanisms by which chemicals interact with PAHs to influence toxicity. A compound may compete for the same metabolic activating enzymes and thereby reduce the toxicity of carcinogenic PAHs, or it may induce the metabolizing enzyme levels to result in a more rapid detoxification of the carcinogenic PAHs (Levin et al. 1982). Chaloupka et al. (1993) showed that a mixture of PAHs, produced as by-products from a manufactured gas plant, was 706 times more potent than expected, based on its benzo[a]pyrene content (0.17%) at inducing mouse hepatic microsomal ethoxyresorufin O-deethylase. Alternatively, compounds may compete for a deactivating pathway, thereby increasing the toxicity of PAHs (Furman et al. 1991). Many monooxygenase inducers are ubiquitous in the environment, and they may have an effect on the toxicity of PAHs. For example, environmental contaminants such as tetrachlorodibenzo-p-dioxin (TCDD), polychlorinated biphenyls (PCBs) and 3,3’,4,4’-tetrachlorobiphenyl (TCBP) can increase microsomal enzyme activity and consequently affect PAH toxicity (Jacob et al. 1987; Kouri et al. 1978). The dermal absorption of benzo[a]pyrene was measured in the presence or absence of complex organic mixtures derived from coal liquefaction processes (Dankovic et al. 1989). The dermal half-life of benzo[a]pyrene was 3.0 hours when applied alone, 6.7 hours when measured as a component of a mixture, and ranged from 7.8 to 29.7 hours in the presence of different mixtures. The authors proposed that these mixtures inhibit the dermal absorption of benzo[a]pyrene by inhibiting the metabolism of benzo[a]pyrene at the application site. Interactions. can thus play important modulatory roles in the expression of PAH toxicity that may not be adequately reflected based on the toxicity of a single PAH.

The majority of human exposures to PAHs occur in the presence of particles that affect the pharmacokinetics of PAHs in a manner that can enhance their carcinogenicity. Coadministration of benzo[a]pyrene and particulate material, such as hematite (Fe_2O_3) and arsenic trioxide (As_2O_3), greatly increases respiratory tract tumor yields in laboratory animals following intratracheal instillation (Pershagen et al. 1984; Saffiotti et al. 1972; Stenback and Rowland 1979; Stenback et al. 1976). The effects of particles on the potential human carcinogenicity of PAHs are likely to be similar. When benzo[a]pyrene is particle-bound, clearance from hamster lungs is slower than that of pure benzo[a]pyrene aerosol, increasing the length of time the lungs are exposed and increasing the dose to the gastrointestinal tract as a result of mucocilliary clearance. Respirable benzo[a]pyrene-containing particulates such as diesel exhaust, when coated with the phospholipid component of a pulmonary surfactant, are genotoxic (Wallace et al. 1987). Dusts can increase the rates of pulmonary cell proliferation (Harris et al. 1971; Stenback and Rowland 1979; Stenback et al. 1976), which in turn increases the cells' susceptibility to an initiation event in the presence of a carcinogen.

Environmental exposure to PAHs can also occur along with exposure to other environmental pollutants. The effects of exposure to SO_2 (either by inhalation or systemically with endogenous sulfite/bisulfite anions that accumulated as a result of induced sulfite oxidase deficiency) on benzo[a]pyrene-induced lung tumors were studied in male Sprague-Dawley rats (Gunnison et al. 1988). The animals, were administered benzo[a]pyrene (1 mg) by weekly intratracheal instillation for 15 weeks during which time they were exposed daily by inhalation to 30 or 60 ppm SO_2 or were maintained on a high tungsten to molybdenum diet. There were no statistically significant differences between the benzo[a]pyrene only and the benzo[a]pyrene + SO_2 or benzo[a]pyrene + sulfite/bisulfite groups with respect to the incidence of squamous cell carcinomas of the lung, latency for tumor development, or rate of appearance. Although benzo[a]pyrene alone induced almost 100% tumor incidence leaving little room for an SO_2-induced enhanced response, a shortened latency or increased rate of appearance would have suggested that SO_2 potentiates the carcinogenicity of benzo[a]pyrene, and this did not occur. Therefore, the authors concluded that SO_2 does not potentiate the carcinogenicity of benzo[a]pyrene in the lung.

Concomitant exposure to solvents may also occur, particularly in an occupational setting. It has been demonstrated that pretreatment of rats with toluene (1 g/kg intraperitoneally) inhibits the total cytochrome P-450 content in microsomes isolated from the lungs (Furman et al. 1991). In addition, formation of 3-hydroxybenzo[a]pyrene (a nontoxic metabolite) was inhibited by 36% by the

microsomes *in vitro* whereas the formation of several diols (reactive intermediates) was unaffected by toluene pretreatment. These results indicate that toluene alters the balance between toxification and detoxification of benzo[a]pyrene by cytochrome P-450 in the lung, favoring the formation of reactive genotoxic/carcinogenic intermediates. Therefore, the authors suggested that concomitant exposure to solvents, such as toluene, and PAHs may result in an increased risk for lung cancer.

Asbestos exerts a synergistic influence on cigarette smoke (which contains several PAHs) in the development of bronchopulmonary cancers. This has important implications for workers occupationally exposed to asbestos, who also smoke. The interaction between cigarette smoke and asbestos may be explained partly by differences in the kinetics of PAH cell uptake when PAHs are preadsorbed on asbestos (Foumier and Pezerat 1986). Plutonium oxide (PuO_2) has also been shown to enhance benzo[a]pyrene-induced lung carcinogenesis following simultaneous inhalation of both compounds (Metivier et al. 1984).

Another component of cigarette smoke, nicotine, may also affect the toxicokinetics of PAHs. When introduced in the perfusion medium with benzo[a]pyrene, nicotine inhibited the elimination of benzo[a]pyrene from the lung (Foth et al. 1988a).

Naturally occurring compounds have been found to induce the enzymes that metabolize PAHs, leading to either increased or decreased toxicity. Compounds that exert a protective effect against the carcinogenicity of PAHs and are enzyme inducers include plant flavonoids, plant phenols, antioxidants, retinoids (vitamin A), garlic oil, selenium, molybdenum, turmeric extracts, nitrates, soy sauce, and Chinese herbs. Plant flavonoids can induce microsomal monooxygenases and reduce the carcinogenicity of benzo[a]pyrene (Weibel 1980). Flavones administered orally or dermally increased benzo[a]pyrene hydroxylase activity in the small intestine and skin, respectively, and prevented the formation of pulmonary adenomas and forestomach and skin tumors initiated by benzo[a]pyrene (Rahimtula et al. 1977; Wattenberg and Leong 1970). A series of flavonoids and isoflavonoids, compounds that are found in fruits and vegetables, were tested for their ability to inhibit metabolism of benzo[a]pyrene in cultured hamster embryo cells (Chae et al. 1992). The results indicated that the flavonoids are generally more active than the isoflavonoids, and that two hydroxyl, two methoxyl, or methyl and hydroxyl substituents at the 5- and 7-positions and a 2,3-double bond are the structural characteristics required for inhibition of benzo[a]pyrene metabolism to reactive intermediates. Two of these compounds, acacetin and kaempferide also inhibited benzo[a]pyrene-induced mutation in Chinese

hamster V79 cells. Therefore, the authors proposed that the protective effect of these compounds may be due to their ability to inhibit metabolism of benzo[a]pyrene to reactive intermediates. Similar results have been obtained with pine cone extracts, tested in the *Salmonella typhimurium* assay (Lee et al. 1993). These results suggest that these compounds may be useful as potential chemopreventive agents in individuals exposed to genotoxic/carcinogenic PAHs.

Dietary plant phenols, such as tannic acid, quercetin, myricetin, and anthraflavic acid exhibit a protective effect against the tumorigenicity of benzo[a]pyrene and other PAHs by altering the metabolic pathways that detoxify and activate PAHs to their ultimate carcinogenic metabolites, thus suppressing PAH metabolism and subsequent PAH-DNA adduct formation. It has been suggested that the possible mechanism for the anticarcinogenic effect of these plant phenols may be an inhibitory effect on the binding of the ultimate carcinogen to the target tissue DNA (Mukhtar et al. 1988). Oral administration of these compounds has been associated with a decrease in tumorigenesis induced by benzo[a]pyrene in mouse forestomach (Katiyar et al. 1993a, 1993b; Zheng et al. 1993). Antioxidants also affect benzo[a]pyrene hydroxylation by rat liver microsomal MFOs, and reduce the bacterial mutagenicity of benzo[a]pyrene in the presence of rat liver microsomes and cofactors (Rahimtula et al. 1977). Antioxidants such as BHA, BHT, phenothiazine, phenothiazine methosulfate, and ethoxyquin all can reduce the quantitative yield of benzo[a]pyrene metabolites in incubations with rat liver microsomes (Sullivan et al. 1978).

Retinoids, of which vitamin A is a member, have demonstrated an antagonistic effect on benzo[a]pyrene-induced carcinogenicity. (Vitamin A has been shown to prevent and/or reverse the genetic damage caused by benzo[a]pyrene.) Similarly, the ability of benzo[a]pyrene (75 mg/kg, oral administration) to induce micronuclei *in vivo* was completely inhibited in Swiss mice orally administered doses of vitamin A ranging from 750 to 1,500 mg/kg 1 hour prior to benzo[a]pyrene treatment (Rao and Nandan 1990). Although the protective mechanism has not been fully elucidated, it has been suggested that vitamin A interferes with the activation of benzo[a]pyrene to its reactive metabolites, thus reducing the amount of benzo[a]pyrene-DNA binding in rat liver and target tissues (i.e., stomach) to prevent the mutagenic action of benzo[a]pyrene. It has also been suggested that vitamin A can enhance DNA repair (McCarthy et al. 1987; Rao et al. 1986). Conversely, vitamin A deficiency enhances the mutagenicity and carcinogenic effect of cigarette smoke and benzo[a]pyrene. This activity is related to a decreased level of free radical scavengers like ascorbic acid and glutathione in the liver (Alzieu et al. 1987). Another study observed that vitamin A deficient animals exposed to

cigarette smoke via inhalation exhibited enhanced benzo[a]pyrene-DNA adduct formation (Gupta et al. 1987, 1990). This has important implications for humans who smoke and consume diets deficient in vitamin A. Mammary tumor incidence was reduced by 27% (from 67% to 40%) in female rats receiving retinyl acetate before, during, and after the administration of either a single dose or eight weekly doses of benzo[a]pyrene. These results demonstrate that retinyl acetate is capable of inhibiting benzo[a]pyrene-induced mammary tumor formation in rats when given before, during, and after carcinogen treatment (McCormick et al. 1981).

The oral gavage administration of 25 mg/kg *n*-acetylcysteine (NAC) prevented the formation of benzo[a]pyrene-diol-epoxide-DNA adducts in rats receiving benzo[a]pyrene by intratracheal instillation for 3 consecutive days (25 mg/kg in 2% Tween 80) (De Flora et al. 1991). Inhibition of DNA adduct formation was more efficient in the liver than in the lungs. Similarly, micronuclei induction in the benzo[a]pyrene-treated rats was completely reversed by NAC. These results suggest that NAC, which is a glutathione precursor, may be effective in preventing or reversing the binding of the reactive intermediates of PAHs to cellular macromolecules and, therefore, may prevent the subsequent toxic effects of PAHs.

Coumarin, also known to be anticarcinogenic, inhibited benzo[a]pyrene-induced micronuclei in male ICR mice pretreated with 65 or 130 mg/kg/day coumarin for 6 days prior to the intraperitoneal administration of 150 mg/kg benzo[a]pyrene (Morris and Ward 1992). However, pretreatment with either dose of coumarin did not alter the genotoxicity of benzo[a]pyrene when females were included in the study.

Garlic oil also exhibits an antagonistic effect on benzo[a]pyrene by inhibiting benzo[a]pyrene-induced skin carcinogenesis in Swiss mice during the initiation phase (Sadhana et al. 1988). A primary constituent of garlic oil, allyl methyl trisulfide (ATM), has also demonstrated an inhibitory effect on benzo[a]pyrene induced neoplasia of the forestomach in mice (Spamins et al. 1986).

Selenium has been shown to reduce the mutagenicity of benzo[a]pyrene as well as AHH activity (Lee and Lin 1988). Selenium also inhibits the metabolism of benzo[a]pyrene *in vitro* (Bompart and Clements 1990). Several different salts of molybdenum inhibited the formation of certain metabolites of benzo[a]pyrene by lung and liver microsomes *in vitro* obtained from rats pretreated with 3-methylcholanthrene (Bompart et al. 1989). In a later study, it was demonstrated that benzo[a]pyrene

metabolism *in vitro* by lung and liver microsomes isolated from rats that were exposed to 40 or 80 mg/kg of ammonium heptamolybdate for 8 weeks was inhibited (Bompart 1990). These results suggest that molybdenum interferes with the cytochrome P-450 enzymes responsible for the activation of benzo[a]pyrene, and thus may have a protective effect against benzo[a]pyrene-induced toxicity/carcinogenicity.

Ferric oxide has been shown to increase the metabolism of benzo[a]pyrene by hamster alveolar macrophages (Greife and Warshawsky 1993). Alveolar macrophages, the primary lung defense cell, have been shown to metabolize benzo[a]pyrene to a more biologically active form, and then release the metabolites. Concurrent exposure of hamster alveolar macrophages to benzo[a]pyrene-coated ferric oxide resulted in a significant increase in the amount of benzo[a]pyrene metabolites and superoxide anions, which have been shown to produce localized lipid peroxidation and edema *in vivo.*

Lindane, an isomer of hexachlorocyclohexane, is an organochlorine pesticide which is extensively used in agricultural and public health programs in developing countries (Khan et al. 1993). Pretreatment of rat lungs with lindane by intratracheal injection inhibited benzo[a]pyrene hydoxlase activity in the lungs. Reduced elimination of intravenously administered benzo[a]pyrene from the lungs of rats after lindane pretreatment was also observed, suggesting that lindane may alter the clearance of benzo[a]pyrene from the lungs.

Prostacyclin has been shown to significantly reduce genetic damage caused by benzo[a]pyrene to mouse bone marrow cells, using the micronucleus test (Koratkar et al. 1993).

Chinese herbs commonly used in anti-cancer drugs have also been demonstrated to inh.ibit the mutagenicity of benzo[a]pyrene (Lee and Lin 1988).

Aqueous extracts of turmeric, curcumin-free aqueous turmeric extract, and curcumin were tested for their ability to inhibit benzo[a]pyrene-induced mutagenicity in the *S. typhimurium* assay and the bone marrow micronucleus test in Swiss mice (Azuine et al. 1992). A dose-dependent inhibition of benzo[a]pyrene-induced mutagenicity was observed in two strains of *Salmonella* in the presence of Aroclor-1254-induced rat liver homogenate, and 3 mg/kg of these three extracts also significantly inhibited benzo[a]pyrene-induced bone marrow micronuclei formation by 43%, 76%, and 65%. Female Swiss mice were treated with either aqueous turmeric extract (3 mg/day), curcumin-free

aqueous tumeric extract (1 mg/day), or curcumin (1 mg/day) 5 days/week for 2 weeks prior to receiving twice weekly gavage administrations of 20 mg/kg benzo[a]pyrene for 4 weeks. The treatment with the turmeric extracts continued for another 2 weeks after the cessation of benzopyrene treatment, and the animals were observed until they were 180 days old. A group receiving just benzo[a]pyrene served as a control. The benzo[a]pyrene-only animals exhibited 100% tumor incidence with 9.1±0.6 papillomas/mouse. All three extracts significantly ($p<0.00l$) inhibited the formation of forestomach papillomas by benzo[a]pyrene by 53%, and the average numbers of papillomas per mouse was also significantly decreased. The authors suggested that turmeric extracts may be useful as chemopreventive agents, but that there are probably several mechanisms of action for these inhibitory effects.

Pumark, a mixture of solvent extracts of tumeric, betel leaf, and catechu, was tested for its chemopreventative activity against benzo[a]pyrene-induced DNA damage (Ghaisas and Bhide 1994) Sister chromatid exchange and micronuclei formation in human lymphocyte culture were used as markers to assess the protective effect of Pumark. Pumark gave 50-60% protection against benzo[a]pyrene-induced chromosomal damage.

Other environmentally ubiquitous substances, such as nitrites and nitrates, have been shown to interact with PAHs. Pyrene is not mutagenic in the *Salmonella typhimurium* assay. However, when injected intraperitoneally into mice at doses of 10-200 mg/kg in combination with inhalation exposure to 50 or 100 ppm nitrous oxide (NO_2) mutagenic metabolites of pyrene were recovered from the urine (Kanoh et al. 1990). In addition, 1-hydroxypyrene (the major urinary metabolite of pyrene) administration in combination with NO_2 exposure also produced mutagenic metabolites. These results suggest that combined exposure to pyrene, a prevalent environmental PAH, and nitrogen compounds could result in the formation of nitrogenated mutagenic metabolites of pyrene. The effects of nitrite (in drinking water) and/or soy sauce (in food) on the forestomach tumors induced by twice weekly gavage administration of eight total doses of benzo[a]pyrene were studied in mice (Benjamin et al. 1988). The combination of nitrite and soy sauce resulted primarily in a significant reduction in the number of tumors per animal induced by benzo[a]pyrene, and also a reduction in tumor incidence. Neither substance alone had much effect on the carcinogenicity of benzo[a]pyrene alone. The mechanism for this protective effect of the combination of nitrite and soy sauce is not known.

The fungicide (prochloraz), the topical antifungal agent (miconazole) and 7,8-benzoflavone (a strong inhibitor of cytochrome P-450) limited the conversion of benzo[a]pyrene to a mutagen in S. *typhimurium.* The order of inhibitory action was 7,8-benzoflavone ≥ prochloraz ≥ miconazole (Antignac et al. 1990).

Diet (i.e., dietary fat levels) can also have an effect on the disposition and toxicity of PAHs. The metabolism of benzo[a]pyrene in hepatocytes *in vitro* from rats fed high-fat (as corn oil) diets was decreased (Zaleski et al. 1991). This effect was not due to a decrease in the activity of AHH. The authors postulated that the high-fat diets allowed benzo[a]pyrene, which is highly lipophilic, to become sequestered in lipid droplets and, therefore, become inaccessible to the P-450 enzymes. Another study suggests that caloric restriction, per se, can reduce the metabolic activation capacity of the liver, thereby reducing the production of mutagenic metabolites from PAHs (Xiao et al. 1993).

Organosulphur compounds, e.g., S-methyl cysteine sulphoxide (SMCSO) and its metabolite methyl methane thiosulphinate, both naturally occurring compounds present in Brassica vegetables (broccoli, cabbage) were found to inhibit benzo[a]pyrene-induced micronucleus formation in mouse bone marrow by 31 and 33%, respectively, after oral administration (Marks et al. 1993).

o-Cresol, often found in conjunction with PAHs in industrial waste from coking, oil processing, shale processing, and other industries, was found to protect mice from benzo[a]pyrene-induced forestomach tumors after oral administration, when o-cresol was administered before or after benzo[a]pyrene (Yanysheva et al. 1993).

Topical application of 1% croton oil twice weekly at 4 weeks of age had an inhibitory effect on tumor formation in offspring of ICF/Ha female mice treated with intraperitoneal injections of benzo[a]pyrene in sesame oil on the llth, 13th and 15th days of pregnancy (Bulay and Wattenberg 1971).

Administration of a diet containing 3% myo-inositol to mice beginning one week after oral benzo[a]pyrene administration reduced the number of pulmonary adenomas by 40% but did not prevent forestomach tumors (Estensen and Wattenberg 1993). Under the same conditions, administration of 0.5% dexamethasone in the diet inhibited pulmonary adenomas by 57% and also inhibited forestomach tumor formation to a similar degree. A combination of the two compounds resulted in additive chemoprevention.

The ubiquitous nature of PAHs in the environment, particularly as constituents of complex mixtures such as automobile emissions, coal tar, coke oven emissions, and combustion products of tobacco, increases the likelihood that the type of interactions discussed will occur. Thus, interactions may play a decisive role in the expression of toxicity and the development of cancer in exposed populations.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to PAHs than will most persons exposed to the same level of PAHs in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

Data suggest that specific subsections of the population may be susceptible to the toxic effects produced by exposure to PAHs. These include people with various conditions, such as aryl hydrocarbon hydroxylase (AHH) that is particularly susceptible to induction, nutritional deficiencies, genetic diseases that influence the efficiency of DNA repair, and imrnunodeficiency due to age or disease. Other subsections of the population that may be susceptible to the toxic effects of PAHs are people who smoke, people with a history of excessive sun exposure, people with liver and skin diseases, and women, especially of child-bearing age. Human fetuses may also be particularly susceptible to the toxic effects produced by exposure to PAHs. Data also indicate that the general population may be at increased risk of developing lung cancer following prolonged inhalation of PAH-contaminated air, and skin cancer following concurrent dermal exposure to PAHs and sunlight. There is some limited evidence that indicates that all people could be sensitive at some point to the toxic effects of environmental contaminants, such as PAHs, as a result of stress and/or circadian rhythms.

Pre- and post-natal exposure to PAHs could produce adverse reproductive and developmental effects in human fetuses. Most PAHs and their metabolites cross the placenta because of their lipid solubility (Calabrese 1978; Shendrikova and Aleksandrov 1974). Fetuses are susceptible to the toxic effects produced by maternal exposure to PAHs, such as benzo[a]pyrene, because of an increased permeability of the embryonic and fetal blood-brain barrier and a decreased liver-enzyme conjugating function (Calabrese 1978; Shendrikova and Aleksandrov 1974). Because of PAH exposure, higher incidences of embryo- and fetolethality, stillbirths, resorptions, and malformations of the kidney and bladder have been observed in animals (Legraverend et al. 1984; Urso and Gengozian 1980; Urso and Johnson 1987). Delayed effects have been observed in the progeny of mothers exposed to PAHs, such as benzo[a]pyrene (Urso and Gengozian 1980). These .delayed effects include sterility of progeny, immune suppression, possible alteration of endocrine function, and cancer in rodents (Csaba and Inczefi-Gonda 1992; Csaba et al. 1991; Legraverend et al. 1984; Mackenzie and Angevine 1981). Tobacco smoke contains both PAHs and particulate matter. These could interact synergistically in pregnant women who smoke to produce decreased birth weight, increased perinatal morbidity and mortality, and other diseases of the newborn (NRC 1983). PAHs in cigarette smoke, such as benzo[a]pyrene, have been associated with the induction of AHH activity in human placental tissue and a decrease in placental size (NRC 1983). Results of *in vitro* studies indicate that benzo[a]pyrene alters human placental endocrine and metabolic function (Avigdor et al. 1992; Bamea and Shurtz-Swirski 1992; Guyda 1991; Guyda et al. 1990).

People with AHH that is particularly susceptible to induction may also be susceptible to the possible carcinogenic effect of exposure to PAHs. This enzyme is mixed function oxidase (MFO) that is involved in the metabolism of PAHs to certain reactive intermediates that can cause cell transformation, mutagenicity, and cytotoxicity. The incidence of this inducible genetic trait is low in 53%, intermediate in 37%, and high in 10% of the white population in the United States (Calabrese 1978). It has been proposed that genetically expressed AHH inducibility is related to the development of bronchogenic carcinoma in persons exposed to PAHs contained in tobacco smoke. On the other hand, individuals with a greater ability to induce AHH may be able to rapidly detoxify PAHs and eliminate them, thus making them less susceptible to the toxic effects of PAHs. Based on the population frequency of genetically controlled AHH induction, some scientists predict that approximately 45% of the general population are considered to be at high risk, and 9% of the 45% are considered to be at very high risk, of developing bronchogenic carcinoma following exposure to PAHs (Calabrese 1978).

Certain nutritional deficiencies have been associated with an increased cancer incidence in PAH-exposed animals. These include deficiencies in vitamins A and C, iron, and riboflavin (Calabrese 1978). It is estimated that at least 25% of all children between the ages of 7 and 12 years and all children of low-income families consume less than the recommended dietary allowance (RDA) of vitamin A. It has also been estimated that between 10% and 30% of the infants, children, and adults of low-income groups consume less than the RDA for vitamin C, 98% of all children consume less than the RDA for iron, and 30% of women and 10% of men between the ages of 30 and 60 years consume less than two-thirds of the RDA for riboflavin (Calabrese 1978). Other nutrients such as vitamin D, selenium, and protein can also influence the cancer incidence in animals exposed to PAHs (NRC 1983; Prasanna et al. 1987). Several studies have been conducted to investigate the interaction between nutrition and PAH exposure by administering benzo[a]pyrene to laboratory animals. The nutritional factors listed above either reduced the amount of benzo[a]pyrene binding to DNA in rat liver or forestomach tissue (McCarthy et al. 1987), prevented or reversed genetic damage (Rao et al. 1986), or reduced the activity of AHH (Prasanna et al. 1987). It has also been observed that fasted rats showed altered toxicokinetics of PAHs resulting from benz[a]anthracene and chrysene exposure. This altered toxicokinetics included reduced hepatic clearance because of decreased AHH activity and the acceleration of the depletion of cytochrome P-450 and other microsomal enzymes required to metabolize PAHs (Fiume et al. 1983).

Individuals who undergo a rapid reduction in body fat may be at risk from increased toxicity because of the systemic release and activation of PAHs that had been stored in fat. The metabolism of benzo[a]pyrene in hepatocytes *in vitro* from rats fed high-fat (as corn oil) diets was decreased (Zaleski et al. 1991). This effect was not due to a decrease in the activity of AHH. The authors postulated that the high-fat diets allowed benzo[a]pyrene, which is highly lipophilic, to become sequestered in lipid droplets and, therefore, become inaccessible to the P-450 enzymes.

People exposed to PAHs in conjunction with particulates from tobacco smoke, fossil-fuel combustion, coal fly ash, and asbestos fibers are at increased risk of developing toxic effects, primarily cancer. Even people not susceptible to the toxic effects of PAHs may become affected when exposure occurs in conjunction with exposure to particulates (NRC 1983). This enhanced effect results from the adsorption of PAHs onto the particulates. They are vacuolized into cells, and distributed differently in tissues depending on the size and type of particulate matter. This increased PAH uptake may result in more efficient induction of AHH activity at low PAH concentrations. This activity also increases the

dose to the gastrointestinal tract as a result of mucocilliary clearance (NRC 1983). This synergistic action between PAHs and particulate matter in air pollution has been associated with the occurrence of stomach cancer in humans (Fraumeni 1975).

Immunocompetence is an important factor in decreasing or preventing human susceptibility to toxicity and disease after exposure to environmental contaminants. Small children have an immature immune system, and the elderly may have a deficient immune system due to age, genetic factors, or disease (Calabrese 1978; NRC 1983). It is possible that individuals whose immune systems are compromised could be at an increased risk of carcinogenesis, including that produced by PAHs. Some genetic diseases that may predispose a person to immune deficiency include ataxia telangiectasia, Wiskott-Aldrich syndrome, Bloom's syndrome, common variable immunodeficiency, selective IgA deficiency, Bruton's agammaglobulinemia, severe combined immunodeficiency, selective IgM deficiency, AIDS, and immunodeficiency with normal or increased immunoglobulins (NRC 1983).

Genetic diseases that reduce DNA-repair capabilities also increase an individual's susceptibility to PAH-related malignancy by reducing the efficiency of DNA repair. In fact, the level of benzo[a]pyrene/DNA adducts in peripheral lymphocytes was slightly but significantly higher in 22 lung cancer patients who had at least one "first-degree" relative with lung cancer than in 30 healthy controls (Nowak et al. 1992). This finding led the authors to speculate that altered metabolic activation and deactivation and increased formation of adducts may indicate a genetic predisposition for lung cancer. Some of the diseases that reduce DNA repair capability are also associated with an abnormality of the immune system (NRC 1983). Diseases that may be associated with DNA-repair deficiencies are classical and variant xeroderma pigmentosum, ataxia telangiectasia, Bloom's syndrome, Fanconi's anemia, familial retinoblastoma, D-deletion retinoblastoma, progeria (Hutchinson-Gilford) syndrome, Down's syndrome, dyskeratosis congenita, Cockayne's syndrome, actinia keratosis, and cutaneous malignant melanoma (NRC 1983).

Women may be at increased risk of reproductive dysfunction following exposure to high levels of PAHs. Data from animal studies indicate that oocyte and follicle destruction occurs following dosing with PAHs (Mattison et al. 1989; Miller et al. 1992; Urso and Gengozian 1980; Urso and Johnson 1987). Benzo[a]pyrene exposure may reduce fertility and the ability to bear children (Mackenzie and Angevine 1981; Rigdon and Rennels 1964). Exposure may also reduce fertility of exposed women by

causing ovarian dysfunction (Swartz and Mattison 1985). However, the doses that produced the effects discussed above are high relative to expected environmental exposures to PAHs.

Subsections of the population that suffer from liver and skin diseases may be at increased risk of developing adverse effects from exposure to PAHs. People with pre-existing skin conditions, such as pemphigus vulgaris and xeroderma pigmentosum, and those with normal skin may be at increased risk of developing adverse dermal effects ranging from rashes to cancer following exposure to some PAHs, such as benzo[a]pyrene, anthracene, benz[a]anthracene, and pyrene (Bingham and Falk 1969; Cavalieri et al. 1977, 1988b; Cottini and Mazzone 1939; Forbes et al. 1976; Habs et al. 1980; Shubik and Porta 1957). Exposure to more than one PAH may enhance or reduce tumor development (Slaga et al. 1979; Van Duuren and Goldschmidt 1976; Van Duuren et al. 1973). Skin cancer induction in laboratory animals has been associated with exposure to benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzohlfluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene.

People with significant exposure to ultraviolet radiation, such as from sunlight, may also be at increased risk of developing skin cancer due to PAH exposure. Ultraviolet radiation has a synergistic influence on PAH-induced skin cancer following dermal exposure. It enhances benzo[a]pyreneinduced skin carcinogenesis in the mouse, which is dependent on the dose of benzo[a]pyrene (Gensler 1988). Combined exposure to anthracene and sunlight could produce mutagenic lesions (Blackbum and Taussig 1975; Forbes et al. 1976). Laboratory animals exposed concurrently to chronic ultraviolet irradiation and to PAHs were at a higher risk of skin tumor induction (Mukhtar et al. 1986).

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to PAHs. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to PAHs. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

General recommendations to reduce absorption follo.wing acute exposure to PAHs include removing the individual from the source of exposure, removing contaminated clothing, and decontaminating exposed areas of the body. It has been suggested that contaminated skin should be washed with soap and water, and eyes exposed to PAHs should be flushed with water or saline (Stutz and Janusz 1988). Administration of activated charcoal following ingestion of PAHs is recommended; however, it has not been proven to reduce absorption of PAHs in the gastrointestinal system (Stutz and Janusz 1988). The use of emetics as a means of gastrointestinal decontamination of PAHs is not recommended (Bronstein and Currance 1988). There is a risk of causing chemical pneumonitis in the patient by the aspiration of the PAHs.

2.8.2 Reducing Body Burden

There are no known methods currently available for reducing the body burden of PAHs. Evidence from acute-duration studies in experimental animals indicates that PAHs are rapidly metabolized and conjugated to form water-soluble metabolites that are essentially completely eliminated in the urine and feces within a matter of days (see Sections 2.3.3 and 2.3.4). No data are available on the kinetics of PAHs following chronic exposure, so it is not known if PAHs or their metabolites bioaccumulate in these exposure situations. Given the relatively rapid and complete excretion observed following short-term exposures, it is not likely that PAHs bioaccumulate to an appreciable degree. However, PAHs are lipophilic, so it is conceivable that unmetabolized parent compound could accumulate in tissue fat stores. In fact, diet (i.e., dietary fat levels) may have an effect on the disposition and toxicity of PAHs. The metabolism of benzo[a]pyrene in hepatocytes *in vitro* from rats fed high-fat (as corn oil) diets was decreased (Zaleski et al. 1991). This effect was not due to a decrease in the activity of AHH. The authors postulated that the high-fat diets allowed benzo[a]pyrene, which is highly lipophilic, to become sequestered in lipid droplets and, therefore, become inaccessible to the P-450 enzymes. Therefore, high-fat diets may favor the accumulation of parent PAHs in lipids so that they are not metabolized to reactive intermediates or water-soluble conjugates. Alternatively, rapid fat loss may result in the release of sequestered parent PAHs, making them available to the P-450 enzymes to be metabolized to reactive intermediates as well as water-soluble conjugates that can be easily excreted. Thus, modulating body fat content may reduce body burden of PAHs by hastening

their metabolism to water-soluble conjugates. However, the result may also be an increase in toxicity due to increased metabolism to reactive intermediates.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

As discussed in Sections 2.3.5 and 2.4, it is currently believed that the toxic and carcinogenic effects of PAHs are mediated by reactive diol-epoxide intermediates that interact directly with DNA and RNA, producing adducts. The formation of these adducts leads to neoplastic transformation as well as interfering with the normal functioning of rapidly proliferating tissues. As discussed above, these reactive intermediates are formed when PAHs are biotransformed by the P-450 enzymes. Interference with these metabolic pathways, by inactivation of the activated diol epoxides, reduction in tissue levels of cytochrome P-450, and direct inhibition of the cytochrome P-450 enzymes responsible for the formation of the reactive intermediates, could reduce the toxic and carcinogenic effects of PAHs. A number of drugs, such as cobaltous chloride, SKF-525-A, and 6-nitro- 1,2,3-benzothioadiazole, have been reported to inhibit P-450 enzymes. In addition, as discussed in Section 2.7, other compounds that exert a protective effect against the carcinogenicity of PAHs by interfering with cytochrome P-450 enzymes include plant flavonoids, plant phenols, antioxidants (such as BHA, BHT, phenothiazine, phenothiazine methosulfate, and ethoxyquin), retinoids (vitamin A), garlic oil, selenium, organosulphur compounds, o-cresol, myo-inositol, lindane, and molybdenum (Bompart 1990; Bompart et al. 1989; Chae et al. 1992; Estensen and Wattenberg 1993; Ghaisas and Bhide 1994; Katiyar et al. 1993a, 1993b; Khan et al. 1993; Lee and Lin 1988; Lee et al. 1993; Marks et al. 1993; Mukhtar et al. 1988; Rahimtula et al. 1977; Rao and Nandan 1990; Sullivan et al. 1978; Weibel 1980, Yanysheva et al. 1994; Zheng et .al. 1993). Reduced caloric intake has also been shown to cause decreased metabolism of PAHs by liver microsomes, thus protecting against genotoxic effects (Xiao et al. 1993). P-450 metabolism also results in products that can be more readily eliminated than can the parent compound. Hence, any side products of the drugs or substances listed above, along with their potential to increase the biological half-life of the PAHs, would also need to be considered in any protocol. Further research to determine which cytochrome P-450 isozymes are involved in the metabolism to the reactive intermediates, as well as which isozymes are involved in enhancing the elimination of PAHs, could lead to the development of strategies to selectively inhibit specific isozymes and, thus, reduce the toxic effects of PAHs.

It has also been suggested that some of these compounds may act at other points in the activation, macromolecular binding sequence described above. For instance, vitamin A can also enhance DNA repair (McCarthy et al. 1987; Rao et al. 1986).

Because PAHs are detoxified by conjugation with substances such as glutathione (see Sections 2.3.3 and 2.3.4), sufficient glutathione stores in the body may reduce the chances of toxic effects following acute exposure to PAHs. For example, the oral gavage administration of NAC prevented the formation of benzo[a]pyrene-diol-epoxide-DNA adducts in rats receiving benzo[a]pyrene (De Flora et al. 1991). Inhibition of DNA adduct formation was more efficient in the liver than in the lungs. Similarly, micronuclei induction in the benzo[a]pyrene-treated rats was completely reversed by NAC. These results suggest that NAC, which is a glutathione precursor, may be effective in preventing or reversing the binding of the reactive intermediates of PAHs to cellular macromolecules and, therefore, may prevent the subsequent toxic effects of PAHs.

2.9 ADEQUACY OF THE DATABASE

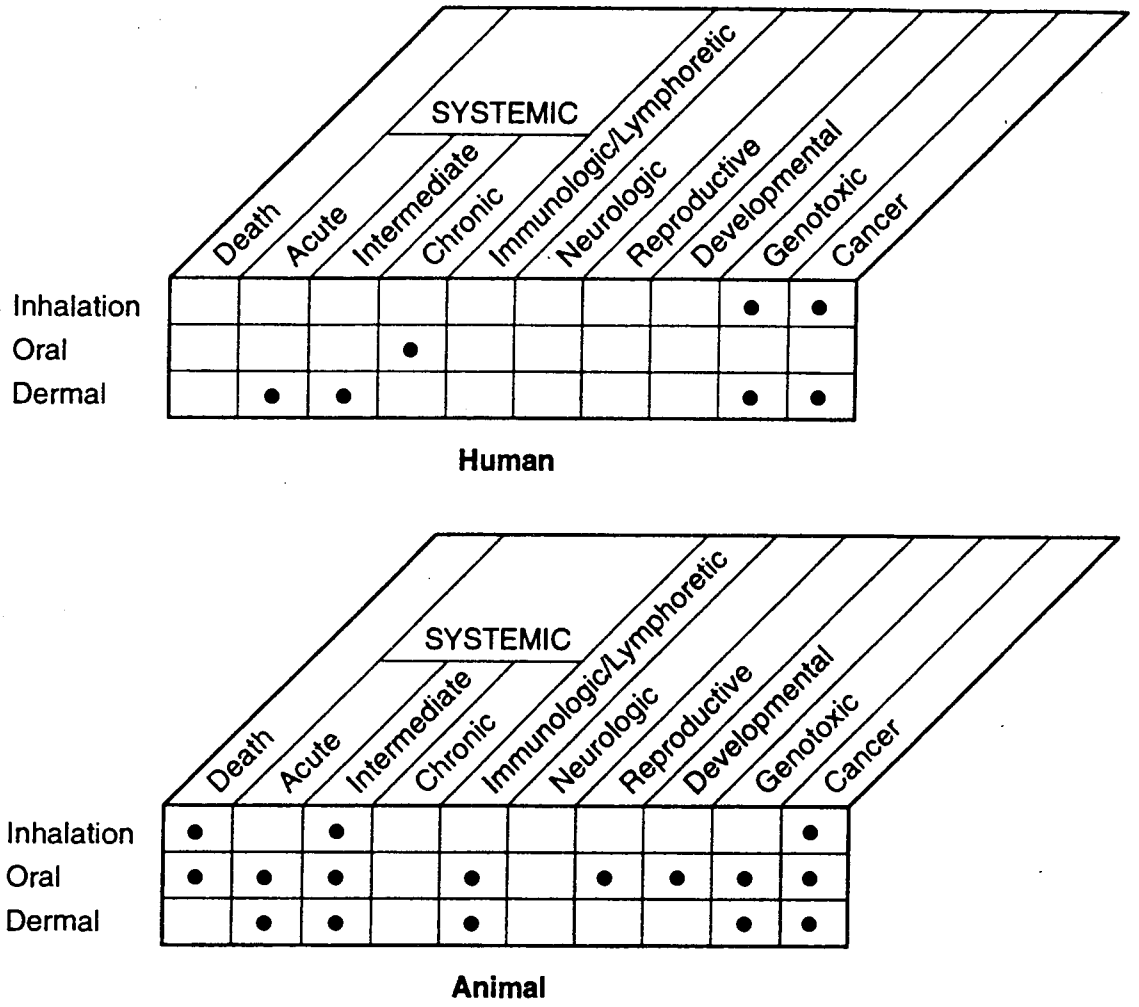
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PAHs is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PAHs.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Polycyclic Aromatic Hydrocarbons

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to PAHs are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing

FIGURE 2-5. Existing Information on Health Effects of Polycyclic Aromatic Hydrocarbons



● Existing Studies

information concerning the health effects of PAHs. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

The vast majority of literature reviewed concerning the health effects of PAHs in humans described case reports and chronic-duration studies in workers linking the occurrence of lung and skin cancer and adverse noncancer skin effects with exposure to PAH-containing mixtures such as coke oven emissions, roofing-tar emissions, shale oils, and soot, and exposure to cigarette smoke. The predominant routes of exposure in the studies are inhalation and dermal, but the possibility of some degree of oral exposure cannot be ruled out, especially in light of muco-cilliary clearance and ingestion following inhalation exposure. Because of the lack of quantitative exposure information and the presence of other potentially carcinogenic substances in these mixtures, it is impossible to evaluate the contribution of an individual PAH or even the PAHs as a class to the effects observed.

The database for the health effects of PAHs in experimental animals consists primarily of older animal studies that would be considered inadequate by current standards, and two-stage dermal carcinogenesis studies. As can be seen in Figure 2-5, very little information is available on the effects of inhalation exposure to PAHs in animals. However, oral and dermal exposures to relatively high doses of PAHs have been shown in numerous studies to induce skin, lung, and forestomach tumors in animals, and noncancer adverse effects in rapidly proliferating tissues such as bone marrow, lymphoid organs, gonads, and intestinal epithelium. Benzo[a]pyrene is by far the most extensively studied of the PAHs; therefore, the adverse effects of other less-studied PAHs must generally be inferred from the results obtained with benzo[a]pyrene. This may over- or underestimate the health risk associated with the various PAHs.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. Little is known regarding the adverse health effects associated with acute-duration inhalation exposure to any of the PAHs in either humans or animals. Limited

information is available on the effects of acute-duration oral and dermal exposures to PAHs in animals; the skin and the liver have been identified as target organs of PAH toxicity in animals (Iwata et al. 1981; Nousiainen et al. 1984). Available information is insufficient to derive an acute inhalation or oral MRL. Identification of target organs (other than the developing fetus) from acute-duration animal studies following inhalation and oral exposures would be helpful in order to assess the risk associated with the acute inhalation of contaminated air or ingestion of PAH-contaminated water or soils by humans living in areas surrounding hazardous waste sites. Additional inhalation and oral studies in animals involving a range of exposure concentrations and employing sensitive histological and biochemical measurements of injury to a comprehensive set of end points would be useful for establishing dose-response relationships and identifying thresholds for these effects. This information would be useful for determining levels of significant exposure to PAHs that are associated with adverse health effects. Both routes are considered significant for individuals living in the vicinity of hazardous waste sites because exposures to particulate PAHs in air and PAHs bound to soil particles, sediments in water, and contaminated food are possible in such areas. Furthermore, the pharmacokinetic data on PAHs are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. Additional studies should be conducted on the effects of PAHs after acute-duration dermal exposure, since dermal exposure may be important to populations around hazardous waste sites. It is known that acute-duration dermal exposure to PAHs results in adverse dermal effects. Further studies determining the relative importance of exposure by this route, with regard to subsequent toxicity, would be useful. Studies describing dermal and oral absorption of PAHs from complex mixtures, including soil and other mixtures that may actually be the vehicles of human exposure, would be useful in furthering understanding of the toxicity of these compounds. The studies should be conducted with benzo[a]pyrene, because this PAH has been found at the highest number of NPL sites and it is a representative altemant PAH; studies should also be conducted with a representative nonaltemant PAH such as fluoranthene, benzo[b]fluoranthene, or benzo[j]fluoranthene. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be cOnducted to determine the most appropriate animal species for extrapolation to humans.

Intermediate-Duration Exposure. Little is known regarding the adverse health effects associated with intermediate-duration inhalation exposure to any of the PAHs in either humans or animals. One inhalation study in rats failed to establish an effect level (Wolff et al. 1989c). Information is available

on the effects of intermediate-duration exposures to some of the PAHs in humans (dermal) and in animals (oral and dermal). Regressive verrucae and other epidermal changes were noted in the skin of human volunteers treated with topically applied benzo[a]pyrene (Cottini and Mazzone 1939). Intermediate-duration dermal exposure to benzo[a]pyrene in patients with preexisting dermal conditions of pemphigus vulgaris and xeroderma pigmentosum was associated with an exacerbation of the abnormal skin lesions (Cottini and Mazzone 1939). Target organs identified in animal studies with some of the PAHs were the skin, the liver, and the hemolymphatic system (Legraverend et al. 1983; Old et al. 1963; Robinson et al. 1975). The available information is insufficient to derive an intermediate inhalation MRL for PAHs because no intermediate-duration inhalation animal studies exist that adequately describe the effects of inhalation exposure to PAHs. Intermediate duration MRLs have been derived for acenaphthene, fluoranthene, fluorene, and anthracene, based on 90-day gavage studies in mice (EPA 1988e; 1989c; 1989d, 1989e). For acenaphthene, fluoranthene, and fluorene, liver effects, supported by effects in other organ systems were identified as the target toxicity. For anthracene, no effect was seen in the liver or any other organ system, even at the highest dose of 1,000 mg/kg/day. The PAHs in these studies were administered by gavage, a route that does not mimic the potential exposure of people living near hazardous waste sites. Identification of target organs from intermediate-duration animal studies following inhalation and oral (drinking water) exposures would be useful in order to assess the risk associated with the intermediate-duration inhalation of contaminated air or ingestion of PAH-contaminated water or soils by humans living in areas surrounding hazardous waste sites. Ninety-day studies in animals by the inhalation and oral (drinking water) routes would be helpful to establish dose-response relationships and to identify other possible target organs or systems in individuals living around hazardous waste sites who can be exposed to low levels of PAHs for an intermediate-duration period of time. Both routes are considered important for individuals living in the vicinity of hazardous waste sites because exposure to particulate PAHs in air and PAHs bound to soil particles, sediments in water, and contaminated food are significant routes of exposure for individuals living in the vicinity of hazardous waste sites. Furthermore, the pharmacokinetic data on PAHs are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. Additional studies should be conducted on the effects of PAHs after intermediate-duration dermal exposure, since dermal exposure may be important to populations around hazardous waste sites. It is known that acute-duration dermal exposure to PAHs results in adverse dermal effects. Further studies determining the relative importance of exposure by this route, with regard to subsequent toxicity, would be useful. Studies describing dermal and oral absorption of PAHs from complex mixtures, including soil and other

mixtures that may actually be the vehicles of human exposure, would be useful in furthering the understanding of the toxicity of these compounds. The studies should be conducted with benzo[a]pyrene, because it has been found at the hi.ghest number of NPL sites and it is a representative altemant PAH, and with a representative nonaltemant PAH such as fluoranthene, benzo[b]fluoranthene, or benzofilfluoranthene. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans.

Chronic-Duration Exposure and Cancer. Few controlled epidemiological studies have been reported in humans on the effects of exposure to PAHs or PAH-containing mixtures; such studies would be difficult to conduct because of the presence of too many confounding factors. However, information is available on the effects of chronic-duration dermal exposures to PAH-containing mixtures in humans. Workers exposed to substances that contain PAHs (e.g., coal tar) experience chronic dermatitis and hyperkeratosis (EPA 1988a). Several chronic ingestion, intratracheal installation, and skin-painting studies have been conducted in animals using various PAHs, but none identified adverse effects other than cancer. Therefore, threshold levels for chronic-duration inhalation and oral exposure have not been thoroughly investigated, and no MRLs have been developed from this database. Although the existing animal studies are inadequate to establish threshold levels and dose-response relationships for toxic effects resulting from chronic exposure to PAHs, the data from 90-day studies recommended above should be evaluated before chronic studies are conducted. Inhalation and ingestion are probably the most significant routes of exposure for individuals living in the vicinity of hazardous waste sites contaminated with PAHs. Low dose chronic studies are needed to mimic these exposures.

Human data on the carcinogenicity of PAHs are available only for mixtures containing PAHs. Animal carcinogenicity data are available for only benzo[a]pyrene following inhalation exposure, for a limited number of PAHs following ingestion, and for almost all of the 17 PAHs following dermal exposure. A large database on carcinogenicity exists on complex mixtures that contain PAHs (such as crude oils, various high boiling point distillates, complex petroleum products, coal tars, creosote, and the products of coal liquification processes). It is difficult to ascertain the carcinogenicity of the component PAHs in these mixtures because of the potential interactions that could occur and the presence of other carcinogenic substances in the mixtures. Furthermore, the levels of PAHs were not quantified in any

of these reports. However, most of the available information on the carcinogenicity of PAHs in humans must be inferred from studies that reported the effects of exposure to complex mixtures that contain PAHs. Epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke oven emissions (Lloyd 1971; Mazumdar et al. 1975; Redmond et al. 1976), roofing-tar emissions (Hammond et al. 1976), and cigarette smoke (Maclure and MacMahon 1980; Wynder and Hoffmann 1967). Despite the limitations inherent in these studies, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs to cause cancer in humans, and more definitive studies in humans on individual PAHs are not recommended at this time.

Inhalation exposure to benzo[a]pyrene has been shown to induce respiratory tract tumors in hamsters (Thyssen et al. 1981). Certain PAHs are carcinogenic to animals by the oral route (e.g., benz[a]anthracene, benzo[a]pyrene, and dibenz[a,h]anthracene), and tumors have been noted in the liver, mammary gland, and respiratory and gastrointestinal tracts following oral administration of these compounds (Neal and Rigdon 1967; Rigdon and Neal 1969). However, only a few PAHs have been assayed by the oral route. The results of dermal studies indicate that benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[l,2,3-c,d]pyrene are tumorigenic in rats and mice following dermal exposure. Although many of these studies would be considered inadequate by current standards, the results nevertheless indicate that these PAHs can induce skin tumors as well as act as tumor initiators and promoters (Habs et al. 1984; Warshawsky and Barkley 1987; Wynder and Hoffmann 1959b). Therefore, additional studies on the carcinogenicity of PAHs in animals are probably not necessary at this time.

Genotoxicity. The genotoxic potential of several of the PAHs (both altemant and nonaltemant) has been extensively investigated using both *in vivo* and *in vitro* assays. All but three of the PAHs (acenaphthene, acenaphthylene, and fluorene) were reported to be mutagenic in at least one *in vitro* assay with the bacteria *S. typhimurium.* No further genotoxicity data are considered necessary at this time.

Reproductive Toxicity. No data were located regarding reproductive effects of PAHs in humans, and the available information regarding reproductive effects of PAHs in animals is limited; data exist on only one of the PAHs (benzo[a]pyrene), and these data are conflicting. Adverse effects such as decreased fertility and total sterility in F1 progeny of CD-1 mice (Mackenzie and Angevine 1981) and

decreased incidence of pregnant female rats at parturition (Rigdon and Rennels 1964) were reported following oral exposure to benzo[a]pyrene. However, no adverse reproductive effects were observed in Swiss mice fed benzo[a]pyrene in their diet (Rigdon and Neal 1965). The metabolic differences and method of benzo[a]pyrene administration could account for the differential response to benzo[a]pyrene-induced toxicity in these studies. Parenteral studies in animals have also demonstrated adverse reproductive effects (Bui et al. 1986; Cervello et al. 1992; Mattison et al. 1992; Miller et al. 1992; Swartz and Mattison 1985). The limited animal data suggest that PAHs may be reproductive toxicants, but these data are not extensive enough to draw firm conclusions. Furthermore, the testes and ovaries contain rapidly proliferating cells and therefore should be considered susceptible to damage by PAHs. The 90-day studies identified above should be conducted with special emphasis on reproductive organ pathology. If reproductive effects are observed in these studies, multigeneration animal studies could then be conducted to evaluate properly the relevance of this end point. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans. Future epidemiological studies should give special emphasis to evaluation of reproductive toxicity.

Developmental Toxicity. No studies were located regarding developmental effects in humans exposed to PAHs by any route. However, results of *in vitro* studies suggest that human placental endocrine and hormonal function may be affected by exposure to benzo[a]pyrene (Avigdor et al. 1992; Bamea and Shurtz-Swirski 1992; Guyda 1991). Only limited data are available in animals on a few PAHs (mostly benzo[a]pyrene). These data indicate that ingested or parenterally administered PAHs have a potential to induce adverse developmental effects such as resorptions and malformations (Legraverend et al. 1984; Shum et al. 1979), sterility in F_1 progeny (Mackenzie and Angevine 1981), testicular changes including atrophy of seminiferous tubules with lack of spermatids and spermatozoa, interstitial cell tumors (Payne 1958), immunosuppression (Urso and Gengozian 1980), and tumor induction (Bulay and Wattenberg 1971; Soyka 1980). However, another study found no developmental effects when benzo[a]pyrene was administered orally to mice (Rigdon and Neal 1965). The available animal data suggest that PAHs may be developmental toxicants. However, most of the data are from parenteral routes of exposure, and there are no inhalation data. The oral data are limited because of conflicting results across studies, the use of inconsistent protocols (e.g., varying numbers of animals, administration of the test compound during different times of gestation), the use of only one

dose, lack of study details, and the fact that data are available only on benzo[a]pyrene. Furthermore, some studies have shown that the toxic manifestations of benzo[a]pyrene are dependent on the route of exposure. Therefore, a two-species developmental toxicity study would be helpful to assess fully the potential for PAHs to affect development in humans. The route of exposure should be determined following evaluation of the reproductive organs in the 90-day studies to see if any particular route of exposure has a greater effect. The pharmacokinetic data on PAHs are insufficient,to determine whether similar effects may be expected to occur across different routes of exposure. Developmental toxicity should also be assessed in future animal reproductive toxicology testing and human epidemiological studies. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans.

Immunotoxicity.No studies were located regarding immunological effects in humans after exposure to PAHs by any route, or in animals following inhalation exposure. In the one oral exposure study in animals that was located, a single dose of fluorene failed to affect thymus or spleen weight (Danz and Brauer 1988). However, there is information available in animals on the immunotoxicity of several PAHs following dermal exposure (contact hypersensitivity) (Old et al. 1963) and intraperitoneal or subcutaneous administration (suppression of both humoral and cellular immunity) (Blanton et al. 1986, 1988; Lubet et al. 1984; Lyte and Bick 1985; White and Holsapple 1984). In general, the degree of immunosuppression correlates with the individual PAH’s carcinogenic potency. Because of the information in animals that suggests that PAHs may affect the immune system, Tier I testing to assess PAH-induced immunotoxicity, as recently defined by the NTP (Luster et al. 1988) is recommended. The parameters that should be measured include immunopathology, humoral-mediated immunity, cell-mediated immunity, and nonspecific immunity. Although relatively high doses of PAHs must be used to obtain immunotoxicity in animals, much information could be gained from these studies. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans. Future epidemiologic studies should also place emphasis on evaluation of this end point.

Neurotoxicity. The potential for short- or long-term neurotoxic effects following exposure to PAHs by any route has not been specifically studied in humans or animals. Although acute-, intermediate-, and chronic-duration studies conducted in animals do not indicate that any of the PAHs tested showed gross evidence of neurotoxicity, these tests were not designed to detect subtle neurological changes. It is recommended that neurobehavioral as well as neuropathological end points be included in future 90-day toxicity testing of PAHs. If these preliminary data indicate that any of the PAHs are neurotoxicants, then a more comprehensive neurotoxicity battery, using sensitive functional and neuropathological tests, could be conducted to characterize further the neurotoxic potential of these PAHs. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans.

Epidemiological and Human Dosimetry Studies. There are no epidemiological studies available that have investigated the effects of single PAHs by any route of exposure. Most of the available information on the effects of PAHs in humans comes from reports of occupational exposures to PAH-containing mixtures. For example, epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke oven emissions (Lloyd 1971; Mazumdar et al. 1975; Redmond et al. 1976), roofing-tar emissions (Hammond et al. 1976), and cigarette smoke (Maclure and MacMahon 1980; Wynder and Hoffmann 1967). Each of these mixtures contains benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene as well as other potentially carcinogenic PAHs and other carcinogenic and potentially carcinogenic chemicals, tumor promoters, initiators, and co-carcinogens such as nitrosamines, coal tar pitch, and creosote. Limitations inherent in these studies include unquantified exposure concentrations and durations, as well as concomitant exposure to other potentially toxic substances. Despite their inadequacies, studies in humans suggest that PAH-containing mixtures are dermal irritants and carcinogens following inhalation and/or derrnal exposure. If either worker or general populations with appropriate exposure can be identified, epidemiologic studies should be undertaken with special emphasis placed upon evaluation of cancer (of the skin and other organs) and other adverse skin effects, reproductive/ developmental toxicity, and immunotoxicity. However, such studies would be difficult to conduct. With a group of chemicals that are as ubiquitous as PAHs, it would be extremely difficult to distinguish between exposed and nonexposed populations. The more these groups overlap, the higher the chance for misclassification bias. In addition, the statistical power of an epidemiological study

depends partially on the variance of the exposure measurements. If there is enormous variation in the exposure levels among the exposed and nonexposed groups, then the population size needed to obtain statistical significance in the study would be unmanageable and would most likely not be found in any one occupational setting or hazardous waste site. Furthermore, because of the size of the population needed, it would be very difficult to control for confounding factors such as smoking, geographical location, lifestyle.

Biomarkers of Exposure and Effect.

Exposure. Sensitive analytical methods are available to quantify PAH exposure in humans. Although PAHs can be detected in the body fluids and tissues, because of the ubiquitous nature of PAHs in the environment, these biomarkers are not specific for any particular source of PAH exposure. PAHs and their metabolites (e.g., 1-hydroxypyrene) can be measured in the urine of exposed individuals. PAHs form DNA adducts that can be measured in body tissues or blood following exposure to PAHs and mixtures that contain PAHs. Studies attempting to identify suitable and reliable biomarkers from phenanthrene, chrysene, and fluoranthene have been conducted (e.g., Grimmer et al. 1988). However, no other biomarkers (specific or otherwise) that have practical utility have been identified following exposure to PAHs. Further work on developing biomarkers that enable exposure to be quantified would be useful to ascertain whether individuals have been exposed to potentially toxic levels of PAHs. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies addressing mixtures of PAHs should be conducted.

Effect. The available biomarkers of effect for PAHs are not specific for effects induced by PAHs. The available genotoxicity data indicate that several of the 17 PAHs considered here are genotoxic in both nonmammalian and mammalian systems and are indirect mutagens (i.e., requiring the presence of an exogenous mammalian metabolic system). There were no tests reported for humans exposed to benzo[a]pyrene (the most widely tested PAH) *in vivo*, but several types of cultured human tissue cells demonstrated positive results for benzo[a]pyrene-induced genotoxicity (as evidenced by the induction of chromosomal aberrations, sister chromatid exchange) and binding of benzo[a]pyrene to DNA. Thus, although these results are exclusively from *in vitro* tests and the limited genotoxicity tests conducted on urine obtained from humans exposed to PAHs have been negative, these genotoxic effects observed in human tissue cells may serve as a biomarker of effects for at least one of the PAHs, benzo[a]pyrene. The formation of benzo[a]pyrene-DNA adducts has been demonstrated, and

this may serve as a biomarker of PAH-induced carcinogenicity. Additional studies on the relative sensitivity of DNA adducts and sister chromatid exchanges to identify threshold levels of exposure that could be detected in human populations would be useful. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies addressing mixtures of PAHs should be conducted.

Absorption, Distribution, Metabolism, and Excretion. The quantitative data on the toxicokinetics of PAHs are based, to a large extent, on short-term exposure to benzo[a]pyrene in animals. Occupational exposure to PAHs generally occurs as a mixture. Therefore, inhalation, oral, and dermal studies exploring how PAHs interact with each other to affect their disposition would be more representative of exposures in humans.

The presence of PAHs and their metabolites in human urine and blood following inhalation, oral, and dermal exposures indicates that PAH absorption occurs in humans (Becher and Bjorseth 1983; Buckley and Lioy 1992; Hecht et al. 1979). However, there was no quantitative information on the extent and rate of PAH absorption in humans. Most of the information regarding the pulmonary and oral absorption and distribution of PAHs in animals is based on acute-duration exposures (Chang 1943; Hecht et al. 1979; Weyand and Bevan 1986, 1987b, 1988; Withey et al. 1991; Wolff et al. 1989c). PAHs appear to be widely distributed in tissues of animals following oral and inhalation exposure; peak tissue concentrations occurred earlier with higher exposure levels. Studies on the absorption and distribution of PAHs following long-term exposures would indicate whether the kinetics are similar to acute-duration exposures. The dermal study conducted by Storer et al. (1984) revealed that several PAHs in a crude coal tar mixture were absorbed, but that benzo[a]pyrene was not. In contrast, animal studies indicate that benzo[a]pyrene was dermally absorbed (Ng et al. 1992; Wester et al. 1990; Yang et al. 1989); however, tissue distribution was not discussed.

PAH metabolism has been extensively reviewed in human and animal tissue homogenates, cultures, and perfused systems (Autrup et al. 1978; Cavalieri et al. 1987; Cohen et al. 1976; Kiefer et al. 1988; Leung et al. 1988). However, these studies are limited to the biotransformation of individual compounds. Since most metabolic pathways have been identified or can be predicted for the individual PAHs, it is now important to understand how these metabolic pathways are affected when the PAHs compete. The carcinogenic and toxic potential of PAHs is associated with their metabolites. Alterations in rates of metabolism and metabolite profiles may affect the toxic consequences of PAHs.

Available data on several of the nonaltemant tumorigenic PAHs discussed in this profile indicate that they exert their adverse effects by mechanisms that differ from those that have been more recently elucidated for altemant PAHs (Amin et al. 1982, 1985b; Rice et al. 1987b). The mechanisms by which benzo[b]fluoranthene and benzo[j]fluoranthene are metabolically activated to genotoxic agents have been elucidated (LaVoie et al. 1993b; Marshall et al. 1993; Weyand et al. 1993a, 1993b). Additional studies designed to assess the potential toxic effects of these reactive metabolites in various species and at various organ sites would be useful.

No studies were located that monitored the rate and extent of PAH excretion in humans. Most studies in animals concentrated on the extent of PAH excretion and the distribution of the compound and its metabolites in urine, feces, and bile following short-term exposures (Bevan and Weyand 1988; Grimmer et al. 1988; Petridou-Fischer et al. 1988; Weyand and Bevan 1986; Wolff et al. 1989c; Yamazaki and Kakiuchi 1989). Data regarding the excretion pattern and rate following long-term exposure to PAHs would be useful to determine if bioaccumulation occurs.

In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans.

Comparative Toxicokinetics. Occupational studies provide evidence that inhaled PAHs are absorbed. Animal studies also show that pulmonary absorption of benzo[a]pyrene occurs, but the extent of absorption is not known. Ingestion of benzo[a]pyrene is low in humans while oral absorption in animals varies among the PAH compounds depending on the lipophilicity. The absorption and distribution of PAHs in various species would be expected to be similar based on the lipophilicity of the compounds. In general, percutaneous absorption of PAHs in several animal species appears to be rapid and high (Ng et al. 1992; Sanders et al. 1986; Wester et al. 1990; Yang et al. 1989). This suggests that dermal absorption in humans may also occur rapidly; however, the extent of absorption may vary depending on the vehicle.

There was no information available on the distribution of PAHs in humans. In general, tissue distribution of benzo[a]pyrene following inhalation exposure is qualitatively similar for different species (Bevan and Weyand 1988; Weyand and Bevan 1986, 1987a, 1988; Wolff et al. 1989c). In

general, orally absorbed PAHs were rapidly and widely distributed in the rat (Bartosek et al. 1984; Withey et al. 1991; Yamazaki and Kakiuchi 1989). Qualitative similarities in distribution among species suggest that distribution in humans would also be similar. Placental transfer of PAHs in mice and rats appears to be limited (Neubert and Tapken 1988; Withey et al. 1992); therefore, human fetuses may be exposed to PAHs, but levels would not be as high as maternal levels.

Qualitatively, metabolism and excretion would be relatively similar in humans and animals, but variability in specific activities of enzymes will alter the metabolic profiles among the species. Knowledge of these differences in enzyme activity in various species would assist in predicting which pathways and metabolites would prevail. For instance, AHH activity is not induced by PAHs in some strains of mice. Therefore, it would be useful to examine the metabolism of those less-well-studied PAHs in several species (i.e., rodent and nonrodent) so that the carcinogenic potential of PAHs in various species could be predicted. The feces (via the bile) appears to be the major excretion route, but the extent of elimination of PAHs varies among species (Bevan and Weyand 1988; Grimmer et al. 1988; Ng et al. 1992; Petridou-Fischer et al. 1988; Sanders et al. 1986; Weyand and Bevan 1986; Wolff et al. 1989c). Further comparative studies on excretion would be useful because differences in human and animal excretion rates are not known. In addition, many of the toxicity tests have used mice, while a larger proportion of toxicokinetic studies have used rats. Thus, more kinetic studies should be conducted in mice to provide data to correspond to the toxicity data. Further, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans.

Methods for Reducing Toxic Effects. Efforts are currently underway to develop ways to mitigate the adverse effects of PAHs, especially with regard to natural products. Efforts to reduce or eliminate cigarette smoking in the general population also contribute toward reducing exposure to and toxic effects of PAHs. The target organs of PAHs have been identified (i.e., the skin and rapidly proliferating tissue such as the hematopoietic and lymphoid systems). Furthermore, several PAHs are considered to be carcinogenic. The mechanism of action for altemant PAH-induced carcinogenicity is fairly well understood. However, additional information would be useful to understand the mechanism of nonaltemant PAH-induced carcinogenicity, how PAHs exert their adverse effects on rapidly proliferating tissue, and how various interactions between PAHs can affect their toxicity and carcinogenicity.

2.9.3 Ongoing Studies

Ongoing research on the health effects and toxicokinetics of PAHs is summarized in Table 2-7.

TABLE 2-7. Ongoing Studies on Polycyclic Aromatic Hydrocarbons[a]

Investigator	Affiliation	Research description	Sponsor
E.J. La Voie	Rutgers State University, New Brunswick, NJ	Environmental polyclics—Metabolism and activation (mice, humans)	National Institute of Environmental Health Sciences
S.P. Mudzinski	Albany Medical College of Union University, Albany, NY	Immunotoxicologic screening of chemical carcinogens (mice)	National Institute of Environmental Health Sciences
W.F. Busby	Massachusetts Institute of Technology, Cambridge, MA	Core—Tumorigenicity testing (mice)	National Institute of Environmental Health Sciences
D.R. Bevan	Virginia Polytechnic Institute, Blacksburg, VA	Disposition of benzo(*a*)pyrene *in vivo*	U.S. Department of Agriculture
R.L. Hill	Florida State University, Tallahassee, FL	The impact of energy-related pollutants on chromosome structure	Not specified
N. Hahon	NIOSH DRDS, Morgantown, WV	Polycyclic aromatic hydrocarbons, particulates and defense mechanisms	National Institute of Occupational Safety and Health
M.K. Sanyal	Yale University, New Haven, CT	Abnormal fetal development during to toxic exposure (humans, rats, mice)	National Institute of Environmental Health Sciences
M. Koreeda	University of Michigan, Ann Arbor, MI	Synthesis and reactions of polycyclic aromatic hydrocarbon metabolites	National Institute of Environmental Health Sciences
L.M. Anderson	National Institutes of Health, Bethesda, MD	Metabolic and pharmacological determinants in perinatal carcinogenesis	National Institutes of Health
K. Frenkel	New York University Medical Center, New York, NY	Tumor promoters affecting base modification in DNA (mice)	National Institutes of Health
M.E. Knuckles	Meharry Medical College, Nashville, TN	Acute and subchronic inhalation and oral toxicity testing of benzo(a)pyrene and fluoranthene	Agency for Toxic Substances and Disease Registry

[a]Information obtained from Federal Research in Progress (October, November 1992) and CRISP (October 1992) databases

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of PAHs is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of PAHs is located in Table 3-2.

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a]

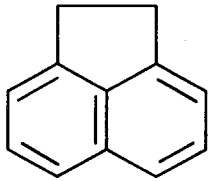
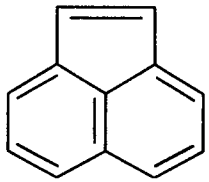
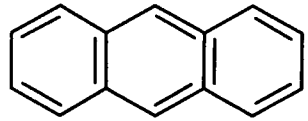
Characteristic	Acenapthene	Acenaphthylene	Anthracene
Synonym(s)	1,2-Dihydroacenaphthylene; 1,8-dihydroacenapthaline; 1,8-ethylenenapthalene; 1,2-dihydroacenapththylene	Cyclopenta[d,e]naphthalene	Anthracin; green oil; paranaphthalene[b]
Registered trade name(s)	No data	No data	Tetra olive NZG; Anthracene oil[d]
Chemical formula	$C_{12}H_{10}$	$C_{12}H_8$	$C_{14}H_{10}$[b]
Chemical structure			
CAS registry	83–29–9	208–96–8	120–12–7[b]
NIOSH RTECS	AB1000000	AB1254000	CA 9350000
EPA hazardous waste	No data	No data	No data
OHM/TADS	8200126	No data	82001222
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	2659	2661	702
NCI	No data	No data	No data

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a] (continued)

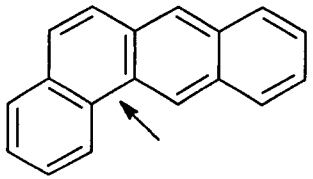
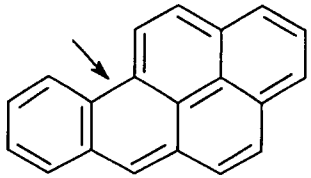
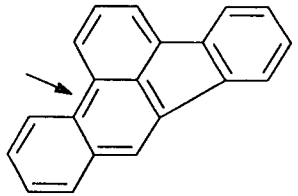
Characteristic	Benzo[a]anthracene	Benzo[a]pyrene	Benzo[b]fluoranthene
Synonym(s)	BA; benz[a]anthracene; 1,2-benzanthracene; benzo[b]-phenanthrene; 2,3-benzophenanthrene; tetraphene[c,d]	Benzo[d,e,f]chrysene; 3,4-benzopyrene, 3,4-benzpyrene; benz[a]pyrene; BP; B[a]P[b]	3,4-Benz[e]acephenanthrylene; 2,3-benzfluoranthene; 3,4-benzfluoranthene; 2,3-benzofluoranthene; 3,4-benzofluoranthene; benzo[e]fluoranthene;B[b]F[b]
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_{18}H_{12}$	$C_{20}H_{12}$[b]	$C_{20}H_{12}$[b]
Chemical structure			
Identification numbers:			
CAS Registry	56–55–3	50–32–8	205–99–2[b]
NIOSH RTECS	CV 9275000[e]	DJ3675000	CU 1400000[e]
EPA Hazardous Waste	U018	U022	No data
OHM/TADS	8200123	No data	8200124[e]
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	4003	2554	4035
NCI	No data	No data	No data

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a] (continued)

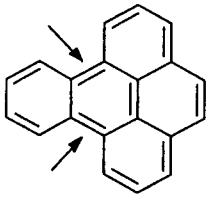
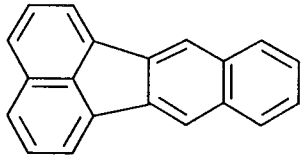
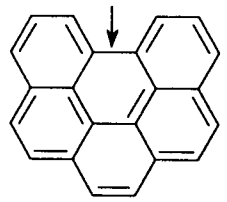
Characteristic	Benzo[e]pyrene	Benzo[k]fluoranthene	Benzo[g,h,i]perylene
Synonym(s)	1.2-Benzopyrene; 1.2-benzpyrene; 4.5 benzopyrene; 4.5-benzpyrene; B[e]P[e]	8.9-Benzfluoranthene; 8.9-benzofluoranthene; 11.12-benzofluoranthene; 2,3,1.8-binaphthylene; dibenzo[b,j,k]fluorene[b]	1,12-Benzoperylene[c]
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_{20}H_{12}$[e]	$C_{20}H_{12}$[b]	$C_{22}H_{12}$[c]
Chemical structure			
CAS registry	192–97–2[e]	207–08–9[b]	191–24–2[c]
NIOSH RTECS	D4500000[e]	DF 350000[e]	DI 6200500[e]
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	8200125[e]	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	4031[e]	6012[e]	6177[e]
NCI	No data	No data	No data

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a] (continued)

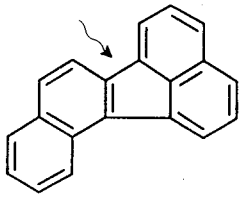
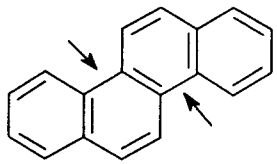
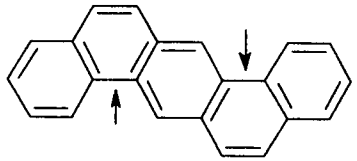
Characteristic	Benzo[j]fluoranthene	Chrysene	Dibenz[a,h]anthracene
Synonym(s)	10.11-Benzofluoranthene; benzo-12.13-fluoranthene; dibenzo[a,j,k]-fluorene; 7.8-benzofluoranthene; B[j]F[e]	1.2-Benzophenanthrene; benzo[a]-phenanthrene; 1,2-benzphenanthrene; benz[a]phenanthrene; 1,2,5,6-dibenzonaphthalene	Dibenz[a,h]anthracene; DB[a,h]A; DBA; 1,2:5,6-dibenz[a]anthracene[b,e]
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_{20}H_{12}$	$C_{18}H_{12}$[b]	$C_{22}H_{14}$[b]
Chemical structure			
CAS registry	205–82–3[e]	218–01–9[b]	53–70–3[b]
NIOSH RTECS	DF 6300000[e]	GC 0700000[e]	HN 2625000[e]
EPA hazardous waste	No data	U050[e]	U063
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	4034[e]	2810	5097
NCI	No data	No data	No data

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a] (continued)

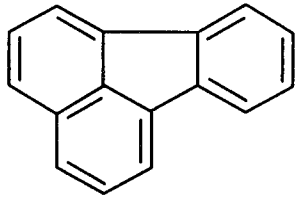
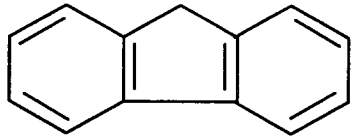
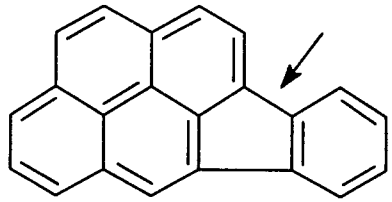
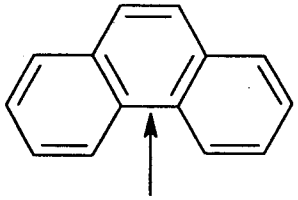
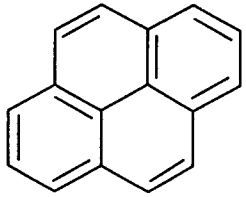
Characteristic	Fluoranthene	Fluorene	Indeno[1,2,3-c,d]pyrene
Synonym(s)	1.2-[1,8-Naphthylene]benzene; 1.2-benzacenaphthene; 1.2-[1.8-naphthalenediyl] benzene; benzo[j,k]fluorene	ortho-Biphenylene methane; diphenylenemethane; 2,2-methylene biphenyl; 2.3-benzidene[b,f]	Indenopyrene; IP; ortho-phenylene pyrene; 1,10-[ortho-phenylene]pyrene; 1,10-[1,2-phenylene]pyrene; 2,3-ortho-phenylene pyrene[b]
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_{16}H_{10}$	$C_{13}H_{10}$[b]	$C_{22}H_{12}$[b]
Chemical structure			
Identification numbers:			
CAS registry	206–44–0	86–73–7[b]	193–39–5[b]
NIOSH RTECS	LL4025000	LL5670000	NK 9300000
EPA hazardous waste	U120	No data	U137
OHM/TADS	8200136	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	5486	2165	5101
NCI	No data	No data	No data

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a] (continued)

Characteristic	Phenanthrene	Pyrene
Synonym(s)	Phenanthrene; Phenantrin[b]	Benzo[d,e,f]phenanthrene; 8-pyrene[b]
Registered trade name(s)	No data	No data
Chemical formula	$C_{14}H_{10}$[b]	$C_{16}H_{10}$[b]
Chemical structure		
Identification numbers:		
CAS registry	85–01–8[b]	129–00–00[b]
NIOSH RTECS	SF7175000	UR 245000[e]
EPA hazardous waste	No data	No data
OHM/TADS	8200140	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	2166	4023
NCI	No data	No data

[a]All information obtained from HSDB 1994, except where noted.
[b]IARC 1983
[c]Eller 1984
[d]Sax and Lewis 1989
[e]HSDB 1992
[f]Weast et al. 1988

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; PAHs = polycyclic aromatic hydrocarbons; RTECS = Registry of Toxic Effects of Chemical Substances; ⟶ = bay region; ⇝ = pseudo bay region

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a]

Property	Acenaphthene	Acenaphthylene	Anthracene
Molecular weight	154.21	152.20	178.2[b]
Color	White	No data	Colorless with violet fluorescence when pure; yellow with green fluorescence when impure
Physical state	Solid (needles)	Solid (prisms/plates)	Solid (tablet or prism)[b]
Melting point	95 °C	92–93 °C	218 °C[b]
Boiling point	96.2 °C	265–275 oC	342 °C[b], 340 °C[e]
Density at 20/4 °C	1.225 g/cm^3 at 0 °C	No data	No data
Specific gravity	1.0242 at 90 °C/4 °C[e]	0.8988 at 16 °C/2 °C	1.25 at 27 °C/4 °C; 1.283 at 25 °C/4 °C[e]
Odor	No data	No data	Weak aromatic odor
Odor threshold:			
Water	0.08 ppm	No data	No data
Air	0.08 ppm	No data	No data
Solubility:			
Water	1.93 mg/L[p]	3.93 mg/L water	0.076 mg/L[p]
Organic solvents	Soluble in alcohol, methanol, propanol, chloroform, benzene, toluene, glacial acetic acid	Alcohol, ether, benzene	Acetone; benzene, carbon disulphide, carbon tetrachloride, chloroform, ether, ethanol, methanol, toluene[e,b]
Partition coefficients:			
Log K_{ow}	3.98[k]	4.07[k]	4.45[k]
Log K_{oc}	3.66[k]	1.40[k]	4.15[k]
Vapor pressure	4.47x10^{-3} mm Hg[m]	0.029 mm Hg at 20 °C[k]	1 mm Hg at 145 °C[b]; 1.7x10^{-5} mm Hg at 25 °C[k]
Henry's law constant	7.91x10^{-5} atm-^{3}/mol[r]	1.45x10^{-3} atm-m^3/mol	1.77x10^{-5} atm-m^3/mol[r]
Autoignition temperature	No data	No data	540 °C[i]
Flashpoint	No data	No data	121 °C(closed cup)[d]
Flammability limits	Dust is moderately flammable[n]	No data	No data
Conversion factors	0	0	0
Explosive limits	No data	No data	Lower, 0.6% by volume[d]

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a] (continued)

Property	Benzo[a]anthracene	Benzo[a]pyrene	Benzo[b]fluoranthene
Molecular weight	228.29[c]	252.3[b]	252.3[b]
Color	Yellow-blue fluorescence[e]	Pale yellow	Colorless
Physical state	Solid (plates)	Solid (plates or needles)[f]	Solid (needles)[e] (recrystallized from benzene/ligroin)
Melting point	158–159 °C[c]; 162 °C[e]	179–179.3 °C[f]	168.3 °C[b]
Boiling point	400 °C[i]; 435 °C sublimes[f]	310–312 °C at 10 mm Hg[f]; 495 °C[j]	No data
Density	1.274 g/cm^3 at 20 °C	1.351 g/cm^{3,h}	No data
Specific gravity	No data	No data	No data
Odor	No data	Faint aromatic odor	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	0.010 mg/L[p]	2.3x10^{-3} mg/L[p]	0.0012 mg/L[q]
Organic solvents	Slightly soluble in acetic acid and hot ethanol; soluble in acetone and diethyl ether; very soluble in benzene[b]	Sparingly soluble in ethanol and methanol; soluble in benzene, toluene, xylene, and ether	Slightly soluble in benzene, acetone[b]
Partition coefficients:			
Log K_{ow}	5.61[k]	6.06[k]	6.04[k]
Log K_{oc}	5.30[k]	6.74[k]	5.74[k]
Vapor pressure	2.2x10^{-8} mm Hg at 20 °C	5.6x10^{-9} mm Hg[k]	5.0x10^{-7} mm Hg at 20–25 °C[r]
Henry's law constant	1x10^{-6} atm–m^3/mol	4.9x10^{-7} atm-m^3/mol[k]	1.22x10^{-5} atm-m^3/mol[k]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	0	0	0
Explosive limits	No data	No data	No data

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a] (continued)

Property	Benzo[e]pyrene	Benzo[k]fluoranthene	Benzo[g,h,i]perylene
Molecular weight	252.30[d]	252.3	276.34[c]
Color	Colorless[b]	Pale yellow	Pale yellow-green
Physical state	Prisms or plates (recrystallized from benzene)[g]	Solid (needles)	Solid (plate)
Melting point	178–179 °C[d]	215.7 °C	273 °C[c]
Boiling point	310–312 °C at 10 mm Hg[g]	480 °C	550 °C
Density	No data	No data	No data
Specific gravity	No data	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	6.3×10^{-3} mg/L at 25 °C[d]	7.6×10^{-4} mg/L at 25 °C	2.6×10^{-4} mg/L at 25 °C
Organic solvents	Acetone[g]	Soluble in benzene, acetic acid, ethanol[b]	Soluable in benzene, dichloromethane, acetone[g]
Partition coefficients:			
Log K_{ow}	No data	6.06[k]	6.50[k]
Log K_{oc}	No data	5.74[k]	6.20[k]
Vapor pressure	5.7×10^{-9} mm Hg at 25 °C[d]	9.59×10^{-11} mm Hg	1.03×10^{-10} mm Hg at 25 °C[k]
Henry's law constant	No data	3.87×10^{-5} atm–m^3/mol[k]	1.44×10^{-7} atm-m^3/mol[k]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	0	0	0
Explosive limits	No data	No data	No data

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a] (continued)

Property	Benzo[j]fluoranthene	Chrysene	Dibenz[a,h]anthracene
Molecular weight	252.32[d]	228.3[b]	278.35[c]
Color	Yellow or orange[d]	Colorless with blue or red-blue fluorescence[b,e]	Colorless[b]
Physical state	Plates (recrystallized from ethanol) or needles (recrystallized from acetic acid)[d,h]	Solid (plates)[e]	Solid (plates or leaftlets)[e]
Melting point	166 °C[d]	255–256 °C[b]	262 °C[c]
Boiling point	No data	448 °C[b]	No data
Density	No data	No data	1.282 g/cm^3[,h]
Specific gravity	No data	1.274 at 20 °C/4 °C[i]	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	6.76x10^{-3} mg/L at 25 °C[d]	2.8x10^{-3} mg/L[p]	5x10^{-4} mg/L[b]
Organic solvent(s)	Slightly soluble in alcohol and acetic acid; soluble in hydrogen sulfide on heating[d]	Slightly soluble in acetone, carbon disulphide, diethyl ether, ethanol glacial acetic acid toluene hot xylene; soluble in benzene[b]	Slightly soluble in ethyl alcohol; soluble in acetone, acetic acid, benzene, toluene and xylene[e]
Partition coefficients:			
Log K_{ow}	6.12[d]	5.16[k]	6.84[k]
Log K_{oc}	4.7–4.8[d]	5.30[k]	6.52[k]
Vapor pressure	1.50x10^{-8} mm Hg at 25 °C[d]	6.3x10^{-7} mm Hg at 25 °C[k]	1x10^{-10} mm Hg at 20 °C[k]
Henry's law constant	1x10^{-6} atm–m^3/mol[d]	1.05x10^{-6} atm-m^3/mol[k]	7.3x10^{-8} atm-m^3/mol[k]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	0	0	0
Explosive limits	No data	No data	No data

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a] (continued)

Property	Fluoranthene	Fluorene	Indeno[1,2,3-c,d]pyrene
Molecular weight	202.26	166.2[g]	276.3[g]
Color	Pale yellow	White[g]	Yellow plates or needles showing a greenish-yellow fluorescence[g]
Physical state	Solid (needles or plates)	Solid (leaflets or flakes; crystalline plates)[g]	Solid (plates or needles)[g]
Melting point	11 °C	116–117 °C[g]	163.6 °C[g]
Boiling point	~375 °C	295 °C[g]	530 °C
Density	No data	No data	No data
Specific gravity	1.252 at 0 °C/4 °C	1.203 at 0 °C/4 °C	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	0.20–0.26 mg/L[g]	1.68–1.98 mg/L[g]	0.062 mg/L[g]
Organic solvents	Alcohol, ether, benzene, acetic acid	Acetic acid, acetone, benzene, carbon disulphide, carbon tetrachloride, diethyl ether, ethanol, pyrimidine, solution, toluene[g]	Soluble in organic solvents[g]
Partition coefficients:			
Log K_{ow}	4.90[k]	4.18[k]	6.58[k]
Log K_{oc}	4.58[k]	3.86[k]	6.20[k]
Vapor pressure	5.0×10^{-6} mm Hg at 25 °C[k]	3.2×10^{-4} mm Hg at 20 °C[d]	~10^{-11}–10^{-6} mm Hg at 20 °C[k]
Henry's law constant	6.5×10^{-6} atm–m^3/mol[k]	1.0×10^{-4} atm-m^3/mol[r]	6.95×10^{-8} atm-m^3/mol[k]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	0	0	0
Explosive limits	No data	No data	No data

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a] (continued)

Property	Phenanthrene	Pyrene
Molecular weight	178.2[b]	202.3[b]
Color	Colorless[b]	Colorless, pale yellow plates (recrystallized from toluene) or slight blue fluorescence (recrystallized from ethanol or sublimation)[b]
Physical state	Solid (plates, crystals, or leaflets)[b]	Solid (plates or tablets)[b]
Melting point	100 °C[b]	156 °C
Boiling point	340 °C	393 °C[e]; 404 °C[l]
Density	0.980 g/cm^3 at 4 °C	1.271 g/cm^3 at 23 °C
Specific gravity	No data	1.271 at 23 °C/4 °C
Odor	Faint aromatic odor	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 25 °C	1.20 mg/L[p]	0.077 mg/L[p]
Organic solvents	Soluble glacial acetic acid, benzene, carbon disulphide, carbon tetrachloride, anhydrous diethyl ether, ethanol, toluene[b]	Soluble in alcohol benzene, carbon disulphide, diethyl ether, ethanol, petroleum ether, toluene, race tone[b]
Partition coefficients:		
Log K_{ow}	4.45[k]	4.88[k]
Log K_{oc}	4.15[k]	4.58[k]
Vapor pressure	6.8x10^{-4} mm Hg at 25 °C[d]	2.5x10^{-6} mm Hg at 25 °C[k]
Henry's law constant	2.56x10^{-5} atm–m^3/mol[r]	1.14x10^{-5} atm-m^3/mol[r]
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	0	0
Explosive limits	No data	No data

[a]All information obtained from HSDB except where noted
[b]IARC 1973
[c]Eller 1984
[d]HSDB 1994
[e]Weast et al. 1988
[f]Weast 1987
[g]IARC 1983
[h]Temperature not specified
[i]Sax and Lewis 1989
[j]Aldrich 1986
[k]Mabey et al. 1982
[l]Windholz 1983
[m]EPA 1987a
[n]ITII 1982
[p]Yalkowsky et al 1993
[q]Sims and Overcash 1983
[r]Nirmalakhandan and Speece 1988

The following equation can be used for the converstion of vapor phase PAHs at 25 °C:

$$\frac{\text{mg/m}^3 \times 24.45}{\text{Mol. wt.}}$$

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

The commercial production of PAHs is not a significant source of these compounds in the environment. The primary source of many PAHs in air is the incomplete combustion of wood and fuel (Perwak et al. 1982). PAHs are a ubiquitous product of combustion from common sources such as motor vehicles and other gas-burning engines, wood-burning stoves and furnaces, cigarette smoke, industrial smoke or soot, and charcoal-broiled foods (IARC 1983). Natural sources include volcanoes, forest fires, crude oil, and shale oil (HSDB 1994).

Of the 17 PAHs included in this profile, only three are produced commercially in the United States in quantities greater than research level: acenaphthene, acenaphthylene, and anthracene. Acenaphthene is manufactured by passing ethylene and benzene or naphthalene through a red hot tube or by heating tetrahydroacenaphthene with sulfur to 180 ºC. It can also be made from acenaphthenone or acenaphthenequinone by high-pressure hydrogenation in decalin with nickel at 180-240 ºC (Windholz 1983). Another manufacturing process involves the isolation and recovery of acenaphthene from a concentrated tar-distillation fraction (Grayson 1978). Technical grades of acenaphthene are typically 98% pure (HSDB 1994). Acenaphthylene is produced by catalytic degradation of acenaphthene (Grayson 1978). Toxic Release Chemical Inventory (TRI) production data for acenaphthylene and acenaphthene are not available (TRI92 1994) and no other data on the production volumes for these compounds in the United States could be found.

Anthracene is produced commercially by recovery from the coal tar distillation fraction known as “anthracene oil” or “green oil.” Purification techniques, including heating and vacuum distillation, are required to remove the major contaminant, potassium carbazole (IARC 1985). Zone melting of solid anthracene and crystallization from benzene followed by sublimation are also effective purification techniques (Hampel and Hawley 1973). Technical grades of anthracene are typically 90-98% pure (HSDB 1994). Table 4-l shows the number of facilities per state that manufacture or process anthracene, as well as a range of the maximum amounts of anthracene present at the facilities (TR192 1994). The following companies have been cited as current U.S. manufacturers of anthracene for sale/distribution: ABC Coke Division (Tarrant City, Alabama); Granite City Steel (Granite City, Illinois); Citizens Gas and Coke Utility (Indianapolis, Indiana); National Steel Corporation (Encore,

Table 4-1. Facilities that Manufacture or Process Anthracene

State[a]	Number of facilities	Range of maximum amounts on site in thousands of pounds[b]	Activities and uses[c]
AL	7	1-1000	1, 4, 6, 8, 9
AR	1	1-10	3, 9
CA	1	10-100	1, 5
FL	2	1-100	8
IL	5	10-10000	1, 2, 4, 5, 6, 8, 10
IN	5	1-1000	1, 4, 5, 8
KY	2	1-100	1, 6, 11
LA	7	0-10000	1, 2, 5, 6, 9
MI	2	1-100	1, 4, 5, 6, 8
MN	1	1-10	1, 4
MO	1	1-10	13
MS	2	1-100	1, 6, 8
NJ	3	10-50000	1, 3, 4, 7, 8, 10
NY	2	1-1000	1, 5, 6, 8
OH	12	0-10000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
OK	1	10-100	2, 3, 9
PA	7	0-10000	1, 4, 5, 6, 7, 8, 10
SC	2	1-10	5, 8
TX	13	0-10000	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 13
UT	2	10-50000	1, 3, 4, 7, 10
VI	1	10000-50000	1, 4, 7
WA	2	10-1000	1, 2, 6, 12
WV	3	10-10000	1, 5, 6, 9, 12

Source: TRI92 1994

[a]Post office state abbreviations used
[b]Data in TRI are maximum amounts on site at each facility.
[c]Activities/Uses

1. Produce
2. Import
3. For on-site use/processing
4. For sale/distribution
5. As a byproduct
6. As an impurity
7. As a reactant
8. As a formulation component
9. As a product component
10. For repackaging
11. As a chemical processing aid
12. As a manufacturing aid
13. Ancillary or other uses

Missouri); Koch Refining Company (Pine Bend, Montana); Amerada Hess Corporation (Port Reading, New Jersey); Reilly Industries, Incorporated (Cleveland, Ohio, and Lone Star, Texas); New Boston Coke Corporation (New Boston, Ohio); Bethlehem Steel Structural (Bethlehem, Pennsylvania); Geneva Steel (Vineyard, Utah); and Hess Oil Virgin Islands Corporation (St. Croix, Virgin Islands). It should be noted that another source (SRI 1994) lists no anthracene processing or manufacturing facilities. In 1982, more than 2,270 kg of anthracene were produced in the United States; more recent production data are not available (HSDB 1994).

The following compounds are not produced commercially in the United States: benz[a]anthracene, benzo[b]fluoranthene, benzo[e]pyrene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, fluoranthene, fluorene, indeno[l,2,3-c,d]pyrene, phenanthrene, and pyrene (HSDB 1994; IARC 1985).

4.2 IMPORT/EXPORT

The most recent data available on U.S. import and export volumes of individual PAHs are as follows: in 1986, 4,000 kg of acenaphthene were imported into the United States; in 1985, 5,730,000 kg of anthracene oil, 882,000 kg of anthracene (≥ 30% purity by weight), 1,040 kg of fluoranthene, and 57,400 kg of pyrene were imported into the United States; in 1984, 79,200 kg of chrysene, 9,440 kg of fluoranthene, 9.1 kg of fluorene, and 551 kg of phenanthrene were imported into the United States; in 1984, 502,000 kg of anthracene oil and pitch of tar coke were exported from the United States, increasing to 3,890,000 kg by 1987 (HSDB 1994; USDOC 1985). In 1985, the United States imported a total of almost 12 million gallons of creosote oil from the Netherlands, France, West Germany, and other countries and almost 185 million pounds of coal tar pitch, blast furnace tar, and oil-gas tar from Canada, Mexico, West Germany, Australia, and other countries (USDOC 1985). The only relevant information found on more recent import and export volumes is for the following group of compounds which contains two PAHs: acenaphthene, chrysene, cymene, and indene (NTDB 1994). Annual import volumes for this group of compounds were $2x10^6$, $3x10^6$, and $9x10^5$ kg for the years 1991, 1992, and 1993, respectively. While these numbers set an upper limit on the import volume for any one of the compounds in this group, they do not provide any further information on import volumes of acenaphthene and chrysene.

4.3 USE

There is no known use for acenaphthylene, benz[a]anthracene, benzo[b]fluoranthene, benzo[e]pyrene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene, or pyrene except as research chemicals (Hawley 1987; HSDB 1994).

Anthracene is used as an intermediate in dye production, in the manufacture of synthetic fibers, and as a diluent for wood preservatives. It is also used in smoke screens, as scintillation counter crystals, and in organic semiconductor research (Hawley 1987). Anthracene is used to synthesize the chemotherapeutic agent, Amsacrine (Wadler et al. 1986). Acenaphthene is used as a dye intermediate, in the manufacture of pharmaceuticals and plastics, and as an insecticide and fungicide (HSDB 1994; Windholz 1983).

Fluorene is used as a chemical intermediate in many chemical processes, in the formation of polyradicals for resins, and in the manufacture of dyestuffs (Hawley 1993; HSDB 1994). Phenanthrene is used in the manufacture of dyestuffs and explosives and in biological research (Hawley 1987; HSDB 1994). Fluoranthene is used as a lining material to protect the interior of steel and ductile-iron drinking water pipes and storage tanks (NRC 1983).

4.4 DISPOSAL

PAHs serve as the basis for listing certain hazardous wastes under the Resource Conservation and Recovery Act (RCRA); they are listed as constituents for groundwater monitoring and are monitored in hazardous wastes as part of the RCRA land disposal restrictions (EPA 1989c). Specific regulations governing the generation, treatment, storage and disposal of hazardous wastes containing PAHs are listed in Chapter 7.

Approximately two-thirds of the PAHs in surface waters are particle-bound and can be removed by sedimentation, flocculation, and filtration processes. The remaining one-third of the dissolved PAHs usually require oxidation for partial removal/transformation (EPA 1980).

Acenaphthene, acenaphthylene, benz[a]anthracene; benzo[a]pyrene, benzo[b]fluoranthene, chrysene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene, and fluoranthene are all good candidates for rotary kiln incineration at temperatures ranging from 820 to 1,600 ºC and residence times of seconds for liquids and gases, and hours for solids (EPA 1981a; HSDB 1994). Benz[a]anthracene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene, and fluoranthene all are good candidates for fluidized-bed incineration at a temperature of 450-980 ºC and residence times of seconds for liquids and gases and longer for solids (EPA 1981a; HSDB 1994). Benz[a]anthracene also is a good candidate for liquid injection incineration at a temperature range of 650-1,600 ºC and a residence time of 0.1 to 2 seconds (EPA 1981a; HSDB 1994). Liquids containing pyrene should be atomized in an incinerator. Combustion is improved by mixing with a more flammable solvent. Solids should be combined with paper or other flammable material prior to incineration (UN 1985). Benz[a]anthracene, chrysene, dibenz[a,h]anthracene, benzo[k]fluoranthene, benzo[j]fluoranthene, benzo[b]fluoranthene, and benzo[a]pyrene laboratory wastes can be oxidized using agents such as concentrated sulfuric acid, potassium dichromate, or potassium permanganate (IARC 1985). Water contaminated with benzo[g,h,i]perylene can be decontaminated by carbon adsorption (EPA 1981c). Anthracene in waste chemical streams may be subjected to ultimate disposal by controlled incineration (HSDB 1994; EPA 1981a).

Bioremediation is emerging as a practical alternative to traditional disposal techniques (Cemiglia 1993; Thomas and Lester 1993; Wilson and Jones 1993). It has only recently been considered as a viable treatment method for contaminated soils but is now being used or is under consideration by the EPA for clean-up in over 135 Super-fund and underground storage tank sites (Carraway and Doyle 1991; Sims 1990; EPA 1989d). *In situ* treatment involves addition of nutrients, an oxygen source, and, sometimes, specifically adapted microorganisms that enhance degradation. Current *in situ* treatments have been used with some success for removal of two- and three-ring PAHs but generally are considered ineffective for removal of most PAHs from soil (Wilson and Jones 1993).

On-site methods such as landfarming also have been used successfully to degrade PAHs with three or fewer aromatic rings. The waste material is applied to the soil as a slurry and the area is fertilized, irrigated, limed, and tilled. The major disadvantage of landfarming is that contaminants can move from the treatment area. To enhance treatment and minimize movement of contaminants, prepared beds have been used. For this type of remediation, the contaminated soil is removed to a specially

prepared area lined with a low permeability material and the bed is managed to optimize degradation (Wilson and Jones 1993).

A third type of bioremediation involves the use of a bioreactor in a dedicated treatment area. The contaminated soil is excavated, slurried with water, and treated in the reactor. The horizontal drum and airlift-type reactors are usually operated in the batch mode but may also be operated in a continuous mode. Because there is considerable control over the operating conditions, treatment often is quick and effective. Contaminated groundwater and effluent also may be treated in either fixed-film' or stirred-tank bioreactors. However, bioreactors are still in the developmental stages and further research is required to optimize their efficiency and cost effectiveness (Wilson and Jones 1993).
A pilot-scale evaluation of the bioreactor method was carried out in a joint Superfund Innovative Technology Evaluation (SITE) project and a project to collect information for the Best Demonstrated Available Technologies (BDAT) database (Lewis 1993). Five 64-L bioslurry reactors were charged with a 30% (wt/vol) ratio of creosote-contaminated soil from a Superfund site, inoculated with PAH degraders, and inorganic nutrients were added. Total PAH -degradation averaged 93.4 ± 3.2% over all reactors during the 12-week study, with 97.4% degradation of the 2- and 3-ring PAHs and 90% degradation of the 4- to 6-ring PAHs.

Huesemann et al. (1993) carried out a 16-week laboratory study to assess the biotreatability of PAHs in refinery American Petroleum Institute (API) oil separator sludge. Two biotic treatments were evaluated: (1) a nutrient-amended, inoculated, aerated slurry reactor, and (2) an oxygen-sparged reactor. A sterile, nitrogen-sparged reactor was used as a control. Naphthalene, anthracene, phenanthrene, and benzo[a]pyrene were completely biodegraded in 4 weeks in both biotic reactors. Chrysene biodegraded in 4 weeks in the aerated reactor and in 16 weeks in the oxygen-sparged reactor. No significant changes in pyrene concentration were observed in the oxygen-sparged reactor and only a 30% degradation was observed in the aerated reactor. The authors concluded that aerobic biotreatment was successful in removing most BDAT PAHs from refinery API oil separator sludge.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

This chapter provides a discussion of the environmental fate and potential for human exposure to 17 PAHs. For the purposes of describing environmental fate, these PAHs have been grouped into low, medium, and high molecular weight classes (see Section 5.3.1, Transport and Partitioning). In general, chemicals within each class have similar environmental fates. When available, data are provided for the individual PAHs that are the subject of the profile. When data on each compound are not available, data on members of the weight class are provided. Data regarding total PAHs or generalizations about PAHs are also used to provide insight into the behavior of the compounds cbvered in this profile.

PAHs are released to the environment through natural and synthetic sources with emissions largely to the atmosphere. Natural sources include emissions from volcanoes and forest fires. Synthetic sources provide a much greater release volume than natural sources; the largest single source is the burning of wood in homes. Automobile and truck emissions are also major sources of PAHs. Environmental tobacco smoke, unvented radiant and convective kerosene space heaters, and gas cooking and heating appliances may be significant sources of PAHs in indoor air. Hazardous waste sites can be a concentrated sources of PAHs on a local scale. Examples of such sites are abandoned wood-treatment plants (sources of creosote) and former manufactured-gas sites (sources of coal tar). PAHs can enter surface water through atmospheric deposition and from discharges of industrial effluents (including wood-treatment plants), municipal waste water, and improper disposal of used motor oil. Several of the PAHs have been detected at hazardous waste sites at elevated levels. In air, PAHs are found sorbed to particulates and as gases. Particle-bound PAHs can be transported long distances and are removed from the atmosphere through precipitation and dry deposition. PAHs are transported from surface waters by volatilization and sorption to settling particles. The compounds are transformed in surface waters by photooxidation, chemical oxidation, and microbial metabolism. In soil and sediments, microbial metabolism is the major process for degradation of PAHs. Although PAHs are accumulated in terrestrial and aquatic plants, fish, and invertebrates, many animals are able to metabolize and eliminate these compounds. Bioconcentration factors (BCFs), which express the concentration in tissues compared to concentration in media, for fish and crustaceans are frequently in

the 10-10,000 range. Food chain uptake does not appear to be a major source of exposure to PAHs for aquatic animals.

The greatest sources of exposure to PAHs for most of the United States population are active or passive inhalation of the compounds in tobacco smoke, wood smoke, and contaminated air, and ingestion of the compounds in foodstuffs. The general population may also be exposed to PAHs in drinking water and through skin contact with soot and tars. Higher than background levels of PAHs are found in foods that are grilled or smoked. Estimates of human exposures to PAHs vary. The average total daily intake of PAHs by a member of the general population has been estimated to be 0.207 µg from air, 0.027 µg from water, and 0.16-l .6 µg from food. The total potential exposure to carcinogenic PAHs for adult males in the United States was estimated to be 3 µg/day. Smokers of unfiltered cigarettes may experience exposures twice as high as these estimates. Persons living in the vicinity of hazardous waste sites where PAHs above background levels have been detected may also be exposed to higher levels.

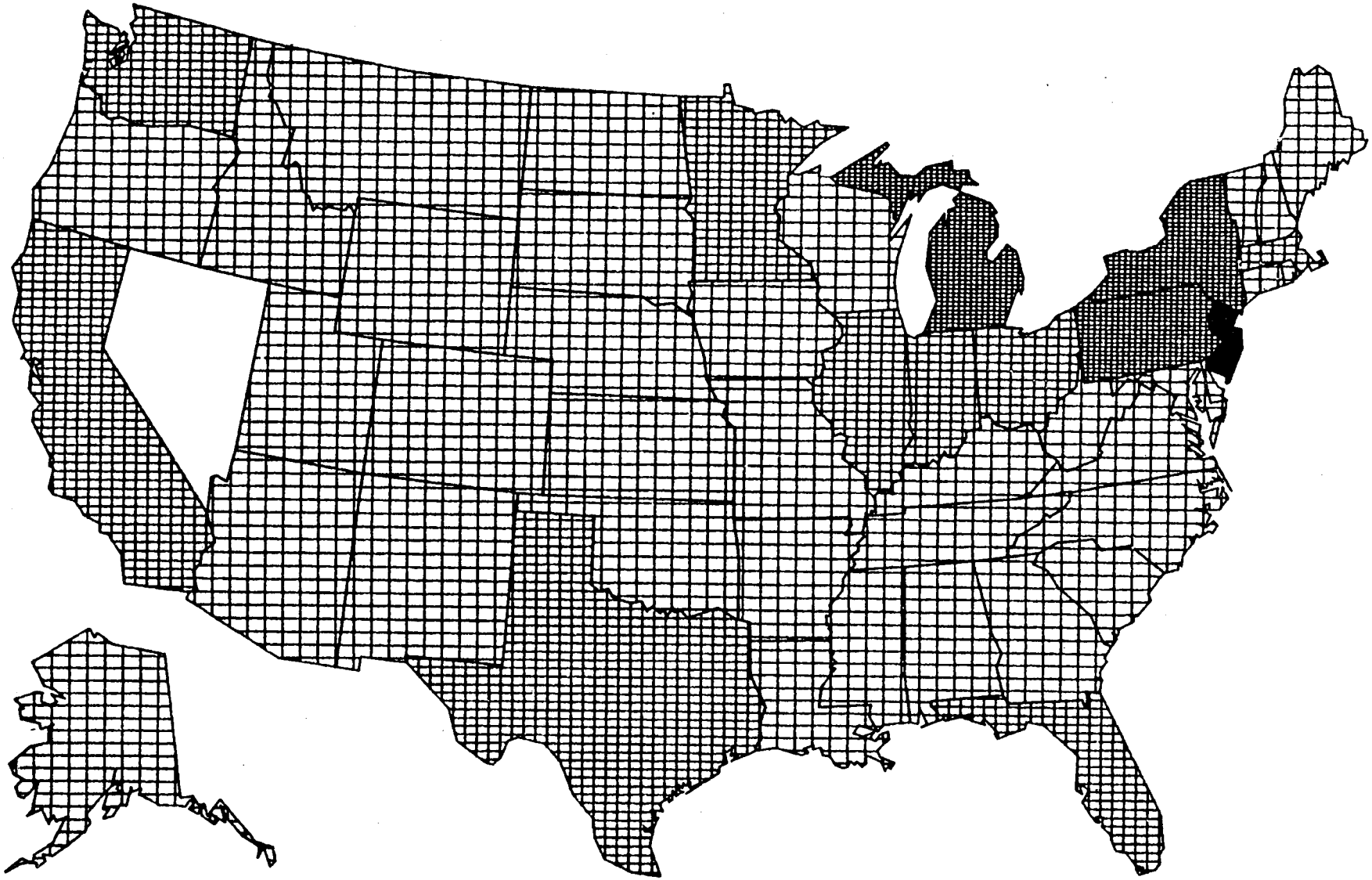
PAHs have been identified in at least 600 of the 1,408 hazardous waste sites that have been proposed for inclusion in the EPA National Priorities List (NPL) (HazDat 1994). However, the number of sites evaluated for PAHs is not known. The frequencies of these sites can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Most of the direct releases of PAHs to the environment are to the atmosphere from both natural and anthropogenic sources, with emissions from human activities predominating. PAHs in the atmosphere are mostly associated with particulate matter; however, the compounds are also found in the gaseous phase (NRC 1983; Yang et al. 1991). The primary natural sources of airborne PAHs are forest fires and volcanoes (Baek et al. 1991; NRC 1983). The residential burning of wood is the largest source of atmospheric PAHs (Peters et al. 1991; Ramdahl et al. 1982); releases are primarily the result of inefficient combustion and uncontrolled emissions (Freeman and Cattell 1990; NRC 1983; Tan et al. 1992). Other important stationary anthropogenic sources include industrial power generation, incineration (Shane et al. 1990; Wild et al. 1992); the production of coal tar, coke, and asphalt; and petroleum catalytic cracking (Baek et al. 1991; Guerin 1978; Perwak et al. 1982; Santodonato 1981).

FIGURE 5-1. FREQUENCY OF NPL SITES WITH PAHs CONTAMINATION*



*Derived from HazDat 1994

Environmental tobacco smoke, unvented radiant and convective kerosene space heaters, and gas cooking and heating appliances may be important sources of PAHs in indoor air (Chuang et al. 1991; Hoffmann and Hoffmann 1993; Mumford et al. 1991; NRC 1986; Traynor et al. 1990). Stationary sources account for about 80% of total annual PAH emissions; the rest are from mobile sources. The most important mobile sources of PAHs are vehicular exhaust from gasoline and diesel-powered engines (Baek et al. 1991; Johnson 1988; Yang et al. 1991). Mobile sources are often the major contributors to PAH releases to the atmosphere in urban or suburban areas (Baek et al. 1991). The amount of anthracene released to the atmosphere in 1992 by U.S. industrial facilities sorted by state is given in Table 5-l (TRI92 1994). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. TRI92 (1994) data were not available for other PAHs included in this profile.

The U.S. annual emissions (from early to mid 1970s) of polycyclic organic matter (a term generally used to describe PAHs, their nitrogen-containing analogs, and their quinone degradation products [Santodonato et al. 1981]) were estimated by NRC (1983) as follows: open buming 4,024 metric tons (39%), residential heating-3,956 metric tons (38%), automobiles and trucks-2,266 metric tons (22%), and industrial boilers-74 metric tons (1%). NRC (1983) estimated that the total amount of benzo[a]pyrene produced in the United States is between 300 and 1,300 metric tons annually. Peters et al. (1981) estimated that a total of 11,031 metric tons of PAHs were released to the atmosphere in the United States on an annual basis, with 36% of the total coming from residential heating, 6% from industrial processes, 1% from incineration, 36% from open burning, 1% from power generation, and 21% from mobile sources. This estimate can be compared to that of Ramdahl et al. (1982), who reported that a total of 8,598 tons of PAHs were emitted to the atmosphere annually from the following sources: (1) residential heating-16%; (2) industrial processes 41%; (3) incineration-l % (4) open burning-13%; (5) power generation-5%; and (6) mobile sources-25%.

The composition of PAH emissions varies with the combustion source. For example, emissions from residential wood combustion contain more acenaphthylene than other PAHs (Perwak et al. 1982), whereas auto emissions contain more benzo[g,h,i]perylene and pyrene (Rogge et al. 1993a; Santodonato et al. 1981). PAHs in diesel exhaust particulates are dominated by three- and four-ring compounds, primarily fluoranthene, phenanthrene, and pyrene (KelIy et al. 1993; Rogge et al. 1993a; Westerholm and Li 1994). Diesel exhaust vapor emissions are dominated by phenanthrene and anthracene (Westerholm and Li 1994). Acenaphthene, fluorene, and phenanthrene have been found to

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Anthracene

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground Injection	Total Environment[c]	POTW Transfer	Off-site Waste Transfer
AL	7	2-3500	0-5	0	0	2-3505	0	0-465000
AR	1	327-327	0	0	0	327-327	0	0
CA	1	1-1	0	0	0	1-1	0	0
FL	2	0-702	0	0	0	0-702	0	0-250
IL	5	126-1000	0	0	0	126-1000	0-250	0-10273
IN	5	0-11090	0	0	0	0-11090	0-88	0
KY	2	20-94	0-78	0	0	20-172	0	0-680
LA	7	0-125	0-9	0	0	0-125	0	0-7370
MI	2	85-4085	0	0	0	85-4085	0-5	0-1190
MN	1	160-160	0	0	0	160-160	0	0
MO	1	10-10	5-5	0	0	15-15	0	0
MS	2	0-250	108-250	0-250	0	108-750	0	0
NJ	3	0-272	0-5	0-7	0	0-272	0	2-250
NY	2	0-910	0	0	0	0-910	0	0
OH	12	0-3700	0-250	0-720	0	0-4425	0-5	0-14112
OK	1	0-0	0	1-1	0	1-1	0	5-5
PA	7	0-997	0-37	0-560	0	0-1594	0	0-7900
SC	2	0-255	0	0	0	0-255	0-250	0-145
TX	13	0-2780	0	0-1532	0	0-2780	0	0-493911
UT	2	2-4	0	0	0	2-4	0	0
VI	1	3879-3879	15-15	0	0	3894-3894	0	0
WA	2	34-5395	11-250	0	0	45-5645	0	0-6650
WV	3	10-1500	0	0	0	10-1500	0	0-250

Source: TRI92 1994

be predominant in total (particle- and vapor-phase) diesel emissions (Lowenthal et al. 1994). Phenanthrene was the most abundant and frequently detected PAH in samples of fly ash and bottom ash collected from municipal refuse incinerators in the United States (Shane et al. 1990), whereas benzo[g,h,i]perylene was the most abundant and frequently detected PAH in fly ash samples collected from municipal solid waste incinerators in the United Kingdom (Wild et al. 1992). Fluoranthene, benzo[a]fluoranthene, benzo[g,h,i]perylene, indeno[1,2,3-c,d]pyrene, phenanthrene, and chrysene were predominant in emission particle samples collected from a municipal waste incinerator, whereas benzo[g,h,i]perylene and benz[a]anthracene were predominant in emission particle samples collected from a municipal and medical/pathological waste incinerator (Williams et al. 1994). Emission particle samples from a pilot scale rotary kiln incinerator charged with polyethylene contained predominantly benz[a]anthracene and phenanthrene when an afterburner was used, whereas pyrene, fluoranthene, and phenanthrene were predominant without an afterburner; total PAH concentrations were reduced by a factor greater than 100 by the use of an afterburner (Williams et al. 1994). In coal tar pitch emissions, concentrations of phenanthrene and pyrene have been reported to be 20-80 times greater than the concentrations of benzo[a]pyrene and benzo[g,h,i]perylene (Sawicki 1962). Chrysene/triphenylene, pyrene, and fluoranthene were dominant among the PAHs found in fine particle emissions from natural gas home appliances (Rogge et al. 1993b). Cigarette mainstream smoke contains a wide variety of PAHs with reported concentrations of benzo[a]pyrene ranging from approximately 5-80 ng/cigarette; sidestream smoke concentrations are significantly higher with sidestream/mainstream concentration ratios for benzo[a]pyrene ranging from 2.5 to 20 (Hoffmann and Hoffmann 1993; IARC 1983).

5.2.2 Water

Important sources of PAHs in surface waters include deposition of airborne PAHs (Jensen 1984), municipal waste water discharge (Barrick 1982), urban storm water runoff (MacKenzie and Hunter 1979), runoff from coal storage areas (Stahl et al. 1984; Wachter and Blackwood 1979), effluents .from wood treatment plants and other industries (DeLeon et al. 1986; Snider and Manning 1982; USDA 1980), oil spills (Giger and Blumer 1974), and petroleum pressing (Guerin 1978). Brown and Weiss (1978) estimated that l-2 tons of benzo[a]pyrene were released from municipal sewage effluents and 0.1-0.4 tons of benzo[a]pyrene were released from petroleum refinery waste waters in the United States in 1977.

Most of the PAHs in surface waters are believed to result from atmospheric deposition (Santodonato et al. 1981). However, for any given body of water, the major source of PAHs could vary. Jensen (1984) studied benzo[a]pyrene loading in a marine coastal area and determined that atmospheric deposition was indeed the major source of benzo[a]pyrene, with lesser amounts contributed by refinery effluent, municipal waste water, urban runoff, and rivers. Prahl et al. (1984) found that combustion-derived PAHs adsorbed to suspended sediments in rivers accounted for the major portion of PAHs in the waters of a Washington coastal area, and other studies have identified industrial effluents, road runoff, and oil spills as the major contributors in specific bodies of water (DeLeon et al. 1986; Santodonato et al. 1981).

The amount of anthracene released to surface water and publicly owned treatment works (POTWs) in 1992 by U.S. industrial facilities sorted by state is shown in Table 5-l (TRI92 1994). The TRI data should be used with caution since only certain facilities are required to report. This is not an exhaustive list. TRI92 (1994) data were not available for other PAHs included in this profile. Because most of the PAHs released to aquatic environments tend to remain near the sites of deposition, lakes, rivers, estuaries, and coastal marine environments near centers of human populations and industrial activity tend to be the major repositories of aquatic PAHs (Neff 1979).

5.2.3 Soil

Most of the PAHs in soil are believed to result from atmospheric deposition after local and long-range transport. The presence of PAHs in the soil of regions remote from any industrial activity supports this contention (Thomas 1986). Other potential sources of PAHs in soil include sludge disposal from public sewage treatment plants, automotive exhaust, irrigation with coke oven effluent, leachate from bituminous coal storage sites, and use of soil compost and fertilizers (Perwak et al. 1982; Santodonato et al. 1981; Stahl et al. 1984; White and Lee 1980). The principal sources of PAHs in soils along highways and roads are vehicular exhausts and emissions from wearing of tires and asphalt. PAHs may also be released to soils at concentrations above background and landfill sites (Black et al. 1989) and industrial sites, including creosote production (Ellis et al. 1991), wood-preserving (Mueller et al. 1991; Weissenfels et al. 1990), and coking plants (Weissenfels et al. 1990; Werner et al. 1988). Soils at the sites of former manufactured gas plants are also heavily contaminated with PAHs (Bewley et al. 1989; Tumey and Goerlitz 1990).

The amount of anthracene released to surface water and publicly owned treatment works (POTWs) in 1992 by U.S. industrial facilities sorted by state is shown in Table 5-l (TRI92 1994). Based on data in Table 5-1, only relatively small amounts of anthracene were discharged in hazardous waste sites from U.S. industrial facilities in 1992. However, some of the anthracene wastes transferred off-site (see Table 5-l) ultimately may be disposed of on land. The TRI data should be used with caution since only certain facilities are required to report. This is not an exhaustive list. TRI92 (1994) data were not available for other PAHs included in this profile.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The global movement of PAHs can be summarized as follows: PAHs released to the atmosphere are subject to short- and long-range transport and are removed by wet and dry deposition onto soil, water, and vegetation. In surface water, PAHs can volatilize, photolyze, oxidize, biodegrade, bind to suspended particles or sediments, or accumulate in aquatic organisms (with bioconcentration factors often in the 10-10,000 range). In sediments, PAHs can biodegrade or accumulate in aquatic organisms. PAHs in soil can volatilize, undergo abiotic degradation (photolysis and oxidation), biodegrade, or accumulate in plants. PAHs in soil can also enter groundwater and be transported within an aquifer.

Transport and partitioning of PAHs in the environment are determined to a large extent by physicochemical properties such as water solubility, vapor pressure, Henry's law constant, octanol-water partition coefficient (K_{ow}), and organic carbon partition coefficient (K_{oc}). In general, PAHs have low water solubilities. The Henry's law constant is the partition coefficient that expresses the ratio of the chemical's concentrations in air and water at equilibrium and is used as an indicator of a chemical's potential to volatilize. The K_{oc} indicates the chemical's potential to bind to organic carbon in soil and sediment. The K_{ow} is used to estimate the potential for an organic chemical to move from water into lipid and has been correlated with bioconcentration in aquatic organisms. Some of the transport and partitioning characteristics (e.g., Henry's law constant, K_{oc} values, and K_{ow}, values) of the 17 PAHs are roughly correlated to their molecular weights. These properties are discussed by grouping these PAHs as follows:

- Low molecular weight compounds (152-l 78 g/mol)-acenaphthene, acenaphthylene, anthracene, fluorene, and phenanthrene;
- Medium molecular weight compounds (202 g/mol)-fluoranthene and pyrene; and
- High molecular weight compounds (228-278 g/mol)-benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, benzo[e]pyrene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene.

As an example, Hattemer-Frey and Travis (1991) found that the low solubility, low vapor pressure and high K_{ow} of benzo[a]pyrene result in its partitioning mainly between soil (82%) and sediment (17%), with ≈1% partitioning into water and <1% into air, suspended sediment and biota.

PAHs are present in the atmosphere in the gaseous phase or sorbed to particulates. The phase distribution of PAHs in the atmosphere is important in determining their fate because of the difference in rates of chemical reactions and transport between the two phases. The phase distribution of any PAH depends on the vapor pressure of the PAH, the atmospheric temperature, the PAH concentration, the affinity of the PAH for the atmospheric suspended particles (K_{oc}), and the nature and concentrations of the particles (Baek et al. 1991). In general, PAHs having two to three rings (naphthalene, acenaphthene, acenaphthylene, anthracene, fluorene, phenanthrene) are present in air predominantly in the vapor phase. PAHs that have four rings (fluoranthene, pyrene, chrysene, benz[a]anthracene) exist both in the vapor and particulate phase, and PAHs having five or more rings (benzo[a]pyrene, benzo[g,h,i]perylene) are found predominantly in the particle phase (Baek et al. 1991; Jones et al. 1992). The ratio of particulate to gaseous PAHs in air samples collected in Antwerp, Belgium, was 0.03 for anthracene, 0.49 for pyrene, 3.15 for summed benz[a]anthracene and chrysene, and 11.5 for summed benzo[a]fluoranthene and benzo[b]fluoranthene (NRC 1983).

Using field data from Osaka, Japan, Pankow et al. (1993) examined the effects of relative humidity. (RH) on measured gas/particle partition coefficients over the range 42% ≥ 95%. They found that for seven PAHs or groups of PAHs (including phenanthrene + anthracene, fluoranthene, and pyrene) sorption decreased with increasing RH.

Atmospheric residence time and transport distance depend on the size of the particles to which PAHs are sorbed and on climatic conditions which will determine rates of wet and dry deposition. About 90-95% of particulate PAHs are associated with particle diameters <3.3 μm, and the peak distributions

are localized between 0.4 and 1.1 μm (Baek et al: 1991). Both coarse particles with aerodynamic diameters >3-5 μm and nucleic particles with diameters <0.1 μm have limited atmospheric residence times. The coarse particles are removed from the atmosphere by wet and dry deposition, while the nucleic particles are removed mainly by coagulation with other nucleic particles or with larger particles, followed by wet and dry deposition. Particles with a diameter range of 0.1-3.0 μm, with which airborne PAHs are principally associated, remain airborne for a few days or longer, due to slower dry deposition and less efficient wet deposition (Baek et al. 1991). Therefore, airborne particulate PAHs in this size range can transport long distances (Lunde and Bjorseth 1977). Larger particles emitted from urban sources tend to settle onto streets and become part of urban runoff. However, PAHs in urban air are primarily associated with submicrometer-diameter soot particles that have residence times of weeks and are subject to long-range transport (Butler and Crossley 1981). Long-range transport of PAHs was examined by Lunde and Bjorseth (1977), Bjorseth et al. (1978a), and Bjorseth and Olufsen (1983) who found that PAHs originating in Great Britain had been transported as far as Norway and Sweden.

The relative importance of wet and dry deposition in removing PAHs from the atmosphere varies with the individual PAH. For example, Perwak et al. (1982) estimated that a total of 23% of benzo[a]pyrene released to the atmosphere is deposited on soil and water surfaces. Dry deposition of benzo[a]pyrene adsorbed to atmospheric aerosols accounts for most of the removal; wet deposition is less significant by a factor of 3-5. In a mass balance study of the atmospheric deposition of PAHs to Siskiwit Lake, which is located on a wilderness island in northern Lake Superior, dry aerosol deposition of particulate phase PAHs was found to be the predominant form of input to surface waters by an average ratio of 9:l over wet deposition (McVeety and Hites 1988).

PAH compounds tend to be removed from the water column by volatilization to the atmosphere, by binding to suspended particles or sediments, or by being accumulated by or sorbed onto aquatic biota. The transport of PAHs from water to the atmosphere via volatilization will depend on the Henry's law constants (Hs) for these compounds. The low molecular weight PAHs have Henry's law constants in the range of 10^{-3}-10^{-5} atm-m^3/mol; medium molecular weight PAHs have constants in the 10^{-6} range; and high molecular weight PAHs have values in the range of 10^{-5}-10^{-8}. Compounds with values ranging from 10^{-3} to 10^{-5} are associated with significant volatilization, while compounds with values less than 10^{-5} volatilize from water only to a limited extent (Lyman et al. 1982). Half-lives for volatilization of benz[a]anthracene and benzo[a]pyrene (high molecular weight PAHs) from water have

been estimated to be greater than 100 hours (Southworth 1979). Southworth et al. (1978) stated that lower molecular weight PAHs could be substantially removed by volatilization if suitable conditions (high temperature, low depth, high wind) were present. Southworth (1979) estimated half-lives for volatilization of anthracene (a low molecular weight PAH) of 18 hours in a stream with moderate current and wind, versus about 300 hours in a body of water with a depth of 1 meter and no current. Even for PAHs susceptible to volatilization, other processes, such as adsorption, photolysis or biodegradation (see Section 5.3.2.2) may become more important than volatilization in slow-moving, deep waters.

Because of their low solubility and high affinity for organic carbon, PAHs in aquatic systems are primarily found sorbed to particles that either have settled to the bottom or are suspended in the water column. It has been estimated that two-thirds of PAHs in aquatic systems are associated with particles and only about one-third are present in dissolved form (Eisler 1987). In an estuary, volatilization and adsorption to suspended sediments with subsequent deposition are the primary removal processes for medium and high molecular weight PAHs, whereas volatilization and biodegradation (see Section 5.3.2.2) are the major removal processes for low molecular weight compounds (Readman et al. 1982). In an enclosed marine ecosystem study, less than 1% of the original amount of radiolabeled benz[a]anthracene added to the system remained in the water column after 30 days; losses were attributed to adsorption to settling particles and to a lesser extent to photodegradation (Hinga and Pilson 1987).

Baker et al. (1991) found that several PAHs were significantly recycled in the water column of Lake Superior. Fluorene and phenanthrene were rapidly removed from surface waters and settled through the water column to the sediment-water interface where a large fraction of the recently settled contaminants were released back into the water column. Higher molecular weight PAHs were found to have lower settling fluxes, but these compounds were efficiently buried in the surficial sediments with little recycling. Settling particles were found to be greatly enriched in hydrophobic organic chemicals.

The K_{oc} of a chemical is an indication of its potential to bind to organic carbon in soil and sediment. The low molecular weight PAHs have K_{oc} values in the range of 10^3-10^4, which indicates a moderate potential to be adsorbed to organic carbon in the soil and sediments. The medium molecular weight compounds have K_{oc} values in the lo4 range. High molecular weight PAHs have K_{oc} values in the

range of 10^5-10^6, which indicates stronger tendencies to adsorb to organic carbon (Southworth 1979). PAHs from lands cleared by slash and bum methods have been found to be deposited in charred litter and to move into soils by partitioning and leaching (Sullivan and Mix 1985). Phenanthrene and fluoranthene (low and medium molecular weight PAHs, respectively) from these areas were incorporated into soil to a greater extent (i.e., less strongly adsorbed to organic carbon in the charred litter) than high molecular weight PAHs such as benzo[g,h,i]pyrene and indeno[1,2,3-c,d]pyrene.

Because mobile colloids may enhance the mobility in porous medias of hydrophobic pollutants such as PAHs, Jenkins and Lion (1993) tested bacterial isolates from soil and subsurface environments for their ability to enhance transport of phenanthrene in aquifer sand. The most mobile isolates tested significantly enhanced the transport of phenanthrene, as a model PAH, in sand.

Sorption of PAHs to soil and sediments increases with increasing organic carbon content and with increasing surface area of the sorbent particles. Karickhoff et al. (1979) reported adsorption coefficients for sorption of pyrene to sediments as follows: sand-9.4-68; silt-1,500-3,600; and clay-l ,400-3,800. Gardner et al. (1979) found that from three to four times more anthracene and about two times more fluoranthene, benz[a]anthracene, and benzo[a]pyrene were retained by marsh sediment than by sand.

PAHs may also volatilize from soil. Volatilization of acenaphthene, acenaphthylene, anthracene, fluorene, and phenanthrene (low molecular weight PAHs) from soil may be substantial (Coover and Sims 1987; Southworth 1979; Wild and Jones 1993). However, of 14 PAHs studied in two soils, volatilization was found to account for about 20% of the loss of 1-methylnaphthalene and 30% of the loss of naphthalene; volatilization was not an important loss mechanism for anthracene, phenanthrene, fiuoranthene, pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, dibenz[a,h]anthracene, benzo[a]pyrene, and indeno[l,2,3-c,d]pyrene (Park et al. 1990).

Physicochemical properties of several phenanthrene and anthracene metabolites [1-hydroxy-2-napthoic acid (lH2NA); 2,3-dihydroxy naphthalene (23DHN); 2-carboxy benzaldehyde (2CBA); and 3,4-dihydroxy benzoic acid (34DHBA)] were experimentally measured and/or estimated and used with a Fugacity Level 1 model to estimate the distribution of the metabolites and their parent compounds in a contaminated soil (Ginn et al. 1994). The volumes of the air, water and soil phases were assumed to be 20%, 30%, and 48%, respectively. A volume of 2% was assumed for nonaqueous phase liquid

(NAPL) phase. The parent compounds, anthracene and phenanthrene, had the greatest tendency to be associated with the NAPL and soil phases. The polar metabolites of phenanthrene, lH2NA and 34DHBA, were associated more with the water phase of the subsurface. The metabolites 2CBA and 23DHN had a stronger affinity for the NAPL phase than for the water phase.

PAHs have been detected in groundwater either as a result of migration directly from contaminated surface waters or through the soil (Ehrlich et al. 1982; Wilson et al. 1986). Fluorene from an abandoned creosote pit was found to migrate through sand and clay into groundwater (Wilson et al. 1986). PAHs have also been shown to be transported laterally within contaminated aquifers (Ehrlich et al. 1982).

PAHs can be accumulated in aquatic organisms from water, sediments, and food. Bioconcentration factors (BCFs) for several species of aquatic organisms are listed in Table 5-2. In fish and crustaceans BCFs have generally been reported in the range of 10-10,000 (Eisler 1987). In general, bioconcentration was greater for the higher molecular weight compounds than for the lower molecular weight compounds. Bioconcentration experiments performed with radiolabeled compounds may overestimate the BCFs of some PAHs. For example, Spacie et al. (1983) estimated BCFs of 900 for anthracene and 4,900 for benzo[a]pyrene in bluegills (whole body) based on total radiolabeled carbon (^{14}C) activity. However, the estimated BCFs based only on the parent compounds were 675 and 490, respectively, indicating that biotransformation of the parent compounds occurred in addition to bioconcentration. Biotransformation by the mixed function oxidase (MFO) system in the fish liver can result in the formation of carcinogenic and mutagenic intermediates; exposure to PAHs has been linked to the development of tumors in fish (Eisler 1987). The ability of fish to metabolize PAHs may explain why benzo[a]pyrene frequently is not detected or found only at very low levels in fish from environments heavily contaminated with PAHs (Varanasi and Gmur 1980, 1981). The breakdown products (polyhydroxy compounds) are eliminated in feces (via bile) and urine. Although fish and most crustaceans evaluated to date have the MFO system required for biotransformation of PAHs, some molluscs and other aquatic invertebrates are unable to metabolize PAHs efficiently (Varanasi et al. 1985). Varanasi et al. (1985) ranked the extent of benzo[a]pyrene metabolism by aquatic organisms as follows: fish > shrimp > amphipod crustaceans > clams. Half-lives for elimination of PAHs in fish ranged from >2 days to 9 days (Niimi 1987).

TABLE 5-2. Polycyclic Aromatic Hydrocarbon (PAHs) Bioconcentration Factors (BCFs) for Selected Species of Aquatic Organisms[a]

PAH compound and organism	Exposure period[b]	BCF
ANTHRACENE		
Mayfly, *Hexagenia* sp.	28 h	3,500
Cladoceran, *Daphnia pulex*	24 h	760–1,200
Cladoceran, *Daphnia magna*	60 m	200
Fathead minnow, *Pimephales promelas*	2–3 d	485
Rainbow trout, *Salmo gairdneri*	72 h	4,400–9,200
BENZ(*a*)ANTHRACENE		
Cladoceran, *D. pulex*	24 h	10,109
BENZO(*a*)PYRENE		
Midge, *Chironomus riparius*, larvae	8 h	166
Mosquito, *Culex pipiens quinquefasciatus*	3 d	11,536
Alga, *Oedogonium cardiacum*	3 d	5,258
Periphyton, mostly diatoms	24 h	9,600
Cladoceran, *D. pulex*	3 d	134,248
Cladoceran, *D. magna*	6 h	2,837
Snail, *Physa* sp.	3 d	82,231
Clam, *Rangia cuneata*	24 h	9–236
Oyster, *Crassostrea virginica*	14 d	242
Northern pike *Esox lucius*	3.3 h–23 d	<55
Mosquitofish, *Gambusia affinis*	3 d	930
Bluegill, *Lepomis macrochirus*	4 h	12
Bluegill, *L. macrochirus*		
No dissolved humic material (DHM)	48 h	2,657
20 mg/L DHM	48 h	225
CHRYSENE		
Clam, *Rangia cuneata*	24 h	8
Pink shrimp, *Penaeus duorarum*		
Cephalothorax	28 d	248–361
Cephalothorax	28 d + 28 d postexposure	21–48
Abdomen	28 d	84–199
Abdomen	28 d + 28 d postexposure	22–91

TABLE 5-2. Polycyclic Aromatic Hydrocarbon (PAHs) Bioconcentration Factors (BCFs) for Selected Species of Aquatic Organisms[a] (continued)

PAH compound and organism	Exposure period[b]	BCF
FLUORENE		
Bluegill	30 d	200–1,800
PHENANTHRENE		
Cladoceran, *D. pulex*	24 h	325
Clam, *R. cuneata*	24 h	32
PYRENE		
Cladoceran, *D. pulex*	24 h	2,702

[a]Data summary from multiple studies; adapted from Eislen (1987)

[b]m = minutes; h = hours; d = days

Mollusks also eliminate accumulated PAHs. Neff (1982) reported that oysters (*Crassostrea gigas*) eliminated the following percentages of accumulated PAHs during a 7-day elimination period: benzo[a]pyrene-0%; benz[a]anthracene-32%; fluoranthene-66%; and anthracene-79%.

Fish and crustaceans readily assimilate PAHs from contaminated food, whereas mollusks and polychaete worms have limited assimilation (Eisler 1987). Biomagnification (a systematic increase in tissue concentrations moving up a food chain) has not been reported because of the tendency of many aquatic organisms to eliminate these compounds rapidly (Eisler 1987). In general, PAHs obtained from the diet contribute to total tissue concentrations only to a limited extent. For example, food chain uptake of anthracene by fathead minnows *(Pimephales promelas)* consuming water fleas *(Daphnia pulex)* was estimated to be about 15% of the amount accumulated from the water (Southworth 1979). In a simple aquatic food chain involving seston (i.e., organic and inorganic particulate matter >0.45 µm), blue mussels, and the common eider duck, significant changes were observed in the composition of 19 PAHs moving through the trophic levels. Decreasing PAH concentrations were found with increasing trophic level, probably as a result of the selective biotransformation capacity of the organisms for different PAHs. The high theoretical flux of PAHs through the food chain did not result in increasing concentrations with increasing trophic level (i.e., biomagnification was not observed), indicating rapid biotransformation of the compounds (Broman et al. 1990).

Sediment-associated PAHs can be accumulated by bottom-dwelling invertebrates and fish (Eisler 1987). For example, Great Lakes sediments containing elevated levels of PAHs were reported by Eadie et al. (1983) to be the source of the body burdens of the compounds in bottom-dwelling invertebrates. Varanasi et al. (1985) found that benzo[a]pyrene was accumulated in fish, amphipod crustaceans, shrimp, and clams when estuarine sediment was the source of the compound. Approximate tissue to sediment ratios were 0.6-1.2 for amphipods, 0.1 for clams, and 0.05 for fish and shrimp.

Some terrestrial plants can take up PAHs from soil via the roots or from air via the foliage; uptake rates are dependent on the concentration, solubility, and molecular weight of the PAH and on the plant species (Edwards 1983). Mosses and lichens have been used to monitor atmospheric deposition of PAHs (Thomas et al. 1984). About 30-70% of atmospheric PAHs (indeno[l,2,3-c,d]pyrene, fluoranthene, and benzo[a]pyrene) deposited on a forest were sorbed onto tree foliage (i.e., leaves and

needles) and then deposited as falling litter (Matzner 1984). Vaughan (1984) stated that atmospheric deposition on leaves often greatly exceeds uptake from soil by roots as a route of PAH accumulation.

The uptake of PAHs from soil to plants and the subsequent biomagnification is generally quite low (Sims and Overcash 1983). Ratios of PAH concentrations in vegetation to those in soil have been reported to range from 0.001 to 0.18 for total PAHs and from 0.002 to 0.33 for benzo[a]pyrene (Edwards 1983). ,In a study of PAH uptake from cropland soils conducted in the United Kingdom, elevated concentrations of PAHs in soils were not correlated with concentrations in plant tissues (Wild et al. 1992). The cropland soils had received repeated applications of PAHs in sewage sludge that was applied to the soils over a number of years. PAH content of the soils substantially increased as a result of the sludge amendments, and residues of some PAHs persisted in the soils for years. Tissues from plants grown in the treated soils were relatively enriched with low molecular weight PAHs (e.g., acenaphthene, fluorene, phenanthrene), but increased PAH concentrations (relative to tissues from plants grown in control plots that did not receive sludge amendments) were not consistently detected. The PAH concentrations in aboveground plant parts were not strongly related to soil PAH levels but were probably the result of atmospheric deposition. The presence of PAHs in root crop tissues was probably due to adsorption of the compounds to root surfaces. In a similar study, Wild and Jones (1993) used carrots. (Daucus carotu) as a test crop to investigate the potential for PAHs to move from sewage sludge amended soil into the human food chain. Due to the over-riding influence of atmospheric delivery of PAHs, there was no evidence that sludge application increased the PAH concentration of the foliage. Low molecular weight PAHs such as fluoranthene and pyrene were relatively enriched in the peel, probably because of their greater bioavailability. Transfer of PAHs from the root peel to the core appeared to be minimal. This again suggests that simple adsorption onto the peel maybe an important process.

Simonich and Hites (1994a) studied the partitioning of PAHs between vegetation and the atmosphere throughout the growing season and under natural conditions. They found the partitioning process to be dependent primarily upon the atmospheric gas-phase PAH concentration and the ambient temperature. During the spring and fall, when ambient temperatures are low, gas-phase PAHs partition into vegetation. In the summer, some PAHs volatilize and return to the atmosphere. They also developed a mass-balance model for PAHs in the northeastern United States and published values for PAH concentrations and fluxes in air, water, sediments, and soils (Simonich and Hites 1994b). Their model showed that 44 ± 18% of PAHs emitted into the atmosphere from sources in the region studied

were removed by vegetation. They further hypothesized that most of the PAHs absorbed by vegetation at the end of the growing season are incorporated into the soil and permanently removed from the atmosphere.

PAHs may accumulate in terrestrial animals through the food chain or by ingestion of soil. The environmental fate of creosote coal tar distillate (which contained 21% phenanthrene and 9% acenaphthene) was studied in a terrestrial microcosm containing soil, rye grass, insects, snails, mealworm larvae, and earthworms by Gile et al. (1982). Two gray-tailed voles (*Microtus canicaudus)* were added 54 days after the start of the experiment, which continued for 19-26 more days. Average surface soil concentrations (measured on an unspecified day) were 0.60 ppm (phenanthrene) and 1.19 ppm (acenaphthene). During the last 3 days of the experiment, the following phenanthrene concentrations were measured: snail-3.27 ppm; pill bugs-l .72 ppm; and earthworm-l 8.30 ppm. The acenaphthene concentrations measured were as follows: snail-11.2 ppm (day 37); pill bugs-0.99 ppm (day 75); and earthworm-71.9 ppm (days 72-75). The whole body concentration in the vole analyzed for phenanthrene was 7.20 ppm; in the vole analyzed for acenaphthene it was 37.00 ppm. The authors found that these compounds were not metabolized in this system. Whole body concentrations in the vole exceeded soil concentrations by a factor of 12 for phenanthrene and 31 for acenaphthene; however, most of the radiolabeled acenaphthene was found as bound residues in the gastrointestinal tract of the animal and, therefore, was not accumulated.

5.3.2 Transformation and Degradation

5.3.2.1 Air

The processes that transform and degrade PAHs in the atmosphere include photolysis and reaction with NO_x, N_2O_5, OH, ozone, sulfur dioxide, and peroxyacetyl nitrate (Baek et al. 1991; NRC 1983). Possible atmospheric reaction products are oxy-, hydroxy-, nitro- and hydroxynitro-PAH derivatives (Baek et al. 1991). Photochemical oxidation of a number of PAHs has been reported with the formation of nitrated PAHs, quinones, phenols, and dihydrodiols (Holloway et al. 1987; Kamens et al. 1986). Some of these breakdown products are mutagenic (Gibson et al. 1978). Reaction with ozone or peroxyacetylnitrate yields diones; nitrogen oxide reactions yield intro and dinitro PAHs. Sulfonic acids have also been formed from reaction with sulfur dioxide.

The rates of homogeneous vapor phase chemical reactions are usually faster than heterogeneous chemical reactions of particulate PAHs with sunlight and oxidants in the atmosphere, particularly due to light shielding and stabilizing (toward both oxidation and photolysis) effects in the adsorbed state (Behymer and Hites 1988).

PAHs have a wide range of volatilities and therefore are distributed in the atmosphere between the gas and particle phases. The 24 ring PAHs exist, at least partially, in the gas phase. Atkinson et al. (1991) calculated atmospheric lifetimes (1.44 times the half-life) of several gas-phase PAHs due to reactions with measured or estimated ambient concentrations of OH radicals, NO_3 radicals, N_2O_5, and O_3. Their laboratory studies showed that, for PAHs not containing cyclopenta-fused rings, the major gas-phase process resulting in atmospheric loss will be reaction with the OH radical. Calculated atmospheric lifetimes for acenaphthene, acenaphthylene, phenanthrene, and anthracene were on the order of a few hours. Nighttime reaction with N_2O_5 was estimated to be a minor source of atmospheric loss. The reactions of PAHs, including fluoranthene and pyrene, with the OH radical (in the presence of NO_x) and with N_2O_5 led to the formation of nitroarenes that have been identified in the ambient air. As a class of compounds, the nitrated PAHs have been found to be much more mutagenic than their parent PAHs (Kamens et al. 1993).

Most PAHs in the atmosphere .are associated with particulates (Baek et al.. 1991). Vu-Due and Huynh (1991) describe two types of chemical reactions that appear to be the predominant mode of transformation of these PAHs: (1) reactions between PAHs adsorbed on the particle surfaces and oxidant gases like NO_2, O_3, and SO_3 that do not appear to be influenced by exposure to UV irradiation and (2) photooxidation of PAHs irradiated either under solar radiation or simulated sunlight which produces a variety of oxidized derivatives such as quinones, ketones, or acids. Kamens et al. (1990) estimate that, even in highly polluted air, photolysis is the most important factor in the decay of particle-sorbed PAHs in the atmosphere, followed by reaction with NO_2, N_2O_5, and HNO_3.

The National Research Council (NRC 1983) noted that compounds adsorbed to soot are more resistant to photochemical reactions than pure compounds. Butler and Crossley (1981) estimated half-lives for degradation of the following PAHs adsorbed to soot particles and exposed to sunlight in air containing 10 ppm nitrogen oxides: benzo[a]pyrene-7 days; benzo[g,h,i]perylene-8 days; benz[a]anthracene-11 days; pyrene-14 days; chrysene-26 days; fluoranthene-27 days; and phenanthrene-30 days. However, Thomas et al. (1968) reported that benzo[a]pyrene adsorbed on

soot was readily photooxidized, with 60% of the compound destroyed within the first 40 minutes of exposure to sunlight. The effect of substrate on PAH photolytic half-lives was investigated by Behymer and Hites (1988). Photolysis of 18 PAHs adsorbed to low-carbon fly ash produced a wjde range of half-lives that indicated a relationship between structure and photochemical reactivity. Photolysis of the same compounds adsorbed to fly ash samples containing >5% carbon produced similar half-lives, indicating that for these fly ash samples, photolysis is dependent on the physical and chemical structure of the adsorbent and independent of PAH structure. The investigators postulated that dark (i.e., high carbon content) substrates stabilize PAHs to photolytic breakdown since they absorb more light, making less light available for photolysis. McDow et al. (1993) hypothesized that PAHs in atmospheric particles may be either dissolved in a liquid organic phase or adsorbed at an organic phase-solid elementai carbon interface. Therefore, the reactivity of PAHs might depend, not only on the surface characteristics of the particle's solid core, but also on the chemical composition of the organic phase that surrounds the core. Experiments revealed that photodegradation of PAHs (including benz [a]anthracene, chrysene, benzo[a]pyrene, benzo[b]fluoranthene, and benzo[k]fluoranthene) in a mixture of methoxyphenols, based on relative amounts collected in actual samples from hardwood burning, was 10-30 times faster than in hexane. Their results demonstrated that variations in chemical composition of different types of particles such as diesel exhaust and wood smoke might strongly affect the reactivity of PAHs. Eisenberg and Cunningham (1985) found that the photochemical reaction products of PAHs (anthracene, phenanthrene, fluoranthene, benz[a]anthracene, chrysene, and benzo[a]pyrene) adsorbed on particulates include singlet oxygen, which may be implicated in the formation of mutagenic compounds.

Some PAHs are degraded by oxidation reactions that have been measured in the dark (to eliminate the possibility of photodegradation). Korfmacher et al. (1980) found that, while fhrorene was completely oxidized, fluoranthene and phenanthrene were not oxidized, and benzo[a]pyrene and anthracene underwent minimal oxidation. These compounds were tested adsorbed to coal fly ash; the authors stated that the form of the compound (adsorbed or pure) and the nature of the adsorbent greatly affected the rate and extent of oxidation.

Several studies have been carried out to investigate the reaction of PAHs with ozone at ambient concentrations (Baek et al. 1991). Alebic-Juretic et al. (1990) found degradation of PAHs on particle surfaces by ozone to be an important pathway for their removal from the atmosphere. Half-lives of PAHs obtained under laboratory conditions were used to predict lifetimes in an atmosphere containing

a constant ozone concentration of 0.05 ppm. The predicted lifetimes were 3 hours for benzo[a]pyrene, 12 hours for pyrene, and 6 days for fluoranthene. Lane and Katz (1977) investigated the kinetics of the dark reaction of several PAHs with ozone and found the reaction to be extremely fast under simulated atmospheric conditions, with a reported half-life of 0.62 hours for benzo[a]pyrene exposed to 190 ppb of ozone.

In an attempt to determine the atmospheric oxidation processes that would result in an arene oxide functional group in PAHs, Murray and Kong (1994) studied the reaction of particle-bound PAHs with oxidants derived from the reactions of ozone with alkenes. Phenanthrene and pyrene were converted to arene oxides under these simulated atmospheric conditions. Control experiments indicated that the oxidant responsible for the transformation was not ozone, but a product of the reaction of ozone with tetramethylethylene (TME), probably the carbonyl oxide or the dioxirane derived from TME.

5.3.2.2 Water

The most important processes contributing to the degradation of PAHs in water are photooxidation, chemical oxidation, and biodegradation by aquatic microorganisms (Neff 1979). Hydrolysis is not considered to be an important degradation process for PAHs (Radding et al. 1976). The contribution of the individual processes,to the overall fate of a PAH will depend largely on the temperature, depth, pollution status, flow rate, and oxygen content of the water. As a result, a process that is a major loss/degradation process for a particular PAH in a certain surface water may not be so in another surface water with different water quality.

The rate and extent of photodegradation vary widely among the PAHs (Neff 1979). Unfortunately, there is no easily defined trend in the rates of photolysis that could be correlated with the chemical structure of PAHs. For example, the rate of aquatic photolysis of naphthalene containing two benzene rings is much slower than anthracene which contains three benzene rings (Anderson et al. 1986). Based on half-life data, photolysis in water may be an important fate determining process for acenaphthene, acenaphthylene, anthracene, pyrene, benzo[a]pyrene, and benz[a]anthracene relative to the other PAHs discussed in this document (Behymer and Hites 1988; Anderson et al. 1986; Zepp and Schlotzhauer 1983). A study by Nagata and Kondo (1977) reported that anthracene, phenanthrene, and benz[a]anthracene were susceptible to photodegradation, and that benzo[a]pyrene, chrysene, fluorene, and pyrene were resistant to photodegradation. In the photooxidation of PAHs, the most common

reactions result in the formation of peroxides, quinones, and diones (NAS 1972). The major photoproducts of anthracene, phenanthrene, and benz[a]anthracene are anthraquinone, 9,10-phenanthrequinone, and 7,12-benz[a]anthraquinone, respectively (David and Boule 1993).

The rate of photolysis is accelerated by the presence of certain sensitizers (Zepp and Schlotzhauer 1983). Conversely, the rate of photolysis is decreased by the presence of certain quenchers in water (e.g., certain carbonyl compounds). The importance of photolysis will also decrease with the increase of depth in a body of water, particularly in turbid water, because of light attenuation and scattering (Zepp and Schlotzhauer 1979).

Generally, oxidation with singlet oxygen and peroxy radicals are the two important oxidative processes for environmental pollutants in water. The rate constants for reactions of PAHs with singlet oxygen and peroxy radicals (Mabey et al. 1981) and the typical concentrations of the two oxidants in environmental waters (Mill and Mabey 1985) suggest that these reactions may not be important in controlling the overall fate of PAHs in water.

PAHs in water can be chemically oxidized by chlorination and ozonation. A high efficiency of PAH degradation from chlorination has been reported by Harrison et al. (1976a, 1976b) for both laboratory and waste-water treatment plant conditions. Pyrene was the most rapidly degraded PAH. Benz[a]anthracene, benzo[a]pyrene, and perylene were also highly degraded. Indeno[1,2,3-c,d]pyrene and benzo[g,h,i]pyrene were intermediate with respect to relative degradation. Benzo[k]fluoranthene and fluoranthene were the most slowly degraded of the compounds tested.

The PAH-related by-products resulting from chlorination are not fully known (Neff 1979). Oyler et al. (1978) identified the following products resulting from the chlorination of PAHs: anthraquinone, a chlorohydrin of fluoranthene; and monochloro derivatives of fluorene, phenanthrene, l-methyl-phenanthrene, and 1-methylnaphthalene. Mori et al. (1993) found that treatment of aqueous benz[a]anthracene (B[a]A) solution with chlorine in both the presence and absence of bromide ion produced a variety of halogenated compounds. The main product was the oxygenated compound, B[a]A-7, l2-dione. A variety of mutagenic halogen substituted and halogen additive (polar) compounds also were produced. The oxidation reaction with chlorine of B[a]A in water was accelerated in the presence of bromide ion.

In water, ozonation is generally slower and less efficient than chlorination in degrading PAHs (Neff 1979). Reaction pathways for ozonation of some PAHs include benz[a]anthracene to 7,12-quinone; benzo[a]pyrene to 3,6-, 1,6-, and 4,5diones; and fluorene to fluorenone (NAS 1972).
In general, PAHs can be significantly metabolized by microbes under oxygenated conditions. However, under anoxic conditions, degradation will be extremely slow (Neff 1979). Concentrations of dissolved oxygen >0.7 mg/L is adequate for biotransformation and the presence of a minimal concentration of PAH is required for biodegradation to proceed (Borden et al. 1989). The minimum total PAH concentration below which biotransformation may be inhibited under ambient nutrient conditions may be 30-70 µg/L (Borden et al. 1989). Some other factors that increase the rates of PAH biodegradation are higher water temperature (summer versus winter) and the presence of adapted microorganisms (Aamand et al. 1989; Anderson et al. 1986; Lee and Ryan 1983). Some PAHs are partially or completely degraded by some species of aquatic bacteria and fungi. The bacterial degradation pathway includes an initial dioxygenase attack to form cis-dihydrodiols (via dioxetane intermediates) that are further oxidized to dihydroxy products. In fungi and mammalian systems (which, unlike bacteria, have cytochrome P-450 enzyme systems), truns-dihydrodiol is produced via an arene oxide intermediate (Anderson et al. 1986; Cemiglia and Heitkamp 1989; Neff 1979). This is significant since the arene oxides have been linked to the carcinogenicity of PAHs. Algae were found to transform benzo[a]pyrene to oxides, peroxides, and dihydrodiols (Kirso et al. 1983; Warshawsky et al. 1983).

Microorganisms in stored groundwater samples completely degraded acenaphthene and acenaphthylene within 3 days (Ogawa et al. 1982). When these reactions occurred under aerobic conditions, there was no evidence of anaerobic degradation of PAHs within the aquifer from which the samples were obtained.

Information on the biodegradation of PAHs by fungi is limited compared to the information that is available about bacteria. However, the fungus *Cunninghamella elegans* has been reported to be capable of metabolizing naphthalene (Cemiglia and Gibson 1979), anthracene, benzo[a]pyrene (Cemiglia and Heitkamp 1989), and fluorene (Pothuluri et al. 1993).

No correlation between biodegradability and molecular weight is evident in three- to four-ring PAHs. For example, phenanthrene with three benzene rings biodegraded in an estuarine water from Savannah,

Georgia, with a half-life of 19 days in August, but anthracene, containing the same number of benzene rings, did not biodegrade at all (Lee and Ryan 1983). Based on estimated reaction rates or half-lives, acenaphthylene, acenaphthylene, and fluorene, the three PAHs that have lower molecular weights than phenanthrene, may not readily biodegrade in water (Lee and Ryan 1983; Mabey et al. 1981). While both naphthalene and phenanthrene biodegraded in water, other PAHs, such as anthracene, benz[a]anthracene, chrysene, and fluorene, did not readily biodegrade in water, but degraded readily in sediment water slurries (Lee and Ryan 1983). On the other hand, PAHs with five or more benzene rings, such as benzo[a]pyrene, dibenz[a,h]anthracene, and benzo[g,h,i]perylene, may not biodegrade readily even in sediment-water slurries (Lee and Ryan 1983; Mabey et al. 1981).

Based on theoretical modeling, photolysis would account for 5% and biodegradation 91% of the transformation/removal of anthracene from deep, slow moving, and somewhat turbid water. The corresponding values in a very shallow, fast-moving, clear water were 47 and 12%, respectively (Southworth 1979).

5.3.2.3 Sediment and Soil

Microbial metabolism is the major process for degradation of PAHs in soil environments. Photolysis, hydrolysis, and oxidation generally are not considered to be important processes for the degradation of PAHs in soils (Sims and Overcash 1983). However, in a study of PAH losses from four surface soils amended with PAHs in sewage sludge, losses due to volatilization and photolysis from sterilized soils were considered to be important for PAHs composed of less than four aromatic rings, whereas abiotic losses were insignificant for PAHs containing four or more aromatic rings (Wild and Jones 1993). Another study that assessed the fate of several PAHs, which included naphthalene, anthracene, phenanthrene, fluoranthene, pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, dibenz[a,h]anthracene, benzo[a]pyrene, dibenzo[a,i]pyrene and indeno[l,2,3-c,d]pyrene, in two soils concluded that abiotic degradation (photolysis and oxidation) accounted for mean losses of 13, 8.3, and 15.8% loss in case of naphthalene, anthracene, and phenanthrene, respectively. No significant abiotic loss was observed for the other PAHs (Park et al. 1990).

The rate and extent of biodegradation of PAHs in soil are affected by environmental factors; the organic content; structure and particle size of the soil; characteristics of the microbial population; the presence of contaminants such as metals and cyanides that are toxic to microorganisms; and the

physical and chemical properties of the PAHs (Wilson and Jones 1993). Based on experimental results, the estimated half-lives (days) of the PAHs in soil were: naphthalene, 2.1-2.2; anthracene, 50-l34; phenanthrene, 16-35; fluoranthene, 268-377; pyrene, 199-260; chrysene, 371-387; benz[a]anthracene, 162-261; benzo[b]fluoranthene, 211-294; benzo[a]pyrene, 229-309; dibenz[a,h]anthracene, 361-420; dibenzo(a,i)pyrene, 232-361; and indeno[l,2,3-c,d]pyrene, 288-289 (Park et al. 1990). Although there are differences in the biodegradation half-life values estimated by different investigators (Park et al. 1990; Wild and Jones 1993; Symons et al. 1988), their results suggest that the biodegradation half-lives of PAH with more than three rings will be considerably longer (>20 days to hundreds of days) than the PAHs with three or fewer rings. Environmental factors that may influence the rate of PAH degradation in soil include temperature, Ph, oxygen concentration, PAH concentrations and contamination history of soil, soil type, moisture, nutrients, and other substances that may act as substrate co-metabolites (Sims and Overcash 1983). The size and composition of microbial populations in turn can be affected by these factors. For example, in low-Ph soils, fungi are dominant over bacteria, and thereby control microbial degradation in these environments. Sorption of PAHs to organic matter and soil particulates also influences bioavailability, and hence, biotransformation potential. Sorption of PAHs by soil organic matter may limit biodegradation of compounds that would otherwise rapidly undergo metabolism (Manila1 and Alexander 1991; Weissenfels et al. 1992).

Although the pathways of microbial degradation are well known for anthracene, benzo[a]pyrene, and phenanthrene, degradation pathways for other PAHs are largely unknown (Sims and Overcash 1983). Metabolism of PAHs by bacteria includes the formation of cis-dihydrodiols through dioxetane intermediates, whereas in fungi (and mammalian systems) trans-dihydrodiols are produced through arene oxide intermediates (Sims and Overcash 1983). MacGillivray and Shiaris (1994) estimated the relative contribution of prokaryotic (bacteria) and eukaryotic (yeast, fungi) microorganisms to PAH biotransformation using phenanthrene as a model compound. They found that the relative contribution of eukaryotic microorganisms to phenanthrene transformation in inoculated sterile sediment was less than 3% of the total activity.

In laboratory studies, Sims et al. (1988) demonstrated extensive degradation of two-ring PAHs in sandy soils, with half-lives of approximately 2 days. The three-ring PAHs, anthracene, and phenanthrene had half-lives of 16 and 134 days, respectively. Four- to six-ring PAHs generally had half-lives >200 days. Anthracene and fluoranthene showed slightly higher biodegradation rates than

benz[a]anthracene or benzo[a]pyrene in a study with fine and medium sands and marsh sediments (Gardner et al. 1979). Degradation rates expressed as a percentage of the mass removed per week for the four compounds were anthracene-2.0-3.0%, fluoranthene-1.9-2.4%, benz[a]anthracene-1.4-l .8%, and benzo[a]pyrene-0.84-1.4%. The ranges of half-lives of phenanthrene and benzo[g,h,i]perylene in four soils amended with PAHs in sewage sludge were 83-193 days and 282-535 days, respectively. Mean half-lives were found to be positively correlated with log K_{ow} and inversely correlated with log water solubility. Previous exposure of the test soils to PAHs enhanced the rate of biodegradation of low molecular weight PAHs but had little effect on the loss of higher molecular weight compounds (Wild and Jones 1993).

Herbes and Schwall (1978) investigated the rates of microbial transformation of PAHs in freshwater sediments from both pristine and oil-contaminated streams. They found that turnover times (l/k) in the uncontaminated sediment were 10-400 times greater than in contaminated sediment. Absolute rates of PAH transformation (micrograms of PAH per gram of sediment per hour) were 3,000-125,000 times greater in the contaminated sediment. Turnover times in the oil-contaminated sediment increased 30-l00-fold per additional ring from naphthalene through benz[a]anthracene; naphthalene was broken down in hours while the turnover times for benz[a]anthracene and benz[a]pyrene were ~400 days and >3.3 years, respectively. Therefore, four- and five-ring PAHs, including the carcinogenic benz[a]anthracene and benz[a]pyrene, may persist even in sediments that have received chronic PAH inputs.

The rate of biodegradation may be altered by the degree of contamination. At hazardous waste sites, half-lives may be longer since other contaminants at the site may be toxic to degrading . microorganisms. Bossert and Bartha (1986) reported reduced biodegradation of PAHs in soil containing a chemical toxic to microorganisms.

Efroymson and Alexander (1994) investigated the effects of nonaqueous phase-liquids (NAPLs) on the biodegradation of hydrophobic compounds, including phenanthrene, in soil and subsoil. Mineralization of phenanthrene in the subsoil was reduced if the compound was dissolved in a NAPL. However, the suppression of the mineralization of phenanthrene in soil by NAPLs was short-lived, suggesting growth of organisms capable of using phenanthrene.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

There is a relatively large body of data characterizing PAH air levels at a variety of U.S. sites. Caution must be used in interpreting and comparing results of different studies, however, because of the different sampling methods used. PAHs occur in the atmosphere in both the particle phase and the vapor phase, as discussed in Section 5.2.1. Three-ring PAH compounds are found in the atmosphere primarily in the gaseous phase, whereas, five- and six-ring PAHs are found mainly in the particle phase; four-ring PAH compounds are found in both phases. To fully characterize atmospheric PAH levels, both particle- and vapor-phase samples must be collected. Many of the earlier monitoring studies used filter sampling methods, which provided information on particle-phase PAH concentrations only, and which did not account for losses of some of the lower molecular weight PAHs by volatilization. As a result, the early use of particulate samples may have resulted in an underestimation of total PAH concentrations. More recent monitoring studies often use sampling methods that collect both particle- and vapor-phase PAHs and that prevent or minimize volatilization losses, thus providing more reliable characterization of total atmospheric PAH concentrations (Baek et al. 1991).

Several monitoring studies indicate that there are higher concentrations of PAHs in urban air than in rural air. Pucknat (1981) summarized 1970 data from the U.S. National Air Surveillance Network and reported that benzo[a]pyrene concentrations in 120 U.S. cities were between 0.2 and 19.3 ng/m^3. Ambient benzo[a]pyrene concentrations in nonurban areas ranged between 0.1 and 1.2 ng/m^3. More recently, Greenberg et al. (1985) evaluated atmospheric concentrations of particulate phase PAHs at four New Jersey sites (three urban and one rural) over two summer and winter seasons during 198l-82. Urban PAH concentrations were approximately 3-5 times higher than those at the rural site; in addition, winter concentrations were approximately 5-10 times higher than summer concentrations. Geometric mean concentrations of ten PAHs (benzo[a]pyrene, benzo[e]pyrene, benzo[b]fluoranthene, benzofi]fluoranthene, benzo[k]fluoranthene, benz[a]anthracene, indeno[l,2,3-c,d]pyrene, benzo[g,h,i]perylene, pyrene, and chrysene) ranged from 0.03 to 0.62 ng/m^3 in urban areas and from 0.01 to 0.12 ng/m^3 in the rural area during the summer seasons. During the winter seasons, geometric mean concentrations of these PAHs ranged from 0.40 to 11.15 ng/m^3 in urban areas and from 0.08 to 1.32 ng/m^3 in the rural area. Geometric mean concentrations of benzo[a]pyrene ranged from 0.11 to

0.23 ng/m^3 (urban) and 0.04 to 0.06 ng/m^3 (rural) during the summer seasons, and from 0.69 to 1.63 ng/m^3 (urban) and 0.17 to 0.32 (rural) during the winter seasons. A more extensive study by Harkov and Greenberg (1985) of atmospheric benzo[a]pyrene concentrations at 27 New Jersey sites indicated similar differences in mean urban (0.6 ng/m^3) and rural (0.3 ng/m^3) concentrations. Significant seasonal trends were also observed, with mean benzo[a]pyrene concentrations during the winter more than an order of magnitude greater than during the summer.

Several other studies provide evidence that atmospheric concentrations of particle-phase PAHs are higher in winter than in summer. In a 1981-82 study conducted in the Los Angeles area; atmospheric concentrations of 10 PAHs (anthracene, fluoranthene, pyrene, chrysene, benz[a]anthracene, combined benzo[e]pyrene and perylene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, and combined benzo[g,h,i]perylene, and indeno[l,2,3-c,d]pyrene) ranged from 0.14 to 1.45 ng/m^3 (with an average of 0.43 ng/m^3) during the summer (August-September), and from 0.40 to 4.46 ng/m^3 (with an average of 1.28 ng/m^3) during the winter (February-March) (Grosjean 1983). A similar seasonal variation in particle-phase PAH concentrations in the Los Angeles atmosphere was seen in an earlier 1974-75 study (Gordon 1976). Quarterly geometric mean concentrations of 11 PAHs (pyrene, fluoranthene, benz[a]anthracene, chrysene, benzo[a]pyrene, benzo[e]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, and indeno[1,2,3-c,d]pyrene) ranged from 0.06 to 2.71 ng/m^3 (with an average of 0.45 ng/m^3) during the May-October period, and from 0.26 to 8.25 ng/m^3 (with an average of 1.46 ng/m^3) during the November-April period. The highest and lowest concentrations were observed during the fourth (November-January) and second (May-July) quarters, respectively. Ratios of fourth quarterly and second quarterly geometric mean concentrations ranged from 3.9 for indeno[l,2,3-c,d]pyrene to 7.5 for benzo[a]pyrene and 9.8 for benz[a]anthracene. Possible factors contributing to these seasonal variations in PAH levels include the following: changes in emission patterns; changes in meteorological conditions (i.e., daylight hours and temperature); and changes in space heating emissions, volatilization, and photochemical activity.

Certain monitoring data suggest that ambient levels of some PAHs may be decreasing. Faoro and Manning (1981) analyzed a limited sample of U.S. National Air Surveillance Network data updated through 1977, which indicated that benzo[a]pyrene concentrations have shown consistent, sizable declines during the period from 1967 to 1977 at 26 urban sites and 3 background sites studied (data not provided).

Over the past two decades, the ambient air levels of PAHs in a number of major cities have been characterized. Although data from studies in different areas cannot be used to indicate definitive temporal trends in PAH air levels, a comparison of the results of these studies yields no strong suggestion that the ambient air levels of PAHs may be decreasing, except in traffic tunnels.

In a 1981-82 study that characterized air levels of 13 PAHs in Los Angeles, Grosjean (1983) reported mean ambient particle-phase PAH concentrations ranging from 0.32 ng/m^3 for benzo[k]fluoranthene to 3.04 ng/m^3 for combined benzo[g,h,i]perylene and indeno[1,2,3-c,d]pyrene. Mean concentrations of anthracene, fluoranthene, pyrene, chrysene, benz[a]anthracene, combined perylene and benzo[e]pyrene, benzo[b]fluoranthene, and benzo[a]pyrene were 0.54; 0.94, 1.62, 0.97, 0.48, 0.43, 0.94, and 0.64 ng/m^3, respectively. Similar results were obtained in an earlier (1974-1975) study of atmospheric particle-phase PAHs in the Los Angeles area, where ambient annual geometric mean concentrations ranged from 0.17 ng/m^3 for benzo[j]fluoranthene to 3.27 ng/m^3 for benzo[g,h,i]perylene (Gordon 1976). The annual geometric mean concentration of benzo[a]pyrene was 0.46 ng/m^3; most individual PAHs had annual geometric mean concentrations of <0.6 ng/m^3. The relatively high levels of benzo[g,h,i]perylene found in these studies.have been attributed to high levels of automobile emissions, which are known to contain high levels of benzo[g,h,i]perylene relative to other PAHs (Santodonato et al. 1981). During the same time period, Fox and Staley (1976) reported somewhat higher ambient average concentrations of particle-phase PAHs in College Park, Maryland, ranging from 3.2 ng/m^3 for benzo[a]pyrene to 5.2 ng/m^3 for pyrene.

In a 1985-86 study, reported average ambient concentrations (combined particle- and vapor-phase) of eight PAHs in Denver ranged between 0.83 ng/m^3 for benzo[k]fluoranthene and 39 ng/m^3 for phenanthrene (Foreman and Bidleman 1990). In a study conducted in Hamilton, Ontario, between May 1990 and June 1991, the concentrations of PAHs in respirable air particulate samples were found to range from 0.6 ng/m^3 for phenanthrene to 4.3 ng/m^3 for benzo[g,h,i]perylene, and 5.1 ng/m^3 for combined benzo[b,j,k]fluoranthenes (Legzdins et al. 1994). In a recent limited study, mean concentrations of particle-phase PAHs in New York City air were reported to range from 0.11 ng/m^3 for anthracene to 4.05 ng/m^3 for benzo[g,h,i]perylene (Tan and Ku 1994).

Atmospheric PAH concentrations have been found to be significantly elevated in areas of enclosed traffic tunnels. In a 1985-86 study in the Baltimore Harbor Tunnel the average concentrations of particle-phase PAHs ranged from 2.9 ng/m^3 for anthracene to 27 ng/m^3 for pyrene (Benner and

Gordon, 1989). These values are up to an order of magnitude lower than those obtained in 1975 by Fox and Staley (1976), which ranged from 66 ng/m^3 for benzo[a]pyrene to 120 ng/m^3 for pyrene. Benner and Gordon (1989) postulated that the observed decrease in PAH concentrations over the 1975-85 decade resulted from the increasing use of catalytic converters in U.S. automobiles over that period, These authors also reported concentrations of PAHs in a typical vapor-phase sample from the Boston Harbor Tunnel for four PAHs included in this profile: anthracene (32.3 ng/m^3), fluoranthene (25.6 ng/m^3), phenanthrene (184 ng/m^3), and pyrene (28.3 ng/m^3). They emphasized that the vapor-phase samples included PAHs inherently present in the vapor phase as well as the more volatile 3- and 4-ring PAHs that may be desorbed from particles during sampling. These results underscore the need to evaluate both particle- and vapor-phase samples to obtain more reliable estimates of total atmospheric PAH concentrations.

5.4.2 Water

PAHs have been detected in surface waters of the United States. In an assessment of STORET data covering the period 1980-82, Staples et al. (1985) reported median concentrations in ambient water of <10 µg/L for 15 PAHs (acenaphthene, acenaphthylene, anthracene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, chrysene, fluoranthene, fluorene, indeno[1,2,3-c,d]pyrene, naphthalene, phenanthrene,. and pyrene). The number of samples ranged from 630 (naphthalene) to 926 (fluoranthene); the percentage of samples in which these PAHs were detected ranged from 1.0 (benzo[g,h,i]perylene) to 5.0 (phenanthrene) and 7.0 (naphthalene).

Basu and Saxena (1978a) reported concentrations of selected PAHs in surface waters used as drinking water sources in four U.S. cities (Huntington, West Virginia; Buffalo, New York; and Pittsburgh and Philadelphia, Pennsylvania). Total concentrations of PAHs ranged from 4.7 ng/L in Buffalo to 600 ng/L in Pittsburgh. Mean concentrations of benzo[a]pyrene in the Great Lakes have been detected at levels between 0.03 and 0.7 ppt (ng/L) (Environment Canada 1991).

DeLeon et al. (1986) analyzed surface water from 11 locations in the Mississippi River. Seventeen PAHs were identified in the samples at levels ranging from 1 ng/L for 6 compounds to a high of 34 ng/L for phenanthrene. The highest concentration of phenanthrene was detected in a sample

collected near New Orleans, Louisiana, near an industrial area, implicating industrial effluent or surface runoff from this area as a possible source.

During April and May 1990, Hall et al. (1993) analyzed 48-hour composite samples from three locations in the Potomac River and three locations in the upper Chesapeake Bay for eight PAHs: perylene, fluorene, phenanthrene, anthracene, fluoranthene, pyrene, benz[a]anthracene, and chrysene. Pyrene was the.only PAH found (0.42 µg/L) in these samples; it was detected in only one of nine Chesapeake Bay samples and not detected in any of the Potomac River samples (detection limit, 0.04 µg/L).

In a more recent study by Pham et al. (1993), raw water samples from 5 areas in the St. Lawrence River and its tributaries were analyzed for 12 PAHs. The highest mean total PAH concentrations were observed in samples collected in the spring (27.3 ng/L) and autumn (21.03 ng/L), which was attributed to snow melt and increased runoff during these respective seasons. The lowest mean total PAH concentration was observed in summer (14.63 ng/L). High molecular weight PAHs were detected more frequently in the spring and autumn samples. Phenanthrene, benzo[b]fluoranthene, fluoranthene, and pyrene were predominant, comprising on average 33.8%, 17.4%, 17.1%, and 12.8% of the total PAHs, respectively: With the exception of anthracene and benzo[b]fluoranthene, a general decrease in concentration with increasing molecular weight was observed.

PAHs have been detected in urban runoff generally at concentrations much higher than those reported for surface water. Data collected as part of the Nationwide Urban Runoff Program indicate concentrations of individual PAHs in the range of, 300-10,000 ng/L, with the concentrations of most PAHs above 1,000 ng/L (Cole et al. 1984). In a recent study by Pitt et al. (1993) which involved the collection and analysis of approximately 140 urban runoff samples from a number of different source areas in Birmingham, Alabama, and under various rain conditions, fluoranthene was one of two organic compounds detected most frequently (23% of samples). The highest frequencies of detection occurred in roof runoff, urban creeks, and combined sewer overflow samples. The maximum reported concentration of fluoranthene in these samples was 130 µg/L.

Industrial effluents also have elevated PAH levels. Morselli and Zappoli (1988) reported elevated PAH levels in refinery waste waters, with concentrations for most PAHs in the range of 400 ng/L (benzo[b]fluoranthene) to 16,000 ng/L (phenanthrene). In an analysis of STORET data covering the

period 1980-88, Staples et al. (1985) reported median concentrations in industrial effluents of <10 µg/L (10,000 ng/L) for 15 PAHs. The number of samples ranged from 1,182 (benzo-[blfluoranthene) to 1,288 (phenanthrene); the percentage of samples in which PAHs were detected ranged from 1.5 (benzo[g,h,i]perylene) to 7.0 (fluoranthene).

Few data are available on the concentrations of PAHs in U.S. groundwater. Basu and Saxena (1978b) reported total PAH concentrations in groundwater from three sites in Illinois, Indiana, and Ohio to be in the range of 3-20 ng/L. Groundwater levels of PAHs near a coal and oil gasification plant and U.S. wood treatment facilities have been found to be elevated. Groundwater samples from the site of a Seattle coal and oil gasification plant which ceased operation in 1956 were found to contain acenaphthylene, acenaphthene, fluorene, phenanthrene, fluoranthene, pyrene, and chrysene at concentrations ranging from not detected (detection limit 0.005 mg/L) to 0.25, 0.18, 0.14, 0.13, 0.05, 0.08, and 0.01 mg/L, respectively (Tumey and Goerlitz 1990). Individual PAHs in the groundwater from 5 U.S. wood treatment facilities were reported at average concentrations of 57 ppb (0.057 mg/L) for benzo[a]pyrene to 1,825 ppb (1.8 mg/L) for phenanthrene (Rosenfeld and Plumb 1991).

An evaluation of the analytical data from 358 hazardous waste sites with over 5,000 wells indicated that anthracene, fluoranthene, and naphthalene were detected (practical quantitation limit, 10-200 µg/L) in groundwater from at least 0.1% of the sites in three of the ten EPA Regions into which the United States is divided (Garman et al. 1987). A review of groundwater monitoring data from 479 waste disposal sites (178 CERCLA or Super-fund sites, 173 RCRA sites, and 128 sanitary/municipal landfill sites) located throughout the United States indicated that 14 of the PAHs included in this profile were detected at frequencies ranging from 2 detections at one site in one EPA Region for indeno[l,2,3-c,d]pyrene, to 85 detections at 16 sites in 4 EPA Regions for fluorene (Plumb 1991). Benzo[a]pyrene was detected 13 times at 6 sites in 6 EPA Regions. Concentrations were not reported.

Data summarized by Sorrel et al. (1980) indicate low levels of PAHs in finished drinking waters of the United States. Reported maximum concentrations for total PAHs (based on measurement of 15 PAHs) in the drinking water of 10 cities ranged from 4 to 24 ng/L; concentrations in untreated water ranged from 6 to 125 ng/L. The low concentrations of PAHs in finished drinking water were attributed to efficient water treatment processes. Shiraishi et al. (1985) found PAHs in tap water at concentrations of 0.1-1.0 ng/L, primarily as chlorinated derivatives of naphthalene, phenanthrene, fluorene, and fluoranthene. The significance to human health of these compounds is not known (Eisler 1987).

5.4.3 Sediment and Soil

PAHs are ubiquitous in soil. Because anthropogenic combustion processes are a major source of PAHs in soils, soil concentrations have tended to increase over the last 100-150 years, especially in urban areas (Jones et al. 1989a, 1989b). Background concentrations for rural, agricultural, and urban soils (from the United States and other countries) are given in Table 5-3. In general, concentrations ranked as follows: urban > agricultural > rural. Evidence of the global distribution of PAHs was given by Thomas (1986) who detected benzo[g,h,i]perylene and fluoranthene at concentrations above 150 µg/kg in arctic soils. Soil samples collected from remote wooded areas of Wyoming contained total PAH concentrations of up to 210 µg/kg.

Recent data on PAH concentrations in soil at contaminated sites are summarized in Table 5-4. Because of the different sampling methods and locations at each site, this tabulation does not provide a reliable inter-site comparison. Additional studies indicate significantly elevated concentrations of PAHs at contaminated sites. Soil samples collected from the Fountain Avenue Landfill in New York City contained PAH concentrations ranging from 400 to 10,000 µg/kg (Black et al. 1989). In a 1988 study at a hazardous waste land treatment site for refinery process wastes, which had been operative since 1958, average PAH concentrations in surface soils (0-30 cm) ranged from not detected (detection limits 0.1-2.0 mg/kg dry weight) for acenaphthylene, acenaphthene, anthracene, benz[a]anthracene, and benzo[k]fluoranthene to 340 mg/kg dry weight for dibenz[a,h]anthracene (Loehr et al. 1993). In addition to dibenz[a,h]anthracene, the three most prevalent compounds at this depth were benzo[a]pyrene (204 mg/kg), benzo[b]fluoranthene (130 mg/kg), and chrysene (100 mg/kg). PAH concentrations decreased with increasing depth and the majority of PAHs were not detected at depths below 60 cm. At 90-135 cm, only phenanthrene (1.4 mg/kg), pyrene (4.0 mg/kg), chrysene (0.9 mg/kg), and dibenz[a,h]anthracene (0.8 mg/kg) were found.

Sediments are major sinks for PAHs, primarily because of the low solubility of these compounds and their strong affinity for organic carbon in particulate matter. PAH concentrations in sediment are generally much higher than those detected in surface water, i.e., in the range of µg/kg (ppb) rather than ng/kg (ppt) .

In an assessment of STORET data covering the period 1980-1982, Staples et al. (1985) reported median concentrations in sediment of ≤500 µg/kg dry weight for 15 PAHs (acenaphthene,

TABLE 5-3. Background Soil Concentrations of Polycyclic Aromatic Hydrocarbons (PAHs)

Compound	Concentrations (μg/kg)		
	Rural soil	Agricultural Soil	Urban Soil
Acenaphthene	1.7	6	
Acenaphthylene		5	
Anthracene		11–13	
Benzo(a)anthracene	5–20	56–110	169–59,000
Benzo(a)pyrene	2–1,300	4.6–900	165–220
Benzo(b)fluoranthene	20–30	58–220	15,000–62,000
Benzo(e)pyrene		53–130	60–14,000
Benzo(g,h,i)perylene	10–70	66	900–47,000
Benzo(k)fluoranthene	10–110	58–250	300–26,000
Chrysene	38.3	78–120	251–640
Fluoranthene	0.3–40	120–210	200–166,000
Fluorene		9.7	
Ideno(1,2,3-c,d)pyrene	10–15	63–100	8,000–61,000
Phenanthrene	30.0	48–140	
Pyrene	1–19.7	99–150	145–147,000

[a]Derived from:

IARC 1973
White and Vanderslice 1980
Windsor and Hites 1979
Edwards 1983
Butler et al. 1984
Vogt et al. 1987
Jones et al. 1987

TABLE 5-4. Soil Concentrations (mg/kg dry weight) Polycyclic Aromatic Hydrocarbons (PAHs) at Contaminated Sites[a]

Compound	Wood-preserving[b]		Creosote production[c]		Wood treatment[d]	Coking plant[d]	Coking plant[e]	Gas works[f]		Gas works[g]
	Surface-soil	Subsoil	mean	range				mean	range	range
Acenaphthene	7	1,368					29	2	0–11	nd–3.0
Acenaphthylene	5	49	33	6–77			187			nd–3.0
Anthracene	10	3,037	334	15–693	766	6	130	156	57–295	nd–3.1
Benz(*a*)anthracene	12	171			356	16	200	317	155–397	nd–8.6
Benzo(*a*)pyrene	28	82			94	14		92	45–159	nd–15
Benzo(*e*)pyrene										nd–12[i]
Benzo(*b*)fluoranthene	38	140						260	108–552	nd–19
Benzo(*k*)fluoranthene								238	152–446	
Benzo(*j*)fluoranthene										nd–1.2[i]
Benzo(*g,h,i*)perylene										nd–16
Chrysene	38	481	614	8–1,586	321	11	135	345	183–597	nd–12
Dibenz(*a,h*)anthracene					101	2		2,451	950–3,836	nd–2.0
Fluoranthene	35	1,629	682	21–1,464	1,350	34		2,174	614–3,664	nd–2.6
Fluorene	3	1,792	650	49–1,294	620	7	245	225	113–233	nd–6.5
Indeno(1,2,3-*c,d*)pyrene	10	23						207	121–316	nd–13
Naphthalene	1	3,925	1,313	<1–5,769	92	56	59			nd[h]–46
Phenanthrene	11	4,434	1,595	76–3,402	1,440	27	277	379	150–716	nd–26
Pyrene	49	1,016	642	19–1,303	983	28	285	491	170–833	nd–4.3

[a]Modified from Wilson and Jones 1993
[b]Mueller et al. 1991—composite samples
[c]Ellis et al. 1991—samples are 1·5 m or 3·5 m
[d]Weissenfels et al. 1990a—no range or sampling details provided
[e]Werner et al. 1988—no range or sampling details provided
[f]Bewley et al. 1989—samples taken from prototype treatment bed
[g]Turney and Goerlitz 1990—samples taken in 1986 from plant inoperative since 1956.
[h]nd = not detected (no detection limit given)
[i]estimated value

acenaphthylene, anthracene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, chrysene, fluoranthene, fluorene, indenopyrene, naphthalene, phenanthrene, and pyrene). The number of samples ranged from 236 (anthracene) to 360 (benzo-[alpyrene, fluoranthene); the percentage of samples in which these PAHs were detected ranged from 6.0 (acenaphthene, benzo[b]fluoranthene, benzo[k]fluoranthene, indeno[1,2,3-c,d]pyrene) to 22.0 (fluoranthene, pyrene).

Eadie et al. (1982) analyzed surficial sediments in southwestern Lake Erie near a large coal-fired power plant. Sediment concentrations for total PAHs were generally in the range of 530-700 µg/kg, although concentrations in river and near-shore sediments reached nearly 4,000 µg/kg (4 ppm). Heit et al. (1981) reported total concentrations of PAHs (3-7 ring PAHs) from two lakes in the Adirondack acid lake region of 2,660 µg/kg and 770 µg/kg (calculated from data presented). Average concentrations of total PAHs in sediments from three coastal South Carolina marinas were reported to range from 35.6 to 352.3 µg/kg (Marcus et al. 1988). Benzo[a]pyrene levels in bottom sediments of the Great Lakes have been reported to range from 34 to 490 ppb (µg/kg) (Environment Canada 1991). Concentrations of PAHs in sediments from Cape Cod and Buzzards Bay in Massachusetts and the Gulf of Maine have been reported to be in the range of 540-1,300 µg/kg (Hites et al. 1980). Concentrations of low molecular weight PAHs (naphthalene, acenaphthylene, fluorene, phenanthrene, anthracene, and 2-methylnaphthalene) and high molecular weight PAHs (fluoranthene, pyrene, benz[a]anthracene, chrysene, benzofluoranthenes, benzo[a]pyrene, indeno[l,2,3-c,d]pyrene, dibenz[a,h]anthracene, and benzo[g,h,i]perylene) in sediment from the highly polluted Boston Harbor have been reported to range from approximately 100 to 11,000 µg/kg dry wt, and 800 to 23,000 µg/kg dry wt, respectively (Demuth et al. 1993).

Total PAH concentrations in bottom sediments from the main stem of the Chesapeake Bay were reported to range from 45 to 8,920 µg/kg for samples collected from 16 stations in 1986 (Huggett et al. 1988). At least 14 PAHs were found to be dominant among pollutants of surface sediments from the Elizabeth River, a subestuary of the James River in Virginia, with a maximum total PAH concentration of 170,000 µg/g (ppm) observed in one sample from a site of two large wood preservative spills (Bieri et al. 1986). In a more recent study, surface sediment samples from the highly contaminated Elizabeth River were found to contain total concentrations of 14 PAHs ranging from 1.5 to 4,230 µg/g (ppm) dry weight (Halbrook et al. 1992). Significantly lower concentrations,

ranging from 0.34 to 0.95 µg/g (340-950 µg/kg) dry weight, were found in sediment samples from the nearby Nansemond River which served as a clean reference site.

Two-thirds of 105 sediment samples collected throughout Florida during the summers of 1989 and 1990 from sites known or suspected to be contaminated with priority pollutants were found to contain at least one of 15 PAH target analytes (Jacobs et al. 1993). Pyrene was detected most frequently (61% of samples); dibenz[a,h]anthracene and naphthalene were detected least frequently (4% of samples). Total PAH concentrations ranged from below the detection limit to 1,090 mg/kg. Mean concentrations for individual PAHs ranged from 0.87 mg/kg (dibenz[a,h]anthracene and naphthalene) to 30.8 mg/kg (acenaphthene).

Drainage stream sediments from a wood-preserving facility near Pensacola, Florida, were found to be highly contaminated with creosote-derived PAHs, with maximum concentrations from two sampling sites ranging from 300 µg/kg for naphthalene to 12,000 µg/kg for phenanthrene and 140,000 µg/kg for anthracene (Elder and Dresler 1988). Fluoranthene, pyrene, benz[a]anthracene, chrysene, acenaphthene, and fluorene were other dominant PAHs. PAHs were not detected in water samples from the drainage stream. Furthermore, no significant PAH contamination was found in surface sediments from estuarine sites adjacent to the drainage stream; PAHs were detected in sediment samples from only one of seven estuarine sites at concentrations ranging from 75 µg/kg for benz[a]anthracene to 190 µg/kg for fluoranthene.

In 1991, Kennicutt et al. (1994) found that sediment samples from Casco Bay in Maine contained total PAH concentrations ranging from 16 to 20,800 µg/kg dry weight. PAHs were found at all 65 locations sampled. PAHs with four or more rings accounted for more than 60% of Casco Bay sedimentary PAHs. The predominance of PAHs with highly condensed ring structures with few alkylations indicated a pyrogenic or combustion source as the major contributor.

Mean total PAH concentrations of sediments collected in 1985-87 from Moss Landing Harbor, Elkhom Slough, and nearshore Monterey Bay, California, were found to range from 1,470 to 3,080, 157 to 375, and 24 to 114 µg/kg dry weight, respectively (Rice et al. 1993). The Moss Landing Harbor and nearshore Monterey Bay ecosystems are subject to PAH contamination from various local industries, harbor-related activities, power generation, municipal waste treatment, and agricultural runoff. The largest Pacific Coast fossil-fueled power plant is located at Moss Landing. Elkhom

Slough is a seasonal estuary which receives freshwater runoff. Combustion PAHs (i.e., benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, benzo[e]pyrene, chrysene, fluoranthene, and pyrene) were predominant, with mean total concentration at these 3 sites ranging from 1,250 to 2,710, to 335, and 11 to 59 ug/kg dry weight, respectively.

Median concentrations of PAHs in sediment coves collected in 1991 from three northern New Jersey waterways (Arthur Kill, Hackensack River, and Passaic River) highly contaminated with petroleum hydrocarbons ranged from 0.47 mg (470 ug/kg) (acenaphthylene) to 5.10 mg (5,100 µg/kg) (pyrene) (Huntley et al. 1993). In addition to pyrene, fluoranthene, chrysene, and benzo[a]pyrene were the most frequently detected PAHs, with median concentrations at the three sites ranging from 2.40 to 4.10, 1.35 to 2.85, and 0.86 to 2.30 mg/kg, respectively. Mean total PAH concentrations at the 29 sampling stations ranged from 0 to 161 mg/kg. A mean total PAH concentration of 139 mg/kg was found at a sampling station downstream from a chemical control Superftmd site. At most sampling stations, PAH concentrations increased with sample depth up to approximately 45-50 cm, indicating a decline in recent loadings relative to historic inputs.

5.4.4 Other Environmental Media

PAHs have been detected in many food products including cereal, potatoes, grain, flour, bread, vegetables, fruits, oils, and smoked or broiled meat and fish. The concentrations in uncooked foods largely depend on the source of the food. For example, vegetables and fruits obtained from a polluted environment may contain higher PAH concentrations than those obtained from nonpolluted environments. Benzo[a]pyrene, dibenz[a,h]anthracene, and chrysene have been detected in vegetables grown near a heavily traveled road (Wang and Meresz 1982). The method of cooking can also influence the PAH content of food; the time of cooking, the distance from the heat source, and the drainage of fat during cooking (e.g., cooking in a pan versus on a grill) all influence PAH content. For example, charcoal broiling increases the amounts of PAHs in meat. In a composite sample characterized to be typical of the U.S. diet, Howard (1979) found that PAH concentrations in all food groups were less than 2 ppb (µg/g). The following ranges of benzo[a]pyrene concentrations (wet or dry weight not specified) were summarized by Santodonato et al. (1981) from studies conducted in many countries:

- cooking oils: 0.5-S ppb (µg/g)
- margarine: 0.2-6.8 ppb

- smoked fish: trace-6.6 ppb
- smoked or broiled meats: trace-105 ppb
- grains and cereals: not detected-60 ppb
- fruits: not detected-29.7 ppb
- vegetables: not detected-24.3 ppb

These data include samples from areas identified as “polluted.”

Gomaa et al. (1993) recently reported the results of a study to screen smoked foods, including turkey, pork, chicken, beef, and fish products, for carcinogenic and noncarcinogenic PAHs. Eighteen commercially available liquid smoke seasonings and flavorings were also evaluated. All smoked meat products and liquid smoke seasonings were purchased from local supermarkets in Michigan. Total PAH concentrations in smoked red meat products ranged from 2.6 µg/kg in cooked ham to 29.8 µg/kg in.grilled pork chops, while those in smoked poultry products ranged from 2.8 µg/kg in smoked turkey breast to 22.4 µg/kg in barbecued chicken wings. Total PAH concentrations in smoked fish products ranged from 9.3 µg/kg in smoked shrimp to 86.6 µg/kg in smoked salmon. Total concentrations of carcinogenic PAHs (benz[a]anthracene, benzo[b]fluoranthene, benzo[a]pyrene, dibenz[a,h]anthracene, and indeno[l,2,3,-c,d]pyrene) ranged from not detected in several red meat products to 7.4 µg/kg in grilled pork chops; from not detected in several poultry products to 5.5 µg/kg in barbecued chicken wings; and from 0.2 µg/kg in smoked trout and shrimp to 14.9 and 16.1 µg/kg in smoked oysters and salmon, respectively. Total PAH concentrations in liquid smoke flavorings and seasonings ranged from 6.3 to 43.7 µg/kg, while total carcinogenic PAH concentrations ranged from 0.3 to 10.2 µg/kg. Smoked meat products processed with natural wood smoke had higher total PAH and total carcinogenic PAH concentrations than those processed with liquid smoke flavorings. Carcinogenic PAHs were not detected in 10% of the smoked food samples and 24% of the samples had concentrations of carcinogenic PAHs <I µg/kg. Benzo[a]pyrene was not detected in 31% of the samples; 45% of the samples had concentrations <l µg/kg. Benzo[a]pyrene was found at concentrations >l µg/kg in 24% of the samples, which included pork sausage (1.8-2.3 µg/kg), grilled pork chops (2.5 µg/kg), whole ham (1.1 µg/kg), beef sausage (1.1 µg/kg), salmon (3.9 µg/kg), and oysters (3.0 µg/kg). Benzo[a]pyrene was detected in 92% (12/13) of liquid smoke flavorings and seasoning samples, with concentrations ranging from 0.1 to 3.4 µg/kg.

Similar results have been obtained in recent investigations of benzo[a]pyrene concentrations in smoked foods in other countries. In Brazil, benzo[a]pyrene was detected in 52% (23/44) of smoked meat

samples; concentrations ranged from 0.1 to 5.9 µg/kg and were generally <1.0 µg/kg (Yabiku et al. 1993). In France, benzo[a]pyrene concentrations in smoked fish, poultry, and pork products were found to range from <0.2 to 1.9, 0.3 to 1.9, and <0.2 to 7.2 µg/kg, respectively; 36% (26/71) of the samples analyzed had benzo[a]pyrene concentrations >1 µg/kg (Moll et al. 1993). Because many imported food products are included in the U.S. food supply, these data may be relevant to estimating dietary PAH exposures of the general U.S. population.

In data summarized by Edwards (1983) the maximum total concentration of PAHs in vegetation near a source was 25,000 ppb (25 µg/g) (dry weight), while concentrations in nonsource areas ranged from 20 to 1,000 ppb (0.02-l .0 µg/g). In general, concentrations in leaves, stems, and fruits were higher than those in roots. Fluoranthene, pyrene, and chrysene/triphenylene were found in concentrations of 1.2, 2.0, and 2.9 µg/g, respectively, in composite samples of green leaves from 62 plant species in the Los Angeles area; corresponding values for dried leaf samples were 0.47, 1.l, and 1.9 µg/g (Rogge et al. 1993d). Edwards (1983) reported that washing removed a maximum of 25% of PAHs on the leaves of plants.

PAHs have been found in the tissues of aquatic organisms. In an assessment of STORET data covering the period 1980-1982, Staples et al. (1985) reported median concentrations in biota of <2.0 mg/kg (ppm) wet weight for 8 PAHs (acenaphthene, acenaphthylene, benz[a]anthracene, benzo[a]pyrene, chrysene, fluoranthene, fluorene, and pyrene) and <2.5 mg/kg wet weight for seven PAHs (anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, indenopyrene, naphthalene, and phenanthrene). The number of samples ranged from 83 (naphthalene) to 140 (acenaphthylene); only benzo[g,h,i]perylene (1 sample, 0.8%) and indenopyrene (1 sample, 0.8%) were found in detectable concentrations.

In summary of data on tissue contamination in mussels and oysters from the first 3 years (1986-1988) of the National Oceanic and Atmospheric Administration (NOAA) Mussel Watch Project, which involved the analysis of samples from 177 coastal and estuarine U.S. sites, overall mean concentrations of low molecular weight PAHs ranged from not detected (detection limits 3.3-67 ng/g dry weight) to 4,200 ng/g dry weight (NOAA 1989). Mean concentrations of low molecular weight PAHs for individual years 1986, 1987, and 1988 ranged up to 9,600, 3,200, and 4,300 ng/g dry weight, respectively. Overall mean concentrations of high molecular weight PAHs ranged from not detected (detection limits 3.9-47 ng/g dry weight) to 11,000 ng/g dry weight. Mean concentrations of high

molecular weight PAHs for 1986, 1987, and 1988 ranged up to 15,000, 10,000, and 11,000 ng/g dry weight, respectively. States with sites ranked among the highest five for concentrations of low molecular weight PAHs in 1986, 1987, 1988, and overall in 1986-1988, were California, Florida, Hawaii, Massachusetts, Mississippi, New York, Oregon, and Washington; for high molecular weight PAHs these states were California, Florida, Hawaii, Massachusetts, New York, and Washington. No consistent trends over the 1986-88 period were observed in the data; significant increases and decreases in concentrations of low and high molecular weight PAHs were observed with almost equal frequency. Low molecular weight PAH concentrations showed significant increasing trends at a single site each in New York, New Jersey, Florida, Texas, California, and Oregon; significant decreasing trends were observed at a single site each in Massachusetts, Maryland, and Mississippi, and at two sites in Texas. High molecular weight PAH concentrations showed significant increasing trends at a single site each in New York and Washington, and at two sites in Florida; significant decreasing trends were observed at a single site each in Connecticut, Maryland, and Florida.

Concentrations of phenanthrene and total PAHs ranged from 2 to 296 and 63 to 2,328 µg/kg (ng/g) wet weight, respectively, in caged mussels *(Elliptio complanata)* after 3 weeks' exposure at various locations in St. Mary's River, which is heavily contaminated from industrial and municipal discharges in the Sault Ste. Marie, Ontario, area (Kauss 1991). PAH concentrations ranging from approximately 50 ng/g wet weight for acenaphthylene to 4,660 nglg wet weight for fluoranthene were found in the digestive glands of the American lobster *(Homerus americancus)* collected in the proximity of a coal-coking plant that had been closed for a decade (King et al. 1993). Benzo[a]pyrene concentration was reported to be 720 nglg wet weight.

In a study to evaluate the concentrations of PAHs in various fish and shellfish species from Prince William Sound, Alaska, following the 1989 Exxon Valdez spill of more than 10 million gallons of crude oil, PAHs were not detected in 18% (72/402) of the samples; trace levels were found in 78% (312/402) of the samples; and individual PAH concentrations ranging from 5 to 12 µg/kg (wet or dry weight not specified) were found in 4% (18/402) of the samples. There was no apparent difference between PAH concentrations in salmon collected from impacted areas and those collected from control areas; however, there was a suggestion that contamination may be increasing with time. No PAHs were detected in 14% (31/221) of samples collected in 1989, trace levels were found in 85% of these samples, and only 1% (3 samples) had individual PAH concentration >5 µg/kg; whereas in the 1990

samples, PAHs were detected in all of the 41 samples, trace levels were found in 87% of the samples, and 13% (6 samples) had individual PAH concentrations >5 µg/kg.

PAHs are present at 1–2 weight percent in crude oils (Guerin 1978). Actual PAH concentrations in crude oil depend on the geological source of the oil (IARC 1989). For example, the NRC (1985) has reported concentrations of seven individual carcinogenic PAHs ranging from 1.2 µg/g for benzo[a]pyrene to 23 µg/g for chrysene in a South Louisiana crude oil and from 0.5 µg/g for benzo[e]pyrene to 6.9 µg/g for chrysene in a Kuwaiti crude oil. PAHs are also found in refined petroleum products including gasoline, kerosene, diesel fuel, some heating oils, and motor oil (Guerin 1978).

PAHs have also been detected in used motor oils. The following concentrations of benzo[a]pyrene and benz[a]anthracene measured in 1,071 samples of used motor oils were reported by Franklin Associates (1984):

Positive	Samples(%)	Mean (mg/kg)	Median (mg/kg)	Range (mg/kg)
Benzo[a]pyrene	58	24.5	10	<1–405
Benz[a]anthracene	74	71.3	12	<5–660

The levels, either in concentration or percent weight, in which several PAHs appear in various other substances are given below. A coal tar sample has been found to contain approximately 0.007 mg/kg benz[a]anthracene, 3 mg/kg benzo[b]fluoranthene, 4 g/kg chrysene, and 30 mg/kg benzo[a]pyrene (Perwak et al. 1982). High-temperature coal tar contains 1,000 mg/kg dibenz[a,h]anthracene (IARC 1985). A sample of coal tar pitch was found to contain <10 mg/kg benz[a]anthracene, <10 mg/kg chrysene, and approximately 10 mg/kg benzo[a]pyrene; creosote oil contains <3 mg/kg benz[a]anthracene, <1 mg/kg chrysene, and <10 mg/kg benzo[a]pyrene (Perwak et al. 1982). Creosote has been reported to contain 21% phenanthrene, 10% fluorene, 10% fluoranthene, 9% acenaphthene, 8.5% pyrene, 3% chrysene, 3% naphthalene, and 2% anthracene (Lorenz and Gjovik 1972).

PAHs have also been reported to occur in chewing tobacco, snuff, and in mainstream and sidestream tobacco smoke. Reported concentrations of some PAHs in various types of tobacco smoke are shown in Table 5-5 (IARC 1983). These data show concentrations of benzo[a]pyrene in cigarette mainstream smoke ranging between 5 and 78 ng/cigarette (IARC 1983). Other studies indicate that concentrations of carcinogenic PAHs in mainstream smoke from unfiltered cigarettes may range from 0.1 to 0.25 µg

per cigarette (Hoffmann and Hecht 1990). Concentrations of PAHs in sidestream smoke are significantly higher than in mainstream smoke with sidestreammainstream concentration ratios for benzo[a]pyrene ranging from 2.5 to 20 (Adams et al. 1987; Evans et al. 1993; Grimmer et al. 1987; Hoffmann and Hoffmann 1993; IARC 1983). Benzo[a]pyrene concentrations of 0.42-63 ppb (ng/g) have been reported in snuff (Brunnemann et al. 1986).

PAH concentrations in a variety of other media have been evaluated. PAH concentrations in fly ash and bottom ash samples from domestic municipal incinerators ranged from not detected to 7,400 µg/kg, with phenanthrene the most abundant and frequently detected compound (Shane et al. 1990). Machado et al. (1993) reported the total concentrations of 16 PAHs (all PAHs in this profile except benzo[e]pyrene) in asphalt and coal tar pitch to be 50, 122 and 294, 300 ppm µg/g), respectively; benzo[a]pyrene concentrations were <6 and 18,100 ppm, respectively. The concentrations of benzo[a]pyrene (250-480 ppm) and several other PAHs in coal tar fumes were higher than those in asphalt fumes by two to three orders of magnitude. The PAH content of asphalt and coal tar pitch fumes increased with increasing generation temperature.

Tire wear particles, brake lining particles, and paved road dust from a residential area had total PAH concentrations of 226.1, 16.2, and 58.7 µg/g, with maximum concentrations of individual PAHs of 54.1 µg/g (pyrene), 2.6 µg/g (benzo[g,h,i]perylene), and 9.4 µg/g (pyrene), respectively (Rogge et al. 1993c). Benzo[a]pyrene concentrations in these media were 3.9, 0.74, and 2.3 µg/g, respectively. Combined particle- and vapor-phase emissions from scrap tire fires have been reported to contain average total PAH concentrations of 3.2 mg/m^3, with average benzo[a]pyrene concentrations ranging from 0.07 to 0.08 mg/m^3 (Lemieux and Ryan 1993). Tire pyrolysis oil, which may be used as a fuel, contains high levels of PAHs, with average total PAH concentrations ranging from 14,540 ppm (µg/g) to over 100,000 ppm (10%); benzo[a]pyrene concentrations ranged from <10 to 600 ppm (Williams and Taylor 1993).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The greatest sources of exposure to PAHs for most of the U.S. population are active or passive inhalation of the compounds in tobacco smoke, wood smoke, and contaminated air, and ingestion of these compounds in foodstuffs. Smoking one pack of cigarettes a day has been estimated to result in exposure to carcinogenic PAHs of up to 5 µg/day (Menzie et al. 1992) and in exposure to

TABLE 5-6. Average Indoor Concentrations (μg/m^3) of Polycyclic Aromatic Hydrocarbons (PAHs) in Different Categories of Sample Homes Occupied by Smokers and Non-smokers[a]

	E/E		Home-type G/E		G/G		
Compound	Smokers	Non-smokers	Smokers	Non-smokers	Smokers	Non-smokers	Outdoor Air
Acenaphthylene	18	11	71	15	33	17	4.2
Anthracene	3.5	1.8	8.3	3.4	8.9	2.2	0.96
Benz[a]anthracene	0.32	0.25	1.7	0.34	1.1	0.55	0.42
Benzo[a]pyrene	0.37	0.30	1.7	0.27	0.96	0.58	0.23
Benzo[e]pyrene	1.4	0.67	5.5	0.52	2.4	1.0	0.46
Benzofluoranthenes	0.79	0.68	1.1	0.97	2.0	2.0	1.1
Benzo[g,h,i]perylene	0.53	0.44	1.4	0.59	1.2	0.75	0.50
Chrysene	0.91	0.76	3.6	0.81	2.3	1.6	1.1
Fluorothene	7.2	7.7	13	7.5	13	16	5.6
Indeno[1,2,3-c,d]pyrene	0.35	0.28	1.1	0.40	0.84	0.64	0.35
Phenanthrene	79	57	130	63	130	110	31
Pyrene	4.3	4.6	11	4.8	5.0	9.3	4.4

[a]Adapted from Chuang et al. (1991)
[b]E/E denotes electric heating and cooking systems; G/E denotes gas heating and electric cooking systems; G/G denotes gas heating and cooking systems

benzo[a]pyrene of 0.4 μg/day (Santodonato et al. 1981). Other potential routes of human exposure are ingestion of contaminated drinking water and food products, and skin contact with soot and tars. PAHs are ubiquitous in the environment, resulting from the incomplete combustion of organic materials, whether natural (forest fires or volcanoes) or synthetic (combustion of fuels for heating and transportation). The amount of PAHs found in food products depends as much on the method of preparation (especially grilling or smoking) as on the origin of the food. Disinfection of public water supplies with chlorine can result in the presence of chlorinated and oxygen substituted PAHs (Shiraishi et al. 1985). Coal tar preparations have been used in the clinical treatment of skin disorders. Contamination of the ambient air can be derived from industrial and construction sources. Eldridge et al. (1983) measured substantial levels of PAHs emitted from freshly laid petroleum road asphalt.

Estimates of general population exposure to total PAHs (μg/day) and carcinogenic PAHs in comparison to readily measured benzo[a]pyrene concentrations were presented by Santodonato et al. (1981), as follows:

Source	Benzo[a]pyrene	Select Carcinogenic PAHs[a]	Total PAHs
Air	0.0095–0.0435	0.038	0.207
Water	0.0011	0.0042	0.027
Food	0.16–1.6	–	1.6–16

[a]Total of benzo[a]pyrene, benzo[j]fluoranthene, and indeno[1,2,3-c,d]pyrene.

The most noteworthy of these estimates are the relatively high exposures from ingestion of contaminate food; however, it was noted that because of the lack of reliable monitoring data for PAHs in food, the uncertainty of the food estimates was greater than the uncertainty of the estimates for air or water. Nevertheless, the authors concluded that estimates from all three exposure sources were probably accurate within one order of magnitude, so that food was predominant among the sources of exposure.

More recent estimates of the potential exposures of American adult males to carcinogenic PAHs were provided by Menzie et al. (1992). The estimates provided by these investigators do not include potential exposures experienced in occupational settings or those resulting from use of consumer products (e.g., cosmetics or asphaltic materials added to roofs or driveways). From the average American diet, the intake of carcinogenic PAHs was estimated to be 1–5 μg/day, mostly from

ingestion of unprocessed grains and cooked meats. This dietary intake estimate was increased to 6-9 µg/day for individuals consuming diets with a large meat content as a result of the additional contribution from charcoal-cooked or smoked meats and fish. Exposure via inhalation of ambient air was estimated to be 0.16 µg/day (median), with a range of 0.02-3 µg/day, assuming an inhalation rate of 20 m^3/day. Smoking one pack of unfiltered cigarettes per day increases this estimate by an additional 2-5 µg/day; chain smokers consuming three packs per day increase their exposure by an estimated 6-15 µg/day. Exposure to carcinogenic PAHs for the typical adult male from ingestion of drinking water and incidental ingestion of soil is minor compared to other potential routes of exposure. Drinking water exposure was estimated to be 0.006 µg/day (median), with a range of 0.0002-0.12 µg/day, assuming a consumption rate of 2 L/day. Assuming incidental ingestion of 50 mg soil/day, which may be more typical for small children than for most adults, the estimated median soil intake of carcinogenic PAHs was 0.06 µg/day (range, 0.003-0.3 µg/day). Therefore, the total potential exposure of carcinogenic PAHs for adult males was estimated to be 3 µg/day (median), with a maximum value of 15 µg/day. Smokers of nonfiltered cigarettes may experience exposures twice as high as these estimates. Ingestion of food appears to be the main source of exposure to PAHs for nonsmokers, although inhalation of ambient air is also an important route.

In a Dutch market-basket survey conducted from 1984 to 1986, the mean daily dietary intake of PAHs by 18-year-old males in composites of 221 different foods from 23 commodity groups was estimated to range from 5 to 17 µg/day. The most frequently detected PAHs were benzo[b]fluoranthene (59% of samples), fluoranthene (48%), and benzo[k]fluoranthene (46%). The largest contribution of PAHs to the total diet came from the sugar and sweets, cereal products, and oils, fats, and nuts commodity groups (de Vos et al. 1990).

Consumption of Great Lakes fish is not expected to contribute significantly to dietary intake unless the fish are smoked (Environment Canada 1991). The estimated exposure from consuming 114 g fish containing 50 ppt (ng/g) benzo[a]pyrene once a week would be 5.7 ng/person/week, or 11.6 pg/kg of body weight per day for a 70-kg individual. However, in some areas of the United States, fish consumption advisories have been issued based on elevated concentrations of PAHs found in locally caught fish or shell fish (see Section 5.6) (RTI 1993).

The average intake of benzo[g,h,i]perylene by adults from drinking water sources has been estimated to be 2 ng/day (assuming a drinking water ingestion rate of 2 L/day), inhalation exposure to the

compound has been estimated to be 10 ng/day (assuming an air intake rate of 20 m^3/day) (EPA 1989a).

Indoor air can be an important source of human exposure to PAHs. Potential indoor combustion sources of PAHs include tobacco smoke, unvented space heaters, and food preparation (Lioy and Greenberg et al. 1990). PAHs are among the major carcinogenic agents in environmental tobacco smoke (ETS), which is comprised primarily of diluted sidestream smoke, with a much smaller contribution from exhaled mainstream smoke (Hoffmann and Hoffmann 1993). Exposure to ETS is of particular concern because it has recently been declared a human lung carcinogen by the U.S. EPA. Concentrations of some PAHs in cigarette smoke-polluted environments are listed in Table 5-5. Chuang et al. (1991) monitored the concentrations of PAHs in the indoor and outdoor air of eight homes in Columbus, Ohio, in the winter of 1986-87 and obtained the indoor air results shown in Table 5-6.

Environmental tobacco smoke was the most significant influence on indoor air PAH levels; homes occupied by smokers had higher average concentrations of most PAHs than homes occupied by nonsmokers. In homes occupied by nonsmokers, the.highest average concentrations of most PAHs were found in homes that had gas cooking and heating appliances, followed by homes with gas heating and electric cooking appliances. Homes equipped with electric cooking and heating had the lowest average concentrations of most PAHs.

The Total Human Environmental Exposure Study (THEES), a multimedia study of human exposure to benzo[a]pyrene, was conducted in a rural town, Phillipsburg, New Jersey, where the major industry was a grey-iron pipe manufacturing plant that contributed to high levels of benzo[a]pyrene in the ambient atmosphere (Butler et al. 1993; Lioy 1990; Lioy et al. 1988; Waldeman et al. 1991). Benzo[a]pyrene concentrations in respirable particulate personal samples from 10 homes in areas near the foundry were measured in the range of 0.1 to 8.1 ng/m^3, depending on personal habits (whether the windows were kept open, how frequently the doors were opened, cooking methods, hobbies, whether home improvements were being made) and sources of home heating. The mean outdoor air concentration of benzo[a]pyrene was 0.9 ng/m^3. In samples of food collected from family meals over a 2-week period, the concentration level of benzo[a]pyrene ranged from 0.004 to 1.2 ng/g (wet weight)., No detectable amounts of benzo[a]pyrene were observed in the drinking water supply (detection limit, 0.1 ng/L). In comparing the inhalation and ingestion pathways in each home, Lioy et

TABLE 5-5. Concentrations of Some Polycyclic Aromatic Hydrocarbons (PAHs) in Tobacco Smoke[a]

Compound	Cigarette main stream smoke (µg/100 cigarettes)	Cigarette side stream smoke (µg/100 cigarettes)	Cigarette smoke-polluted environments (µg/m^3)	Cigar smoke (µg/100 g)	Pipe smoke (µg/100 g)
Anthracene	2.3–23.5			11.9	110.0
Benz(*a*)anthracene	0.4–7.6	4–20	0.1–100	2.5–3.9	
Benzo(*b*)fluoranthene	0.4–2.2		0.1–35[b]		
Benzo(*j*)fluoranthene	0.6–2.1				
Benzo(*k*)fluoranthene	0.6–1.2				
Benzo(*g,h,i*)fluoranthene	0.1–0.4				
Benzo(*g,h,i*)perylene	0.3–3.9	9.8	0.4–17		
Benzo(*a*)pyrene	0.5–7.8	2.5–19.9	0.4–760	1.8–5.1	8.5
Benzo(*e*)pyrene	0.2–2.5	13.5	0.4–18		
Chrysene	0.6–9.6		2.6–16		
Dibenz(*a,h*)anthracene	0.4		<0.1–13		
Fluoranthene	1–27.2	126	0.2–99	20.1	
Fluorene	present				
Indeno(1,2,3-*c,d*)pyrene	0.4–2.0		0.6–1		
Phenanthrene	8.5–62.4		4–87	115	
Pyrene	5–27	39–101	0.8–66	17.6	75.5

[a]Adapted from a tabulation of data from several studies in IARC (1983) and Guerin et al. (1992)
[b]Benzofluoranthenes

al. (1988) found that potential intake could be similar in each medium. Of the 20 weeks of exposure (10 homes over a 2-week exposure period), 10 had higher food benzo[a]pyrene exposures and 10 had higher inhalation benzo[a]pyrene exposures. The range of estimated food exposures (l0-4,005 ng/week) was much greater than the range of estimated air exposures (78-385 ng/week). The dominance of one pathway or the other seemed to depend on indoor combustion sources (e.g., cigarette smoke or coal-burning stoves) and personal eating habits. For smokers, inhalation of tobacco smoke was the main source of benzo[a]pyrene exposure; intake from this source was much higher than inhalation of ambient and indoor air or ingestion of food. Smokers also had higher exposure through food intake than nonsmokers. For the average nonsmoker, ingestion of food was the most important route of exposure (Lioy 1990).

Occupational exposures to PAHs can result from processes such as petroleum refining, metalworking, the production of coke, the manufacture of anodes, and the production of aluminum. In reviewing the available data on occupational exposures, it is important to understand that it cannot be implied that the results of a study at one industrial site would be valid for another site or for the same site at another time.

Occupational exposures to PAHs are possible in all operations involved in extraction and processing of crude oil, including drilling, pumping and treating, transport, storage, and refinement (Suess et al. 1985). The main route of exposure is inhalation, although there is also potential for significant dermal exposure (IARC 1989). Workers in petroleum refineries are exposed to PAHs from a variety of sources, including atmospheric distillation, catalytic cracking, residual fuel oil, lubricant oil processing, bitumen processing and loading, coking, and waste-water treatment (IARC 1989). In a study of nine US refineries, total PAH concentrations of 10 $\mu g/m^3$ were reported in personal samples taken in the fluid catalytic cracking and delayed coker units (Futagaki 1983). Total PAH concentrations ranging from approximately 1 to 40 $\mu g/m^3$ were observed in area samples from bitumen processing units. Total PAH concentrations in personal samples from the de-asphalting unit in one refinery were found to range from 2.5 to 49.8 $\mu g/m^3$. At least 85% of the total PAH in these samples was comprised of two-ring compounds (i.e., naphthalene and its derivatives) and 94% of two- or three-ring compounds. PAHs with five or more rings were found to contribute from <0.1% at the catalytic cracker unit to 2.5% at the delayed coker unit. The highest combined concentration of benzo[a]pyrene and benzo[e]pyrene was 9.3 $\mu g/g^3$ in a personal sample from a coker cutter; however, these two PAHs were not detected in most samples (detection limit, 0.01 µg/m3). Exposures to four- to six-ring PAHs

of <0.1 μg/m^3 have been associated with loading road tankers with bitumen in refineries (Brandt and Molyneux 1985). In an evaluation of turn-around operations on reaction and fractionator towers, concentrations of anthracene, benzo[a]pyrene, chrysene, and pyrene in personal samples were either too low to be detected or ≤1 μg/m^3; naphthalene and its methyl derivatives accounted for >99% of the total PAH measured in personal samples (Dynamac Corp. 1985). Area samples taken at various sites during shut-down, leak testing and start-up operations after turn-arounds showed the same distribution pattern of individual PAHs with total PAH concentrations generally ≤100 μg/m^3 (maximum 400 μg/m^3).

Metalworkers may also be exposed to PAHs from refined mineral oils used in machining operations, with the level of exposure depending on the type of oil refinement procedure used (IARC 1984). Acid refined mineral oils have a significant PAH content and have been shown to cause skin cancer in workers exposed to them (Jarvholm and Easton, 1990). Solvent refining procedures almost completely remove PAHs from mineral oils and, therefore, should almost completely eliminate the risks of exposure to carcinogenic PAHs (Bingham et al. 1965; Doak et al. 1983; IARC 1984). There is evidence, however, that the concentration of carcinogenic PAHs in solvent-refined cutting oils may increase during use, particularly during operations such as quenching where the oil is severely heated (Agarwal et al. 1986; Apostoli et al. 1993; IARC 1984; La Fontaine 1978; Thony et al. 1976). Total PAH concentrations in air samples from work areas related to the use of cutting, hardening, and extruding oilshave been reported to be 66, 90, and 106 ng/m^3, respectively (Apostoli et al. 1993).

In a summary of data on industrial exposures in IARC (1984), concentrations of airborne benzo[a]pyrene in aluminum production facilities from 1959 to 1982 in several countries ranged from not detected to 975 μg/m^3; concentrations in a U.S. aluminum reduction plant ranged from 0.03 to 53.0 μg/m^3, depending on the work site. Concentrations of airborne benzo[a]pyrene in coke oven operations ranged from 0 to 383 μg/m^3 depending on the work area; average concentrations in a U.S. plant were reported to range from 0.15 to 6.72 μg/m^3. More recently, inhalation exposures to phenanthrene, pyrene, and benzo[a]pyrene of 485, 108, and 48 μg/8 hours, respectively, have been reported for workers in a German coke plant (Grimmer et al. 1994). However, Van Rooij et al. (1993b) has recently concluded that among coke oven workers dermal absorption is a major route of exposure to PAHs, accounting for an average of 75% and 51% of total absorbed pyrene and benzo[a]pyrene, respectively; the mean dermal and respiratory uptakes of pyrene in 12 workers were reported to range from 4 to 34 and 0.5 to 32 μg/day, respectively.

The use of coal tar, pitch, asphalt, creosote, soot, and anthracene oil is widespread in the manufacture of fuel, dyes, plastics, paints, insulating materials, impregnating materials, building materials, road-building materials, embedding material, rubber, inks, and brushes (Hueper 1949). Faulds et al. (1981) faund that PAHs in diesel engine exhaust attach to respirable dust particles and travel long distances in underground mines, resulting in exposure of mine workers far removed from engine sites. Mechanics may also be exposed to PAHs resulting from the pyrolytic decomposition of the organic fractions of abraded particles from clutch and brake linings (Knecht et al. 1987). Potential exposure to PAHs in road sealing work involving coal tar and bitumen was discussed by Darby et al. (1986). In a study to evaluate inhalation and dermal exposures of 10 roofers removing an old coal tar pitch roof and applying a new asphalt roof, the PAH content of forehead skin wipes taken at the end of the workshift (0.097 µg/cm^2; equivalent to an estimated daily skin exposure of 19.4 µg/day) was found to correlate with the PAH concentrations in personal air samples (10.2 µg/m^3) (Wolff et al. 1989c). Relative concentrations of PAHs in air and wipe samples were: fluoranthene > pyrene > benz[a]anthracene > benzo[a]pyrene > benzo[b]fluoranthene > benzo[g,h,i]perylene > benzo[k]fluoranthene. Anthracene was found in the air samples but was not detected in the wipe samples.

Data on PAH exposures in the United States for many other occupations are limited. Most of the recent studies have been conducted in other countries. PAH concentrations (combined particle- and vapor-phase) in two work areas in a silicon carbide plant ranged from not detected (detection limit, 0.01 mg/m^3) for benzo[a]pyrene and benzo[e]pyrene, to 0.99 mg/m^3 for fluoranthene and 3.46 mg/m^3 for naphthalene (Dufresne et al. 1987). Higher ambient concentrations were observed in the furnace area, ranging from 0.04 mg/m^3 for benzo[a]pyrene and benzo[e]pyrene to 3.85 mg/m^3 for fluoranthene and 58.0 mg/m^3 for naphthalene. Total PAH concentrations in areas near cooking fume sources in the food and catering industries in Finland have been reported to range from 0.2 to 31.8 µg/m^3 (Vainiotalo and Matveinen 1993). Benzo[a]pyrene concentrations of <l-44 ng/m^3 in the breathing zone of urban bus drivers in France have been reported (Limasset et al. 1993). The mean particulate total PAH exposure level in a Swedish electrode paste plant was found to vary from 4.3 to 84.6 µg/m^3 over various work operations, with an overall mean particulate PAH exposure level in the plant of 14.4 µg/m^3 (Ovrebo et al. 1994). The mean PAH exposure level in a Belgian graphite electrode plant was reported to be 19.7 µg/m^3 (Van Hummelen et al. 1993). Drivers of large diesel-powered trucks in Switzerland were not found to have exposures to total PAHs or benzo[a]pyrene that were significantly different from controls (Guilleman et al. 1992).

Preliminary data from the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, estimated the number of workers potentially exposed to various chemicals in the workplace from 1981 to 1983 (NIOSH 1990). Data for the seven PAHs included in the survey are summarized below:

Chemical	Number of industry/ occupation categories	Number of workers potentially exposed
Anthracene	5	2,303
Benz[a]anthracene	4	2,310
Benzo[a]pyrene	1	896
Chrysene	2	9,358
Fluoranthene	36	21,339
Fluorene	6	2,912
Pyrene	3	9,368

The NOES database does not contain information on the frequency, level, or duration of exposure of workers to any of the chemicals listed. It provides only estimates of workers potentially exposed to the chemicals.

PAHs have generally not been detected in surveys of human tissue, presumably because the compounds are fairly rapidly metabolized. Phenanthrene was the only PAH detected in the 1982 National Human Adipose Tissue Survey; it was found in trace concentrations in 13% of the samples (EPA 1986). Acenaphthylene, acenaphthene, fluorene, and chrysene were not found at levels below the detection limit (0.010 µg/g; 10 ppt). However, autopsies performed on cancer-free corpses found PAH levels of 11–2,700 ppt (ng/g) in fat samples (Obana et al. 1981). Several PAHs were detected, including anthracene, pyrene, benzo[e]pyrene, benzo[k]fluoranthene, benzo[a]pyrene, and benzo[g,h,i]perylene, with pyrene being detected in the highest concentrations. A similar study done on livers from autopsied cancer-free corpses found levels of 6–500 ppt (ng/g) of all of the same PAHs except benzo[e]pyrene, which was not detected (Obana et al. 1981). As in the fat sample studies, pyrene appeared in the highest concentrations in the liver, but the overall levels were less than in fat.

Human exposure to PAHs can be monitored through analytical determination of PAHs and metabolites (e.g., 1-hydroxypyrene) in the urine of exposed individuals (Jongeneelen et al. 1985, 1987; Tolos et al. 1991; Weston et al. 1994). For example, Clonfero et al. (1990) detected increased levels of PAH metabolites in the urine of individuals occupationally (i.e., aluminum plant workers) and

therapeutically (i.e., psoriatic patients) exposed to coal tar, as compared to unexposed subjects. Weston et al. (1994) reported similar results for coal-tar treated psoriasis patients. Tolos et al. (1991) and Van Rooij et al. (1994) reported significant increases in the average 1-hydroxypyrene concentrations in the urine of smokers over nonsmokers. Significant increases in urinary 1-hydroxypyrene levels have also been observed in children living in areas of high density automobile traffic over those of children in suburban areas (Kanoh et al. 1993). Several researchers have reported substantial increases in the urinary concentrations of 1-Hydroxypyrene and other PAH metabolites among workers exposed to PAHs in a variety of occupational settings, including coke plants (Grimmer et al. 1994; Jongeneelen et al. 1990; Van Hummelen et al. 1993), graphite electrode plants (Van Hummelen et al. 1993), foundries (Santella et al. 1993), and creosote wood treatment plants (Viau et al. 1993) and during clean-up of dump sites contaminated with coal tars (Viau et al. 1993), handling of petroleum coke (Jongeneelen et al. 1989), and road surfacing operations (Jongeneelen et al. 1988). Most of these increases were statistically significant over controls. There is conflicting evidence regarding an exposure-response relationship between PAH exposures levels and urinary PAH metabolite concentrations. For example, Grimmer et al. (1994) reported a good correlation between PAH inhalation exposures and levels of urinary metabolites of benzo[a]pyrene, phenanthrene, and pyrene, whereas Jongeneelen et al. (1990) did not find a strong relationship between air monitoring data and urinary levels of 1-hydroxypyrene. In a study of PAH inhalation exposures of aluminum plant workers, Becher and Bjorseth (1983) found that the high concentrations in the occupational setting did not correspond to the measured concentrations of urinary PAH metabolites. The authors suggested that PAHs adsorbed to airborne particulate matter may not be bioavailable and that the exposure-uptake relationship may not be linear over the entire PAH concentration range. When urinary 1-hydroxypyrene excretion is used in the assessment of PAH exposure, the contributions of alternative routes of exposure (i.e., inhalation and dermal) and the variability in the baseline excretion among individual PAH metabolites due to tobacco smoking and dietary PAH intake should be taken into account (Van Rooij et al. 1993b, 1994). Assays for other biomarkers of PAH exposure are currently being developed in animal models (Singh and Weyard 1994), but have not been evaluated in humans.

The detection of PAH-DNA adducts in urine, blood and other tissues by immunoassay and ^{32}P-postlabelling has also been used as an indicator of exposure (Harris et al. 1985; Herikstad et al. 1993; Ovrebo et al. 1994; Perera et al. 1993; Santella et al. 1993).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Human exposure to PAHs is expected to be highest among certain occupational groups (e.g., individuals working with coal tar and its products, foundry workers, miners, chimney sweeps), smokers and nonsmokers living or working in close proximity to smokers, members of the general population who heat their homes with wood-burning stoves, individuals living in the vicinity of emission sources or using products containing PAHs, and people living in the vicinity of NPL sites where PAHs have been detected above background levels. People who consume grilled or smoked food may ingest high levels of these compounds. Anyone who works extensively with products such as roofing materials, asphalt, and other PAH-containing substances may be exposed through inhalation or skin contact.

Recreational and subsistence fishers that consume appreciably higher amounts of locally caught fish from contaminated waterbodies may be exposed to higher levels of PAHs associated with dietary intake (EPA 1993b). PAH contamination has triggered the issuance of several human health advisories. As of September 30, 1993, PAHs were identified as the causative pollutants in five fish consumption advisories in three different states. This information is summarized in Table 5-7 (RTI 1993). EPA is considering including PAHs as target analytes and has recommended that these chemicals be monitored in fish and shellfish tissue samples collected as part of state toxics monitoring programs. EPA recommends that residue data obtained from these monitoring programs be used by states to conduct risk assessments to determine the need for issuing fish and shellfish consumption advisories for the protection of the general public as well as recreational and subsistence fishers (EPA 1993b).

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PAHs is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PAHs.

Table 5-7. Fish Consumption Advisories

State	Waterbody	Extent
Massachusetts	Hocomoco Pond	Entire pond
Michigan	Hersey River	Downstream from Reed City
Ohio	Black River	6.2 miles from the 31st Street Bridge (Loraine) to the harbor (includes confined disposed facility)
Ohio	Little Scioto River	3.9 miles from Holland Road (Marion) south to St. Rt. 739
Ohio	Mahoning River	29.24 miles from Northwest Bridge Street (Warren) to Pennsylvania border

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties (K_{ow}, K_{oc}, vapor pressure, Henry's law constant, etc.) have been sufficiently characterized for most of the 17 PAHs and allow prediction of their environmental fate.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1992, .became available in May of 1994. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

PAHs are produced primarily as a result of combustion processes both from anthropogenic and natural sources (HSDB 1994; IARC 1982). Of the 17 PAH compounds discussed in this profile, only acenaphthene, acenaphthylene, and anthracene are produced commercially. However, several other PAH compounds were imported into the United States in 1984 and 1985 (see Section 4.2).

There is no known commercial use for most of the 17 PAHs discussed in this profile. Anthracene, acenaphthene, fluorene, and phenanthrene are chemical intermediates used in the manufacture of dyes, plastics, pesticides, explosives, and chemotherapeutic agents (Hawley 1987; HSDB 1992; Windholz 1983). Fluoranthene is used as a lining material to protect the interior of steel and ductile iron drinking water pipes and storage tanks (NRC 1983).

PAHs are most likely to be released directly in the atmosphere. Other contaminated media of relevance to human exposure include foods and drinking water.

Rules governing the disposal of PAHs have been promulgated by EPA. Although information regarding recommended remedial techniques is available for most of the 17 PAHs discussed in this profile (EPA 1980, 1981a; HSDB 1992; IARC 1985), additional information about the amounts of these compounds disposed of by these remediation methods would be helpful in determining important routes of human exposure.

Environmental Fate. The environmental fate of PAHs is well characterized. No further studies are needed. PAHs are transported in and partitioned to the air, water, and soil. Transformation and degradation processes of PAHs in the air, water, and soil have been well studied. Atmospheric halflives of PAHs are generally less than 30 days. Photochemical oxidation of a number of PAHs has been reported (EPA 1988a). The National Research Council (NRC 1983) noted that compounds adsorbed to soot are more resistant to photochemical reactions than pure compounds. In surface water, PAHs can volatilize, photodegrade, oxidize, biodegrade, bind to particulates, or accumulate in aquatic organisms (with bioconcentration factors often in the 100-2,000 range). Half-lives for volatilization of benz[a]anthracene and benzo[a]pyrene (high molecular weight PAHs) from water have been estimated to be greater than 100 hours (Southworth 1979), and the half-life for volatilization of anthracene (a low molecular weight PAH) was estimated to be 18 hours (Southworth et al. 1978). Hydrolysis is not considered to be an important degradation process for PAHs (Radding et al. 1976). The rate and extent of photodegradation varies widely among the PAHs (Neff 1979). PAHs in soil can biodegrade or accumulate in plants. Microbial metabolism is the major process for degradation of PAHs in soil environments. Photolysis, hydrolysis, and chemical oxidation are not considered important processes for the degradation of PAHs in soils (Sims and Overcash 1983).

Bioavailability from Environmental Media. Limited information is available regarding the bioavailability of PAHs from plants grown in contaminated soils. PAHs can be absorbed following inhalation, oral, or dermal exposure. All of these routes are of concern to humans because PAHs have been shown to contaminate the air, drinking water, soil, and food. There is a need to conduct additional studies on the bioavailability of PAHs from plants grown in contaminated soils and from contaminated soils. However, bioavailability of PAHs from contaminated air, water, and food is of primary concern, and some information is available concerning bioavailability following exposure by these routes. Indirect evidence indicates that PAHs are absorbed by humans following inhalation exposure (Becher and Bjorseth 1983). Furthermore, indirect evidence suggests that benzo[a]pyrene may be absorbed following oral exposure in humans. The concentration of benzo[a]pyrene in human

feces was studied after eight volunteers ingested broiled meat that contained approximately 9 µg of benzo[a]pyrene (Hecht et al. 1979). Less than 0.1 µg/person of benzo[a]pyrene was measured in the feces of these individuals, suggesting absorption and perhaps metabolism of the compound. More direct data are needed on the extent of bioavailability of PAHs, particularly those that are particlebound, following the three major routes of exposure.

Food Chain Bioaccumulation. PAHs can bioaccumulate in plants, aquatic organisms, and animals from intake of contaminated water, soil, and food. Extensive metabolism of the compounds by high-trophic-level consumers, including humans, has been demonstrated; therefore, food chain biomagnification of the compounds does not appear to be significant (Edwards 1983; Eisler 1983; Gile et al. 1982; Wild et al. 1992). However, in some areas of the United States, fish consumption advisories have been issued based on elevated concentrations of PAHs found in locally caught fish or shellfish (see Section 5.6) (RTI 1993). Additional information is needed on levels of PAHs in aquatic organisms that are of concern for human health.

Exposure Levels in Environmental Media. PAHs have been produced and used in large volumes in the environment, home, and industry and. are widely distributed in the environment. They have been detected in air, water, sediment, soil, and food. Although some studies of background levels in different media have been conducted, additional site-specific concentration data in the vicinity of hazardous waste sites are needed. Studies should focus particularly on ambient air, in order to estimate exposure of the general population through inhalation of contaminated air as well as ingestion of or dermal contact with contaminated water or soil. Levels of PAHs tend to be higher in urban air than in rural air (Greenberg et al. 1985; Pucknat 1981). One study reported benzo[a]pyrene air levels of 0.2-19.3 ng/m^3 for urban air and 0.1-0.2 ng/m^3 in rural air (Pucknat 1981). Higher levels of other PAHs have been measured in urban areas. Basu and Saxena (1978a) reported concentrations of selected PAHs in surface waters used as drinking water sources in four U.S. cities (Huntington, West Virginia; Buffalo, New York; and Pittsburgh and Philadelphia, Pennsylvania) as ranging from 4.7 ng/L in Buffalo to 600 ng/L in Pittsburgh. Data collected as part of the Nationwide Urban Runoff Program indicate concentrations of individual PAHs in the range of 300-10,000 ng/L, with the concentrations of most PAHs above 1,000 ng/L (Cole et al. 1984). Few data are available on the concentrations of PAHs in U.S. groundwater. Basu and Saxena (1978b) reported total PAH concentrations in groundwater from three sites in Illinois, Indiana, and Ohio to be in the range of 3-20 ng/L. Data summarized by Sorrel et al. (1980) indicate low levels of PAHs in finished drinking waters of the

United States. Reported maximum concentrations for total PAHs (based on measurement of 1.5 PAHs) in the drinking water of 10 cities ranged from 4 to 24 ng/L. PAHs have been detected in unprocessed cereal, potatoes , grain, flour, bread, vegetables, fruits, and refined fats and oils. The concentrations in uncooked foods largely depend on the source of the food. The amount of PAHs found in food products depends as much on the method of preparation (especially grilling, smoking, or pickling) as on the origin of the food.

Reliable monitoring data for the levels of PAHs in contaminated media at hazardous waste sites and associated background sites are needed so that the information obtained on levels of PAHs in the environment can be used in combination with the known body burden of PAHs to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. No data are available regarding the levels of PAHs in body tissues or fluids for populations living near hazardous waste sites. PAHs and their metabolites can be measured in the urine of exposed individuals. In workers exposed to PAHs, the PAH metabolite 1-hydroxypyrene has been detected in the urine at concentrations of 0-40 µg/g creatinine (Jongeneelen et al. 1985). No correlation was found between occupational exposure levels and urine levels, so it is not known whether-urine metabolites could be detected following exposure to low levels of PAHs (as might be expected to occur in individuals living in the vicinity of hazardous waste sites).

PAHs have generally not been detected in surveys of human tissue, presumably because the compounds are fairly rapidly metabolized. Phenanthrene was the only PAH detected in the 1982 National Human Adipose Tissue Survey; it was found in trace concentrations in 13% of the samples (EPA 1986). Acenaphthylene, acenaphthene, fluorene, and chrysene were not found at levels below the detection limit (0.010 µg/g; 10 ppt). However, autopsies performed on cancer-free corpses found PAH levels of 11-2,700 ppt (ng/g) in fat samples (Obana et al. 1981). Several PAHs were detected, including anthracene, pyrene, benzo[e]pyrene, benzo[k]fluoranthene, benzo[a]pyrene, and benzo[g,h,i]perylene, with pyrene being detected in the highest concentrations. A similar study done on livers from cancer-free patients found levels of 6-500 ppt of all of the same PAHs except benzo[e]pyrene, which was not detected (Obana et al. 1981). As in the fat sample studies, pyrene appeared in the highest concentrations in the liver, but the overall levels were less than in fat.

A few exposure estimates for the general population have been made from inhalation of ambient air and ingestion of contaminated drinking water and food, but sparse monitoring data limit the reliability of these estimates. Relatively recent estimates of the size of the workforce exposed to a few of the PAHs (such as benzo[a]pyrene) are available from NIOSH. However, monitoring data on workplace exposure levels are generally inadequate, partially because of the complexity of air emissions in terms of number of compounds detected. Information on exposure levels in humans is needed to better define exposure estimates in the general population and workforce, and to examine the relationship between levels of PAHs in the environment, human tissue levels, and the subsequent development of health effects. These data should be collected simultaneously with data on levels of PAHs air, water, and soil. For a sound database to serve as a foundation for higher level environmental or toxicological research, it should contain information on human exposure levels to PAHs, particularly for individuals living near hazardous waste sites.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for PAHs were located. These substances are not currently compounds for which a subregistry has been established in the National Exposure Registry. The substances will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 Ongoing Studies

The National Institute of Environmental Health Sciences is funding research at Miami University, Oxford, Ohio, to evaluate the transfer of benzo[a]pyrene from sediments directly to a sediment-feeding fish. Specific objectives are to (1) to examine the effects of seasonal parameters (i.e., temperature, body lipids, gonadal development) on the rate and pattern of metabolism of benzo[a]pyrene in a range of size, age, and sexual maturity classes; and (2) evaluate the relative importance of sediment and water as vectors of uptake of benzo[a]pyrene.

The National Institute of Environmental Health Sciences is funding research at the State University of New York at Albany to determine the aquatic bioavailability of PAHs from sediments collected near

discharge points from two aluminum manufacturing plants in the Massena area of the St. Lawrence River. The results of this study should provide a better understanding of the relative contributions of individual industries to pollution of fish and wildlife consumed by area residents.

The National Institute of Environmental Health Sciences is funding research at the State University of New York at Albany to conduct an epidemiologic study of Mohawk women and infants to test the hypotheses that exposure to PAHs, polychlorinated biphenyls (PCBs), polychlorinated dibenzo-pdioxins and dibenzofurans (PCDD/Fs) from a nearby Superfund hazardous waste site elevates body burdens and affects the cytochrome P-450-dependent mixed function monooxygenase system. Determination of 15 PAHs in breast milk will be among the analyses included in this study. The results of the study should enhance our understanding of how these important classes of chemicals arising from hazardous waste bioaccumulate in human adults and infants and whether P-450IA2 induction is a sensitive biomarker of their early biologic effect.

The National Institute of Environmental Health Sciences is funding research at Johns Hopkins University to investigate the molecular dosimetry of ingested PAHs from cooked meats in humans, and identify susceptibility factors that modulate the formation of DNA and protein adducts with these dietary carcinogens. Ultimately, molecular biomonitoring may allow quantitation of biological dose from ingested PAHs, thus accounting for variation in exposure, cooking processes, and metabolism.

The National Institute of Environmental Health Sciences is funding the Massachusetts Institute of Technology to continue studies with fluoranthene by using a modification of a ^{32}P-postlabelling assay to detect and quantify DNA adducts in mice and human lymphoblast cell lines from eventual application as a dosimeter to monitor DNA damage in tissues from occupationally or environmentally exposed human populations.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring PAHs, its metabolites, and other biomarkers of exposure and effect to PAHs. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Several analytical techniques have been used to determine trace levels of PAHs in biological tissues and fluids including adipose tissue, lungs, liver, skin, hair, blood, urine, and feces (Table 6-l). These include gas chromatography coupled with flame ionization detection (GC/FID), gas chromatography coupled with a mass spectrometry (GC/MS), high-performance liquid chromatography (HPLC) coupled with an ultraviolet (UV) or fluorescence detector, and thin-layer chromatography (TLC) with fluorescence detection.

Recently, Liao et al. (1988) developed a relatively simple and rapid procedure for purifying human and bovine adipose tissue extracts so that trace levels of complex mixture of target analytes (including PAHs) could be detected and quantified by capillary GC/MS. By employing an activated Florisil column, Liao and co-workers showed that lipid contaminants bind effectively (more than 99.75%) with Florisil, thereby producing a relatively clean sample extract. A detection limit at a low ng/g level and an average sample recovery of 85% were achieved (Gay et al. 1980; Liao et al. 1988; Modica et al. 1982).

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Biological tissues (adipose)	Homogenization in 8% benzene in hexane; clean-up on Florisil column	GC/MS	5–50 ng/g	52–95	Liao et al. 1988
	Extraction into pentane; clean-up on Florisil and silica column	GC/MS	0.05 ng/sample	27–100	Gay et al. 1980
	Extraction into cyclohexane; clean-up on alumina column; concentration	GC/FID	50 ng/sample	83–95	Modica et al. 1982
Lungs	Homogenization in hexane; extraction with 25% DMSO in water (discarding aqueous phase); washing with water; concentration	SF	No data	95	Mitchell 1979
	Extraction into cyclohexane; centrifugation; dry with Na_2SO_4; concentration; analysis in acetonitrile	HPLC/UV	20 ng/g	93.7 (fluoranthene); 65.3 (pyrene); 65 (benzo[a]-anthracene)	Brandys et al. 1989

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Lungs (cont.)	Tissue digestion; extraction and precipitation of DNA with spermine; hydrolysis of DNA in 0.1 M HCl	HPLC/radioisotope counting	13.3–32.7x10^{-15} mol BPDE bound/mg DNA	No data	Weyand and Bevan 1987a
	Tissue digestion; extraction of DNA; isolation of BPDE-DNA adducts (immunoaffinity chromatography); hydrolysis to tetrahydrotetrols	HPLC/fluorescence detector	6 pg B[a]P-tetrol/mL	26–66	Weston and Bowman 1991
Human lymphocytes	Isolation and hydrolysis of DNA to tetrahydrotetral; oxidization to dicarboxylic acid with potassium superoxide; derivatization and clean up on silica	GC/NIEC-MS (BaP adduct)	5 adduct/10^{7} nucleotide	47	Allan et al. 1993
Liver	Homogenization with DMSO; incubation with S-9 mixture at 37 °C; extraction with ethyl acetate; concentration; analysis for metabolites of indeno[1,2,3-c,d]pyrene	HPLC/UV-VIS	No data	No data	Rice et al. 1985b

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liver (cont.)	Homogenization with DMSO; incubation with S-9 mixture at 37 °C; extraction with ethyl acetate; concentration and analysis for metabolites of indeno[1,2,3-c,d]pyrene and benzo[b]fluoranthene	HPLC/UV-VIS	No data	No data	Amin et al. 1982
	Homogenization; saponification; extraction into hexane; clean-up on silica or alumina column	HPLC/fluorescence detector	0.006–0.46 ng/g range	No data	Obana et al. 1981
Skin	Digestion and deproteinization of PAH-treated skin tissue; extraction and precipitation of DNA; hydrolysis with 1.2 M HCl	HPLC/fluorescence detector	10^{-15} mol BPDE/sample	No data	Shugart et al. 1983
	Modification of PAH-treated skin DNA *in vitro*; labelling of PAH-DNA adduct by ^{32}P-postlabeling technique	TLC/ autoradiography	90–1,210x10^{-15} mol PAH adduct/ mg DNA	No data	Phillips et al. 1987

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish bile	Hydrolysis of the conjugated PAH metabolite; extraction of the free metabolite into n-hexane; concentration and methylation with methyl iodide; extraction of methylated product	LESS (3-hydroxy-BaP)	0.005 ng/mL	No data	Ariese et al. 1993b
Blood	Hydrolysis of BPDE-DNA adduct with 0.1 M HCl; analysis of hydrolysis products (benzo[a]pyrene-tetrols and triols)	SLS	No data	No data	Haugen et al. 1986
	Extraction into cyclohexane; centrifugation; drying with Na_2SO_4; concentration; analysis in acetonitrile solution	HPLC/UV	20 ng/mL	107 (fluoranthene); 108.6 (pyrene); 101 (benzo[a]-anthracene)	Brandys et al. 1989

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (cont.)	Treatment with 2% horse serum; incubation with rabbit anti-BPDE-DNA antiserum; incubation with alkaline phosphatase-conjugated goat anti-rabbit IgG, PNPP, radiolabeled PNPP, and $MgCl_2$; separation of hydrolyzed radiolabeled PNPP; measurement of radioactivity	USERIA	$0.38–2.2x10^{-15}$ mol/μg DNA	No data	Haugen et al. 1986
	Incubation of equal volumes rabbit anti-serum and sample; wash; incubation with reconstituted biotinylated anti-rabbit IgG; wash; incubation with buffered europium-labeled streptovidin; shaking with enhancement solution at room temperature	Time-related fluorometry (PAH-DNA adduct)	<1 adduct/10^8 nucleotides	No data	Schoket et al. 1993
Blood	Incubation of BPDE-DNA adduct sample with goat antihuman IgG reagent, horseradish peroxidase and substrate solution	ELISA	$0.38–2.2x10^{-15}$ mol BPDE/μg DNA	No data	Haugen et al. 1986

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (cont.)	Separation and isolation of white blood cell DNA by standard RNase and phenol treatment	ELISA	$1x10^{-15}$ mol BPDE/0.001 mg DNA	No data	Perera et al. 1988
			$2–120x10^{-15}$ BPDE/50 µg DNA	No data	Shamsuddin et al. 1985
	Separation of hemoglobin (hb) by lysis and centrifugation; isolation of BPDE-hb adduct by acid hydrolysis; clean-up on Sep-Pak and cellulose column	HPLC/fluorescence detector	$5x10^{-12}$ g BPDE/sample	No data	Shugart 1986
	Isolation of PAH-DNA adduct from white blood cells; digestion of adduct with [gamma ^{32}P] ATP; resolution and quantitation of the ^{32}P-labelled adduct by TLC;	TLC and auto-radiography	$0.3x10^{-15}$ mols adduct/µg DNA	No data	Phillips et al. 1988
	Collection of lymphocyte cells; isolation of BPDE-DNA adduct by standard treatment; assay of BPDE-DNA adduct by immunoassay; analyses by SLS	ELISA/USERIA; SLS	$0.06–0.23x10^{-15}$ mol BPDE/µg DNA	No data	Harris et al. 1985

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Feces	Extraction with benzene:MeOH (4:1); add MeOH:H_2O (4:1); clean-up on silica gel column	HPLC/UV	0.05 µg/g	No data	Hecht et al. 1979
Urine	Acidify to pH 3 with HCl; clean-up on activated Sep-Pak C_{18} cartridge column; reduction with hydriodic acid	HPLC/fluorescence detector	<1 µg PAH/mmol creatinine	10–85	Becher and Bjorseth 1983
	Extraction into cyclohexane; concentration; reduction with hot acid	GC/FID	1.2–6.48 µg PAH/mmol creatinine	No data	Becher and Bjorseth 1985
	Hydrolysis; isolation of tetrol by Sep-Pak chromatography; clean up by immunoaffinity chromatography (anti BP-tetrol-modified guanosine column)	HPLC/SFS (7,8,9,10-BaP tetrol)	0.01 pmol/mL	>30	Weston et al. 1993a
	Isolation on a Sep-Pak column, washing with water followed by 10% MeOH; elution with 100% MeOH; concentration; addition of 0.1 M HCl with heating	SLS	25 pg metabolite/mL	No data	Uziel et al. 1987

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (cont.)	Collection of radiolabeled benzo[a]pyrene urine sample; addition of MeOH; isolation on C_{18} Sep-Pak column; elution with aqueous MeOH	HPLC/UV	$5x10^{-12}$ mol 7-BPDE-Gua/10 µg of labelled benzo[a]-pyrene	No data	Autrup and Seremet 1986
	Buffer to pH=5.5; enzymatic hydrolysis with β-glucuronidase/sulfatase (4 hours at 37.5 °C); clean-up using Sep-Pak C_{18} cartridge; isolation of 1-pyrenol	HPLC/fluorescence detector	0.45 nmol/L (1-pyrenol)	No data	Tolos et al. 1990
	Dilution; extraction into $CHCl_3$; precipitation of protein; wash extract with CH_3OH; evaporation and analysis of residue	HPLC/UV; FLNS	~1 fmol (BP tetrol)	No data	Rogan et al. 1990
Feces	Homogenization and drying; extraction with $CHCl_3$; evaporation and analysis of residue	HPLC/UV; FLNS	~1 fmol (BP tetrol)	No data	Rogan et al. 1990
Hair	Incubation of hair follicle with (-)-B[a]P-7,8-diol for 24 hours; addition of acetone; centrifugation; analysis of supernatant	HPLC/fluorescence detector	~0.3 fmol of tetrols	No data	Alexandrov et al. 1990

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Thymus and liver	Preparation of fluoranthene-modified DNA *in vitro*; digestion with enzyme; isolation of adducts using disposable C_{18} cartridge; nuclease P1 pretreatment to remove residual unmodified nucleotides; labelling of fluoranthene-DNA adduct by ^{32}P-postlabelling technique; nuclease P1 digestion	HPLC/radioisotope counting	0.1 fmol adduct (3 adducts/10^8 nucleotides in 1 µg DNA)	10–15	Gorelick and Wogan 1989
Thymus	Preparation of B[a]P-DNA adduct; digestion; labelling of adduct by ^{35}S-postlabelling technique	HPLC/radioisotope counting	1 adduct/10^8 nucleotides for 60 µg DNA	20	Lau and Baird 1991
Embryo and thymus	Preparation of PAH-DNA adduct; digestion; labelling of adduct by ^{35}P-postlabelling; separation of steroisomers by immobilized boronate chromatography	IP-RP-HPLC/radioisotope flow detects (+) and (–) enantiomers of anti- and syn- PAH-DE-DNA adduct	No data	No data	Baird et al. 1993

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Placenta	Hydrolysis of DNA; addition of phosphate-buffered saline; neutralization with NaOH; incubation of sensor in sample	FIS	$14x10^{-18}$ mol BPT	No data	Vo-Dinh et al. 1991

ATP = adenosine triphosphate; B[a]P = benzo[a]pyrene; BPDE = 7_{β},8α-dihydroxy-[9α, 10α]-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene; BPT = benzo[a]pyrene tetrol; $CHCl_3$ = chloroform; CH_3OH = methanol; DMSO = dimethyl sulfoxide; DNA = deoxyribonucleic acid; ELISA = enzyme linked immunosorbent assay; FIS = fluoroimmunosensor; FLNS = fluorescence line narrowing spectrometry; fmol = femtomole; GC/FID = gas chromatography/flame ionization detector; GC/MS = gas chromatography/mass spectrometry; Gua = Guanosine; H_2O = water; HCl = hydrogen chloride; HPLC = high performance liquid chromatography; IgG = immunoglobin; IP-RP-FPLC = ion-paired reverse phase high pressure liquid chromatography; KOH = potassium hydroxide; LESS = laser-excited Stepol'skii spectroscopy; M = molar; MeOH = methanol; $MgCl_2$ = magnesium chloride; mmol = millimole; $NADP^+$ = oxidized nicotinamide adenosine dinucleotide; NaOH = sodium hydroxide; Na_2SO_4 = sodium sulfate; ng = nanogram; NIEC-MS = negative ionization electron capture mass spectrometry; nmol = nanomole; PAHs = polycyclic aromatic hydrocarbons; pg = picogram; pmol = picomole; PNPP = para nitrophenyl phosphate; SF = spectrofluorometry; SFS = synchronous fluorescence spectroscopy; SLS = synchronous luminescence spectroscopy; TLC = thin-layer chromatography; USERIA = ultra sensitive enzyme radioimmuno assay; UV = ultraviolet; UV-VIS = UV-visible detector.

Obana et al. (1981) reported the identification and quantification of six PAHs on EPA's priority pollutant list: anthracene, pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, and benzo[g,h,i]perylene using the HPLC/fluorescence detector technique. Levels measured in human. tissue ranged from 0.006 to 0.460 ng/g. Following extraction of the PAHs from the sample matrices by saponification with KOH, the extract was cleaned on alumina and silica gel columns, prior to quantitation. The known carcinogens, benz[a]anthracene and dibenz[a,h]anthracene, were not detected (detection limit <0.005 ng/g). The HPLC/UV detection technique has also been used to simultaneously determine fluoranthene, benz[a]anthracene, and pyrene in blood and lung tissues (Brandys et al. 1989). A detection limit of ppb (ng/g or ng/mL), satisfactory recoveries (65-109%), and adequate precision (119% relative standard deviation [RSD]) were achieved (Brandys et al. 1989).

In addition to direct measurement of PAHs in biological tissues, it is also possible to determine the concentration of metabolites in biological fluids. Pyrene is predominantly excreted as a 1-hydroxypyrene conjugate (glucoronate and sulfate), although 1,2-dihydroxy- 1,2-dihydropyrene conjugates are .also excreted in urine (Grimmer et al. 1993). Phenanthrene, on the other hand, is mainly excreted as dihydrodiol conjugates. The metabolites of phenanthrene that have been detected in human urine are 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 4-hydroxyphenanthrene, 9-hydroxyphenanthrene, 1,2-dihydroxy-1,2-dihydrophenanthrene, 3,4-dihydroxy-3,4-dihydro-phenanthrene, and 9,10-dihydroxy-9,10-dihydrophenanthrene (Grimmer et al. 1993). There are apparently individual variations in the phenanthrol (hydroxyphenanthrene) and phenanthrene dihydrodiol conjugates excreted in the 24-hour urine sample (Grimmer et al. 1993). The major metabolite of benzo[a]pyrene in human tissue and body fluid is 7,8,9,10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene (Weston et al. 1993a, 1993b).

Becher and Bjorseth (1983, 1985) and Becher (1986) developed an HPLC method for biological monitoring of PAHs and PAH metabolites in the urine of humans following occupational exposure to PAHs. Using the HPLC/fluorescence detector technique, recoveries of the individual PAH compounds varied between 10 and 85% with the more volatile 3-ring PAHs having the lowest recoveries. A detection limit of less than 1 µg of PAHs per mmol of creatinine was obtained. HPLC equipped with a fluorescence detector has also been used to measure 1-pyrenol (1-hydroxypyrene, a pyrene metabolite) in urine of workers exposed to PAHs in coal tar pitch with a detection limit of

0.45 nmol/L (Tolos et al. 1990). Recovery and precision data were not reported. A strong correlation was observed between the concentrations of urinary 1-hydroxypyrene in workers and environmental PAHs, indicating that pyrene may be used as a biomarker of exposure for assessing worker exposure to coal tar pitch containing pyrene (Tolos et al. 1990). Since 1-Hydroxypyrene glucuronide is approximately 5 times more fluorescent than 1-hydroxypyrene, the former may be a more sensitive biomarker for PAH exposure (Strickland et al. 1994). A sensitive HPLC/synchronous fluorescence spectroscopic method is available for the determination of 1-hydroxypyrene glucuronide (Strickland et al. 1994). Hecht et al. (1979) employed an HPLC analytical technique for determining the concentrations of benzo[a]pyrene and its metabolites in the feces of humans and rats following consumption of charcoal-broiled beef. A detection limit of 0.05 µg of benzo[a]pyrene metabolites per gram of sample was noted with HPLC/UV detection.

There is considerable evidence that PAHs are enzymatically converted to highly reactive metabolites that bind covalently to macromolecules such as DNA, thereby causing mutagenesis and carcinogenesis in experimental animals. Thus, benzo[ajpyrene, a prototype of the carcinogenic PAHs and the most thoroughly studied PAH, is activated by microsomal enzymes to 7β, 8α-dihydroxy-(9α,10α)-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDE) and binds covalently to DNA, resulting in formation of BPDE-DNA adducts (Harris et al. 1985; Haugen et al. 1986; Uziel et al. 1987). Sensitive methods are available to detect PAH-DNA adducts in the blood and tissues of humans and animals. These include immunoassays, i.e., enzyme-linked immunosorbent assays (ELISA), radioimmunoassay (RIA), dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA), and ultrasensitive enzyme radioimmunoassay (USERIA); ^{32}P- and ^{35}S-postlabelling with radioactivity counting; surface-enhanced Raman spectroscopy; and synchronous luminescence spectroscopy (SLS) (Gorelick and Wogan 1989; Gorelick and Reeder 1993; Harris et al. 1985; Haugen et al. 1986; Helmenstine et al. 1993; Herikstad et al. 1993; Lau and Baird 1991; Perera et al. 1988; Phillips et al. 1987; Schoket et al. 1993).

The ELISA technique is used for detection of antibodies in serum bound to BPDE-DNA adducts. The USERIA method involves measuring the immunological response of BPDE-DNA in the presence of rabbit anti-serum. Several researchers have employed the immunoassay techniques for detecting PAH-DNA adducts at 10^{-l5} mol levels in the blood and tissues of humans occupationally exposed to

PAHs (Harris et al. 1985; Haugen et al. 1986; Newman et al. i988; Perera et al. 1988; Shamsuddin et al. 1985; Weston et al. 1988).

^{32}P-postlabelling is a highly sensitive and specific method for detecting PAH-DNA adducts in the blood and tissues of humans and animals (Gorelick and Wogan 1989; Phillips et al. 1988, 1987; Willems et al. 1991). Detection limits ranging from $0.3x10^{-15}$ mol of PAH adduct per µg of DNA (<1 adduct in 10^7 nucleotides) to $<10^{-18}$ mol of adduct per ug of DNA have been achieved (Phillips et al. 1988, 1987; Willems et al. 1991). Further advantages of the ^{32}P-postlabelling technique are that adducts do not need to be fully characterized in order to be detected, and that the method is particularly suited to occupational exposure to a complex mixture of PAHs. Coupling ^{32}P-postlabelling methodology with HPLC analysis has improved the resolution of the labeled nucleotides and can be used to identify and quantify specific PAH-DNA adducts such as fluoranthene-DNA adducts (Gorelick and Wogan 1989). A detection limit of 0.1 femtomole (fmol) of adduct (3 adducts per 10^8 nucleotides in 1 µg DNA) has been achieved. The advantage of this method is that it is not limited with respect to the amount of DNA that can be analyzed; therefore, sensitivity can be enhanced by analyzing larger quantities of DNA. Average recovery was 10-15% at 3 adducts per 10^6 nucleotides. Recovery was greater (30-40%) from DNA containing higher levels of adducts (Gorelick and Wogan 1989). The ^{32}P-postlabelling assay and a combination of thin-layer and reverse-phase HPLC was also used to separate DNA adducts of 6 nitrated PAHs (King et al. 1994). PAH-DNA adducts have also been detected and identified using [^{35}S]phosphorothioate postlabelling combined with HPLC analysis (Lau and Baird 1991). The sensitivity of this assay is 1 adduct per 10^8 nucleotides for a 60-µg DNA sample with an overall adduct recovery of 20%. An advantage of ^{35}S-postlabelling over ^{32}P-postlabelling is that ^{35}S has a longer half-life (87 days) than ^{32}P (14 days). This allows longer storage times between labeling and adduct analysis with minimal loss in sensitivity. ^{35}S also has a lower radioactive decay energy than ^{32}P, which reduces the risk of human radiation exposure and eliminates the need for the radioisotope-shielding equipment that is required for studies with high specific radioactivity. On the other hand, ^{35}S is also less sensitive than the ^{32}P-postlabelling analysis because of the lower specific activity of [^{35}S]adenosine triphosphatase (ATP) compared to [^{32}P]ATP and because of the requirement for more radioactivity per adduct for accurate HPLC analysis. However, if large samples of DNA are available, the sensitivity of ^{35}S-postlabelling/HPLC can be increased substantially (Lau and Baird 1991).

HPLC/UV detection and HPLC/fluorescence detection have been used for determining concentrations of PAH-DNA adduct and hydrolyzed PAH-DNA adducts in biological tissues and fluids (Alexandrov et al. 1990; Autrup and Seremet 1986; Jongeneelen et al. 1986; Rice et al. 1985b; Rogan et al. 1990; Salhab et al. 1987; Shugart 1986; Shugart et al. 1983; Weston and Bowman 1991; Weston et al. 1988). A detection limit of l0-l5 mol of tetrols per sample was achieved (Haugen et al. 1986; Shugart et al. 1983; Weyand and Bevan 1987a). HPLC with a fluorescence detector has been used to measure the stereospecific formation of benzo[a]pyrene tetrols from cytochrome P-450-dependent metabolism of (-)-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene to BPDE in human hair (Alexandrov et al. 1990). This assay is simple, requiring only three human hair follicles and a low (0.5-2 µmol) substrate concentration. The limit of detection is ≈0.3 fmol of tetrols (Alexandrov et al. 1990). This is a rapid and noninvasive method that could be used to determine an individual's capacity to activate carcinogens to DNA-binding intermediates (Alexandrov et al. 1990). HPLC with fluorescence detection has also been used to detect BPDE-DNA adducts in human lung tissues (Weston and Bowman 1991). A detection limit of 6 pg benzo[a]pyrene-tetrol/mL (1 adduct in 10^8 nucleotides) was achieved (Weston and Bowman 1991). Recoveries ranged from 26 to 66% for the procedure. HPLC/UV has been used to identify and quantify a benzo[a]pyrene-DNA adduct, specifically 7-(benzo[a]pyrene-6-yl)guanine (BP-N7Gua) in urine and feces in the femtomole range (Rogan et al. 1990). The structure of the adduct was established by fluorescence line narrowing spectrometry (FLNS). Recovery and precision data were not reported (Rogan et al. 1990).

Using benzo[a]pyrene as a model carcinogen, Vahakangas et al. (1985), Haugen et al. (1986), and Harris et al. (1985) have developed an synchronous luminescence spectroscopy (SLS) technique for detecting trace levels of PAH-DNA adducts in the blood of humans occupationally exposed to high levels of PAHs. Vahakangas et al. (1985) detected less than 1 benzo[a]pyrene moiety per 10^7 DNA molecules by SLS technique following *in vitro* acid hydrolysis of BPDE-DNA adduct. Fiber-optic antibody-based fluoroimmunosensor (FIS) has been used to measure DNA adducts of benzo[a]pyrene in biological samples such as human placenta (Tromberg et al. 1988; Vo-Dinh et al. 1991). The FIS is used to detect the highly fluorescent benzo[a]pyrene 7,8,9,10-tetrol (BPT) after release from the weakly fluorescent BPDE-DNA by mild hydrolysis. The FIS is highly specific because of the antigen-antibody reaction. This assay is highly sensitive, achieving a detection limit of 14×10^{-18} mol

of BPT (Vo-Dinh et al. 1991). FIS precision is adequate (6.2-15% RSD) (Tromberg et al. 1988). Recovery data were not reported.

6.2 ENVIRONMENTAL SAMPLES

One of the difficulties associated with determination of PAHs in environmental samples is the complexity of PAH mixture in these samples. Even after extensive and rigorous clean-up, the PAH fraction may contain hundreds of compounds. Analytical methods that offer combinations of good chromatographic resolving power and detector selectivity are usually required to quantify selected compounds in such mixtures. There is essentially a three-step procedure for the analysis and determination of PAHs in environmental samples: (1) extraction and isolation of PAHs from the sample matrix; (2) clean-up of the PAH mixtures from impurities and fractionation of PAH into subgroups; and (3) identification and quantitative determination of the individual components in each of these subgroups.

The collection of PAHs from air for quantification requires special considerations. Some of the PAHs, especially those with lower molecular weights, exist primarily in the vapor phase while PAHs with higher molecular weights exist primarily in the particulate phase (Santodonato et al. 1981). Therefore, a combination of a particulate filter (usually glass-fiber filter) and an adsorbent cartridge (usually XAD-2 or polyurethane foam) is used for the collection of PAHs (Andersson et al. 1983; Harvath 1983; Hawthorne et al. 1993). Therefore, collection methods that use either a filtration system or an adsorbent alone may be incapable of collecting both particulate and vapor phase PAHs. In addition, a few PAHs are known to be susceptible to oxidation by ozone and other oxidants present in the air during the collection process (Santodonato et al. 1981).

The commonly used methods for the extraction of PAHs from sample matrices are Soxhlet extraction, sonication, or partitioning with a suitable solvent or a solvent mixture. Dichloromethane, cyclohexane, benzene, and methanol have been widely used as solvents (see Table 6-2). Supercritical fluid extraction (SFE) of heterogeneous environmental samples with carbon dioxide in the presence of a modifier, such as 5-10%. methanol or dichloromethane is preferable to the conventional extraction method because SFE is much less time consuming and has comparable or better PAH extraction

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on XAD and glass-fiber filters with 2-D labeled PAH internal standards; extraction with toluene; fractionation and clean-up on activated silica and alumina	HRGC/MS	0.001–0.03 ng/m^3	No data	Hippelein et al. 1993
	Collection on glass-fiber filter; extraction with methylene chloride; clean-up on silica gel column; analysis at 254 nm	GC/DAD	0.2–4.8 ng/sample	75–100	Desilets et al. 1984
	Collection of on glass-fiber filter; extraction with benzene:MeOH (4:1); concentration; fractionation into acid/neutral/base fractions; clean-up neutral fraction by column chromatography; concentration	GC/FID; HPLC/fluor-escence detector	0.05 ng/m^3	No data	Matsumoto and Kashimoto 1985
	Collection on a glass-fiber filter; thermal desorbtion of filter onto GC column	GC/LIMF	1–15 µg/sample	No data	Galle and Grennfelt 1983
	Collection on a glass-fiber filter; extraction with 35% methylene chloride in cyclohexane	HPLC/fluorometric detector	<0.01 ng/sample	No data	Golden and Sawicki 1978
	Collection on filter; extraction with organic solvent	TLC; GC/MS	<1 pg/sample	No data	Majer et al. 1970

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (cont.)	Collection on fiber-glass filter; extraction with cyclohexane; concentration	GC/GPFD	$1x10^{-6}$ ppm	100.5	Mulik et al. 1975
	Collection on filter; extraction with toluene; acid/base fractionation; drying and concentration	HPLC; GC/MS	0.11 ppm	>85	Naikwadi et al. 1987
	Collection on glass-fiber filter; ultrasonic extraction with benzene; concentration; fractionation by HPLC	HRGC/FID	low ng/m^3	8–100	Tomkins et al. 1982
	Collection on filter; extraction with cyclohexane; clean-up on silica column	GC/MS	0.001–0.002 ppm	No data	Oehme 1983
	Collection on glass-fiber filter (particulates) and XAD-2 resin (vapor); extraction with benzene or methylene chloride	HPLC; GC/MS	0.001–0.1 ppm	No data	Harvath 1983
	Collection on glass-fiber filter; extraction with benzene; concentration	HPLC/fluor-escence detector	0.000025 ppm	92–100	Fox and Staley 1976
	Collection through filter onto XAD-2 resin; extract with benzene, cyclohexane or methylene chloride (NIOSH Methods 5506 and 5515)	HPLC; GC/FID	<1 ppm	No data	NIOSH 1984

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (cont.)	Collection on a glass-fiber filter; extraction with cyclohexane; clean-up by partitioning to DMSO and pentane	GC/MS	0.00001 ppm	No data	Karlesky et al. 1987
	Collection of air particulates with high-volume sampler; ultrasonic extraction with acetonitrile	HPLC/fluor-escence detector	10–50 pg	No data	Miguel and DeAndrade 1989
Sea water	Extraction with hexane or carbon tetrachloride; acid-base fractionation; and clean-up on silica and alumina column	GC/FID	0.024–0.045 µg/L	44–85	Desiderie et al. 1984
Water	Collection on a column containing XAD-4:XAD-8 (1:1) resin; elution with acetone followed by chloroform	HPLC/UV; GC/MS	0.01–3 µg/L	No data	Thruston 1978
	Extraction with cyclohexane	HPLC with time-resolved fluorescence detection	180×10^{-15} g/sample	89–100	Furuta and Otsuki 1983
	Filtration into flotation vessel; adjustment to pH 3; addition of Triton X-100; bubbling nitrogen through mixture; collection of foam, and extraction with methylene chloride; evaporation and dissolution of residue in methanol	HPLC/fluor-escence detector	low ng/L	86–107	Xu and Fang 1988

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water (cont.)	Extraction at neutral pH with methylene chloride (EPA Methods 8100, 8250,and 8310)	HPLC/fluor-escence detector GC/FID GC/MS	0.64–0.013 µg/L 2.0–45.1 µg/L 1.9–7.8 µg/L	No data	EPA 1986
	Collection through sampling cartridges containing XAD-2 resin; elution with acetone:hexane (15:85)	GC/MS	0.00005 µg/L	57–100	Beniot et al. 1979
Municipal and industrial waste water	Extraction with methylene chloride; reconstitution in cyclohexane; clean-up on silica gel column (EPA Method 610)	HPLC/UV fluorescence detector	0.013–2.3 µg/L	78–116	EPA 1982
	Adjustment to pH >11.0; extraction with methylene chloride; drying with sodium sulfate; concentration (EPA Method 625)	GC/MS	1.6–7.8 µg/L	41–83	EPA 1982
Sediments	Extraction with methylene chloride; clean-up on alumina column	TLC; GC/MS	0.2–2.7 µg/g	86–89	John and Nickless 1977
	Freeze drying, sieving and homogenization; extraction with methylene chloride; clean-up on silica gel followed by sephadex column	HPLC/DAD/MS	pg range	No data	Quilliam and Sim 1988

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediments (cont.)	Extraction of dry sample with methylene chloride; injection into supercritical fluid extracting system	GC/MS	2.8–7.3 µg/g	91–97	Hawthorne and Miller 1987a, 1987b
	Extraction of dried sample with benzene; clean-up on silica gel and alumina column	GC/FID; GC/MS	0.014–0.093 µg/g	76–110	Szepesy et al. 1981
Sediments	Direct sampling of sediment in sample insert of SSJ/LIF	SSJ/LIF	1.8 ppm (B[a]P); 0.4 ppm (pyrene)	No data	Lai et al. 1990
	Extraction by sonication; clean-up on silica mini-columns	Spectrofluoro-metry	0.008–4.5 ng/mL	80–95	Saber et al. 1991
Waste water and sediments	Freeze drying; extraction with chloroform:MeOH (2:1); concentration of crude extract; clean-up by TLC followed by HPLC	GC/FID	0.12–0.46 µg/g	51–100	Readman et al. 1986
Water and sediments	Extraction in organic solvent	GC/FT-IR	0.01–0.06 µg/g	No data	Gurka et al. 1987
Soil	Extraction in organic solvent; concentration	GC/FT-IR	0.025–0.25 µg/sample	0.998–0.85 correlation coefficient	Gurka and Pyle 1988
	Ultrasonic extraction of sieved sample with acetonitrile; filtration through teflon filter	HPLC/SF	0.017 µg/g	No data	Tanaka and Saito 1988

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediments/ suspended matter (river), airborne particulate, dust and soil	Extraction of dried sample with methylene chloride; clean-up on activated copper column followed by sephadex	GC/FID; GC/MS	0.03–0.09 µg/g	99–113	Giger and Shaffner 1978
Diesel exhaust particulate and dust	Collection on fiber filter; extraction with hexane; concentration; partitioning with DMSO; concentration of organic extract	HPTLC; FSD	1–50 pg/sample	No data	Butler et al. 1984a
Cigarette smoke	Collection in trap of smoking machine; dissolution in benzene:MeOH:H_2O (2:1:2); clean-up on silicic acid and gel filtration column	GC/FID	No data	92–95	Severson et al. 1976
	Collection on filter pad; extraction with cyclohexane	HPLC/fluore-scence detector	3 pg/sample	89–108	Risner 1988
Cooking oil fume	Collection on glass-fiber filter; extraction with acetone; concentration, then dissolution in cyclohexane; clean-up by partitioning in DMF and reconstitution in cyclohexane	TLC/FSD	0.11–0.41 ng	96–99	Shuguang et al. 1994
Coal-fly ash	Drying at 150 °C, cooling in desiccator; ultrasonic extraction with methylene chloride; concentration	GC/MS	No data	No data	Low et al. 1986

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Highly refined coal- and petroleum-derived fuels	Dissolution in methylene chloride	HPLC/HPLC/fluorescence detector	3.5–46 µg/L	56–100	Tomkins and Griest 1987
	Collection in brown Winchester bag; addition of 20% aqueous MeOH with shaking; clean-up on Sep-Pak C_{18} cartridge column	HPLC/UV and fluorescence detector	0.1–7.1 µg/L	45–95	Symons and Crick 1983
	Dissolution in hexane; clean-up on silica and alumina gel column	TLC; SPF	µg/L range	No data	Monarca and Fagioli 1981
Highly refined coal- and petroleum-derived fuels (con.)	Dissolution in methylene chloride	HPLC/UV-VIS; GC/MS	2000 µg/L	No data	Tomkins et al. 1986
Solvent refined coal	Crushing into fine particles; dissolution in benzene; filtration	N-SSL R-SSL	$7x10^{-7}$ M $7x10^{-5}$ M	No data	Lin et al. 1991
Shale and fuel oil	Dissolution in cyclohexane; fractionation into acid and base/neutral fractions; clean-up base/neutral fraction on alumina followed by alumina-silica column	XEOL	10 ng/sample	No data	Woo et al. 1980
	Dilution in ethanol	RTP SLS	No data No data	±15 RSD ±4 RSD	Vo-Dinh et al. 1984
Sun tan oil	Extraction with hexane; clean-up on silica gel column	TLC; SPF	Low µg/L	79–93	Monarca et al. 1982

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
White petroleum products	Collection on silica gel column; elution with pentane:ether (1.5:1); concentration; clean-up on basic and acidic alumina column	FPS	µg/L range	No data	Popl et al. 1975
Sewage sludge	Homogenization; extraction with cyclohexane; centrifugation; separation and concentration of organic phase	2-Dimensional TLC/fluorescence detector	<1 µg/g	80–100	McIntyre et al. 1981
Smoked foods (e.g., fish and meat)	Saponification; extraction with cyclohexane; clean-up on Florisil column	HPLC/fluorescence detector GC/FID GC/MS	2–27 pg/sample 10 pg/sample 1,000 pg/kg	28–142	Lawrence and Weber 1984
	Soxhlet extraction of homogenized sample with acetone; saponification with ethanolic KOH; extraction with cyclohexane; drying and concentration; clean-up on alumina column; concentration, then dilution in methanol	HPLC/fluorescence detector	0.1–µg/kg	75–90	Moll et al. 1993
Charcoal-broiled beef	Extraction of ground sample with benzene:MeOH (4:1); evaporation to dryness; dissolution of residue in MeOH:H_2O (4:1); clean-up on silica gel column	HPLC/fluorescence detector	20–50 ng/g	No data	Hecht et al. 1979

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Seafoods	Saponification of homogenized sample with ethanolic KOH; extraction with 1,1,2-trichlorotrifluoroethane; concentration; clean-up by silica, alumina and C_{18} cartridge (modified FDA method)	GC-MS	1–5 µg/kg	73–144	Nyman et al. 1993
	Saponification of homogenized sample with ethanolic KOH; extraction with 1,1,2-trichlorotrifluoroethane; concentration; clean-up by silica alumina and gel permeation HPLC (NMFS method)	GC/MS	1–5 µg/kg	63–106	Nyman et al. 1993
Cooked beef	Saponification of ground sample with methanolic KOH; extraction with cyclohexane, DMF, and n-hexane; concentration	LT-MLS SLS HPLC/ fluorescence detector	0.9 ppb 0.2 ppb 1.0 ppb	75–85 (extraction efficiency)	Jones et al. 1988
Food (meat/fish, dried dairy products, cereals, leafy vegetables, and oils)	Digestion with alcoholic KOH; partitioning into cyclohexane or isooctane; removal of lipids by solvent partitioning with dimethylformamide or dimethylsulfoxide/water; clean-up on silica gel, Florisil, or Sephadex	HPLC/fluor-escence detector; GC-MS/SIM	2–90 ng/kg	20.6–92.5 (ocean perch); 34.2–62.7 (bran cereal); 98 (powdered milk)	Lawrence and Das 1986

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Cereal products	Saponification; extraction with cyclohexane; reextraction with 15% caffeine in formic acid; dilution in sodium chloride solution; reextraction with cyclohexane; clean-up on silica gel; concentration	GC/MS	20 pg/inj	40–100	Tuominen et al. 1988
Vegetable oil	Dilution with *n*-pentane	LC-GC/MS	1 pg/sample	No data	Vreuls et al. 1991
Fat products	Dissolution in light petroleum; extraction with caffeine in formic acid; dilution in sodium chloride solution; reextraction with light petroleum; clean-up on silica gel column	HPLC/fluor-escence detector	0.1–0.5 ppb	76–85	Van Heddeghem et al. 1980
Barley malt	Homogenization; ultrasonic extraction with cyclohexane; centrifugation; clean-up of supernatant on silica gel-alumina column	HPLC/UV and fluorescence detector	2.5–5 ng/g	78–97	Joe et al. 1982
Alcoholic beverage	Continuous extraction with cyclohexane for 20 hours	HPLC/UV; GC/FID	1 µg/L	60	Toussaint and Walker 1979
Tea	Saponification; extraction with hexane; addition of DMSO with shaking; clean-up on silica gel	TLC; FSD	2–12 ng/g	92–95	Poole et al. 1987

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish tissue	Homogenization with 1.15% KCl solution; isolation on extraction cartridges packed with a styrene-divinylbenzene copolymer resin; washing with water; extraction with acetone:MeOH (1:1); extraction with methylene chloride:2-propanol (75:25)	HPLC/fluorescence detector; GC/MS	50–1,100 ng/g	>90	Krahn and Malins 1982
	Homogenization with distilled water and KOH pellets; reflux, then extraction with methylene chloride; clean-up on basic alumina column	GC/MS	<0.2 ng/g	72	Vassilaros et al. 1982
	Homogenization in methylene chloride; centrifugation; clean-up on alumina column	HPLC/UV; GC/MS	No data	89–98	Krahn et al. 1988
B[a]P metabolite formulation	Dissolution in MeOH	HPLC/MS	low ng/sample	No data	Bieri and Greaves 1987
PAH formulation	Dissolution in methylene chloride	GC/MS with laser multiphoton ionization detection	200×10^{-15} g sample	No data	Rhodes et al. 1983
	Dissolution in acetonitrile	UV-RRS	<1 ppb	No data	Asher 1984
	Dissolution in ethanol	HPLC/fluorescence detector	500–16,000 ppb	No data	Su et al. 1982

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
PAH formulation (cont.)	Conversion to nitroaromatic compound (packing sample in glass tube between glass-wool plugs, passing reagent gas through tube for 3 to 5 seconds); analysis for nitroaromatic compound	TQMS	100–500 ppb	No data	Hunt et al. 1983

B[a]P = benzo[*a*]pyrene; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EPA = Environmental Protection Agency; EtOH = ethanol; FPS = fluorescence and phosphorescence spectrometry; FSD = fluorescence scanning densitometry; GC = gas chromatography; GC/FID = gas chromatography/flame ionization detector; GC/DAD = gas chromatography/diode array detector; GC/LIMF = gas chromatography/laser induced molecular fluorescence; GC/GPFD = gas chromatography/gas phase fluorescence detector; GC/MS = gas chromatography/mass spectrometry; GC/FT-IR = gas chromatography/fourier transform-infra-red spectrometry; HPLC = high performance liquid chromatography; HCl = hydrochloric acid; HPLC/HPLC = high performance liquid chromatography/high performance liquid chromatography; HPLC/UV = high performance liquid chromatography/ultraviolet; HPLC/DAD/MS = high performance liquid chromatography/diode array detector/mass spectrometry; HPLC/SF = high performance liquid chromatography/spectrofluoremetry; HPTLC = high performance thin-layer chromatography; HPTLC/UV = high performance thin-layer chromatography/ultraviolet; H_2O = water; H_2SO_4 = sulfuric acid; inj = injection; KOH = potassium hydroxide; LC = liquid chromatography; LT-MLS = low temperature-molecular luminescence spectrometry; LC-GC/MS = liquid chromatography-gas chromatography/mass spectrometry; M = molar; MeOH = methanol; ng = nanogram; NMFS = National Marine Fisheries Service; PAHs = polycyclic aromatic hydrocarbons; R/N-SSL = resonant/nonresonant-synchronous scan luminescence; RSD = relative standard deviation; RTP = room temperature phosphorescence; SF = spectrofluorometry; SLS = synchronous luminescence spectroscopy; SSJ/LIF = supersonic jet/laser induced fluorescence; SIM = selected ion monitoring; SJS/SFC = supersonic jet spectroscopy/supercritical fluid chromatography; SP = spectrophotometer; SPF = spectrophotofluorometer; TCTFE = 1,1,2-trichloro-1,2,2-trifluoroethane; TLC = thin-layer chromatography; TQMS = triple quadruple mass spectrometer; UV-RRS = ultraviolet-resonance raman spectrometer; UV-VIS = UV-visible detector; XEOL = x-ray excited optical luminescence

recovery than the conventional methods (Burford et al. 1993; Dankers et al. 1993; Hawthorne et al. 1993; Hill and Hill 1993).

Column chromatography on silica, alumina, Sephadex or Florisil has been used most often for the clean-up and fractionation of PAHs in the sample extract (Desiderie et al. 1984; Desilets et al. 1984; Oehme 1983; Quilliam and Sim 1988). HPLC can also be used for the clean-up and fractionation of PAHs in sample extract (Readman et al. 1986). A disposable Sep-Pak cartridge with an amino stationary phase was used for the clean-up of benzo[a]pyrene in cigarette smoke condensate (Dumont et al. 1993). Some soil and sediment samples containing high amounts of sulfur may require clean-up on an activated copper column (Giger and Schaffner 1978).

A variety of analytical methods has been used for determining trace concentrations of PAHs in environmental samples (Table 6-2). These include GC with various detectors, HPLC with various detectors, and TLC with fluorimetric detectors. Various detection devices used for GC quantification include FID, MS, Fourier transform infrared spectrometer (FT-IR), laser induced molecular fluorescence detector (LIMF), diode array detector (DAD), and gas phase fluorescence detector (GPFDA). GC/MS and HPLC with UV or spectrofluorimetric detectors are perhaps the most prevalent analytical methods for determining concentrations of PAHs in environmental samples.

Oehme (1983) and Low et al. (1986) employed capillary GC coupled with negative ion chemical ionization MS for detecting and differentiating isomeric PAHs (including PAHs on EPA’s priority pollutant list). This procedure was successfully used to differentiate the isomers benzolj]fluoranthene and benzo[b]fluoranthene at low ppb levels in complex matrices, such as air particulate matter and coal fly ash. An alternative method for the elucidation of PAH isomers is GC coupled with a charge-exchange and chemical ionization MS (Simonsick and Hites 1985). Simonsick and Hites (1985) demonstrated that the structural isomers pyrene, fluoranthene, aceanthrylene and acephenanthrylene can be identified on the basis of their first ionization potential and $(M+l)^+/M^+$ mass ion ratio.

HPLC has been one of the most widely used analytical methods for determining PAHs in complex environmental samples. The development of a chemically nonpolar stationary phase for HPLC has

provided a unique selectivity for separation of PAH isomers that are often difficult to separate by GC columns. For example, chrysene, benz[a]anthracene, and triphenylene are baseline resolved with a C-18 reverse phase column packing. A detection limit of subpicogram to picogram levels of PAHs per sample has been achieved by HPLC with fluorescence detector (Fox and Staley 1976; Furuta and Otsuki 1983; Futoma et al. 1981; Golden and Sawicki 1978; Lawrence and Weber 1984; Marcomini et al. 1987; Miguel and De Andrade 1989; Nielsen 1979; Risner 1988; Ton&ins et al. 1982). HPLC equipped with a fluorescence detector has selectively measured 10 PAHs (phenanthrene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, benzo[g,h,i]perylene, and indeno[l,2,3-c,d]pyrene) in ambient air (Miguel and De Andrade 1989). Detection limits for the 10 PAHs were in the range of 10-50 pg and RSD was <10%. Recovery data were not reported. PAH levels in the ng/L range have also been successfully determined in water using flotation enrichment and HPLC/fluorescence detection (Xu and Fang 1988). Good recoveries (86-107%) were achieved, and RSD was 2.7-13.6% RSD. A quenchofluorometric detection system provides an inexpensive method to achieve selective detection for the fluoranthenic PAHs as a group (Konash et al. 1981). UV detectors have been used to measure PAHs in fats and oil samples; however, these detectors lacked the sensitivity and specificity of the fluorescence detectors for determining PAHs at low levels (ppb and lower) (Van Heddeghem et al. 1980).

A number of less commonly used analytical techniques are available for determining PAHs. These include synchronous luminescence spectroscopy (SLS), resonant (R)/nonresonant (NR)-synchronous scan luminescence (SSL) spectrometry, room temperature phosphorescence (RTP), ultravioletresonance Raman spectroscopy (UV-RRS), x-ray excited optical luminescence spectroscopy (XEOL), laser-induced molecular fluorescence (LIMF), supersonic jet/laser induced fluorescence (SSJ/LlF), low-temperature fluorescence spectroscopy (LTFS), high-resolution low-temperature spectrofluorometry, low-temperature molecular luminescence spectrometry (LT-MLS), and supersonic jet spectroscopy/capillary supercritical fluid chromatography (SJS/SFC) (Asher 1984; Garrigues and Ewald 1987; Goates et al. 1989; Jones et al. 1988; Lai et al. 1990; Lamotte et al. 1985; Lin et al. 1991; Popl et al. 1975; Richardson and Ando 1977; Saber et al. 1991; Vo-Dinh et al. 1984; Vo-Dinh and Abbott 1984; Vo-Dinh 1981; Woo et al. 1980). More recent methods for the determination of PAHs in environmental samples include GC-MS with stable isotope dilution calibration (Bushby et al. 1993), capillary electrophoresis with UV-laser excited fluorescence detection (Nie et al. 1993), and

laser desorption laser photoionization time-of-flight mass spectrometry of direct determination of PAH in solid waste matrices (Dale et al. 1993).

Among the less commonly used spectroscopic methods, SLS and room temperature phosphorescence (RTP) are used for determining trace levels of PAHs in environmental media. Vo-Dinh (1981), Vo-Dinh and Abbott (1984), and Vo-Dinh et al. (1984) reported a cost-effective and relatively simple SLS and RTP technique for determining trace amounts of PAHs (less than $1x10^{-9}$ g per sample) in air particulate extracts collected at a wood-burning area. Improved selectivity is the main advantage of SLS and RTP over conventional luminescence or fluorescence spectroscopy. Additionally, R/N-SSL spectrometry has been applied to determine trace amounts of anthracene and its derivatives in solvent-refined coal (Lin et al. 1991). The sensitivity of N-SSL ($7x10^{-7}$ M) is about two orders of magnitude better than that of R-SSL spectrometry (7x10-5 M). The detection limit for N-SSL is several times better than that of conventional fluorescence spectrometry ($3x10^{-6}$ M). The better sensitivity comes from a higher efficiency in fluorescence collection (Lin et al. 1991). The combination of R- and N-SSL spectrometries provides a sensitive and selective analytical method because of the spectral simplicity of R-SSL and the high sensitivity of N-SSL spectrometry (Lin et al. 1991). This spectrometric method is also applicable to other PAHs in the environment, such as benzo[a]pyrene in airborne particulates.

Low temperature-molecular luminescence spectrometry (LT-MLS), SLS, and HPLC/fluorescence detection have been used to measure pyrene in broiled hamburger (Jones et al. 1988). A comparison of the three methods showed that sensitivity for all three methods was in the low-ppb range and that all methods were comparably reproducible (6-9% RSD). Adequate recovery (75-85%) was obtained from the extraction procedure for all three methods. While HPLC is the least expensive and easiest to operate, it has the longest analysis time (30 minutes), and it provides the least resolution of components. LT-MLS is the fastest technique (5 minutes), and it gives mores spectral information than the other two methods. SLS, with an analysis time of 15 minutes, offers no real advantages over LT-MLS other than cost of equipment.

Methods 8100, 8250, and 8310 are the test methods recommended by EPA (1986) for determining PAHs in a variety of matrices at solid waste sites. EPA Methods 610 and 625, recommended for

municipal and industrial waste water have been used to measure PAHs in groundwater contaminated by petroleum hydrocarbons at detection limits in the low-ppb range (Thomas and Delfino 1991). Recovery and precision data were not reported. NIOSH (1985) has recommended methods 5506 and 5515 as the analytical methods for determining PAHs in air samples at concentrations below ppm level.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PAHs is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PAHs.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Adequate methods are available to separate and quantify PAHs in biological materials such as adipose tissue (Gay et al. 1980; Liao et al. 1988; Modica et al. 1982), lungs (Brandys et al. 1989; Mitchell 1979; Tomingas et al. 1976; Weston and Bowman 1991; Weyand and Bevan 1987a), liver (Amin et al. 1982; Obana et al. 1981; Rice et al. 1985b), skin (Phillips et al. 1987; Shugart et al. 1983), hair (Alexandrov et al. 1990), blood (Brandys et al. 1989; Harris et al. 1985; Haugen et al. 1986; Perera et al. 1988; Phillips et al. 1988; Shamsuddin et al. 1985; Shugart 1986), urine (Au&up and Seremet 1986; Becher and Bjorseth 1985; Rogan et al. 1990; Tolos et al. 1990; Uziel et al. 1987), and feces (Hecht et al. 1979; Rogan et

al. 1990). These methods include GC/FID, GCMS, HPLC, TLC, and spectrofluorometry (SF). The difficulties involved in recovering bound benzo[a]pyrene from feces hinder studies on absorption and bioavailability in humans after exposure to benzo[a]pyrene. Therefore, there is a need to develop a satisfactory analytical method for the determination of benzo[a]pyrene in feces. Immunoassays (i.e., ELISA and USERIA, ^{32}P-arid ^{35}S-postlabelling, SLS, and FIS) are methods currently being developed to detect the presence of carcinogenic PAH adducts bound covalently to macromolecules (e.g., DNA). The parent compound is generally measured in biological tissues, but both the parent compound and its metabolites can be measured in biological fluids, particularly urine. However, improved methods for identifying and characterizing conjugated PAH metabolites from various biological fluids would be useful. PAH-DNA adducts can be measured in blood, serum, and other tissues. These methods are accurate, precise, and sensitive enough to measure background levels in the population and levels at which biological effects occur. Additional quantitative information regarding the relationships between body and environmental levels of PAHs for both short- and long-term exposures might allow investigators to predict environmental exposure levels from measured body levels.

The urinary level of 1-Hydroxypyrene has the potential to be used as a biomarker for exposure to PAHs, and analytical methods for the detection of the hydroxy metabolite in urine of exposed and non-exposed control persons are available (Ariese et al. 1993a; Jongeneelen et al. 1988; Kanoh et al. 1993; Mercado Calderon 1993; Van Hummelen et al. 1993). The correlation coefficient between total PAHs in air of a coke production plant and hydroxypyrene in urine of workers was 0.77 ($p<0.0001$) (Mercado Calderon 1993). A study attempted to use benzo[a]pyrene metabolite 3-hydroxy-benzo[a]pyrene in urine as a biomarker for occupational exposure to PAH (Ariese et al. 1993a). Since the level of 3-hydroxybenzo[a]pyrene is about 3 orders of magnitude lower than 1-hydroxypyrene, a sensitive method was developed to estimate levels of 3-hydroxybenzo[a]pyrene in occupational groups (Ariese et al. 1993a). However, no significant correlation between the metabolite and levels of airborne benzo[a]pyrene was found.

The available biomarkers of effect for PAHs are not specific for effects induced by PAHs other than cancer or genotoxicity. PAHs form DNA adducts that can be measured in body tissues or blood following exposure to PAHs and mixtures that contain PAHs. The formation of benzo[a]pyrene-DNA adducts has been demonstrated, and this may serve as a biomarker of PAH-induced carcinogenicity.

HPLC and immunoassays, (i.e., ELISA and USERIA, ^{32}P-and ^{35}S-postlabelling, SLS, and FIS) are sensitive, selective, and reproducible methods being developed to detect the presence of carcinogenic PAH adducts bound covalently to macromolecules (e.g., DNA) (Gorelick and Wogan 1989; Haugen et al. 1986; Lau and Baird 1991; Phillips et al. 1988; Weston and Bowman 1991). Chromosomal aberration and sister chromatid exchange methods were used to show that several types of cultured human tissue cells demonstrated positive results for benzo[a]pyrene-induced genotoxicity (Abe et al. 1983a, 1983b; Huh et al. 1982; Lo Jacono et al. 1992; Van Hummelen et al. 1993; Weinstein et al. 1977; Wienke et al. 1990). However, statistically significant correlation between the cytogenetic markers and airborne occupational PAH levels was not found (Van Hummelen et al. 1993).

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Standardized methods are available that are reliable, reproducible, and sensitive enough to separate and quantify PAHs in air (Andersson et al. 1983; Fox and Staley 1976; Golden and Sawicki 1978; Harvath 1983; Karlesky et al. 1987; Majer et al. 1970; Miguel and De Andrade 1989; Naikwadi et al. 1987; NIOSH 1984; Oehme 1983; Tomkins et al. 1982; Matsumoto and Kashimoto 1985), water (Beniot et al. 1979; Desiderie et al. 1984; EPA 1986; Furuta and Otsuki 1983; Thomas and.Delfino 1991; Thruston 1978; Xu and Fang 1988), soil and sediment (Hawthorne and Miller 1987a, 1987b; John and Nickless 1977; Saber et al. 1991; Szepesy et al. 1981; Tanaka and Saito 1988), and other media, such as food (Hecht et al. 1979; Joe et al. 1984; Jones et al. 1988; Krahn and Malins 1982; Krahn et al. 1988; Lawrence and Das 1986; Lawrence and Weber 1984; Poole et al. 1987; Toussaint and Walker 1979; Tuominen et al. 1988; Van Heddeghem et al. 1980; Vassilaros et al. 1982; Vreuls et al. 1991), cigarette smoke (Risner 1988; Severson et al. 1976), coal tar (Alben 1980; Goates et al. 1989; Low et al. 1986), and fuels (Lin et al. 1991; Monarca and Fagioli 1981; Symons and Crick 1983.; Ton&ins and Griest 1987; Vo-Dinh et al. 1984; Woo et al. 1980). These methods include GC, HPLC, TLC, and others. Various detection devices used for GC quantification include FID, MS, FT-IR, LIMF, DAD, or GPFDA. GC/MS and HPLC are perhaps the most prevalent analytical methods for determining concentrations of PAHs in environmental samples. These methods are adequate to measure environmental levels that may be associated with adverse human effects. All of the available analytical methods for PAHs in soil and food items are sensitive down to levels of <1 ppb.

6.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health and Injury Control, Centers for Disease Control and Prevention, is developing methods for the analysis of PAHs and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry, which gives detection limits in the low parts per trillion (ppt) range.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding polycyclic aromatic hydrocarbons (PAHs) in air, water, and other media are summarized in Table 7-1.

An MRL of 0.6 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to acenaphthene, based on a minimal LOAEL of 175 mg/kg/day for liver weight in mice (EPA 1989c).

An MRL of 0.4 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to fluoranthene, based on a minimal LOAEL of 125 mg/kg/day for increased liver weight in mice (EPA 1988e).

An MRL of 0.4 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to fluorene, based on a minimal LOAEL of 125 mg/kg/day for relative liver weight in mice (EPA 1989e).

Reference doses have been developed by EPA for anthracene (0.3 mg/kg/day), acenaphthene (0.06 mg/kg/day), fluoranthene (0.04 mg/kg/day), fluorene (0.04 mg/kg/day), and pyrene (0.03 mg/kg/day). No reference concentrations exists for any of the PAHs.

PAHs are regulated under The Emergency Planning and Community Right-to-Know (EPCRA) standards of 40 CFR Subpart J. EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use these chemicals to report annually their release of those chemicals to any environmental media.

OSHA regulates the benzene soluble fraction of coal tar pitch volatiles and mineral oil mist, which contain several of the PAH compounds. Employers of workers who are occupationally exposed must institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PEL). The employer must use engineering and work controls, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 0.2 mg/m^3 for coal tar pitch volatiles and 5 mg/m^3 for mineral oil mist.

7. REGULATIONS AND ADVISORIES

PAHs are regulated by the Clean Water Effluent Guidelines in Title 40, Sections 400-475, of the Code of Federal Regulations. For each point source category, PAHs may be regulated as a group of chemicals controlled as Total Toxic Organics, may have a specific regulatory limitation, or may have a zero discharge limitation. The point source categories for which the PAHs are controlled as a Total Toxic Organic include electroplating, and metal molding and casting. The point source categories for which the PAHs have specific regulatory limitations include organic chemicals, plastics, and synthetic fibers; cokemaking; and nonferrous metals manufacturing.

Under the Resource Conservation and Recovery Act (RCRA), several PAHs are listed as hazardous wastes when they are discarded commercial chemical products, off-specification species, container residues, and spill residues (40 CFR 261.33).

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons

Agency	Description	Information	Reference
INTERNATIONAL			
IARC	Carcinogenic classification[a]		IARC 1987; IARC 1984; IARC 1984; IARC 1983; IARC 1973
	(B[a]A; B[a]P)	Group 2A[b]	
	(B[b]F; B[j]F; B[k]F; I[123cd]P)	Group 2B[c]	
	(Anthracene; B[ghi]P; B[e]P; Chrysene; Fluoranthene; Fluorene; Phenanthrene; Pyrene)	Group 3[d]	
	(Mineral oil mists)	Group 1	
			IARC 1984
	Occupational exposure limits		
	Oil mists, mineral		
	Australia, Belgium, German Democratic Republic, Italy, Netherlands, Switzerland	5 mg/m^3 (TWA	
	Japan, Finland, Sweden	3 mg/m^3 (TWA)	
	Coal-tar pitch volatiles	0.2 mg/m^3 (TWA)	
	Australia, Belgium, Italy, Netherlands, Switzerland, Yugoslavia		
WHO	European standard for drinking water[e]	0.2 µg/L	WHO 1971
NATIONAL			
Regulations:			
a. Air:		0.2 mg/m^3	
OSHA	PEL, TWA		29 CFR 1910.1000
	Coal tar pitch volatiles-benzene soluble fraction[f]		29 CFR 1910.1002 OSHA 1993 ACGIH 1991
	Oil mist, mineral	5 mg/m^3	29 CFR 1910.1000
EPA	Hazarouds Air Pollutants: Proposed Regulations Governing Constructed, Reconstructed or Modified Major Sources	Yes	59 FR 15504 April 1, 1994 (40 CFR 63.44)
b. Non-specific media:			
EPA	Solid Waste		40 CFR Subchapter I
	Criteria for municipal solid waste landfills		40 CFR 258
	List of hazardous inorganic and organic constituents (all PAHs)	Yes	40 CFR App. II
	Identification and Listing of Hazardous Waste	Yes	40 CFR 261
	Off-specification and discarded materials, and residues (B[a]A, B[a]P, Chrysene, DB[a,h]A, DB[a,i]P, Fluoranthene, I[1,2,3-cd]P)		40 CFR 261.33

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Basis for listing hazardous waste (Acenaphthylene; B[a]A; B[a]P; B[b]F; B[k]F; Chrysene; DB[a,h]A; Fluoranthene; I[1,2,3-cd]P)	Yes		40 CFR 261, App. VII
	Hazardous constituents of waste (B[a]A; B[b]F; B[j]F; B[k]F; B[a]P; Chrysene; DB[a,e]P; DB[a,h]P; DB[a,i]P; Fluoranthene, I[1,2,3-cd]P)	Yes		40 CFR 261, App. VIII
	Waste excluded from nonspecific sources	Yes		40 CFR 261, App. IX
	Carbamate production identification and listing of hazardous waste: oral and inhalation toxicity information for waste constituents (Notice of proposed rulemaking)	Yes		59 FR 9808 March 1, 1994 (40 CFR 261.32) EPA 1994
	Standards for Owners, and Operators of Hazardous Waste Treatment, Storage & Disposal Facilities	Yes		40 CFR 264
	Groundwater monitoring list (all PAHs)			40 CFR 264, App. IX
	Standards for the Management of Specific Hazardous Wastes and Specific Types of Hazardous Waste Management Facilities			40 CFR 266
	Limits for exclusion of waste-derived residues			40 CFR 266, App. VII
	(B[a]A)	$1x10^{-4}$ mg/kg		
	(DB[a,h]A)	$7x10^{-6}$ mg/kg		
	Land Disposal Restrictions			40 CFR 268
	Waste to be evaluated (B[a]A; B[a]P; Chrysene; DB[a,h]A; I[1,2,3-cd]P)	Yes		40 CFR 268.10
	List of wastes to be identified by May 8, 1990	Yes		40 CFR 268.12
	Land disposal treatment concentrations			40 CFR 268.43
	Waste No. F039	Wastewaters (mg/L)	Non-wastewaters (mg/kg)	
	Acenaphthalene	0.059	3.4	
	Acenaphthene/Anthracene/ Fluorene	0.059	4.0	
	B[a]A; Chrysene	0.059	8.2	
	B[b]F; B[k]F	0.055	3.4	
	B[g,h,i]P	0.055	1.5	
	B[a]P	0.061	8.2	
	DB[a,h]A	0.055	8.2	
	DB[a,e]P	0.061	NA	
	Fluoranthene	0.068	8.2	
	Phenanthrene	0.059	3.1	
	Pyrene	0.067	8.2	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description		Information	Reference
NATIONAL (cont.)	Waste No. K035			
	Acenaphthrene; Anthracene, B[a]P; DB[a,h]A; Fluorene; I[1,2,3-cd]P	NA	3.4	
	B[a]A; Chrysene; Phenanthrene	0.059	3.4	
	Fluoranthene	0.068	3.4	
	Pyrene	0.067	8.2	
	Waste No. K048			
	B[a]P	0.047	12	
	Chrysene	0.043	15	
	Fluorene	0.011	14	
	Phenanthrene	0.033	42	
	Pyrene	0.047	36	
	Waste No. K087			
	Acenaphthalene; Chrysene; Fluoranthene; I[1,2,3-cd]P; Phenanthrene	0.028	3.4	
	Waste No. K049			
	Anthracene	0.039	28	
	B[a]P	0.047	12	
	Chrysene	0.043	15	
	Phenanthrene	0.033	42	
	Pyrene	0.047	3.6	
	Waste No. K051			
	Acenaphthene	0.05	NA	
	Anthracene	0.039	28	
	B[a]A	0.043	20	
	Phenanthrene	0.011	14	
	Pyrene	0.033	42	
	Waste No. U018, U050 (B[a]A; Chrysene)	0.059	8.2	
	U022 (B[a]P)	0.061	8.2	
	U063 (DB[a,h]A)	0.055	8.2	
	U120 (Fluoranthene)	0.068	8.2	
	U137 (I[1,2,3-cd]P)	0.0055	8.2	
	Requirements Authorization of State Hazardous Waste Programs			40 CFR 271

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)	Regulations implementing the HSWA of 1984	Yes	40 CFR 271.1
	Proposed rule: Universal treatment standards for organics	Yes	58 FR 48092 Sept. 14, 1993
	Maximum grab sample (non-wastewaters)		(40 CFR 148, 260, 261, 268, 271)
	Acenaphthalene; acenaphthene; anthracene; B[a]A; B[a]P; chrysene; fluoranthene; fluorene; I[1,2,3-cd]P	3.4 mg/kg	
	B[b]F; B[k]F	6.8 mg/kg	
	B[g,h,i]P	1.8 mg/kg	
	DB[a,h]A; pyrene	8.2 mg/kg	
	Phenanthrene	5.6 mg/kg	
	Maximum grab sample (wastewaters)		
	Acenaphthalene; acenaphthene; anthracene; B[a]A; chrysene; fluorene; phenanthrene	0.059 mg/L	
	B[a]P; DB[a,e]P	0.061.mg/L	
	B[b]F; B[k]F	0.11 mg/L	
	B[g.h,i]P; I[1,2,3-cd]P	0.0055 mg/L	
	DB[a,h]A	0.055 mg/L	
	Fluoranthene	0.068 mg/L	
	Pyrene	0.067 mg/L	
	Proposed rule: BDAT standard		
	Maximum grab sample (non-wastewaters)		
	B[a]A; B[a]P; chrysene; I[1,2,3-cd]P	3.4 mg/kg	
	B[b]F; B[k]F	6.8 mg/kg	
	DB[a,h]A	8.2 mg/kg	
	Maximum grab samples (wastewaters)		
	B[a]A; chrysene	0.059 mg/L	
	B[a]P	0.061 mg/L	
	B[b]F; B[k]F	0.11 mg/L	
	I[1,2,3-cd]P	0.0055 mg/L	
	DB[a,h]A	0.055 mg/L	
	Superfund, Emergency Planning, and Community Right-To-Know Programs		40 CFR Subchapter J

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)	Designation, Reportable Quantities and Notification		40 CFR 302
	Designation and Reportable Quantities of Hazardous Waste		40 CFR 302.4
	Acenaphthene; chrysene, fluoranthene, I[1,2,3-cd]P	100 pounds	
	Acenaphthylene; anthracene, B[k]F; B[g,h,i]P; fluorene; phenanthrene, pyrene	5,000 pounds	
	B[a]A	10 pounds	
	B[b]F; B[a]P; DB[a,h]A	1 pound	
	Emergency Planning and Notification		40 CFR 355
	List of extremely hazardous substances and threshold planning quanitties		40 CFR 355, App. A
	Pyrene	1,000/10,000 lbs.	
	Toxic Chemical Release Reporting: Community Right-to-Know		40 CFR 372
	Toxic chemical listing (anthracene)	Yes	40 CFR 272.65
	Proposed Rule: National oil and hazardous substance pollution contingency plan; QA/QC of chemical analysis of oil compositoin using GC/MS	Yes	58 FR 54702 October 22, 1993 40 CFR 300
	Proposed Rule: Addition of certain chemicals; toxic chemical release reporting; comunity right-to-know	Yes	59 FR 1788 January 12, 1994 40 CFR 372
	Toxic Substances Control Act		40 CFR Subchapter R
	Reporting and Recordkeeping Requirements		40 CFR 704
	Chemical substance matrix for CAIR reporting (Phenanthrene, pyrene)	Yes	40 CFR 704.225
	Health and Safety Data Reporting		40 CFR 716
	Listing of substances and mixtures (anthracene)	Yes	40 CFR 716.120
	Significant New Uses of Chemical Substances		40 CFR 721
	Fluorene substituted aromatic amines	Yes	40 CFR 721.3764
	Provisional Test Guidelines		40 CFR 795

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Protocol for determining anaerobic microbiological transformation rate data for chemicals in the subsurface environment	Yes		40 CFR 795.54
DOT	Hazardous materials transport	Yes		49 CFR 171 DOT 1991
c. Water				
EPA	Water Programs			40 CFR Subchapter D
	National Pollution Discharge Elimination System (NPDES)			40 CFR 122
	Testing requirements for NPDES permits			
	B[a]P; acenaphthene; aenaphthalene	Yes		40 CFR 122, App. D
	Guidelines Establishing Test Procedures for the Analysis of Pollutants			40 CFR 136
	Guidelines for testing pollutants under the CWA (all PAHs)			40 CFR 136.3
	Testing procedures for PAHs base/neutrals and acids, semivolatile organic compounds (all PAHs)	Yes		40 CFR 136, App. A Methods 610, 625, 1625 (Revision B)
	National Primary Drinking Water Regulations			40 CFR 141
	Effective dates (B[a]P)	Yes		40 CFR 141.6
	Sampling and Analytical Requirements for organic chemicals (B[a]P)	Yes		40 CFR 141.24
	Public notification under the SDWA (B[a]P)	0.002 ppm		40 CFR 141.32
	Special monitoring for organic and inorganic compounds (B[a]P)	Yes		40 CFR 141.40
	Maximum contaminant levels for organic contaminants (B[a]P)	0.0002 mg/L		40 CFR 141.61
	Final Rule: Water quality standards; numeric criteria for priority toxic pollutants; states' compliance	Yes		57 FR 60848 Dec. 22, 1992 (40 CFR 131)
	Human health (10^{-6} risk for carcinogens); for consumption of (µg/L):	Water and Organism	Organism Only	
	Anthracene	9,600	110,000	
	B[a]A; B[a]P; B[b]F; B[k]F; chrysene; DB[a,h]A; I[1,2,3-cd]P	0.0028	0.031	
	Fluoranthene	300	370	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Fluorene	1,300	14,000	
	Pyrene	960	11,000	
	Proposed Rule: National primary and secondary drinking water regulations; analytical methods for regulated drinking water contaminants (B[a]P)	Yes		58 FR 5622 Dec. 15, 1993 (40 CFR 141, 143)
	Effluent Guidelines and Standards			40 CFR Subchapter N
	General Provisions			40 CFR 401
	Toxic pollutants under Sec. 307(a) of the CWA (Acenaphthene, fluoranthene)	Yes		40 CFR 401.15
	General Pretreatment Regulations for Existing and New Sources of Pollution			40 CFR 403
	Pretreatment regulations for POTWs (acenaphthene, fluoranthene)	Yes		40 CFR 403, App. B
	Electroplating Point Source Category			40 CFR 413
	Definition of total toxic organic (TTO) (all PAHs, excluding acenaphthene)	Yes		40 CFR 413.02
	Organic Chemicals, Plastics, and Synthetic Fiber			40 CFR 414
	Toxic effluent standards for point sources that use end-of-pipe biological treatment	Daily maximum (µg/L)	Monthly Maximum (µg/L)	40 CFR 414.91 (58 FR 36872) July 9, 1993
	Acenaphthene; acenaphthylene; anthracene; B[a]A; B[k]F; Chrysene; fluorene; phenanthrene	59	22	
	Fluoranthene	68	25	
	B[a]P	61	23	
	Pyrene	67	25	
	Toxic pollutant standards for point sources that do not use end-of-pipe biological treatment			58 FR 36872 (40CFT 414.101
	Acenaphthene; acenaphthylene; anthracene; B[a]A; B[k]F; Chrysene; fluorene; phenanthrene	47	19	
	B[a]P; pyrene	48	20	
	Fluoranthene	54	22	
	Toxic pollutant standards for indirect discharge point sources			58 FR 36872 40 CFR 414.111
	Acenaphthene; anthracene; fluorene; phenanthrene	47	19	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Fluoranthene	54	22	
	Pyrene	48	20	
	Iron and Steel Manufacturing Point Source Category			40 CFR 420
	Definition (B[a]P)	Yes		40 CFR 420.02
	Effluent limitations attainable using BAT for cokemaking B[a]P--1 day maximum (kg/kkg of product)			40 CFR 420.13
	cokemaking--iron and steel	0.0000319		
	--iron and steel with physical chemical treatment	0.0000215		
	--merchant	0.0000355		
	--merchant with physical chemical treatment	0.0000250		
	New source performance standards (B[a]P)--1 day maximum (kg/kkg of product)	Yes		40 CFR 420.14
	cokemaking--iron and steel	0.0000319		
	--merchant	0.0000355		
	Nonferrous Metals Manufacturing Point Source Category			40 CFR 421
	Definition of B[a]P for primary aluminum smelting	Yes		40 CFR 421.21
	Effluent limitations attainable by application of BAT for primary aluminum smelting plants (mg/kg)	Max. 1-day limit	Max. monthly avg.	40 CFR 421.23
	Anode and cathode plastic plant wet air pollution control	0.005	0.002	
	Anode contact cooling and briquette quenching	0.007	0.003	
	Anode bake plant wet air pollution control (closed top)	0.146	0.067	
	Anode bake plant wet air pollution control (open top ring furnace with spray tower only	0.002	0.001	
	Anode bake plant wet air pollution control (open top ring furnace with wet ESP and spray tower)	0.025	0.011	
	Anode bake plant wet air pollution control (tunnel kiln)	0.038	0.018	
	Cathode reprocessing (with dry potline scrubbing and not commigled)	1.181	0.547	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Cathode reprocessing (with wet potline scrubbing)	0.000	na	
	Potline wet air pollution control (w/o cathode reprocessing)	0.028	0.013	
	Potline wet air pollution control (w/cathode reprocessing and not commingled)	0.028	0.013	
	Potline wet air pollution control (w/cathode reprocessing and commingled)	0.028	0.013	
	Pot room wet air pollution control	0.056	0.026	
	Potline SO_2 emissions wet air pollution control	0.045	0.021	
	Degreasing wet air pollution control	zero	zero	
	Pot repair and pot soaking	0.000	na	
	Direct chill casting contact cooling	zero	zero	
	Continuous rod casting contact cooling	zero	zero	
	Stationary casting or shot casting contact cooling	0.000	na	
	New Source Performance Standards for Primary Aluminum Smelting (B[a]P) (mg/kg)	Max. 1-day limit	Max. monthly avg.	40 CFR 421.24
	Anode and cathode paste plant wet air pollution control	0.000	na	
	Anode contact cooling and briquette quenching	0.007	0.003	
	Anode bake plant wet air pollution control	0.000	na	
	Cathode reprocessing (operating with dry potline scrubbing and commingled)	1.181	0.547	
	Potline wet air pollution control	0.000	na	
	Potroom wet air pollution control	0.000	na	
	Potline SO_2 emissions wet air pollution control	0.045	0.021	
	Degassing wet air pollution control	0.000	na	
	Pot repair and pot soaking	0.000	na	
	Direct chill casting contact cooling	zero	zero	
	Continuous rod casting contact cooling	zero	zero	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Stationary casting or shot casting contact cooling	0.000	na	
	Pretreatment standards for primary aluminum smelting sources (B[a]P) (mg/kg)	Max. 1-day limit	Max. monthly avg.	40 CFR 421.26
	Anode and cathode paste plant wet air pollution control	0.000	na	
	Anode contact cooling and briquette quenching	0.007	0.003	
	Anode bake plant wet air pollution control	0.000	na	
	Cathode reprocessing (operating with dry potline scrubbing and not commingled)	1.181	0.547	
	Cathode reprocessing (operating with dry potline scrubbing and commingled)	1.181	0.547	
	Potline wet air pollution control	0.000	na	
	Potroom wet air pollution control	0.000	na	
	Potline SO_2 emissions wet air pollution control	0.045	0.021	
	Degassing wet air pollution control	0.000	na	
	Pot repair and pot soaking	0.000	na	
	Direct chill casting contact cooling	zero	zero	
	Continuous rod casting contact cooling	zero	zero	
	Stationary casting or shot casting contact cooling	0.000	na	
	Steam Electric Power Generating Point Source Category			40 CFR 423
	Priority pollutants for steam power generators (all PAHs)	Yes		40 CFR 423, App. A
	Metal Finishing Point Source Category			40 CFR 433
	Definition of total toxic organics (TTO) for metal refinishing (all PAHs)	Yes		40 CFR 433.11
	Metal Molding and Casting Point Source Category			40 CFR 464
	Definition of TTO for aluminum casting (Acenphthene; anthracene; B[a]A; B[a]P; chrysene; fluorene; fluoranthene; phenanthrene; pyrene)	Yes		40 CFR 464.11

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)	Definition of TTO for copper casting (Acenphthene; acenaphthylene; anthracene; B[a]A; B[b]F; chrysene; phenanthrene; pyrene)	Yes	40 CFR 464.21
	Definition of TTO for ferrous casting (Acenaphthene; chrysene; acenaphthylene; anthracene; fluoranthene; fluorene; phenanthrene; pyrene)	Yes	40 CFR 464.31
	Definition of TTO for zinc casting (Acenaphthene; fluoranthene)	Yes	40 CFR 464.41
	Aluminum Forming Point Source Category		40 CFR 467
	Definition of TTO for aluminum casting (Acenaphthene; acenaphtylene; anthracene; B[k]F; B[a]P; B[g,h,i]P; chrysene; DB{a,h]A; fluoranthene; fluorene, I[1,2,3-cd]P; phenanthrene; pyrene)	Yes	40 CFR 467.02
	Copper Forming Point Source Category		40 CFR 468
	Definition of TTO for copper forming (Anthracene; phenanthrene)	Yes	40 CFR 468.02
Guidelines:			
a. Air:			
ACGIH	TLV TWA; Confirmed human carcinogens		ACGIH 1991
	Coal tar pitch volatiles-benzene soluble fraction	0.2 mg/m^3	
	Phenanthrene: cyclohexane extractable fraction	1030 mg/m^3	
	Oil mist, mineral		
	TWA	5 mg/m^3	ACGIH 1991
	STEL	10 mg/m^3	
NIOSH	REL TWA		NIOSH 1992
	Coal tar pitch volatiles; B[a]P; cyclohexane extractable fraction	Ca[g]; 0.1 mg/m^3	
	Chrysene	Ca[g]; lowest feasible concentration	
	Oil mist, mineral		
	TWA	5 mg/m^3	
	STEL	10 mg/m^3	
b. Water:			
EPA OWRS	Ambient water quality criteria for protection of human health		IRIS 1994
	Ingestion of water and organisms[h]		
	PAHs	0.0028 µg/L	
	Fluoranthene	42 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)	Ingestion of organisms only PAHs Fluoranthene	0.031 µg/L 54 µg/L	
	Organoleptic effects (acenaphthene)	0.02 mg/L	
EPA OW	Drinking water standards and health advisories		EPA 1994
	Maximum contaminant level goal (B[a]P) for organic chemicals	0 mg/L	40 CFR 141.50
	Maximum contaminant level (B[a]A) (B[a]P, B[b]F, B[k]F, chrysene) (DB[ah]A) (I[123cd]P)	 0.0001 mg/L 0.0002 mg/L 0.0003 mg/L 0.0004 mg/L	
EPA	Clean Water Act: Toxic pollutants subject to the effluent standards of the Clean Water Act section 301(a)(l)		EPA 1981b (40 CFR 401.15) EPA 1991b (40 CFR 129)
	Polynuclear aromatic hydrocarbons (include: acenaphthene; benzanthracene; benzopyrenes; benzofluoranthene; chrysenes; dibenzoanthracenes; indenopyrenes; fluoranthenes)	Yes	
c. Non-specific media: EPA	Carcinogenic classification[i]		IRIS 1994
	(Fluoranthene, anthracene, acenaphthylene)	Group D	
	(B[a]A, I[123cd]P, DB[ah]A, chrysene, B[k]F, B[b]F, B[a]P)	Group B	
EPA	RfD (Oral)		IRIS 1994
	Anthracene	0.3 mg/kg/day (u.f. 3000)	
	Acenaphthene	0.06 mg/kg/day (u.f. 3000)	
	Fluoranthene	0.04 mg/kg/day (u.f. 3000)	
	Fluorene	0.04 mg/kg/day (u.f. 3000)	
	Pyrene	0.03 mg/kg/day (u.f. 3000)	
	Acenaphthylene; B[a]P; B[e]P; B[a]A; B[b]F; B[ghi]P; B[k]F; B[j]F; chrysene; DB[ah]A; I[123cd]P; BP; phenanthrene	No data	
OSHA	NRC recommendations concerning chemical hygiene in laboratories (B[a]P)	Yes	29 CFR 1910.1450, App. A

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE			
Regulations and Guidelines:			
a. Air			
	Average acceptable ambient air concentrations		NATICH 1992
Arizona			
(B[a]P; B[a]A; DB[ah]A)	1-hour average	0.79 $\mu g/m^3$	
	24-hour average	0.21 $\mu g/m^3$	
	Annual	0.00057 $\mu g/m^3$	
Connecticut			
(B[a]P;)	8-hour average	0.1000 $\mu g/m^3$	
(Coal tar pitch volatiles)	8-hour average	2.0000 $\mu g/m^3$	
(Fluorene)	8-hour average	50.000 $\mu g/m^3$	
(Naphthalene)	8-hour average	10000.0000 $\mu g/m^3$	
Florida- Ft Ldle			
Coal tar pitch volatiles	8-hour average	2.00×10^{-3} $\mu g/m$	
Florida-Pinella			
(B[a]P)	Annual	0.0003 $\mu g/m^3$	
(B[a]A)	8- and 24-hour average	0.00 $\mu g/m^3$	
	Annual	0.00110 $\mu g/m^3$	
(DB[ah]A)	Annual	7.10×10^{-5} $\mu g/m^3$	
Coal tar pitch volatiles	8-hour average	2.00 $\mu g/m^3$	
	24-hour average	0.48 $\mu g/m^3$	
Indiana			
(B[a]P)	8-hour average	0.100 $\mu g/m^3$	
	Annual	0.0006 $\mu g/m^3$	
Kansas			
(B[a]P)	Annual	3.03×10^{-4} $\mu g/m^3$	
(Coal tar pitch volatiles)	Annual	0.00161 $\mu g/m^3$	
Kansas-KC		3.03×10^{-4} $\mu g/m^3$	
(B[a]P)	Annual		
Louisiana			
(Fluoranthene)	Annual	0.0600 $\mu g/m^3$	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
Maryland (B[a]P; B[a]A; DB[ah]A; Fluorene; Fluoranthene; Acenaphthene; Acenaphthylene; Anthracene; B[b]F; B[k]F; B[ghi]P; Chrysene; I[123cd]P; Phenanthrene; Pyrene; B[e]P)		0.00 $\mu g/m^3$	
Maine (B[a]P)	Annual	5.70×10^{-4} $\mu g/m^3$	
Michigan (B[a]P)	Annual	3.00×10^{-4} $\mu g/m^3$	
Nevada (Coal tar pitch volatiles)	8-hour average	0.0050 mg/m^3	
New York (B[a]P)		0.00 $\mu g/m^3$	NATICH 1992
North Carolina (B[a]P)	Annual	3.30×10^{-5} mg/m^3	
(Coal tar pitch volatiles)	Annual	3.30×10^{-5} mg/m^3	
North Dakota (B[a]P; B[a]A; DB[ah]A; B[b]F; Chrysene; I[123cd]P)		0.00 $\mu g/m^3$	
Pennsylvania-Phila (B[a]P)	1-year average Annual	7.00×10^{-4} $\mu g/m^3$ 7.00×10^{-4} $\mu g/m^3$	
(Coal tar pitch volatiles)	1-year average	0.4800 $\mu g/m^3$	
Texas (B[a]P)	30-minute average Annual	0.03 $\mu g/m^3$ 0.003 $\mu g/m^3$	
(Chrysene)	30-minute average Annual	0.500 $\mu g/m^3$ 0.05 $\mu g/m^3$	
Virginia (B[a]P; chrysene)	24-hour average	0.00 $\mu g/m^3$	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
(Coal tar pitch volatiles)	24-hour average	2.0000 $\mu g/m^3$	
Vermont			
(B[a]P)	Annual	$3.00x10^{-14}$ $\mu g/m^3$	
(Phenanthrene)	Annual	1.30 $\mu g/m^3$	
(Pyrene)	Annual	3.40 $\mu g/m^3$	
Washington-SWest (B[a]P)	Annual	$6.00x10^{-4}$ $\mu g/m^3$	
Kentucky	Significant emission levels of toxic air pollutants		401 KAR 63:022 NREPC 1991
	B[a]P; B[b]F; B[a]A; DB[ah]A; I[123cd]P	$5.100x10^{-7}$ pounds/hour	
	Chrysene; coal tar pitch volatiles	$5.103x10^{-5}$ pounds/hour	
b. Water:			
	Water quality standards		NYSDEC 1994
New York Acenaphthene		20 $\mu g/L$	
	Drinking water quality standards		
Arizona (B[a]P)		0.003 $\mu g/L$	FSTRAC 1990
Kansas (B[a]P)		0.03 $\mu g/L$	
(All other PAHs)		0.029 $\mu g/L$	
Maine (PAHs)		25 $\mu g/L$	
Minnesota (PAHs)		0.028 $\mu g/L$	
New Hampshire (B[a]P)		0.003 $\mu g/L$	
New Mexico (B[a]P)		10 $\mu g/L$	
(All other PAHs)		30 $\mu g/L$	
New Jersey (All PAHs)		1 $\mu g/L$	NJDEP 1989

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
State (cont.)			
	ACENAPHTHYLENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	** (no value recorded)	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria	0.003 µg/L	
	Domestic Water Supply (DWS)	0.002 µg/L	
	Fish Consumption (FC)	0.12 µg/L	
	Full Body Contact (FBC)	NNS (no numerical standard)	
	Partial Body Contact (PBC)		
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply (This concentration is allowed for each of a goup of PAHs)	0.003 µg/L	
	Groundwater	0.003 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	ACENAPHTHENE		
	Water Quality: Human Health		CELDS 1994
AL	Consumption of Water and Fish	20(0) µg/L	
	Fish Consumption Only	20(0) µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	420 µg/L	
	Fish Consumption (FC)	2600 µg/L	
	Full Body Contact (FBC)	8400 µg/L	
	Partial Body Contact (PBC)	8400 µg/L	
MO	Class II Human Health Protection-Fish Consumption	2700 µg/L	
	Class III Drinking Water Supply	20 µg/L	
WI	Threshold conc. for substances causing taste and odor in water (not toxic to humans)	20 µg/L	
OH	Water Supply Public Water Supply Outside mixing zone Human health 30 day-average	20 µg/L	
DC	Numerical Standards for Water Quality Criteria for Classes (Maximum)		
	Classes A, B, C	50.0 µg/L	
	Classes D, E	20.0 µg/L	
	Water Quality: Aquatic Life		CELDs 1994
AZ	Acute Criteria for Aquatic and Wildlife Uses		
	Cold Water Fishery (A&Wc)	850	
	Warm Water Fishery (A&Ws)	850	
	Effluent Dominated Water (A&Wedw)	850	
	Ephemeral (A&We)	NNS	
	Chronic Criteria for Aquatic and Wildlife Uses	550 µg/L	
	Cold Water Fishery (A&Wc)	5,500 µg/L	
	Warm Water Fishery (A&Ws)	NNS	
	Effluent Dominated Water (A&Wedw)		
	Ephemeral (A&We)		
CO	Aquatic life segments-organic compounds to the second power		
	Standard (acute)	1,700 µg/L	
	Standard (chronic)	520 µg/L	
HI	Numeric Standards for Toxic Pollutants		
	Applied to All Waters	570 µg/L	
	Freshwater (acute)	320 µg/L	
	Saltwater (acute)	NS (no standard developed)	
	Fish Consumption		
OH	Aquatic Life Habitat-Coldwater		
	Outside mixing zone (maximum)	67 µg/L	
	Outside mixing zone (30-day average)	67 µg/L	
	Inside mixing zone (maximum)	134 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside mixing zone (maximum)	67 µg/L	
	Inside mixing zone (maximum)	134 µg/L	
NY	Water Classes-A, A-S, AA, AA-S		
	Standards µg/L	20 µg/L	
	Type-health (water source)		
	Basis code-chem.correlation		
	Groundwater Monitoring		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Groundwater Quality Standards		CELDs 1994
MO	Class VII-Groundwater	20 µg/L	
	ANTHRACENE		
	Water Quality: Human Health		CELDs 1994
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	2100 µg/L	
	Fish Consumption (FC)	6300 µg/L	
	Full Body Contact (FBC)	420000µg/L	
	Partial Body Contact (PBC)	NNS	
MO	Human Health Protection-Fish	0.03 µg/L	
	Consumption	0.003 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater		
OH	Water Supply		
	Public Water Supply		

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	Outside mixing zone Human Health 30-day average	0.028 0.003 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CA		Yes	
IL		Yes	
KY		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater Outside mixing zone Human Health 30-day average	0.31 µg/L*	
	Aquatic Life Habitat-Limited Resource Warmwater Outside mixing zone Human Health 30-day average	0.31 µg/L*	
	*This value applies to the sum of PAHs		
	BENZ(a)ANTHRACENE		
	Hazardous Constituents		CELDs 1994
AL		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NH		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
NJ		Yes	
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	Water Quality: Human Health		CELDs 1994
AL	Human Health Criteria:		
	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
	-Classified as a carcinogen		
AZ	Numeric Water Quality Criteria:		
	Domestic Water Source (DWS)	0.03 µg/L	
	Fish Consumption (FC)	0.00008 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
	-known, probable, or possible human carcinogen		
MO	Human Health Protection-Fish		
	Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
	Water Supply		
	Public Water Supply		
OH	Outside mixing zone		
	Human health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria*		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	*Human cancer criteria for PAHs are applicable to any combination of 10 PAHs (specific)		

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WI	Human Cancer Criteria*		
	Non-Public Water Supplies		
	Warmwater Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	*Human cancer criteria are applicable to any combination of 9 PAHs.		
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater		
	Outside mixing zone		
	Human Health		
	30-day average	0.31 µg/L*	
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside mixing zone		
	Human Health		
	30-day average	0.31 µg/L*	
	* This value applied to the sum of 13 PAHs		
	BENZO(b)FLUORANTHENE		
	Water Quality: Human Health		CELDs 1994
OH	Water Supply-Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L*	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 µg/L	
	Cold Water Communities	0.023 µg/L	
	Great Lakes	0.023 µg/L	
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 mg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
IL		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
LA		Yes	
KY		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	BENZO(k)FLUORANTHENE		
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater Outside Mixing Zone Human Health 30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater Outside Mixing Zone Human Health 30-day average	0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
IL		Yes	
MD		Yes	
MT		Yes	
NE		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WY		Yes	
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.00001 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
OH	Water Supply		
	Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	BENZO(g,h,i)PERYLENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.0001 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
OH	Water Supply		
	Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	BENZO(a)PYRENE		
	Water Quality: Human Health Criteria		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only -Carcinogen	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Supply (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.002 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply*	0.003 µg/L	
	Groundwater*	0.003 µg/L	
	*These conclusions are allowed for each of the PAHs		
NM	Groundwater Standards		
	Human Health Standards	0.0007 mg/L	
OH	Water Supply-Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
OK	Maximum Allowable Levels for Organic Chemicals	0.4 mg/L	
TN	National Primary Drinking Water		
	Standard Organic Chemicals	0.002 mg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Human Cancer Criteria		
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	Special Monitoring, Reporting and Public Notification Requirements for Unregulated Organic and Inorganic Contaminants Nonregulated Organic Contaminants	Yes	
	Water Quality: Aquatic Life		CELDs 1994
NY	Water Classes-GA Standards (µg/L)-ND Type-H(WS) Basis code-F		
OH	Aquatic Life Habitat-Coldwater Outside Mixing Zone Human Health 30-day average	0.31 µg/L*	
	Aquatic Life Habitat-Limited Resource Warm Water Outside Mixing Zone Human Health 30-day average	0.31 µg/L*	
	*This value applies to the sum of 13 PAHs		
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Groundwater Quality Standards		CELDs 1994
NY	Groundwater Effluent Standard	Not detectable	
WI	Public Health Groundwater Quality Standards		
	Enforcement Standard	0.003 µg/L	
	Preventive Action	0.0003 µg/L	
	CHRYSENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Supply (DWS)	0.03 µg/L	
	Fish Consumption (FC)	0.0001 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
OH	Water Supply-Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Human Cancer Criteria		
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WI		Yes	
WV		Yes	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	DIBENZ(a,j)ACRIDINE		
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
IL		Yes	
LA		Yes	
KY		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
MD		Yes	
MN		Yes	
MT		Yes	
NE		Yes	
ND		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	DIBENZO(a,h)ANTHRACENE		
	Water Quality: Human Health		CELDs 1994
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
AL	Human Health Criteria		
	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Supply (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.00003 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
OH	Water Supply-Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Human Cancer Criteria		
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		©ELDs 1994

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
OH	Aquatic Life Habitat-Coldwater Outside Mixing Zone Human Health 30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater Outside Mixing Zone Human Health 30-day average	0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
C0		Yes	
IL		Yes	
KY		Yes	
LA		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CA		Yes	
CO		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	FLUORANTHENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	280 µg/L	
	Fish Consumption (FC)	130 µg/L	
	Full Body Contact (FBC)	5600 µg/L	
	Partial Body Contact (PBC)	5600 µg/L	
IN	Continuous Criterion Concentration (4-Day) Average for Human Health		
	Outside of Mixing Zone	54 (T)*	
	Point of Water	42	
	*(T) - T is derived from threshold toxicity		
KY	Water Quality Criteria for Protection of Human Health from the Consumption of Fish Tissue Substances Not Linked to Cancer	54 µg/L	
	Organics		
	Domestic Water Supply Source Criteria Substances Not Linked to Cancer		
	Maximum Contaminant Level (organics)	0.042 mg/L	
MO	Drinking Water Supply	40 µg/L	
	Human Health Protection-Fish Consumption	54 µg/L	
	Groundwater	40 µg/L	
OH	Water Supply-Public Water Supply Outside Mixing Zone Human Health		
	30-day average	42 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WI	Human Threshold Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	28 µg/L	
	Cold Water Communities	9.1 µg/L	
	Great Lakes	9.3 µg/L	
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	32 µg/L	
	Cold Water Communities	9.5 µg/L	
	Warm Water and Limited Fish and Limited Aquatic	41,000 µg/L	
HI	(Water Quality Standards: Basic Water Quality Criteria for All Waters)		
	Numeric Standards for Toxic Pollutants Applicable to All Waters		
	Freshwater		
	Acute	1,300 µg/L	
	Chronic	NS	
	Saltwater		
	Acute	13 µg/L	
	Chronic	NS	
	Fish Consumption	18 µg/L	
	Water Quality: Aquatic Life		CELDs 1994
AZ	Acute Criteria for Aquatic and Wildlife Uses	2000 µg/L	
	A&Wc: Cold Water Fishery	2000 µg/L	
	A&Ws: Warm Water Fishery	2000 µg/L	
	A&Wedw: Effluent Dominated Water	NNS	
	A&We: Ephemeral		
	Chronic Criteria for Aquatic and Wildlife Uses	1600 µg/L	
	A&Wc: Cold Water Fishery	1600 µg/L	
	A&Ws: Warm Water Fishery	1600 µg/L	
	A&Wedw: Effluent Dominated Water	NNS	
	A&We: Ephemeral		
CO	Aquatic Life Segments (organic compounds to the second power)	3,980 µg/L	
	Standard (acute)		
FL	Maximum Concentration Levels for Mixing Zone Pollutants	540 µg/L	
OH	Aquatic Life Habitat-Coldwater		
	Outside mixing zone		
	Maximum	200 µg/L	
	30-day average	8.9 µg/L	
	Human Health		
	30-day average	54 µg/L	
	Inside Mixing Zone		
	Maximum	400 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	Outside Mixing Zone Maximum Human Health 30-day average	200 µg/L 54 µg/L	
	Inside Mixing Zone Maximum	400 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	FLUORENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	280 µg/L	
	Fish Consumption (FC)	580 µg/L	
	Full Body Contact (FBC)	5600 µg/L	
	Partial Body Contact (PBC)	5600 µg/L	
MO	Human Health Protection-Fish	0.03 µg/L	
	Consumption	0.003 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater		
OH	Water Supply		
	Public Water Supply		
	Outside mixing zone		
	Human Health 30-day average	0.028 µg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater		
	Outside mixing zone		
	Human Health		
	30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside mixing zone		
	Human Health		
	30-day average	0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	INDENO(1,2,3-CD)PYRENE		
	Water Quality: Human Health Criteria		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Supply (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.000003 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS µg/L	
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
OH	Water Supply-Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Human Cancer Criteria		
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
OH	Aquatic Life Habitat-Coldwater Outside mixing zone Human Health 30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater Outside mixing zone Human Health 30-day average	0.31 µg/L*	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	PHENANTHRENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Supply (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.0005 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Non-Public Water Supplies		
	Warm water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994s
AZ	Acute Criteria for Aquatic and Wildlife Uses	30 µg/L	
	A&Wc: Cold Water Fishery	30 µg/L	
	A&Ws: Warm Water Fishery	540 µg/L	
	A&Wedw: Effluent Dominated Water	NNS	
	A&We: Ephemeral		

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	Chronic Criteria for Aquatic and Wildlife Uses	6.3 µg/L	
	A&Wc: Cold Water Fishery	6.3 µg/L	
	A&Ws: Warm Water Fishery	6.3 µg/L	
	A&Wedw: Effluent Dominated Water	NNS	
	A&We: Ephemeral		
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	PYRENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	210 µg/L	
	Fish Consumption (FC)	1100 µg/L	
	Full Body Contact (FBC)	4200 µg/L	
	Partial Body Contact (PBC)	4200 µg/L	
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
OH	Water Supply		
	Public Water Supply		
	Outside mixing zone		
	Human Health		
	30-day average	0.028 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WI	Human Cancer Criteria Public Water Supplies Warm Water Sport Fish Communities Cold Water Communities Great Lakes	 0.023 mg/L 0.023 mg/L 0.023 mg/L	
	Human Cancer Criteria Non-Public Water Supplies Warm Water Sport Fish Communities Cold Water Communities Warm Water and Limited Fish and Limited Aquatic	 0.1 mg/L 0.1 mg/L 6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater Outside mixing zone Human Health 30-day average	 0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater Outside mixing zone Human Health 30-day average	 0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	

[a]Degree of evidence in animals revised on the basis of data that appeared after the most recent monograph and/or on the basis of present criteria. Overall evaluation based on evidence of carcinogenicity in monograph 32, 1983.

[b]Group 2A = Probable human carcinogen

[c]Group 2B = Possible human carcinogen

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

[d]Group 3 = Not classifiable as to carcinogenicity

[e]The following PAHs were used as indicators in deriving this standard: B[a]P; B[b]F; B[a]F; B[k]F; fluoranthene; and I[123cd]P. Source: EPA 1986b.

[f]Includes anthracene, B[a]P, phenanthrene, acridine, chrysene, and pyrene

[g]Agent recommended by NIOSH to be treated as a potential occupational carcinogen.

[h]Because of their carcinogenic potential, the EPA-recommended concentration for PAHs in ambient water is zero. However, because attainment of this level may not be possible, the recommended criteria requires a E-G estimated incremental lifetime cancer risks.

[i]Group D = not classifiable as to human carcinogenicity, Group B2 = Probable Human Carcinogen

[j]When "all PAHs" are listed, it includes the following compounds, unless specified otherwise:
Anthracene, Acenaphthylene, Acenaphthene, B[a]A, B[a]P, B[b]F, B[h]F, B[g,h,i]P, Chrysene, DB[a,h]A, Fluoranthene, Flourene, I[1,2,3-cd]P, Phenanthrene, Pyrene

ACHIH = American Conference of Govemmental Industrial Hygienists; B[a]A = Benzo[a]Anthracene; B[a]P = Benzo[a]Pyrene; B[b]F = Benzo[b]Fluoranthene; B[e]P = Benzo[e]Pyrene; B[ghi]P = Benzo(ghi)perylene; B[j]F = Benzo[j]Fluoranthene; B[k]F = Benzo[k]Fluoranthene; B[ghi]P = Benzo[ghi]perylene; BP = Benzopyrene; DB[a,h]A = Dibenz[a,h]Anthracene; DB[a,e]P = Dibenzo[a,e]pyrene; DB[a,i] = Dibenzo[a,i]pyrene; DOT = Department of Transportation; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; I[123cd]P = Indeno[1,2,3-c,d]Pyrene; ng = nanogram; NIOSH = Natinonal Institute for Occupational Safety and Health; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OWRS = Office of Water Regulations and Standards; PAH = Polycyclic Aromatic Hydrocarbons; PEL = Permissible Exposure Limit; RCRA = Resource Conservation and Recovery Act; REL = Recommended Exposure Limit; RfD = Reference Dose; TLV = Threshold Limit Value; TWA = Time-Weighted Average; u.f. = Uncertainty Factor; WHO = World Health Organization

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9. GLOSSARY

Acute Exposure-Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc})-The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF)-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL)-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory-An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity-The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In vivo-Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})-A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1^*-The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity-The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)-The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity-This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50})-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-l) 2-2, and 2-4) and figures (2-1, 2-2, and 2-3) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15 to 364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 " 18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [chemical x] via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(I 2) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphical!y illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the' entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

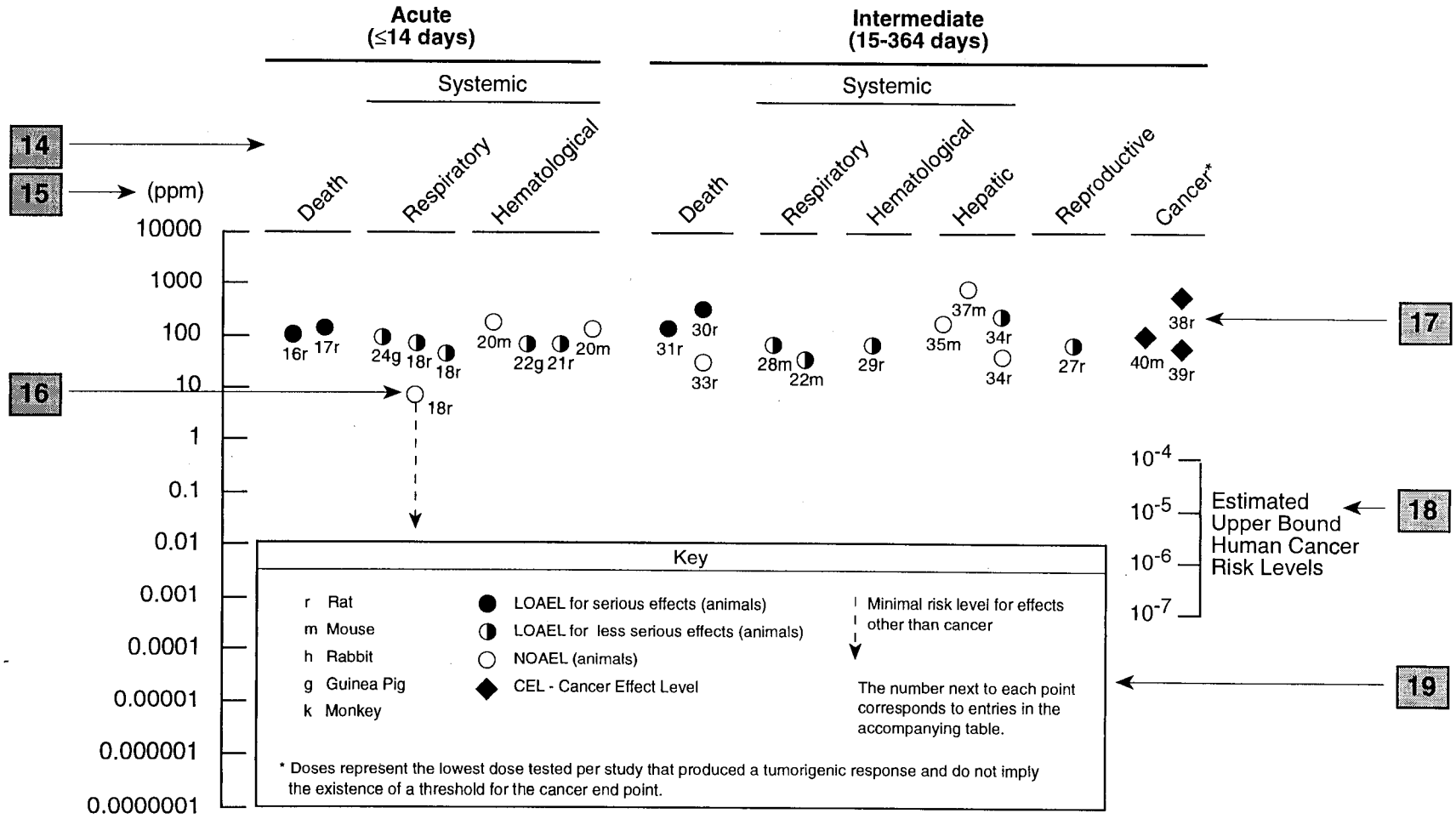
[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Chemicals”, and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
dL	deciliter
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient

K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification

SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram
μM	micromolar

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TOXICOLOGICAL PROFILE FOR THALLIUM

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

July 1992

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about thallium and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Thallium has been found in at least 18 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for thallium. As EPA evaluates more sites, the number of sites at which thallium is found may change. This information is important for you to know because thallium may cause harmful health effects and because these sites are potential or actual sources of human exposure to thallium.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as thallium, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS THALLIUM?

Pure thallium is a soft, bluish-white metal that is widely distributed in trace amounts in the earth's crust. In its pure form, it is odorless and tasteless. It can be found in pure form or mixed with other metals in the form of alloys. It can also be found combined with other substances such as bromine, chlorine, fluorine, and iodine to form salts. These combinations may appear colorless to white or yellow. Thallium remains in the environment since it is a metal and cannot be broken down to simpler substances.

Thallium exists in two chemical states (thallous and thallic). The thallous state is the more common and stable form. Thallous compounds are the most likely form to which you would be exposed in the environment. Thallium is present in air, water, and soil. We do not know how much time it takes for thallium to move from one medium to another.

Thallium is used mostly in the manufacture of electronic devices, switches, and closures. It also has limited use in the manufacture of special glasses and for medical procedures that evaluate heart disease. Up until 1972 thallium was used as a rat poison, but was then banned because of its potential harm to man. Thallium is no longer produced in the United States.

All the thallium used in the United States since 1984 has been obtained from imports and thallium reserves.

More information on the properties and uses of thallium and how it behaves in the environment may be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO THALLIUM?

You can be exposed to thallium in air, water, and food. However, the levels of thallium in air and water are very low. The greatest exposure occurs when you eat food, mostly home-grown fruits and green vegetables contaminated by thallium. Small amounts of thallium are released into the air from coal-burning power plants, cement factories, and smelting operations. This thallium falls out of the air onto nearby fruit and vegetable gardens. Thallium enters food because it is easily taken up by plants through the roots. Very little is known on how much thallium is in specific foods grown or eaten. Cigarette smoking is also a source of thallium. People who smoke have twice as much thallium in their bodies as do nonsmokers. Although fish take up thallium from water, we do not know whether eating fish can increase thallium levels in your body. It has been estimated that the average person eats, on a daily basis, 2 parts thallium per billion parts (ppb) of food. Even though rat poison containing thallium was banned in 1972, accidental poisonings from old rat poison still occur, especially in children.

Thallium is produced or used in power plants, cement factories, and smelters. People who work in these places can breathe in the chemical or it may come in contact with their skin. Information on the amount of thallium in workplace air in the United States could not be found. Hazardous waste sites are also possible sources of exposure to thallium. An average of 23 ppb of thallium in surface water and 11 ppb in groundwater have been found at hazardous waste sites. Since thallium compounds mix easily in water, you can be exposed if you live near a chemical waste site where thallium emissions have contaminated the water. An average of 1.7 parts of thallium per million parts (ppm) of soil was found at hazardous waste sites. Since thallium sticks to soil, you can be exposed at hazardous waste sites if you swallow or touch contaminated soil. Thallium-contaminated dust in the air can also be swallowed after it is cleared from the lungs. Thallium is naturally found in soil at levels from 0.3 to 0.7 ppm.

More information on how you might be exposed to thallium is given in Chapter 5.

1.3 HOW CAN THALLIUM ENTER AND LEAVE MY BODY?

Thallium can enter your body when you eat food or drink water contaminated with thallium, breathe thallium in the air, and when your skin comes in contact with it. When thallium is swallowed most of it is absorbed and rapidly goes to various parts of your body, especially the kidney and

liver. Thallium leaves your body slowly. Most of the thallium leaves your body in urine and to a lesser extent in feces. It can be found in urine within 1 hour after exposure. After 24 hours, increasing amounts are found in feces. It can be found in urine as long as 2 months after exposure. About half the thallium that enters various parts of your body leaves them within 3 days.

The significant, likely routes of exposure near hazardous waste sites are through swallowing thallium-contaminated soil or dust, drinking contaminated water, and skin contact with contaminated soil. More information on how thallium enters and leaves the body is given in Chapter 2.

1.4 HOW CAN THALLIUM AFFECT MY HEALTH?

Thallium can affect your nervous system, lung, heart, liver, and kidney if large amounts are eaten or drunk for short periods of time. Temporary hair loss, vomiting, and diarrhea can also occur and death may result after exposure to large amounts of thallium for short periods. Thallium can be fatal from a dose as low as 1 gram. No information was found on health effects in humans after exposure to smaller amounts of thallium for longer periods. Birth defects observed in children of mothers exposed to small amounts of thallium did not occur more often than would be expected in the general population. The length of time and the amount of thallium eaten by the mothers are not known exactly. As in humans, animal studies indicate that exposure to large amounts of thallium for brief periods of time can damage the nervous system and heart and can cause death. Animal reproductive organs, especially the testes, are damaged after drinking small amounts of thallium-contaminated water for 2 months. These effects have not been seen in humans. No information was found on effects in animals after exposure to small amounts of thallium for longer periods of time. No studies were found on whether thallium can cause cancer in humans or animals.

More information on the health effects of thallium in humans and animals can be found in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO THALLIUM?

Reliable and accurate ways to measure thallium in the body are available. The presence of thallium in the urine and hair can indicate exposure to thallium. Tests of your urine can detect thallium up to 2 months. The normal amount of thallium in human urine amounts to less than 1 ppm and 5-10 ppb in human hair. Although thallium can be measured in blood, this tissue is not a good indicator of exposure since thallium stays there too short a time. We do not know yet whether thallium levels measured in the body can be used to predict possible health effects.

More information on how thallium can be measured in exposed humans is presented in Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has set standards and guidelines to protect individuals from the possible effects of excessive thallium exposure. The EPA has determined a water quality criteria level of 13 ppb in surrounding waters to protect humans from the harmful effects of drinking water and eating food containing thallium.

The Occupational Safety and Health Administration (OSHA) has established an occupational limit of 0.1 mg of soluble thallium compounds per cubic meter of workplace air (mg thallium/m^3/skin) for an 8-hour workday over a 40-hour workweek. "Skin" indicates that measures must be taken to prevent skin exposure to thallium.

Additional information on governmental regulations regarding thallium can be found in Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of thallium and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for thallium based on toxicological studies and epidemiological investigations.

Pure thallium exists in nature but is usually found combined with other elements in inorganic compounds. Thallium forms compounds in both the monovalent and trivalent states; however, the monovalent state is the more stable. This document includes nine of the commonly used thallium compounds. Toxicity data were found for five of these compounds (thallium sulfate, thallium oxide, thallium nitrate, thallium acetate, and thallium carbonate).

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing noobserved-adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

2. HEALTH EFFECTS

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989c), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding lethality in humans or animals after inhalation exposure to thallium.

2.2.1.2 Systemic Effects

No studies were located in humans or animals regarding the effects on the respiratory, hematological, musculoskeletal, hepatic, renal, and dermal/ocular systems after inhalation exposure to thallium. Limited occupational data show the cardiovascular and gastrointestinal systems were not susceptible to thallium.

Cardiovascular Effects. There are few data in humans on the cardiovascular effects of thallium following inhalation. Data are limited to a study evaluating the health of workers employed in a magnesium sea water battery plant in England (Marcus 1985). There were no statistically significant differences in cardiovascular effects in a cohort of 86 exposed workers compared with 79 unexposed controls in the same factory. However, the authors did not clearly define the cardiovascular parameters measured. Workplace air levels were 0.014 and 0.022 mg/m^3 in machining and alloying operation areas. Occupational exposure is expected to involve multiple compound exposures. However, the authors did not provide data on other chemicals to which workers have been exposed concomitantly.

No studies were located regarding cardiovascular effects in animals after inhalation exposure to thallium.

Gastrointestinal Effects. Based on available medical records, there were no differences in gastrointestinal effects in a cohort of 86 exposed workers in a magnesium sea water battery plant in England compared with 79

unexposed controls (Marcus 1985). Maximum thallium levels in workplace air were 0.014 and 0.022 mg/m^3 during machining and alloying operations, respectively.

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to thallium.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to thallium.

2.2.1.4 Neurological Effects

Human occupational studies indicate that thallium may affect the nervous system following inhalation. Thirty-six workers involved in cement production for 5-44 years (mean of 22.9) exhibited paresthesia, numbness of toes and fingers, the "burning feet" phenomenon, and muscle cramps (Ludolph et al. 1986). Peripheral conduction was impaired and there were changes in somatosensory action potential. Electroencephalographic recordings revealed no abnormalities. This study did not evaluate an unexposed control group. It should be further noted that 50% of the patients suffered concurrent disease including diabetes, obesity, malabsorption syndrome, (alcoholic) liver disease, disorders of joints and connective tissues, and hypertensive vascular disease. These may have contributed to the neurological effects observed.

No studies were located regarding neurological effects in animals after inhalation exposure to thallium.

No studies were located regarding the following effects in humans or animals after inhalation exposure to thallium:

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after inhalation exposure to thallium.

2.2.2 Oral Exposure

2.2.2.1 Death

There are numerous case reports of human lethality following acute oral exposure to thallium. Death occurred in one individual 9 days following intentional ingestion of a single estimated dose of 54-110 mg thallium/kg (as thallium nitrate) (Davis et al. 1981). Cranial and peripheral nerves showed axonal degeneration with preservation of most of the overlying myelin, suggesting that thallium damaged axons. Two of three subjects who ingested thallium (thallous acetate) also died; however death occurred 1 month after onset of symptoms (Cavanagh et al. 1974). Dose could not be determined since exposure occurred in three divided doses for unspecified durations. Distal peripheral axon degeneration with preserved proximal fibers was reported in one case (Cavanagh et al. 1974). Other studies (de Groot et al. 1985; Heath et al. 1983; Roby et al. 1984) have reported that thallium (as thallium sulfate, dose not specified) is lethal following ingestion, and there was evidence for central-peripheral distal axonopathy (Roby et al. 1984). While the finding of neurological effects was consistent among case reports, death was attributable to cardiac or respiratory failure. No studies were located concerning intermediate or chronic exposures.

In rats, estimates of LD_{50} for thallium compounds were 32 and 39 mg thallium/kg (as thallium acetate and thallic oxide, respectively) (Downs et al. 1960). The lowest oral doses of thallium compounds showing lethality ranged from 12 (guinea pig) to 29 (rat) mg thallium/kg (as thallium acetate) and 5 (guinea pig) to 30 (dog and rabbit) mg thallium/kg (as thallic oxide) (Downs et al. 1960). Rats exposed for 15 weeks to diets containing thallium showed increased mortality at a dose of 4.5 mg thallium/kg/day (as thallic oxide) and 2.3 mg thallium/kg/day (as thallium acetate) (Downs et al. 1960). Continuous administration via drinking water of approximately 1.4 mg thallium/kg/day to rats (as thallium sulfate) resulted in 15%-21% mortality after 40 and 240 days of treatment, respectively (Manzo et al. 1983). When rats were administered up to 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days, no deaths were reported (Stoltz et al. 1986).

A NOAEL value and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.2 Systemic Effects

No studies were located regarding hematological effects in humans or animals following oral exposure to thallium. Case studies in humans who ingested various thallium compounds show the respiratory and cardiovascular systems as well as the liver, kidney, and muscles are susceptible. Hair loss may also occur. These effects are discussed below. The highest NOAEL values and all reliable LOAEL values for these systemic effects for each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

TABLE 2-1. Levels of Significant Exposure to Thallium and Compounds - Oral

Key to figure[a]	Species		Exposure frequency/ duration	System	NOAEL (mg Tl/kg/day)	LOAEL (effect) Less serious (mg Tl/kg/day)	LOAEL (effect) Serious (mg Tl/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Rat	(F)	1x				39 (LD50-7 days)	Downs et al. 1960	Tl_2O_3
2	Rat	(F)	1x				20 (lowest lethal dose)	Downs et al. 1960	Tl_2O_3
3	Rat	(F)	1x				32 (LD50-7 days)	Downs et al. 1960	$TlC_2H_3O_2$
4	Gn pig	(F)	1x				5 (lowest lethal dose)	Downs et al. 1960	Tl_2O_3
Systemic									
5	Rabbit	(F)	1x	Cardio		56 (electrocardial alterations)		Grunfeld et al. 1963	Tl_2SO_4
Developmental									
6	Rat	(G)	4 d 1x/d Gd 6,7,8,9			0.08 (performance deficit)		Bornhausen and Hagen 1984	Tl_2SO_4
INTERMEDIATE EXPOSURE									
Death									
7	Rat	(F)	15 wk				4.5 (increased mortality)	Downs et al. 1960	Tl_2O_3
8	Rat	(F)	15 wk				2.3 (increased mortality)	Downs et al. 1960	$TlC_2H_3O_2$
9	Rat	(G)	90 d 1x/d		0.2			Stoltz et al. 1986	Tl_2SO_4
10	Rat	(W)	36 wk				1.4 (increased mortality)	Manzo et al. 1983	Tl_2SO_4

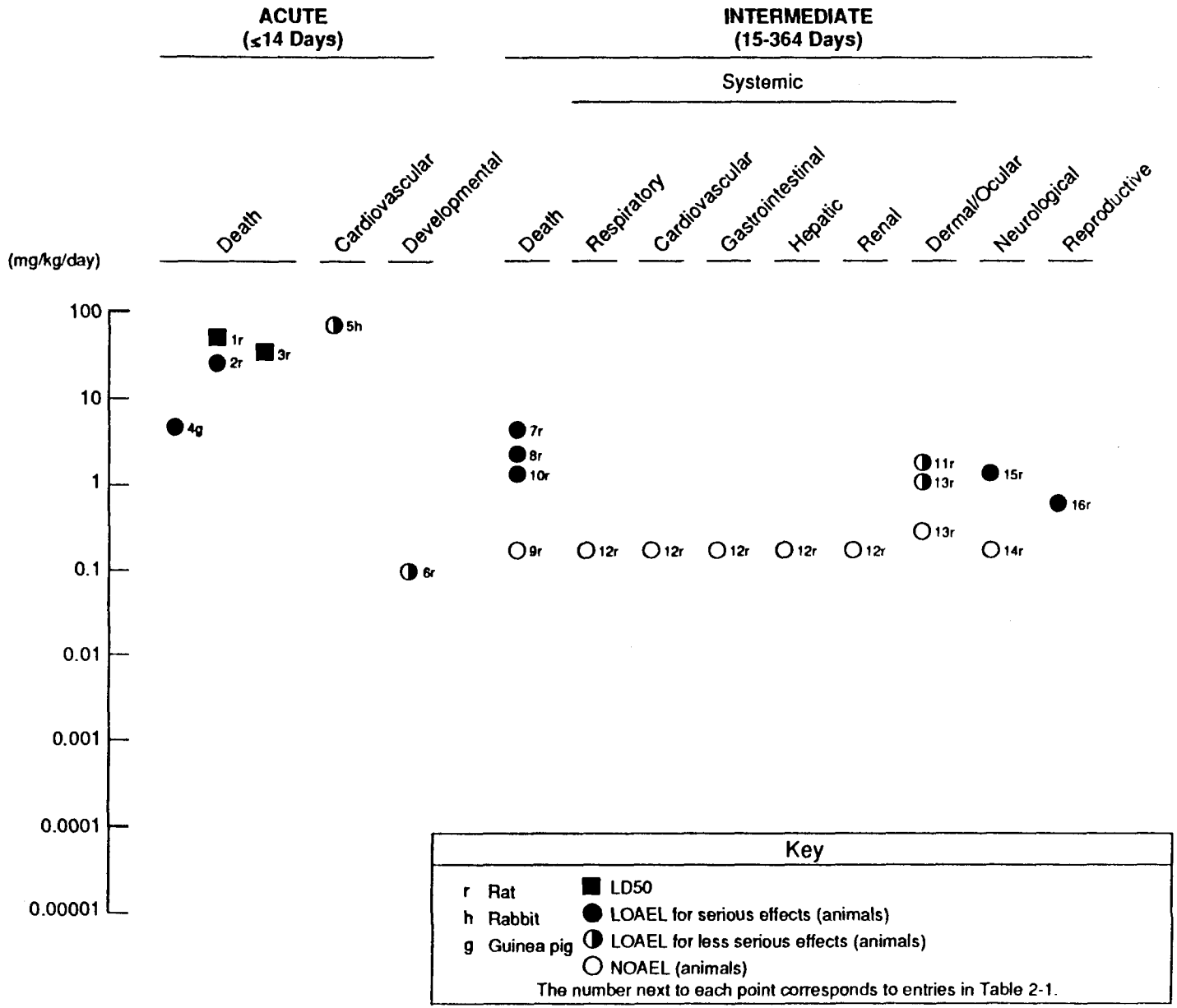
TABLE 2-1 (Continued)

Key to figure[a]	Species		Exposure frequency/ duration	System	NOAEL (mg Tl/kg/day)	LOAEL (effect) Less serious (mg Tl/kg/day)	LOAEL (effect) Serious (mg Tl/kg/day)	Reference	Form
Systemic									
11	Rat	(F)	15 wk	Derm/oc		1.8 (hair loss)		Downs et al. 1960	Tl_2O_3
12	Rat	(G)	90 d 1x/d	Hepatic Renal Cardio Gastro Resp	0.2 0.2 0.2 0.2 0.2			Stoltz et al. 1986	Tl_2SO_4
13	Rat	(F)	15 wk	Derm/oc	0.4	1.2 (hair loss)		Downs et al. 1960	$TlC_2H_3O_2$
Neurological									
14	Rat	(G)	90 d 1x/d		0.2			Stoltz et al. 1986	Tl_2SO_4
15	Rat	(W)	36 wk				1.4 (peripheral nerve damage)	Manzo et al. 1983	Tl_2SO_4
Reproductive									
16	Rat	(W)	30-60 d				0.7 (histological alteration of testis)	Formigli et al. 1986	Tl_2SO_4

[a]The number corresponds to entries in Figure 2-1.

Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; Gn = guinea; LD50 = lethal dose, 50% mortality; LOAEL = lowest-observed-adverse-effect level; mg thallium/kg/day = milligram thallium per kilogram body weight per day; NOAEL = no-observed-adverse-effect level; Resp = respiratory; Tl_2SO_4 = thallium sulfate, Tl_2O_3 = thallium carbonate, $TlC_2H_3O_2$ = thallium acetate

FIGURE 2-1. Levels of Significant Exposure to Thallium – Oral



2. HEALTH EFFECTS

Respiratory Effects. Limited data in humans show that thallium can cause respiratory damage. Lungs showed diffuse alveolar damage with hyaline membrane and focal organization in one case following acute ingestion of an estimated 54-110 mg thallium/kg (as thallium nitrate). Bronchopneumonia was also reported in this study (Davis et al. 1981). Similar findings were reported after ingestion of thallium acetate; however, the doses that produced these effects were not clearly defined (Cavanagh et al. 1974; de Groot et al. 1985; Roby et al. 1984).

One study was located in animals. No adverse effects were observed on the respiratory system of rats administered 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days (Stoltz et al. 1986).

Cardiovascular Effects. Cardiovascular damage was reported in humans after ingestion of a single estimated lethal dose of 54-110 mg thallium/kg (as thallium nitrate) (Davis et al. 1981). There was extensive damage of the myocardium with myofiber thinning, accumulation of lipid droplets, myocardial necrosis, and inflammatory reaction (Davis et al. 1981). Sinus bradycardia, ventricular arrhythmias, and T-wave anomalies were reported in two additional case reports; however, the authors did not provide data on dose and duration (Roby et al. 1984).

Limited studies were located regarding cardiovascular effects in animals after oral exposure to thallium. Electrocardiographic changes were observed in rabbits administered 56 mg thallium/kg/day (as thallous sulfate), which was also lethal (Grunfeld et al. 1963). Abnormalities reported included T-wave fluttering, prolonged Q-T intervals, heart block, atria1 and ventricular ectopic rhythms, and ST-segment depression or elevation (Grunfeld et al. 1963). While thallium was detected in heart tissue (16-45 μg/g tissue), histological examination did not reveal damage to the myocardium. When rats were administered up to 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days, no cardiovascular effects were observed (Stoltz et al. 1986).

Gastrointestinal Effects. In humans, acute ingestion of thallium sulfate caused gastroenteritis, diarrhea or constipation, vomiting, and abdominal pain (Davis et al. 1981; de Groot et al. 1985; Grunfeld and Hinostroza 1964). Gastrointestinal disturbances were also reported in 189 cases of thallium poisoning which occurred in China from 1960 to 1977 (Dai-xing and Ding-nan 1985). High levels of thallium were detected in urine and hair samples. The authors attributed exposure to ingestion of cabbage from contaminated gardens.

Data in animals are sparse. When rats were administered up to 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days, no adverse effects were observed on the gastrointestinal system (Stoltz et al. 1986).

Musculoskeletal Effects. Data are sparse regarding the muscular effects in humans. Histopathological examination of muscle biopsies from two cases revealed myopathic changes associated with thallium poisoning (Limos et al. 1982). Fiber necrosis, central nucleation, and fiber splitting were reported. No data were provided on exposure levels.

Hepatic Effects. Case reports in humans demonstrate that the liver is susceptible to thallium toxicity. Centrilobular necrosis with fatty changes has been reported (Cavanagh et al. 1974; Davis et al. 1981). It was not clear whether the effects observed were a result of a direct effect on the liver or secondary to other effects. Serum glutamic oxaloacetic transaminase, serum pyruvic oxaloacetic transaminase, and alkaline phosphatase levels were elevated.

Data in animals are sparse. No adverse effects were observed on the liver when rats were administered 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days (Stoltz et al. 1986).

Renal Effects. Human case studies report that thallium can affect the kidneys (Cavanagh et al. 1974; Gastel 1978). Histological examination of the kidneys in one case revealed extensive recent necrosis of the cortex (Cavanagh et al. 1974). The authors reported that the effects were probably the result of infarction. Renal function is also impaired following thallium exposure. Diminished creatinine clearance, a raised blood urea, and proteinuria are common (Cavanagh et al. 1974).

In animals, there were no adverse renal effects in rats administered 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days (Stoltz et al. 1986).

Dermal/Ocular Effects. Ingestion of thallium has been associated with hair loss in humans. Loss can occur as early as 8 days after exposure (Grunfeld and Hinostroza 1964). Several cases have reported loss of body hair, full beard, and scalp hair (Grunfeld and Hinostroza 1964). In other instances, body and pubic hair have been spared (Gastel 1978; Grunfeld and Hinostroza 1964). Hair loss is temporary, and no local skin changes have been reported.

In animals, hair loss was observed in rats exposed to $\geq$ 1.2 mg thallium/kg/day (as thallium acetate or thallium oxide) for 15 weeks (Downs et al. 1960). Histological examination revealed that 1.8 mg thallium/kg/day (as thallium oxide) caused atrophy of the hair follicles and there was a decrease in size of sebaceous glands.

No studies were located regarding the direct effects of thallium on the eyes of humans. However, thallium caused damage to certain cranial nerves which lead to eye disturbances. Decreased visual acuity due to bilateral central scotomas and progressive optic atrophy have been associated with optic.

nerve damage (Moeschlin 1980). Also, there are degenerative changes in cranial nerves which innervate the extraocular muscles. Ptosis and disconjugate eye movements are common manifestations of eye disturbances (Cavanagh et al. 1974; Davis et al. 1981).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to thallium.

2.2.2.4 Neurological Effects

Human case studies revealed that the nervous system is susceptible *to* thallium toxicity after acute oral exposure at high doses. Severe cranial and peripheral neuropathy were reported following ingestion of a single estimated dose of 54-110 mg thallium/kg (as thallium nitrate), which was also lethal (Davis et al. 1981). Examination of nerves obtained on days 7 and 9 demonstrated axonal degeneration with secondary myelin loss. Axons were swollen and contained distended mitochondria and vacuoles (Davis et al. 1981). Distal peripheral axonal degeneration with preserved proximal fibers was observed in another case in which death occurred; however, reliable exposure data (dose and duration) were not reported (Cavanagh et al. 1974; Roby et al. 1984).

No studies were located regarding neurological effects in humans after intermediate oral exposure to thallium. Peripheral neuropathy was reported in 189 cases of thallium poisoning in China from 1960 to 1977 (Dai-xing and Ding-nan 1985). Thallium was detected in urine samples of the exposed group at higher levels (0.6-2.25 mg/L, P>0.0l) than in the unexposed individuals (0.14-0.31 mg/L). Similarly, levels in the hair were 21.8-31.5 mg/kg (P>0.0l) compared to 5.80-11.3 mg/kg in the unexposed group. The authors attributed exposure to ingestion of cabbage grown in thallium-contaminated gardens. No other details were provided.

In animals, structural and functional changes were observed in peripheral nerves in rats at 240 days, following treatment with 1.4 mg thallium/kg/day (as thallium sulfate), but effects were not found at 40 days (Manzo et al. 1983). There was a 44% decrease in the amplitude of motor action potential (MAP), a 30% decrease in the amplitude of the sensory action potential, and a 25% increase in MAP latency. Wallerian degeneration of scattered fibers and vacuolization and delamination of the myelin sheath of 10% of the fibers were reported in 50% of the test animals (Manzo et al. 1983). Ultrastructural examination of fibers with Wallerian degeneration showed complete destruction of the axon, with mitochondrial degeneration, neurofilamentous clustering, and evidence of extensive lysosomal activity

(Manzo et al. 1983). However, when rats were administered up to 0.20 mg thallium/kg (as thallium sulfate) by gavage for 90 days, light microscopic examination did not reveal neurological effects (Stoltz et al. 1986). No electron microscopic evaluations were performed in this study.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.5 Developmental Effects

Thallium can cross the human placenta; however, data are limited regarding the developmental effects. A retrospective study was conducted to assess the teratogenic potential of thallium in 297 children born to mothers living in the vicinity of a cement plant in Germany that discharged thallium into the atmosphere (Dolgner et al. 1983). Maternal intake was presumed to have been due to consumption of home-grown vegetables and fruits contaminated with thallium. Levels of thallium in 24-hour urine samples were determined to assess the degree of past thallium exposure, s!nce there were no relaible data on exposure during pregnancy. Maternal urinary levels were 0.6-2.2 μg/L compared to less than 1 μg/L for the general population. In the absence of reliable exposure data, no firm conclusions can be made about the developmental toxicity of thallium in humans. The incidence of congenital malformations and anomalies in the exposed group did not exceed the number of expected birth defects in the general population.

Data in animals are sparse. Rats were administered 0, 0.08, 0.4 or 1.6 mg thallium/kg/day as thallium sulfate on days 6-9 of gestation to determine the effect of prenatal exposure on learning ability. The study involved a conditioning program in which lever pressing was rewarded with a food pellet (Bornhausen and Hagen 1984). Rats showed impairment of learning after prenatal exposure at doses of 0.08 mg thallium/kg/day or greater but no dose-response relationship was observed. The LOAEL of 0.08 mg thallium/kg/day is recorded in Table 2-l and plotted in Figure 2-1. While performance deficits suggest impairment of brain function, no structural alterations were reported at any dose tested.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to thallium.

In animals, abnormalities in testicular morphology, function, or biochemistry were evident in rats which received an average daily intake of 0.27 mg thallium/day (approximately 0.7 mg/thallium/kg/day, as thallium sulfate) during a 60-day treatment period (Formigli et al. 1986). Males exposed to thallium for 60 days exhibited epididymal sperm with increased number of immature cells and significantly reduced motility. Histological

examination revealed disarrangement of the tubular epithelium. In addition, Sertoli cells showed cytoplasmic vacuolization and distension of the smooth endoplasmic reticulum. Testicular ,β-glucuronidase activity was reduced significantly ($p<0.0l$) in the thallium-treated males, but plasma testosterone levels were unaffected. Abnormalities in testicular morphology, function, or biochemistry were not observed in rats exposed for 30 days (Formigli et al. 1986); however, thallium levels were not measured in this dose group. The LOAEL of 0.7 mg thallium/kg/day is recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to thallium. However, thallium caused dominant lethal mutations in rats after oral exposure at a dose of 0.04 pg thallium/kg/day as thallium carbonate (Zasukhina et al. 1983). Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans or animals after oral exposure to thallium.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to thallium.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular effects in humans or animals after dermal exposure to thallium.

No studies were located regarding the following health effects in humans or animals after dermal exposure to thallium:

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to thallium.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No quantitative studies were located regarding absorption in humans or animals after inhalation exposure to thallium.

2.3.1.2 Oral Exposure

Limited data show direct gastrointestinal tract absorption in humans. Indirect oral exposure may also occur through breathing contaminated airborne dust. The mucociliary clearance mechanism moves most particulates with a mass median aerodynamic diameter (MMAD) of l-5 μm out of the lungs and into the gastrointestinal tract. Larger particles (greater than 5 μm) impacting in the nasopharyngeal region would also be eventually ingested.

Limited data were located regarding absorption in humans after oral exposure to thallium. Following oral administration of a single tracer dose of 500 microcuries (μCi) of thalliumz^{204} (as thallium nitrate) and 45 mg daily for 5 days of thallium sulfate in a patient with terminal osteogenic sarcoma, 0.4% of the administered radioactivity was recovered in feces and 11% in urine during a 72-hour collection period. In 5.5 days, the patient had excreted 15.3% of the administered dose in the urine. These data suggest that most of the thallium was absorbed (Barclay et al. 1953).

Animal studies suggest that thallium is completely absorbed when ingested. Lie et al. (1960) administered a single trace dose of thallium^{204} (as thallium nitrate) orally to rats at a dose of 0.767 mg thallium/kg. The body burden of thallium^{204}, as percent dose, decreased with a single exponential function which extrapolated to 100% at zero time. The authors, therefore, concluded that thallium is completely absorbed from the gastrointestinal tract.

2.3.1.3 Dermal Exposure

No reliable quantitative studies were located regarding absorption in humans or animals after dermal exposure to thallium.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to thallium.

2.3.2.2 Oral Exposure

There is little information on distribution of thallium in humans. Analysis of human tissues indicate that thallium is distributed throughout the body. A female cancer patient was administered a tracer dose of 1.8 mg thallium^{204} (as thallium nitrate) orally and thereafter an oral dose of 36 mg thallium/kg (as thallium sulfate) (Barclay et al. 1953). The thallium tissue levels, reported as percent of average body distribution per gram, were highest in scalp hair (420%), renal papilla (354%), renal cortex (268%), heart (236%), bone tumor (233%) and spleen (200%). Lower levels were found in the brain (45%-70%).

In animals distribution of thallium from the blood stream is rapid and widespread. Thallium was found to accumulate in the kidney (17 μg/g) followed by the heart (7 μg/g), brain (6 μg/g), bone (8 μg/g), skin (3 μg/g), and blood (0.67 μg/g) in rats administered approximately 1.4 mg thallium/kg (as thallium sulfate) in drinking water (Manzo et al. 1983). In male rats administered 740 μg thallium/kg (as thallium sulfate) in drinking water, 6.3 μg thallium/g tissue was found in the testes compared to less than 0.08 μg thallium/g tissue in untreated controls (Formigli et al. 1986). In rats fed 2.3-3.0 mg thallium/kg (as thallium acetate or thallic oxide), the largest amount of thallium was detected in the kidney (24-31 μg/g wet tissue) with lower levels in the liver (13-16 μg thallium/g) and bone (19 μg thallium/g). Smaller amounts (5-9 μg/g) were found in the brain, lung, and spleen (Downs et al. 1960).

Lie et al. (1960) studied the tissue distribution of thallium in rats administered a single tracer dose of thallium^{204} (as thallium nitrate) orally at a dose of 0.76 mg thallium/kg. Approximately 7 days post-treatment, the highest level of thallium was detected in kidneys (4.7% of the body burden per gram of tissue). Lesser amounts were detected in salivary glands (1.08%), testes (0.88%), muscle (0.79%), bone (0.74%), gastrointestinal tract (0.62%), spleen (0.56%), heart (0.54%), liver (0.52%), respiratory system (0.47%), hair (0.37%), skin (0.37%), and brain (0.27%). The biological half-life for thallium was 3.3 days.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to thallium.

2.3.2.4 Other Exposure

Parenteral studies also indicate extensive tissue distribution of thallium. Adult white mice dosed intraperitoneally with thallium^{204} at a dose of 4 mg thallium/kg as thallous sulfate showed high thallium concentrations in bone tissue, kidney (particularly in the medulla), pancreas, and large intestine approximately 1 hour after dosing (Andre et al. 1960). Thallium levels in bone decreased after 10 days or more, but thallium was still detectable 28 days posttreatment. Parenteral administration of thallium resulted in peak concentrations in the brain, spinal cord, spleen, liver, and kidney. Half-lives for depletion from several tissues in rats were estimated at 2.7 days for the brain to 6.0 days for the spleen (Ducket et al. 1983).

Thallium^{204} as thallous sulfate has been shown to cross the placenta and locate in the fetus within 15 minutes following intraperitoneal injection (50 μCi, specific activity not stated) (Olsen and Jonsen 1982) and 32 minutes after intravenous administration (0.16-5.2 mg thallium/min/kg) (Rade et al. 1982). The concentration of thallium in the fetus was substantially lower than that in maternal tissues by both routes of administration.

2.3.3 Metabolism

No studies were located regarding metabolism of thallium in humans or animals.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

In humans, thallium urinary levels ranging from ≤50 μg/L to 236 μg/L were found in 39 workers exposed to thallium in a magnesium seawater battery plant (Marcus 1985). Workers employed in a cement factory showed urinary levels between 0.3-6.3 μg thallium/g creatinine (Schaller et al. 1980).

No studies were located regarding excretion in animals after inhalation exposure to thallium.

2.3.4.2 Oral Exposure

In humans, 15.3% of the administered radioactivity was detected in urine 5.5 days postdosing and 0.4% in feces in 3 days (Barclay et al. 1953). An excretion half-life of 21.7 days was estimated (EPA 1980a).

In rats administered 10 mg thallium/kg (as thallium sulfate) by gavage, 32% of the administered dose was eliminated in feces and 21% in urine (Lehman and Favari 1985) by 8 days postdosing.

Lie et al. (1960) administered a single tracer dose of thallium^{204} (as thallium nitrate) orally to rats at a dose of 767 μg thallium/kg. The ratio of fecal to urinary excretion of thallium increased from about 2 to 5 between days 2 and 16.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to thallium.

2.4 RELEVANCE TO PUBLIC HEALTH

As discussed in Section 2.2, estimates of levels of exposure to thallium posing minimal risk to humans (MRLs) were to have been made, where data were believed reliable, for the most sensitive noncancer effect for each route and exposure duration. Because no data were located on effects of acute-duration or intermediate-duration inhalation exposure to thallium in humans or animals, and because available information concerning effects of chronic-duration inhalation exposure in humans was not quantitative, no inhalation MRLs were derived. Limited data on human and animal acute oral exposure to thallium suggests that the nervous system may be the target organ, but reliable doseresponse data were not available (Bornhausen and Hagen 1984; Cavanagh et al. 1974; Davis et al. 1981; Roby et al. 1984). Data on effects of intermediateduration oral exposure in animals do not reliably identify the most sensitive target organ or the threshold for adverse effects. No data on effects of chronic-duration oral exposure to thallium were located. Therefore, acuteduration, intermediate-duration, and chronic-duration oral MRLs were not derived. Acute-duration, intermediate-duration, and chronic-duration dermal MRLs were not derived for thallium due to the lack of an appropriate methodology for the development of dermal MRLs.

Inhalation and oral studies in humans and oral studies in animals demonstrate that thallium compounds such as thallium oxide and thallium sulfate can be lethal at relatively low doses (about 1 gram). However, these doses are high compared to exposure levels that would be expected from thallium at NPL sites. Thallium compounds can affect the respiratory, cardiovascular, and gastrointestinal systems, liver, kidneys, and the male reproductive system. Temporary hair loss has also been associated with ingestion of thallium in humans. Thallium compounds can also affect the peripheral and central nervous systems. The rate of congenital malformations among children of mothers exposed to thallium did not exceed the rate expected for the general population. No studies have been located regarding thallium exposure and development of cancer in humans or animals.

Death. Thallium was lethal in humans following acute oral exposure at doses of 54-110 mg thallium/kg of body weight as thallium sulfate (Davis et al. 1981). The estimated lethal dose for the average adult for thallium is 1 g (approximately 14-15 mg/kg) (Gosselin et al. 1984). No studies were

located concerning intermediate and chronic exposures in humans by oral, inhalation, or dermal route.

Death has been reported in animals exposed to low doses for brief periods. The lowest doses showing lethality ranged from 5 to 30 mg thallium/kg for several species (Downs et al. 1960). Exposure to low doses of thallium (1.4 mg thallium/kg/day, as thallium sulfate) for longer durations (40-240 days) can also cause death (Manzo et al. 1983). No studies were located on chronic oral exposures or inhalation or dermal exposure for any duration in animals.

Mortality data of exposed humans and results of studies in several animal species suggest that humans are at risk of death from exposure to high concentrations of thallium. Neurological damage was a consistent feature among humans who died following thallium exposure. However, death was regularly attributed to cardiac or respiratory failure. Ingestion of lethal doses readily resulted in cardiac and respiratory depression which generally overshadowed the characteristic manifestation of neuropathy.

Systemic Effects.

Respiratory Effects. Human case studies reported respiratory effects following acute oral exposure. Alveolar damage, hyaline membrane formation, and pulmonary edema have been reported (Davis et al. 1981; Roby et al. 1984). It has been suggested that thallium may have a direct effect on pulmonary epithelial and endothelial cells. Alveolar damage suggests that respiratory effects may be an area of concern following thallium exposure.

Cardiovascular Effects. Studies in humans demonstrated cardiovascular effects following oral exposure to thallium. Myocardial damage and electrocardiographic changes were observed (Davis et al. 1981; Roby et al. 1984). Following a single oral dose (56 mg thallium/kg as thallium sulfate), rabbits showed electromyographic abnormalities without changes in the myocardium (Grunfeld et al. 1963). The precise mechanism of thallium-induced cardiovascular injury is not clear. However, parenteral injection of thallium causes a direct effect on the cardiovascular system. Intravenously applied thallium caused a significant dose-dependent decrease in mean arterial pressure and heart rate, the maximum fall in blood pressure occurring within 3-5 minutes (Lameijer and van Zwieten 1976). The authors presumed a direct influence of thallium on the sinus node. Based on human and animal data, cardiovascular effects may be an area of concern following thallium exposure.

Musculoskeletal Effects. Very little information was found on the effects of thallium on muscles. Myopathic changes included fiber necrosis, fiber splitting, and central nucleation (Limos et al. 1982). It should be noted that these effects occurred in cases involving axon degeneration of the nerve. It is, therefore, not clear if the effects observed were due to a

direct toxic effect on muscle or were the result of rapid atrophy of the paralyzed muscle secondary to severe axonal degeneration.

Hepatic Effects. Oral studies in humans suggest that the liver is susceptible to thallium toxicity. Necrosis, fatty changes, and altered serum enzyme levels were reported. No studies were located demonstrating that thallium causes liver toxicity in humans or animals by inhalation or dermal exposure. Parenteral injection in animals has been observed to cause liver effects. Single intraperitoneal doses of 33-132 mg thallium/kg/day (as thallium chloride) were associated with ultrastructural.and biochemical changes in the liver consistent with injury to the membranes of subcellular organelles in the hepatocytes (Woods and Fowler 1986). In rats administered subcutaneous injections of thallium (7.8-15.5 mg thallium/kg, as thallium acetate), there were degenerative changes in mitochondria and increased glycogen deposits (Herman and Bensch 1967). The precise mechanism for liver toxicity is not known; however, thallium may combine with the sulfhydryl groups of mitochondria, interfering with oxidative phosphorylation. Because these effects occurred under conditions not likely to result in human exposure, it is not clear whether similar effects on subcellular organelles will occur in humans following relevant routes of exposure.

Renal Effects. Very little information was found on the effects of thallium on the kidney in humans. Tubular necrosis has been reported in some cases following ingestion. However, these effects were reportedly due to infarction rather than a direct affect on kidney tissue. Thallium did not cause injury to the kidneys of rats following oral exposure. No studies were located regarding renal effects in humans or animals after inhalation or dermal exposure to thallium. Parenteral exposure studies in animals demonstrate that thallium can affect the kidney following subcutaneous administration. Accumulation of debris in the lumen of the convoluted tubules and progressive changes in the mitochondria of the tubule cell were observed (Herman and Bensch 1967). By 12 weeks, many cup-shaped mitochondria were present, and, in some mitochondria, partial loss of cristae was evident. This route of exposure is not likely to result in significant human exposure. Therefore, it is not clear if similar effects will occur in humans by relevant exposure routes.

Dermal/Ocular Effects. Hair loss has been reported in humans following exposure to thallium. However, the effect is reversible. Animal studies confirm human findings. However, these studies should be interpreted with caution since rodent hair does not continue to grow as does cycling human head hair. Animal studies suggest that thallium affects hair follicles directly or that hair loss is the result of effects of thallium on the sympathetic nervous system (Carson et al. 1986). No direct ocular effects of thallium have been reported. However defects of the oculomotor nerve, ocular muscle, and ptosis have been reported (Cavanagh et al. 1974; Davis et al. 1981).

Immunological Effects. No studies were located regarding the immunological effects in humans or animals after inhalation, oral, or dermal exposure to thallium. In the absence of histopathologic evaluation and direct tests of immune functions, the potential for thallium to affect the immune system in humans cannot be determined.

Neurological Effects. Human case reports demonstrated that thallium caused disturbances of the peripheral and central nervous systems following acute oral exposure. Ataxia, tremor, and multiple cranial palsies have been reported following oral exposure to thallium as has numbness of toes and fingers, "burning feet" phenomenon, and muscle cramps. Convulsions and death can also occur. While thallium characteristically produces distal, predominantly sensory neuropathy in humans, structural alterations underlying the changes have not been firmly established. Histological evaluations have shown axonal degeneration and myelin loss.

The mechanism by which thallium exerts its effects is not clear. However, parenteral studies in animals suggest that the effects observed may be due in part to the depletion or inhibition of critical enzyme systems. There was depletion of succinic dehydrogenase and guanine deaminase in the rat cerebrum after intraperitoneal injection of 5 mg thallium/kg (as thallium acetate) (Hasan et al. 1977a, 1977b) as well as depletion of monoamine oxidase, acid phosphatase, and cathepsin activity (Hasan et al. 1977b). Adenosine triphosphatase and adenosine deaminase activities were unaffected. At the same dose, sequestrated axons were observed in the hypothalamus, and there were increased Golgi zones and electron dense bodies in the hypothalamus and hippocampus (Hasan et al. 1977a, 1978). Also, the protein content of the corpus striatum was significantly increased (Hasan et al. 1977b). Furthermore, there was a significant increase in the spontaneous discharge rate of cerebellar Purkinje neurons of rats administered intraperitoneal injections of 5 mg thallium/kg/day (as thallium acetate) (Marwaha et al. 1980).

The effects in the hypothalamus, hippocampus, and corpus striatum are consistent with a reported differential distribution of thallium in the brain. In rats that received a single intraperitoneal injection of 13-39 mg thallium/kg/day (as thallium sulfate), the highest thallium concentrations were found in the hypothalamus and the lowest in the cortex (Rios et al. 1989). It was also noted that thallium accumulated more rapidly in the hypothalamus than in other brain regions (Rios et al. 1989). Differential distribution of thallium suggests that some areas of the brain may be affected more severely than others. Brown et al. (1985) provided data suggesting a dose-related selective toxicity between brain regions. Lipid peroxidation rates and P-galactosidase activity were increased in the cerebellum and brainstem following intraperitoneal injections of 3 mg thallium/kg/day (as thallium acetate). However, when 6 mg thallium/kg/day (as thallium acetate) were administered, lipid peroxidation rates were increased in the cerebellum,

brainstem, striatum, and cortex. β-Galactosidase activity was also increased in the cerebellum, cortex, hippocampus, and brainstem.

Developmental Effects. A retrospective study was conducted to compare the incidence of congenital abnormalities in children born to mothers who had been exposed to thallium during pregnancy (Dolgner et al. 1983). The number of anomalies in the exposed group did not exceed the number of expected birth defects for the general population.

Existing evidence suggests that thallium causes alterations in the functional competence of the nervous system. There was impairment of learning in rats prenatally exposed to 0.08 mg thallium/kg/day or greater during gestation but no dose-response relationship was found (Bornhausen and Hagen 1984). No structural alterations in the brain were reported in this study. It should be noted that these effects were reported to occur at dose levels below those at which other neurological effects (e.g. structural and functional alterations of peripheral nerves) have been observed. While existing data suggest, in part, that thallium may be a potential developmental neurotoxicant, additional testing batteries are needed. These studies would be useful in determining the full spectrum of behavioral alterations and for assessing the relative importance of this finding and human health risk.

In animals, cultured rat embryos exposed to thallium at concentrations of 10, 30, or 100 μg/mL showed dose-related growth retardation at all levels, suggesting embryotoxic effects (Anschutz et al. 1981). Complete growth inhibition was reported at 100 μg/mL. At 3 μg/mL (lowest dose tested), the treated and control embryos did not differ significantly. Administration by intraperitoneal injection to pregnant rats at a dose of 2.0 mg thallium/kg/day (as thallium sulfate) during gestation days 8-10 resulted in reduced fetal body weights, hydronephrosis, and the absence of vertebral bodies (Gibson and Becker 1970). While these data suggest that thallium is a developmental toxicant, the evidence is limited and does not allow a conclusive decision about the human health implications.

Reproductive Effects. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to thallium.

In rats, thallium administered in the drinking water at 0.74 mg/kg/day (as thallium sulfate) for 60 days caused decreased sperm motility, inhibition of β-glucuronidase activity and histopathological alterations of the testes (Formigli et al. 1986). Mutagenicity studies employing dominant lethal assays in mice provide some evidence of the potential reproductive effects of thallium (see Genotoxic Effects). There was increased embryolethality following oral exposure. While there are no human data regarding the reproductive effects of thallium, animal data suggest that the male reproductive system may be susceptible to the toxic action of thallium.

Genotoxic Effects. No studies were located regarding the genotoxic effects of thallium in humans. Results of animal and bacterial assays suggest thallium is genotoxic. Thallium induced dominant lethals in male rats *in vivo*. The overall embryonic mortality increased at doses of 0.04 μg thallium/kg/day or greater as thallium carbonate (Zasukhina et al. 1983). *In vitro* DNA damage tests employing rat embryo cells were positive (Table 2-2). Thallium enhanced viral-induced transformations in Syrian hamster embryo cells (Table 2-2). The significance of this response in the overall assessment of the mutagenic potential of thallium is reduced since this end point is not well understood. *In vitro* tests employing bacterial assays were positive (Table 2-2). Existing data suggest that genotoxicity may be an area of concern for thallium exposure in humans.

Cancer. No studies were located regarding carcinogenicity in humans or animals after inhalation, oral, or dermal exposure to thallium. In the absence of epidemiological studies or long-term animal bioassays, the potential for thallium to cause cancer in humans cannot be determined.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites 'in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to thallium are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or

TABLE 2-2. Genotoxicity of Thallium In Vitro

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms:					
Bacillus subtilis	$TlNO_3$	DNA damage/repair	Not tested	+	Kanematsu et al. 1980
Mammalian cells:					
CBA mouse embryo cells; Rat embryo fibroblast	Tl_2CO_3	DNA damage/repair	Not tested	+	Zasukhina et al. 1981, 1983
Syrian hamster embryo cells/SA7	$TlC_2H_3O_2$	Enhancement of viral transformation	Not tested	+	Casto et al. 1979

+ = positive result; $TlC_2H_3O_2$ = thallium acetate; Tl_2CO_3 = thallium carbonate; $TlNO_3$ = thallium nitrate

cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by thallium are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose,. or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Thallium

Thallium levels in urine, blood, and hair have been used as indications of exposure to thallium. The determination of thallium in urine has been the most widely used of biological indicators of thallium exposure. Typical thallium levels in unexposed individuals are below 1 μg/g creatinine (Schaller et al. 1980). Because of the quantitative renal excretion of creatinine and its rather consistent rate of production, creatinine constitutes an endogenous substance suitable for clearance testing. Higher values have been detected in areas where thallium is used or emitted. Urinary levels in cement workers ranged between <0.3 and 6.3 μg thallium/g creatinine (Schaller et al. 1980). A mean urinary thallium level of 76 μg/L was reported in a population living in the vicinity of a cement production plant (Brockhaus et al. 1981). Apostoli et al. (1988) reported mean urinary thallium levels of 0.38 and 0.33 μg/L in two groups of workers employed in two cement production plants and two cast iron foundries. Unexposed subjects showed lower mean levels CO.22 μg/L). Urinary levels in toxic cases may be 3,100 μg/L (Gastel 1978) and ≥ 5,000 μg/L in fatal cases (Roby et al. 1984).

While thallium can be detected in blood, it is cleared from the blood very rapidly. In one case in which a patient with osteogenic sarcoma was administered oral doses of 1.8 mg thallium^{204} (as thallium nitrate) (approximately 4 ng thallium/kg), 3% of the administered dose was detected in blood within 2 hours post-treatment while 1.6% was detected within 24 hours (Barclay et al. 1953). Since measurements of blood thallium reflect only recent exposures, it is not generally considered to be a reliable means of monitoring human populations for exposure to thallium.
Thallium is excreted in hair and measurement of hair levels may be an indicator of thallium exposure. The normal concentration range of thallium in human hair is approximately 5-10 ng/g. Seven percent of the administered

radioactivity was detected in scalp hair of a cancer patient who had been administered 1.8 mg thallium^{204} (as thallium nitrate) (Barclay et al. 1953). It should be noted that thallium may adsorb to hair and become incorporated into the hair matrix, making it difficult to distinguish between thallium incorporated into the hair from the body burden and external deposition of thallium.

2.5.2 Biomarkers Used to Characterize Effects Caused by Thallium

Neurological damage is the primary toxic effect associated with exposure to thallium. Various effects on the nervous system of people exposed to thallium can be detected by monitoring the incidence of signs and symptoms such as ataxia, lethargy, painful extremities and numbness of toes and fingers. Electromyographic measurements of nerve conduction velocity and amplitude can be monitored to detect early signs of neurotoxicity. However, since neurological damage occurs with other compounds, these tests are not specific for thallium exposure. Also, thallium accumulates in hair. Dark pigmentation of the hair roots and hair loss are common diagnostic features (Gastel 1978). Depletion and inhibition of several enzymes in the brain have been associated with thallium exposure. Hasan et al. (1977a, 1977b) reported depletion of succinic dehydrogenase and guanine deaminase in the rat cerebrum after parenteral administration of 5 mg thallium/kg (as thallium acetate) as well as depletion of monoamine oxidase, acid phosphatase, and cathepsin activity (Hasan et al. 1977b). However, the usefulness of the data is reduced since the procedure is highly invasive.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Studies have shown that trace metals can influence the toxicity of thallium. Potassium has been shown to increase renal excretion of thallium (Gehring and Hammond 1967; Lund 1956a), decrease the degenerative effects of thallium on epiphysial cartilage in mouse limb bud cultures, decrease placental transport of thallium (Sabbioni et al. 1980), and increase the lethality of thallium in animals (Gehring and Hammond 1967). Other interactions can influence thallium toxicity through accelerated elimination.
Potent diuretics such as furosemide enhanced the urinary excretion of thallium in rats (Lameijer and van Zwieten 1977a, 1978; Lehman and Favari 1985). Oral administration of activated charcoal and Prussian blue accelerated the elimination of orally administered thallium in rats (Lehman and Favari 1985; Lund 1956b). These agents adsorb thallium in the gastrointestinal tract, and are themselves unabsorbed, thus reducing gastrointestinal absorption of thallium.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Limited toxicity data suggest there are certain subgroups of the general population which may be more susceptible to thallium exposure than other

groups. People with preexisting neurological disease, kidney, and liver damage may be at risk.

Neurological injury is a major effect associated with exposure to thallium in humans (Cavanagh et al. 1974; Davis et al. 1981; Ludolph et al. 1986; Roby et al. 1984). In people with neurological damage of other etiology, thallium may add to or magnify the effect on the nervous system.

Other subgroups that are potentially more sensitive to thallium exposure are individuals with liver and kidney disease. In humans, necrosis of the liver with fatty changes and elevated serum enzymes have been observed (Cavanagh et al. 1974; Davis et al. 1981). Individuals with preexisting liver disease may sustain additional liver damage at lower than usual dose levels producing liver injury. Renal damage has also been associated with thallium exposure. Tubular necrosis and renal failure may occur (Cavanagh et al. 1974; Gastel 1978). In people with renal disease, there may be decreased capacity to excrete thallium. Also, individuals with potassium deficiency may be at risk since potassium has been shown to increase renal excretion of thallium (Gehring and Hammond 1967; Lund 1956a).

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to thallium. This section is intended to inform the public of existing clinical practice and the status of research concerning such methods. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to thallium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Exposure to thallium may occur by inhalation, ingestion, or dermal absorption, but ingestion appears to be the predominant route of exposure for humans (see Chapter 5). Thallium ingestion causes acute gastrointestinal symptoms and multiple systemic effects, including respiratory, neurological, cardiovascular, hepatic, and renal damage and alopecia (see Section 2.2).

Procedures that have been suggested following acute, high-level exposure to thallium consist of measures to reduce or eliminate further absorption. Following inhalation exposure, these measures are removal of the victim and administration of high-flow, humidified oxygen (Bronstein and Currance 1988; Stutz and Janusz 1988). Following dermal exposure, contaminated clothing is removed and skin thoroughly washed. Following ocular exposure, the eyes are. flushed (Bronstein and Currance 1988; Stutz and Janusz 1988). Treatment for acute, high-level oral exposure to thallium is designed to remove thallium from the gastrointestinal tract as quickly as possible, to prevent absorption of any remaining thallium and to increase excretion of thallium (Proctor et al. 1988). However, some of the methods recommended to accomplish these aims

are controversial. Emptying the stomach by gastric lavage or administration of syrup of ipecac has been suggested within the first few hours following exposure, if the victim is alert and has an intact gag reflex. Following gastric emptying, it has been suggested that serial doses of activated charcoal be administered to adsorb residual and rescreted thallium, and a mild cathartic also used to accelerate fecal excretion (Ellenhorn and Barceloux 1988; Stutz and Janusz 1988).

Prussian blue (potassium ferric ferrocyanide) binds with thallium in the intestine and neither the Prussian blue nor its complex with thallium is absorbed systemically. The oral or duodenal administration of this compound effectively prevents absorption and increases fecal excretion (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Proctor et al. 1988). However, this use of Prussian blue has not been approved by the U.S. Food and Drug Administration (FDA), but is approved for use in Europe (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990).

Oral administration of potassium chloride in large doses has been recommended in victims with intact renal function to enhance thallium clearance from tissue storage sites and increase renal excretion. However, there may be a transient worsening of symptoms following this treatment due to the redistribution of thallium from tissue stores into the serum, and there is some controversy concerning the efficacy of potassium chloride administration (Ellenhorn and Barceloux 1988; Proctor et al. 1988).

Hemodialysis or hemoperfusion may be beneficial in cases of severe poisoning. Hemodialysis has been found to be quite effective in reducing thallium concentrations in the blood in some cases and only minimally effective in others. Hemoperfusion may give better results than hemodialysis. These procedures may be used in cases where renal failure and paralytic bowel render other treatments ineffective (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Proctor et al. 1988).

It is unlikely that populations surrounding hazardous waste sites would be exposed to thallium at levels that would result in symptoms requiring any of these measures. Supportive follow-up medical care is likely to be the only treatment for long-term neurological effects of thallium exposure. Additional details regarding the treatment of acute, high-level thallium poisoning may be obtained from the cited references.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of thallium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP),

is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of thallium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Thallium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to thallium are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of thallium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

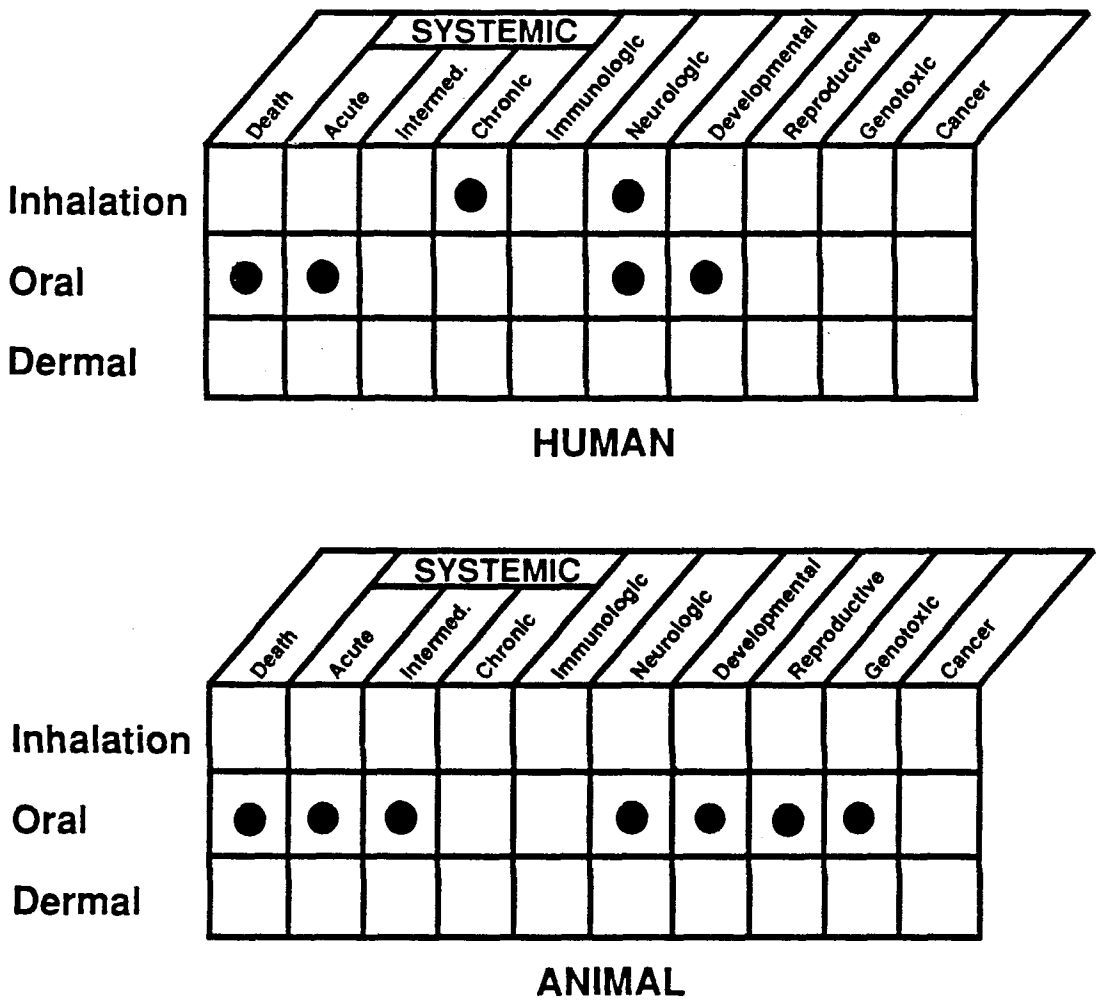
Most of the information concerning the health effects of thallium in humans is found in case reports of accidental or intentional acute ingestion of thallium. No information was found on effects after intermediate and chronic exposures. Reports of chronic inhalation exposure in the workplace exist; however, these are limited to sites outside the United States. No information was found on effects of thallium after acute and intermediate inhalation exposure or on effects after acute, intermediate, or chronic dermal exposures.

In animals, information exists on acute and intermediate oral exposures to thallium in several species. However, no studies were located regarding chronic oral exposures and on effects following acute, intermediate, and chronic inhalation or dermal exposures.

2.9.2 Data Needs

Acute-Duration Exposure. No studies were found on the adverse effects of acute-duration inhalation exposure in humans or animals. Inhalation is not likely to lead to significant exposure of the general population near hazardous waste sites. Thallium and compounds are not volatile and are subject to precipitation washout. The available information on effects of acute-duration exposure to thallium and compounds in humans is limited to case reports that indicate neurological, gastrointestinal, lung, liver, kidney, and heart effects following oral exposure (Cavanagh et al. 1976; Davis et al. 1982; deGroot et al. 1985; Roby et al. 1984). Some studies did not report

FIGURE 2-2. Existing Information on Health Effects of Thallium



reliable exposure data. Estimated dose levels were provided in other cases,but these doses far exceeded those expected to occur in the environment. Human exposure data were not sufficient to derive an acute oral MEL since reliable NOAEL and LOAEL values could not be determined. Since thallium binds tightly to soil particles, dermal contact may be significant, particularly in children who may ingest thallium-contaminated soil. Additional dermal studies would be useful to determine if soil-bound thallium is bioavailable. Acute oral data in animals demonstrated lethal (Downs et al. 1960) and developmental neurological effects (Bornhausen and Hagen 1984) of thallium, but data were not sufficient to derive an acute oral MEL. Additional studies in other species would be useful to identify the most sensitive effect and a doseresponse relationship following acute oral exposure to thallium. Information was not available to derive acute inhalation and dermal MRLs.

Intermediate-Duration Exposure. No studies are available on adverse health effects of intermediate-duration inhalation exposure in humans to thallium and compounds. Since thallium is not volatile, this route may not be a major concern to humans exposed near hazardous waste sites. No information is available on the effects of intermediate-duration inhalation exposure in animals. Limited oral studies in animals demonstrated neurological and reproductive effects (Formigli et al. 1986; Manzo et al. 1983). Data from these studies were not sufficient to derive an intermediate MEL. These studies employed one dose level, precluding dose-response evaluations. Additional oral studies employing other animal species and additional dose levels would be useful in identifying susceptible organs and intermediate-duration threshold for effects. There are no data on intermediate-duration exposure in humans or animals and toxicokinetics data are lacking. Additional studies would be useful in determining potential target organs and critical effects levels.

Chronic-Duration Exposure and Cancer. A few studies are available evaluating the effects on humans chronically exposed to thallium in workplace air (Ludolph et al. 1986; Marcus 1985). One study demonstrated that the nervous system is adversely affected by inhalation exposure (Ludolph et al. 1986); however, no exposure data are provided. In the absence of quantitative exposure data, available studies are not sufficient to derive a chronic-duration MRL. Because thallium is not volatile and is subject to precipitation washout from the atmosphere, exposure by this route may not be a major concern at hazardous waste sites. No studies are available on the effects of chronic oral or dermal exposure in humans or in animals by any route of exposure. Because long-term environmental exposure to thallium can occur in humans at hazardous waste sites, oral chronic animal studies of various species at several dose levels would be useful in identifying susceptible target organs and defining chronic thresholds.

No studies are available on the carcinogenic effects of inhalation, oral, or dermal exposure in humans or animals to thallium and compounds. Considering the positive results of the genotoxicity assays (Casto et al.

1979; Kanematsu et al. 1980; Zasukhina et al. 1981, 1983), studies to assess the carcinogenic potential would be useful. There are some populations in the vicinity of hazardous waste sites that might be exposed to low doses of thallium for long periods of time.

Genotoxicity. No information was available on the genotoxic effects of thallium and compounds in humans. Microbial and in vitro and in vivo mammalian assays evaluating DNA damage and repair were positive (Kanematsu et al. 1980). Additional in vivo studies evaluating structural and numerical chromosomal aberrations would be useful to confirm the genotoxic potential of thallium in humans.

Reproductive Toxicity. No epidemiological studies have been conducted in humans to establish a relationship between thallium exposure and adverse effects on reproduction. Subchronic oral studies in rats suggest that the testes may be susceptible (Formigli et al. 1986). These studies evaluated only one dose level precluding dose-response evaluations. Results of dominant lethal assays (Zasukhina et al. 1983) suggest thallium may act through a genotoxic mechanism resulting in adverse reproductive effects. Subchronic oral studies in other animal species evaluating various dose levels would be helpful in confirming potential reproductive effects and identifying a threshold for this effect.

Developmental Toxicity. No studies were found in humans on the developmental toxicity of thallium and compounds following inhalation exposure. As stated previously, inhalation exposure is not expected to be an important source of exposure in the general population living near hazardous waste sites. There is one human study involving the ingestion of contaminated homegrown vegetables (Dolgner et al. 1983). It failed to clearly establish any relationship between thallium exposure and occurrence of developmental effects. Animal studies show that thallium can cross the placenta by the parenteral route (Olsen and Jonsen 1982; Rade et al. 1982) and suggest that it is a developmental, neurological toxicant by the oral route (Bornhausen and Hagen 1984). While data are limited on thallium-induced alterations on the functional competence of the nervous system, it should be noted that these effects were reported to occur at dose levels below those at which other neurological effects occurred. Additional animal studies involving other species and employing various dose levels by oral exposure during critical developmental periods would be helpful in confirming this effect and determining a threshold level for this effect. Since dermal exposure through soil contact may be a significant source of exposure in children living near hazardous waste sites, studies are needed to determine if soil-bound thallium is bioavailable.

Immunotoxicity. No studies were located regarding immunotoxicity in humans or animals following inhalation, oral or dermal exposures. Since subchronic studies do not suggest the immune system is a target, additional studies are not essential at this time.

Neurotoxicity. Clinical neurological signs as well as histological lesions in cranial and peripheral nerves have been demonstrated in humans following inhalation (Ludolph et al. 1986) or oral (Cavanagh et al. 1974; Davis et al. 1981; Dai-xing and Ding-nan 1985; Roby et al. 1984) exposure. Exposure levels were not provided or if available, levels far exceeded those expected to occur in the environment. No studies are available on effects following dermal exposure. Structural and functional changes in peripheral nerves in animals following oral exposure (Manzo et al. 1983) confirm findings in humans. Since studies evaluated only one dose level and one additional study using multiple doses did not demonstrate neurological effects (Stoltz et al. 1986), data gaps exist relative to dose-response relationships for this target tissue. Additional oral studies would be useful in identifying a threshold for this effect. Further, parenteral studies in animals demonstrated biochemical changes in various parts of the brain suggesting a doserelated selective toxicity between brain regions (Brown et al. 1985; Hasan et al. 1977a,b, 1978; Rios et al. 1989). Additional animal studies to evaluate preferential deposition of thallium in certain brain regions would be useful in confirming the extent of neurological damage induced by thallium.

Epidemiological and Human Dosimetry Studies. Epidemiological studies evaluating the potential health effects of thallium are limited. One study reported peripheral neuropathy in a group of cement workers exposed to thallium (Ludolph et al. 1986). The relative usefulness of this study is limited since an unexposed control group was not evaluated, exposure concentrations were not reported, and the study population was small. Since thallium is nonvolatiie, inhalation exposure may not be a major concern near hazardous waste sites. However, there is potential for oral exposure. Long-term epidemiological studies by the oral route evaluating low-dose exposure would be useful in characterizing the nature of organ changes produced by thallium. Since neurological effects are well characterized, these studies should consider reproductive effects based on animal data suggesting that the male organs are susceptible to thallium toxicity (Formigli et al. 1986).

Biomarkers of Exposure and Effect. The presence of thallium in urine is the most reliable biomarker of exposure. The metal can be detected in urine more than several days after exposure (Brockhaus et al. 1981; Schaller et al. 1980).

Alopecia and changes in the nervous system are characteristic of thallium exposure (Dai-zing and Ding-nan 1985; Gastel 1978; Grunfeld and Hinostroza 1964; Ludolph et al. 1986). Electromyographic measurements of nerve conduction velocity and amplitude can be monitored to detect early signs of neurotoxicity in people exposed to thallium. While such tests are not specific for thallium-induced toxicity, they do identify potential health impairment. Studies to develop more specific biomarkers of thallium-induced effects would be useful in assessing the potential health risk of thallium exposure near hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. No quantitative information is available on absorption of thallium in humans or animals by inhalation or dermal exposure. However, animal studies following intratracheal administration suggested that uptake through respiratory epithelium was rapid and complete (Lie et al. 1960). Data regarding absorption in humans are limited. In one study in which a patient with terminal osteogenic sarcoma was given a single oral dose of thalliumzo4, complete absorption was suggested based on an increased urinary radioactivity over a 72-hour period (Barclay et al. 1953). Additional oral studies that provide data on rate and extent of absorption would be useful since this appears to be the primary exposure route. In one study in which rats were administered radiolabel thallium nitrate by oral exposure, body burden of radioactivity was expressed as a percent of administered dose over time, suggesting virtually complete and rapid uptake by this route (Lie et al. 1960).

No information was found on the distribution of thallium following inhalation or dermal exposure. There are a few studies by oral exposure, which indicate that thallium is found in many tissues of the body (Barclay et al. 1953). Data in humans reported tissue levels are highest in the scalp hair, kidney, heart, bone, and spleen. Lower levels were found in the brain (Barclay et al. 1953). Animal studies confirmed that thallium is widely distributed (Downs et al. 1960; Grunfeld et al. 1963; Lie et al. 1960). However, in animals, thallium is chiefly distributed to the kidneys and liver. Additional studies are needed as a basis for understanding species differences in distribution of thallium. Data exist suggesting that thallium can cross the placental barrier by parenteral administration (Olsen and Jonsen 1982; Rade et al. 1982). However, in human studies evaluating developmental toxicity, the increase of congenital malformation and anomalies in the exposed group did not exceed the number of expected defects in the general population (Dolgner et al. 1983). Additional animal studies by the oral route would be useful in confirming that thallium can locate in the fetus and providing a basis for assessing if there is potential human health risk.

No information is available on the metabolism of thallium. Additional studies are needed to determine if thallium is transformed in the body and would provide a basis for understanding target organ toxicity.

No data are available on excretion of thallium in humans or animals by inhalation or dermal exposure. There are data on excretion in humans and animals by oral exposure. In one study in which a patient was administered radiolabel thallium nitrate, one half of the radioactivity was detected in the urine 21.7 days after exposure, suggesting that thallium is slowly excreted from the body (Barclay et al. 1953). In animals, excretion is more rapid (e.g., half in 3.3 days) and occurs primarily via feces (Lehman and Favan 1985; Lie et al. 1960). Additional studies of other animal species by all routes of exposure would be useful in clarifying differences in excretion patterns.

Comparative Toxicokinetics. Since human and animal toxicokinetics data are limited, very little data exist on comparative kinetics across species. Human data are limited to one study (Barclay et al. 1953) and animal data are primarily in rats (Downs et al. 1960; Lehman and Favan 1985; Lie et al. 1960). These data suggest some kinetics differences, particularly in distribution and excretion patterns. Additional studies using other animal species would be useful in clarifying species differences.

Mitigation of Effects. Recommended methods for the mitigation of the acute effects of thallium poisoning involve prevention of thallium absorption from the gastrointestinal tract by administration of emetics, cathartics, and/or binding agents and removal of absorbed thallium from the serum by hemodialysis or hemoperfusion or by administration of potassium chloride (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Proctor et al. 1988). No information was located concerning mitigation of effects of lower-level or longer-term exposure to thallium. Further information on techniques to mitigate such effects would be useful in determining the safety and effectiveness of possible methods for treating thallium-exposed populations surrounding hazardous waste sites.

2.9.3 On-going Studies

A number of research projects are in progress investigating the toxicity of thallium. These projects are summarized in Table 2-3.

TABLE 2-3. On-going Studies on the Health Effects of Thallium

Investigator	Affiliation	Research description	Sponsoring agency
S. J. Adelstein	Shields Warren Radiation Lab	The kinetics of uptake and intracellular microscopic distribution of thallium radiolabeled with Auger emitters will be measured in cell culture and their relationship to biological effects determined. Cytogenetic effects, transformation, and mutagenesis will also be scored in cell cultures exposed to Auger and alpha emitters.	NIH
B. J. Hoffer	University of Colorado, Denver	The effects of chronic perinatal and acute exposure on the histological organization and electrophysiological function in selected areas of the brain will be studied. These studies may provide some insight into the mechanism of thallium-induced neurotoxicity.	NIH, NIEHS
B. Weiss	University of Rochester	Thallium levels in various tissues in rats exposed to thallium in drinking water and subsequently treated with diethyldithiocarbamate will be determined. Behavioral measures, derived from a modified running wheel apparatus, will be used to trace the appearance of neurotoxicity.	NIH

NIH = National Institutes of Health; NIEHS = National Institute of Environmental Health Sciences

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Table 3-1 lists common synonyms, trade names, and other pertinent identification information for thallium and a number of thallium compounds.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of thallium and selected thallium compounds.

TABLE 3-1. Chemical Identity of Thallium and Compounds[a]

Characteristic	Thallium	Thallium acetate	Thallium chloride	Thallium nitrate	Thallium oxide	Thallium sulfate
Synonyms	Ramor[b]	Thallous acetate; thallium (1+) salt	Thallic chloride	Thallous nitrate; nitric acid, thallium (1+) salt	Thallic oxide	Thallous sulfate
Trade name	No data	No data	No data	No data	No data	No data
Chemical formula	Tl	$TlC_2H_3O_2$	$TlCl_3$	$TlNO_3$	Tl_2O_3	Tl_2SO_4
Chemical structure	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Identification numbers:						
CAS Registry	7440-28-0	563-68-8	13453-32-2	10102-45-1	1314-32-5	7416-18-6
NIOSH RTECS	XG3425000[c]	AJ5425000[c]	No data	XG5950000[c]	XG2975000[c]	No data
EPA Hazardous Waste	No data	V214[b]	No data	V217[b]	P113[b]	No data
OHM/TADS	7216925[b]	7217306[b]	No data	No data	No data	No data
DOT/UN/NA/ IMCO Shipping	UN1707[b] IMCO 6.1[b]	UN1707[b] IMCO 6.1[b]	No data No data	UN2727[b] IMCO 6.1[b]	UN1707[b] IMCO 6.1[b]	No data No data
HSDB	4496[b]	855[b]	No data	No data	6055[b]	No data
NCI	No data	No data	No data	No data	No data	No data

TABLE 3-1 (Continued)

Characteristic	Thallium carbonate	Thallium bromide	Thallium iodide	Thallium fluoride
Synonyms	Thallous carbonate; carbonic acid; dithallium carbonate	Thallium monobromide; thallous bromide	Thallous iodide	Thallum monofluoride; Thallous fluoride
Trade name	No data	No data	No data	No data
Chemical formula	Tl_2CO_3	TlBr	TlI	TlF
Chemical structure	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Identification numbers:				
CAS Registry	6533-73-9	7789-40-0	7790-30-9	7789-27-7
NIOSH RTECS	XG4000000[c]	XG3850000[c]	XG5425000[c]	XG4900000[c]
EPA Hazardous Waste	V215[b]	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/ IMCO Shipping	UN1707[b] IMCO6.1[b]	No data No data	No data No data	No data No data
NCI	No data	No data	No data	No data

[a]All information obtained from EPA 1988a, except where noted.
[b]HSDB 1989
[c]Sax 1984

CAS = Chemical Abstracts Service
DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code
EPA = Environmental Protection Agency
HSDB = Hazardous Substances Data Bank
NCI = National Cancer Institute
NIOSH = National Institute for Occupational Safety and Health
OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System
RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of Thallium and Compounds[a]

Property	Thallium	Thallium acetate	Thallium chloride	Thallium nitrate	Thallium oxide	Thallium sulfate
Molecular weight	204.38	263.43	310.74	266.39	456.76	504.82
Color	Blush-white	White	White[b]	White[b]	Colorless	Colorless
Physical state	Metal	Solid	Solid	Solid	Solid	Solid
Melting point	303.5°C	131°C	25°C	206°C[c]	717±5°C	632°C
Boiling point	1457±10°C	No data	Decomposes	430°C[c]	-20 at 875°C	Decomposes[c]
Density at 20°C	11.85	3.76 at 137°C	No data	5.5[b]	9.65-10.19 at 21°C	6.77
Odor	Odorless[d]	Odorless[d]	No data	Odorless[d]	No data	No data
Odor threshold:						
Water	No data	No data	No data	No data	No data	No data
Air	No data	No data	No data	No data	No data	No data
Solubility:						
Water at 20°C	Insoluble	Very soluble	Very soluble	95.5 g/L	Insoluble	48.7 g/L
Organic solvents	Soluble in nitric or sulfuric acid,	Very soluble in alcohol; insoluble in acetone	Soluble in alcohol and ether	Insoluble in alcohol; Soluble in acetone	Soluble in acids; Insoluble in alkalies	No data
Partition coefficients:						
Log octanol/water	No data	No data	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data	No data	No data
Vapor Pressure at 1000°C	10 mmHg[c]	No data	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data	No data	No data

TABLE 3-2 (Continued)

Property	Thallium carbonate	Thallium bromide	Thallium iodide	Thallium fluoride
Molecular weight	468.78	284.29	331.29	223.38
Color	Colorless	Yellowish-white	Yellow red (at 170°C)	Colorless
Physical state	Solid	Solid	Solid	Solid
Melting point	273°C	480°C	440°C[c]	327°C
Boiling point	No data	815°C	824°C[c]	655°C
Density at 20°C	7.11	7.56 at 17.3°C	7.29	8.23 at 4°C
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20°C	40.3 g/L at 15.5°C	0.5 g/L at 25°C	0.006 g/L	786 g/L at 15°C
Organic solvents	Insoluble in alcohol, ether, and acetone	Soluble in alcohol, insoluble in acetone	Insoluble in alcohol, slightly soluble in nitric acid	Slightly soluble in alcohol
Partition coefficients:				
Log octanol/water	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor Pressure at 1000°C	No data	10 mmHg at 517°C[c]	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data

[a]All information obtained from Weast 1985, except where noted.
[b]Windholz 1983
[c]EPA 1988a
[d]HSDB 1989

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

The domestic production of thallium ceased in 1981. Prior to this, thallium had been recovered as a byproduct from the flue dust and residuals that resulted from the smelting of zinc, copper, and lead ores through treatment by electrolysis, precipitation, or reduction (HSDB 1989; Sax and Lewis 1987; U.S. Bureau of Mines 1983, 1988). Based upon the estimated thallium content of zinc ores, United States mine production of thallium was 0.45 metric tons in 1986 and 1987 and 14.06 metric tons in the rest of the world (U.S. Bureau of Mines 1983, 1988). No data were located regarding the production of thallium acetate, thallium nitrate, thallium chloride, thallium sulfate or thallium oxide.

There are six facilities in the United States that either import thallium, use thallium and its compounds in manufacturing processes, or produce them as byproducts. These facilities are listed in Table 4-l.

4.2 IMPORT/EXPORT

Currently all thallium used in the United States is obtained from thallium reserves or is imported. The combined import of thallium and thallium compounds ranged from 1.27 metric tons in 1983 to 2.04 metric tons in 1987. Between 1983-1986 the countries from which thallium and thallium compounds were imported were Belgium (54%), the Netherlands (16%), the Federal-Republic of Germany (14%), the United Kingdom (6%), and other sources (10%) (U.S. Bureau of Mines 1988).

No information was located regarding the export of thallium or thallium compounds.

4.3 USE

Today's primary user of thallium is the semiconductor industry which in 1987 used 60%-70% of total U.S. thallium imports in its production of switches and closures. The remainder of thallium used was in the pharmaceutical industry to produce thallium for cardiac imaging, and to manufacture highly refractive optical glass (HSDB 1989; U.S. Bureau of Mines 1988; Windholz 1983).

Thallium compounds have a variety of uses. Thallium sulfate is used in the semiconductor industry and in low range thermometers, optical systems, and photoelectric cells, and as a chemical intermediate for other thallium compounds and thallium metals (HSDB 1989). Thallium acetate is used to prepare solutions of high specific gravity for use in separating ore constituents by flotation (HSDB 1989). Thallium chloride is used as a catalyst in chlorination (Windholz 1983). Thallium nitrate is used with other

TABLE 4-1. Facilities That Manufacture or Process Thallium and Compounds[a]

Facility	Location	Maximum Amount on site (lbs)	Use
Philips Industries, Inc., Dexter Axle Div	Albion, IN	10,000-99,999	Import; as a manufacturing aid
Tenneco Oil Company	Chalmette, LA	0-99	As a processing aid
Koch Refining Company	Saint Paul, MN	1,000-9,999	As an impurity
River Cement Company	Festus, MO	100,000,000-499,999,999	As a reactant
Sohio Oil Company Toledo Refinery	Oregon, OH	100-999	As an impurity
Dana Corporation	Reading, PA	0-99	As an impurity

[a]Derived from TRI 1989

compounds and resins for use as signals at sea. It is also used in the production of low melting glass, photocells, fireworks and as an oxidizing agent in organic syntheses (HSDB 1989; Weast 1985). Thallium oxide is used in the manufacture of highly refractive glass and for the production of artificial gems (Windholz 1983). Thallium and compounds were once used as a pesticide for control of rodents and insects, but the use of thallium as a pesticide was banned in 1972 (EPA 1985b).

4.4 DISPOSAL

Thallium is listed as a hazardous substance, therefore, disposal of waste thallium is controlled by a number of federal regulations, including land disposal restrictions (see Chapter 7). Industries producing or using thallium reported off-site waste transfers of about 40,000 pounds of thallium in 1987 (TRI 1989). Land disposal restrictions were implemented by EPA in 1987. Prior to this time disposal of pesticides had been to municipal and industrial landfills. Since thallium is relatively stable in the environment, we can assume that landfills, as well as other superfund sites, contain thallium or thallium-containing products.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Thallium is a heavy metallic element that exists in the environment mainly combined with other elements (primarily oxygen, sulfur, and the halogens) in inorganic compounds. Thallium is quite stable in the environment, since it is neither transformed nor biodegraded.

Compounds of thallium are generally soluble in water and the element is found primarily as the monovalent ion (Tl^+). Thallium tends to be sorbed to soils and sediments (Frantz and Carlson 1987; Mathis and Kevern 1975; Wallwork-Barber et al. 1985) and to bioconcentrate in aquatic plants, invertebrates, and fish (Barrows et al. 1978; Zitko and Carson 1975). Terrestrial plants can also absorb thallium from soil (Ewers 1988; Sharma et al. 1986).

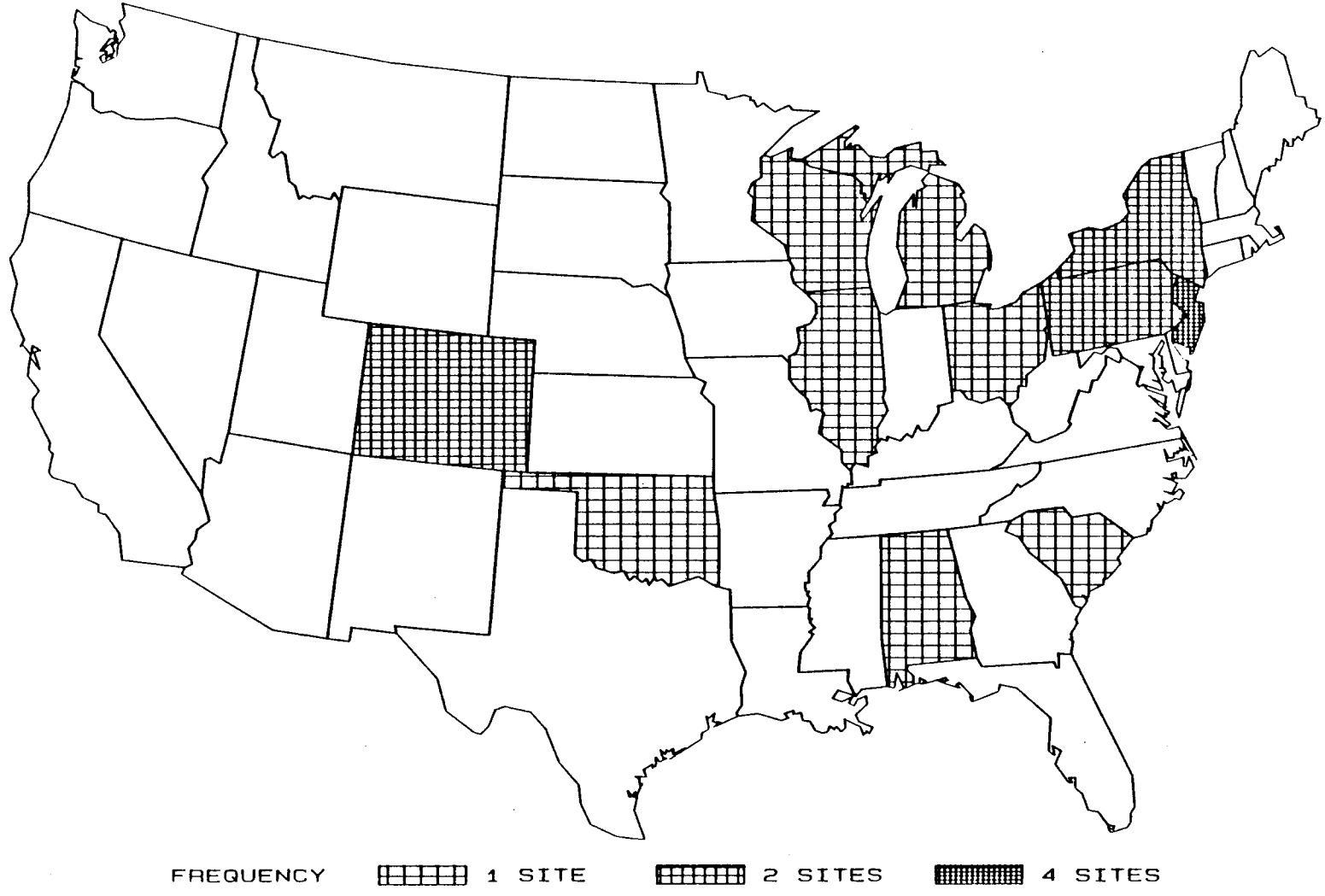
Major releases of thallium to the environment are from processes such as coal-burning and smelting, in which thallium is a trace contaminant of the raw materials, rather than from facilities producing or using thallium compounds. Humans may be exposed to thallium by ingestion, inhalation, or dermal absorption. However, the general population is exposed most frequently by ingestion of thallium-containing foods, especially home-grown fruits and green vegetables. Inhalation of contaminated air near emission sources or in the workplace may also contribute to thallium exposure of some individuals.

The EPA has identified 1,177 NPL sites. Thallium has been found at 18 of the sites evaluated for this chemical. However, we do not know how many of the 1,177 sites have been evaluated for this chemical. As more sites are evaluated, these numbers may change (View 1989). The frequency of these sites within the United States can be seen in Figure 5-l. Seventeen sites are located in the United States and 1 site is located in the commonwealth of Puerto Rico (not shown).

5.2 RELEASES TO THE ENVIRONMENT

Manufacturers, processors, and users of thallium and thallium compounds are required to report quantities of releases of these substances to environmental media annually (EPA 1988c). According to the SARA Section 313 Toxics Release Inventory (TRI), an estimated total of 56,511 pounds of thallium were released to the environment from manufacturing and processing facilities in the United States in 1987 (Table 5-l) (TRI 1989). The TRI data should be used with caution since the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list. However, the major sources of

FIGURE 5-1. FREQUENCY OF NPL SITES WITH THALLIUM CONTAMINATION *



* Derived from View 1989

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Thallium and Compounds[a]

Facility	Location	Total (lbs)						
		Air	Underground injection	Water	Land	Environment	POTW[b] transfer	Off-site transfer
Philips Industries, Inc., Dexter Axle Div	Albion, IN	54,411	0	0	0	54,411	0	39,639
Tenneco Oil Company	Chalmette, LA	0	No Data	0	0	0	No Data	3
Koch Refining Company	Saint Paul, MN	0	0	1,100	0	1,100	No Data	0
River Cement Company	Festus, MO	250	0	0	0	250	0	0
Sohio Oil Company Toledo Refinery	Oregon, OH	0	0	750	0	750	0	0
Dana Corporation	Reading, PA	No Data	No Data	No Data	0	No Data	0	250
Totals		54,661	0	1850	0	56511	0	39892

[a]Derived from TRI 1989
[b]POTW -- publicly-owned treatment works

thallium releases to the environment are not from facilities that produce or use thallium and its compounds, but from processes such as coal-burning or smelting in which thallium is a trace element of the raw materials (Schoer 1984). Data on thallium emissions from these sources are not included in the TRI.

5.2.1 Air

Thallium is released to the atmosphere mainly from coal-burning power plants, cement factories, and ferrous and nonferrous smelting operations (EPA 1988a; Ewers 1988; Sharma et al. 1986). Thallium emissions in the United States were estimated at 140 tons/year each from coal-burning power plants and from iron and steel production (Ewers 1988; Schoer 1984; Smith and Carson 1977). Total air releases reported from industrial sources were about 27 tons in 1987 (TRI 1989).

Davison et al. (1974) reported concentrations of thallium on airborne fly ash emitted from a coal-burning power plant ranging from 29 to 76 μg/g, the thallium concentration increasing with decreasing particle size. The highest concentrations (greater than 60 μg/g) were on particles less than 7.3 μm in diameter. The authors reported that these concentrations were representative of eight other United States power plants burning various types of coal. The highest thallium concentrations were also found on the smaller diameter (0.2 – 0.8 μm) particles of fly dust emitted from a West German cement plant (Ewers 1988).

No quantitative estimates of thallium emissions from other domestic sources were located. However, additional sources of airborne thallium may include manufacturers of alloys, artificial gems, electronics equipment, optical glass, and domestic heating plants (EPA 1987a; Sharma et al. 1986; Valerio et al. 1988).

5.2.2 Water

The major sources of thallium releases to water include nonferrous metals, iron and steel manufacturers and various mining, inorganic chemicals, refining, and ore-processing industries (EPA 1980a, 1983c; Ewers 1988). Thallium concentrations in raw or treated waste waters from these industries ranged up to 2 g/L (EPA 1983c). Thallium has been detected in urban waste waters, apparently from commercial and industrial sources (Callahan et al. 1979a; Levins et al. 1979). Total water releases reported from industrial sources were 1,850 pounds in 1987 (TRI 1989). Thallium has been detected in both surface and groundwater samples at hazardous waste sites. Data from the Contract Laboratory Program (CLP) Statistical Database indicate that thallium occurred in surface water at 1% of sites at a geometric mean concentration of 23 ppb in positive samples and in groundwater at 7% of sites at a mean concentration of 11 ppb in positive samples (CLPSD 1989). Note that the Contract Laboratory Program (CLP) Statistical Database includes data from both

NPL and non-NPL sites. No other quantitative estimates of total thallium releases to water were located.

5.2.3 Soil

Thallium releases to soil are mainly solid wastes from coal combustion and smelting operations (Ewers 1988). Thallium was detected at a geometric mean concentration of 1.7 ppm in positive soil samples from 3.5% of an unspecified number of hazardous waste sites (CLPSD 1989). Although direct soil releases are likely to be small, since thallium-containing wastes are subject to EPA land disposal restrictions, atmospheric thallium pollution may contribute to soil contamination in the vicinity of thallium emission sources (Brockhaus et al. 1981). It should be noted that land disposal restrictions were implemented by EPA in 1987. Prior to this time disposal of pesticides had been to municipal and industrial landfills. Since thallium is relatively stable in the environment, we can assume that landfills, as well other Superfund sites, contain thallium or thallium-containing products.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Thallium is a nonvolatile heavy metal, and if released to the atmosphere by anthropogenic sources, may exist as an oxide (thallium oxide), hydroxide (TlOH), sulfate (thallium sulfate), or as the sulfide Tl_2S (EPA 1988a). These thallium compounds are not volatile (EPA 1983c; Weast 1970). It has been speculated that thallium sulfate and TlOH will partition into water vapor (such as clouds and rain drops) because they are soluble in water and thus, precipitation may remove these forms of thallium from the atmosphere (EPA 1988a). Thallium oxides are less soluble in water, and may be subject to only atmospheric dispersion, and gravitational settling. No corroborative information was located. The atmospheric half-life of suspended thallium particles is unknown.

Thallium exists in water primarily as a monovalent ion (thallium$^+$); thallium may be trivalent ($T1^{3+}$) in very oxidizing water (Callahan et al. 1979b). Tl^+ forms complexes in solution with halogens, oxygen, and sulfur (Lee 1971). Thallium may precipitate from water as solid mineral phases. However, thallium chloride, sulfate, carbonate, bromide, and hydroxide are very soluble in water. For example, the solubility of thallium sulfate at 0°C is about 27 g/L (EPA 1980a). In extremely reducing water, thallium may precipitate as a sulfide (Tl_2S), and in oxidizing water, $T1^{3+}$ may be removed from solution by the formation of $Tl(OH)_3$ (Lee 1971). Stephenson and Lester (1987a, 1987b) argued that the partial removal of thallium from water was the result of precipitation of unknown solids during the treatment of sewage sludge.

5. POTENTIAL FOR HUMAN EXPOSURE

Thallium may partition from water to soils and sediments. Mathis and Kevern (1975) presented indirect evidence that thallium was adsorbed by lake sediments. Furthermore, thallium may be adsorbed by micaceous clays in solution (Frantz and Carlson 1987).

Partition coefficients such as adsorption constants describe the tendency of a chemical to partition to solid phases from water. Adsorption constants for inorganic ions such as Tl+ cannot be predicted a priori, but must be measured for each adsorbent. Thallium adsorption data in Magorian et al. (1974) for a hectorite clay (a rare montmorillonite clay mineral) at pH 8.1 suggest that an adsorption constant for this specific system may be approximately 19 L/g. No other information on the adsorption of thallium by earth materials was located.

Thallium may be bioconcentrated by organisms from water. A bioconcentration factor (BCF) relates the concentration of a chemical in the tissues of aquatic animals or plants to the concentration of the chemical in the water in which they live. Experimentally-measured BCF values have been reported: 18.2 for clams and 11.7 for mussels (Zitko and Carson 1975). Bioconcentration factors for the muscle tissue of juvenile Atlantic salmon have ranged from 27 to 1,430 (Zitko et al. 1975). The maximum BCF for bluegill sunfish was 34 in the study of Barrows et al. (1978). Thallium is absorbed by plants from soil and thereby enters the terrestrial food chain (Ewers 1988; Sharma et al. 1986). Cataldo and Wildung (1983) demonstrated that thallium could be absorbed by the roots of higher plants from the rhizophere.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Metallic thallium oxidizes slowly in air (Lee 1971), and thallous chloride is photosensitive (Cotton and Wilkinson 1980). However, there was no evidence that thallium is transformed significantly by photochemical reactions in the atmosphere (Callahan et al. 1979b).

5.3.2.2 Water

Little is known about thallium transformation in water by either abiotic or biotic processes (EPA 1988a). Pertinent data regarding the photolysis or hydrolysis of common thallium compounds were not located.

5.3.2.3 Soil

Callahan et al. (1979b) concluded that there was no evidence that thallium is biotransformed in the environment. No other information was located.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Data on thallium levels in ambient air are sparse. In six United States cities, the thallium concentrations ranged from 0.02 to 0.1 ng/m^3, with a typical concentration of 0.04 ng/m^3 (EPA 1980a, 1988a). Concentrations of thallium in Chadron, Nebraska reportedly ranged from 0.04 to 0.48 ng/m^3 (EPA 1980a, 1988a), and geometric mean concentrations measured during 1985-1986 in Genoa, Italy were about 0.015 μg/m^3 (Valerio et al. 1988). The estimated thallium concentration near a coal-burning power plant was 0.7 μg/m^3 (EPA 1988a).

Thallium levels have also been measured in workplace air. Marcus (1985) reported maximum thallium levels in workplace air at 0.014 and 0.022 mg/m^3 during machining and alloying operations, respectively, of a magnesium alloy used in batteries at a plant in England. Air samples in two cement plants and two foundries in Italy had thallium concentrations of less than 1 μg /m^3 (Apostoli et al. 1988).

5.4.2 Water

Since thallium is a naturally-occurring element, it may be present in ambient waters in trace amounts. However, monitoring data indicate elevated thallium concentrations near industrial and commercial sources and hazardous waste sites.

A survey of tap water from 3,834 homes in the United States detected thallium in 0.68% of samples at an average thallium concentration of 0.89 μg/L (EPA 1980a, 1988a). Thallium was detected in 10% of urban stormwater runoff samples at concentrations ranging from 1 to 14 μg/L (Cole et al. 1984). Thallium has been measured in seawater at 0.01-14.00 μg/L (Sharma et al. 1986).

Water concentrations of thallium in rivers in the United States and Canada that receive mining operations effluents ranged from 0.7 to 88.3 μg/L (EPA 1980a, 1988a; Zitko et al. 1975).

5.4.3 Soil

Estimates of thallium concentration in the earth's crust range from 0.3 to 0.7 ppm (EPA 1988a), so thallium is likely to be present in soils in trace amounts. The limited data available indicate that soil thallium levels may be increased near thallium-emitting industrial sources and at hazardous waste sites. Measured thallium concentrations in lake sediments ranged from 0.13 to 0.27 μg/g in four remote Rocky Mountain lakes (Heit et al. 1984) to 2.1-23.1 mg/kg (mean value 13.1 mg/kg) in a Michigan lake reportedly polluted by airborne particulate matter (EPA 1988a). Up to 5 mg/kg thallium was

reported in stream sediments near metal industry runoff areas (Wallwork-Barber et al. 1985).

5.4.4 Other Environmental Media

Trace amounts of thallium are found in most foods (Ewers 1988), but few foods, except vegetables grown in thallium-polluted soil, are likely to have significant thallium concentrations (Ewers 1988; Sharma et al. 1986).

Data on thallium content of specific foods grown and consumed in the United States were not located. However, a recent study of the thallium content of food in the United Kingdom reports levels of thallium in meat, fish, fats, and green vegetables (Sherlock and Smart 1986).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Human exposure to thallium may occur by inhalation, ingestion, or dermal absorption. The general population is exposed most frequently by ingestion of thallium-containing foods (EPA 1980a, 1988a; Ewers 1988). From the very limited data available, EPA estimated daily intakes for the general adult population from drinking water, air, and food (EPA 1980a). More recent data on thallium concentrations in food and dietary intake of the general population (Sherlock and Smart 1986) confirm that food (green vegetables in particular) is probably the major source of thallium exposure. Although these data are from the United Kingdom, it is not likely that the thallium content of the food supply of the United States would be significantly different. Limited data on thallium concentrations in cigars and cigarettes suggest smoking may be a source of thallium. The extent of exposure from this source is not clear since thallium levels in cigarette smoke are not known. Table 5-2 summarizes the estimated typical daily intakes from water, food, and air.

Occupational exposure to thallium may be significant for workers in smelters, power plants, cement factories, and other industries that produce or use thallium compounds or alloys. Exposure may occur by dermal absorption from handling thallium-containing compounds, ores, limestone, or cement or by inhalation of workplace air (Ewers 1988; Marcus 1985; Schaller et al. 1980).

Urinary thallium levels are considered the most reliable indicator of thallium exposure. Although data on exposure levels in workplace air are rare (see Section 5.4.1), studies associating workplace exposure and elevated urinary thallium confirm the occurrence of industrial exposures in Europe (Apostoli et al. 1988; Marcus 1985; Schaller et al. 1980). Similar data were not located for U.S. workplaces. However, NIOSH estimated that more than

TABLE 5-2. Summary of Typical Human Exposure to Thallium[a]

Parameter	Exposure medium		
	Water	Air	Food
Typical concentration in medium	0.89 μg/L	0.48 ng/m^3	ND-50 μg/kg
Assumed intake of medium by 70-kg adult	2 L/day	20 m^3/day	1.5 kg
Assumed absorption fraction	1.0	0.35	1.0
Estimated daily intake by 70-kg adult	≈2 μg	3.4 ng	5 μg

[a]Adapted from EPA 1980a, 1988a; Sherlock and Smart 1986

ND = not detected

1,600 people are occupationally exposed to thallium in the United States (NOES 1989). The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. This survey provides only estimates of the number of workers potentially exposed to chemicals in the workplace.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations with potentially high exposures are those living near coal-Burning power plants, metal smelters, or cement plants (Sharma et al. 1986). The airborne particulate emissions from these plants may have high thallium levels, especially on the small-diameter, respirable particles (Davison et al. 1974; Ewers 1988). Human populations living in the vicinity of these plants may be exposed by inhalation or by ingestion of fruits and vegetables homegrown in contaminated soils (Brockhaus et al. 1980, 1981; EPA 1988a; Sharma et al. 1986).

Workers in industries producing or using thallium-containing materials also have potentially high exposures as noted above (Section 5.5).

Limited data suggest that smokers may have potentially high exposure to thallium. Although recent authoritative evaluations of cigarette smoke constituents do not include thallium, thallium was detected at 0.057-0.170 μg/g in cigar stubs and 0.024 μg/g in cigarette tobacco (EPA 1980a; Smith and Carson 1977). One study indicates that the urinary excretion of thallium in smokers is about twice that of nonsmokers (EPA 1980a; Smith and Carson 1977).

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of thallium is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of thallium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. Additional measurements of the aqueous solubility of environmentally relevant thallium compounds would provide a more accurate basis for applying mineral equilibria to predict the fate of thallium in water (EPA 1988a).

Production, Import/Export, Use, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Data on production, use, and disposal (HSDB 1989; TRI 1989; U.S. Bureau of Mines 1988) are adequate. Additional information is unlikely to significantly affect estimates of human exposure.

Environmental Fate. Little information is available on partitioning of thallium in the atmosphere (EPA 1988a). This lack of data is not important since thallium is nonvolatile. The reaction mechanisms controlling the fate of thallium in water are not well known. Adsorption-desorption reactions with soils and sediments (Frantz and Carlson 1987; Magorian et al. 1974; Mathis and Kevern 1975) suggest that movement of thallium can be reduced. Additional research would provide a more accurate basis for predicting the fate of thallium in water. Very little is known about potential transformation mechanisms for thallium in air, water, or soil (Callahan et al. 1979b; EPA 1988a), but this lack of detailed data may not be a major limitation because many transition metals are not susceptible to transformation or degradation-type processes.

Bioavailability From Environmental Media. Thallium can be absorbed following inhalation of contaminated workplace air, ingestion of contaminated food, or dermal contact (Dai-xing and Ding-nan 1985; Dolgner et al. 1983; Marcus 1985). The most significant routes of exposure near hazardous waste sites are likely to be through drinking thallium-contaminated water and skin contact with or ingestion of thallium that is attached to soil particles. Information on the percent of thallium taken into the body from environmental media that is actually absorbed or bioavailable would be useful in clarifying the toxic potential of thallium in humans. The relative absorption of different species/forms of thallium from inorganic and biological matrices would also be useful.

Food Chain Bioaccumulation. There are no specific data on the bioaccumulation of thallium or its potential to be transferred from lower trophic levels to higher organisms. Because thallium can be bioconcentrated, it may be that it can also be accumulated in living tissues. We know that

thallium may be bioconcentrated by aquatic plants, invertebrates, and fish (Barrows et al. 1978; Zitko and Carson 1975; Zitko et al. 1975). Information on biotransformation in aquatic biota would provide further insight into the extent of chemical speciation and forms of thallium to which humans could be exposed near hazardous waste sites. Terrestrial plants absorb thallium from soil (Cataldo and Wildung 1983). Additional measurements of the bioconcentration of thallium by plants and animals and information on soil types and conditions which enhance thallium uptake by plants would be helpful to better define the tendency of thallium to partition to living tissues. Detectable levels of thallium have been found in many foods (Ewers 1988; Sharma et al. 1986; Sherlock and Smart 1986). However, no data were located on biomagnification of thallium in the food chain. Information on food chain bioaccumulation would be useful in assessing the potential for human exposure to thallium from food.

Exposure Levels in Environmental Media. Data on thallium levels in all environmental media are sparse (EPA 1988a). More research using sensitive analytical methods for all media, especially in the vicinity of potential thallium pollution sources and waste sites, and specific data on the thallium content of the American diet would increase the accuracy of human exposure estimates.

Exposure Levels in Humans. Thallium has been detected in human urine and urinary thallium excretion is used as a measure of thallium absorption (Dai-xing and Ding-nan 1985; Dolgher et al. 1983; Marcus 1985). Reliable data on urinary thallium in unexposed individuals and correlating urinary thallium levels with environmental exposures at hazardous waste sites would help to identify populations at risk in the vicinity of these sites from thallium exposure.

Exposure Registries. No exposure registries for thallium were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

Remedial investigations and feasibility studies conducted at the 18 NPL sites known to be contaminated with thallium will add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries.

No other information was located on any on-going studies on the fate, transport, or potential for human exposure for thallium.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring thallium in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify thallium. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect thallium in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

Thallium is almost always determined as total metal, rather than specific thallium compounds. Among the wide range of techniques that can be used to measure thallium are spectrophotometry, mass spectrometry, voltammetry, neutron activation analysis, and x-ray fluorimetry (Sharma et al. 1986). However, direct aspiration atomic absorption analysis is the most widely used and straightforward method for determining thallium; furnace atomic absorption analysis is used for very low analyte levels and inductively coupled plasma atomic emission analysis for multianalyte analyses that include thallium.

6.1 BIOLOGICAL MATERIALS

Methods for detection of thallium in biological materials are summarized in Table 6-1. Normally, for determination in biological samples, the sample is digested in an oxidizing acid mixture, such as 3:l:l (v/v/v) nitric:perchloric:sulfuric acid mixture (Kneip and Crable 1988), followed by atomic spectrometric determination. Alternatively, thallium can be extracted from biological samples such as blood or urine by chelating agents such as diethylthiocarbamate in methylisobutylketone and measured by atomic absorption analysis.

6.2 ENVIRONMENTAL SAMPLES

Methods for the determination of thallium in environmental samples are summarized in Table 6-2. Thallium is readily measured in multielement analyses of air, water, and solid waste samples by inductively coupled plasma atomic emission spectroscopy. For individual analyses of thallium, direct aspiration atomic absorption spectroscopy is a very convenient method of analysis; if lower detection limits are needed, furnace atomic absorption analysis can be employed. Other sensitive means of measuring thallium include anodic stripping voltammetry and laser-excited atomic fluorescence spectroscopy, which have been used for biological samples (see Table 6-2).

TABLE 6-1. Analytical Methods for Determining Thallium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Biotic materials	Combustion in oxygen stream	ASV and AAS	No data	No data	Kaiser and Tolg 1986
Blood and tissue	Acid digestion	ICP/AES	No data	131% recovery at 10 mg/sample	Kneip and Crable 1988
Blood and urine	Extraction into methyl-isobutylketone with diethyldithiocarbamate chelating agent	AAS	<3 µg/L[a]	No data	Baselt 1988
Blood and tissue	Acid digestion	ICP/AES	1 µg/100g blood, 0.2 µg/g tissue	106% 4.9% RSD	*NIOSH* 1984a
Bovine liver, mouse brain tissue	No data	LEAFS	No data	No data	Dougherty et al. 1988
Liver, kidney	Digestion by proteolytic enzyme	AAS	No data	No data	Carpenter 1981
Urine	Acid digestion	ASV	1 µg/L	95% recovery at 16 µg/L	Angerer and Schaller 1985
Urine	Extraction into toluene with sodium diethylthio-carbamate chelting agent	AAS	0.1 µg/L	95%-98% 3.5%-4.4% RSD	Chandler and Scott 1984
Urine	Dilution	AAS	0.5 µg/L	No data	Paschal and Bailey 1986

[a]Estimated from cited values of normal blood thallium concentration.

AAS = atomic absorption spectroscopy; ASV = anoidc stripping voltammetry (inverse voltammetry); ICP/AES = inductively coupled plasma atomic emission spectroscopy; LEAFS = laser excited atomic fluorescence spectroscopy; RSD = relative standard deviation

TABLE 6-2. Analytical Methods for Determining Thallium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on filter, workup in acid	AAS	No data	No data	Sittig 1985
Air	Collection on filter; workup in acid	ICP/AES	1 µg per sample	103% recovery at 2.5 µg per sample	NIOSH 1984b
Water	Acidify with nitric acid	AAS (direct aspiration)	0.1 mg/L	98±1.7% at 3 mg/L	APHA 1985
Water	Acidify with nitric acid	AAS (direct aspiration)	0.1 mg/L	No data	EPA 1983a
Water	Acidify with nitric acid	AAS (furnace technique)	1 µg/L	No data	EPA 1983b
Water	Digestion for total thallium, filtration through 0.45 micron filter followed by digestion for dissolved thallium	AAS	No data	No data	Sittig 1985
Wastewater	Acid digestion	ICP/AES	40 µg/L	No data	EPA 1985a
Solid waste	Acid digestion	AAS (direct aspiration)	0.1 mg/L[a]	98±1.7% at 3 mg/L	EPA 1986a
Solid waste	Acid digestion	AAS (furnace technique)	1 µg/L[a]	No data	EPA 1986b
Solid waste	Acid digestion	ICP/AES	40 µg/L[a]	No data	EPA 1986c
Solid environmental samples	No data	AAS (electrothermal)	No data	No data	DeRuck et al. 1989

[a]Detection limit for thallium in liquid sample digestate.

AAS = atomic absorption spectroscopy; ICP/AES = inductively coupled plasma atomic emission spectroscopy

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of thallium is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of thallium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Methods for Biomarkers of Exposure and Effect. The only means available to indicate exposure to thallium is detection of thallium in tissue and biological fluids. Sensitive, specific, readily used atomic spectrometric techniques are available for the detection and quantitative measurement of thallium after the sample matrix in which it is contained has been digested with oxidant acids or after thallium has been extracted with methylisobutylketone (Baselt 1988). The determination of specific compounds that contain thallium are relatively unimportant because of the uncomplicated chemistry of this element and there is no evidence in the literature for the production of metabolites. If such metabolites do in fact exist, methods for their determination would be useful in monitoring exposure to thallium. Studies are needed to determine whether solid tissues provide a "matrix effect" biasing the accuracy of determinations from tissues. Thallium exists in both stable univalent (I) and trivalent (III) states. Additional studies would be useful in clarifying if relative concentration of thallium in various tissues would be affected by the valence or if there is a biochemical conversion of Tl^{+} and $T1^{3+}$ into a single species.

Biomarkers for effects of thallium intoxication are alopecia, neurological effects, and albuminuria (Baselt 1988), which are indicative of exposure to many other toxicants as well. Therefore, methods are needed for more specific biomarkers for effects of thallium exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining the parent compound, thallium, in water, air, and waste samples with excellent selectivity and sensitivity are well developed (EPA 1983a,b, 1985a, 1986a, b,c; NIOSH 1984b), so the database in this area is good and undergoing constant improvement.

Sampling methodologies for very low-level elemental pollutants such as thallium continue to pose problems such as nonrepresentative samples, insufficient sample volumes, contamination, and labor-intensive, tedious extraction and purification procedures (Green and LePape 1987).

6.3.2 On-going Studies

Examination of the literature suggests that studies are underway to improve means for determining thallium and other heavy metals in biological samples and environmental media. Improvements continue to be made in detection limits and ease and speed of analysis.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for thallium by various national and state agencies. These values are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Thallium and Compounds

Agency	Description	Information	Reference
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA (soluble compounds, as Tl)	0.1 mg/m³	OSHA 1989 (29 CFR 1910.1000) Table Z-1-A
b. Water:			
EPA OWRS	General permits under NPDES	Yes	40 CFR 122, Appendix D, Table II
	General pretreatment regulations for existing and new sources of pollution	Yes	40 CFR 403
	Hazardous substance		EPA 1989a
	Thallium sulfate	Yes	(40 CFR 116)
	Reportable quantity		40 CFR 117.3
	Thallium sulfate	100 pounds	
c. Nonspecific media:			
EPA OERR	Reportable quantity		EPA 1989a (40 CFR 302.4)
	Thallium	1,000 pounds	
	Thallium (1) acetate	100 pounds	
	Thallium (1) chloride	100 pounds	
	Thallium (1) nitrate	100 pounds	
	Thallic oxide	100 pounds	
	Thallium (1) sulfate	100 pounds	
	Thallium (1) carbonate	100 pounds	
	Thallium selenite	1,000 pounds	
	Extremely hazardous substance TPQ		EPA 1987b (40 CFR 355)
	Thallium sulfate	100/10,000 pounds	
	Thallous chloride	100/10,000 pounds	
	Thallous sulfate	100/10,000 pounds	
	Thallous carbonate	100/10,000 pounds	
	Thallous malonate	100/10,000 pounds	
EPA OPP	Cancellation of all pesticide products containing thallium sulfate 03/09/72	Yes	EPA 1985b
EPA OSW	Hazardous waste constituent (Appendix VIII) (Thallium and Compounds)	Yes	EPA 1980c (40 CFR 261)
	Groundwater monitoring list (Appendix IX)	Yes	EPA 1987c (40 CFR 264)
	Land disposal restrictions	Yes	EPA 1988d, 1987d (40 CFR 264, 268)
EPA OTS	Toxic chemical release reporting	Yes	EPA 1988c (40 CFR 372)
	Health and safety data reporting rule	Yes	EPA 1988e (40 CFR 716)

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	Reference
Guidelines:			
a. Air:			
ACGIH	TLV TWA (soluble compounds as Tl)	0.1 mg/m^3	ACGIH 1986
NIOSH	IDLH (soluble compounds as Tl)	20 mg/m^3	NIOSH 1985
b. Water:			
EPA OWRS	Ambient water quality criteria		EPA 1980a
	Ingesting water and organisms	13 µg/L	
	Ingesting organisms only	48 µg/L	
c. Other:			
EPA	Carcinogenic classification	Group D[a]	EPA 1988a
	Thallium and salts		
	RfD (oral)		IRIS 1989
	Thallium (insoluble salts)	$7x10^{-5}$ mg/kg/day	EPA 1991
	Thallium (I) sulfate	$8x10^{-5}$ mg/kg/day	
	Thallium (I) acetate	$9x10^{-5}$ mg/kg/day	
	Thallium (I) chloride	$8x10^{-5}$ mg/kg/day	
	Thallium (I) nitrate	$9x10^{-5}$ mg/kg/day	
	Thallium (I) carbonate	$8x10^{-5}$ mg/kg/day	
STATE			
Regulations:			
a. Air:	Acceptable ambient air concentration		NATICH 1989
Connecticut		2.0 µg/m^3 (8 hr)	
Florida (Tampa)		0.001 mg/m^3 (8 hr)	
Kansas (Kansas City)		0.238 µg/m^3 (1 yr)	
Nevada		0.002 mg/m^3 (8 hr)	
New York		0.330 µg/m^3 (1 yr)	
North Dakota		0.001 mg/m^3 (8 hr)	
Pennsylvania (Philadelphia)		2.47 µg/m^3 (1 yr)	
		2.40 µg/m^3 (annual)	
Virginia		1.60 µg/m^3 (24 hr)	
Wisconsin		2.4 µg/m^3 (24 hr)	
b. Water:	Drinking water		FSTRAC 1988
Kansas		13 µg/L	
Wisconsin		6.5 µg/L	

[a] Group D = not classified as to human carcinogenicity. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; IDLH = Immediately Dangerous to Life or Health Level; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Products; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time-Weighted Average

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for thallium by various national and state agencies. These values are summarized in Table 7-l.

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9. GLOSSARY

Acute Exposure - Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) - The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) - The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) - The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) - The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen - A chemical capable of inducing cancer.

Ceiling Value - A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure - Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity - The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity - Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory - An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) - The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure - Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity - The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro - Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo - Occurring within the living organism.

Lethal Concentration $_{(LO)}$ (LC_{LO}) - The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration $_{(50)}$ (LC_{50}) - A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose $_{(LO)}$ (LD_{LO}) - The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose $_{(50)}$ (LD_{50}) - The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time $_{(50)}$ (LT_{50}) - A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) - The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations - Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level - An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen - A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

9. GLOSSARY

Neurotoxicity - The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) - The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) - The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) - An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* - The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m^3 for air).

Reference Dose (RfD) - An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) - The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity - The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) - The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

9. GLOSSARY

Target Organ Toxicity - This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen - A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) - A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) - An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) - A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) - A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people ,living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and end point and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minima1 Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented- below demonstrate the application of these tables and figures. A representative example of LSE Table 2-l and Figure 2-1 are shown. The numbers in the left columrn of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate mute of exposure. When sufficient data exist,

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

2) Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

5) Species The test species, whether animal or human, are identified in this column.

6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance XI via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

7) System This column further defines the systemic effects. These systems include: respiratory9 cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key nmber 18, one systemic effect (respiratory)was investigated in this study.

8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects, These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to

quantify the adverse effect accompanies the LOAEL. The “Less Serious” respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

10) Reference The complete reference citation is given in Chapter 8 of the profile.

11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer9 but the text may report doses which did not cause a measurable increase in cancer.

12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables ate found in the footnotes. Footnote “b” indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

13) Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

14) Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

15) Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale “y” axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

16) NOAEL In this example, 1% NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key numbr 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRI, of 0.005 ppm (see footnote “b” in the LSE table).

17) CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

APPENDIX

18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5 ↓	6 ↓	7 ↓	8 ↓	9 ↓		10 ↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer						11 ↓	
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

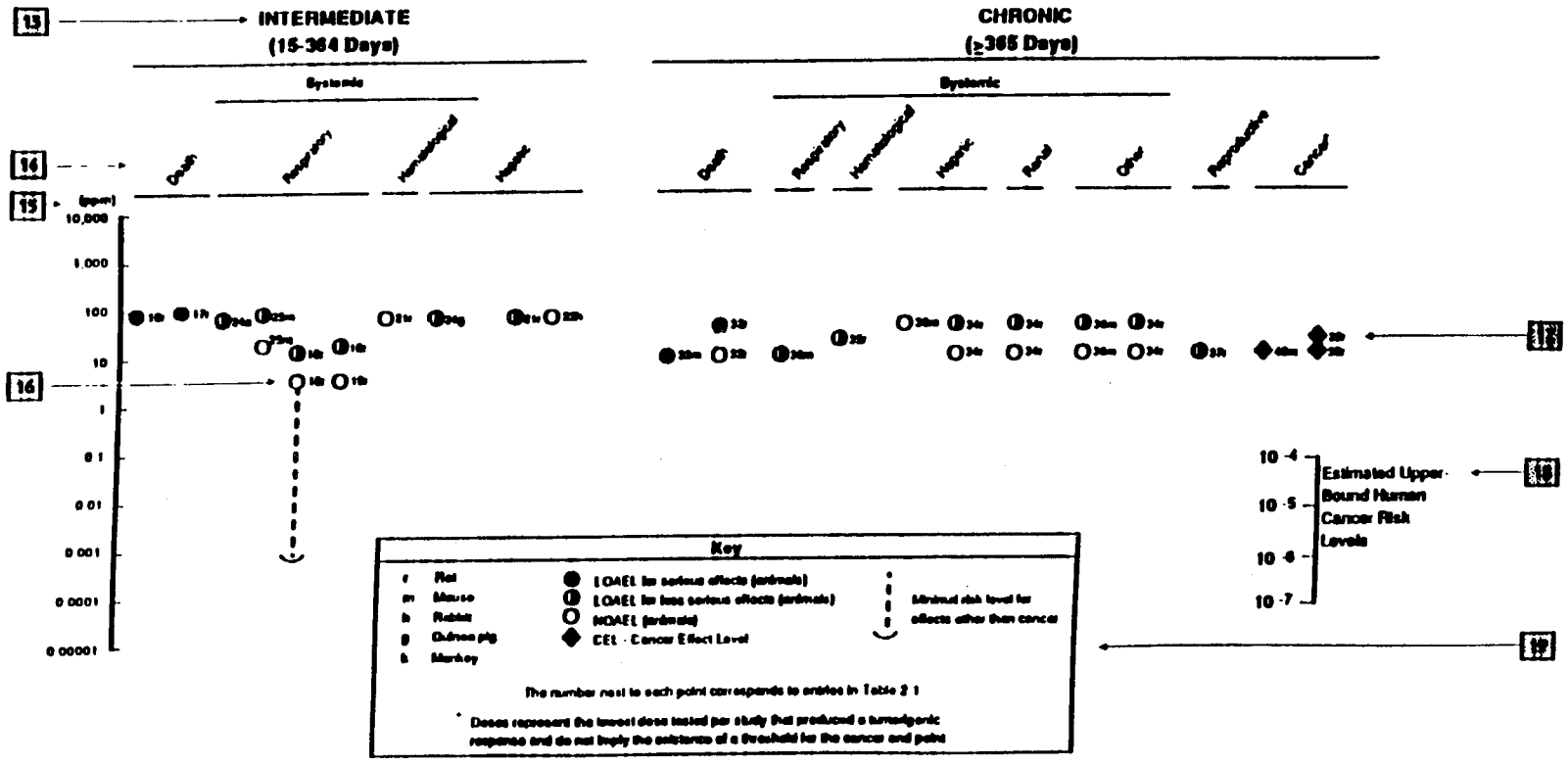

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around
   hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potiency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute - intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic informationknown about the substance. Other sections such as 2.6, “Interactions with Other Chemicals” and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MEL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f_1	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
Koc	octanol-soil partition coefficient
Kow	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration low
LC_{50}	lethal concentration 50 percent kill
LD_{Lo}	lethal dose low
LD_{50}	lethal dose 50 percent kill
LOAEL	lowest-observed-adverse-effect level

APPENDIX B

LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average

APPENDIX B

U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for thallium. The panel consisted of the following members: Dr. Curtis Klaassen, Associate Director, Environmental Health Science Division, Dept. of Pharmacology and Toxicology, University of Kansas; Dr. David Brown, Director, Toxicology Programs, Northeastern University; Dr. Kenneth Reuhl, Associate Professor, Department of Pharmacology and Toxicology, Rutgers University College of Pharmacology. These experts collectively have knowledge of thallium's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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DRAFT
TOXICOLOGICAL PROFILE FOR
VANADIUM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2009

DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Vanadium was released in 1992. This present edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-62
Atlanta, Georgia 30333

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information. Each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

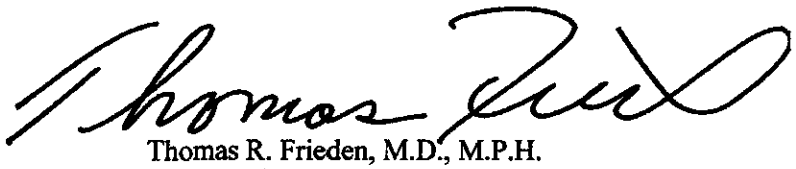
Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road, N.E.
Mail Stop F-62
Atlanta, Georgia 30333

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Howard Frumkin, M.D., Dr. P.H.
Director, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry



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Administrator, Agency for Toxic Substances and Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for vanadium. The panel consisted of the following members:

1. Janusz Z. Byczkowski, Ph.D., DABT, Independent Consultant, Fairborn, Ohio;

2. David Dorman, Ph.D., D.V.M., DABT, Associate Dean for Research and Graduate Studies, North Carolina State University, Raleigh, North Carolina; and

3. Anna Fan, Ph.D., DABT, Chief, Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland/Sacramento, California.

These experts collectively have knowledge of vanadium's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about vanadium and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Vanadium has been found in at least 319 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which vanadium is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to vanadium, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS VANADIUM?

Description	Vanadium is a naturally occurring element. It is widely distributed in the earth's crust at an average concentration of approximately 100 mg/kg. Vanadium is found in about 65 different minerals. Depending on its form, vanadium can be a gray-white metal or light gray or white lustrous powder. Pure vanadium is a bright white, soft, and ductile metal.

Uses	
• **Vanadium metal**	Vanadium is used in producing rust-resistant, spring, and high-speed tool steels. It is an important carbide stabilizer in making steels.
• **Vanadium pentoxide**	Vanadium pentoxide is used in ceramics and as a catalyst as well as in the production of superconductive magnets.
• **Vanadyl sulfate and sodium metavanadate**	Vanadyl sulfate and sodium metavanadate have been used in dietary supplements.

For more information on the physical and chemical properties of vanadium and its production, disposal and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO VANADIUM WHEN IT ENTERS THE ENVIRONMENT?

Sources	Vanadium occurs naturally in soil, water, and air. Natural sources of atmospheric vanadium include continental dust, marine aerosol, and volcanic emissions. Releases of vanadium to the environment are mainly associated with industrial sources, especially oil refineries and power plants using vanadium rich fuel oil and coal. Global human-made atmospheric releases of vanadium has been estimated to be greater than vanadium releases due to natural sources. Natural releases to water and soil are far greater overall than human-made releases to the atmosphere.

Break down	Vanadium cannot be destroyed in the environment. It can only change its form or become attached or separated from airborne particulate, soil, particulate in water, and sediment.
• **Air**	Vanadium particles in the air settle to the ground or are washed out of the air by rain. Smaller particles, such as those emitted from oil-fueled power plants, may stay in the air for longer times and are more likely to be transported farther away from the site of release.
• **Water and soil**	The transport and partitioning of vanadium in water and soil is influenced by many factors including acidity of the water or soil and the presence of particulates. Vanadium can either be dissolved in water as dissolved ions or may become adsorbed to particulate matter.

1.3 HOW MIGHT I BE EXPOSED TO VANADIUM?

Food–primary source of exposure	Most foods have naturally occurring low concentrations of vanadium. Seafood generally contains higher concentrations of vanadium than meat from land animals. Daily intakes of vanadium from food ranging from 0.01 to 0.02 mg have been reported. Average vanadium concentrations in tap water are approximately 0.001 mg/L. Assuming that you drink approximately 2 L of water a day, a daily intake of approximately 0.002 mg of vanadium from tap water can be estimated for adults. Vanadium also may be found in various commercial nutritional supplements and multivitamins in amounts ranging from 0.0004 to 12.5 mg, depending on the serving size recommended by the manufacturer. Consumption of some vanadium-containing supplements may result in intakes of vanadium that would exceed intakes from food and water. Populations in areas with high levels of residual fuel oil consumption may also be exposed to above-background levels of vanadium, both from increased particulate deposition upon food crops and soil in the vicinity of power plants.

Air	Most people take in very little vanadium from breathing. The general population may also be exposed to airborne vanadium through inhalation, particularly in areas where use of residual fuel oils for energy production is high. Individuals exposed to cigarette smoke may also be exposed to higher than background levels of vanadium. Approximately 0.0004 mg of vanadium is given off by in the smoke of one cigarette.
Water and soil	Vanadium concentrations in surface water can range from approximately 0.04 to 220 µg/L depending on geographical location.

For more information on how you might be exposed to vanadium, see Chapter 6.

1.4 HOW CAN VANADIUM ENTER AND LEAVE MY BODY?

Enter your body • **Inhalation**	Some of the vanadium you breathe will enter your body through your lungs; however, we do not know how much will enter.
• **Ingestion**	A small amount of vanadium in food and water (3–20%) will enter your body through the digestive tract. The vanadium compounds you are exposed to will determine how much is absorbed.
• **Dermal contact**	We do not know how much vanadium will enter your body through your skin. It is likely that very little will pass through the skin.

For more information about how vanadium enters and leaves your body, see Chapter 3.

1.5 HOW CAN VANADIUM AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Workers **• Inhalation**	Breathing air with vanadium pentoxide can result in coughing which can last a number of days after exposure.
Laboratory animals **• Inhalation**	Damage to the lungs, throat, and nose have been observed in rats and mice exposed to vanadium pentoxide.
Humans **• Oral**	Nausea, mild diarrhea, and stomach cramps have been reported in people taking sodium metavanadate or vanadyl sulfate for the experimental treatment of diabetes. Stomach cramps were also reported in a study of people taking about 13 mg vanadium/day.
Laboratory animals **• Oral**	A number of effects have been found in rats and mice ingesting several vanadium compounds. The effects include: • Decreases in number of red blood cells • Increased blood pressure • Mild neurological effects
Cancer	Lung cancer has been found in mice exposed to vanadium pentoxide. The International Agency for Research on Cancer (IARC) has determined that vanadium is possibly carcinogenic to humans.

For more information on health effects in people and animals after breathing, eating, or touching vanadium, see Chapter 3.

1.6 HOW CAN VANADIUM AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in children	The health effects seen in children from exposure to toxic levels of vanadium are expected to be similar to the effects seen in adults. We do not know if children will be more sensitive to vanadium toxicity than adults.
Birth defects	We do not know whether vanadium can cause birth defects in people. Studies in animals exposed during pregnancy have shown that vanadium can cause decreases in growth and increases in the occurrence of birth defects. These effects are usually observed at levels which cause effects in the mother.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO VANADIUM?

Food	Vanadium is a naturally occurring element that is widely distributed in the environment. It is found in many foods, typically in small amounts. You cannot avoid exposure to vanadium. Exposure to the levels of vanadium that are naturally present in food and water are not considered to be harmful.
Consumer products	Consumption of some vanadium-containing supplements may result in intakes of vanadium that would exceed intakes from food and water. You should check with your physician before taking supplements containing vanadium to determine if such supplements are appropriate for you. As a precaution, such products should have child-proof caps or should be kept out of reach of children so that children will not accidentally ingest them.

Air	Individuals exposed to cigarette smoke may also be exposed to higher-than-background levels of vanadium. Avoiding exposure to cigarette smoke may reduce exposure of you and your family to vanadium.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO VANADIUM?

Detecting exposure	All people have small amounts of vanadium in their bodies. It can be measured in many tissues and fluids including blood, urine, and hair.
Measuring exposure	Measurements of vanadium concentrations in blood and urine can tell you whether you have been exposed to larger-than-normal amounts of vanadium. Blood and urinary vanadium levels are considered the most reliable indicators of occupational exposure to vanadium. Measuring the concentration of vanadium in breathing air, drinking water, and food can help in determining how much vananium you are exposed to. Measuring vanadium levels in hair is not a good indicator of occupational or environmental exposure to vanadium.

For more information on ways to tell whether you have been exposed to vanadium see Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it.

Some regulations and recommendations for vanadium include the following:

Workplace air	OSHA set a legal limit of 0.5 mg/m^3 for vanadium pentoxide respirable dust averaged over an 8-hour work day. A limit of 0.1 mg/m^3 for vanadium pentoxide fume has also been established.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO VANADIUM IN THE UNITED STATES

Vanadium is the 22nd most abundant element in the earth's crust with an average concentration of 100 ppm. It exists in oxidation states ranging from -1 to +5 with 3+, 4+, and 5+ being the most common oxidation states. Vanadium is primarily used in the production of rust-resistant, spring, and high-speed tool steels; vanadium pentoxide is used in ceramics. Vanadium is released to the environment by continental dust, marine aerosols, volcanic emissions, and the combustion of coal and petroleum crude oils. It is naturally released into water and soil as a result of weathering of rock and soil erosion. Ambient air concentrations of vanadium are low, with urban areas having higher concentrations. Average vanadium concentrations were 3.0–3.7 ng/m^3 in urban areas of Illinois; in rural areas, the vanadium concentrations were 0.8–1.2 ng/m^3. Higher vanadium levels have been measured in the eastern United States due to the high density of oil fired power plants using vanadium-rich residual fuel oil. An average vanadium air concentration of 620 ng/m^3 was measured in Eastern cities compared to 11 ng/m^3 in cities throughout the United States. Vanadium residence time in the environment is inversely related to the particle size. In water, vanadium is converted from trivalent forms to pentavalent forms. The levels of vanadium in surface water range from 0.04 to 104 µg/L. Vanadium levels of 1.2–1.0 µg/L were measured in tap water samples collected in several U.S. states.

Food is the primary route of exposure for the general population; foods with the highest vanadium content include ground parsley, freeze-dried spinach, wild mushrooms, and oysters. Vanadium in food is mainly ingested as VO^{2+} (vanadyl, V^{4+}) or HVO_4^{2-} (vanadate, V^{5+}). Estimates of dietary vanadium intake range from 0.09 to 0.34 µg/kg/day in adults. Humans are potentially exposed to a variety of vanadium compounds, the most common being vanadium pentoxide, sodium metavanadate, sodium orthovanadate, vanadyl sulfate, and ammonium metavanadate. Organic anthropogenic vanadium compounds, such as bis(maltolato)oxyvanadium (IV) or vanadyl acetyl acetonate, are used in the treatment of diabetes and cancer; these compounds have different toxicokinetic properties than inorganic vanadium compounds and are not discussed in this toxicological profile.

Although there is some evidence to suggest that vanadium is an essential nutrient, a functional role for vanadium in humans has not been established; increases in abortion rates and decreased milk production have been observed in vanadium-deprived goats. Vanadium mimics insulin and stimulates cell proliferation and differentiation. In animal models, particularly streptozotoxin-induced diabetes in rats,

vanadium has been shown to normalize blood glucose and lipid levels, improve insulin sensitivity, and prevent or reverse secondary complications such as cardiomyopathy, cataract development, and impaired antioxidant status.

2.2 SUMMARY OF HEALTH EFFECTS

The general population can be exposed to vanadium primarily through oral (ingestion of vanadium in food) and inhalation routes of exposure. Based on occupational exposure studies, human experimental studies, and studies in laboratory animals, the respiratory tract following inhalation exposure and the gastrointestinal tract, hematological system, and developing organism following oral exposure are the primary targets of toxicity.

Adverse respiratory effects have been reported in humans and animals exposed to vanadium compounds at concentrations much higher than those typically found in the environment. Although the available data in humans are limited, signs of airway irritation (e.g., coughing, wheezing, sore throat) have been reported in subjects acutely exposed to 0.6 mg vanadium/m^3 and in workers exposed to vanadium pentoxide dust. These effects have persisted for days to weeks after exposure termination and are often not associated with alterations in lung function. Studies in laboratory animals provide strong support that the respiratory tract is the most sensitive target following inhalation exposure to vanadium. A variety of lung lesions including alveolar/bronchiolar hyperplasia, inflammation, and fibrosis have been observed in rats and mice exposed to vanadium pentoxide; the severity of the lesions is related to concentration and duration. The lung effects have been observed following acute exposure to 0.56 mg vanadium/m^3 and chronic exposures to 0.28 mg vanadium/m^3 and have been observed after 2 days of exposure. Longer duration exposures also result in inflammation and hyperplasia in the larynx and hyperplasia in nasal goblet cells. These histological alterations result in restrictive impairments in lung function; respiratory distress is observed at vanadium pentoxide concentrations of $\geq$4.5 mg vanadium/m^3.

Other sensitive targets of vanadium toxicity include the gastrointestinal system following oral exposure and hematological system following inhalation or oral exposure. Symptoms of gastrointestinal irritation (diarrhea, cramps, nausea) have been observed in humans following bolus administration of sodium metavanadate or vanadyl sulfate; it appears that with repeated exposure, humans develop a tolerance to these effects. Diarrhea has also been observed in rats and mice orally exposed to lethal doses of vanadium. Microcytic erythrocytosis (evidenced by decreases in hematocrit, hemoglobin, and mean cell volume and increases in reticulocytes and nucleated erythrocytes) has been observed in rats exposed to

1.1 mg vanadium/m^3 as vanadium pentoxide for at least 4 days. Hematological effects, including decreases in erythrocyte levels, decreases in hemoglobin, and increases in reticulocytes have also been observed in rats orally exposed to 1.18 mg vanadium/kg/day as ammonium metavanadate for 4 weeks.

Information on the potential of vanadium to induce developmental effects in humans is limited, but developmental effects have been observed in laboratory animals. Decreases in pup growth have been observed at maternal doses of ≥2.1 mg vanadium/kg/day. At higher doses, decreases in pup survival and gross, skeletal, and visceral malformations and anomalies have been reported; marked decreases in maternal body weight are also observed at these dose levels.

No studies have examined the carcinogenic potential of vanadium in humans. An increase in lung carcinoma incidence has been observed in mice chronically exposed to vanadium pentoxide; there is also marginal evidence for lung cancer in male rats (incidence of carcinoma was higher than historical controls but not concurrent controls). Carcinogenicity has not been adequately assessed in laboratory animals following oral exposure. One study classified vanadium pentoxide in group 2B (possibly carcinogenic to humans) based on inadequate evidence in humans and sufficient evidence in animals. The Department of Health and Human Services and EPA have not classified carcinogenicity of vanadium.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for vanadium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these types of levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic

bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

Acute-Duration Inhalation MRL

- An MRL of 0.0008 mg vanadium/m^3 has been derived for acute-duration inhalation exposure (14 days or less) to vanadium pentoxide dust.

Data on acute toxicity of vanadium in humans are limited to an experimental study in which a small number of subjects were exposed to vanadium pentoxide dust for 8 hours (Zenz and Berg 1967). A persistent cough lasting for 8 days developed in two subjects exposed to 0.6 mg vanadium/m^3; at 0.1 mg vanadium/m^3, a productive cough without any subjective complaints or impact on work or home activities were observed in five subjects. The available studies in laboratory animals focused on potential respiratory tract effects. Impaired lung function, characterized as airway obstructive changes (increased resistance and decreased airflow), was observed in monkeys exposed to 2.5 or 1.7 mg vanadium/m^3 as vanadium pentoxide for 6 hours (Knecht et al. 1985, 1992); the highest no-observed-adverse-effect level (NOAEL) for this effect was 0.34 mg vanadium/m^3. In female rats exposed to 0.56 mg vanadium/m^3 6 hours/day, 5 days/week for 13 days, minimal inflammation and histiocytic infiltration were observed (NTP 2002). Alveolar and bronchiolar epithelial hyperplasia and inflammation were observed in the lungs of mice similarly exposed to 1.1 mg vanadium/m^3 as vanadium pentoxide (NTP 2002). Although the Knecht et al. (1985, 1992) or NTP (2002) studies did not include examination of potential end points outside of the respiratory tract, longer-duration studies have identified the respiratory tract as the most sensitive target of toxicity (NTP 2002). The NTP (2002) rat study was selected as the basis of the acute-duration inhalation MRL.

In the NTP (2002) study, groups of male and female F344 rats received whole-body exposure to 0, 1, 2, or 4 mg vanadium pentoxide/m^3 (0, 0.56, 1.1, or 2.2 mg vanadium/m^3) as particulate aerosols 6 hours/day, 5 days/week. On days 6 and 13, 10 rats/group were killed and a histopathological examination of the lungs was conducted. Four rats per group were killed for examination of the onset and extent of lung lesions after 1, 2, 5, 10, or 16 days of exposure. Hyperplasia of alveolar epithelium and bronchiole epithelium were observed in 100% of the female rats exposed to 1.1 or 2.2 mg vanadium/m^3 for 6 or 13 days. Significant increases in the incidence of histiocytic infiltrate and inflammation were observed in rats exposed to 1.1 or 2.2 mg vanadium/m^3 for 6 or 13 days and in rats exposed to 0.56 mg vanadium/m^3 for 13 days. A significant increase in fibrosis was observed in rats exposed to 2.2 mg vanadium/m^3 for

13 days. No histopathological alterations were observed in the four female rats killed after 1 day of exposure; by day 2, inflammation and histiocytic infiltrates (increased number of alveolar macrophages) were observed in the rats exposed to 2.2 mg vanadium/m^3. Hyperplasia of the alveolar and bronchiolar epidthelium was first observed on day 5 in rats exposed to 1.1 or 2.2 mg vanadium/m^3.

A benchmark dose (BMD) approach was considered for derivation of the acute-duration inhalation MRL; however, the fit was not considered adequate due to the limited amount of information from the study on the shape of the exposure-response curve for lung inflammation; more information regarding the BMD analysis is presented in Appendix A. A NOAEL/lowest-observed-adverse-effect level (LOAEL) approach was used to derive the MRL. The LOAEL of 0.56 mg vanadium/m^3 for lung inflammation was selected as the point of departure for the MRL. This LOAEL was converted to a human equivalent concentration ($LOAEL_{HEC}$) of 0.073 mg vanadium/m^3 (see Appendix A for more information on the calculation of the $LOAEL_{HEC}$) and divided by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for animal to human extrapolation using dosimetric adjustments, and 10 for human variability), resulting in an acute-duration inhalation MRL of 0.0008 mg vanadium/m^3.

Intermediate-Duration Inhalation MRL

The available data on the toxicity of vanadium following intermediate-duration inhalation exposure are limited to several rat and mouse studies (NTP 2002) involving exposure to vanadium pentoxide for 6 hours/day, 5 days/week. These studies demonstrate that the respiratory tract is the most sensitive target of toxicity. Signs of respiratory distress (rapid respiration, difficulty breathing) have been observed in rats exposed to 4.4 mg vanadium/m^3 as vanadium pentoxide for at least 4 weeks (NTP 2002). A 3-month exposure resulted in increased incidences of lung lesions in rats and mice and nasal lesions in rats. Lung effects included alveolar and bronchiolar epithelial hyperplasia, histiocytic infiltrates, inflammation, and fibrosis. A NOAEL of 0.56 mg vanadium/m^3 was identified in both species. At 1.1 mg vanadium/m^3, epithelial hyperplasia and inflammation (male rats and female mice only) were observed. In mice, the severity of the lesions was graded as minimal. In rats, the epithelial hyperplasia was graded as mild in males and minimal to mild in females and the inflammation was graded as mild. These data suggest that at a given air concentration, rats are more sensitive than mice based on the severity of the lesions. In both species, the severity of the lesions increased with increasing concentrations. Significant alterations in pulmonary function suggestive of a restrictive disease were observed in rats exposed to 2.2 or 4.4 mg vanadium/m^3; lung function tests were not performed in mice. Nasal effects in rats included hyperplasia and squamous metaplasia of the respiratory epithelium and inflammation. The NOAEL and LOAEL for

nasal effects were 2.2 and 4.5 mg vanadium/m^3 in males and 1.1 and 2.2 mg vanadium/m^3 in females. In addition to the respiratory tract effects, mild microcytic erythrocytosis was observed in rats exposed to ≥1.1 mg vanadium/m^3.

The lowest LOAEL identified in intermediate-duration studies is 1.1 mg vanadium/m^3 for lung epithelial hyperplasia and inflammation in rats exposed 6 hours/day, 5 days/week for 13 weeks (NTP 2002); the NOAEL for these effects is 0.56 mg vanadium/m^3. However, this NOAEL is the same as the LOAEL for lung inflammation in rats exposed for 13 days (NTP 2002). As summarized in Table 2-1, lung inflammation was observed in rats exposed to 0.56 mg vanadium/m^3 for 6 days (not significant), 13 days, and 2 years. Although the three studies were conducted for the National Toxicology Program (NTP), the 13-week study was conducted at a different laboratory using the same strain of rats and vanadium pentoxide dusts with similar particles sizes as the acute and chronic studies. An explanation for the inconsistent findings is not apparent from the available data. Because an intermediate-duration inhalation MRL based on the NOAEL identified in the 13-week study would be higher than the acute-duration inhalation MRL, the database is not considered adequate for derivation of an intermediate-duration inhalation MRL. However, it would be expected that the acute-duration inhalation MRL would be protective of intermediate-duration exposure to vanadium.

Chronic-Duration Inhalation MRL

- An MRL of 0.0001 mg vanadium/m^3 has been derived for chronic-duration inhalation exposure (1 year or longer) to vanadium pentoxide dust.

Two-year rat and mouse studies conducted by NTP (2002) examined the chronic toxicity of inhaled vanadium pentoxide 6 hours/day, 5 days/week for 2 years. At the lowest concentration tested in rats (0.28 mg vanadium/m^3), lung (increases in the incidence of alveolar and bronchiolar epithelial hyperplasia), larynx (degeneration and hyperplasia of the epiglottis epithelium), and nasal (goblet cell hyperplasia in respiratory epithelium) effects were observed. Similar lung and larynx effects were observed in mice at the lowest concentration tested (0.56 mg vanadium/m^3). The nasal effects observed in mice exposed to 0.56 mg vanadium/m^3 included goblet cell hyperplasia in the respiratory epithelium and nasal olfactory epithelial atrophy and hyaline degeneration. In addition to these effects, a significant increase in alveolar/bronchiolar carcinoma incidence was also observed in mice exposed to ≥0.56 mg vanadium/m^3. In male rats, an increased combined incidence of alveolar/bronchiolar adenoma or carcinoma was also observed; however, the incidence was not significantly higher than concurrent

Table 2-1. Lung Effects Observed in Rats Exposed to Vanadium Pentoxide 6 Hours/day, 5 Days/week for 6 or 13 Days, 3 Months, or 2 Years

	mg vanadium/m^3						
Air concentration	0	0.28	0.56	1.1	2.2	4.5	9.0
			6-Day study				
Alveolar hyperplasia	0/10		0/10	10/10[a] (1.1)[b]	8/10[a] (1.4)		
Bronchiole hyperplasia	1/10 (1.0)		0/10	10/10[a] (1.7)	10/10[a] (1.8)		
Histiocytic infiltrate	2/10 (1.0)		6/10 (1.3)	10/10[a] (1.4)	10/10[a] (1.8)		
Inflammation	0/10		3/10 (1.0)	10/10[a] (1.5)	10/10[a] (2.5)		
			13-Day study				
Alveolar hyperplasia	0/10		3/10 (1.0)	10/10[a] (1.0)	10/10[a] (2.0)		
Bronchiole hyperplasia	0/10		0/10	10/10[a] (1.0)	10/10[a] (1.8)		
Histiocytic infiltrate	0/10		10/10[a] (1.3)	10/10[a] (1.9)	10/10[a] (2.2)		
Inflammation	0/10		8/10 (1.3)	10/10[a] (1.7)	10/10[a] (2.0)		
Fibrosis	0/10		0/10	0/10	6/10[a] (1.5)		
			3-Month study (males)				
Epithelial hyperplasia	0/10		0/10	10/10[a] (2.0)	10/10[a] (3.0)	10/10[a] (3.6)	10/10[a] (3.3)
Inflammation	0/10		0/10	9/10[a] (1.0)	10/10[a] (1.0)	10/10 (1.6)	10/10[a] (2.1)
Fibrosis	0/10		0/10	2/10 (1.0)	10/10[a] (1.9)	10/10[a] (3.2)	10/10 (3.1)
			3-Month study (females)				
Epithelial hyperplasia	0/10		0/10	10/10[a] (1.3)	10/10[a] (2.9)	10/10[a] (3.5)	10/10[a] (3.2)
Inflammation	0/10		0/10	0/10	10/10[a] (1.0)	10/10[a] (1.9)	10/10[a] (1.2)
Fibrosis	0/10		0/10	0/10	10/10[a] (1.0)	10/10[a] (2.9)	10/10[a] (3.2)

Table 2-1. Lung Effects Observed in Rats Exposed to Vanadium Pentoxide 6 Hours/day, 5 Days/week for 6 or 13 Days, 3 Months, or 2 Years

	mg vanadium/m^3						
Air concentration	0	0.28	0.56	1.1	2.2	4.5	9.0
			2-Year study (males)				
Alveolar hyperplasia	7/50 (2.3)	24/49[a] (2.0)	34/48[a] (2.0)	49/50[a] (3.3)			
Bronchiole hyperplasia	3/50 (2.3)	17/49[a] (2.2)	31/48[a] (1.8)	49/50[a] (3.3)			
Inflammation	5/50 (1.6)	8/49 (1.8)	24/48[a] (1.3)	42/50[a] (2.4)			
Fibrosis	7/50 (1.4)	7/49 (2.0)	16/48[a] (1.6)	38/50[a] (2.1)			
Histiocyte infiltration	22/50 (1.3)	40/49[a] (2.0)	45/48[a] (2.3)	50/50[a] (3.3)			
			2-Year study (females)				
Alveolar hyperplasia	4/49 (1.0)	8/49 (1.8)	21/50[a] (1.2)	50/50[a] (3.1)			
Bronchiole hyperplasia	6/49 (1.5)	5/49 (1.6)	14/50[a] (1.3)	48/50[a] (3.0)			
Inflammation	10/49 (1.5)	10/49 (1.1)	14/50 (1.2)	40/50[a] (1.7)			
Fibrosis	19/49 (1.4)	7/49[a] (1.3)	12/50 (1.6)	32/50[a] (1.4)			
Histiocyte infiltration	26/49 (1.4)	35/49[a] (1.3)	44/50[a] (2.0)	50/50[a] (1.9)			

[a]$p \leq 0.05$
[b]Average severity grade of lesions in affected animals: 1=minimal; 2=mild, 3=moderate; 4=marked

Source: NTP 2002

controls, but was higher than historical controls. Because the rat study identified a lower LOAEL for lung, larynx, and nasal effects, it was selected as the basis of a chronic-duration inhalation MRL.

In the NTP (2002) study, groups of 50 male and 50 female F344 rats were exposed to 0, 0.5, 1, or 2 mg vanadium pentoxide/m^3 (0, 0.28, 0.56, and 1.1 mg vanadium/m^3) 6 hours/day, 5 days/week for 104 weeks. No significant alterations in survival or body weight gain were observed in the vanadium-exposed rats. Alveolar histiocytic infiltrates were observed in males and females exposed to ≥0.28 mg vanadium/m^3. Significant increases in the incidence of hyperplasia of the alveolar and bronchiolar epithelium were observed in males exposed to ≥0.28 mg vanadium/m^3 and females exposed to ≥0.56 mg vanadium/m^3. Squamous metaplasia was observed in alveolar epithelium of males and females exposed to 1.1 mg vanadium/m^3 and in the bronchiolar epithelium of males exposed to 1.1 mg vanadium/m^3. Chronic inflammation was observed in males exposed to 0.56 or 1.1 mg vanadium/m^3 and females exposed to 1.1 mg vanadium/m^3 and interstitial fibrosis was observed in males exposed to 1.1 mg vanadium/m^3 and females exposed to 0.28 or 1.1 mg vanadium/m^3. An increased incidence of brownish pigment in alveolar macrophages was observed in males exposed to 1.1 mg vanadium/m^3 and females exposed to 0.56 or 1.1 mg vanadium/m^3; this effect was considered to be of little biological relevance. Chronic inflammation, degeneration and hyperplasia of the epiglottis were observed in the larynx of males and females exposed to ≥0.28 mg vanadium/m^3; squamous metaplasia of the epiglottis respiratory epithelium was also observed in males exposed to ≥0.28 mg vanadium/m^3 and in females exposed to 1.1 mg vanadium/m^3. Goblet cell hyperplasia of the nasal respiratory epithelium was observed in males exposed to ≥0.28 mg vanadium/m^3 and in females exposed to 1.1 mg vanadium/m^3.

BMD analyses of the incidence data for alveolar and bronchiolar epithelial hyperplasia, chronic inflammation of the larynx, degeneration of epiglottis respiratory epithelium, and hyperplasia of nasal respiratory epithelial goblet cells in male rats were used to determine the point of departure for the MRL. As described in greater detail in Appendix A, the $BMCL_{10}$ values for these effects were 0.09, 0.10, 0.07, 0.04, and 0.16 mg vanadium/m^3, respectively.

These $BMCL_{10}$ values were converted to a human equivalent concentrations (as described in detail in Appendix A); the $BMCL_{HEC}$ values were 0.008, 0.017, 0.005, 0.003, and 0.012 mg vanadium/m^3 for alveolar epithelial hyperplasia, bronchiolar epithelial hyperplasia, chronic inflammation of the larynx, degeneration of epiglottis respiratory epithelium, and hyperplasia of nasal respiratory epithelial goblet cells, respectively. The $BMCL_{HEC}$ of 0.003 mg vanadium/m^3 for degeneration of epiglottis respiratory epithelium was selected as the point of departure. This value was divided by an uncertainty factor of

30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability), resulting in a chronic-duration inhalation MRL of 0.0001 mg vanadium/m^3.

Oral MRLs

Acute-Duration Oral MRL

Gastrointestinal effects (diarrhea, cramps, nausea, and vomiting) have been observed in diabetic patients administered vanadyl sulfate or sodium metavanadate capsules as a supplement to their diabetes treatment (Boden et al. 1996; Cusi et al. 2001; Goldfine et al. 1995). The gastrointestinal effects subsided within the first couple of weeks of exposure. The concentrations in the capsules ranged from 16 to 24 mg and daily doses ranged from 0.35 to 0.66 mg vanadium/kg/day. A small number of studies in laboratory animals have examined the acute toxicity of vanadium following oral exposure. Significant increases in reticulocyte levels in peripheral blood and polychromatophilic erythroblasts in the bone marrow were observed in rats exposed to 27.72 mg vanadium/kg/day as ammonium metavanadate in drinking water for 2 weeks (Zaporowska and Wasilewski 1989). The remaining nonlethality studies reported developmental effects in the offspring of rats and mice administered 7.5–8.4 mg vanadium/kg/day via gavage during gestation (Paternain et al. 1987, 1990; Sanchez et al. 1991). The observed developmental effects included decreases in fetal growth, increases in resorptions, and gross, visceral, and skeletal malformations and anomalies.

Although the human studies identified the lowest LOAEL values, they were not considered suitable as the basis of an MRL. These studies used a small number of diabetic subjects (5–10 subjects per study) and no control group. The lowest LOAEL identified in an animal study is 7.5 mg vanadium/kg/day for developmental effects (Paternain et al. 1990). In this study, significant increases in early resorptions, decreases in fetal body weight and length, and increases in the incidence of soft tissue anomalies/ malformations (hematomas in facial area, neck, and dorsal area, cleft palate), and skeletal defects (delayed ossification of supraoccipital bone, carpus, tarsus, and sternebrae) were observed in the offspring of Swiss mice administered via gavage 7.5 mg vanadium/kg/day as vanadyl sulfate on gestation days 6–15. This dose was also associated with significant decreases in maternal body weight gain (during gestation days 6–15, the dams gained 46% less weight than controls); no significant alterations in food intake were observed. Because 7.5 mg vanadium/kg/day is a serious LOAEL in the dams (ATSDR defines serious effects as those that evoke failure in a biological system and can lead to morbidity or mortality), this study is not suitable for derivation of an acute-duration oral MRL. It is ATSDR's policy to not use a LOAEL for serious health effects as the basis of an MRL.

Intermediate-Duration Oral MRL

- An MRL of 0.01 mg vanadium/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to vanadium.

Two human studies have examined the oral toxicity of vanadium. No significant alterations in hematological parameters, liver function (as measured by serum enzymes), cholesterol and triglyceride levels, kidney function (as measured by blood urea nitrogen), body weight, or blood pressure were observed in subjects administered via capsule 0.12 or 0.19 mg vanadium as ammonium vanadyl tartrate or vanadyl sulfate for 6–12 weeks (Dimond et al. 1963; Fawcett et al. 1997). Studies in laboratory animals have identified several sensitive effects including alterations in erythrocyte and reticulocyte levels, increased blood pressure, neurobehavioral alterations, and developmental toxicity. The lowest LOAEL identified in an intermediate-duration study was 0.12 mg vanadium/kg/day for increases in blood pressure observed in rats exposed to sodium metavanadate in drinking water for 210 days (Boscolo et al. 1994); several other studies by these investigators have reported similar effects at higher doses (Carmagnani et al. 1991, 1992). However, other studies have not found significant alterations in blood pressure at higher doses (Bursztyn and Mekler 1993; Sušić and Kentera 1986, 1988). Significant decreases in erythrocyte levels have been observed in rats exposed to 1.18 mg vanadium/kg/day as ammonium metavanadate in drinking water for 4 weeks (Zaporowska et al. 1993); at higher concentrations, decreases in hemoglobin and increases in reticulocyte levels have been observed (Ścibior 2005; Ścibior et al. 2006; Zaporowska and Wasilewski 1990, 1991, 1992a, 1992b; Zaporowska et al. 1993). However, other intermediate-duration studies have not found significant alterations at doses as high as 9.7 mg vanadium/kg/day (Dai et al. 1995; Mountain et al. 1953). At 1.72 mg vanadium/kg/day, impaired performance on neurobehavioral tests (open field and active avoidance tests) was observed in rats exposed to administered sodium metavanadate for 8 weeks (Sanchez et al. 1998). No other studies have examined the neurotoxic potential of vanadium. As with acute-duration exposure, the developing organism is a sensitive target of vanadium toxicity. Decreases in pup body weight and length were observed in the offspring of rats administered 2.1 mg vanadium/kg/day as sodium metavanadate for 14 days prior to mating and throughout gestation and lactation (Domingo et al. 1986). At higher doses (6, 10, or 12 mg vanadium/kg/day), decreases in pup survival, and increases in the occurrence of gross, visceral, or skeletal malformations and anomalies were observed (Elfant and Keen 1987; Morgan and El-Tawil 2003; Poggioli et al. 2001).

The animal database suggests that the most sensitive targets of vanadium toxicity are blood pressure, erythroctyes, nervous system, and the developing organism with LOAEL values of 0.12, 1.18, 1.72, and

2.1 mg vanadium/kg/day, respectively. Two approaches for derivation of an intermediate-duration oral MRL were considered. In the first approach, the NOAEL of 0.12 mg vanadium/kg/day identified in the Fawcett et al. (1997) study was used as the point of departure for the MRL. The Fawcett et al. (1997) study was selected over the Dimond et al. (1963) study, which identified a slightly higher NOAEL (0.19 mg vanadium/kg/day) because more subjects (six subjects in Dimond study compared to 15–16 subjects in Fawcett study) were examined and the results of the study are described in greater detail. In the Fawcett et al. (1997) study, groups of men and women enrolled in a weight training program for at least 1 year were administered capsules containing 0 (11 men and 4 women) or 0.12 mg vanadium/kg/day as vanadyl sulfate trihydrate (12 men and 4 women) for 12 weeks. Fasting blood samples were collected at 0 and 12 weeks and analyzed for hematological (erythrocyte count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, platelet count, and total and differential leukocyte count) and serum chemistry (cholesterol, high density lipoprotein, triglycerides, albumin, total protein, total and direct bilirubin, alkaline phosphatase, alanine amino-transferase) parameters. Body weight and blood pressure were measured at weeks 4, 8, and 12. No significant alterations in blood pressure, body weight, or hematological or clinical chemistry parameters were found. Using the NOAEL of 0.12 mg vanadium/kg/day and an uncertainty factor of 10 for human variability, the MRL would be 0.01 mg vanadium/kg/day.

Several animal studies were also considered as the basis of an MRL. Although an increase in blood pressure was observed at the lowest adverse effect level (0.12 mg vanadium/kg/day; Boscolo et al. 1994), this end point was not selected as the basis for an intermediate-duration oral MRL. This effect has not been consistently observed among rat studies and no alterations in blood pressure were observed in a study of healthy adults exposed to 0.12 mg vanadium/kg/day for 12 weeks (Fawcett et al. 1997). The next highest LOAEL of 1.18 mg vanadium/kg/day for a decrease in erythrocyte levels in rats (Zaporowski et al. 1993) was considered as the principal study for the MRL. In the Zaporowski et al. (1993) study, groups of 2-month-old male and female Wistar rats (15–16/sex/group) were exposed to ammonium metavanadate in drinking water for 4 weeks at doses of 0, 1.18, and 4.93 mg vanadium/kg/day (males) or 1.50 and 6.65 mg vanadium/kg/day (females). No alterations in behavior or motor activity were observed. A significant decrease in water consumption (14% less than controls) was observed in males exposed to 4.93 mg vanadium/kg/day. No significant alterations in body weight gain were observed. As summarized in Table 2-2, alterations in erythrocyte, hemoglobin, hematocrit, and reticulocyte levels were observed. This study identified a minimal LOAEL of 1.18 mg vanadium/kg/day for decreases in erythrocyte and hematocrit levels in male rats. The alteration in erythrocyte levels was considered minimally adverse because the magnitude of the change was small (approximately 11%). Dividing this

Table 2-2. Hematological Effects in Rats Exposed to Ammonium Metavanadate for 4 Weeks

	Dose (mg vanadium/kg/day)		
Males	0	1.18	4.93
Erythrocytes ($x10^{12}/dm^3$)	8.32	7.38[a]	7.47[b]
Hemoglobin (mmol/L)	9.37	8.94	8.65[a]
Hematocrit (L)	0.48	0.47[b]	0.47[a]
Reticulocytes (%)	2.55	2.64	3.82[b]
Females	0	1.50	6.65
Erythrocytes ($x10^{12}/dm^3$)	8.24	7.38[c]	7.12[c]
Hemoglobin (mmol/L)	9.41	8.76	8.72[a]
Hematocrit (L)	0.48	0.47	0.47
Reticulocytes (%)	2.55	2.91	3.64[b]

[a]Significantly different from control group ($p<0.01$)
[b]Significantly different from control group ($p<0.05$)
[c]Significantly different from control group ($p<0.001$)

Source: Zaporowska et al. 1993

minimal LOAEL by an uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability) results in an MRL of 0.004 mg vanadium/kg/day.

Although an MRL based on the Zaporwska et al. (1993) rat study would be approximately 3 times lower than an MRL based on the Fawcett et al. (1997) human study, the Fawcett et al. (1997) study was selected as the basis of the intermediate-duration oral MRL because greater confidence was given to an MRL based on a reliable human study. Thus, the intermediate-duration oral MRL is 0.01 mg vanadium/kg/day.

Chronic-Duration Oral MRL

No studies examining the chronic toxicity of vanadium in humans were identified. Although several laboratory animal studies have examined chronic toxicity, most tested low doses and did not find effects. No adverse effects were observed in rats and mice exposed to 0.7 or 4.1 mg vanadium/kg/day, respectively, as vanadyl sulfate in drinking water for 2–2.5 years (Schroeder et al. 1970; Schroeder and Balassa 1967). In rats exposed to 28 mg vanadium/kg/day as vanadyl sulfate in drinking water, a 20% decrease in body weight gain was observed; no alterations in lungs, heart, liver, or kidneys histopathology, hematological parameters, or blood pressure were observed at 19 mg vanadium/kg/day (Dai and McNeill 1994; Dai et al. 1994a, 1994b). Because the most sensitive target of vanadium toxicity following chronic-duration oral exposure have not been identified, the animal studies that mostly identified free-standing NOAEL values were not considered suitable for derivation of an MRL.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of vanadium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

Elemental vanadium does not occur in nature; however, vanadium compounds exist in over 50 different mineral ores and in association with fossil fuels. It has six oxidation states (1-, 0, 2+, 3+, 4+, and 5+) of which 3+, 4+, and 5+ are the most common. The toxicologically significant compounds are vanadium pentoxide (V_2O_5), sodium metavanadate ($NaVO_3$), sodium orthovanadate (Na_3VO_4), vanadyl sulfate ($VOSO_4$), and ammonium vanadate (NH_4VO_3). Vanadium pentoxide dust is usually encountered in occupational settings, and humans would be exposed via the inhalation route. Organic vanadium compounds, such as bis(maltolato)oxyvanadium (IV), bis(ethylmaltolato)oxyvanadium (IV), and vanadyl acetyl acetonate, have been synthesized for use in the treatment of diabetes and cancer. Because these compounds likely have different toxicokinetic properties from inorganic vanadium compounds, they are not included in this toxicological profile.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress

or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to vanadium.

Increases in mortality have been observed in several studies of laboratory animals exposed to vanadium pentoxide. Deaths occurred in rabbits exposed to 114 mg vanadium/m^3 for 1 hour, but not in rabbits exposed to 43 mg vanadium/m^3 (Sjöberg 1950). Exposure to 18 mg vanadium/m^3 as vanadium pentoxide resulted in death in three of five rats exposed for 6 days (NTP 2002). Intermediate-duration exposure resulted in deaths in rats exposed to 9 mg vanadium/m^3 and mice exposed to 18 mg vanadium/m^3 (NTP

2002). A decrease in survival was observed in mice chronically exposed to 2.2 mg vanadium/m^3 (NTP 2002). The LOAEL values are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Although a number of studies have reported respiratory effects in humans exposed to vanadium, in particular vanadium pentoxide, very few provide reliable quantitative exposure data. In an experimental study, persistent coughing lasting 8 days after exposure termination was observed in two subjects exposed to 0.6 mg vanadium/m^3 for 8 hours; no alterations in lung function (lung function parameters assessed: forced vital capacity, 0.5 and 1 second forced expiratory volume, maximal expiratory flow, 200–1,200 cc flow rate, maximal midexpiratory time, and forced inspiratory vital capacity) were observed (Zenz and Berg 1967). At 0.1 mg vanadium/m^3, five subjects reported productive coughing without other subjective complaints, alterations in lung function, or changes in daily activities; this concentration level was considered a NOAEL. Workers exposed to a range of vanadium pentoxide dust levels for as little as 1 day (Levy et al. 1984; Musk and Tees 1982; Thomas and Stiebris 1956; Zenz et al. 1962) or as long as ≥6 years (Irsigler et al. 1999; Lewis 1959; NIOSH 1983; Sjöberg 1956; Vintinner et al. 1955; Wyers 1946), show mild respiratory distress, such as cough, wheezing, chest pain, runny nose, or sore throat. One study of chronically-exposed workers showed increased neutrophils in the nasal mucosa (Kiviluoto 1980; Kiviluoto et al. 1979b, 1981a). More severe pathology has not been reported. Symptoms are reversible within days or weeks after exposure ceases. Data were not located to assess the relationship of exposure level or duration to severity of response. Chest x-rays and pulmonary function tests were normal in most cases. Chronic effects were infrequently reported. In a study of 40 vanadium pentoxide workers with persistent respiratory symptoms (Irsigler et al. 1999), 12 were found to have bronchial hyperresponsiveness to inhaled histamine or exercise challenge. No significant alterations in baseline lung function were found. The mean urine vanadium level (assessed via spot urine samples) in the hyperresponsive group was 52.7 µg/g creatinine compared to 30.7 µg/g creatinine in 12 matched subjects with persistent respiratory symptoms and without bronchial hyperreactivity; statistical comparisons of the two groups were not made. Five to 23 months after removal from exposure, bronchial hyperreactivity was still present in nine of the subjects, although the response was less severe in five of them and more severe in one subject.

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rabbit	1 d 7 hr/d (NS)				114 (2/4 died)	Sjoberg 1950 VANADIUM PENTOXIDE	
Systemic								
2	Monkey (Cynomolgus)	6 hr (NS)	Resp	0.34 M	2.5 M (impaired lung function)		Knecht et al. 1985 VANADIUM PENTOXIDE	
3	Monkey (Cynomolgus)	6 hr	Resp	0.28 M	1.7 M (impaired lung function)		Knecht et al. 1992 VANADIUM PENTOXIDE	
4	Rat (Fischer- 344)	6 hr/d 5 d/wk 6 or 13 d	Resp		0.56[b] F (histiocytic infiltrate and inflammation in lungs)		NTP 2002 VANADIUM PENTOXIDE	
5	Mouse (B6C3F1)	6 hr/d 5 d/wk 6 or 13 d	Resp		1.1 F (hyperplasia of alveolar and bronchiole epithelium and inflammation in lungs)		NTP 2002 VANADIUM PENTOXIDE	
INTERMEDIATE EXPOSURE								
Death								
6	Rat (Fischer- 344)	6 hr/d 5 d/wk 16 d				18 M (3/5 males died)	NTP 2002 VANADIUM PENTOXIDE	
7	Rat (Fischer- 344)	6 hr/d 5 d/wk 3 mo				9 (7/10 males and 3/10 females died)	NTP 2002 VANADIUM PENTOXIDE	

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
8	Mouse (B6C3F1)	6 hr/d 5 d/wk 16 d				18 M (5/5 males died)	NTP 2002 VANADIUM PENTOXIDE	
Systemic								
9	Monkey (Cynomolgus)	6 hr/d 5 d/wk 26 wk	Resp		0.62 M (audible wheezing and coughing in 3/8 monkeys)		Knecht et al. 1992 VANADIUM PENTOXIDE	
10	Rat (Fischer- 344)	6 hr/d 5 d/wk 16 d	Resp	1.1	2.2 (localized inflammatory response)		NTP 2002 VANADIUM PENTOXIDE	
			Bd Wt	4.5	9 (12-13% decreased body weight gain)	9 (25-40% decreased body weight gain)		
11	Rat (Fischer- 344)	6 hr/d 5 d/wk 3 mo	Resp	0.56	1.1 (epithelial hyperplasia and inflammation in lungs)		NTP 2002 VANADIUM PENTOXIDE	
			Cardio	4.5				
			Gastro	4.5				
			Musc/skel	4.5				
			Hepatic	4.5				
			Renal	4.5				
			Dermal	4.5				
			Bd Wt	4.5		9 (30-60% decreased body weight gain)		

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
12	Mouse (B6C3F1)	6 hr/d 5 d/wk 16 d	Resp	1.1	2.2 (lung inflammation)		NTP 2002 VANADIUM PENTOXIDE	
			Bd Wt	9		18 (28% decreased body weight gain)		
13	Mouse (B6C3F1)	6 hr/d 5 d/wk 3 mo	Resp	0.56	1.1 (lung inflammation and epithelial hyperplasia)		NTP 2002 VANADIUM PENTOXIDE	
			Cardio	9				
			Gastro	9				
			Hepatic	9				
			Renal	9				
			Bd Wt	4.5 F	9 F (12% decreased body weight gain)			
Immuno/ Lymphoret								
14	Rat (Fischer- 344)	6 hr/d 5 d/wk 16 d			2.2 (decr phagocytosis and incr bactericidal activity)		NTP 2002 VANADIUM PENTOXIDE	
15	Mouse (B6C3F1)	6 hr/d 5 d/wk 16 d		18			NTP 2002 VANADIUM PENTOXIDE	
Reproductive								
16	Rat (Fischer- 344)	6 hr/d 5 d/wk 3 mo		9 M 2.2 F	4.5 F (increased estrous cycle length)		NTP 2002 VANADIUM PENTOXIDE	

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
17	Mouse (B6C3F1)	6 hr/d 5 d/wk 3 mo		2.2 M 9 F	4.5 M (decreased epididymal spermatozoa motility)		NTP 2002 VANADIUM PENTOXIDE	
CHRONIC EXPOSURE								
Death								
18	Mouse (B6C3F1)	6 hr/d 5 d/wk 2 yr				2.2 M (decreased survival in males)	NTP 2002 VANADIUM PENTOXIDE	
Systemic								
19	Rat (Fischer- 344)	6 hr/d 5 d/wk 2 yr	Resp		0.28[c] (hyperplasia of alveolar and bronchiolar epithelium, degeneration and hyperplasia of epiglottis epithelium, and goblet cell hyperplasia in nasal respiratory epithelium)		NTP 2002 VANADIUM PENTOXIDE	
			Cardio	1.1				
			Gastro	1.1				
			Musc/skel	1.1				
			Hepatic	1.1				
			Renal	1.1				
			Bd Wt	1.1				

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)		LOAEL Serious (mg V/m³)		Reference Chemical Form	Comments
20	Mouse (B6C3F1)	6 hr/d 5 d/wk 2 yr	Resp		0.56	(hyperplasia and chronic inflammation in lungs; squamous metaplasia of epiglottis epithelium and nasal respiratory epithelium; atrophy and degeneration of nasal olfactory epithelium)			NTP 2002 VANADIUM PENTOXIDE	
			Cardio	2.2						
			Gastro	2.2						
			Hepatic	2.2						
			Renal	2.2						
			Dermal	2.2						
			Bd Wt	0.56	1.1	(15-20% decreased body weight gain)	2.2	(20-29% decreased body weight gain)		
Cancer										
21	Rat (Fischer- 344)	6 hr/d 5 d/wk 2 yr					0.28 M	(lung tumor incidence higher than historical controls)	NTP 2002 VANADIUM PENTOXIDE	

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
22	Mouse (B6C3F1)	6 hr/d 5 d/wk 2 yr				0.56 (alveolar/bronchiolar carcinoma)	NTP 2002 VANADIUM PENTOXIDE	

a The number corresponds to entries in Figure 3-1

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.0008 mg vanadium/m3; concentration adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days), multiplied by the Regional Deposited Dose Ratio (RDDR) of 0.732 for the thoracic region, and divided by an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to human with dosimetric adjustment, and 10 for human variability).

c Used to derive a chronic-duration inhalation MRL of 0.0001 mg vanadium/m3 calculated using benchmark dose analysis. The BMCL10 of 0.04 mg vanadium/m3 was adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days), multiplied by the RDDR of 0.423 for the extrathoracic region, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = Female; Gastro = gastrointestinal hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to Vanadium - Inhalation

Acute (≤14 days)

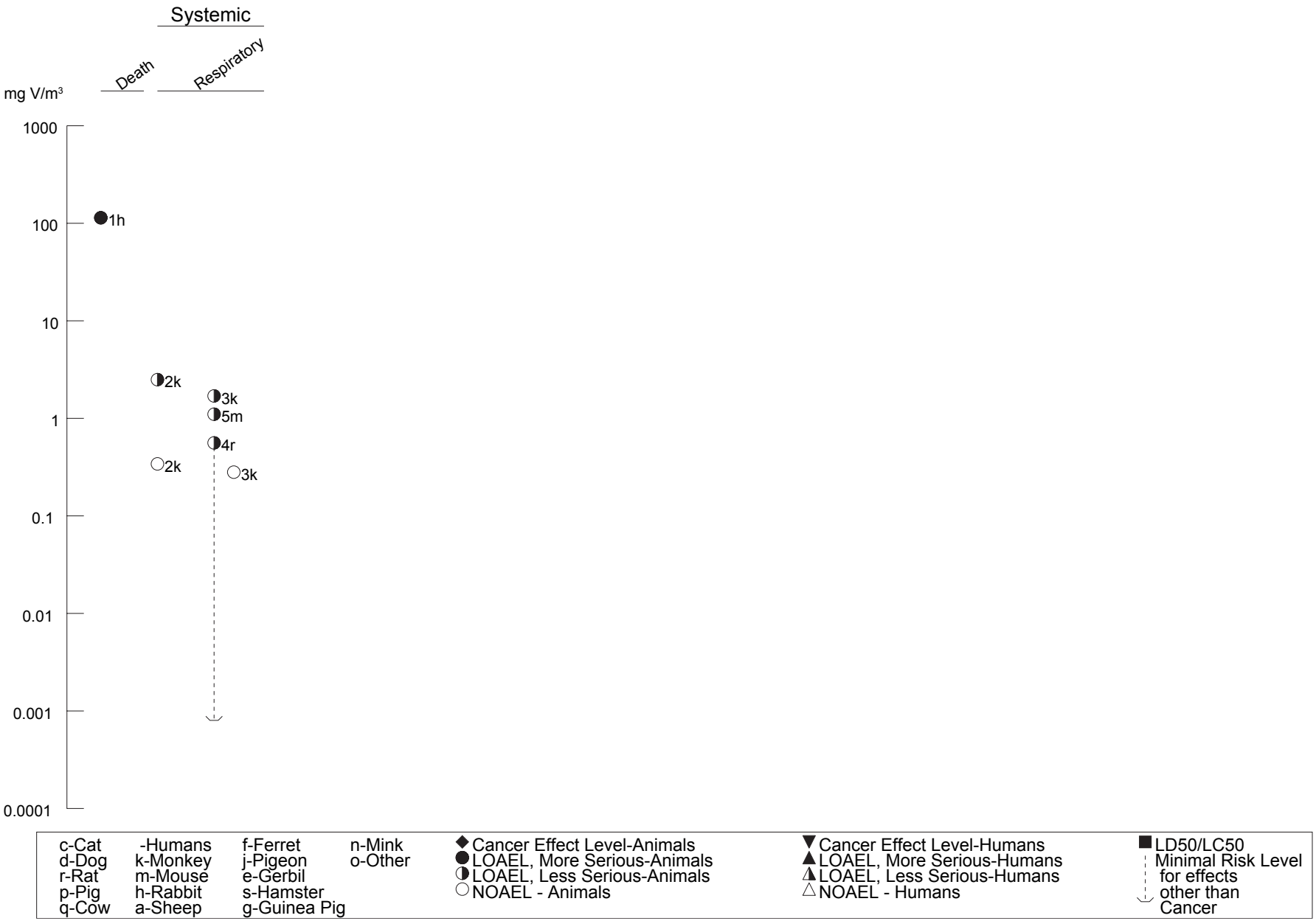


Figure 3-1 Levels of Significant Exposure to Vanadium - Inhalation *(Continued)*

Intermediate (15-364 days)

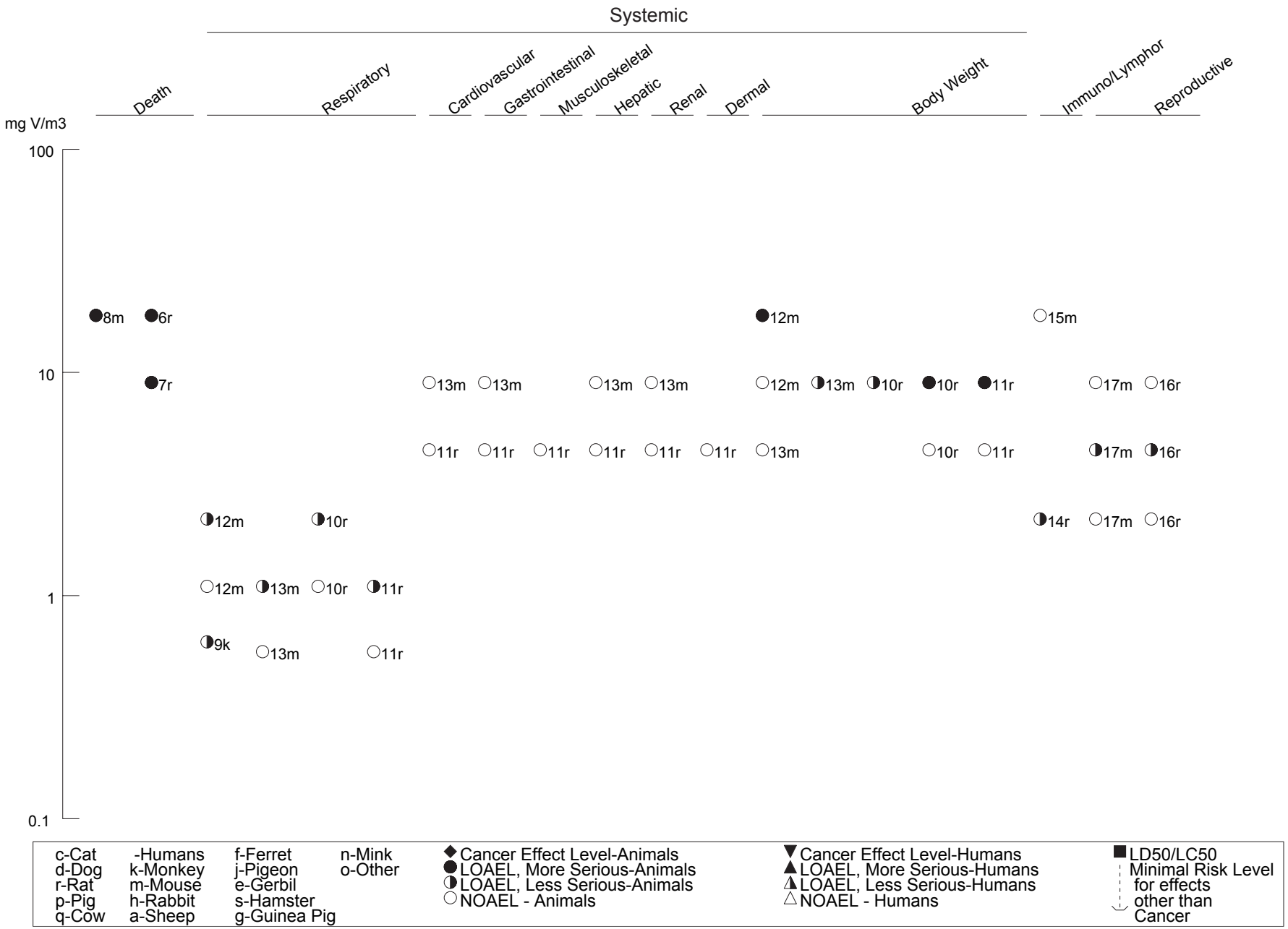
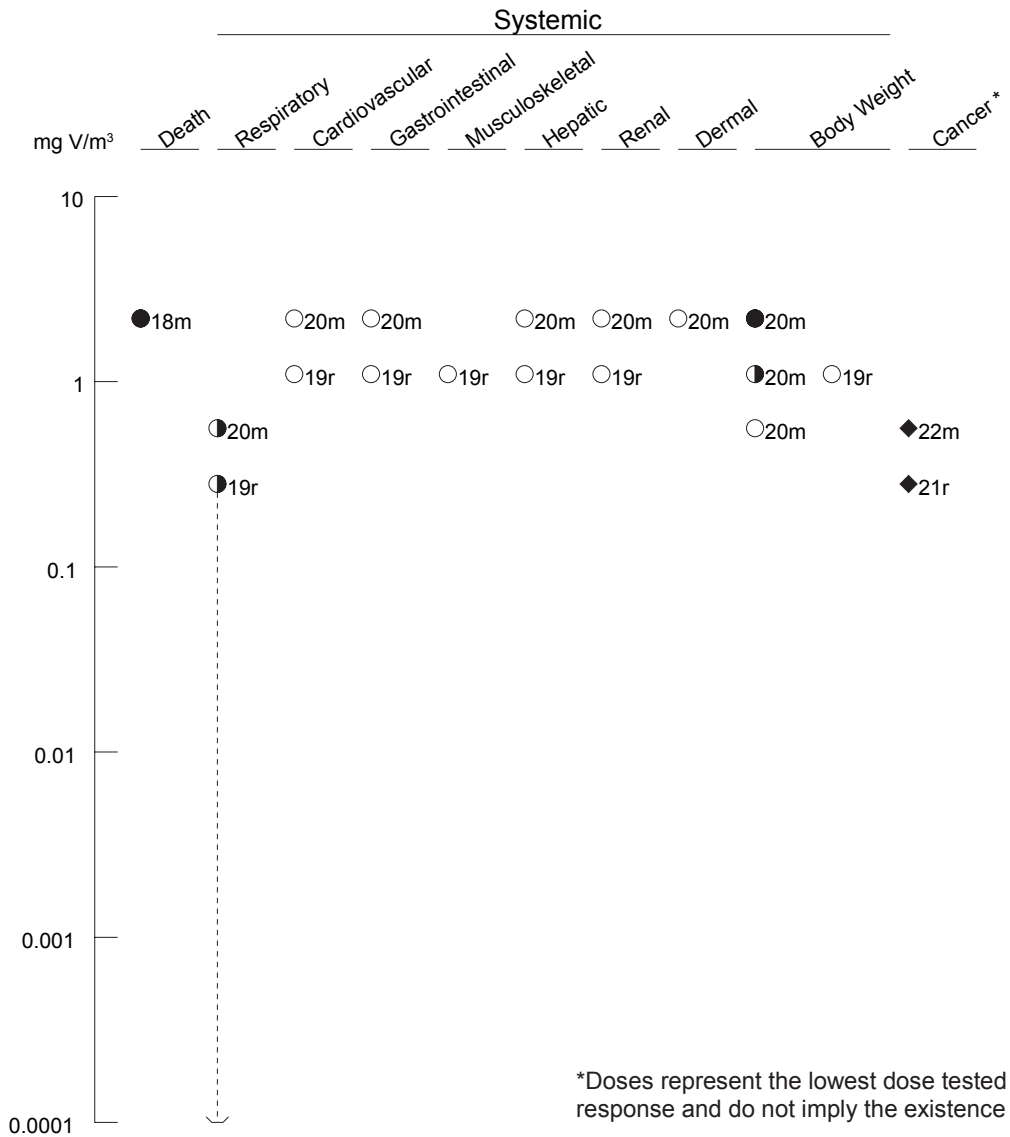


Figure 3-1 Levels of Significant Exposure to Vanadium - Inhalation *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Animal data support the human findings and provide additional evidence that vanadium compounds are respiratory toxicants. Signs of respiratory distress, impaired lung function, increased pulmonary reactivity, and histological alterations in the lungs, larynx, and nasal cavity have been observed in laboratory animals. Rapid respiration during the exposure period was observed in rats exposed to 9.0 mg vanadium/m^3 as vanadium pentoxide for 16 days or 4.5 mg vanadium/m^3 for 4 weeks. In rats exposed to 9.0 mg vanadium/m^3 for 9 weeks, abnormal respiration was also observed during periods between vanadium exposures (NTP 2002). Audible wheezing and coughing were observed in monkeys exposed to 0.62 mg vanadium/m^3 for 6 hours; respiratory symptoms were not observed at 0.14 or 0.028 mg vanadium/m^3 as vanadium pentoxide (Knecht et al. 1992).

Decreases in pulmonary function were observed in rats exposed to ≥2.2 mg vanadium/m^3 6 hours/day, 5 days/week for 13 weeks (NTP 2002). Exposure to 2.2 or 4.5 mg vanadium/m^3 resulted in alterations characterized as restrictive based on reduced lung compliance, changes in breathing measurements, impaired capacity to diffuse carbon monoxide, reduced static and dynamic lung volumes, and exaggerated airflow. The changes in breathing mechanics, static lung volumes, and forced expiratory maneuvers observed at 9.0 mg vanadium/m^3 were suggestive of an obstructive lung disease; however, the investigators noted that these alterations may have been due to the deteriorating condition of the rats rather than an obstructive disease. Increased pulmonary resistance was observed in monkeys 1 day after a 6-hour exposure to 2.8 mg vanadium/m^3 (Knecht et al. 1985). Pulmonary reactivity, as evidenced by an obstructive pattern of impaired pulmonary function, was also observed in monkeys following a 6-hour exposure to 1.7 mg vanadium/m^3 as vanadium pentoxide (Knecht et al. 1992); an increase in the total number of inflammatory cells present in the lungs was also observed. A similar degree of pulmonary reactivity was observed when the monkeys were re-challenged with methacholine following a 26-week exposure to 0.28 mg vanadium/m^3 (6 hours/day, 5 days/week). Pulmonary reactivity was not significantly affected by a provocation challenge with 0.28 mg vanadium/m^3 before or after the 26-week exposure (Knecht et al. 1992).

NTP (2002) conducted a series of studies to evaluate the toxicity of vanadium pentoxide in rats and mice exposed 6 hours/day, 5 days/week for acute, intermediate, and chronic durations. Histological alterations were observed in the lungs, larynx, and nose. In the lungs, hyperplasia of alveolar and bronchiolar epithelium occurred at 1.1 mg vanadium/m^3 in rats and mice exposed for 6, 13, or 90 days, 0.28 mg vanadium/m^3 in rats exposed for 2 years, and 0.56 mg vanadium/m^3 in mice exposed for 2 years. Lung inflammation and histiocytic infiltration (alveolar macrophages) were observed at similar concentrations in the acute, intermediate, and chronic duration studies. Fibrosis was also observed in rats exposed to

2.2 mg vanadium/m^3 for 13 or 90 days or 0.28 mg vanadium/m^3 for 2 years and in mice exposed to 1.1 mg vanadium/m^3 for 2 years. In both species, the severity of the lung lesions increased with increasing exposure duration and vanadium pentoxide exposure level. NTP (2002) also conducted several studies to examine the time course of the lung lesions. In rats exposed to 2.2 mg vanadium/m^3, histiocytic infiltrates and inflammation were observed after 2 days of exposure and alveolar and bronchiolar epithelial hyperplasia were first observed after 5 days of exposure to 1.1 or 2.2 mg vanadium/m^3. In rats exposed to 0.56 mg vanadium/m^3, hyperplasia was only observed in a few animals after 542 days of exposure; however, at the end of the 2-year study, there was a significant increase in the incidence at this exposure level. In mice, lung lesions were not observed after 1 or 2 days of exposure. Bronchiolar epithelial hyperplasia and inflammation were observed after 5 days of exposure to 2.2 mg vanadium/m^3. At the lower exposure levels, lung lesions were observed after 12 days of exposure to 1.1 mg vanadium/m^3 and 54 days of exposure to 0.56 mg vanadium/m^3.

The nasal effects observed in rats consisted of hyperplasia and squamous metaplasia of respiratory epithelium at 2.2 mg vanadium/m^3 for 13 weeks, inflammation at 9.0 mg vanadium/m^3 for 13 weeks, and goblet cell hyperplasia of the respiratory epithelium at 0.28 mg vanadium/m^3 for 2 years. In mice exposed to vanadium pentoxide for 2 years, the nasal effects included suppurative inflammation at 1.1 mg vanadium/m^3, olfactory epithelium atrophy at 0.56 mg vanadium/m^3, hyaline degeneration of olfactory and respiratory epithelium at 0.56 mg vanadium/m^3, and squamous metaplasia of respiratory epithelium at 0.56 mg vanadium/m^3. Chronic exposure also resulted in damage to the larynx; degeneration and hyperplasia of the epiglottis epithelium were observed in rats exposed to 0.28 mg vanadium/m^3 and squamous metaplasia of epiglottis epithelium was observed in rats exposed to 1.1 mg vanadium/m^3 and mice exposed to 0.56 mg vanadium/m^3.

Cardiovascular Effects. Workers exposed chronically to vanadium pentoxide dusts at incompletely documented exposure levels had normal blood pressure values (Vintinner et al. 1955). No other cardiovascular parameters were investigated in this study, but another study revealed normal electrocardiograms in vanadium workers (Sjöberg 1950).

No significant alterations in heart rate, blood pressure, or electrocardiogram readings were observed in rats exposed to 4.5 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks (NTP 2002). Decreases in heart rate and blood pressure were found in rats exposed to 9.0 mg vanadium/m^3; however, this was attributed to the poor condition of the animals rather than a direct cardiotoxic effect. No histological alterations were observed in the hearts of rats exposed to 4.5 or 1.1 mg vanadium/m^3

6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively (NTP 2002).

Gastrointestinal Effects. No gastrointestinal complaints were reported by subjects exposed to 0.6 or 0.1 mg vanadium/m^3 vanadium pentoxide dusts for 8 hours (Zenz and Berg 1967). Workers exposed to vanadium in oil-burner ashes also did not show gastrointestinal symptoms (Sjöberg 1950). One study found that workers exposed chronically to vanadium dusts in factories sometimes complained of nausea and vomiting (Levy et al. 1984), but these symptoms can have a number of causes (such as exposure to other substances) and cannot be directly attributed to the vanadium. No histological alterations were observed in the gastrointestinal tract of rats exposed to 4.5 or 1.1 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively, (NTP 2002).

Hematological Effects. No hematological alterations were observed in humans following acute (Zenz and Berg 1967) or occupational exposure (Kiviluoto et al. 1981a; Sjöberg 1950; Vintinner et al. 1955) to vanadium dusts.

During the first 23 days of a 13-week study, minimal erythrocyte microcytosis (as evidenced by decreases in hematocrit values, hemoglobin, mean cell volume, and mean cell hemoglobin) was observed in rats exposed to vanadium pentoxide 6 hours/day, 5 days/week (NTP 2002). The alterations in hematocrit and hemoglobin were observed after 4 days of exposure to 1.1 mg vanadium/m^3, mean cell volume and mean cell hemoglobin were decreased after 23 or 90 days of exposure to 2.2 mg vanadium/m^3. At 13 weeks, the microcytosis was replaced by erythrocytosis (as evidenced by increases in hemoglobin, hematocrit, nucleated erythrocytes, and reticulocytes) in rats exposed to 4.5 or 9.0 mg vanadium/m^3.

Musculoskeletal Effects. Muscular strength was not altered in one study of workers exposed to vanadium pentoxide (Vintinner et al. 1955). No significant histological alterations were observed in the bone or muscle following a 13-week or 2-year exposure of rats to 9.0 or 1.1 mg vanadium/m^3 as vanadium pentoxide, respectively, or mice to 9.0 or 2.2 mg vanadium/m^3, respectively.

Hepatic Effects. Workers exposed chronically to 0.01–0.5 mg/m^3 of vanadium dusts had normal serum levels of four enzymes (serum alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase) that are commonly used to detect possible liver damage (Kiviluoto et al. 1981a).

Significant increases in serum ALT levels were observed in rats exposed to 4.5 mg vanadium/m^3 6 hours/day, 5 days/week for 13 weeks (NTP 2002). However, this alteration was not considered to be biologically relevant because it was not associated with histological alterations in the liver. No histological alterations were observed in the livers of rats exposed to 4.5 or 1.1 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively (NTP 2002).

Renal Effects. Workers exposed chronically to 0.01–0.5 mg/m^3 of vanadium dusts had normal serum levels of electrolytes, creatinine, and urea, suggesting no alterations in renal function (Kiviluoto et al. 1981b). Workers in other studies of chronic exposure to vanadium had normal urine levels of substances used to detect kidney disease (casts, protein levels, urea) (Sjöberg 1950; Vintinner et al. 1955).

Significant increases in serum urea nitrogen concentration were observed in male rats exposed to 4.5 mg vanadium/m^3 for 13 weeks and females exposed to 2.2 mg vanadium/m^3 for 23 days (but not after 13 weeks of exposure) (NTP 2002). However, because decreases in total protein and creatinine concentration were also observed, the urea nitrogen alteration was attributed to decreased body weight rather than an effect on renal clearance. A decrease in overnight urine volumes and increase in urine specific gravity were observed in rats exposed to 2.2 mg vanadium/m^3 for 13 weeks (NTP 2002). No alterations in urine volume or specific gravity were observed in urine samples collected after a 16-hour water deprivation period, suggesting that the alterations observed in the overnight urine sample were reflective of dehydration rather than altered kidney function. No histological alterations were observed in the kidneys of rats exposed to 4.5 or 1.1 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively (NTP 2002).

Dermal Effects. No increases in the occurrence of dermatitis were observed in vanadium pentoxide workers (Vintinner et al. 1955); increases in skin rashes were observed in some workers (NIOSH 1983). No histological alterations of the skin were observed in rats and mice following intermediate- or chronic-duration exposure to vanadium pentoxide (NTP 2002).

Ocular Effects. Workers chronically exposed to vanadium dusts in factories had slight to moderate eye irritation (Levy et al. 1984; Lewis 1959; Sjöberg 1950; Thomas and Stiebris 1956; Vintinner et al. 1955). Brief exposure to vanadium dust can also cause conjunctivitis (Zenz et al. 1962).

Body Weight Effects. Workers exposed to vanadium ore dust reported weight loss (Vintinner et al. 1955). Significant decreases in body weight gain have been observed in rats and mice exposed to vanadium pentoxide (6 hours/day, 5 days/week) for intermediate or chronic durations (NTP 2002). The LOAELs were 9.0 mg vanadium/m^3 for rats exposed for 16 or 90 days, 18 mg vanadium/m^3 for mice exposed for 16 days, 9.0 mg vanadium/m^3 for mice exposed for 90 days, and 1.1 mg vanadium/m^3 for mice exposed for 2 years. At lower concentrations, the decreases were within 10% of the controls. Marked decreases in body weight gain (approximately 30% or higher) were observed at lethal concentrations.

3.2.1.3 Immunological and Lymphoreticular Effects

The only human data located found that workers chronically exposed to unspecified levels of vanadium dusts in factories showed no significant signs of allergic reactions on the skin or in the respiratory system (Sjöberg 1950). This, however, cannot be considered to be an adequate evaluation of immunological function. Systemic immunity was evaluated in rats and mice exposed to vanadium pentoxide 6 hours/day, 5 days/week for 16 days (NTP 2002). Significant decreases in *in vitro* phagocytosis and increases *in vivo* bactericidal activity were observed in rats exposed to ≥2.2 mg vanadium/m^3. No adverse effect on the response to *Klebsiella pneumoniae* or to the influenza virus were observed in mice exposed to 18 mg vanadium/m^3.

3.2.1.4 Neurological Effects

Most workers exposed to vanadium dusts did not report major adverse neurological signs (Sjöberg 1956; Vintinner et al. 1955). However, some workers complained of dizziness, depression, headache, or tremors of the fingers and arms (Levy et al. 1984; Vintinner et al. 1955), which may or may not have been specifically due to vanadium exposure. No histological alterations were observed in the nervous system following a 13-week or 2-year exposure of rats to 4.5 or 1.1 mg vanadium/m^3, respectively, or mice to 9.0 or 2.2 mg vanadium/m^3, respectively (NTP 2002). Because the NTP (2002) study did not assess neurological function, these NOAELs are not listed in Table 3-1 or Figure 3-1.

3.2.1.5 Reproductive Effects

No studies were located regarding the reproductive effects in humans after inhalation exposure to vanadium. There are limited data on the potential reproductive toxicity of vanadium in animals following

inhalation exposure. No histological alterations were observed in rats exposed to 9.0 mg vanadium/m^3 as vanadium pentoxide for 3 months or 1.1 mg vanadium/m^3 for 2 years or in mice exposed to 9.0 mg vanadium/m^3 for 3 months or 2.2 mg vanadium/m^3 for 2 years (NTP 2002). No significant alterations in sperm count, motility, or concentration were observed in rats exposed to 9.0 mg vanadium/m^3 for 3 months (NTP 2002). In females exposed to 4.5 mg vanadium/m^3 as vanadium pentoxide for 3 months, significant increases in estrous cycle length were observed (NTP 2002); at 9.0 mg vanadium/m^3, the number of cycling females was significantly reduced. No studies examined reproductive function.

3.2.1.6 Developmental Effects

No studies were located regarding the developmental effects in humans or animals after inhalation exposure to vanadium.

3.2.1.7 Cancer

No studies were located regarding the carcinogenicity in humans after inhalation exposure to vanadium. NTP (2002) examined the carcinogenic potential of vanadium in rats and mice exposed to vanadium pentoxide 6 hours/day, 5 days/week for 2 years. Increases in the incidence of alveolar/bronchiolar adenoma, carcinoma, or the combined incidences of adenoma and carcinoma were observed in male rats. As indicated in Table 3-2, the incidences of these tumors were not statistically different from controls; however, the incidence of adenomas at 0.28 mg vanadium/m^3 and combined incidence of adenoma and carcinoma at 0.56 or 1.1 mg vanadium/m^3 were greater than historical control levels. Due to the rarity of these tumors, NTP considered the increases in adenoma and carcinoma observed in male rats to be related to vanadium pentoxide exposure. In female rats, no significant increases in lung tumors were observed. In the 0.28 mg vanadium/m^3 group, the incidence of alveolar/bronchiolar adenoma exceeded the historical control range. NTP (2002) noted that this may be related to vanadium pentoxide exposure; however, because it was only observed at the lowest vanadium pentoxide concentration, a clear relationship between lung neoplasms and vanadium pentoxide could not be determined in female rats. In male mice, significant increases in the incidence of alveolar/bronchiolar carcinoma and the combined incidence of alveolar/bronchiolar adenoma and carcinoma were observed at 0.56, 1.1, and 2.2 mg vanadium/m^3; an increased incidence of alveolar/bronchiolar adenoma was observed at 1.1 mg vanadium/m^3. In female mice, the incidences of alveolar/bronchiolar adenoma or carcinoma and the combined incidence of adenoma and carcinoma were significantly elevated in the 0.56, 1.1, and 2.2 mg vanadium/m^3 groups. As presented in Table 3-2, the tumor incidences in the male and female mice were not concentration-related. Based on vanadium lung burden studies in female rats and mice exposed to vanadium pentoxide, NTP

Table 3-2. Incidence of Lung Tumors in Rats and Mice Exposed to Vanadium Pentoxide for 2 Years[a]

	Concentration (mg vanadium/m^3)			
	0	0.28	0.56	1.1
Rats				
Male				
Alveolar/bronchiolar adenoma, multiple	0/50	2/49	0/48	0/50
Alveolar/bronchiolar adenoma (includes multiple)[b]	4/50	8/49	5/48	6/50
Alveolar/bronchiolar carcinoma, multiple	0/50	1/49	0/48	0/50
Alveolar/bronchiolar carcinoma (includes multiple)[c]	0/50	3/49	1/48	3/50
Alveolar/bronchiolar adenoma or carcinoma[d]	4/50	10/49	6/48	9/50
Female				
Alveolar/bronchiolar adenoma	0/49	3/49	1/50	0/50
Alveolar/bronchiolar carcinoma	0/49	0/49	0/50	1/50
Alveolar/bronchiolar adenoma or carcinoma	0/49	3/49	1/50	1/50
Mice	0	0.56	1.1	2.2
Male				
Alveolar/bronchiolar adenoma, multiple	1/50	1/50	11/50[e]	5/50
Alveolar/bronchiolar adenoma (includes multiple)	13/50	16/50	26/50[e]	15/50
Alveolar/bronchiolar carcinoma, multiple	1/50	10/50[e]	16/50[e]	13/50[e]
Alveolar/bronchiolar carcinoma (includes multiple)	12/50	29/50	30/50	35/50
Alveolar/bronchiolar adenoma or carcinoma	22/50	42/50[e]	43/50[e]	43/50[e]
Female	0	0.28	0.56	1.1
Alveolar/bronchiolar adenoma, multiple	0/50	3/50	5/50[e]	6/50[e]
alveolar/bronchiolar adenoma (includes multiple)	1/50	17/50[e]	23/50[e]	19/50[e]
Alveolar/bronchiolar carcinoma, multiple	0/50	9/50[e]	5/50[e]	5/50[e]
Alveolar/bronchiolar carcinoma (includes multiple)	0/50	23/50[e]	18/50[e]	22/50[e]
Alveolar/bronchiolar adenoma or carcinoma	1/50	32/50[e]	35/50[e]	32/50[e]

[a]Animals were exposed for 6 hours/day, 5 days/week
[b]Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ±standard deviation): 4.2±3.5%, range 0–12%; with inhalation chamber controls given NIH-07 diet: 1.7±2.4%, range 0–10%
[c]Historical incidence for NTP-2000: diet 0.4±0.8%, range 0–2%; NIH-07 diet: 0.8±1.2%, range 0–10%
[d]Historical incidence for NTP-2000: diet 4.5±3.9%, range 0–14%; NIH-07 diet: 2.5±2.6%, range 0–10%
[e]$p \leq 0.01$

Source: NTP 2002

(2002) estimated that the total vanadium lung "doses" were 130, 175, and 308 µg vanadium in rats exposed to 0.28, 0.56, or 1.1 mg vanadium/m^3 for 540 days and 153, 162, and 225 µg vanadium in mice exposed to 0.56, 1.1, or 2.2 mg vanadium/m^3 for 553 days. In both species, the similarity of the total dose at the two lower concentrations (total lung doses of 130 and 175 µg vanadium in rats exposed to 0.28 and 0.56 mg vanadium/m^3 and 153 and 162 µg vanadium in mice exposed to 0.56 and 1.1 mg vanadium/m^3) provides a partial explanation for the flat dose-response curve for lung tumors. NTP (2002) also suggested that the differences in lung tumor responses between the rats and mice may be due to finding that mice received considerably more vanadium on a body weight basis than rats.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans after oral exposure to vanadium.

The 14-day LD_{50} values for sodium metavanadate are 41 mg vanadium/kg in rats and 31.2 mg vanadium/kg in mice (Llobet and Domingo 1984). Deaths have been reported in rat dams exposed to 17 mg vanadium/kg/day as sodium orthovanadate on gestation days 6–15 (Sanchez et al. 1991) and in rats exposed to 22.06 or 24.47 mg vanadium/kg/day as ammonium metavanadate for 4 weeks (Zaporowska and Wasilewski 1989, 1990). Although the cause of death was not determined, marked decreases in body weight, food intake, and water consumption and increases in the occurrence of diarrhea were observed in animals dying early. Chronic exposures of up to 19 mg vanadium/kg as vanadyl sulfate in food or water did not affect mortality in rats or mice (Dai et al. 1994a, 1994b; Schroeder and Balassa 1967; Schroeder et al. 1970).

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

No studies were located regarding musculoskeletal or dermal/ocular effects in humans or animals following oral exposure to vanadium.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to vanadium. Rats receiving sodium metavanadate in the drinking water for 3 months had

Table 3-3 Levels of Significant Exposure to Vanadium - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat	1 d 1 x/d (GW)				41 (LD50)	Llobet and Domingo 1984 SODIUM METAVANADATE	
2	Mouse	once (GW)				31 (LD50)	Llobet and Domingo 1984 SODIUM METAVANADATE	
3	Mouse (Swiss)	Gd 6-15 (G)				17 F (17/19 dams died)	Sanchez et al. 1991 SODIUM ORTHOVANADATE	
Systemic								
4	Rat (Wistar)	2 wk (W)	Hemato		27.72 M (increased reticulocytes, increased polychromatophilic erythroblasts in bone marrow)		Zaporowska and Wasilewski 1989 AMMONIUM METAVANADATE	
			Bd Wt	27.65 F				
5	Mouse (Swiss)	Gd 6-15 (G)	Bd Wt			7.5 F (46% decrease in maternal weight gain)	Paternain et al. 1990 VANADYL SULFATE	
Developmental								
6	Rat	Gd 6-14 (G)		4.2	8.4 (facial hemorrhages)		Paternain et al. 1987 SODIUM METAVANADATE	

Table 3-3 Levels of Significant Exposure to Vanadium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
7	Mouse (Swiss)	Gd 6-15 (G)			7.5 F (increased early resorptions, decreased fetal growth, increased soft tissue and skeletal defects)		Paternain et al. 1990 VANADYL SULFATE	
8	Mouse (Swiss)	Gd 6-15 (G)		4.2	8.3 (decreased number of ossified sacrococcygeal vertebrae)		Sanchez et al. 1991 SODIUM ORTHOVANADATE	
INTERMEDIATE EXPOSURE								
Death								
9	Rat (Wistar)	4 or 8 wk (W)				24.47 M (10/32 animals died by week 4)	Zaporowska and Wasilewski 1989 AMMONIUM METAVANADATE	
10	Rat (Wistar)	4 wk (W)				22.06 M (12/20 rats died)	Zaporowska and Wasilewski 1990 AMMONIUM METAVANADATE	
Systemic								
11	Human	45-68 d (C)	Hemato	0.19			Dimond et al. 1963 AMMONIUM VANADYL TARTRATE	
			Hepatic	0.19				
			Renal	0.19				

Table 3-3 Levels of Significant Exposure to Vanadium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
12	Human	daily 12 wk (C)	Cardio	0.12			Fawcett et al. 1997 VANADYL SULFATE	
			Hemato	0.12[b]				
			Hepatic	0.12				
			Bd Wt	0.12				
13	Rat (Wistar)	10 wk (F)	Hemato	1 F	2.1 F (decreased hemoglobin and hematocrit, increased reticulocyte)		Adachi et al. 2000 SODIUM METAVANADATE	
			Bd Wt	2.1 F				
14	Rat (Swiss)	60 d (G)	Cardio		31 M (decreased aorta diameter)		Akgun-Dar et al. 2007 VANADYL SULFATE	
			Metab	31 M				
15	Rat (Sprague-Dawley)	210 d (W)	Resp	4.7 M			Boscolo et al. 1994 SODIUM METAVANADATE	
			Cardio		0.12 M (increased blood pressure)			
			Hepatic	4.7 M				

Table 3-3 Levels of Significant Exposure to Vanadium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Rat (Sabra)	4 wk (W)	Cardio	22 M			Bursztyn and Mekler 1993 SODIUM METAVANADATE	
			Metab	22 M				
17	Rat (Sprague-Dawley)	7 mo (W)	Cardio		12 M (increased blood pressure and heart rate)		Carmagnani et al. 1991 SODIUM METAVANADATE	
18	Rat (Sprague-Dawley)	7 mo (W)	Cardio		1.2 M (increased blood pressure)		Carmagnani et al. 1992 SODIUM METAVANADATE	
19	Rat (Wistar)	12 wk (W)	Hemato	9.7 M			Dai et al. 1995 AMMONIUM METAVANADATE	
			Bd Wt	9.7 M				
20	Rat (Wistar)	12 wk (W)	Hemato	7.6 M			Dai et al. 1995 VANADYL SULFATE	
			Bd Wt	7.6 M				
21	Rat (Sprague-Dawley)	Gd 0- Ld 21 (F)	Bd Wt		6 F (19% decrease in maternal body weight gain)		Elefant and Keen 1987 SODIUM METAVANADATE	
22	Rat (Wistar)	60 d (G)	Bd Wt	31 M			Jain et al. 2007 VANADYL SULFATE	

Table 3-3 Levels of Significant Exposure to Vanadium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
23	Rat (Wistar)	75 or 103 d (F)	Hemato	6.6 M			Mountain et al. 1953 VANADIUM PENTOXIDE	
			Bd Wt	6.6 M		30 M (53% decrease in body weight gain)		
24	Rat (Sprague-Dawley)	8 wk (G)	Bd Wt	3.42 M	6.84 M (10% decrease in body weight gain)		Sanchez et al. 1998 SODIUM METAVANADATE	
25	Rat (Wistar)	6 wk (W)	Hemato		8.35 M (increased erythrocyte levels)		Scibior 2005 SODIUM METAVANADATE	
			Bd Wt	8.35 M				
26	Rat (Wistar)	6 wk (W)	Hemato		10.69 M (decreased erythrocyte and hemoglobin levels)		Scibior et al. 2006 SODIUM METAVANADATE	
27	Rat (Long- Evans)	2 mo (F)	Cardio		10 M (increased ventricular pressure)		Susic and Kentera 1986 AMMONIUM METAVANADATE	
28	Rat (Sprague-Dawley)	7.4 wk (W)	Metab	13 M			Yao et al. 1997 VANADYL SULFATE	

Table 3-3 Levels of Significant Exposure to Vanadium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
29	Rat (Wistar)	4 or 8 wk (W)	Hemato		24.47 M (decreased erythroctyes, increased reticulocytes)		Zaporowska and Wasilewski 1989 AMMONIUM METAVANADATE	
30	Rat (Wistar)	4 wk (W)	Hemato		22.06 M (decreased erythrocyte, increased reticulocyte)		Zaporowska and Wasilewski 1990 AMMONIUM METAVANADATE	
31	Rat (Wistar)	4 wk (W)	Hemato		19.73 M (decreased hemoglobin and erythrocyte and increased reticulocyte)		Zaporowska and Wasilewski 1991 AMMONIUM METAVANADATE	
32	Rat (Wistar)	4 wk (W)	Gastro		19.73 (diarrhea)		Zaporowska and Wasilewski 1992a AMMONIUM METAVANADATE	
			Hemato		19.73 M (decreased hemoglobin and erythrocyte and increased reticulocyte)			
33	Rat (Wistar)	4 wk (W)	Hemato		12.99 M (decreased hemoglobin and erythrocyte and increased reticulocyte)		Zaporowska and Wasilewski 1992b AMMONIUM METAVANADATE	

Table 3-3 Levels of Significant Exposure to Vanadium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
34	Rat (Wistar)	4 wk (W)	Hemato		1.18 M (decreased erythrocyte levels)		Zaporowska et al. 1993 AMMONIUM METAVANADATE	
			Bd Wt	4.93 M				
35	Rabbit (NS)	24, 129, or 171 d (W)	Hemato		1.8 (decreased erythrocyte levels)		Kasibhatla and Rai 1993 Not Reported	
Immuno/ Lymphoret								
36	Rat (Wistar)	10 wk (F)		1 F	2.1 F (decreased B-cell, IgG, and IgM levels)		Adachi et al. 2000 SODIUM METAVANADATE	
Neurological								
37	Rat (Sprague-Dawley)	8 wk (G)			1.72 M (impaired performance on neurobehavioral tests)		Sanchez et al. 1998 SODIUM METAVANADATE	
38	Rat (Sprague-Dawley)	daily 8 wk (GW)			6.84 M (impaired response in active avoidance tests)		Sanchez et al. 1999 SODIUM METAVANADATE	
Reproductive								
39	Rat (Sprague-Dawley)	60 d (GW)		8.4			Domingo et al. 1986 SODIUM METAVANADATE	

Table 3-3 Levels of Significant Exposure to Vanadium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
40	Rat (Wistar)	60 d (G)			31 M (decreased fertility, sperm count, and motility)		Jain et al. 2007 VANADYL SULFATE	
41	Rat (Sprague-Dawley)	M: 70 d F:14 d premating, mating, gestation, lactation (W)			10 M (decreased fertility) 12 F (decreased fertility)		Morgan and El-Tawil 2003 AMMONIUM METAVANADATE	
42	Mouse (Swiss)	64 d (W)		17 M	25 M (decreased fertility and spermatozoa count)		Llobet et al. 1993 SODIUM METAVANADATE	
Developmental								
43	Rat (Sprague-Dawley)	60 d (G)			2.1 (reduced pup weight and length)		Domingo et al. 1986 SODIUM METAVANADATE	
44	Rat (Sprague-Dawley)	Gd 0- Ld 21 (F)				6 (decreased pup survival and body weight)	Elefant and Keen 1987 SODIUM METAVANADATE	

Table 3-3 Levels of Significant Exposure to Vanadium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
45	Rat (Sprague-Dawley)	M: 70 d F:14 d premating, mating, gestation, lactation (W)			10 M (decreased viability, increased gross, skeletal and visceral anomalies, decreased pup body weight)		Morgan and El-Tawil 2003 AMMONIUM METAVANADATE	
					12 F (decreased viability, increased gross, skeletal and visceral anomalies, decreased pup body weight)			
46	Rat (Wistar)	Gd 19- Ld 25, pups exposed until pnd 100 (W)				10 (decreased pup survival)	Poggioli et al. 2001 VANADYL SULFATE	
CHRONIC EXPOSURE								
Death								
47	Rat	2.5 yr (W)		0.7			Schroeder et al. 1970 VANADYL SULFATE	
48	Mouse	2 yr (F)		4.1			Schroeder and Balassa 1967 VANADYL SULFATE	
49	Mouse	2.5 yr (W)		0.54			Schroeder and Mitchner 1975 VANADYL SULFATE	

Table 3-3 Levels of Significant Exposure to Vanadium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL: Less Serious (mg V/kg/day)	LOAEL: Serious (mg V/kg/day)	Reference Chemical Form	Comments
Systemic								
50	Rat (Wistar)	52 wk (W)	Resp	19 M			Dai and McNeill 1994; Dai et al. 1994a, 1994b VANADYL SULFATE	
			Cardio	19 M				
			Hemato	19 M				
			Hepatic	19 M				
			Renal	19 M				
			Bd Wt	17 M	28 M (20% decrease in body weight gain)			
			Metab	19 M				
51	Rat	2.5 yr (W)	Renal	0.7			Schroeder et al. 1970 VANADYL SULFATE	
			Bd Wt	0.7				
52	Mouse	2 yr (F)	Resp	4.1			Schroeder and Balassa 1967 VANADYL SULFATE	
			Cardio	4.1				
			Hemato	4.1				
			Renal	4.1				
			Bd Wt	4.1				
53	Mouse	2.5 yr (W)	Bd Wt	0.54			Schroeder and Mitchner 1975 VANADYL SULFATE	

Table 3-3 Levels of Significant Exposure to Vanadium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
54	Mouse	2 yr (F)		4.1			Schroeder and Balassa 1967 VANADYL SULFATE	

a The number corresponds to entries in Figure 3-2

b Used to derive an intermediate-duration oral MRL of 0.01 mg vanadium/kg/day; dose divided by an uncertainty factor of 10 for human variability.

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; pnd = post-natal day; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Vanadium - Oral

Acute (≤14 days)

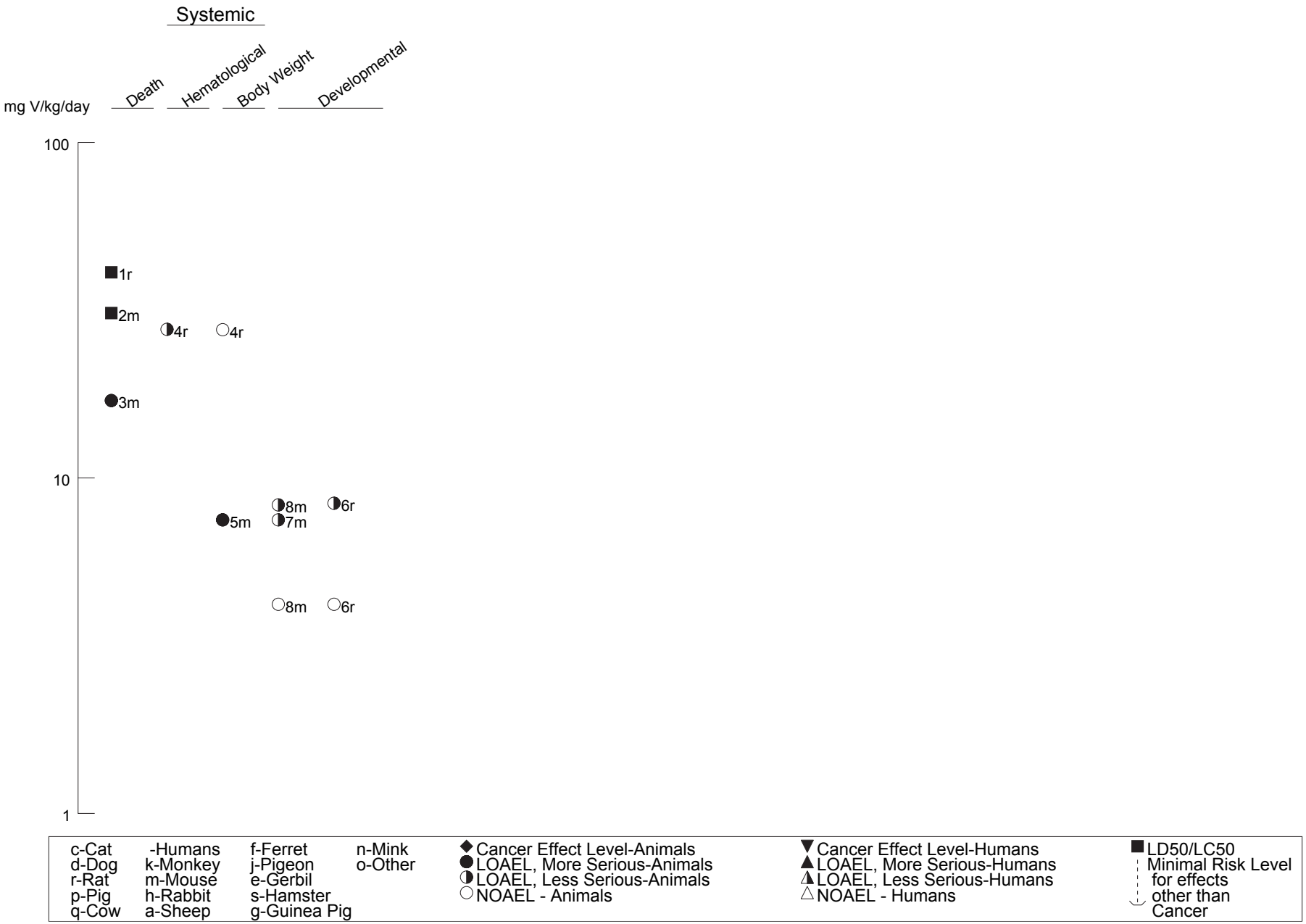


Figure 3-2 Levels of Significant Exposure to Vanadium - Oral *(Continued)*

Intermediate (15-364 days)

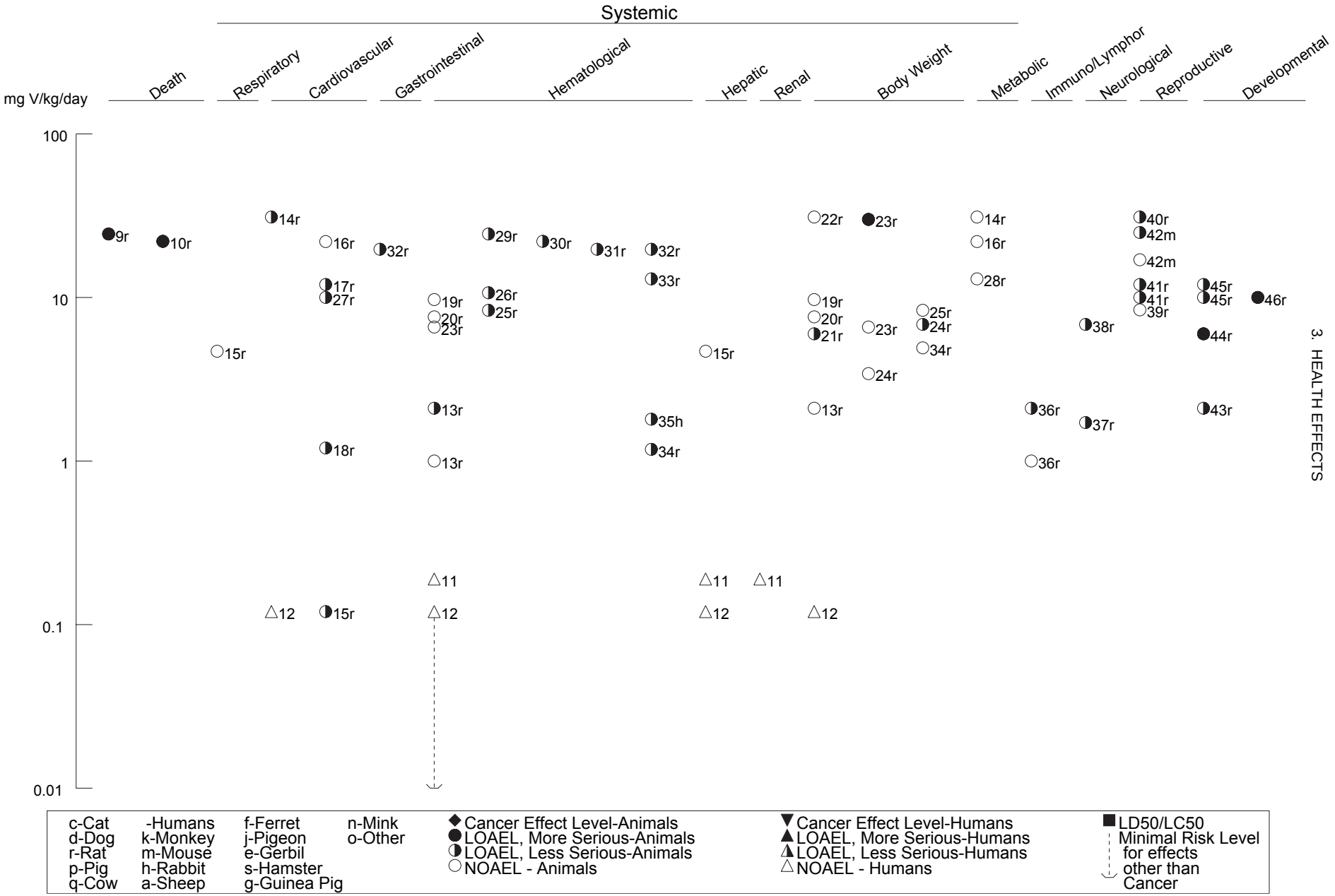
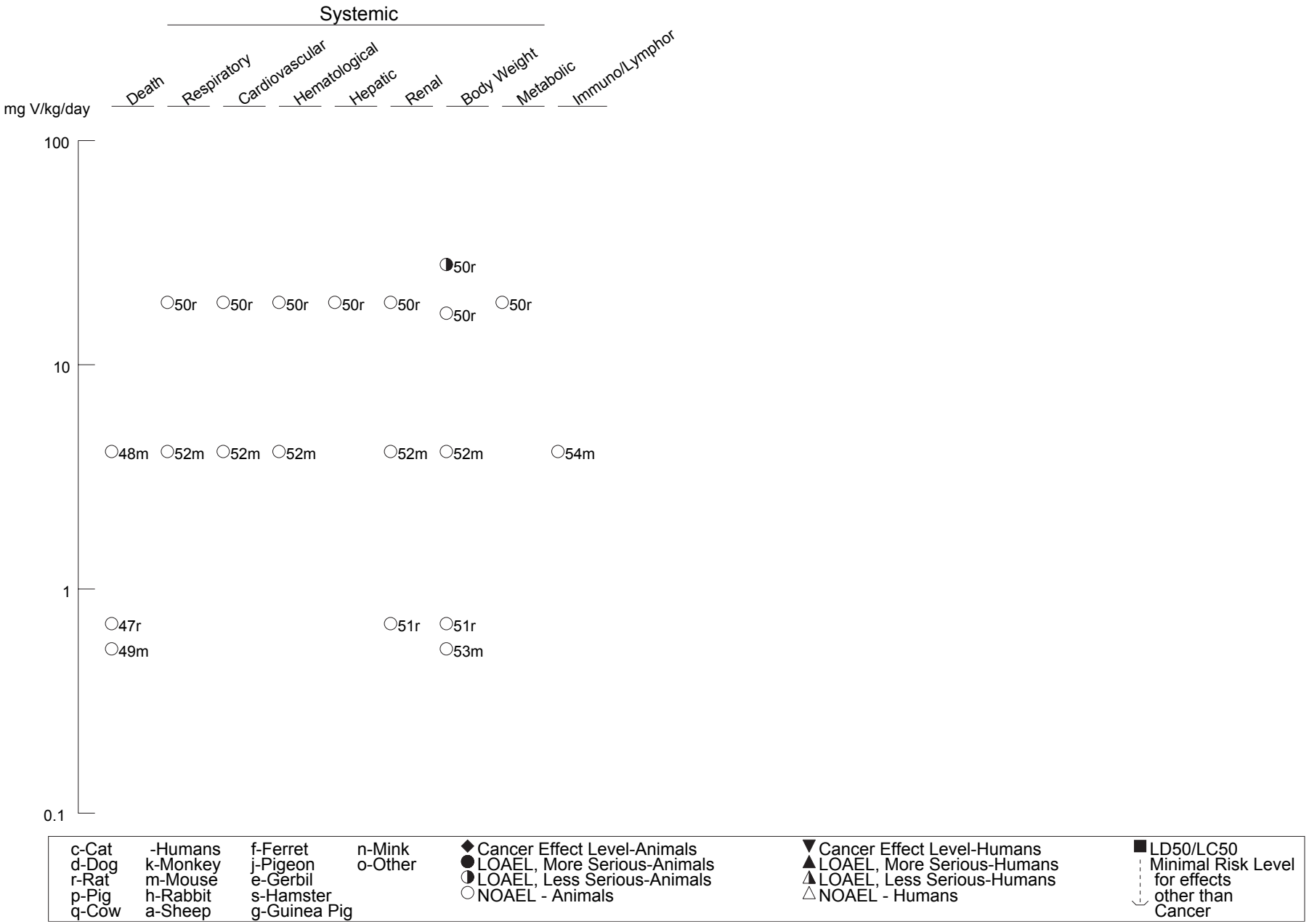


Figure 3-2 Levels of Significant Exposure to Vanadium - Oral *(Continued)*

Chronic (≥365 days)



mononuclear cell infiltration, mostly perivascular, in the lungs; the investigators noted that the effects were more evident at the highest dose level (3.5 mg vanadium/kg/day), but incidence data were not reported (Domingo et al. 1985).

Cardiovascular Effects. No significant alterations in systolic or diastolic blood pressure were observed in adults exposed to 0.12 mg vanadium/kg/day as vanadyl sulfate for 4, 8, or 12 weeks via capsules taken at mealtime (Fawcett et al. 1997).

Several studies have examined the effects of vanadium on blood pressure in laboratory animals. The results are inconsistent; however, differences in the methods used to measure blood pressure and the strains of rats tested complicate cross study comparisons. Significant increases in systolic, diastolic, and/or mean blood pressure were observed in Sprague-Dawley rats exposed to 0.12–12 mg vanadium/kg/day as sodium metavanadate in drinking water for 180–210 days (measured in femoral artery of anesthetized rats; Boscolo et al. 1994), in Sprague-Dawley rats exposed to 1.2–12 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (measured in the aorta of anesthetized rats; Carmagnani et al. 1991, 1992), and Long-Evans rats exposed to 10 mg vanadium/kg/day as ammonium vanadate in the diet for 60 days (measured in ventricle of anesthetized rats; Sušić and Kentera 1986). In contrast, no alterations in blood pressure were observed in rats exposed to 10 mg vanadium/kg/day as ammonium vanadate in the diet for 60 days (Long-Evans rats, measured in femoral artery; Sušić and Kentera 1986), 22 mg vanadium/kg/day as sodium metavanadate in drinking water for 4 weeks (Sabra rats, measured via tail cuff; Bursztyn and Mekler 1993), 32 mg vanadium/kg/day as vanadyl sulfate in drinking water for 52 weeks (Wistar rats, measured via tail cuff; Dai and McNeill 1994), or 63 mg vanadium/kg/day as sodium metavanadate in the diet for 24 weeks (Long-Evans rats, measured via tail cuff or femoral artery; Sušić and Kentera 1988). Studies in compromised animals have also found alterations in blood pressure. Increases in arterial blood pressure (measured via tail cuff) were observed in salt-induced hypertensive rats exposed to 22 mg vanadium/kg/day as sodium metavanadate in drinking water for 4 weeks compared to hypertensive controls (Bursztyn and Mekler 1993). Similar increases in blood pressure (measured via tail cuff) were observed in uninephrectomized rats exposed to 6 mg vanadium/kg/day as sodium metavanadate in the diet for 18 weeks (Sušić and Kentera 1988) or 5 mg vanadium/kg/day as sodium orthovanadate in the diet (Steffen et al. 1981). Alterations in the renin-angiotensin-aldosterone system and alterations in urinary excretion of electrolytes observed in the Boscolo et al. (1994) study provide suggestive evidence that altered renal function may play a role in vanadium-induced hypertension. Significant increases in plasma renin activity, plasma aldosterone levels, and increases in kallikrein (enzyme that releases vasodilating kinins from plasma proteins), and

kininases I and II activities were observed in rats exposed to 1.2 or 4.7 mg vanadium/kg/day as sodium metavanadate in the drinking water for 7 months.

Other alterations in the cardiovascular system included significant decreases in aorta diameter and the aorta tunica intima thickness in rats administered 31 mg vanadium/kg/day as vanadyl sulfate via gavage for 60 days (Akgün-Dar et al. 2007) and an increase in heart rate in rats exposed to 12 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (Carmagnani et al. 1991, 1992), but not in rats exposed to ≤4.7 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (Boscolo et al. 1994; Carmagnani et al. 1992) or 10 mg vanadium/kg/day as ammonium vanadate in the diet for 2 months (Sušić and Kentera 1986).

Gastrointestinal Effects. The limited data available for assessing gastrointestinal effects suggest that exposure to vanadium may cause mild gastrointestinal irritation. Intestinal cramping and diarrhea were observed in subjects exposed to an average dose of 0.19 mg vanadium/kg/day as ammonium vanadyl tartrate administered via capsules for 45–68 days (Dimond et al. 1963). Several clinical studies investigating the efficacy and mechanism of action of sodium metavanadate and vanadyl sulfate for the treatment of diabetes mellitus have found mild gastrointestinal effects (Boden et al. 1996; Cusi et al. 2001; Goldfine et al. 1995). Mild diarrhea was reported by 4/10 insulin- and noninsulin-dependent diabetes patients administered 0.66 mg vanadium/kg/day as sodium metavanadate as capsules administered 3 times/day (0.26 mg vanadium/kg at breakfast and lunch and 0.13 mg vanadium/kg at dinner) for 14 days (Goldfine et al. 1995); another subject reported nausea and vomiting that subsided when the dose was decreased to 0.13 mg vanadium/kg 3 times/day. In another study of eight noninsulin dependent diabetics administered 0.35 mg vanadium/kg/day as vanadyl sulfate as capsules 2 times/day for 4 weeks, diarrhea and abdominal cramps were reported during the first week of treatment, but not reported thereafter (Boden et al. 1996). Similarly, insulin-independent diabetics reported diarrhea and abdominal discomfort during the first 2 weeks of exposure to vanadyl sulfate (Cusi et al. 2001). The initial dose of 0.2 mg vanadium/kg/day administered presumably as capsules 2 times/day was increased every 2–3 days and reached 0.6 mg vanadium/kg/day by week 2. Several animal studies have reported diarrhea in rats exposed to ≥8.35 mg vanadium/kg/day as sodium metavanadate or ammonium metavanadate (Ścibior 2005; Zaporowska and Wasilewski 1989, 1990, 1992a); the diarrhea was often observed at doses associated with marked decreases in food intake and water consumption.

Hematological Effects. No alterations in reticulocyte or platelet counts (Dimond et al. 1963) or erythrocyte, hemoglobin, hematocrit, or platelet levels (Fawcett et al. 1997) were observed in adults

exposed to 0.19 mg vanadium/kg/day as ammonium vanadyl tartrate for 6–10 weeks or 0.12 mg vanadium/kg/day as vanadyl sulfate for 12 weeks, respectively.

A series of studies conducted by Zaporowska and associates examined the hematotoxicity of ammonium metavanadate administered in drinking water to rats for acute or intermediate durations. A 2-week exposure to 27.72 mg vanadium/kg/day resulted in significant increases in reticulocyte levels and increases in the percentage of polychromatophilic erythroblasts in the bone marrow in male rats (Zaporowska and Wasilewski 1989); a nonsignificant increase in erythrocytes was also observed at this dose level. Exposures to 12.99–24.47 mg vanadium/kg/day for 4 weeks resulted in decreases in erythrocyte levels and hemoglobin levels and increases in reticulocyte levels (Zaporowska and Wasilewski 1989, 1990, 1991, 1992a, 1992b). However, death and decreases in body weight gain, food intake, and water consumption were also observed at these dose levels. Similar effects were observed in rats exposed to 8.35 or 10.69 mg vanadium/kg/day as sodium metavanadate for 6 weeks (Ścibior 2005; Ścibior et al. 2006). One study in this series tested lower concentrations which did not result in frank toxicity. Significant decreases in erythrocyte and hematocrit levels were observed in rats exposed to 1.18 or 4.93 mg vanadium/kg/day as ammonium metavanadate for 4 weeks (Zaporowska et al. 1993); significant increases in reticulocyte levels were observed at 4.93 mg vanadium/kg/day. The decreases in erythrocyte levels were small (approximately 11% less than controls) and not dose-related. Decreases in hemoglobin and hematocrit and increases in reticulocytes were observed in rats exposed to 2.1 mg vanadium/kg/day as sodium metavanadate for 10 weeks (Adachi et al. 2000a) and decreases in erythrocyte counts were observed in rabbits exposed to 1.8 mg vanadium/kg/day of an unknown metavanadate compound for 24 days (Kasbhatla and Rai 1993). However, other investigators have not found hematological alterations in rats exposed to 19 mg vanadium/kg/day as vanadyl sulfate for 1 year (Dai and McNeill 1994), 9.7 mg vanadium/kg/day as ammonium metavanadate for 12 weeks (Dai et al. 1995), 7.6 mg vanadium/kg/day as vanadyl sulfate for 12 weeks (Dai et al. 1995), or 6.6 mg vanadium/kg/day as vanadium pentoxide for 10–15 weeks (Mountain et al. 1953). As suggested by Ścibior et al. (2006), the differences may be due to the duration of exposure, compound administered, or age of the animals.

Hepatic Effects. No significant alterations in serum AST, cholesterol, triglyceride, phospholipid, and/or bilirubin levels were observed in humans administered, via capsules, 0.19 mg vanadium/kg as ammonium vanadyl tartrate for 45–68 days (Dimond et al. 1963) or 0.12 mg vanadium/kg/day as vanadyl sulfate for 12 weeks (Fawcett et al. 1997).

Several studies in laboratory animals examining cholesterol and triglyceride levels (Adachi et al. 2000a; Dai et al. 1994a) or serum enzyme levels (ALT or AST) (Adachi et al. 2000a; Dai et al. 1994b; Yao et al. 1997) have not found biologically relevant alterations. The highest NOAEL values for these effects are 13 mg vanadium/kg/day (Yao et al. 1997) following intermediate-duration exposure and 19 mg vanadium/kg/day following chronic-duration exposure (Dai et al. 1994a, 1994b). No histological alterations were observed in the livers of rats exposed to 3.5 mg vanadium/kg/day as sodium metavanadate in drinking water for 3 months (Domingo et al. 1985), 4.7 mg vanadium/kg/day as sodium metavanadate in drinking water for 210 days (Boscolo et al. 1994), or 19 mg vanadium/kg/day as vandyl sulfate in drinking water for 1 year (Dai et al. 1994b).

Renal Effects. Humans given 0.19 mg vanadium/kg as ammonium vanadyl tartrate capsules for 45–68 days did not show any changes in urinalysis for albumin, hemoglobin, or formed elements. Blood urea nitrogen levels were also unchanged (Dimond et al. 1963).

There are limited data on the renal toxicity of vanadium compounds. Narrowing of the lumen of the proximal tubules was observed in rats exposed to 4.7 or 12 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (Boscolo et al. 1994; Carmagnani et al. 1991); however, neither study reported the incidence of the lesion or statistical significance. Similarly, corticomedullar micro-hemorrhagic foci were observed in the kidneys of rats exposed to sodium metavanadate in drinking water for 3 months (Domingo et al. 1985); the investigators noted that the effect was more evident at the highest dose (3.5 mg vanadium/kg/day), but incidence data or statistical analyses were not included in the paper. This study also found significant increases in serum total protein, urea, and uric acid levels in rats exposed to 3.5 mg vanadium/kg/day. No statistically significant increases in the incidence of histological alterations were observed in rats exposed to 19 mg vanadium/kg/day as vanadyl sulfate in drinking water for 1 year (Dai et al. 1994b). No histological alterations were observed in the kidneys of rats exposed to 0.7 mg vanadium/kg/day (Schroeder et al. 1970) as vanadyl sulfate in drinking water for 2.5 years or in mice exposed to 4.1 mg vanadium/kg/day as vanadyl sulfate in the diet for 2 years (Schroeder and Balassa 1967).

Body Weight Effects. No significant alterations in body weight were observed in adults exposed to 0.12 mg vanadium/kg/day as vanadyl sulfate administered via capsules for 12 weeks (Fawcett et al. 1997). Numerous studies have reported significant decreases in body weight gain in rats or mice exposed to vanadium compounds. In general, intermediate-duration exposure to <10 mg vanadium/kg/day did not result in >10% decreases in body weight gain (Adachi et al. 2000a; Dai et al. 1995; Sanchez et al. 1998;

Ścibior 2005; Zaporwska et al. 1993). At higher concentrations, a considerable amount of variability in the magnitude of decreases in body weight gain was observed. Decreases of 12–15% were observed in rats or mice exposed to 10.69, 13, 20.93, 22.06, or 33 mg vanadium/kg/day as vanadyl sulfate, ammonium metavanadate, or sodium metavanadate in drinking water (Llobet et al. 1993; Ścibior et al. 2006; Yao et al. 1997; Zaporowski and Wasilewski 1989, 1990). However, decreases of ≥37% were observed in rats exposed to 12.99 or 19.73 mg vanadium/kg/day as ammonium vanadate in drinking water (Zaporowski and Wasilewski 1991, 1992a, 1992b); these decreases in body weight gain were accompanied by marked decreases in food intake and water consumption. A severe decrease in body weight gain (54%) and weight loss were observed in rats exposed to 30 or 55 mg vanadium/kg/day, respectively, as vanadium pentoxide for 75 days (Mountain et al. 1953). In contrast, no alterations in body weight gain were observed in rats exposed to 22 mg vanadium/kg/day as sodium metavanadate in drinking water (Bursztyn and Mekler 1993) or administered via gavage at 31 mg vanadium/kg/day as vanadyl sulfate (Akgün-Dar et al. 2007; Jain et al. 2007). Significant decreases in maternal weight gain have been observed in rats exposed to 6 mg vanadium/kg/day as sodium metavanadate (Elfant and Keen 1997) and mice administered 7.5 mg vanadium/kg/day as vanadyl sulfate (Paternain et al. 1990). Following chronic exposure, a 20% decrease in body weight gain was observed in rats exposed to vanadyl sulfate in drinking water for 1 year (Dai et al. 1994a). No alterations in body weight gain were observed in mice exposed to 4.1 or 0.54 mg vanadium/kg/day as vanadyl sulfate (Schroeder and Balassa 1967; Schroeder and Mitchener 1975) or rats exposed to 0.7 mg vanadium/kg/day as vanadyl sulfate (Schroeder et al. 1970).

It is likely that the decreases in body weight in a number of these studies are secondary to decreases in water consumption (possibly due to palatability). Decreases in food intake and body weight gain have been observed in rats placed on a water restricted diet (Crampton and Lloyd 1954); young rats were particularly sensitive to the effect (2-month-old rats were used in the Zaporowski and Wasilewski studies). Thus, LOAELs for decreases in body weight gain in drinking water studies reporting decreases in water consumption (possibly due to palatability) are not presented in Table 3-3 or Figure 3-2; similarly, LOAELs were not listed for studies that did not report whether there was an effect on drinking water consumption.

Metabolic Effects. No studies were located regarding metabolic effects in healthy humans after oral exposure to vanadium. No significant alterations in blood glucose or insulin levels were observed in rats exposed to 22 mg vanadium/kg/day as sodium metavanadate in drinking water for 4 weeks (Bursztyn and Mekler 1993), rats administered 31 mg vanadium/kg/day as vanadyl sulfate for 60 days (Akgün-Dar et al.

2007), or rats exposed to 19 mg vanadium/kg/day as vanadyl sulfate in drinking water for 1 year (Dai et al. 1994a). Additionally, no alterations in the response to an oral glucose tolerance test were observed in rats exposed to 13 mg vanadium/kg/day as vanadyl sulfate in drinking water for 7.4 weeks (Yao et al. 1997).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to vanadium. Minimal information on immunological effects in animals was located. Mice exposed to 0.13, 1.3, or 6.5 mg vanadium/kg/day as sodium orthovanadate in the drinking water for 6 weeks showed a dose-related, but nonsignificant, decrease in the antibody-forming cells in the spleen when challenged with sheep erythrocytes (Sharma et al. 1981). The number of plaques formed was 46, 69, and 78%, respectively, lower than the response in the controls; the investigators noted that statistical significance was not achieved due to the large variation in the control group. Decreases in B-cell levels and IgG and IgM levels were observed in rats exposed to 2.1 mg vanadium/kg/day as sodium metavanadate in the diet for 10 weeks (Adachi et al. 2000a). Mild spleen hypertrophy and hyperplasia were seen in rats exposed to sodium metavanadate in the drinking water for 3 months (Domingo et al. 1985); the investigators noted that the effects were more evident at the highest dose (3.5 mg vanadium/kg/day), but incidence data were not reported. The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to vanadium. Data on the neurotoxicity of vanadium are limited to two studies in rats. In one study, decreases in travelling distance and horizontal movement in an open field test and poorer avoidance performance and higher latency period in an active avoidance test were observed in rats administered 1.72 mg vanadium/kg/day as sodium metavanadate for 8 weeks (Sanchez et al. 1998). In the second study, no alterations in travelling distance or vertical movements were observed in an open field test in rats administered 6.84 mg vanadium/kg/day as sodium metavanadate for 8 weeks (Sanchez et al. 1999). A decrease in the number of avoidance responses to conditioned stimuli and increases in the latency period were also observed in these rats. These LOAEL values are recorded in Table 3-3 and Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to vanadium. Decreases in fertility have been observed in female rats mated to unexposed males (Ganguli et al. 1994b; Morgan and El-Tawil 2003) and in male rats or mice mated with unexposed females (Jain et al. 2007; Llobet et al. 1993; Morgan and El-Tawil 2003). The lowest LOAEL values for decreased fertility are 12 and 10 mg vanadium/kg/day for females and males, respectively (Morgan and El-Tawil 2003). No alterations in fertility were observed in male and female rats administered 8.4 mg vanadium/kg/day as sodium metavanadate (Domingo et al. 1986). Decreases in sperm count and motility have also been observed in rats administered 31 mg vanadium/kg/day as vanadyl sulfate for 60 days (Jain et al. 2007). This NOAEL value and reliable LOAEL values are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to vanadium. A variety of fetal malformations/anomalies have been observed in animals following gestational exposure to vanadium. Exposure on gestation days 6–14 or 6–15 resulted in increases in facial hemorrhages (Paternain et al. 1987), hematomas in facial, neck, and dorsal areas (Paternain et al. 1990), and delayed ossification (Paternain et al. 1990; Sanchez et al. 1991); the rat and mouse dams were administered 7.5–8.3 mg vanadium/kg/day as vanadyl sulfate, sodium metavanadate, or sodium orthovanadate. One study also reported increases in early resorptions and decreases in fetal growth in the offspring of mice administered 7.5 mg vanadium/kg/day as vanadyl sulfate (Paternain et al. 1990); marked decreases in maternal body weight were also observed at this dose level. Vanadium exposure throughout gestation and lactation resulted in decreases in pup body weight and length at ≥2.1 mg vanadium/kg/day (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003). Increases in stillbirths and decreases in pup survival were observed at 6 mg vanadium/kg/day (Elfant and Keen 1987); this dose level was associated with decreases in maternal food intake and body weight. Increases in gross, skeletal, and visceral anomalies were observed in the offspring of rats exposed to 12 mg vanadium/kg/day as ammonium metavanadate (Morgan and El-Tawil 2003); similar effects were observed in unexposed dams mated with males exposed to 10 mg vanadium/kg/day (Morgan and El-Tawil 2003). In rats exposed to 10 mg vanadium/kg/day as vanadyl sulfate in drinking water during gestation and lactation and exposed until postnatal day 100, significant decreases in survival were observed (Poggioli et al. 2001). This study also found significant decreases in the number of rearings in an open field test and no alterations in locomotor activity or working memory. A two-generation, one-dose study in rats showed altered lung collagen metabolism in fetuses of adults with lifetime exposure (Kowalska 1988). The toxicological significance

of this finding is also not known. Reliable LOAEL values from these studies are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located that specifically studied cancer in humans or animals after oral exposure to vanadium. However, some studies designed to test other end points noted no increase in tumor frequency in rats and mice chronically exposed to 0.5–4.1 mg vanadium/kg as vanadyl sulfate in drinking water (Schroeder and Balassa 1967; Schroeder and Mitchener 1975; Schroeder et al. 1970). Although results of these oral studies were negative for carcinogenicity, they were inadequate for evaluating carcinogenic effects because insufficient numbers of animals were used, it was not determined whether or not a maximum tolerated dose was achieved, a complete histological examination was not performed, and only one exposure dose per study was evaluated.

3.2.3 Dermal Exposure

No studies were located regarding the following health effects in humans or animals after dermal exposure to vanadium:

3.2.3.1 Death
3.2.3.2 Systemic Effects
3.2.3.3 Immunological and Lymphoreticular Effects
3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.3 GENOTOXICITY

The *in vitro* and *in vivo* data on the genotoxicity of vanadium compounds are summarized in Tables 3-4 and 3-5, respectively. In workers exposed to vanadium pentoxide, no alterations in the occurrence of sister chromatid exchange (Ivancsits et al. 2002) or deoxyribonucleic acid (DNA) strand breaks (Ehrlich et al. 2008; Ivancsits et al. 2002) were observed; however, an increase in micronuclei formation was observed in lymphocytes (Ehrlich et al. 2008). Similarly, increases in the micronuclei formation were observed in mouse bone marrow cells following oral exposure to vanadyl sulfate (Ciranni et al. 1995;

Table 3-4. Genotoxicity of Vanadium and Compounds *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Bacillus subtilis	Recombination repair	No data	+ + +	Kada et al. 1980	V_2O_5 $VOCl_2$ NH_4VO_3
B. subtilis	Recombination repair	No data	+ + +	Kanematsu et al. 1980	V_2O_5 $VOCl_2$ NH_4VO_3
Escherichia coli	Gene mutation	No data	– –	Kanematsu et al. 1980	V_2O_5 NH_4VO_3
Salmonella typhimurium	Gene mutation	No data	– –	Kanematsu et al. 1980	V_2O_5 NH_4VO
S. typhimurium	Gene mutation	–	–	NTP 2002	V_2O_5
Saccharomyces cerevisiae	Induction of diploid spores	No data	+	Sora et al. 1986	$VOSO_4$
S. cerevisiae	Reverse point mutation	+	+	Bronzetti et al. 1990	NH_4VO_3
S. cerevisiae	Mitotic gene conversion	+	+	Bronzetti et al. 1990	NH_4VO_3
Mouse erythroleukemia cells	DNA repair	No data	+	Foresti et al. 2001	$NaVO_3$
Mouse 3T3 and 3T6 cells	DNA synthesis	No data	+	Smith 1983	Na_3VO_4 $VOSO_4$
Chinese hamster ovary cells	DNA protein crosslinks	No data	+	Cohen et al. 1992	NH_4VO_3
Hamster V79 fetal lung fibroblasts	*hprt* mutation frequency	No data	+	Cohen et al. 1992	NH_4VO_3
Chinese hamster V79 cells	*hprt* mutation frequency	No data	+	Klein et al. 1994	NH_4VO_3
Chinese hamster V79 cells	*gpt* mutation frequency	No data	–	Klein et al. 1994	NH_4VO_3
Chinese hamster V79 cells	*hprt* mutation frequency	No data	–	Zhong et al. 1994	V_2O_5
Syrian hamster ovary cells	Micronuclei formation	No data	–	Gibson et al. 1997	V_2O_5
Chinese hamster V79 cells	Micronuclei formation	No data	+	Zhong et al. 1994	V_2O_5
Chinese hamster ovary cells	Sister chromatid exchange	+ + +	+ + +	Owusu-Yaw et al. 1990	$VOSO_4$ V_2O_3 NH_4VO_3
Chinese hamster V79 cells	Sister chromatid exchange	No data	–	Zhong et al. 1994	V_2O_5

Table 3-4. Genotoxicity of Vanadium and Compounds *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Zhong et al. 1994	V_2O_5
Chinese hamster ovary cells	Chromosomal aberrations	+ + +	+ + +	Owusu-Yaw et al. 1990	$VOSO_4$ V_2O_3 NH_4VO_3
Human tumor cells	Colony formation	No data	+	Hanauske et al. 1987	<0.1 pM V
Human tumor cells	Colony formation	No data	−	Hanauske et al. 1987	>0.1 pM V
Human leukocytes	DNA strand break	No data	+	Birnboim 1988	Na_3VO_4
Human fibroblasts	DNA strand break	No data	+	Ivancsits et al. 2002	V_2O_5
Human erythrocytes, lymphocytes	DNA strand break	No data	−	Ivancsits et al. 2002	V_2O_5
Human nasal epithelial cells	DNA strand break	No data	−	Kleinsasser et al. 2003	V_2O_5
Human lymphocytes	DNA strand break	No data	+	Kleinsasser et al. 2003	V_2O_5
Human lymphocytes	DNA strand break	No data	+	Wozniak and Blasiak 2004	$VOSO_4$
Human cervical cancer cells (HeLa)	DNA strand break	No data	+	Wozniak and Blasiak 2004	$VOSO_4$
Human lymphocytes	DNA strand break	No data	±	Rojas et al. 1996	V_2O_5
Human leukocytes	DNA strand break	No data	+	Rojas et al. 1996	V_2O_5
Human lymphocytes	Chromosomal aberrations	No data	+ + + +	Migliore et al. 1993	NH_4VO_3, $NaVO_3$, Na_3VO_4, $VOSO_4$
Human lymphocytes	Structural chromosomal aberrations	No data	−	Roldán and Altamirano 1990	V_2O_5
Human lymphocytes	Numerical chromosomal aberrations	No data	+	Roldán and Altamirano 1990	V_2O_5
Human lymphocytes	Sister chromatid exchange	No data	−	Roldán and Altamirano 1990	V_2O_5
Human lymphocytes	Sister chromatid exchange	No data	− − − −	Migliore et al. 1993	NH_4VO_3, $NaVO_3$, Na_3VO_4, $VOSO_4$

Table 3-4. Genotoxicity of Vanadium and Compounds *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Human lymphocytes	Micronuclei formation	No data	+ +	Migliore et al. 1995	Na_3VO_4, $VOSO_4$
Human lymphocytes	Micronuclei formation	No data	+ + + +	Migliore et al. 1993	NH_4VO_3, $NaVO_3$, Na_3VO_4, $VOSO_4$

— = negative result; + = positive result; ± = weakly positive; DNA = deoxyribonucleic acid; hprt = hypoxanthine phosphoribosyltransferase; $NaVO_3$= sodium metavanadate; Na_3VO_4 = sodium orthovanadate; NH_4VO_3 = ammonium metavanadate; V_2O_5 = vanadium pentoxide; V_2O_3 = vanadium trioxide; $VOSO_4$ = vanadyl sulfate; $VOCl_2$ = vanadyl dichloride

Table 3-5. Genotoxicity of Vanadium and Compounds *In Vivo*

Species (test system)	End point	Exposure Route	Result	Reference	Form
Human leukocytes	Sister chromatid exchange	Inhalation (occupational)	–	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	Sister chromatid exchange	Inhalation (occupational)	–	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	Micronuclei formation	Inhalation (occupational)	+	Ehrlich et al. 2008	V_2O_5
Human leukocytes	DNA strand breaks	Inhalation (occupational)	–	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	DNA strand breaks	Inhalation (occupational)	–	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	DNA strand breaks	Inhalation (occupational)	–	Ehrlich et al. 2008	V_2O_5
CD-1 mouse bone marrow	Micronuclei formation	Drinking water	–	Villani et al. 2007	$VOSO_4$
CD-1 mouse blood reticulocytes	Micronuclei formation	Drinking water	±	Villani et al. 2007	$VOSO_4$
CD-1 mouse bone marrow	Micronuclei formation	Gavage	+ + +	Ciranni et al. 1995	$VOSO_4$ Na_3VO_4 NH_4VO_3
B6C3F1 mouse erythrocytes	Micronuclei formation	Inhalation	–	NTP 2002	V_2O_5
CD-1 mouse bone marrow	Chromosome aberrations	Gavage	+ + +	Ciranni et al. 1995	$VOSO_4$ Na_3VO_4 NH_4VO_3
CD-1 mouse bone marrow	DNA damage	Drinking water	–	Villani et al. 2007	$VOSO_4$
CD-1 mouse testis cells	DNA damage	Drinking water	–	Villani et al. 2007	$VOSO_4$

– = negative result; + = positive result; ± = weakly positive; DNA = deoxyribonucleic acid; V_2O_5 = vanadium pentoxide; $VOSO_4$ = vanadyl sulfate; Na_3VO_4 = sodium orthovanadate; NH_4VO_3 = ammonium metavanadate

Villani et al. 2007), sodium orthovanadate (Ciranni et al. 1995), or ammonium metavanadate (Ciranni et al. 1995); however no increases in micronuclei formation were observed in mouse erythrocytes following intermediate duration inhalation exposure to vanadium pentoxide (NTP 2002). Increases in chromosomal aberrations were also observed in mouse bone marrow following a single gavage exposure to vanadyl sulfate, sodium orthovanadate, or ammonium metavanadate (Ciranni et al. 1995). As with the vanadium workers, DNA damage was not observed in mouse bone marrow or testis cells following intermediate duration exposure to vanadyl sulfate in drinking water.

Conflicting results have been found for genotoxicity tests in prokaryote assays. Impaired recombination repair were found in *Bacillus subtilis* following exposure to vanadium pentoxide, vanadyl dichloride, or ammonium metavanadate (Kada et al. 1980; Kanematsu et al. 1980). No alterations in gene mutation frequency were found in *Escherichia coli* or *Salmonella typhimurium* for vanadium pentoxide (Kanematsu et al. 1980; NTP 2002) or ammonium metavanadate (Kanematsu et al. 1980). In nonmammalian eukaryotes, increases in reverse point mutations and mitotic gene conversion were found in *Saccharomyces cerevisiae* (Bronzetti et al. 1990). In general, alterations in DNA repair, synthesis, formation of cross links or strand breaks, and gene mutation frequency were observed in mammalian cells for vanadium pentoxide, ammonium metavanadate, vanadyl sulfate, sodium orthovanadate (Birnboim 1988; Cohen et al. 1992; Foresti et al. 2001; Ivancsits et al. 2002; Klein et al. 1994; Kleinsasser et al. 2003; Rojas et al. 1996; Smith 1983; Wozniak and Blasiak 2004; Zhong et al. 1994). *In vitro* human data suggest cell-specific differences in the ability of vanadium compounds to induce DNA strand breaks. DNA strand breaks were found in fibroblasts and lymphocytes (Ivancsits et al. 2002; Kleinsasser et al. 2003; Wozniak and Blasiak 2004) but not in erythrocytes or nasal epithelial cells (Ivancsits et al. 2002; Kleinsasser et al. 2003). Increases in the occurrence of chromosomal aberrations were observed in Chinese hamster V79 cells exposed to vanadium pentoxide (Zhong et al. 1994), Chinese hamster ovary cells exposed to vanadyl sulfate, vanadium trioxide, or ammonium metavanadate (Owusu-Yaw et al. 1990), and human lymphocytes exposed to ammonium metavanadate, sodium metavanadate, sodium orthovanadate, vanadium pentoxide, or vanadyl sulfate (Migliore et al. 1993; Roldán and Altamirano 1990). An increase in sister chromatid exchange was found in Chinese hamster ovary cells exposed to vanadyl sulfate, vanadium trioxide, or ammonium metavanadate (Owusu-Yaw et al. 1990), but not in Chinese hamster V79 cells exposed to vanadium pentoxide (Zhong et al. 1994) or human lymphocytes exposed to vanadium pentoxide, ammonium metavanadate, sodium metavanadate, sodium orthovanadate, or vanadyl sulfate (Migliore et al. 1993; Roldán and Altamirano 1990). Increases in micronuclei formation were also found in Chinese hamster V79 cells exposed to vanadium pentoxide (Zhong et al. 1994) and in human lymphocytes exposed to sodium orthovanadate, vanadyl sulfate, ammonium

metavanadate, or sodium metavanadate (Migliore et al. 1993, 1995), but not in Syrian hamster ovary cells exposed to vanadium pentoxide (Gibson et al. 1997). Thus, the available data provide evidence that vanadium compounds are genotoxic, both clastogenic effects and DNA damage have been observed in *in vitro* and *in vivo* studies.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Several occupational studies indicate that absorption can occur in humans following inhalation exposure. An increase in urinary vanadium levels was found in workers exposed to <1 ppm of vanadium (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983). The vanadium concentration in serum was also reported to be higher than the nonoccupationally exposed controls following exposure to vanadium pentoxide dust (Kiviluoto et al. 1981b).

Indirect evidence of absorption after inhalation of vanadium in animals is indicated in studies involving inhalation exposure or intratracheal administration. In rats and mice exposed to 0.28–2.2 mg vanadium/m^3 as vanadium pentoxide for 14 days or 2 years (6 hours/day, 5 days/week), marginal increases in blood vanadium levels were observed, suggesting that vanadium pentoxide was poorly absorbed or rapidly cleared from the blood (NTP 2002); in the 2-year studies, the increase in blood vanadium levels were somewhat concentration-related. Intratracheal studies suggest that soluble vanadium compounds are readily absorbed through the lungs. Initial pulmonary clearance is rapid in rats. There was rapid 100% absorption of vanadium in rats receiving radiolabeled vanadyl chloride (Conklin et al. 1982). The greatest absorption of a radioactive dose, ^{48}V, was found to occur 5 minutes after administration (Roshchin et al. 1980). Most of the vanadium, 80 and 85% of the tetravalent (V4+) and pentavalent (V5+) forms of vanadium, respectively, cleared from the lungs 3 hours after intratracheal exposure (Edel and Sabbioni 1988). After 24 hours, >50% of vanadyl oxychloride was cleared from the lungs of male rats (Oberg et al. 1978), and at 3 days, 90% of vanadium pentoxide was eliminated from the lungs of female rats (Conklin et al. 1982). In another study 50% was cleared in 18 minutes, and the rest within a few days (Rhoads and Sanders 1985).

3.4.1.2 Oral Exposure

No studies were located regarding the rate and extent of absorption in humans after oral exposure to vanadium.

The absorption of vanadium through the gastrointestinal tract of animals is low. Less than 0.1% of an intragastric dose was detectable in the blood of rats at 15 minutes postexposure, and less than 1% at 1 hour (Roshchin et al. 1980). Similarly, only 2.6% of an orally administered radiolabeled dose of vanadium pentoxide was absorbed 3 days after exposure in rats (Conklin et al. 1982). In contrast, 16.5% of vanadium was absorbed in rats exposed to sodium metavanadate in the diet for 7 days (Adachi et al. 2000b). Vanadium was reported in tissues and urine within hours after a single (Edel and Sabbioni 1988) and repeated oral exposure in rats (Bogden et al. 1982; Parker and Sharma 1978), suggesting that it is rapidly absorbed. Young rats that consumed vanadium in the drinking water and feed were found to have higher tissue vanadium levels 21 days after birth than they did 115 days after birth (Edel et al. 1984). The data suggest that there is a higher absorption of vanadium in these young animals due to a greater nonselective permeability of the undeveloped gastrointestinal barrier.

3.4.1.3 Dermal Exposure

No specific studies were located regarding absorption in humans or animals after dermal exposure to vanadium, although absorption by this route is generally considered to be very low (WHO 1988). Absorption through the skin is thought to be quite minimal due to its low lipid/water solubility.

3.4.2 Distribution

Vanadium has been detected in the lungs (in 52% of the cases) and intestines (in 16% of the cases) of humans with no known occupational exposure, collected from autopsy data (Schroeder et al. 1963). In the gastrointestinal tract, it was primarily found in the ileum (37%), cecum (45.1%), sigmoid colon (15.9%), and rectum (26.2%). The heart, aorta, brain, kidney, muscle, ovary, and testes were found to have no detectable vanadium concentrations. Bone was not tested.

3.4.2.1 Inhalation Exposure

There are limited data on the distribution of vanadium in workers; serum vanadium levels in workers were highest within a day after exposure followed by a rapid decline in levels upon cessation of exposure

(Gylseth et al. 1979; Kiviluoto et al. 1981b). Analytical studies have shown low levels of vanadium in human kidneys and liver, with even less in brain, heart, and milk. Higher levels were detected in hair, bone, and teeth (Byrne and Kosta 1978). Inhalation exposure and intratracheal administration studies in laboratory animals have examined the distribution of vanadium. In rats chronically exposed to 0.56 or 1.1 mg vanadium/m^3 as vanadium pentoxide (6 hours/day, 5 days/week), vanadium lung burdens peaked after 173 days of exposure and declined for the remainder of the study (day 542); lung burden levels never reached steady state (NTP 2002). In contrast, lung burdens appeared to reach steady state by exposure day 173 in rats exposed to 0.28 mg vanadium/m^3 (NTP 2002). Similarly, lung burdens did not reach steady state in mice exposed to 1.1 or 2.2 mg vanadium/m^3 as vanadium pentoxide, 6 hours/day, 5 days/week for 542 days (NTP 2002). Rather, lung burdens peaked near day 54 and declined through day 535. Steady state was achieved in mice exposed to 0.56 mg vanadium/m^3 during the first 26 days of exposure. These data suggest that vanadium is cleared more rapidly from the lungs of mice compared to rats.

Vanadium is rapidly distributed in tissues of rats after acute intratracheal administration. Within 15 minutes after exposure to 0.36 mg/kg vanadium oxychloride, radiolabeled vanadium was detectable in all organs except the brain. The highest concentration was in the lungs, followed by the heart and kidney. The other organs had low levels. Maximum concentrations were reached in most tissues between 4 and 24 hours (Oberg et al. 1978). Vanadium is found to have a two-phase lung clearance after a single acute exposure (Oberg et al. 1978; Rhoads and Sanders 1985). The initial phase is rapid with a large percentage of the absorbed dose distributed to most organs and blood 24 hours postexposure, followed by a slower clearance phase. Vanadium is transported mainly in the plasma. It is found in appreciable amounts in the blood initially and only at trace levels 2 days after exposure (Roshchin et al. 1980). The pentavalent and tetravalent forms of vanadium compounds were found to have similar distribution patterns (Edel and Sabbioni 1988). Three hours after intratracheal exposure to the pentavalent or tetravalent form, 15–17% of the absorbed dose was found in the lung, 2.8% in the liver, and 2% in the kidney (Edel and Sabbioni 1988). Although levels in the kidney are high after exposure, the bone had greater retention of vanadium.

Skeletal levels of vanadium peaked 1–3 days postexposure (Conklin et al. 1982; Rhoads and Sanders 1985; Roshchin et al. 1980) and have been reported to persist after 63 days (Oberg et al. 1978).

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to vanadium.

Acute studies with rats showed the highest vanadium concentration to be located in the skeleton. Male rats had approximately 0.05% of the administered ^{48}V in bones, 0.01% in the liver, and <0.01% in the kidney, blood, testis, or spleen after 24 hours (Edel and Sabbioni 1988). Similar findings were noted by other authors who found that the bone had the greatest concentration of radiolabeled vanadium, followed by the kidney (Roshchin et al. 1980). Conklin et al. (1982) reported that after 3 days, 25% of the absorbed vanadium pentoxide was detectable in the skeleton and blood of female rats. In female rats exposed to sodium metavanadate in the diet for 7 days, the highest concentrations of vanadium were found in bone, followed by the spleen and kidney (Adachi et al. 2000b); the lowest concentration was found in the brain. As summarized in Table 3-6, vanadium elimination half-times in various tissues were 3.57–15.95 or 3.18–13.50 days following a 1-week exposure to 8.2 mg vanadium/kg/day as sodium metavanadate or vanadyl sulfate, respectively, administered in a liquid diet (Hamel and Duckworth 1995). Although the elimination half-times were longer in rats administered sodium metavanadate compared to vanadyl sulfate, no statistical comparisons were made.

Oral exposure for an intermediate duration produced the highest accumulation of vanadium in the kidney. Adult rats exposed to 5 or 50 ppm vanadium in the drinking water for 3 months had the highest vanadium levels in the kidney, followed by bone, liver, and muscle (Parker and Sharma 1978). The retention in bone may have been due to phosphate displacement. All tissue levels plateaued at the third week of exposure. A possible explanation for the initially higher levels in the kidney during intermediate-duration exposure is the daily excretion of vanadium in the urine. When the treatment is stopped, levels decrease in the kidney. At the cessation of treatment, vanadium mobilized rapidly from the liver and slowly from the bones. Other tissue levels decreased rapidly after oral exposure was discontinued. Thus, retention of vanadium was much longer in the bones (Edel et al. 1984; Parker and Sharma 1978).

In rats exposed to approximately 100 mg/L vanadium in drinking water as vanadyl sulfate or ammonium metavanadate for 12 weeks, significant increases, as compared to controls, in bone, kidney, and liver vanadium levels were observed; no alterations in vanadium muscle levels were found (Thompson et al. 2002). The highest concentration of vanadium was found in the bone, followed by the kidney and liver. Tissue vanadium concentrations were significantly higher in rats exposed to ammonium metavanadate as compared to animals exposed to vanadyl sulfate.

Table 3-6. Vanadium Elimination Half-Times in Various Organs in Rats Exposed to 8.2 mg Vanadium/kg/day for 1 Week

	Half-time (days)	
Organ	Sodium metavanadate	Vanadyl sulfate
Liver	3.57	3.18
Kidney	3.92	3.27
Fat	4.06	5.04
Lung	5.52	4.45
Muscle	6.11	4.49
Heart	7.03	5.05
Spleen	9.13	5.15
Brain	11.17	9.17
Testes	15.95	13.50

Source: Hamel and Duckworth 1995

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans and animals after dermal exposure to vanadium.

3.4.2.4 Other Routes of Exposure

After intraperitoneal administration to rats, vanadium is distributed to all organs. After 24 hours, the highest concentrations were found in the bones and kidney, although initial levels were highest in the kidney (Roshchin et al. 1980; Sharma et al. 1980). This is similar to the distribution seen following inhalation and oral exposure.

3.4.3 Metabolism

Vanadium is an element, and as such, is not metabolized. In the oxygenated blood, it circulates as a polyvanadate (isopolyanions containing pentavalent vanadium) but in tissues, it is retained mainly as the vanadyl cation (cationic form of tetravalent vanadium). Depending on the availability of reducing equivalents (such as reduced glutathione-SH, NADPH, NADH) and oxygen, vanadium may be reduced, reoxidized, and/or undergo redox cycling (Byczkowski and Kulkarni 1998).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Occupational studies showed that urinary vanadium levels significantly increased in exposed workers (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983; Zenz et al. 1962). Male and female workers exposed to 0.1–0.19 mg/m^3 vanadium in a manufacturing company, had significantly higher urinary levels (20.6 µg/L) than the nonoccupationally exposed control subjects (2.7 µg/L) (NIOSH 1983). The correlation between ambient vanadium levels and urinary levels of vanadium is difficult to determine from these epidemiological studies (Kiviluoto et al. 1981b). In most instances, no other excretion routes were monitored. Analytical studies have shown very low levels in human milk (Byrne and Kosta 1978). Evidence from animal studies supports the occupational findings. Vanadium administered intratracheally to rats was reported to be excreted predominantly in the urine (Oberg et al. 1978) at levels twice that found in the feces (Rhoads and Sanders 1985). Three days after exposure to vanadium pentoxide, 40% of the ^{48}V dose was excreted, mostly in the urine while 30% remained in the skeleton (5 days after exposure) (Conklin et al. 1982).

In female rats exposed to 0.56 or 1.1 mg vanadium/m^3 as vanadium pentoxide for 16 days (6 hours/day, 5 days/week), lung clearance half-times during an 8-day recovery period were 4.42 and 4.96 days, respectively (NTP 2002). In mice similarly exposed to 1.1 or 2.2 mg vanadium/m^3, lung clearance half-times were 2.55 and 2.40 days, respectively (NTP 2002). In contrast to the 16-day exposure data, the lung clearance half-times in female rats exposed to 0.28, 0.56, or 1.1 mg vanadium/m^3 for 2 years (6 hours/day, 5 days/week) were 37.3, 58.6, and 61.4 days, respectively (NTP 2002). In mice, the half-times were 6.26, 10.7, and 13.9 days at 0.56, 1.1, and 2.2 mg vanadium/m^3 exposure levels (NTP 2002). These data suggest that vanadium is more rapidly cleared from the lungs following a short exposure period compared to longer periods.

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to vanadium.

Since vanadium is poorly absorbed in the gastrointestinal tract, a large percentage of vanadium is excreted unabsorbed in the feces in rats following oral exposure. More than 80% of the administered dose of ammonium metavanadate or sodium metavanadate accumulated in the feces after 6 or 7 days (Adachi et al. 2000b; Patterson et al. 1986). After 2 weeks of exposure, 59.1±18.8% of sodium metavanadate was found in the feces (Bogden et al. 1982). However, the principal route of excretion of absorbed vanadium is through the kidney in animals. Approximately 0.9% of ingested vanadium was excreted in the urine of rats exposed to sodium metavanadate in the diet for 7 days (Adachi et al. 2000b). An elimination half-time of 11.7 days was estimated in rats exposed to vanadyl sulfate in drinking water for 3 weeks (Ramanadham et al. 1991).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to vanadium.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various

combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in

humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for vanadium exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK models for vanadium were located.

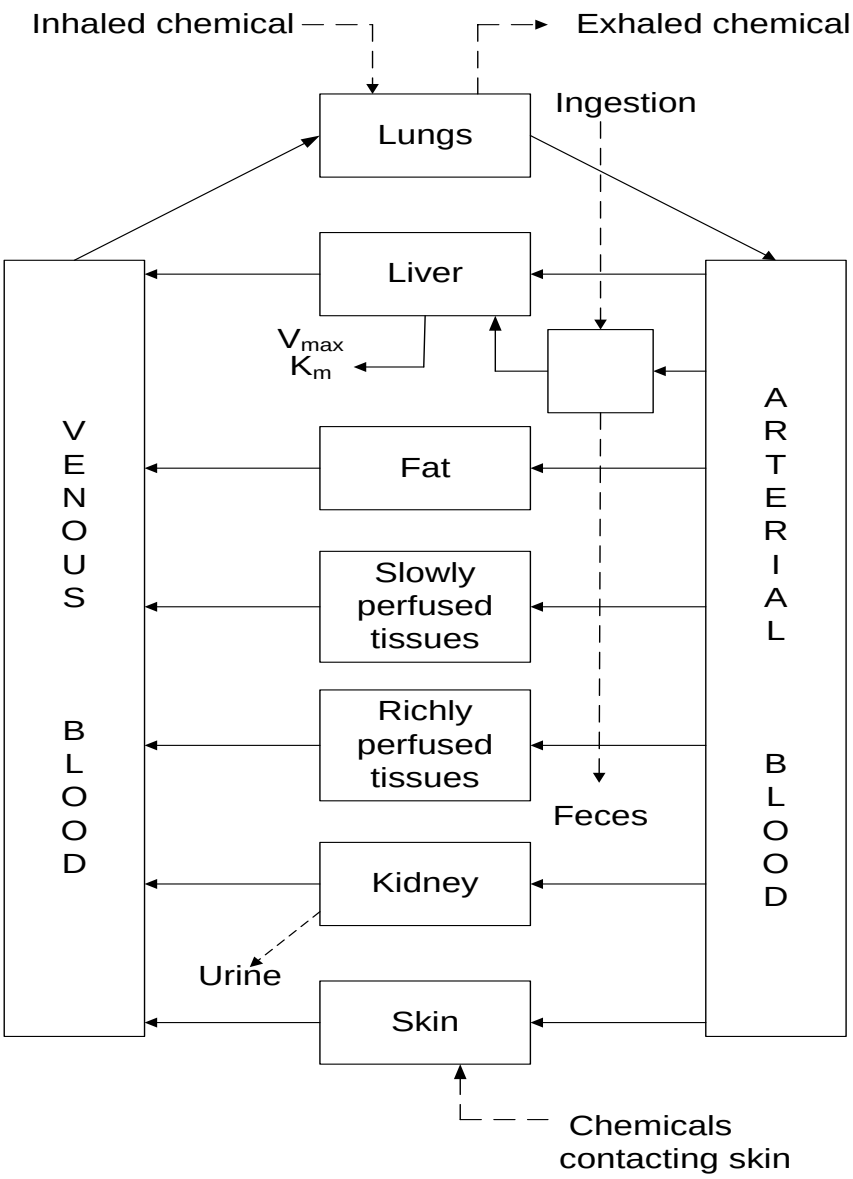
3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

In the body, there is an interconversion of two oxidation states of vanadium, the tetravalent form, vanadyl (V^{+4}), and the pentavalent form, vanadate (V^{+5}). Vanadium can reversibly bind to transferrin protein in the blood and then be taken up into erythrocytes. Vanadate is considered more toxic than vanadyl because vanadate is reactive with a number of enzymes and is a potent inhibitor of the Na+K+-ATPase of plasma membranes (Harris et al. 1984; Patterson et al. 1986). There is a slower uptake of vanadyl into erythrocytes compared to the vanadate form. Five minutes after an intravenous administration of radiolabeled vanadate or vanadyl in dogs, 30% of the vanadate dose and 12% of the vanadyl dose is found in erythrocytes (Harris et al. 1984). It is suggested that this difference in uptake is due to the time required for the vanadyl form to be oxidized to vanadate. When V^{+4} or V^{+5} is administered intravenously, a balance is reached in which vanadium moves in and out of the cells at a rate that is comparable to the rate of vanadium removal from the blood (Harris et al. 1984). Initially, vanadyl leaves the blood more rapidly than vanadate, possibly due to the slower uptake of vanadyl into cells (Harris et al. 1984). Five hours after administration, blood clearance is essentially identical for the two forms. A decrease in glutathione-SH, NADPH, and NADH occurs within an hour after intraperitoneal injection of sodium vanadate in mice (Bruech et al. 1984). It is believed that the redox cycling of vanadium V^{+5}/V^{+4}, depending on the local availability of oxygen in tissues, depletes reducing equivalents that are necessary for activity of cytochrome P-450.

Vanadium in the plasma can exist in a bound or unbound form (Bruech et al. 1984). Vanadium as vanadyl (Patterson et al. 1986) or vanadate (Harris and Carrano 1984) reversibly binds to human serum transferrin at two metal-binding sites on the protein. With intravenous administration of vanadate or vanadyl, there is a short lag time for vanadate binding to transferrin, but at 30 hours, the association is

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

identical for the two vanadium forms (Harris et al. 1984). The vanadium-transferrin binding is most likely to occur with the vanadyl form as this complex is more stable (Harris et al. 1984). The transferrin-bound vanadium is cleared from the blood at a slower rate than unbound vanadium in rats, which explains a biphasic clearance pattern (Sabbioni and Marafante 1978). The metabolic pathway appears to be independent of route of exposure (Edel and Sabbioni 1988).

3.5.2 Mechanisms of Toxicity

In vitro studies (as reviewed by Barceloux 1999; Etcheverry and Cortizo 1998; Harland and Harden-Williams 1994; Léonard and Gerber 1994; Mukherjee et al. 2004) have shown that vanadium acts as a phosphate analog and, as such, interferes with various ATPases, phosphatases, and phosphate-transfer enzymes. Vanadium has been shown to inhibit Na+K+ATPase, Ca2+ATPase, H+K+ATPase, K+ATPase, Ca+Mg+ATPase, dynein ATPase, actomyosin ATPase, acid and alkaline phosphatases, glucose-6-phosphatase, ribonuclease, phosphodiesterase, and phosphotryosyl-phosphatase. It has also been shown to stimulate tyrosine kinase phosphorylase, NADPH oxidase, and adenylate cyclase. Additionally, vanadium has been shown to have insulin-mimetic properties, particularly the ability to stimulate glucose uptake and oxidation and glycogen synthesis, and the ability to induce cell proliferation. The effect of vanadium on various enzymes may be responsible for the diverse effects observed in animals exposed to vanadium. However, little information is available regarding the mechanism of vanadium toxicity *in vivo*.

3.5.3 Animal-to-Human Extrapolations

There are little data available to evaluate potential toxicokinetic differences between humans and laboratory animals. Similar effects have been reported in humans and animals following inhalation or oral exposure to vanadium; however, this conclusion is based on the limited human toxicity data. In absence of data to the contrary, rats or mice appear to be valid models for extrapolation to humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to

develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997b). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No *in vivo* or *in vitro* studies were located regarding endocrine disruption in humans and/or animals after exposure to vanadium.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There are limited data on the toxicity of vanadium in children. One study examined the influence of age on the renal toxicity of vanadium in male rats administered 10 mg/kg/day sodium orthovanadate via intraperitoneal injection for 8 days. Similar morphological effects were observed in the kidneys of 22-day-old rats and 62-day-old rats; however, the effects were more severe in the older rats (de la Torre et al. 1999). The difference in lesion severity is likely due to the significantly lower renal vanadium concentration in the young rats.

Edel et al. (1984) examined age-related changes in the distribution of vanadium in rats exposed to background levels of vanadium. At 21 days of age, the highest concentrations of vanadium (ng vanadium/g wet weight) were found in the kidney, heart, lung, brain, and liver. By 115 days of age, the highest concentration was in the femur; levels in the heart, lung, brain, spleen, and muscle were approximately 3–4 times lower. The concentrations of vanadium in the kidney, liver, and lungs significantly decreased with increasing age of the rat. The investigators suggested several mechanisms that may be responsible for the age-related changes in vanadium tissue concentration, including higher gastrointestinal absorption of vanadium in young rats, which may be due to increased bioavailability of vanadium in breast milk compared to the diet, or a higher vanadium retention capacity in undeveloped tissue due to a greater affinity or lower elimination rate.

As discussed in Section 3.2, a number of developmental effects including decreases in growth, increases in malformation and anomalies, and death have been observed in developmental toxicity studies (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003; Paternain et al. 1990); however most of these effects occurred at doses associated with significant maternal toxicity.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is

available at http://www.cdc.gov/exposurereport/. The biomonitoring data for vanadium from this report is discussed in Section 6.5. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to vanadium are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by vanadium are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Vanadium

Several biomarkers of exposure have been identified for vanadium but none of them can be used to quantitatively determine exposure levels. Elevated levels of vanadium have been found in the serum

(Gylseth et al. 1979; Kiviluoto et al. 1981b) and urine (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983; Zenz et al. 1962) of exposed workers. However, relationships between exposure levels and serum or urine vanadium levels have not been established. Some vanadium workers develop a characteristic green tongue, as a result of direct accumulation of the vanadium dusts on the tongue (Lewis 1959). One report from the 1950s states that vanadium exposure was associated with decreased cystine content in the fingernails of vanadium workers (Mountain et al. 1955). However, alterations in cystine levels can also be associated with dietary changes and with other disease states, so this is not specific for vanadium exposure. No other commonly measured cellular changes have been identified with vanadium exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by Vanadium

The primary effects of inhalation exposure to vanadium dusts are coughing, wheezing, and other respiratory difficulties. These effects, however, are not specific to vanadium and can be found following inhalation of many types of dusts.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Vanadium in the drinking water of mice had no influence on tumor induction by the known carcinogen 1,2-dimethylhydrazine given by subcutaneous injection (Kingsnorth et al. 1986), but dietary vanadium did decrease mammary tumors in mice caused by 1-methyl-1-nitrosourea administered concurrently (Thompson et al. 1984). The latter effect may have been due to interaction with DNA.

The combination of manganese and vanadium or of nickel and vanadium administered to pregnant mice caused some alterations in behavioral development of the pups as compared to either element administered alone (Hoshishima et al. 1983). Oral administration of vanadium in rats interfered with copper metabolism, probably by inhibiting the intestinal absorption of copper (Witkowska et al. 1988).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to vanadium than will most persons exposed to the same level of vanadium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of vanadium, or compromised function of organs

affected by vanadium. Populations who are at greater risk due to their unusually high exposure to vanadium are discussed in Section 6.7, Populations with Potentially High Exposures.

No unusually susceptible populations have been identified, but persons with pre-existing respiratory disorders such as asthma or chronic obstructive pulmonary disease (COPD) may be expected to have increased adverse effects from breathing vanadium dusts. Due to the insulin-mimetic effects of vanadium, individuals with hypoglycemia may be unusually susceptible to exposure to high levels of vanadium.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to vanadium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to vanadium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to vanadium:

Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Company, 1033.

Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 406-407.

3.11.1 Reducing Peak Absorption Following Exposure

There is no known treatment to decrease absorption after inhaling vanadium and/or its compounds. Following oral exposure, dilution with water or milk is one way to decrease overall absorption (Stutz and Janusz 1988). To decrease gastrointestinal absorption, especially for organic vanadium compounds, it has been suggested that activated charcoal be ingested. If vanadium gets onto the skin, washing the contaminated area with soapy water has been advised. For ocular exposure, it is suggested that the eyes be flushed with large amounts of saline or water (Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

Several studies have evaluated the effectiveness of chelating agents in reducing vanadium body burden. Significant increases in urinary excretion of vanadium were observed in rodents treated with ascorbic acid

(Domingo et al. 1990), tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate) (Domingo et al. 1990; Gomez et al. 1991), deferoxamine mesylate (Gomez et al. 1988, 1991), or 2-mercaptosuccinic (Domingo et al. 1990) following intramuscular injection of vanadyl sulfate (Domingo et al. 1990) or 6-week oral exposure to sodium metavanadate or vanadyl sulfate (Gomez et al. 1991). Administration of EDTA, 2-mercaptosuccinic or tiron also significantly reduced kidney vanadium levels (Domingo et al. 1990) and tiron reduced spleen and kidney vanadium levels (Gomez et al. 1991). Administration of calcium disodium EDTA resulted in increases in urinary excretion of vanadium in calves exposed to high levels of dietary vanadium (Gummow et al. 2006); however, no difference in vanadium excretion was observed after vanadium exposure was terminated. Other studies have examined the potential of chelating agents to reduce toxicity. Humans or animals with vanadium poisoning have not been helped by the chelating agent dimercaprol (BAL), which is often effective in lessening the toxicity of other metals (Lusky et al. 1949). Intraperitoneal injections of ascorbic acid and of ethylene diamine tetraacetate (EDTA) reduced vanadium-induced morbidity in mice and rats (Jones and Basinger 1983; Mitchell and Floyd 1954). Administration of tiron 0, 24, 48, or 72 hours after pregnant mice received a 25 mg/kg sodium metavanadate intraperitoneal injection on gestation day 12 resulted in significant reductions in vanadium-induced abortions, early deliveries, fetal deaths, and incidence of reduced ossification (Domingo et al. 1993a). Administration of tiron after a 6-week exposure to sodium metavanadate reverted the vanadium-induced impairment in performance on neurobehavioral tests (Sanchez et al. 1999). Co-exposure to calcium disodium EDTA did not significantly alter the toxicity of ingested vanadium in calves (Gummow et al. 2006).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

There are limited data on treatments which interfere with the mechanism of action for vanadium toxicity. Moderate to severe morphological alterations (average severity score of 3.0) were observed in the kidneys 25 days after rats were administered 1 mg vanadium/kg/day as ammonium metavanadate via subcutaneous injection (Al-Bayati et al. 2002). Administration of the antifibrotic agent, pirfenidone, for 41 days after exposure termination resulted in a decrease in the severity of the kidney lesions; the lesions were scored as very mild with a severity score of 1.42. Although the mechanism associated with the reduction in toxicity was not determined, it is possible that the pirfenidone-induced reduction in collagen-deposition in the kidney may have contributed to the diminished toxicity. Chandra et al. (2007a) demonstrated a reduction in testes toxicity in rats administered 0.4 mg vanadium/kg/day as sodium metavanadate via intraperitoneal injection for 26 days and 50 or 100 mg/kg vitamin E acetate simultaneously in the diet compared to rats administered vanadium only. The likely mechanism is that

vitamin E interrupts the chain reactions of lipid peroxidation and scavenges ROS generated during the univalent reduction of molecular oxygen and normal activity of oxidative enzymes; thus its prevents the detrimental effect of vanadium on testis by inhibiting the oxidative stress.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of vanadium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of vanadium.

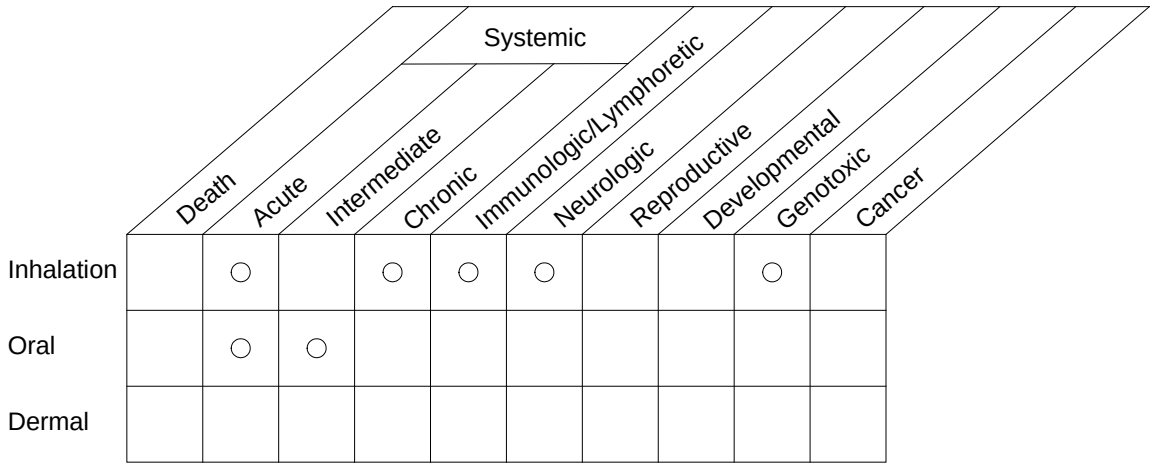
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Vanadium

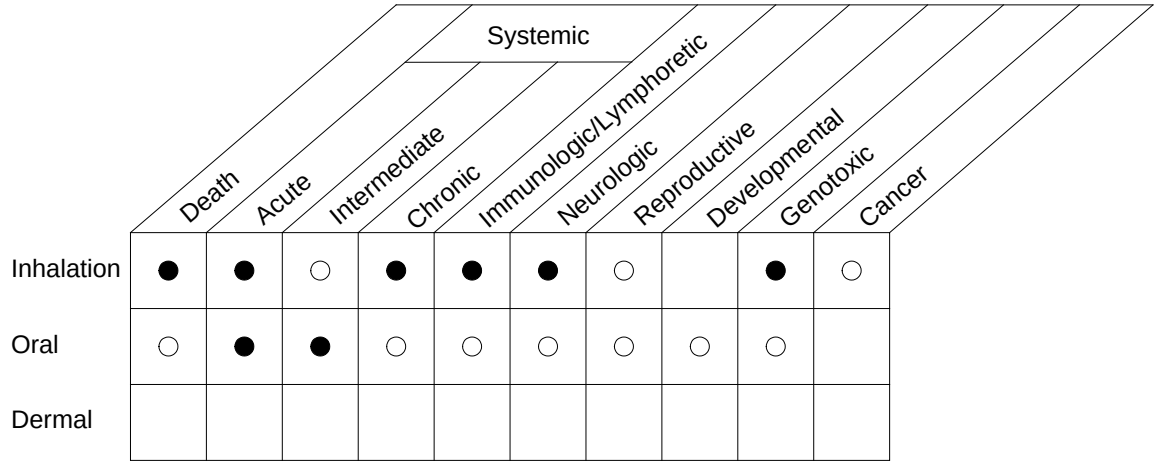
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to vanadium are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of vanadium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Data are available from humans regarding acute, intermediate, and chronic inhalation exposure to vanadium pentoxide and on immunologic and neurologic effects, primarily from case studies of factory

Figure 3-4. Existing Information on Health Effects of Vanadium and Compounds



Human



Animal

● Existing Studies

workers. Data regarding acute effects are available from volunteers who ingested ammonium vanadyl tartrate in capsules for intermediate periods. No human dermal data were located.

Data are available regarding the effects of inhalation of vanadium pentoxide in rats, mice, and monkeys following acute, intermediate, and chronic exposures. Data are available in humans orally exposed to vanadyl sulfate or ammonium metavanadate. Data are available following acute, intermediate, and chronic oral exposures in animals, including information on death (from ammonium metavanadate, sodium metavanadate, or vanadyl sulfate), systemic toxicity (from vanadyl sulfate, sodium metavanadate, sodium orthovanadate, or ammonium metavanadate), immunological (from sodium orthovanadate), neurological (from vanadium pentoxide), developmental (from vandyl sulfate, sodium orthovanadate, ammonium metavanadate, or sodium metavanadate), and reproductive effects (from sodium metavanadate, ammonium metavanadate, or vanadyl sulfate). No animal dermal data were located.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information on the acute toxicity of inhaled vanadium in humans is limited to the finding of symptoms of respiratory irritation (persistent coughing) in a small number of subjects exposed to vanadium pentoxide dust for 8 hours (Zenz and Berg 1967). Several animal studies confirm that the respiratory tract is the most sensitive target of vanadium toxicity (Knecht et al. 1985, 1992; NTP 2002). These studies only examined the respiratory tract; however, longer duration studies have confirmed the respiratory tract as the most sensitive target following inhalation exposure. At lower concentrations, the observed effects included lung inflammation and alveolar and bronchiolar epithelial hyperplasia in rats and mice exposed to vanadium pentoxide for 6 or 13 days (NTP 2002); the severity of the lung effects increased with increasing vanadium concentrations. Impaired lung function was reported in monkeys exposed to fairly low concentrations of vanadium pentoxide for 6 hours (Knecht et al. 1985, 1992). The animal data were sufficient to derive an acute-duration inhalation MRL for vanadium based on lung inflammation in rats (NTP 2002).

There are limited data on human toxicity following ingestion of vanadium; gastrointestinal effects (diarrhea, cramps, nausea, vomiting) have been reported in patients given vanadium supplement as part of a diabetes treatment plan (Boden et al. 1996; Cusi et al. 2001; Goldfine et al. 1995). However, these studies are limited by the small number of subjects and the lack of control groups. A small number of studies in laboratory animals have examined the acute toxicity of vanadium following oral exposure. At the lowest doses tested, marked developmental toxicity (decreases in fetal growth, increases in resorptions

and gross, visceral, and skeletal malformations and anomalies) was observed in rat and mouse offspring (Paternain et al. 1987, 1990; Sanchez et al. 1991). In adult rats, hematological effects (including increases in reticulocyte levels and polychromatophilic erythroblasts in bone marrow) were observed at higher doses than the developmental effects (Zaporowska and Wasilewski 1989). The database was considered inadequate for derivation of an acute-duration oral MRL due to the limitations in the human studies and the serious effects observed at the lowest animal dose tested. At the lowest adverse effect level, a 46% decrease in weight gain (considered a serious health effect) was observed in the rat dams (Paternain et al. 1990); it is ATSDR policy to not use serious LOAELs as the basis of an MRL. Additional studies which examine a variety of end points are needed to identify the most sensitive effect following acute oral exposure. These additional studies might provide a suitable basis for an acute-duration oral MRL.

No dermal exposure studies were identified in humans or animals. Studies are needed to establish the potential toxicity of vanadium compounds applied to the skin.

Intermediate-Duration Exposure. No human studies examined the toxicity of vanadium following intermediate-duration inhalation exposure. Animal data come from 16-day and 13-week exposure studies in rats and mice (NTP 2002). These studies clearly identify the respiratory tract as the most sensitive target of toxicity. At low concentrations of vanadium pentoxide, alveolar and bronchiolar epithelial hyperplasia were observed in both species. At higher concentrations, nasal effects were also observed. Although the NTP (2002) study is a high quality study which identified NOAEL and LOAEL values for a sensitive end point, an intermediate-duration inhalation MRL was not derived because the NOAEL value was the same as the LOAEL for lung inflammation in rats exposed to vanadium pentoxide for 13 days (NTP 2002). An explanation for the inconsistent findings is not apparent from the available data. An additional study designed to examine respiratory effects after various exposure durations may provide insight into the inconsistent findings of the NTP study and may be useful for derivation of an MRL.

Data on the toxicity of vanadium following intermediate-duration oral exposure come from two human studies and a number of animal studies. The human studies examined a number of potential end points in subjects exposed to relatively low doses of vanadium for 6–12 weeks; no adverse effects were observed (Dimond et al. 1963; Fawcett et al. 1997). Animal studies have identified several sensitive effects including hematological alterations (decreased erythrocyte levels and increased reticulocyte levels) (Ścibior 2005; Ścibior et al. 2006; Zaporowska and Wasilewski 1990, 1991, 1992a, 1992b; Zaporowska et al. 1993), increased blood pressure (Boscolo et al. 1994; Carmagnani et al. 1991, 1992), alterations in

neurobehavioral performance tests (Sanchez et al. 1998), and developmental toxicity (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003; Poggioli et al. 2001). However, the findings are inconsistent and a cause of the conflicting results has not been identified. Additional animal studies examining hematological, blood pressure, and neurological end points are needed to support the findings of the animal studies. An intermediate-duration oral MRL based on the NOAEL identified in one of the human studies (Fawcett et al. 1997) was derived.

No dermal exposure studies were identified in humans or animals. Studies utilizing several vanadium compounds would be useful for assessing the potential dermal toxicity of vanadium.

Chronic-Duration Exposure and Cancer. Sufficient information is available in occupationally exposed humans to identify the respiratory system as a target organ following chronic inhalation exposure (Lewis 1959; NIOSH 1983; Sjöberg 1956; Vintinner et al. 1955; Wyers 1946). Two-year rat and mouse studies (NTP 2002) confirm the identification of the respiratory tract as the most sensitive target of inhaled vanadium pentoxide. At the lowest concentrations tested, histological alterations in the lungs (alveolar and bronchiolar epithelial hyperplasia), larynx (degeneration and hyperplasia of epiglottis epithelium), and nasal cavity (goblet cell hyperplasia) were observed. The NTP (2002) rat study was used as the basis of a chronic-duration inhalation MRL for vanadium.

No studies examining the chronic oral toxicity of vanadium in humans were identified. Several studies have examined chronic oral toxicity in rats and mice (Dai and McNeill 1994; Dai et al. 1994a, 1994b; Schroeder and Balassa 1967; Schroeder et al. 1970); however, the doses tested did not result in adverse effects, with the exception of a decrease in body weight gain, and the most sensitive targets of vanadium toxicity following chronic exposure have not been identified. Additional studies examining a variety of end points, including potential hematological and cardiovascular effects (sensitive targets following intermediate-duration exposure), are needed to identify sensitive targets and establish dose-response relationships.

Data are not available to determine target organs in humans from chronic dermal exposure. Dermal exposure studies which could be used to identify targets of toxicity and dose-response relationships are needed.

No studies were located regarding the carcinogenicity in humans after inhalation, oral, or dermal exposure to vanadium. Significant increases in the incidence of lung tumors (alveolar/bronchiolar adenoma and/or

carcinoma) were observed in mice exposed to airborne vanadium pentoxide for 2 years (NTP 2002). Suggestive evidence of lung carcinogenicity was also observed in male rats chronically exposed to vanadium pentoxide (NTP 2002). Although several oral studies did not find increases in tumor frequency in rats or mice exposed to vanadyl sulfate in drinking water (Schroeder and Balassa 1967; Schroeder and Mitchener 1975; Schroeder et al. 1970), these studies were considered inadequate for carcinogenicity assessment due to the small number of animals tested, low doses (maximum tolerated dose was not achieved), incomplete histological examination, and the use of one exposure dose per study. No studies examined the potential carcinogenicity of vanadium following dermal exposure. Additional studies are needed to evaluate the potential carcinogenicity of vanadium following oral and dermal exposure.

Genotoxicity. *In vivo* genotoxicity assays have been conducted in vanadium pentoxide workers (Ehrlich et al. 2008; Ivancsits et al. 2002), in mice exposed to airborne vanadium pentoxide (NTP 2002), in mice exposed to vanadyl sulfate in drinking water (Villani et al. 2007), and in mice administered a gavage dose of vanadyl sulfate, ammonium metavanadate, or sodium orthovanadate (Ciranni et al. 1995). Most of the *in vitro* genotoxicity assays have been conducted in mammalian systems, although there are also mutagenicity assays in cultured bacteria (Kada et al. 1980; Kanematsu et al. 1980; NTP 2002) and yeast (Bronzetti et al. 1990; Sora et al. 1986). In mammalian systems, mutagenicity (Cohen et al. 1992), DNA damage (Birnboim 1988; Foresti et al. 2001; Ivancsits et al. 2002; Kleinsasser et al. 2003; Rojas et al. 1996; Smith 1983; Wozniak and Blasiak 2004), and clastogenicity (Gibson et al. 1997; Migliore et al. 1993, 1995; Owusu-Yaw et al. 1990; Roldán and Altamirano 1990; Zhong et al. 1994) have been observed. In general these studies provide evidence that vanadium compounds damage DNA and induce clastogenic alterations. However, there are a number of inconsistencies in the results and additional studies are needed.

Reproductive Toxicity. No studies were located regarding the reproductive effects in humans after inhalation, oral, or dermal exposure to vanadium. Following inhalation exposure, alterations in estrous cycle were observed in female rats exposed to vanadium pentoxide for 3 months (NTP 2002); no alterations in sperm characteristics were observed. Studies examining reproductive function are needed to evaluate whether the alterations observed in female rats would result in impaired fertility. Decreases in male and/or female fertility were observed in rats and mice orally exposed to vanadium (Ganguli et al. 1994b; Jain et al. 2007; Llobet et al. 1993; Morgan and El-Tawil 2003). Dermal exposure studies are needed to evaluate whether the reproductive system is also a target of toxicity for this route.

Developmental Toxicity. The potential developmental toxicity of vanadium has not been assessed in humans. Oral exposure studies in animals provide evidence that developmental toxicity is a sensitive end point. The observed effects include decreases in fetal/pup growth, increased mortality, and increases in gross, skeletal, and visceral malformations and anomalies (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003; Paternain et al. 1987, 1990; Poggioli et al. 2001). Most of these effects occurred at doses associated with decreases in maternal food intake and body weight. Additional studies utilizing doses not associated with maternal toxicity would be useful in determining whether the observed effects are secondary to maternal toxicity or whether the developing organism is a primary target. No studies were located regarding the developmental effects in animals after inhalation or dermal exposure to vanadium. Studies are needed to determine whether developmental toxicity would also be a sensitive target following inhalation or dermal exposure.

Immunotoxicity. Data regarding the immunotoxicity of vanadium in humans are limited to a study of vanadium workers which did not find signs of allergic reactions on the skin or in the respiratory tract (Sjöberg 1950). No alterations in immune response to bacteria and/or viruses were observed in mice exposed to airborne vanadium pentoxide for 16 days (NTP 2002); an altered response was observed in rats. An altered response to sheep red blood cells in mice exposed to sodium orthovanadate in drinking water for 6 weeks (Sharma et al. 1981) and decreases in B-cell, IgG, and IgM levels in rats exposed to sodium metavanadate in the diet for 10 weeks (Adachi et al. 2000a) were observed. No dermal exposure studies examining immunological end points were identified. Although the animal data provide some suggestive evidence of immunotoxicity, additional inhalation and oral exposure studies testing a full immunology battery are needed to establish the potential of vanadium to induce immunotoxicity.

Neurotoxicity. Some workers exposed to vanadium dust complained of dizziness, depression, headache, or tremors of the fingers and arms (Levy et al. 1984; Vintinner et al. 1955); however, these effects may not have been specifically due to vanadium exposure. Neurotoxicity was not evaluated in humans following oral or dermal exposure. In animals, alterations in performance on neurobehavioral tests were observed in rats orally exposed to sodium metavanadate (Sanchez et al. 1998, 1999). No histological alterations in the nervous system were observed in rats or mice exposed to airborne vanadium pentoxide (NTP 2002). Neurotoxicity potential was not assessed in animals following dermal exposure. Additional studies performing a complete neurological battery of tests are needed to fully evaluate the potential of vanadium to induce neurotoxicity, particularly since the Sanchez et al. (1998) study provides suggestive evidence that this may be a sensitive target following oral exposure.

Epidemiological and Human Dosimetry Studies. Studies of health effects on people who have inhaled vanadium in the workplace clearly show that the target organ is the respiratory system (Domingo et al. 1985; Levy et al. 1984; Lewis 1959; Musk and Tees 1982; NIOSH 1983; Sjöberg 1950, 1956; Thomas and Stiebris 1956; Vintinner et al. 1955; Wyers 1946; Zenz and Berg 1967; Zenz et al. 1962). The dose-response relationship is not known, because exposure levels are not well quantified. Further information on exposure levels associated with respiratory effects would be useful. However, people living near hazardous waste sites are unlikely to come in contact with amounts of vanadium dusts large enough to cause adverse health effects. Further epidemiological studies may be useful in revealing adverse health effects in people living near boiler ash dumps. Additional information on potentially susceptible populations, such as those people with asthma or other respiratory problems, would be useful. There are limited data regarding the oral toxicity of vanadium in humans. Studies in diabetics have shown that bolus administration can result in symptoms of gastrointestinal irritation (Boden et al. 1996; Cusi et al. 2001; Goldfine et al. 1995). Two studies in healthy individuals (Dimond et al. 1963; Fawcett et al. 1997) examined a wide variety of potential targets of vanadium toxicity. However, both studies used a small number of subjects and additional studies are needed to evaluate the long-term toxicity of vanadium in humans, particularly since vanadium is present in a number of nutritional supplements and there is a potential for human exposure. An intermediate-duration oral study (Fawcett et al. 1997) which found no adverse effects in subjects administered vanadyl sulfate via capsules was used as the basis of an MRL.

Biomarkers of Exposure and Effect.

Exposure. Biomarkers specific for exposure to vanadium include the presence of vanadium in the urine (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983; Zenz et al. 1962) and serum (Gylseth et al. 1979) and a green discoloration of the tongue (Lewis 1959), the latter resulting from the direct accumulation of vanadium pentoxide. Further studies would be helpful in correlating urinary or serum vanadium levels with exposure levels. Vanadium can also be measured in the hair (Stokinger et al. 1953), and studies could be performed to determine if a correlation exists between levels of vanadium in hair and exposure levels. In the 1950s, decreased cystine content of the hair or fingernails was described as a possible biomarker of exposure (Mountain et al. 1955). However, this is not specific for vanadium since other factors, such as diet or disease, can also affect cystine content.

Effect. There are no specific biomarkers of effects. It is possible that further biochemical studies might show specific effects. For example, it is possible that specific effects may be seen on lung cells, which can be examined by lavage.

Absorption, Distribution, Metabolism, and Excretion. Data are available from human and animal studies regarding the kinetics of vanadium following inhalation and oral exposure. Specific data from dermal exposure are lacking; although significant absorption of vanadium by this route in humans is unlikely (WHO 1988), data are needed to confirm this hypothesis. No animal studies were located that evaluated absorption efficiency following inhalation exposure, although NTP (2002) reported marginal, but concentration-related, increases in blood vanadium in rats exposed to vanadium pentoxide for 14 days or 2 years. Additionally, information is available from intratracheal exposures (Conklin et al. 1982; Edel and Sabbioni 1988; Oberg et al. 1978; Rhoads and Sanders 1985). Oral exposure studies suggest that approximately 3–17% of ingested vanadium is absorbed and that absorption efficiency may vary among vanadium compounds (Adachi et al. 2000b; Conklin et al. 1982). Intratracheal administration and oral exposure suggest similar patterns of distribution and excretion (Adachi et al. 2000b; Conklin et al. 1982; Ramanadham et al. 1991; Rhoads and Sanders 1985) for the two routes of exposure. Additional studies are needed to provide information on the toxicokinetic properties of vanadium following inhalation and dermal exposure. Additionally, there are limited data comparing the absorption and distribution of various vanadium compounds; inhalation, oral, and dermal exposure studies are needed to evaluate whether there are compound-specific differences.

Comparative Toxicokinetics. Animal data (Conklin et al. 1982; Oberg et al. 1978; Rhoads and Sanders 1985; Roshchin et al. 1980) and limited human (Dimond et al. 1963; Gylseth et al. 1979; Schroeder et al. 1963) data are available on the kinetics of vanadium. There is little reason to believe that vanadium toxicokinetics would differ between animals and humans. The data indicate that the kinetics are similar in both. However, as with any particulate substance, extrapolations on inhalation absorption rates from animals to humans would be difficult. Studies are available in humans, rats, mice, and dogs.

Methods for Reducing Toxic Effects. No vanadium-specific information on reducing the absorption of vanadium following inhalation, oral, or dermal exposure were identified; such information would be useful in the treatment of persons who may have been exposed to vanadium and/or its compounds near hazardous waste sites. Several animal studies have explored the use of chelating agents for reducing the vanadium body burden. Administration of ascorbic acid, tiron, deferoxamine mesylate, or 2-mercaptosuccinic have been shown to increase urinary excretion of vanadium or reduce kidney levels

(Domingo et al. 1990; Gomez et al. 1988, 1991), and EDTA and tiron have been shown to reduce toxicity (Domingo et al. 1993a; Jones and Basinger 1983; Mitchell and Floyd 1954; Sanchez et al. 1999), presumably by reducing the body burden. There is some evidence that pirfenidone (an antifibrotic agent) (Al-Bayati et al. 2002) and vitamin E (Chandra et al. 2007a) may interfere with the mechanism of vanadium toxicity. Additional data are needed, particularly studies examining methods for reducing the toxicity of inhaled vanadium.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are limited data on the susceptibility of children to vanadium toxicity. No human or animal studies examined possible age-related differences in toxicity following inhalation, oral, or dermal exposure. An intraperitoneal study found decreases in the severity of renal lesions in young rats (22 days of age) compared to older rats (62 days of age) (de la Torre et al. 1999). Additional studies are needed to evaluate if there are age-related differences in vanadium toxicity or toxicokinetic properties.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing studies examining the toxicity or toxicokinetics of vanadium were identified.

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Vanadium is a naturally occurring element that appears in group 5(B5) of the periodic table (Lide 2008). Vanadium is widely distributed in the earth's crust at an average concentration of 100 ppm (approximately 100 mg/kg), similar to that of zinc and nickel (Byerrum 1991). Vanadium is the 22nd most abundant element in the earth's crust (Baroch 2006). Vanadium is found in about 65 different minerals; carnotite, roscoelite, vanadinite, and patronite are important sources of this metal along with bravoite and davidite (Baroch 2006, Lide 2008). It is also found in phosphate rock and certain ores and is present in some crude oils as organic complexes (Lide 2008). Table 4-1 lists common synonyms and other pertinent identification information for vanadium and representative vanadium compounds.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Vanadium is a gray metal with a body-centered cubic crystal system. It is a member of the first transition series. Because of its high melting point, it is referred to as a refractory metal (Baroch 2006). When highly pure, it is a bright white metal that is soft and ductile. It has good structural strength and a low-fission neutron cross section. Vanadium has good corrosion resistance to alkalis, sulfuric and hydrochloric acid, and salt water; however, the metal oxidizes readily above 660 °C (Lide 2008). The chemistry of vanadium compounds is related to the oxidation state of the vanadium (Woolery 2005). Vanadium has oxidation states of +2, +3, +4, and +5. When heated in air at different temperatures, it oxidizes to a brownish black trioxide, a blue black tetraoxide, or a reddish orange pentoxide. It reacts with chlorine at fairly low temperatures (180 °C) forming vanadium tetrachloride and with carbon and nitrogen at high temperatures forming VC and VN, respectively. The pure metal in massive form is relatively inert toward oxygen, nitrogen, and hydrogen at room temperature (HSDB 2009). Vanadium pentoxide is an industrially important vanadium compound (Lide 2008). Table 4-2 lists important physical and chemical properties of vanadium and vanadium compounds.

Table 4-1. Chemical Identity of Vanadium and Compounds[a]

Characteristic	Vanadium	Vanadium pentoxide	Vanadyl sulfate
Synonym(s)	Vanadium, elemental	Vanadium oxide; vanadium(V) oxide; vanadic anhydride; divanadium pentoxide	Vanadic sulfate; vanadium oxide sulfate
Registered trade name(s)			
Chemical formula	V	V_2O_5	$VOSO_4$
Identification numbers:			
CAS registry	7440-62-2	1314-62-1	27774-13-6
EINECS	231-171-1	215-239-8	248-652-7
RTECS[b]	YW1355000	YW2450000	YW1925000
EPA hazardous waste	No data	P120	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	UN2862	UN2931
HSDB	1022	1024	1026
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Vanadium and Compounds[a]

Characteristic	Sodium metavanadate	Sodium orthovanadate	Ammonium metavanadate
Synonym(s)	Sodium vanadate(V); vanadic acid, monosodium	Sodium o-vanadate; sodium pervanadate; sodium vanadium oxide; vanadic(II) acid, trisodium salt	Ammonium vanadate(V); ammonium monovanadate; ammonium vanadium oxide; ammonium vanadium trioxide; vanadic acid, ammonium salt
Registered trade name(s)			
Chemical formula	$NaVO_3$	Na_3VO_4	NH_4VO_3
Identification numbers:			
CAS registry	13718-26-8	13721-39-6	7803-55-6
EINECS	237-272-7	237-287-9	232-261-3
RTECS[b]	YW1050000	YW1120000	YW0875000
EPA hazardous waste	No data	No data	P119
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	UN2859
HSDB	No data	No data	6310
NCI	No data	No data	No data

[a]All information obtained from ChemIDPlus 2009 and HSDB 2009, except where noted.
[b]RTECS 2009

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Vanadium and Compounds[a]

Property	Vanadium	Vanadium pentoxide	Vanadyl sulfate dihydrate
Molecular weight	50.9415	181.88	199.035[c]
Color	Light gray or white lustrous powder, fused hard lumps or body-centered cubic crystals. Pure vanadium is bright white, soft and ductile.	Yellow to rust-brown orthorhombic crystals. Yellow-orange powder or dark-gray flakes dispersed in air. Yellow to red crystalline powder.	Blue crystalline powder[c]
Physical state	Solid[b]	Solid[b]	Solid
Melting point	1,910 °C	690 °C	
Boiling point	3,407 °C	1,750 °C (decomposes)	
Density at 18.7 °C	6.11	3.357	No data
Odor	No data	Odorless	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Insoluble	1 g dissolves in approximately 125 mL water	Soluble in water[c]
Other solvents	Soluble in nitric, hydrofluoric, and concentrated sulfuric acids; attacked by alkali, forming water soluble vanadates	Soluble in concentrated acids, alkalies; insoluble in alcohol	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	2.34×10^{-2} mm Hg at 1,916 °C (extrapolated)	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Vanadium and Compounds[a]

Property	Sodium metavanadate	Sodium orthovanadate	Ammonium metavanadate
Molecular weight	121.830[c]	183.909[c]	116.98
Color	Colorless, monoclinic, prismatic crystals or pale-green crystalline powder[b]	Colorless, hexagonal prisms[b]	White or slightly yellow, crystalline powder
Physical state	Solid	Solid	Solid
Melting point	630°C[b]	850–866 °C[b]	200 °C
Boiling point	No data	No data	No data
Density	No data	No data	2.326 g/cm^3
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	21 g/100 g water at 25 °C[c]	Soluble in water[c]	Slightly soluble in cold water
Other Solvents	No data	Insoluble in ethanol[c]	Insoluble in alcohol, ether, ammonium chloride
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	Noncombustible[b]	No data	Nonflammable[b]
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

[a]All information obtained from HSDB 2009, except where noted.
[b]Lewis 2007
[c]Lide 2008
[d]Vanadyl sulfate pentahydrate - Ethereal blue solid; readily soluble in water

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

TRI information is available in the TRI database on facilities that manufacture or process vanadium (except when contained in an alloy) and vanadium compounds for Release Year 2007, in accordance with Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (TRI07 2009).

Seven U.S. firms produced ferrovanadium, vanadium pentoxide, vanadium metal, and vanadium-bearing chemicals or specialty alloys by processing materials such as petroleum residues, spent catalysts, utility ash, and vanadium-bearing pig iron slag (USGS 2009a).

Vanadium occurs in uranium-bearing minerals of Colorado, in the copper, lead, and zinc vanadates of Africa, and with certain phosphatic shales and phosphate rocks in the western United States. Commercial production from petroleum ash holds promise as an important source of vanadium. It is a constituent of titaniferous magnetites that are widely distributed in Russia, South Africa, Finland, People's Republic of China, eastern and western United Sates, and Australia. The vanadium deposits from sulfide and vanadate ores in the Peruvian Andes have been depleted. Most reserves are in deposits where vanadium would be a by-product or co-product with other minerals, including phosphate, titanium, iron, and petroleum (Baroch 2006). High-purity ductile vanadium can be obtained by reduction of vanadium chloride with magnesium or with magnesium-sodium mixtures. Much of the vanadium metal now being produced is made by calcium reduction of V_2O_5 in a pressure vessel (Lide 2008).

World mine production reported for 2008 (in metric tons) was: China, 20,000; Russia, 16,000; South Africa, 23,000; and other countries, 1,000, or about 60,000 metric tons for the world (USGS 2009a).

Table 5-1 lists the facilities in each state that manufacture or process vanadium (except when contained in an alloy), the intended use, and the range of maximum amounts of this material that are stored on site. Table 5-2 lists the facilities in each state that manufacture or process vanadium compounds, the intended use, and the range of maximum amounts of this material that are stored on site. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI07 2009). Only certain types of facilities were required to report (EPA 2005b). Therefore, this is not an exhaustive list.

Current U.S. manufacturers of vanadium and selected vanadium compounds are given in Table 5-3.

Table 5-1. Facilities that Produce, Process, or Use Vanadium (Except When Contained in an Alloy)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	7	100	49,999,999	1, 2, 3, 5, 7, 12, 13, 14
AR	4	0	99,999	1, 5, 13, 14
AZ	5	10,000	9,999,999	1, 2, 3, 4, 5, 6, 12, 13, 14
CA	12	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
CT	2	10,000	999,999	1, 4, 5, 9, 12
FL	8	0	999,999	1, 4, 5, 9, 10, 12, 13, 14
GA	1	1,000,000	9,999,999	1, 11, 13
ID	3	100,000	999,999	1, 3, 5, 12
IL	9	0	999,999	1, 5, 7, 12, 13
IN	3	0	999,999	8, 10, 14
KS	4	100	999,999	1, 5, 11, 12, 14
KY	6	0	99,999	1, 5, 7, 8, 11, 12
LA	7	0	999,999	1, 2, 3, 6, 7, 10, 12, 13, 14
MD	3	0	99,999	1, 5
MI	2	1,000	99,999	2, 5, 7, 8, 11, 14
MO	1	1,000	9,999	12
MS	3	10,000	999,999	2, 3, 8, 10
NC	1	1,000	9,999	8
ND	1	100,000	999,999	1, 5, 12
NE	3	10,000	99,999	1, 3, 4, 5, 9, 12, 13
NJ	1	10,000	99,999	2, 13
NM	2	10,000	9,999,999	12
NY	3	100	999,999	1, 5, 6
OH	14	0	9,999,999	1, 3, 4, 5, 7, 8, 11, 12, 13, 14
OK	2	10,000	99,999	1, 5, 11, 14
PA	8	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 12
PR	1	0	0	0
SC	10	0	999,999	1, 3, 4, 5, 6, 9, 12, 13
TN	4	100	9,999	1, 2, 3, 5, 9, 13, 14
TX	24	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	3	0	99,999	1, 2, 5, 12, 13, 14
WI	1	1,000	9,999	7, 8

Table 5-1. Facilities that Produce, Process, or Use Vanadium (Except When Contained in an Alloy)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WV	2	1,000	99,999	10, 12
WY	2	10,000	99,999	10, 12

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI07 2009 (Data are from 2007)

Table 5-2. Facilities that Produce, Process, or Use Vanadium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	25	0	999,999	1, 3, 4, 5, 7, 8, 9, 12, 13, 14
AR	16	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
AZ	19	1,000	99,999,999	1, 3, 4, 5, 6, 9, 10, 12, 13, 14
CA	28	0	49,999,999	1, 2, 3, 4, 5, 6, 9, 10, 11, 12, 13, 14
CO	21	100	999,999	1, 4, 5, 9, 12, 13, 14
CT	5	100	9,999	1, 4, 5, 9, 12, 13
DE	10	0	999,999	1, 2, 5, 9, 10, 12, 13
FL	51	0	9,999,999	1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14
GA	27	0	49,999,999	1, 3, 4, 5, 7, 9, 10, 12, 13, 14
HI	1	100	999	1, 5
IA	14	0	999,999	1, 3, 4, 5, 9, 12, 13, 14
ID	11	0	49,999,999	1, 2, 3, 5, 6, 10, 14
IL	45	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 14
IN	52	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
KS	19	0	999,999	1, 3, 4, 5, 9, 10, 12, 13, 14
KY	23	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14
LA	50	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	10	1,000	99,999	1, 2, 5, 9, 11, 12, 13, 14
MD	16	0	999,999	1, 4, 5, 6, 7, 9, 12, 13, 14
ME	7	0	99,999	1, 5, 12, 13
MI	37	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
MN	10	100	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14
MO	21	0	999,999	1, 3, 5, 9, 10, 12, 13, 14
MS	14	0	9,999,999	1, 2, 3, 4, 5, 8, 9, 10, 13, 14
MT	5	100	999,999	1, 5, 9, 12, 14
NC	32	0	9,999,999	1, 2, 3, 4, 5, 7, 9, 12, 13, 14
ND	6	10,000	999,999	1, 5, 9, 12, 13, 14
NE	9	10,000	999,999	1, 3, 4, 5, 9, 12, 13
NH	7	0	999,999	1, 5, 9
NJ	20	100	999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 12, 13, 14
NM	8	1,000	999,999	1, 3, 4, 5, 9, 12, 13, 14
NV	22	0	499,999,999	1, 2, 3, 5, 6, 9, 10, 12, 13, 14
NY	21	0	999,999	1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 14
OH	46	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	14	1,000	99,999	1, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14
OR	3	1,000	99,999	1, 3, 4, 5, 9, 14
PA	59	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Vanadium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PR	8	0	99,999	1, 2, 5, 10, 13
SC	18	0	9,999,999	1, 3, 4, 5, 7, 8, 9, 12, 13, 14
SD	2	10,000	99,999	1, 5, 9, 13, 14
TN	25	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
TX	69	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
UT	26	100	49,999,999	1, 2, 3, 4, 5, 7, 9, 10, 11, 12, 13, 14
VA	21	0	999,999	1, 3, 4, 5, 8, 9, 10, 12, 13, 14
VI	1	100,000	999,999	10, 14
WA	3	10,000	999,999	1, 3, 4, 5, 9, 12, 13
WI	17	0	999,999	1, 3, 4, 5, 9, 12, 13, 14
WV	26	0	999,999	1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 14

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI07 2009 (Data are from 2007)

Table 5-3. Current U.S. Manufacturers of Vanadium and Selected Vanadium Compounds[a]

Company	Location
Vanadium	
International Specialty Alloys	New Castle, Pennsylvania
Vanadium pentoxide	
Denison Mines (USA) Corp.	Blanding, Utah
Gulf Chemical & Metallurgical Corp.	Freeport, Texas
Stratcor, Inc.	Hot Springs, Arizona
Vanadyl sulfate	
The Shepherd Chemical Co.	Cincinnati, Ohio
Shieldalloy Metallurgical Corp.; Specialty Products Division	Cambridge, Ohio
Stratcor, Inc.	Hot Springs, Arizona
Sodium metavanadate	
Denison Mines (USA) Corp.	Blanding, Utah
Shieldalloy Metallurgical Corp.; Specialty Products Division	Cambridge, Ohio
Sodium orthovanadate	
Shieldalloy Metallurgical Corp.; Specialty Products Division	Cambridge, Ohio
Ammonium metavanadate	
Denison Mines (USA) Corp.	Blanding, Utah
Shieldalloy Metallurgical Corp.; Specialty Products Division	Cambridge, Ohio
Stratcor, Inc.	Hot Springs, Arizona

[a]Stanford Research Institute (SRI 2008), except where otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed.
[b]USGS 2009b

5.2 IMPORT/EXPORT

Import sources of ferrovanadium from 2004 to 2007 were 76% of the Czech Republic, 7% from Swaziland, 6% from Canada, 6% from the Republic of Korea and 5% from other sources. Vanadium pentoxide import sources in this same time period were 59% from South Africa, 20% from China, 18% from Russia, and 3% from other sources (USGS 2009a).

5.3 USE

Vanadium is used in producing rust-resistant, spring, and high-speed tool steels. It is an important carbide stabilizer in making steels. About 80% of the vanadium produced is used as ferrovanadium as a steel additive. Vanadium foil is used as a bonding agent in cladding titanium to steel. Vanadium pentoxide is used in ceramics and as a catalyst as well as in producing a superconductive magnet with a field of 175,000 gauss (Lide 2008). Metallurgical use as an alloying agent for iron and steel accounted for approximately 92% of domestic vanadium consumption in 2008 (USGS 2009a).

Vanadium, as elemental vanadium or vanadyl sulfate, also may be found in various commercial nutritional supplements and multivitamins (NLM 2009). Vanadyl sulfate and sodium metavanadate have been used in supplements for individuals with diabetes, as well by weight training athletes (Barceloux 1999; IOM 2001; Smith et al. 2008).

5.4 DISPOSAL

Waste material contaminated with vanadium should be disposed of in a manner not hazardous to employees. The disposal method must conform to applicable local, state, and federal regulations and must not constitute a hazard to the surrounding population or environment. Chemical precipitation has been investigated as a possible wastewater treatment technology for vanadium (EPA 1982).

Approximately 8.8×10^5 and 7.0×10^5 pounds of vanadium (except when contained in an alloy) and vanadium compounds, respectively, were reported for on-site disposal and other releases in 2007. On-site disposal or other releases include emissions to the air, discharges to bodies of water, disposal at the facility to land, and disposal in underground injection wells. Approximately 1.2×10^6 and 9.6×10^6 pounds of vanadium (except when contained in an alloy) and vanadium compounds, respectively, were reported for off-site disposal and other releases in 2007. An off-site disposal or other release is a discharge of a

toxic chemical to the environment that occurs as a result of a facility's transferring a waste containing a TRI chemical off-site for disposal or other release (TRI07 2009). The TRI data should be used with caution because only certain types of facilities are required to report (EPA 2005b). This is not an exhaustive list.

Some tool steel scrap was recycled mainly for its vanadium content, and vanadium was recycled from spent chemical process catalysts; however, these two sources together accounted for only a small percentage (USGS 2009a).

6. POTENTIAL FOR HUMAN EXPOSURE

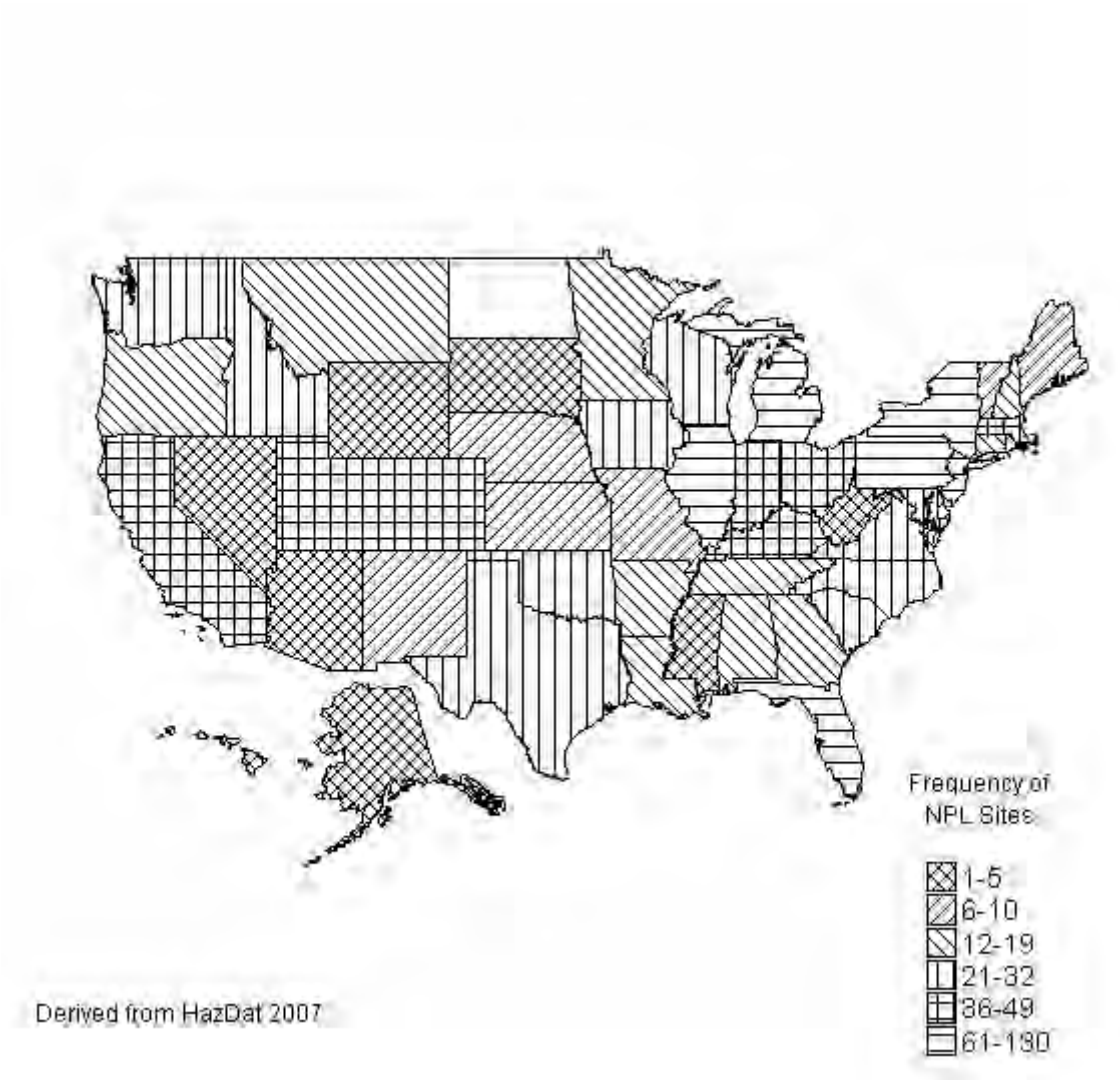
6.1 OVERVIEW

Vanadium has been identified in at least 319 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for vanadium is not known. The frequency of these sites can be seen in Figure 6-1. All of these sites are located within the United States.

Vanadium is widely distributed in the earth's crust at an average concentration of 100 ppm (approximately 100 mg/kg), similar to that of zinc and nickel (Byerrum 1991). Vanadium is the 22nd most abundant element in the earth's crust (Baroch 2006). There are about 65 different vanadium-containing minerals; carnotite, roscoelite, vanadinite, and patronite are important sources of this metal along with bravoite and davidite (Baroch 2006; Lide 2008). It is also found in phosphate rock and certain ores and is present in some crude oils as organic complexes (Lide 2008).

Vanadium is released naturally to the atmosphere by the formation of continental dust, marine aerosols, and volcanic emissions. Vanadium is a constituent of nearly all coal and petroleum crude oils. Eastern U.S. coal has an average vanadium content of approximately 30 ppm, while coal from western states has average content of 15 ppm, and coal from the interior portion of the United States contains an average vanadium concentration of 34 ppm (Byerrum et al. 1974). The average vanadium content of bituminous and anthracite coal is 30 and 125 ppm, respectively (Byerrum et al. 1974). The most important anthropogenic sources of vanadium include the combustion of fossil fuels, particularly residual fuel oils, which constitute the single largest overall release of vanadium to the atmosphere. While the levels of vanadium in residual fuel oil vary by source, levels of 1–1,400 ppm have been reported (Byerrum et al. 1974). Natural gas and distillate fuel oils contain very low or undetectable levels (<0.05 ppm) of vanadium and are not considered a significant source of vanadium to the environment, except in the case of large accidental spills. The natural release of vanadium to water and soils occurs primarily as a result of weathering of rocks and soil erosion. This process usually involves the conversion of the less-soluble trivalent form to the more soluble pentavalent form. Deposition of atmospheric vanadium is also an important source both near and far from industrial plants burning residual fuel oils rich in vanadium. Other anthropogenic sources include leachates from mining tailings, vanadium-enriched slag heaps, municipal sewage sludge, and certain fertilizers. Natural releases to water and soil are far greater overall than anthropogenic releases to the atmosphere.

Figure 6-1. Frequency of NPL Sites with Vanadium Contamination



Ambient atmospheric levels of vanadium are generally low (parts per trillion range) in rural and remote areas and greater in urban locations; however, vanadium levels in both rural and urban locations in the eastern United States tend to be significantly higher than in other areas throughout the country, particularly during winter months. A high density of oil fired power plants that consume vanadium-rich residual fuel oil stretching from southern New York to North Carolina are likely to be the greatest potential source of the high vanadium levels observed in the eastern United States (Polissar et al. 2001). In 2007, the Department of Energy reported that nearly 80% of the residual fuel oil consumed for power generation was purchased in the East Coast districts (DOE 2008).

The general population is exposed to background levels of vanadium primarily through ingestion of food. Vanadium in food is mainly ingested as VO^{2+} (vanadyl, V^{4+}) or HVO_4^{2-} (vanadate) (Sepe et al. 2003). Vanadium, as elemental vanadium or vanadyl sulfate, is also found in some dietary supplements and multivitamins; consumption of some vanadium-containing supplements may result in intakes of vanadium that would exceed those from food. Workers in industries processing or using vanadium compounds are commonly exposed to higher than background levels of vanadium as vanadium oxides via the inhalation pathway. Exposure to vanadium oxides through inhalation may also be of importance in urban areas, particularly in the northeastern United States where large amounts of residual fuel oil are burned. Other populations possibly exposed to higher-than-background levels, include those ingesting foodstuffs contaminated by vanadium-enriched soil, fertilizers, or sludge. Populations in the vicinity of vanadium-containing hazardous waste sites may also be exposed to higher than background levels. Individuals exposed to cigarette smoke may also be exposed to higher-than-background levels of vanadium.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005b). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities

primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005b).

6.2.1 Air

Estimated releases of $8.1x10^4$ pounds (~37 metric tons) of vanadium (except when contained in an alloy) to the atmosphere from 49 domestic manufacturing and processing facilities in 2007, accounted for about 3.8% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). Estimated releases of $6.0x10^5$ pounds (~270 metric tons) of vanadium compounds to the atmosphere from 520 domestic manufacturing and processing facilities in 2007, accounted for about 1.4% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). These releases are summarized in Tables 6-1 and 6-2.

Natural sources of atmospheric vanadium include continental dust, marine aerosol, and volcanic emissions (Byerrum et al. 1974; Van Zinderen Bakker and Jaworski 1980; Zoller et al. 1973). The quantities entering the atmosphere from each of these sources are uncertain; however, continental dust is believed to account for the largest portion of naturally emitted atmospheric vanadium followed by marine aerosols. Contributions from volcanic emissions are believed to be negligible when compared with the other two sources (Zoller et al. 1973).

Combustion of heavy fuels, especially in oil-fired power plants, refineries, and industrial boilers, and coal are the major source of anthropogenic emissions of vanadium into the atmosphere (Mamane and Pirrone 1998; Sepe et al. 2003). Global anthropogenic atmospheric emission of vanadium as been estimated to be $2.1x10^5$ metric tons (MT)/year, 3 times higher than vanadium releases due to natural sources. However, other estimates indicated that anthropogenic releases of particulate-bound vanadium ($9x10^4$ MT/year) were more similar to releases due natural sources, such as continental or volcanic dusts, which have releases of $7x10^4$ and $1x10^4$ MT/year, respectively) (Mamane and Pirrone 1998).

Fuel oils may contain vanadium in concentrations ranging from 1 to 1,400 ppm, depending on their origin (Byerrum et al. 1974). During the combustion of residual oils organovanadium compounds found in fuel oils are oxidized and transformed into various compounds (e.g., vanadium pentoxide, vanadium tetroxide, vanadium trioxide, and vanadium dioxide). These compounds are emitted as fly ash into the atmosphere (Mamane and Pirrone 1998).

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Vanadium (Except When Contained in an Alloy)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	1	17,181	0	0	3,436	0	20,617	0	20,617
AR	2	6	0	0	0	1,739	6	1,739	1,745
AZ	2	77	0	0	187,092	0	187,167	2	187,169
CA	4	252	310	0	127,011	5	76,332	51,246	127,578
ID	1	38	0	0	244,713	0	244,751	0	244,751
IL	1	0	0	0	3,068	0	0	3,068	3,068
KS	3	5,709	0	0	102,300	608,717	11,009	705,717	716,726
KY	1	14	0	0	0	0	14	0	14
LA	2	140	5,152	0	56,388	0	5,292	56,388	61,680
MO	1	0	0	0	0	20	0	20	20
MS	1	0	0	0	131,300	0	0	131,300	131,300
ND	1	48,088	0	0	86,381	0	90,782	43,687	134,469
NE	1	140	0	0	13,000	0	13,140	0	13,140
NY	1	0	0	0	949	64,880	0	65,828	65,828
OH	6	1,614	1,674	2	138,507	26,328	48,265	119,860	168,125
PA	3	3,279	0	0	5	35,104	3,284	35,104	38,388
PR	1	0	0	0	0	0	0	0	0
SC	1	1,000	1,972	0	107	0	3,079	0	3,079
TN	1	10	0	0	1,512	274	10	1,786	1,796
TX	12	3,212	19,799	0	17,938	5	25,004	15,950	40,954
VA	1	83	15	0	4,108	4	98	4,112	4,210
WV	1	0	0	0	52,255	0	52,255	0	52,255

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Vanadium (Except When Contained in an Alloy)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WY	1	201	0	0	100,057	0	100,258	0	100,258
Total	49	81,043	28,922	2	1,270,126	737,076	881,362	1,235,808	2,117,170

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI07 2009 (Data are from 2007)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Vanadium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	21	14,224	9,379	0	1,694,971	27	1,711,492	7,109	1,718,601
AR	8	16,188	169,170	0	1,709,832	1,858	1,895,125	1,923	1,897,048
AZ	7	1,099	0	0	244,363	0	245,462	0	245,462
CA	13	187	1,052	0	86,238	15	994	86,498	87,492
CO	10	1,375	119	0	303,890	7,052	163,631	148,805	312,436
CT	2	0	0	0	20,009	0	0	20,009	20,009
DE	4	1,743	17,501	0	428,513	179,436	56,244	570,949	627,193
FL	21	54,752	1,481	33,315	4,958,132	28,031	1,785,451	3,290,260	5,075,711
GA	15	27,261	20,059	0	1,873,231	0	1,881,251	39,300	1,920,551
IA	7	1,571	5	0	173,500	12,644	168,976	18,744	187,720
ID	2	3,819	1,405	0	616,407	1,620	621,632	1,620	623,252
IL	22	28,755	10,927	0	418,991	321	341,886	117,108	458,994
IN	29	19,920	12,250	0	3,311,659	18,648	2,693,285	669,192	3,362,477
KS	8	11,820	1	0	259,993	0	271,382	432	271,814
KY	23	20,580	21,751	0	3,198,893	124,137	3,054,104	311,257	3,365,361
LA	24	147,927	55,994	0	332,235	6,722	436,791	106,087	542,878
MA	4	4,938	2,491	0	64,314	0	38,274	33,469	71,743
MD	8	5,704	1,597	0	159,347	260,048	56,863	369,833	426,697
ME	2	1,500	4,662	0	21,274	0	27,436	0	27,436
MI	17	6,036	7,869	0	832,882	2,358	622,845	226,300	849,145
MN	5	2,070	863	0	392,039	3,182	277,956	120,198	398,154
MO	11	6,124	25	0	262,566	0	268,310	405	268,715
MS	8	1,037	67,469	1,261,497	2,701,215	0	4,030,172	1,046	4,031,218
MT	2	2,832	10	0	215,880	12,930	218,722	12,930	231,652
NC	20	15,186	8,878	0	1,373,808	15,355	1,350,201	63,027	1,413,228
ND	3	1,115	0	0	143,171	679	136,742	8,223	144,965
NE	3	2,615	0	0	78,511	0	81,126	0	81,126
NH	3	1,075	0	0	10,380	0	2,975	8,480	11,455
NJ	7	1,638	16,250	0	5,018	6,300	17,638	11,568	29,206
NM	5	1,971	830	0	490,597	0	493,398	0	493,398
NV	5	17	0	0	2,201,622	0	2,201,639	0	2,201,639
NY	9	20,512	3,276	0	585,147	247,051	551,640	304,346	855,986
OH	26	106,896	1,139	1,810	2,159,259	162,350	1,793,794	637,660	2,431,454
OK	10	2,842	11	0	126,270	0	77,723	51,400	129,123

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Vanadium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
OR	1	305	0	0	9,900	0	10,205	0	10,205
PA	29	13,634	1,127	0	1,499,090	550	936,936	577,465	1,514,401
PR	1	0	0	0	0	0	0	0	0
SC	16	4,754	4,227	0	276,695	322	263,725	22,274	285,999
SD	1	104	0	0	17,100	0	13,104	4,100	17,204
TN	15	3,931	30,351	0	1,508,290	0	1,268,104	274,468	1,542,572
TX	33	25,734	6,258	11,292	1,652,925	120,018	1,642,602	173,625	1,816,227
UT	9	1,021	1,000	0	284,148	28,151	285,391	28,929	314,320
VA	16	4,059	5,687	0	693,368	38,974	632,757	109,331	742,088
VI	1	37	8,387	0	24,878	0	11,990	21,312	33,302
WA	1	387	182	0	96,659	0	97,228	0	97,228
WI	14	4,914	868	0	577,355	131,721	106,054	608,803	714,857
WV	15	4,775	991	0	2,085,660	38,000	1,681,804	447,622	2,129,425
WY	4	1,913	0	0	244,462	0	176,966	69,409	246,375
Total	520	600,897	495,542	1,307,914	40,424,686	1,448,501	34,702,024	9,575,516	44,277,540

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI07 2009 (Data are from 2007)

Vanadium has not been identified in air collected at current or former NPL hazardous waste sites where vanadium was detected in some environmental media (HazDat 2007).

6.2.2 Water

Estimated releases of $2.9x10^4$ pounds (~13 metric tons) of vanadium (except when contained in an alloy) to surface water from 49 domestic manufacturing and processing facilities in 2007, accounted for about 1.4% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). Estimated releases of $5.0x10^5$ pounds (~230 metric tons) of vanadium compounds to surface water from 520 domestic manufacturing and processing facilities in 2007, accounted for about 1.1% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). These releases are summarized in Tables 6-1 and 6-2.

Natural sources of vanadium release to water include wet and dry deposition, soil erosion, and leaching from rocks and soils. The largest amount of vanadium release occurs naturally through water erosion of land surfaces. It has been estimated that approximately 32,300 tons of vanadium are dissolved and transported to the oceans by water, and an additional 308,650 tons are thought to be transported in the form of particulate and suspended sediment (Van Zinderen Bakker and Jaworski 1980).

Anthropogenic releases to water and sediments are far smaller than natural sources (Van Zinderen Bakker and Jaworski 1980). Such sources of vanadium in water may include leaching from the residue of ores and clays, vanadium-enriched slags, urban sewage sludge, and certain fertilizers, all of which are subjected to rain and groundwater drainage, as well as leachate from ash ponds and coal preparation wastes (Byerrum et al. 1974; Van Zinderen Bakker and Jaworski 1980). Leaching may potentially occur from landfills and from the airborne particulate matter that is deposited in areas with high residual fuel oil combustion, although neither of these release sources is documented.

Vanadium has been identified in groundwater and surface water at 224 and 129 sites, respectively, of the 319 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

6.2.3 Soil

Estimated releases of 1.3 million pounds (~580 metric tons) of vanadium (except when contained in an alloy) to soils from 49 domestic manufacturing and processing facilities in 2007, accounted for about 60%

of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). An additional 2 pounds (~0.9 kilograms) of vanadium were released via underground injection (TRI07 2009). Estimated releases of 40 million pounds (~$1.8x10^4$ metric tons) of vanadium compounds to soils from 520 domestic manufacturing and processing facilities in 2007, accounted for about 91% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). An estimated 1.3 million pounds (~590 metric tons) of vanadium compounds were released via underground injection from 520 domestic manufacturing and processing facilities in 2007, accounted for about 3.0% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). These releases are summarized in Tables 6-1 and 6-2.

Natural releases of vanadium to soil result from weathering of rock-bearing vanadium minerals, precipitation of vanadium particulate from the atmosphere, deposition of suspended particulate from water, and plant and animal wastes. The largest amount of vanadium released to soil occurs through the natural weathering of geological formations (Byerrum et al. 1974; Van Zinderen Bakker and Jaworski 1980).

Anthropogenic releases of vanadium to soil are less widespread than natural releases and occur on a smaller scale. These include the use of certain fertilizers containing materials with a high vanadium content such as rock phosphate (10–1,000 mg/kg vanadium), superphosphate (50–2,000 mg/kg vanadium), and basic slag (1,000–5,000 mg/kg vanadium) (Van Zinderen Bakker and Jaworski 1980) as well as disposal of industrial wastes such as slag heaps and mine tailings. Additional release to the environment may also result from the disposal of vanadium-containing wastes in landfills, although this has not been specifically documented, and from wet and dry deposition of airborne particulate, particularly in areas with high levels of residual fuel oil combustion (Byerrum et al. 1974).

Vanadium has been identified in soil at 172 sites and in sediment at 44 sites collected from 319 NPL hazardous waste sites, where vanadium was detected in some environmental media (HazDat 2007).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

The global biogeochemical cycling of vanadium is characterized by releases to the atmosphere, water, and land by natural and anthropogenic sources, long-range transportation of particles in both air and water, wet and dry deposition, adsorption, and complexing. Vanadium generally enters the atmosphere as an

aerosol. From natural sources, vanadium is probably in the form of mineral particles; it has been suggested that these may frequently be in the less-soluble trivalent form (Byerrum et al. 1974; Zoller et al. 1973). From human-made sources, almost all of the vanadium released to the atmosphere is in the form of simple or complex vanadium oxides (Byerrum et al. 1974).

The size distribution of vanadium-bearing particles in the atmosphere is substantially altered during long-range transportation (Zoller et al. 1973). Natural sources of vanadium, as well as man-made sources such as ore-processing dust, tend to release large particles that are more likely to settle near the source. Smaller particles, such as those emitted from oil-fueled power plants, have a longer residence time in the atmosphere and are more likely to be transported farther away from the site of release (Zoller et al. 1973). Vanadium transported within the atmosphere is eventually transferred to soil and water on the earth's surface by wet and dry deposition and dissolution in sea water (Duce and Hoffman 1976; Van Zinderen Bakker and Jaworski 1980). Eventually, in the course of biogeochemical movement between soil and water, these particulates are adsorbed to hydroxides or associated with organic compounds and are deposited on the sea bed (WHO 1988).

Deposition rates ranging from 20.5 to 84.9 μg/cm^2/day of vanadium were reported in urban dust collected between March and September 2002 from six locations Adapazarí, Turkey (Dundar 2006). Vanadium is considered a marker of air pollution emitted from residual oil and coal combustion (Mamane and Pirrone 1998).

The transport and partitioning of vanadium in water and soil is influenced by pH, redox potential, and the presence of particulate. In fresh water, vanadium generally exists in solution as the vanadyl ion (V^{4+}) under reducing conditions and the vanadate ion (V^{5+}) under oxidizing conditions, or as an integral part of, or adsorbed onto, particulate matter (Wehrli and Stumm 1989). The chemical formulas of the vanadyl species most commonly reported in fresh water are VO^{2+} and $VO(OH)^{+}$, and the vanadate species are $H_2VO_4^-$ and HVO_4^{2-} (Wehrli and Stumm 1989). The partitioning of vanadium between water and sediment is strongly influenced by the presence of particulate in the water. Both vanadate and vanadyl species are known to bind strongly to mineral or biogenic surfaces by adsorption or complexing (Wehrli and Stumm 1989). Thus, vanadium is transported in water in one of two ways: solution or suspension. It has been estimated that only 13% is transported in solution, while the remaining 87% is in suspension (WHO 1988).

Upon entering the ocean, vanadium in suspension or adsorbed and/or absorbed onto particulate is deposited upon the sea bed (WHO 1988). The fate of the remaining dissolved vanadium is more complex. Only about 0.001% of vanadium entering the oceans is estimated to persist in soluble form (Byerrum et al. 1974). Adsorption/absorption and biochemical processes are thought to contribute to the extraction of vanadium from sea water (WHO 1988). Adsorption to organic matter as well as to manganese oxide and ferric hydroxide, demonstrated by the high particle-water partition coefficient of $5.7x10^5$ L/kg for the adsorption of manganese oxide in sea water, results in the precipitation of the dissolved vanadium (Wehrli and Stumm 1989; WHO 1988). Biochemical processes are also of importance in the partitioning from sea water to sediment (WHO 1988). Some marine organisms, in particular the ascidians (sea squirts), bioconcentrate vanadium very efficiently, attaining body concentrations approximately 10,000 times greater than the ambient sea water (Byerrum et al. 1974). Upon the death of the organism, the body burden adds to the accumulation of vanadium in silt (WHO 1988). The extent to which either bioconcentration or adsorption dominates is uncertain (WHO 1988).

In general, marine plants and invertebrates contain higher levels of vanadium than terrestrial plants and animals. In the terrestrial environment, bioconcentration is more commonly observed amongst the lower plant phyla than in the higher, seed-producing phyla. The vanadium levels in terrestrial plants are dependent upon the amount of water-soluble vanadium available in the soil, pH, and growing conditions. It has been found that the uptake of vanadium into the above-ground parts of many plants is low, although root concentrations have shown some correlation with levels in the soil (Byerrum et al. 1974). Certain legumes, such as *Astralagus preussi*, have been shown to be vanadium accumulators. Vanadium is believed to replace molybdenum as a specific catalyst in nitrogen fixation (Cannon 1963), and the root nodules of these plants may contain vanadium levels three times greater than those of the surrounding soil (Byerrum et al. 1974). Of the few plants known to actively accumulate vanadium, *Amanita muscaria*, a poisonous mushroom, has been demonstrated to contain levels up to 112 ppm (dry weight). Vanadium appears to be present in all terrestrial animals, but, in vertebrates, tissue concentrations are often so low that detection is difficult. The highest levels of vanadium in terrestrial mammals are generally found in the liver and skeletal tissues (Van Zinderen Bakker and Jaworski 1980; WHO 1988). No data are available regarding biomagnification of vanadium within the food chain, but human studies suggest that it is unlikely; most of the 1–2% vanadium that appears to be absorbed by humans following ingestion is rapidly excreted in the urine with no evidence of long-term accumulation (Fox 1987).

The form of vanadium present in the soil is determined largely by the parent rock. Ferric hydroxides and solid bitumens (organic) constitute the main carriers of vanadium in the sedimentation process. Iron acts

as a carrier for trivalent vanadium due to the high affinity between trivalent vanadium and trivalent iron, and is responsible for its diffusion through molten rocks where it becomes trapped during crystallization. The mobility of vanadium in soils is affected by the pH of the soil. Relative to other metals, vanadium is fairly mobile in neutral or alkaline soils, but its mobility decreases in acidic soils (Van Zinderen Bakker and Jaworski 1980). Similarly, under oxidizing, unsaturated conditions, some mobility is observed, but under reducing, saturated conditions, vanadium is immobile (Van Zinderen Bakker and Jaworski 1980). In a 30-month field study to examine the movement of metal ions through a profile of an acidic loamy sand soil from the Upper Coastal Plain (South Carolina), <3% of the applied vanadium, as dissolved salt (vanadyl sulfate), was found to move below the surface 7.5 cm region (Martin and Kaplan 1998). Buchter et al. (1989) reported log K_d values for various metal ions in 11 soils from 7 states in the U.S. (Louisiana, South Carolina, Hawaii, Iowa, New Hampshire, New Mexico, and Florida). Log K_d values for vanadium (applied as ammonium vanadate) ranged from 1.035 in Calciorthid soil from New Mexico (pH 8.5, 0.44% total organic carbon [TOC], 70.0% sand, 19.3% silt, 10.7% clay) to 3.347 in Kula soil from Hawaii (pH 5.9, 6.62% TOC, 73.7% sand, 25.4% silt, 0.9% clay).

6.3.2 Transformation and Degradation

As an element, vanadium cannot be degraded in the environment, but may undergo various precipitation or ligand exchange reactions. Vanadium in compounds may undergo oxidation-reduction reactions under various environmental conditions. Vanadium can be complexed by various ligands present in the environment (e.g., fulvic and humic acids). Despite forming complexes with organic matter, it is generally not incorporated into organic compounds. Thus, transformation occurs primarily between various inorganic compounds during its movement through the environment, and biotransformation is not considered to be an important environmental fate process. Vanadium can exist in many different oxidation states, ranging from -2 to +5; however, under environmental conditions, vanadium can exist in the +3, +4, or +5 oxidation states, with the +5 oxidation state being the most prevalent under most environmental conditions (Crans et al. 1998).

6.3.2.1 Air

Vanadium-containing particulates emitted to the atmosphere from anthropogenic sources are frequently simple or complex oxides (Byerrum et al. 1974) or may be associated with sulfates (Zoller et al. 1973). Generally, lower oxides formed during combustion of coal and residual fuel oils, such as vanadium trioxide, undergo further oxidation to the pentoxide form, often before leaving the stacks (EPA 1985a). The average residence time for vanadium in the atmosphere is unknown as the particle size varies

considerably. An estimated residence time of about 1 day has been proposed for the settling of fly ash vanadium pentoxide when associated with hydrogen sulfate (EPA 1985a).

6.3.2.2 Water

Vanadium entering water by leaching from vanadium-containing rocks is rapidly oxidized from less-soluble vanadium(III) to more-soluble vanadium(V), which is the most common oxidation state of vanadium found in surface waters (Byerrum et al. 1974; Crans et al. 1998). In water, vanadium can undergo hydrolytic reactions, forming oligomeric anionic species. The equilibrium of vanadium(V) in solution is sensitive to vanadium concentration, pH, ionic strength, and oxidation-reduction potential (Crans et al. 1998). The species of vanadium most likely to be found in sea water are $(H_2V_4O_{13})^{4-}$, HVO_4^{2-}, and VO^{3-} (Van Zinderen Bakker and Jaworski 1980). Vanadium(III) is only found in very reducing environments or is complexed to organic ligands (Crans et al. 1998). Vanadium is continuously precipitated from sea water by ferric hydroxides and organic matter (WHO 1988) and forms sediments on the seabed.

6.3.2.3 Sediment and Soil

There are about 65 different vanadium-containing minerals (Baroch 2006; Lide 2008). The main vanadium-containing minerals include carnotite, cuprodescloizite, descloizite, mottramite, patronite, roscoelite, and vanadinite (Crans et al. 1998). Vanadium exists in its +3 to +5 oxidation states in these minerals. Vanadium(V) is more soluble and is easily leached from soils into water. The vanadium oxides, carnotite, cuprodescloizite, descloizite, mottramite, and vanadinite, are mostly vanadium(V) minerals and comprise most of the vanadium-containing minerals. Roscoelite contains vanadium(III), and the exact chemical composition of patronite is not known (Crans et al. 1998). Weathering of rocks and minerals during soil formation may extract vanadium in the form of a complex anion that may remain in the soil or enter the hydrosphere. Vanadium remains in the soil after being precipitated from the weathering solution. This can be brought about by precipitation with polyvalent cations such as divalent calcium and divalent copper, by binding with organic complexing agents, adsorbing onto anion exchangers such as clay particles in the soil, and coprecipitating and adsorbing to hydrous ferric oxide in the soil (Van Zinderen Bakker and Jaworski 1980). In the presence of humic acids, mobile metavanadate anions can be converted to the immobile vanadyl cations resulting in local accumulation of vanadium (Van Zinderen Bakker and Jaworski 1980).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to vanadium depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of vanadium in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on vanadium levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring vanadium in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Levels of vanadium measured in ambient air vary widely between rural and urban locations, time of season, and geographical location. In general, urban locations often tend to have greater atmospheric levels of vanadium as compared to rural sites since there is a larger density of combustion sources capable of emitting particulate matter containing vanadium to the environment. Sweet et al. (1993) reported average vanadium concentrations of 3.0 and 3.0 ng/m^3 (fine particles, <2.5 μm) and 3.7 and 3.0 ng/m^3 (coarse particles, 2.5–10 μm) in samples of inhalable particulate matter collected over a 3-year sampling period in southeast Chicago and East St. Louis Illinois, respectively. Average vanadium concentrations in fine and coarse particulate matter collected from a rural site in Bondville, Illinois were 0.8 and 1.2 ng/m^3, respectively (Sweet et al. 1993). Aerosol sampling ($PM_{2.5}$ fraction) was conducted from 1988 to 1995 at a rural location in Underhill, Vermont (Polissar et al. 2001). A geometric mean concentration of 0.82 ng/m^3 was reported for vanadium, with seasonal maxima occurring during the winter and spring months and minimum concentrations observed during the summer months. A factor analysis method applied to the data determined that the most likely sources of the vanadium were oil fired power plants predominantly located in eastern Virginia, Pennsylvania, southern New York, New Jersey, Maryland, and Delaware (Polissar et al. 2001). Measurements obtained at five different rural sites in northwestern Canada were found have average vanadium concentrations of 0.72 ng/m^3 (range 0.21–1.9 ng/m^3) (Zoller et al. 1973). Between the years 1965 and 1969, average ambient vanadium concentrations in rural air in the United States ranged from <1 to 40 ng/m^3 (Byerrum et al. 1974), although some rural areas may have levels as high as 64 ng/m^3 due to localized burning of fuel oils with a high vanadium content (WHO 1988). Vanadium concentrations in air samples collected from a rural forest in Denmark that received heavy deposition from European cities were 11.5 and 4.4 ng/m^3 in samples from 1979 to 1980 and 2002 to 2005, respectively (Hovmand et al. 2008).

Northeastern locations in the United States typically have higher atmospheric levels of vanadium as compared to other regions of the country. U.S. cities were divided into two groups based on the levels of vanadium present in the atmosphere and geographic location (Zoller et al. 1973). The first group of cities is widely distributed throughout the United States and is characterized by ambient air vanadium concentrations that range from 3 to 22 ng/m^3, with an average concentration of 11 ng/m^3 (approximately 20 times that of remote areas). Cities in the second group, primarily located in the northeastern United States, had vanadium concentrations in air that ranged from 150 to 1,400 ng/m^3 with an average of 620 ng/m^3 (Zoller et al. 1973). The variation is attributed to the use of large quantities of residual fuel oil for the generation of heat and electricity, particularly during winter months

Atmospheric levels of vanadium at remote sites tend to be lower since both natural and anthropogenic emissions are typically negligible. Vanadium concentrations measured over the South Pole ranged from 0.001 to 0.002 ng/m^3 (WHO 1988) and are frequently 2 orders of magnitude smaller than those over the ocean at middle latitudes (WHO 1988). For example, vanadium concentrations in air measurements taken at nine rural sites located in the Eastern Pacific averaged 0.1 ng/m^3 (range 0.02–0.8 ng/m^3). Atmospheric aerosols were collected from Mt. Everest in May–June, 2005; vanadium concentrations ranged from 0.9 to 3.8 ng/m^3, with a mean of 1.4 ng/m^3 (Cong et al. 2008). Vanadium concentrations at other remote locations of 0.044 and 0.0039 ng/m^3 were reported for Greenland, 1988–1989 and Terra Nova Bay, Antarctica, 2000–2001, respectively (Cong et al. 2008; Mosher et al. 1993).

Vanadium was detected in exhaust aerosol collected from the Elbtunnel, a major highway tunnel in Hamburg, Germany, at an average concentration of 14.8 ng/m^3 (range: 7.6–36.9 ng/m^3) (Dannecker et al. 1990). Fine atmospheric particulate $PM_{2.5}$ (particles with diameters of <2.5 μm) were collected from November 2000 to September 2001 in Guaynabo, Puerto Rico, an urban industrialized area, and in Fajardo, Puerto Rico, a less polluted reference site (Figueroa et al. 2006). Vanadium concentrations in the $PM_{2.5}$ were 40 and 1.4 ng/m^3 for Guaynabo and Fajardo, respectively. Mean urban vanadium concentrations in winter and summer air (fine and course particulate combined) collected from the Birmingham University campus, Edgbaston, United Kingdom in January-February 1992 and July-August 1992 were 11.2 and 3.5 ng/m^3, respectively. Vanadium concentrations were higher in the fine particle fraction, 7.6 and 2.3 ng/m^3 (winter and summer), as compared to the coarse particle samples, 3.6 and 1.2 ng/m^3 (winter and summer) (Harrison et al. 1996). Mean vanadium concentrations in air samples from a central Copenhagen street (January–March 1992 and February–March 1993) and a city park (January–March 1992) were reported to be 12 and 10 ng/m^3, respectively (Nielsen 1996). Smith et al. (1996) reported mean vanadium concentrations in air samples collected from a city site, a rural site, and

an industrial site in Lahore, Pakistan in 1992–1993 of 127, 161, and 253 ng/m^3, respectively. Mean vanadium concentrations in air samples of 10, 180, and 110 ng/m^3 were reported in Karachi, Pakistan; Calcutta, India; and Bombay, India, respectively (Smith et al. 1996). Schroeder et al. (1987) reported concentration ranges of vanadium associated with particulate matter in the atmosphere: 0.001–14 ng/m^3 (remote areas); 2.7–97 ng/m^3 (rural); 10–130 ng/m^3 (urban Canada); 0.4–1,460 ng/m^3 (urban United States); 11–73 ng/m^3 (urban Europe); and 1.7–180 ng/m^3 (urban other).

Vanadium and nickel were measured in air particulate samples collected during and after the Kuwait oil fires (from March 1991 to July 1992) at Dhahran, Saudi Arabia (Sadiq and Mian 1994). Vanadium concentrations ranged from not detected to 1,165.8 ng/m^3 in the inhalable (PM_{10}, <10 μm) and from not detected to 160.26 ng/m^3 in the total suspended particulate. The minimum vanadium concentration was found in samples collected in December 1991 and gradually increased through May 1992.

Air sampling in homes in two New York counties in the winter of 1986 measured various contaminants in the indoor air (Koutrakis et al. 1992). Mean vanadium concentrations in indoor air of non-source homes (no kerosene heaters, wood stoves, or cigarette smokers), wood-burning homes, kerosene heater homes, and smoking homes were 5, 4, 6, and 6 ng/m^3, respectively. Miguel et al. (1995) reported vanadium concentrations in samples of indoor air from non-industrial office workplaces and restaurants in the cities of Sao Paulo and Rio de Janeiro, Brazil in the summer of 1993 ranging from less than the detection limit to 0.360 μg/m^3. Kinney et al. (2002) reported mean winter and summer vanadium concentrations of 9.49 and 4.17 ng/m^3 in indoor air (particle-associated) in 38 homes sampled in 1999 in the West Central Harlem section of New York City. A mean vanadium concentration of 0.8 ng/m^3 was reported inside patrol cars of ten nonsmoking North Carolina State Highway Patrol troopers during 25 work days (3 pm to midnight shift) during August–October of 2001 (Riediker et al. 2003).

6.4.2 Water

Levels of vanadium in fresh water illustrate geographic variations produced by differences in effluents and leachates, from both anthropogenic and natural sources, entering the water table. Vanadium concentrations in water can range from approximately 0.2 to >100 μg/L depending on geographical location (Sepe et al. 2003). Vanadium was detected in 3,387 of 3,625 surface water samples recorded in the STORET database for 2007–2008 at concentrations ranging from 0.04 to 104 μg/L in samples where vanadium was detected (EPA 2009a). Measurements of vanadium in such natural fresh waters as the Animas, Colorado, Green, Sacramento, San Joaquin, and San Juan Rivers, as well as some fresh water

supplies in Wyoming, range from 0.3 to 200 µg/L (Byerrum et al. 1974; Van Zinderen Bakker and Jaworski 1980). The presence of naturally occurring uranium ores resulted in rivers in the Colorado Plateau containing vanadium concentrations of up to 70 µg/L, and in Wyoming, vanadium concentrations in water were found to range from 30 to 220 µg/L (Byerrum et al. 1974).

Taylor et al. (2001) reported vanadium concentrations of <0.05 µg/L in water collected in June and September 1994 from the Alamosa River, Colorado and 6.2 µg/L in water collected in September 1992 from Big Arsenic Spring, New Mexico. Saleh and Wilson (1999) reported various metal concentrations in surface water from the Houston Ship Channel, Texas; vanadium concentrations ranged from 4.062 to 115.600 µg/L in samples from Buffalo Bayou and the Washburn Tunnel, respectively. Coal mining activity in the west-central region of Indiana has resulted in a number of sites where surface waters are contaminated with acidic mine drainage. Surface water samples collected from 12 locations in west-central Indiana that have been contaminated with acidic mine drainage were reported to contain vanadium at concentrations ranging from 0.17 to 0.66 mg/L (Allen et al. 1996). Kennish (1998) reported vanadium concentrations ranging from 1.0 to 38 nmol/L (0.05–1.9 µg/L) in waters from U.S. estuaries and 32 nmol/L (1.6 µg/L) in U.S. coastal marine waters.

Levels in sea water are considerably lower than those in fresh water because much of the vanadium is precipitated (Byerrum et al. 1974; Van Zinderen Bakker and Jaworski 1980). Vanadium concentrations measured usually average 1–3 µg/L (Sepe et al. 2003; Van Zinderen Bakker and Jaworski 1980), although levels as high as 29 µg/L have been reported (Byerrum et al. 1974). The total content of vanadium in sea water has been estimated to be $7.5x10^{12}$ kg ($7.5x10^{9}$ metric tons) (Byerrum et al. 1974). Mean vanadium concentrations ranging from 2.08 to 2.60 µg/L were reported in seawater samples collected along the Saudi coast of the Arabian Gulf (Sadiq et al. 1992b).

Fiorentino et al. (2007) measured vanadium concentrations in groundwater collected from the southwest of the Province of Buenos Aires, Argentina; all samples contained vanadium, and concentrations ranged from 0.05 to 2.47 mg/L. Groundwater samples collected from 104 monitoring wells from shallow aquifers beneath an industrial city in the Eastern Province of Saudi Arabia contained vanadium concentrations that ranged from 0.04 to 55.69 µg/L, with a mean concentration of 7.46 µg/L (Sadiq and Alam 1997).

Vanadium is on the EPA Drinking Water Contaminant Candidate List (CCL). The contaminants on this list are known or anticipated to occur in public water systems; however, they are currently not regulated

by existing national primary drinking water regulation. Research in ongoing to determine whether regulations are needed (EPA 2008b).

Mean vanadium concentrations in tap water collected from homes participating a dietary study in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin) for the National Human Exposure Assessment Survey (NHEXAS) were 1.2 and 1.0 µg/L, respectively, in samples collected after running the water at high velocity for 3 minutes (flushed tap water) and after there had been no usage of any tap water or toilet in the home for the previous 4 hours (standing tap water) (Thomas et al. 1999).

As part of the National Water-Quality Assessment Program of the U.S. Geological Survey (USGS), water samples were collected during 1991–2004 from domestic wells (private wells used for household drinking water) for analysis of drinking-water contaminants. Vanadium was detected in 452 of 662 samples, with a median concentration of 1.29 µg/L (USGS 2009c).

Lagerkvist et al. (1986) summarized older reports from the 1960s and 1970s regarding vanadium concentrations in drinking water. One report stated that 91% of drinking water samples analyzed from U.S. sources had vanadium concentrations below 10 µg/L, with an average concentration of 4.3 µg/L. In another report, the typical vanadium concentrations in drinking water were about 1 µg/L.

6.4.3 Sediment and Soil

Vanadium is widely distributed in the earth's crust at an average concentration of 100 ppm (approximately 100 mg/kg) (Byerrum 1991). The level of vanadium measured in soil is closely related to the parent rock type (Van Zinderen Bakker and Jaworski 1980; Waters 1977). A range of 3–310 mg/kg has been observed, with tundra podsols and clays exhibiting the highest concentration, 100 and 300 mg/kg, respectively (Byerrum et al. 1974). The average vanadium content of soils in the United States is 200 mg/kg (Byerrum et al. 1974) and seems to be most abundant in the western United States, especially the Colorado Plateau (Cannon 1963; Grayson 1983).

Gallagher et al. (2008) measured various metal concentrations in soils collected during the summer of 2005 from a site in Jersey City, New Jersey on the west bank of Upper New York Bay. This land was originally an intertidal mud flat and a salt marsh that was filled during 1860–1919 with material consisting of mostly debris from construction projects and refuse from New York City. It was used as a railroad yard until 1967. The site was then transferred to the New Jersey Division of Parks and Forestry

in 1970. Vanadium concentrations in soil collected from this site ranged from below the detection limit (<0.01 µg/g) to 317 µg/g, with a median value of 56.4 µg/g (Gallagher et al. 2008). Metal concentrations were measured in two alluvial soils from the lower Mississippi River Delta. Median vanadium concentrations of 3.2 and 3.8 µg/g were reported in freshly deposited alluvium soil from Bonnet Carré Spillway and in urban soil samples from New Orleans, respectively (Mielke at el. 2000).

Various trace elements were measured in 13 surface soils collected from southwestern Saskatchewan, Canada (Mermut et al. 1996). Fertilizers and pesticides are the two major anthropogenic sources of trace elements in the Canadian Prairies. Vanadium concentrations ranged from 31.75 mg/kg in Hatton soil (0–13 cm, pH 6.2, 1.32% organic content [OC], 6% clay) to 180.06 mg/kg in Sceptre soil (90–105 cm, pH 8.0, 0.85% OC, 73% clay). Clay soils were found to contain more vanadium that other soils (Mermut et al. 1996). Vanadium concentrations in 16 soil samples collected in May 2000 in the vicinity of a cement plant in Catalonia, Spain ranged from 5.6 to 12.4 mg/kg dry weight. These values were generally lower than vanadium levels found in urban areas (Schuhmacher et al. 2002). The geometric mean vanadium concentrations in 112 samples street dust and 40 samples of urban soil collected in Aviles, Northern Spain were 28.1 (range 25.0–34.0) and 34.1 (22.0–67.0) µg/g, respectively (Ordóñez et al. 2003).

Metal contamination was determined in soil samples collected from 10 locations in the Hafr Al Batin Area (Saudi Arabia) near the Saudi/Kuwaiti border following the Gulf War (1990–1991) (Sadiq et al. 1992a). Oil burning in Kuwait, atmospheric fallout of particulates form the use of explosives in the Gulf War, and other war-related ground activities created air pollution problems in the countries neighboring Kuwait. Vanadium concentrations in soil ranged from 2 mg/kg collected at the most distant sampling site from the Kuwaiti border (15–25 cm depth) to 59 mg/kg collected from a sampling site near the border (0–5 cm depth). Vanadium concentrations in soil samples were found to decrease with increasing distance from the border (Sadiq et al. 1992a). Various metal concentrations were determined in 25 surface soil samples from Surat, India, an industrial area. Vanadium concentrations ranged from 141.9 to 380.6 mg/kg with a mean 284.8 mg/kg (Krishna and Govil 2007).

Mean vanadium concentration of 44 and 82 mg/kg were reported in the sediments of Lake Huron and Lake Superior. Vanadium was detected in sediment samples from the Georgian Bay and North Channel (Lake Huron) at mean concentrations of 67 and 66 mg/kg, respectively (International Joint Commission 1978). Heit et al. (1984) reported vanadium concentrations in Rocky Mountain Lake sediments of 27.3 and 15 mg/kg dry weight in Lake Husted surface (0–2 cm) and subsurface sediments, respectively, and 35 and 32.8 mg/kg dry weight in Lake Louise surface and subsurface sediments, respectively.

Vanadium concentrations of 55 and 43 mg/kg dry weight were reported in surface sediments from Lake Haiyaha and The Loch, two other Rocky Mountain lakes. Total vanadium concentrations of 136 and 222 mg/kg dry weight were reported in sediment samples from the Texas City channel and Ashtabula River, Ohio (Engler 1979).

Four sediment cores collected January 1996 from Central Park Lake New York City, New York were analyzed for various metals including vanadium; average vanadium concentrations ranged from 87 µg/g at a depth of 44–47 cm to 665 µg/g at a depth of 12–14 cm (Chillrud et al. 1999). In 1966, approximately 35% of the residual fuel oil used in New York City was from Venezuela. Vanadium is enriched in the sulfur-rich petroleum from Venezuela. Comparison of the approximate year of deposition to vanadium concentration in the sediment for Central Park Lake showed that vanadium levels in sediments from Central Park Lake were found to decrease after restrictions on sulfur content of fuel oils used in New York City were introduced starting in 1966. The average vanadium concentration peaks at 665 µg/g in sediments from 12 to 14 cm depth, which correlates with approximately with the mid 1960s (Chillrud et al. 1999). Trace metal concentrations were measured in sediment cores collected in February 1992 from the Gulf of Mexico; the average vanadium concentration was 47.78 µg/g and ranged from 15.6 to 117.5 µg/g (Macias-Zamora et al. 1999). Metal concentrations were measured in sediment collected during early and late autumn of 1993 and 1994 from 16 locations in Lake Erie, the Niagara River, and Lake Ontario; vanadium concentrations ranged from 6.0 to 31.1 µg/kg dry weight in these sediment samples (Lowe and Day 2002).

Vanadium concentrations in surface sediments collected during 1988–1991 from the Great Astrolabe Lagoon, Fiji ranged from 2 to 726 mg/kg dry weight. This lagoon, which encompasses a number of small volcanic islands, is considered to be a pristine marine environment with minimal human impact in this study (Morrison et al. 1997).

A diesel oil spill occurred in April 2002 from a pipeline on the Pacific side of Mexico, in Salina Cruz into the San Pedro stream, Xadani estuary, and the Superior Lagoon mouth (Salazar-Coria et al. 2007). Vanadium concentrations in sediment collected after the spill during the dry and rainy seasons were 110.5 and 123.0 mg/kg dry weight at the San Pedro site, 95.4 and 148.9 mg/kg dry weight at the Piedra Estuary, 113.3 and 107.7 mg/kg dry weight at the Xadani estuary, and <5.0 mg/kg dry weight at Superior Lagoon, respectively. Vanadium concentrations in a reference site, upstream from the spill were below the limit of detection, <5.0 mg/kg dry weight.

Chemical contamination was measured in sediment from the Shuaiba Industrial Area (SIA), a coastal area in Kuwait that receives industrial effluent (Beg et al. 2001). The SIA contains a petrochemical company, three refineries, two power desalination plants, a melamine company, an industrial gas corporation, a paper products company, and other smaller industrial plants, as well as a large harbor. Vanadium concentrations were reported to range from 9.8 to 146.0 mg/kg dry weight in sediment from Shuaiba coastal area (Beg et al. 2001).

6.4.4 Other Environmental Media

The majority of foods have naturally occurring low concentrations of vanadium, many of them ≤1 ng/g (Byrne and Kosta 1978). Food items containing the highest levels of vanadium include ground parsley (1,800 ng/g dry weight), freeze-dried spinach (533–840 ng/g), wild mushrooms (50–2,000 ng/g dry weight), and oysters (455 ng/g wet weight) (Byrne and Kosta 1978). Intermediate levels are found in food types such as certain cereals (ranging from 0.7 ng/g in maize to 30 ng/g in Macedonian rice), fish (ranging from 3.5 ng/g in mackerel to 28 ng/g in freeze-dried tuna), and liver (ranging from 7.3 ng/g in beef to 38 ng/g in chicken) (Byrne and Kosta 1978). In general, seafoods have been found to be higher in vanadium than terrestrial animal tissues (WHO 1988). Vanadium concentrations in cow milk ranging from about 0.2 to 10 µg/kg also have been reported in older reports from the late 1970s and early 1960s, respectively (Lagerkvist et al. 1986). Pennington and Jones (1987) surveyed 234 foods from a 1984 collection of the FDA's Total Diet Study for various trace elements including vanadium. Sixty-four percent of the Total Diet Foods had vanadium concentrations of <0.5 µg/100 g and 88% had vanadium concentrations of <2 µg/100 g. Foods with the highest vanadium concentrations included breakfast cereals, canned fruit juices, fish sticks, several vegetables, sweeteners, wine, and beer. The data from this survey are summarized in Table 6-3.

Vanadium, as elemental vanadium or vanadyl sulfate, also may be found in various commercial nutritional supplements and multivitamins; vanadium concentration can range from 0.0004 to 12.5 mg in these supplements depending on the serving size recommended by the manufacturer (NLM 2009). Vanadium has been used in supplements for individuals with diabetes; intakes of 30–150 mg/day for vanadyl sulfate (9–47 mg V/day) and 125 mg/day for sodium metavanadate (52 mg V/day) have been reported (IOM 2001; Smith et al. 2008).

Table 6-3. Vanadium Levels in Food

Food item	Mean (µg/100 g)	Range (µg/100 g)
Adult foods		
Milk, yogurt, and cheese	0.1	0–0.6
Meat, fish, and poultry	1.0	0–11.9
Eggs	0.3	0.2–0.4
Nuts	0.6	0.2–1.0
Legumes	0.1	0–0.3
Grains and grain products	2.3	0–14.7
Fruits and fruit juices	0.6	0–7.1
Vegetables	0.6	0–7.2
Mixed dishes and soups	0.6	0–2.0
Desserts	0.9	0–2.9
Sweeteners	2.3	0.4–4.7
Fats and sauces	0.3	0–0.6
Beverages	0.7	0–3.3
Infant foods		
Formulas	0.1	0–0.2
Meat and poultry	0.5	0–0.8
Cereals	1.6	1.2–2.0
Fruit and juices	1.6	0–13.4
Vegetables	0.4	0–1.1
Mixed dishes	0.2	0–0.6
Custard	0.2	No data

Source: Pennington and Jones 1987

Gummow et al. (2005) reported a study that looked at the commonly consumed tissues and milk concentrations of vanadium in cattle in South Africa that were extensively farmed over a 5-year period (1999–2004) in an area adjacent to a vanadium processing plant that was known to have higher-than-normal background levels of vanadium. The group of cattle included two groups, one group of 10 cattle that was farmed adjacent to the mine, with an average exposure of 1,229 mg V/day, and another group of 20 cattle that was farmed 2–3 km from the first group with an exposure about half that of the high exposure group (mean=532 mg V/day). Cattle in the trial were monitored over a 5-year period and six cohorts of animals were slaughtered over this period. Concentrations of vanadium in commonly consumed tissues (liver, kidney, fillet, and triceps) ranged from <0.05 to 11.51 mg/kg (wet-weight) in triceps and liver, respectively, over both groups. The median concentration of vanadium in milk was 0.23 mg/kg (range: <0.05–1.92 mg/kg) over both groups. Concentrations of vanadium in tissues from the group raised adjacent to the mine and those raised 2–3 km away were not differentiated in the presentation of the data.

Concentrations of various metals, including vanadium, were measured in samples of six fish species collected during 1997 and 1998 along the coast of the Adriatic Sea. Vanadium concentrations (µg/kg fresh weight) were 45.3–74.4 (anchovy), <4.0–4.8 (angler), <4.0 (hake), 6.7–29.8 (mackerel), 11.8–32.4 (red mullet), and <4.0–2.9 (sole) (Sepe et al. 2003).

Vanadium is found in almost all coals used in the United States, with levels ranging from extremely low to 10 g/kg (Byerrum et al. 1974; WHO 1988). Eastern U.S. coal has an average content of 30 ppm, western coal has an average content of 15 ppm, and coal from the interior contains an average of 34 ppm (Byerrum et al. 1974). The average vanadium content of bituminous and anthracite coal is 30 and 125 ppm, respectively (Byerrum et al. 1974).

Vanadium is usually the most abundant trace metal found in petroleum samples (Amorim et al. 2007). Vanadium concentrations in petroleum may be as high as 1,500 mg/kg, while some crude oils contain <0.1 mg/kg. Vanadium occurs predominantly as the vanadyl ion (VO^{2+}) in the form of organometallic complexes with porphyrins. Vanadyl porphyrins originated from the formation of crude oil; the vanadyl ion was substituted for magnesium ion (Mg^{2+}) in the chlorophylls of plants. Other vanadium complexes in petroleum include non-porphyrin and organic acid complexes (Hovmand et al. 2008). Mamane and Pirrone (1998) reported that residual fuel oils manufactured from U.S. crude oils contain 25–50 ppm of vanadium. Venezuelan, Middle Eastern, and North African residual oils have vanadium concentrations of 200–300, 10–20, and 50–90 ppm, respectively. Vanadium is highly enriched relative to other elements in

heavy fuel oils due to vanadium porphyrins. Because of this, vanadium is used as a marker for emissions from fuel oil combustion (Mamane and Pirrone 1998).

Vanadium concentrations ranging from 0.49 to 5.33 µg/g in were measured in 45 different brands of whole unsmoked cigarettes. Mean vanadium concentrations of 1.11, 0.67, 0.09, and 0.33 µg/cigarette in whole unsmoked cigarettes, ash, filter, and smoke of six different brands of cigarettes, respectively (Adachi et al. 1998a).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Food is the main source of vanadium intake for humans (Lagerkvist et al. 1986). Higher dietary intake levels are possible when food is grown in soil contaminated with greater than background levels of vanadium. Vanadium in food is mainly ingested as VO^{2+} (vanadyl, V^{4+}) or HVO_4^{2-} (vanadate) (Sepe et al. 2003). Byrne and Kučera (1991) reported a daily intake of vanadium of 10–20 µg. The dietary intake of vanadium estimated from the combined total intake of solids and liquids from a dietary study in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin) for the NHEXAS was 0.34 µg/kg of body weight/day (Thomas et al. 1999). Pennington and Jones (1987) surveyed 234 foods from a 1984 collection of the FDA's Total Diet Study for various trace elements including vanadium. Based on this survey, estimated daily intakes of vanadium ranged from 6.2 µg/day for 60–65-year-old females to 18.3 µg/day for 25–30-year-old males. Table 6-4 summarizes the estimated daily intakes of vanadium for the various age groups in this study.

Various metal concentrations were determined in foods (meat, fish and seafood, pulses [lentil, bean], cereals, vegetables, fruits, tubers, whole milk, yogurt, eggs, and sugar) purchased from local markets, supermarkets, and grocery stores in zones of Tarragona County (Catalonia, Spain) near a hazardous waste incinerator, which has been operating since 1999 (Bocio et al. 2005). A dietary intake for vanadium of 28.9 µg/day was estimated for an average adult man (70 kg body weight) in Tarragona County (Catalonia, Spain). Fish and seafood (hake, sardine, and mussels) were the only foods that contributed to this value; vanadium was not detected in any other foods that were surveyed. The detection limit for vanadium in this study was 0.25 µg/g (Bocio et al. 2005). Sepe et al. (2003) reported an 11–34% contribution to the daily vanadium ingestion from fish collected during 1997 and 1998 along the coast of the Adriatic Sea for the population in this area.

Table 6-4. Estimated Daily Vanadium Intake

Age group	Intake (µg/day)
6–11 Months	6.7
2 Years	6.5
14–16 Years, female	7.1
14–16 Years, male	11.0
25–30 Years, female	8.1
25–30 Years, male	18.3
60–65 Years, female	6.2
60–65 Years, male	10.6

Source: Pennington and Jones 1987

Gummow et al. (2005) estimated dietary intakes of vanadium from the consumption of cattle in South Africa that were raised over a 5-year period (1999–2004) in an area adjacent to a vanadium processing plant that was known to have higher-than-normal background levels of vanadium. The median potential daily intakes of vanadium in the diet of humans consuming beef from these cattle were estimated to be 1.9, 1.8, 2.9, and 1.2 µg/kg body weight/day for consuming fillet, triceps, liver, and kidney, respectively. The median potential daily intake of vanadium from drinking milk of these cattle was estimated to be 4.6 µg/kg body weight/day (Gummow et al. 2005).

As compared to food, drinking water is a less important source of vanadium exposure for the general population. Thomas et al. (1999) reported mean vanadium concentrations of 1.2 and 1.0 µg/L in flushed tap water and standing tap water samples from Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin, respectively. Assuming a daily intake of 2 L of water (EPA 1988), a daily intake of approximately 2 µg of vanadium from tap water can be estimated.

Vanadium is present in many dietary supplements, including multivitamin and mineral supplement formulations, as well as products marketed for weight control, bodybuilding, and diabetes control (NTP 2008). The National Library of Medicine's (NLM's) Dietary Supplements Label Database lists >100 products containing vanadium (NLM 2009). Many of these products contain <10 µg of vanadium. Some of these products contain up to 12.5 mg of vanadium depending on the serving size recommended by the manufacturer. Three containing vanadyl sulfate are also listed on the NLM's Dietary Supplements Label Database, containing 0.01–1.66 mg of vanadyl sulfate (0.003–0.52 mg vanadium) depending on the serving size recommended by the manufacturer (NLM 2009). According to the Third National Health and Nutrition Examination Survey on supplement use of vanadium, the median intake of supplement vanadium by adults was approximately 9 µg/day (IOM 2001). Vanadium has been used in supplements for individuals with diabetes. Intakes of 30–150 mg/day for vanadyl sulfate (9–47 mg V/day) and 125 mg/day for sodium metavanadate (52 mg V/day) have been reported (IOM 2001; Smith et al. 2008). Vanadyl sulfate supplements have been used as well by weight training athletes at levels up to 60 mg/day (18.6 mg V/day) (Barceloux 1999). Consumption of some vanadium-containing supplements may result in intakes of vanadium that would exceed those from food and water.

The general population may also be exposed to airborne vanadium through inhalation, particularly in areas where use of residual fuel oils for energy production is high (Zoller et al. 1973). Assuming air concentrations of approximately 50 ng/m^3, Byrne and Kosta (1978) estimated a daily intake of 1 µg vanadium, assuming an average inhalation rate of 20 m^3/day. In addition, cigarette smoke can contribute

vanadium exposure. Koutrakis et al. (1992) estimated an emission rate for vanadium from cigarette smoke of 373 ng/cigarette; approximately 0.04 µg of vanadium is given off by in the smoke of one cigarette.

Lin et al. (2004) reported vanadium concentrations in the blood of 52 Taiwanese college students (19–42 years old). None of these students had occupational exposure to vanadium and five of the students (all male) were smokers. The average vanadium concentration in was 0.42 ng/mL in all students, with a range of 0.01–1.20 ng/mL. The average vanadium concentration in blood for the female students was 0.37 ng/L and the average concentration for nonsmoking male students was 0.44 ng/L; the average for the five smokers was 0.47 ng/mL. Concentrations of vanadium in human blood reported in the literature range from 0.032 to 0.095 ng/mL (Kučera et al. 1992; Lin et al. 2004; Sabbioni et al. 1996). The average vanadium concentration in blood of individuals that have occupational exposure is 33.2 (3.10–217) ng/mL (Lin et al. 2004). Sabbioni et al. (1996) surveyed the literature for reports on vanadium determination in human blood, serum, and urine and reported that vanadium concentrations in blood and/or serum ranged from 0.45–18.4 nmol/L (0.022–0.937 µg/L) and concentrations in urine ranged from 4.16–15.7 nmol/L (0.212–0.800 µg/L). Normal concentrations of vanadium in blood and serum were reported to be around 1 nmol/L (0.05 µg/L) and around 10 nmol/L (0.5 µg/L) for urine. Nixon et al. (2002) reported similar values for vanadium concentrations of 0.05 and 0.24 µg/L in serum and urine, respectively, in healthy individuals from a literature survey. Vanadium concentrations ranging from 30 to 160 µg/kg have been reported in hair (Fernandes et al. 2007; Kučera et al. 1992). No functional role for vanadium in higher animals or humans has been identified (IOM 2001).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths,

sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Similar to adults, dietary intake of vanadium through the ingestion of food is the primary exposure route for children. This route of exposure is particularly relevant when the food is contaminated with soil because soil contains an average of about 10,000 times as much vanadium as is found in many biological materials (Byrne and Kosta 1978). Since young children tend to ingest soil and dust during daily activities, children may be exposed to vanadium through the ingestion of soil or dust. Cigarette smoke can contribute vanadium exposure of children. Approximately 0.04 µg of vanadium is given off by in the smoke of one cigarette (Koutrakis et al. 1992).

Blood and hair samples were collected from 23 children living in the vicinity of a metallurgical plant producing vanadium pentoxide (V_2O_5) approximately 20 km from Prague, Czechoslovakia (Kučera et al. 1992). These children may have been exposed to vanadium due to contamination of well water. A control group consisted of 17 children from a nonpolluted rural area about 30 km from Prague. Median vanadium concentrations in hair samples from the exposed and control groups did not differ significantly, and were 98 and 88 µg/kg, respectively. The median vanadium concentration in the blood of the exposed children and the children in the control group were 0.078 and 0.042 µg/L, respectively, and were considered significantly different (Kučera et al. 1992).

Concentrations of vanadium in human breast milk of 0.46, 0.27, 0.21, 0.11, 0.69, and 0.13 µg/g have been reported in samples from Nigeria, Zaire, Guatemala, Hungary, Philippines, and Sweden, respectively (Nriagu et al. 1992). Ikem et al. (2002) reported mean vanadium concentrations of 0.001, 0.002, and 0.003 µg/mL in milk-based liquid formulas from the United Kingdom, milk based powdered formulas from the United States, and soy-based powder formulas from the United States, respectively. Vanadium was not detected in milk-based powdered formulas from Nigeria and the United Kingdom. Daily intakes of vanadium for infants in the United States were estimated to be 0.05, 3.5, and 2.8 µg/day for milk-based powder formulas, soy-based powder formulas, and hypoallergenic powder formulas from the United States, respectively (Ikem et al. 2002).

Pennington and Jones (1987) reported concentrations in infant foods that ranged from 0.1 µg/100 g in formulas to 1.6 µg/100 g in cereals, fruits, and juices. Daily intakes of vanadium of 6.7, 6.5, 7.1, and 11.6 µg/day for children aged 6–11 months, 2 years, 14–16 years (female), and 14–16 years (male),

respectively, were estimated based on this food survey. A summary of these data are found in Tables 6-3 and 6-4.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations consuming foods grown in soils supplemented with fertilizers or sludge containing vanadium or in soils naturally high in vanadium content may be exposed to concentrations higher than background levels. This is due primarily to surface deposition.

Populations in areas with high levels of residual fuel oil consumption may also be exposed to above-background levels of vanadium, both from increased particulate deposition upon food crops and soil in the vicinity of power plants and higher ambient air levels (Zoller et al. 1973). Cities in the northeastern United States frequently fall into this category, where ambient air levels often range from 150 to 1,400 ng/m^3 (Zoller et al. 1973).

Personal exposure measurements were conducted on 18 boilermakers and 11 utility workers before and during a 3-week overhaul of a large oil-fired power plant (Liu et al. 2005). Utility workers included mechanics, welders, laborers, painters, precipitator operators, work crew supervisors, and laboratory workers. During the overhaul, boilermakers worked both inside and outside the boiler and were more likely to be exposed to ash. Utility workers worked outside the boiler in adjacent areas and had little direct contact with the ash. Time-weighted average exposures for the boilermakers and the utility workers were 1.20 and 1.10 µg/m^3, respectively, before the overhaul work and 8.9 and 1.4 µg/m^3, respectively, during the overhaul work (Liu et al. 2005).

Full-shift, personal breathing sampling was conducted on nine employees working in the finishing and cut-off areas (torch cutting, pneumatic hammer, water blast, and the five finishing workstations) of a titanium investment casting plant in Redmond, Oregon during July 7–10, 2003. Respirable vanadium pentoxide concentrations ranged from 0.0005 to 0.0089 mg/m^3, with the highest measurement of 0.123 mg/m^3 in the torch cutting area (NIOSH 2004).

Vanadium, as elemental vanadium or vanadyl sulfate, may be found in various commercial nutritional supplements and multivitamins; vanadium concentration can range from 0.0004 to 12.5 mg in these supplements depending on the serving size recommended by the manufacturer (NLM 2009). Vanadium supplements have be used and studied as supplements for diabetic individuals. Intakes of 30–150 mg/day

for vanadyl sulfate (9–47 mg V/day) and 125 mg/day for sodium metavanadate (52 mg V/day) have been reported (IOM 2001; Smith et al. 2008). Vanadyl sulfate supplements have been used as well by weight training athletes at levels up to 60 mg/day (18.6 mg V/day) (Barceloux 1999). Consumption of some vanadium containing supplements may result in intakes of vanadium that would exceed that from food and water.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of vanadium is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of vanadium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of vanadium and its compounds are reasonably well documented (see Tables 4-1 and 4-2). No data needs are indentified.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2007, became available in March of 2009. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Companies involved in the vanadium production industry (see Table 5-3), uses of vanadium and various vanadium compounds (Lide 2008; USGS 2009a), and various sources of release are also available (see Table 6-1). There is little information available describing the amounts of vanadium consumed in each

use category or the quantities recycled and disposed of within the United States. Few details were found regarding the specific disposal methods used (HSDB 2009; USGS 2009a). Information in each of these areas would provide an indication of the potential for human exposure as a result of disposal practices.

Environmental Fate. The relative contributions of natural (Byerrum et al. 1974; Zoller et al. 1973) and anthropogenic sources (Byerrum et al. 1974; TRI07 2009) of vanadium to the different environmental media are available. Partitioning between the various media is described, in particular from soil to water and from water to sediment (Wehrli and Stumm 1989; WHO 1988), but specific coefficients are not available in many studies. Information on the transport of vanadium within each media is available (Duce and Hoffman 1976; Martin and Kaplan 1998; Wehrli and Stumm 1989; WHO 1988; Zoller et al. 1973).

Bioavailability from Environmental Media. Occupational studies on the uptake of vanadium via the inhalation route exist; however, data suggesting that this route is relevant with regard to hazardous waste sites are lacking. Dermal absorption data are limited; however, it is likely that absorption via this route is low since vanadium, like other metals, has low solubility in lipids (WHO 1988). The daily intakes of vanadium from air, food, and water are generally small (Bocio et al. 2005; Thomas et al. 1999; Zoller et al. 1973). Seafood or milk from cows raised in an area with vanadium contamination can be a more significant dietary contribution of vanadium (Gummow et al. 2005; Sepe et al. 2003). No data needs are identified.

Food Chain Bioaccumulation. The uptake of vanadium in aquatic plants and animals is reasonably well documented; levels of vanadium present in different species have been established (Byerrum et al. 1974; WHO 1988). Levels present in terrestrial plants (Byerrum et al. 1974; Cannon 1963) and animals (Van Zinderen Bakker and Jaworski 1980; WHO 1988) have been established for several species. Uptake of vanadium by terrestrial plants grown on sludge-amended, or vanadium-containing fertilized fields has been studied. Vanadium does not appear to concentrate in above-ground portions of terrestrial plants (Byerrum et al. 1974). No data needs are identified.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of vanadium in contaminated media at hazardous waste sites are needed so that the information obtained on levels of vanadium in the environment can be used in combination with the known body burden of vanadium to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Estimates of human exposure to vanadium from food (Bocio et al. 2005; Byrne and Kosta 1978; Byrne and Kučera 1991; Gummow et al. 2005; Pennington and Jones 1987; Sepe et al. 2003; Thomas et al. 1999; WHO 1988), drinking water (USGS 2009c; Lagerkvist et al. 1986; Thomas et al. 1999), and air (Byrne and Kosta 1978) are limited. Current information on emission levels from the combustion of residual fuel oil would enable a more complete picture of populations potentially exposed to higher than background ambient air levels. A data need is identified regarding vanadium levels found in environmental media in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Limited information was located describing levels of vanadium present in human tissues for the general population (Byrne and Kosta 1978; Fernandes et al. 2007; Kučera et al. 1992; Lin et al. 2004; Nixon et al. 2002; Sabbioni et al. 1996). Little information is available on tissue levels found in populations near hazardous waste sites. A data need for vanadium levels in blood samples of the general population and those residing near hazardous waste sites is identified.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Measurements of the vanadium in blood and hair of children who have been exposed to vanadium, as well as unexposed children, are limited (Kučera et al. 1992). Additional information monitoring vanadium concentrations in children are needed. Specific data on the intake of vanadium from food eaten by children and from their diet are also limited (Ikem et al. 2002; Pennington and Jones 1987).

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for vanadium were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

No long-term research studies on the environmental fate of vanadium were identified. No ongoing studies or long-term research concerning occupational or general population exposures to vanadium were identified (FEDRIP 2009).

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring vanadium, its metabolites, and other biomarkers of exposure and effect to vanadium. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

Vanadium can be determined as the total metal, as well as in its different oxidation states (species). The various oxidation states of vanadium can interconvert between the oxidation state depending on conditions such as, oxidation-reduction potential, pH, and salinity. In natural waters, dissolved vanadium exists as vanadium(IV) or vanadium(V) and these species have different toxic properties; therefore, determination of the vanadium species present in a sample can be more important than the total vanadium content of the sample in order to best evaluate human exposure (Pyrzyńska and Wierzbicki 2004).

Analytical techniques for the determination of species of vanadium include standard atomic spectroscopic techniques and separations methods coupled with sensitive detectors. Separation methods include capillary electrophoresis (CE) and liquid chromatography (LC). Atomic spectroscopic methods used for the determination of vanadium include atomic absorption spectroscopy (AAS) with flame and graphite tube atomizers, inductively coupled plasma optical emission spectrometry (ICP-OES), inductively coupled plasma mass spectrometry (ICP-MS), x-ray fluorescence spectrometry (XRF), and spectrophotometric methods (Chen and Owens 2008).

Sample preparation is one of the most important steps in the analysis of vanadium in biological and environmental samples. Direct analysis of vanadium species using atomic spectroscopic or separation techniques is generally not feasible due to the relatively low concentrations of vanadium found in samples as compared to other metals. In addition, the complexity of the matrices of biological and environmental samples can interfere with the determination of vanadium species, and it is often necessary to remove the matrices prior to vanadium analysis (Pyrzyńska and Wierzbicki 2004; Chen and Owens 2008).

The main methods for matrix removal are liquid-liquid extraction (LLE) and solid phase extraction (SPE). LLE is based on the distribution of the analyte between two immiscible solvents and involves the formation of an uncharged chemical species in the aqueous phase by chelation or ion-association of the vanadium ion, followed by extraction into an organic solvent. Example of complexing reagents (chelates) used to bind vanadium species include, vanadium(IV) with bis(salicylaldehyde) tetramethylethylene-diimine in a chloroform/water mixture, vanadium(V) with N-benzoyl-N-phenylhydroxylamine (BPHA) in a chloroform/water mixture, and vanadium(V) with 2-(5-bromo-2-pyridylazo)-5-(N-propyl-N-sulfopropy-lamino)-phenol (5-Br-PAPS) in a xylene/water mixture. Each of these LLE steps was followed by separation using liquid chromatography with UV detection. Other complexing agents that have been studied include dibenzo-18-crown-6 and N-phenyl-(1,2-methanofullerene)-formohydroxamic acid (PMFFA) (Chen and Owens 2008; Pyrzyńska and Wierzbicki 2004).

SPE is based on the transfer of metal ions from an aqueous phase to the active sites of a solid phase. Compared to LLE, SPE is simpler and more convenient to automate. It also uses less solvent and requires fewer manipulations. Several ion-exchange resins, functionalized cellulose sorbents, and chelating resins have been studied for the selective preconcentration and separation of vanadium species. Cellulose sorbent with phosphonic acid exchange groups gives excellent enrichment of vanadium(IV) and vanadium(V) and can be simultaneously eluted using an ethylenediamine tetraacetic acid (EDTA) solution. Other solid phases used to separate and preconcentrate vanadium species include Sephadex DEAE A-25 with Eriochrome Cyanide R complexation, C_{18} microcolumn or XAD-7 resin with complexation using 2-(5-bromo-2-pyridylazo)-5-diethylaminophenol or dithizone or 8-hydroxyquinoline (8-HQ), and Chelex 100 (Chen and Owens 2008; Pyrzyńska and Wierzbicki 2004).

Vanadium concentrations in biological and environmental samples are typically very low, and vanadium analysis requires powerful analytical methods. Analytical methods with sufficient sensitivity include neutron activation analysis (NAA), electrothermal atomic absorption spectrometry (ETAAS), inductively coupled plasma atomic emission spectrometry (ICP-AES), ICP-MS, and some UV-vis spectrophotometric methods (Pyrzyńska and Wierzbicki 2004). ETAAS is routinely used for the determination of trace concentrations of vanadium. ICP-MS has better sensitivity than ETAAS; however, interference from the sample matrix can complicate the analysis. The species $^{16}O^{35}Cl^{+}$ and $^{34}S^{16}OH^{+}$ from the sample matrix can overlap with the most abundant isotope of vanadium at *m/z*=51 (Nixon et al. 2002; Pyrzyńska and Wierzbicki 2004).

Due to the low levels of vanadium that are typically found in biological and environmental samples, care must be exercised during sample handling in order to avoid contamination. Vanadium may be found in disposable steel needles, collection vials, storage containers, and chemicals and reagents (Kučera and Sabbioni 1998).

7.1 BIOLOGICAL MATERIALS

Methods for determination of vanadium in biological samples are summarized in Table 7-1.

NAA has been widely used to measure trace elements (including vanadium) in biological samples (Allen and Steinnes 1978; Lavi and Alfassi 1988; Martin and Chasteen 1988; Mousty et al. 1984). In NAA, the sample is bombarded with neutrons, and the element of interest is made radioactive. The amount of the element present in the sample is then determined by measurement of the radioactivity or radioactive decay products. When ^{51}V is bombarded with neutrons, it becomes ^{52}V (half-life 3.75 minutes and γ emission of 1.433 MeV). The resultant γ emission is detected with an efficient detector with high spectral resolution such as a well-type germanium detector combined with a multichannel analyzer. The concentration of vanadium is determined through its short-lived half-life of ^{52}V (Seiler 1995). Detection limits of low- to sub-ppb (µg/L) levels of vanadium in blood and urine samples have been obtained (Allen and Steinnes 1978; Lavi and Alfassi 1988; Mousty et al. 1984). The advantages of the NAA technique are its sensitivity and multi-elemental capability. The disadvantages of this technique include its high cost and the limited availability of nuclear facilities for NAA analysis (Seiler 1995).

Sabbioni et al. (1996) surveyed the literature for reports on vanadium determination in human blood, serum, and urine. Many analytical methods have been used to determine vanadium concentrations in blood, serum, and urine samples, including spectrography, colorimetry, catalytic reactions, XRF, particle induced x-ray emission (PIXE), ICP-AES, isotope dilution mass spectrometry (ID-MS), graphite furnace AAS (GF-AAS), and NAA. Only ID-MS, NAA, and GF-AAS can determine vanadium concentrations at levels of a few picograms (pg) of vanadium; GF-AAS and NAA are used most frequently (Kučera and Sabbioni 1998; Nixon et al. 2002; Sabbioni et al. 1996).

Nixon et al. (2002) reported the use of a Dynamic Reaction Cell™ ICP-MS (DRC-ICP-MS) for the analysis of vanadium in serum and urine. Generally, Zeeman graphite furnace atomic absorption spectrometry (ZGFAAS) and NAA are routinely used for the determination of vanadium in urine and serum. While ICP-MS as been routinely used to determine heavy metal concentrations in blood, serum,

Table 7-1. Analytical Methods for Determining Vanadium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood/urine	Digest sample and evaporate; redissolve in acid; extract with MIBK; evaporate; redissolve in acid	NAA	~1 µg/L (blood); 2–4 µg/L (urine)	No data	Allen and Steinnes 1978
Urine	Wet ashing with HNO_3; chelation with cupferron; extraction into MIBK	GFAAS	1 µg/L	96–100%	Buchet et al. 1982
Serum/urine	Digestion in $H_2SO_4/HClO_4/HNO_3$ add $KMnO_4$, sulfamic acid, and HCl; extract with BTA in benzene	ETAAS	0.008 µg/L	90.3% (serum); 90.8% (urine)	Ishida et al. 1989
Serum	Coprecipitate sample with lead nitrate or bismuth nitrate; dry and irradiate	NAA	0.7 µg/L	No data	Lavi and Alfassi 1988
Blood	Microwave digestion with HNO_3	ICP-MS	0.0078 µg/L	No data	Lin et al. 2004
Serum/urine	Dilution with 1% HNO_3 and addition of internal standard	DRC-ICP-MS	0.028 µg/L	No data	Nixon et al. 2002
Hair	Washing and drying of hair samples, followed by cryogenic grinding; powdered hair samples prepared as slurries in mixtures of HNO_3 and a slurry stabilizer	ETAAS	0.28–0.34 µg/L	No data	Fernandes et al. 2007

BTA = N-benzoyl-N-(o-tolyl)hydroxylamine; DRC-ICP-MS = Dynamic Reaction Cell™ inductively coupled mass spectrometry; MIBK = methyl isobutyl ketone; NAA = neutron activation analysis

and urine, and ICP-MS quantitation is at least an order of magnitude better than ZGFAAS for elements such as arsenic, lead, selenium, and cadmium, interference from $^{16}O^{35}Cl^{+}$, which is produced in the argon plasma of the instrument, has limited the use of ICP-MS for the determination of vanadium. In this study it was found that with proper dynamic reaction cell conditions, OCl^{+} interference can be eliminated. The detection limit for vanadium (0.028 µg/L) was also found to be superior to that of ZGFAAS (1.9 µg/L) (Nixon et al. 2002).

Fernandes et al. (2007) reported on a method to analyze hair samples using ETAAS. Samples were powdered using cryogenic grinding and hair slurries contained nitric acid, Triton X-100 (a nonionic surfactant), and water soluble tertiary amines. Limits of detection of 0.28 and 0.34 µg/L were reported using longitudinal heating and transversal heating graphite furnace atomizers, respectively.

7.2 ENVIRONMENTAL SAMPLES

Standard methods are available to measure vanadium concentrations in air, surfaces, water, soil, sediment, and plant and animal tissue (EPA 1983a, 1983b, 1983c, 1994a, 1994b, 1997a, 2003a; NIOSH 2003a, 2003b, 2003c, 2003d; OSHA 2002; USGS 1987, 1993, 1996, 1998, 2006, 2007). Atomic spectroscopic methods are generally used in these methods as well as ICP-MS and spectrophotometric methods. NIOSH Method 7504 (1994) and OSHA Method ID-185 (1991) can be used to measure vanadium oxides in air samples using XRF. Methods for determination of vanadium in environmental samples are summarized in Table 7-2.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of vanadium is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of vanadium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean

Table 7-2. Analytical Methods for Determining Vanadium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Vanadium					
Air	Collect sample on MCE or PVC filter, followed by $HNO_3/HClO_4$ ashing	ICP-AES	0.028 µg/filter	98.3–103.2% (MCE) 102.5–108.3% (PVC)	NIOSH 2003a (Method 7300)
Air	Collect sample on MCE or PVC filter, followed by aqua regia ashing	ICP-AES	0.028 µg/filter	101.3–106.0% (MCE) 77.8–96.1% (PVC)	NIOSH 2003b (Method 7301)
Air	Collect sample on MCE filter, followed by hot block/HCl/HNO_3 digestion	ICP-AES	0.003 µg/mL	No data	NIOSH 2003c (Method 7303)
Wipes	Wipe surface; ash wipe with $HNO_3/HClO_4$	ICP-AES	0.01 µg/wipe	No data	NIOSH 2003d (Method 9102)
Air, wipe, or bulk	Digestion of filters with HNO_3/ H_2SO_4/H_2O_2	ICAP-AES	1.9 µg	No data	OSHA 2002 (Method ID-125G)
Water	Acid solubilization	ICP-MS	0.014 µg/L	97–109.2%	EPA 1997a (EPA Method 200.10)
Water	Sample is mixed with HNO_3/HCl and heated	AVICP-AES	0.2 µg/L	93%	EPA 2003 (EPA Method 200.5)
Water	Acidified with HNO_3	FAAS	200 µg/L	95–100%	EPA 1983a, 1983b (EPA Method 286.1)
Water	Acidified with HNO_3	GFAAS	4 µg/L	No data	EPA 1983a, 1983c (EPA Method 286.2)
Water	Filter and acidified samples	ICP-AES	6 µg/L	No data	USGS 1987 (USGS Method I-1472-87)
Water	Filter and acidified samples	ICP-MS	0.08 mg/L	64–105%	USGS 1998 (USGS Method I-2477-92)

Table 7-2. Analytical Methods for Determining Vanadium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Treatment with an ammonium persulfate phosphoric acid reagent and gallic acid solution	Colorimetric	1 µg/L	No data	USGS 1993 (USGS Method I-2880)
Water	Filter and acidified samples	ICP-OES	5 µg/L	98%	USGS 1998 (USGS Method I-4471-97)
Water (filtered)	Filtered (0.045 µm membrane); preserved with HNO_3	ICP-MS	0.05 µg/L	No data	USGS 2006 (USGS Method I-2020-05)
Water (unfiltered)	Preserved with HNO_3 followed by digestion	ICP-MS	0.05 µg/L	No data	USGS 2006 (USGS Method I-4020-05)
Water/waste water/solid wastes	Digestion with nitric and hydrochloric acid	ICP-AES	3 µg/L	84–104%	EPA 1994a (EPA Method 200.7)
Water/wastes	Digestion with nitric and hydrochloric acid	ICP-MS	2.5 µg/L	74.9–113.4%	EPA 1994b (EPA Method 200.8)
Water/waste water/solid wastes	Acid digestion	ICP-AES	5 µg/L	No data	EPA 2007 (EPA Method 6010 C)
Soil/sediment	Air-dried and sieved; digestion with HNO_3 using a closed-vessel microwave digestion procedure	ICP-MS	0.01 µg/L	No data	USGS 2006 (USGS Method I-5020-05)
Animal tissue	Acid digestion	ICP-MS	0.06 µg/g	101%	USGS 1996 (USGS Method B-9001-95 [ICP-MS])
Animal tissue	Acid digestion	ICP-AES	Not calculatable	96%	USGS 1996 (USGS Method B-9001-95 [ICP-AES])

Table 7-2. Analytical Methods for Determining Vanadium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Biota	Digestion with HNO_3 using a closed-vessel microwave digestion procedure	ICP-MS	0.01 µg/L	No data	USGS 2006 (USGS Method I-9020-05)
Vanadium oxides					
Air	Collect sample on PVC filter, dissolve filter in THF; redeposit on silver filter	XRD	4–28 µg (V_2O_5), 5–62 µg (V_2O_3), 7–50.3 µg (NH_4VO_3)	No data	NIOSH 1994 (Method 7504)
Vanadium pentoxide					
Air	Collect sample on PVC filter, dissolve filter in THF; suspension is produced with the collected dust, which is transferred to silver membrane	XRD	25 µg at 65 s	163.4–190.2% (respirable dust); 85.9–91.1% (fine-respirable dust)	OSHA 1991 (Method ID-185)

AVICP-AES = axially viewed inductively coupled plasma-atomic emission spectrometry; EPA = Environmental Protection Agency; FAAS = flame atomic absorption spectrometry; GFAAS : graphite furnace atomic absorption spectrometry; ICAP-AES = inductively coupled argon plasma-atomic emission spectroscopy; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively couples plasma-mass spectrometry; ICP-OES = inductively coupled plasma-optical emission spectroscopy; MCE = mixed cellulose ester; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PVC = polyvinyl chloride; THF = tetrahydrofuran; USGS = United States Geological Survey; XRD = X-ray diffraction

that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Sensitive and selective methods are available for the detection and quantitative measurement of vanadium after the sample matrix in which it is contained as been properly treated. Atomic spectroscopic methods used for the determination of vanadium include AAS with flame and graphite tube atomizers, ICP-OES, ICP-MS, XRF, and spectrophotometric methods (Chen and Owens 2008). No data needs are identified.

Exposure. Methods exist to determine vanadium levels in environmental samples and human tissues. While several biomarkers of exposure have been indentified, none of them can be used to quantitatively determine exposure levels (Rydzynski 2001). Kučera et al. (1998) reported that blood and urinary vanadium levels are considered the most reliable indicators of occupational exposure to vanadium. No data needs are identified.

Effect. No well-documented biomarkers of effect specific for vanadium have been report (Rydzynski 2001). The primary effects of exposure to vanadium dusts are coughing, wheezing, and other respiratory difficulties; however, these effects are not specific to vanadium and can be found following inhalation of many types of dusts (Rydzynski 2001). No data needs are identified.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining vanadium in water, air, and waste samples with adequate selectivity and sensitivity are well developed and undergoing constant improvement. No data needs are identified.

7.3.2 Ongoing Studies

No ongoing studies regarding methods for measuring vanadium in biological and environmental samples were located (FEDRIP 2009).

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an acute-duration inhalation MRL of 0.0008 mg vanadium/m^3 based on a LOAEL of 0.56 mg vanadium/m^3 for lung inflammation in rats exposed to vanadium pentoxide 6 hours/day, 5 days/week for 13 days (NTP 2002). The MRL was derived by dividing the human equivalent concentration of the LOAEL (0.073 mg vanadium/m^3) by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for animal to human extrapolation with dosimetric adjustments, and 10 for human variability).

ATSDR has derived a chronic-duration inhalation MRL of 0.0001 mg vanadium/m^3 based on a $BMCL_{10}$ of 0.04 mg vanadium/m^3 for degeneration of epiglottis respiratory epithelium of rats exposed to vanadium pentoxide 6 hours/day, 5 days/week for 2 years (NTP 2002). The MRL was derived by dividing the human equivalent concentration of the $BMCL_{10}$ (0.003 mg vanadium/m^3) by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustments and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.01 mg vanadium/kg/day based on a NOAEL of 0.12 mg vanadium/kg/day for hematological and blood pressure effects in humans exposed to vanadyl sulfate for 12 weeks (Fawcett et al. 1997) and an uncertainty factor of 10 for human variability.

IRIS (2009) has derived an oral reference dose (RfD) of 0.009 mg/kg/day for vanadium pentoxide based on a NOAEL of 0.89 mg/kg/day for decreased hair cysteine levels in rats exposed to vanadium pentoxide for 2.5 years (Stokinger et al. 1953) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 to protect against unusually susceptible individuals).

EPA has not derived an inhalation reference concentration (RfC) for vanadium and vanadium compounds.

OSHA has required employers of workers who are occupationally exposed to vanadium peroxide to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs) (OSHA 2009). The employer must use engineering and work practice

controls to reduce exposures to not exceed 0.5 mg/m^3 for vanadium peroxide as respirable dust (as V_2O_5) and 0.1 mg/m^3 as fume (as V_2O_5) at any time (OSHA 2009).

Vanadium pentoxide, vanadyl sulfate dehydrate, and ammonium metavanadate are on the list of chemicals appearing in “Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" and has been assigned a reportable quantity (RQ) limit of 1,000 pounds each (EPA 2009d). Vanadium pentoxide is also considered to be an extremely hazardous substance (EPA 2009e). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

The international and national regulations, advisories, and guidelines regarding vanadium and compounds in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Vanadium and Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2009
	Vanadium pentoxide	Group 2B[a]	
WHO	Air quality guidelines		WHO 2000
	Vanadium		
	TWA based on effects other than cancer or odor/annoyance using an averaging time of 24 hours	1 µg/m^3	
	Drinking water quality guidelines	No data	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)[b]		ACGIH 2008
	Vanadium pentoxide (respirable fraction of dust or fume, as V_2O_5)	0.05 mg/m^3	
	TLV Basis	Irritation and lung	
AIHA	ERPG values	No	AIHA 2008
EPA	Second AEGL chemical priority list		EPA 2008a
	Vanadium and compounds	Yes[c]	
	Hazardous air pollutant	No	EPA 2009b 42 USC 7412
NIOSH	REL (15-minute ceiling)		NIOSH 2005
	Vanadium pentoxide[d]	0.05 mg/m^3	
	IDLH	35 mg/m^3	
	Target organ	Eyes, skin, and respiratory system	
OSHA	PEL (ceiling limit) for general industry		OSHA 2009 29 CFR 1910.1000, Table Z-1
	Vanadium pentoxide		
	Respirable dust (as V_2O_5)	0.5 mg/m^3	
	Fume (as V_2O_5)	0.1 mg/m^3	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2009h 40 CFR 116.4
	Vanadium pentoxide	Yes	
	Vanadyl sulfate dehydrate	Yes	
	Drinking water contaminant candidate list		EPA 1998b

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Vanadium and Compounds

Agency	Description	Information	Reference
	Vanadium	Yes	63 FR 10274
NATIONAL *(cont.)*			
EPA	Drinking water standards and health advisories	No	EPA 2006a
	National primary drinking water standards	No	EPA 2003b
	National recommended water quality criteria	No	EPA 2006b
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2009c 40 CFR 117.3
	Vanadium pentoxide	1,000 pounds	
	Vanadyl sulfate dehydrate	1,000 pounds	
c. Food			
FDA	EAFUS[e]	No	FDA 2008
d. Other			
ACGIH	Carcinogenicity classification	A4[f]	ACGIH 2008
	Biological exposure indices (end of shift at end of workweek)		
	Vanadium in urine	50 µg/g creatinine	
EPA	Carcinogenicity classification	No	IRIS 2009
	RfC	No	
	RfD		
	Vanadium pentoxide	$9x10^{-3}$ mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and their reportable quantities		EPA 2009d 40 CFR 302.4
	Vanadium pentoxide[g]	1,000 pounds	
	Vanadyl sulfate dehydrate[h]	1,000 pounds	
	Ammonium metavanadate[i]	1,000 pounds	
	Effective date of toxic chemical release reporting		EPA 2009f 40 CFR 372.65
	Vanadium (except when contained in an alloy)	01/01/2000	
	Extremely hazardous substance and its threshold planning quantity		EPA 2009e 40 CFR 355, Appendix A
	Vanadium pentoxide	100/10,000 pounds	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Vanadium and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	TSCA chemical lists and reporting periods		EPA 2009g 40 CFR 712.30
	Vanadium, vanadium pentoxide, vanadyl sulfate dehydrate, sodium metavanadate, sodium orthovanadate, and ammonium metavanadate		
	Effective date	07/11/2003	
	Reporting date	09/09/2003	
DHHS	Carcinogenicity classification	No data	NTP 2005
IOM	Upper Tolerable Limit	1.8 mg/day	IOM 2001

[a]Group 2B: possibly carcinogenic to humans
[b]Vanadium peroxide is included in the 2008 Notice of Intended Changes in which the substance and its corresponding values and notations for which the withdrawal of the Documentation and adopted TLV are proposed.
[c]Vanadium and compounds are included on the list of 371 priority chemicals that are acutely toxic and represent the selection of chemicals for AEGL development by the NAC/AEGL committee during the next several years.
[d]The REL applies to all vanadium compounds except vanadium metal and vanadium carbide.
[e]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[f]A4: not classifiable as a human carcinogen
[g]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act and Section 3001 of the Resource Conservation and Recovery Act.
[h]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.
[i]Designated CERCLA hazardous substance pursuant to Section 3001 of the Resource Conservation and Recovery Act.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; IOM = Institute of Medicien; NAC = National Advisory Council; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vanadium compounds
CAS Numbers: 7440-62-2
Date: August 2009
Profile Status: Pre-Public Comment, Final Draft
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 4
Species: Rat

Minimal Risk Level: 0.0008 [ ] mg/kg/day [X] mg vanadium/m^3

Reference: NTP. 2002. NTP toxicology and carcinogenesis studies of vanadium pentoxide (CAS No. 1314-62-1) in F344/N rats and B6C3F1 mice (inhalation). Natl Toxicol Program Tech Rep Ser (507):1-343.

Experimental design: Groups of 40–60 female F344 rats were exposed to 0, 1, 2, or 4 mg vanadium pentoxide/m^3 (0, 0.56, 1.1, and 2.2 mg vanadium/m^3) 6 hours/day, 5 days/week for 16 days. On days 6 and 13, 10 rats/group were killed and a histopathological examination of the lungs was conducted. Four animals per group were killed for examination of onset and extent of lung lesions on days 1, 2, 5, 10, and 16. The remaining animals were used to measure blood and lung concentrations of vanadium, lung clearance half-times, and cell proliferation rates.

Effect noted in study and corresponding doses: Hyperplasia of alveolar epithelium and bronchiole epithelium were observed in 100% of the female rats exposed to 1.1 or 2.2 mg vanadium/m^3 for 6 or 13 days. Significant increases in the incidence of histiocytic infiltrate and inflammation were observed in rats exposed to 1.1 or 2.2 mg vanadium/m^3 for 6 or 13 days and in rats exposed to 0.56 mg vanadium/m^3 for 13 days. A significant increase in fibrosis was observed in rats exposed to 2.2 mg vanadium/m^3 for 13 days. No histopathological alterations were observed in the four female rats killed after 1 day of exposure; by day 2, inflammation and histiocytic infiltrates (increased number of alveolar macrophages) were observed in the rats exposed to 2.2 mg vanadium/m^3. Hyperplasia of the alveolar and bronchiolar epidthelium was first observed on day 5 in rats exposed to 1.1 or 2.2 mg vanadium/m^3.

Dose and end point used for MRL derivation: Increase in the incidence of lung inflammation in rats exposed to 0.56 mg vanadium/m^3 as vanadium pentoxide for 13 days.

[ ] NOAEL [X] LOAEL

A BMD analysis was considered for determining the point of departure for the inflammation in female rats exposed to vanadium pentoxide for 13 days. All available dichotomous models in the EPA benchmark dose software ([BMDS] version 2.1) were fit to the incidence data for lung inflammation (0/10, 8/10, 10/10, and 10/10 in rats exposed to 0, 0.56, 1.1, or 2.2 mg vanadium/m^3) using the extra risk option. The multistage model was run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Adequate model fit is judged by three criteria: goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all the models providing adequate fit to the data, the lowest lower bound on the BMC (BMCL) is selected as the point of departure when the difference between the BMDLs estimated from these models are more three-fold; otherwise, the BMCL from the model with the lowest AIC is chosen. In accordance with U.S. EPA (2000) guidance,

benchmark concentrations (BMCs) and BMCLs associated with an extra risk of 10% are calculated for all models.

Table A-1. Model Predictions for the Incidence of Inflammation in Female Rats Exposed to Vanadium Pentoxide 6 Hours/Day, 5 Days/Week for 13 Days

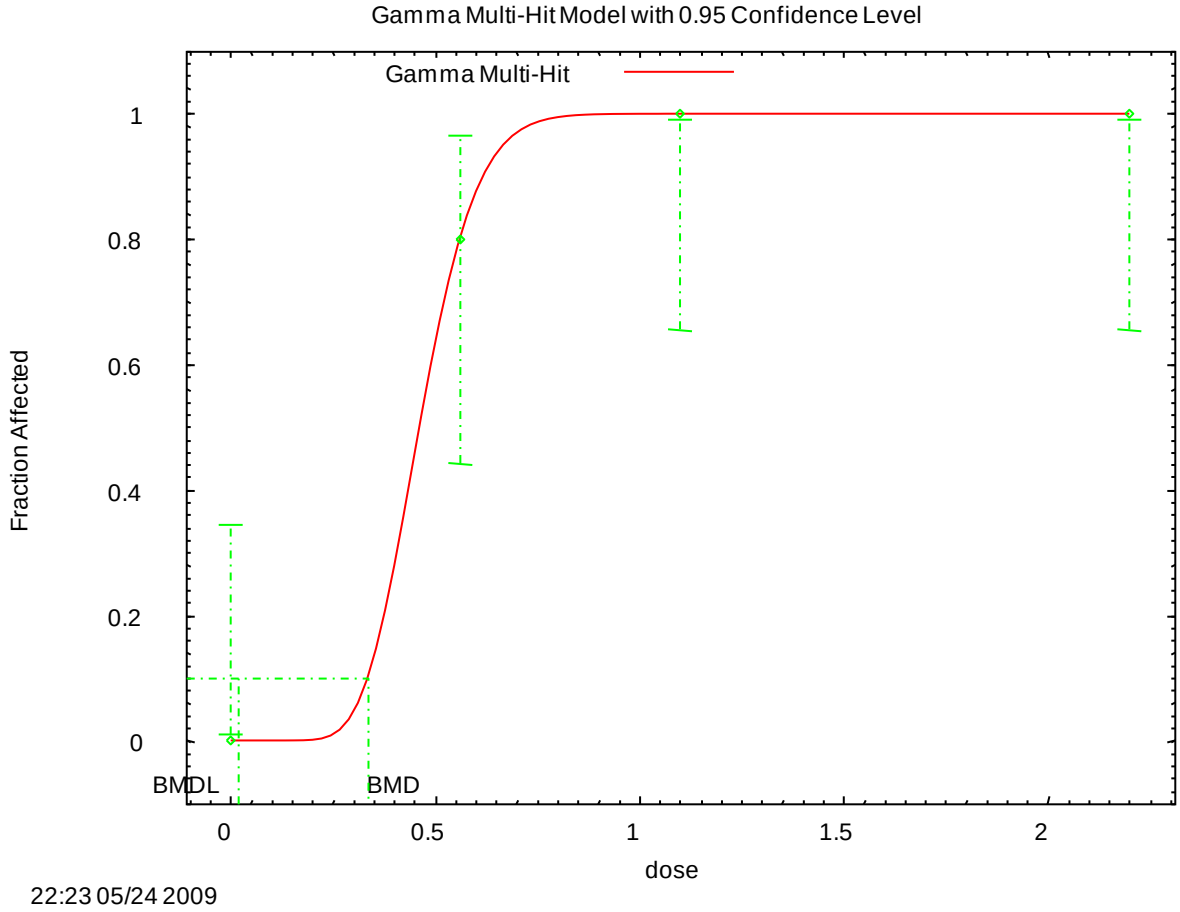
Model	χ^2 Goodness of fit p-value[a]	AIC	BMC_{10} (mg V/m^3)	$BMCL_{10}$ (mg V/m^3)
Gamma[b]	**1.00**	**12.01**	**0.33**	**0.02**
Logistic	1.00	14.01	0.46	0.10
LogLogistic	1.00	12.01	0.46	0.01
LogProbit	1.00	14.01	0.42	0.03
Multistage[c]	0.93	12.69	0.03	0.02
Probit	1.00	14.01	0.38	0.09
Weibull[b]	1.00	14.01	0.25	0.02
Quantal-linear	0.93	12.69	0.03	0.02

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria
[b]Power restricted to ≥1
[c]Betas restricted to ≥0; 1-degree polynomial

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC

Source: NTP 2002

Figure A-1. Fit of Gamma Model to Data on the Incidence of Inflammation in Female Rats Exposed to Vanadium Pentoxide for 13 Days



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

Although the data provide an adequate statistical fit, the estimated $BMCL_{10}$ of 0.02 mg vanadium/m^3 appears to be an overly conservative estimate of a no-adverse-effect level, which may be a reflection of the limited amount of information from the study on the shape of the exposure-response relationship (incidences of lung inflammation were 0/10 in controls and 8/10 at the lowest vanadium concentration). In a chronic-duration study conducted by NTP (2002), no significant alterations in the incidence of lung inflammation were observed in male and female rats exposed to 0.28 mg vanadium/m^3; the LOAEL for lung inflammation was 0.56 mg vanadium/m^3 in males and 1.1 mg vanadium/m^3 in females.

Due to the low confidence in the $BMCL_{10}$, a NOAEL/LOAEL approach was used to determine the point of departure for the acute MRL.

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

The duration-adjusted LOAEL of 0.1 mg vanadium/m^3 was converted to a human equivalent concentration ($LOAEL_{HEC}$) using the following equation:

$$LOAEL_{HEC} = LOAEL_{ADJ} \times RDDR_{TH}$$
$$LOAEL_{HEC} = 0.1 \text{ mg vanadium/m}^3 \times 0.732$$
$$LOAEL_{HEC} = 0.073 \text{ mg vanadium/m}^3$$

where:
The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal to the predicted inhalation particulate exposure concentration for a human. The RDDR program (EPA 1990) was used to calculate a multiplier of 0.732 for the thoracic region was determined using a default body weight of 0.124 kg (EPA 1994c) and a particle size MMAD of 1.2 µm with a geometric standard deviation of 1.9

Was a conversion used from intermittent to continuous exposure? The LOAEL was adjusted for intermittent exposure as follows:

$$LOAEL_{ADJ} = LOAEL \times 6 \text{ hours/day} \times 5 \text{ days/week}$$
$$LOAEL_{ADJ} = 0.56 \text{ mg vanadium/m}^3 \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days}$$
$$LOAEL_{ADJ} = 0.1 \text{ mg vanadium/m}^3$$

Other additional studies or pertinent information that lend support to this MRL: Data on acute toxicity of vanadium in humans are limited to an experimental study in which a small number of subjects were exposed to vanadium pentoxide dust for 8 hours (Zenz and Berg 1967). A persistent cough lasting for 8 days developed in two subjects exposed to 0.6 mg vanadium/m^3; at 0.1 mg vanadium/m^3, a productive cough without any subjective complaints or impact on work or home activities were observed in 5 subjects. The available studies in laboratory animals focused on potential respiratory tract effects. Impaired lung function characterized as airway obstructive changes (increased resistance and decreased airflow) were observed in monkeys exposed to 2.5 or 1.7 mg vanadium/m^3 as vanadium pentoxide for 6 hours (Knecht et al. 1985, 1992); the highest NOAEL for this effect was 0.34 mg vanadium/m^3. Alveolar and bronchiolar epithelial hyperplasia and inflammation were observed in the lungs of mice exposed to 1.1 mg vanadium/m^3 6 hours/day, 5 days/week for 13 days (NTP 2002). Although the Knecht et al. (1985, 1992) or NTP (2002) studies did not include examination of potential end points outside of the respiratory tract, longer-duration studies have identified the respiratory tract as the most sensitive target of toxicity (NTP 2002).

Agency Contacts (Chemical Managers): Jessilynn Taylor, Sam Keith, Larry Cseh

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vanadium compounds
CAS Numbers: 7440-62-2
Date: August 2009
Profile Status: Pre-Public Comment, Final Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 19
Species: Rat

Minimal Risk Level: 0.0001 [ ] mg/kg/day [X] mg vanadium/m^3

Reference: NTP. 2002. NTP toxicology and carcinogenesis studies of vanadium pentoxide (CAS No. 1314-62-1) in F344/N rats and B6C3F1 mice (inhalation). Natl Toxicol Program Tech Rep Ser (507):1-343.

Experimental design: Groups of 50 male and 50 female F344 rats were exposed to 0, 0.5, 1, or 2 mg vanadium pentoxide/m^3 (0, 0.28, 0.56, and 1.1 mg vanadium/m^3) 6 hours/day, 5 days/week for 104 weeks. The following parameters were used to assess toxicity: clinical observations, body weights (every 4 weeks from week 5 to 89 and every 2 weeks from week 92 to 104), complete necropsy, and microscopic examination of major tissues and organs.

Effect noted in study and corresponding doses: No significant alterations in survival or body weight gain were observed in the vanadium-exposed rats. A summary of selected non-neoplastic respiratory tract lesions is presented in Table A-2. Alveolar histiocytic infiltrates were observed in males and females exposed to ≥0.28 mg vanadium/m^3. Significant increases in the incidence of hyperplasia of the alveolar and bronchiolar epithelium were observed in males exposed to ≥0.28 mg vanadium/m^3 and females exposed to ≥0.56 mg vanadium/m^3. Squamous metaplasia was observed in alveolar epithelium of males and females exposed to 1.1 mg vanadium/m^3 and in the bronchiolar epithelium of males exposed to 1.1 mg vanadium/m^3. Chronic inflammation was observed in males exposed to 0.56 or 1.1 mg vanadium/m^3 and females exposed to 1.1 mg vanadium/m^3 and interstitial fibrosis was observed in males exposed to 1.1 mg vanadium/m^3 and females exposed to 0.28 or 1.1 mg vanadium/m^3. An increased incidence of brownish pigment in alveolar macrophages was observed in males exposed to 1.1 mg vanadium/m^3 and females exposed to 0.56 or 1.1 mg vanadium/m^3; this effect was considered to be of little biological relevance. Chronic inflammation, degeneration, and hyperplasia of the epiglottis were observed in the larynx of males and females exposed to ≥0.28 mg vanadium/m^3; squamous metaplasia of the epiglottis respiratory epithelium was also observed in males exposed to ≥0.28 mg vanadium/m^3 and in females exposed to 1.1 mg vanadium/m^3. Goblet cell hyperplasia of the nasal respiratory epithelium was observed in males exposed to ≥0.28 mg vanadium/m^3 and in females exposed to 1.1 mg vanadium/m^3. A positive trend for increased incidences of uterine stromal polyp was observed; NTP did not consider it to be related to vanadium pentoxide exposure. An increased incidence of nephropathy was observed in male rats exposed to 0.56 or 1.1 mg vanadium/m^3; NTP considered the finding to be of marginal biological significance because there was a lack of increase in severity, as compared to controls, and significant findings in female rats. No significant increases in the incidence of lung neoplasms were observed; however, the incidence of alveolar/bronchiolar adenoma in males exposed to 0.28 mg vanadium/m^3 and alveolar/bronchiolar carcinoma or combined incidence of adenoma and carcinoma in males exposed to 0.28 or 1.1 mg vanadium/m^3 were higher than historical controls. These increases in lung tumors were considered to be related to vanadium pentoxide exposure.

Table A-2. Selected Respiratory Tract Effects Observed in Rats Exposed to Vanadium Pentoxide 6 Hours/Day, 5 Days/Week for 2 Years

Air concentration (mg vanadium/m^3)	0	0.28	0.56	1.1
Males				
Lungs				
Alveolar hyperplasia	7/50 (2.3)	24/49[b] (2.0)	34/48[b] (2.0)	49/50[b] (3.3)
Bronchiole hyperplasia	3/50 (2.3)	17/49[b] (2.2)	31/48[b] (1.8)	49/50[b] (3.3)
Inflammation	5/50 (1.6)	8/49 (1.8)	24/48[b] (1.3)	42/50[b] (2.4)
Fibrosis	7/50 (1.4)	7/49 (2.0)	16/48[c] (1.6)	38/50[b] (2.1)
Histiocyte infiltration	22/50 (1.3)	40/49[b] (2.0)	45/48[b] (2.3)	50/50[b] (3.3)
Larynx				
Chronic inflammation	3/49 (1.0)	20/50[b] (1.1)	17/50[b] (1.5)	28/49[b] (1.6)
Degeneration of epiglottis respiratory epithelium	0/49	22/50[b] (1.1)	23/50[b] (1.1)	33/50[b] (1.5)
Hyperplasia of epiglottis respiratory epithelium	0/49	22/50[b] (1.1)	23/50[b] (1.1)	33/49[b] (1.5)
Squamous metaplasia of epiglottis respiratory epithelium	0/49	18/50[b] (1.5)	34/50[b] (1.5)	32/49[b] (1.9)
Nose				
Hyperplasia of respiratory epithelium goblet cell	4/49 (1.8)	15/50[b] (1.8)	12/49[c] (2.0)	17/48[b] (2.1)
Female				
Lung				
Alveolar hyperplasia	4/49 (1.0)	8/49 (1.8)	21/50[b] (1.2)	50/50[b] (3.1)
Bronchiole hyperplasia	6/49 (1.5)	5/49 (1.6)	14/50[c] (1.3)	48/50[b] (3.0)
Inflammation	10/49 (1.5)	10/49 (1.1)	14/50 (1.2)	40/50[c] (1.7)
Fibrosis	19/49 (1.4)	7/49 (1.3)	12/50 (1.6)	32/50[b] (1.4)
Histiocyte infiltration	26/49 (1.4)	35/49[c] (1.3)	44/50[b] (2.0)	50/50[b] (1.9)
Larynx				
Chronic inflammation	8/50 (1.8)	26/49[b] (1.5)	27/49[b] (1.3)	37/50[b] (1.4)
Degeneration of epiglottis respiratory epithelium	2/50 (1.0)	33/49[b] (1.2)	26/49[b] (1.2)	40/50[b] (1.5)
Hyperplasia of epiglottis respiratory epithelium	0/50	25/49[b] (1.4)	26/49[b] (1.3)	33/50[b] (1.5)
Squamous metaplasia of epiglottis respiratory epithelium	2/50 (2.0)	7/49 (1.9)	7/40 (1/7)	16/50[b] (1.4)
Nose				
Hyperplasia of respiratory epithelium goblet cell	13/50 (2.0)	18/50 (2.0)	16/50 (1.9)	30/50[b] (2.0)

[a]Average severity grade of lesions in affected animals: 1=minimal; 2=mild, 3=moderate; 4=marked
[b]$p \leq 0.01$
[c]$p \leq 0.05$

Source: NTP 2002

Dose and end point used for MRL derivation: The human equivalent concentration of the $BMCL_{10}$ for degeneration of respiratory epithelium of the epiglottis, 0.003 mg vanadium/m^3, was used as the point of departure for the chronic-duration inhalation MRL.

[ ] NOAEL [ ] LOAEL [X] $BMCL_{10}$

BMD analysis was used to determine the point of departure for select respiratory tract lesions in rats exposed to vanadium pentoxide for 2 years. A number of lesions were observed in male and female rats exposed to 0.28 mg vanadium/m^3 including hyperplasia of the alveolar and bronchiolar epithelium, chronic inflammation of the larynx, degeneration of the epiglottis, and hyperplasia of respiratory epithelial goblet cells. The incidence of these lesions in male rats were modeled using all available dichotomous models in the EPA BMDS (version 2.1) that were fit to the incidence data for alveolar hyperplasia, bronchial hyperplasia, using the extra risk option. The multistage model was run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Adequate model fit is judged by three criteria: goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMCL is selected as the point of departure when the difference between the BMCLs estimated from these models are more three-fold; otherwise, the BMCL from the model with the lowest AIC is chosen. In accordance with U.S. EPA (2000) guidance, BMCs and BMCLs associated with an extra risk of 10% are calculated for all models.

The results of the BMD analyses are presented in Table A-3 and Figures A-2 through A-6.

Table A-3. Model Predictions for Respiratory Effects in Rats Exposed to Vanadium Pentoxide for 2 Years

Model	χ^2 Goodness of fit p-value[a]	AIC	BMC_{10} (mg V/m^3)	$BMCL_{10}$ (mg V/m^3)
Alveolar hyperplasia in male rats				
Gamma[b]	0.25	183.50	0.12	0.04
Logistic	0.52	181.44	0.11	0.09
Log-Logistic	0.08	185.40	NA	NA
Log-Probit	0.13	184.60	0.15	0.08
Multistage[c]	0.21	184.00	0.05	0.04
Probit	**0.57**	**181.29**	**0.10**	**0.09**
Weibull[b]	0.33	183.11	0.10	0.05
Quantal-Linear	0.21	184.00	0.05	0.04
Bronchiolar hyperplasia in male rats				
Gamma[b]	0.28	165.38	0.17	0.10
Logistic	0.60	163.19	0.15	0.12
Log-Logistic	0.08	167.58	NA	NA
Log-Probit	0.12	166.67	0.19	0.13
Multistage[c]	0.56	164.51	0.13	0.07
Probit	**0.71**	**162.87**	**0.14**	**0.12**
Weibull[b]	0.45	164.73	0.15	0.09
Quantal-linear	0.03	170.74		

Table A-3. Model Predictions for Respiratory Effects in Rats Exposed to Vanadium Pentoxide for 2 Years

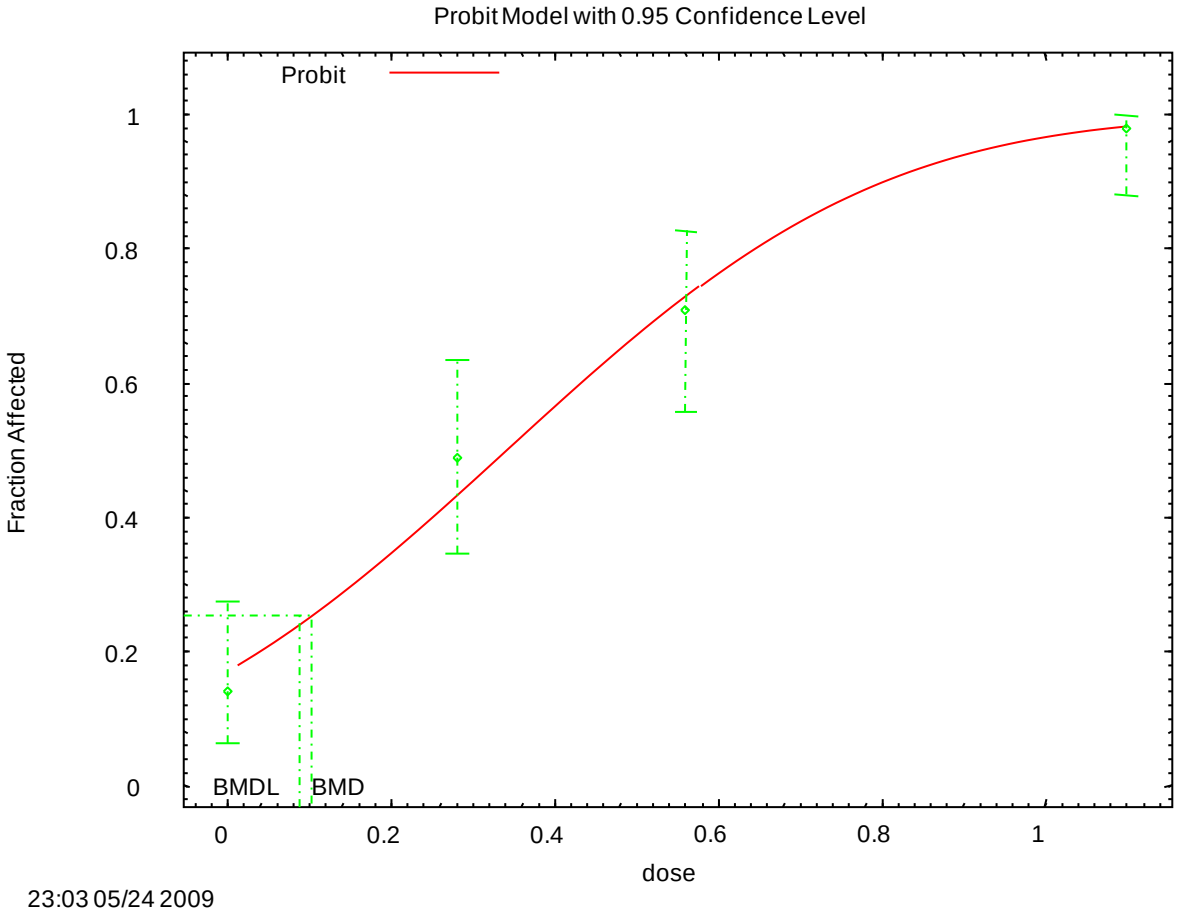
Model	χ^2 Goodness of fit p-value[a]	AIC	BMC_{10} (mg V/m^3)	$BMCL_{10}$ (mg V/m^3)
Chronic inflammation in larynx of male rats				
Gamma[b]	0.04	230.93	NA	NA
Logistic	0.01	235.47	NA	NA
Log-Logistic	**0.11**	**229.28**	**0.10**	**0.07**
Log-Probit	0.00	235.73	NA	NA
Multistage[c]	0.04	230.93	NA	NA
Probit	0.01	235.09	NA	NA
Weibull[b]	0.04	230.93	NA	NA
Quantal-linear	0.04	230.93	NA	NA
Degeneration of epiglottis respiratory epithelium in male rats				
Gamma[b]	0.06	210.55	NA	NA
Logistic	0.00	230.64	NA	NA
Log-Logistic	**0.47**	**206.17**	**0.06**	**0.04**
Log-Probit	0.01	214.79	NA	NA
Multistage[c]	0.06	210.55	NA	NA
Probit	0.00	229.81	NA	NA
Weibull[b]	0.06	210.55	NA	NA
Quantal-linear	0.06	210.55	NA	NA
Hyperplasia of nasal respiratory epithelial goblet cells in male rats				
Gamma[b]	0.12	213.84	0.32	0.20
Logistic	0.07	215.11	NA	NA
Log-Logistic	**0.15**	**213.35**	**0.27**	**0.16**
Log-Probit	0.03	216.79	NA	NA
Multistage[c]	0.12	213.84	0.32	0.20
Probit	0.07	214.97	NA	NA
Weibull[b]	0.12	213.84	0.32	0.20
Quantal-linear	0.12	213.84	0.32	0.20

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria
[b]Power restricted to ≥1
[c]Betas restricted to ≥0; 1-degree polynomial

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD; NA = not applicable

Source: NTP 2002

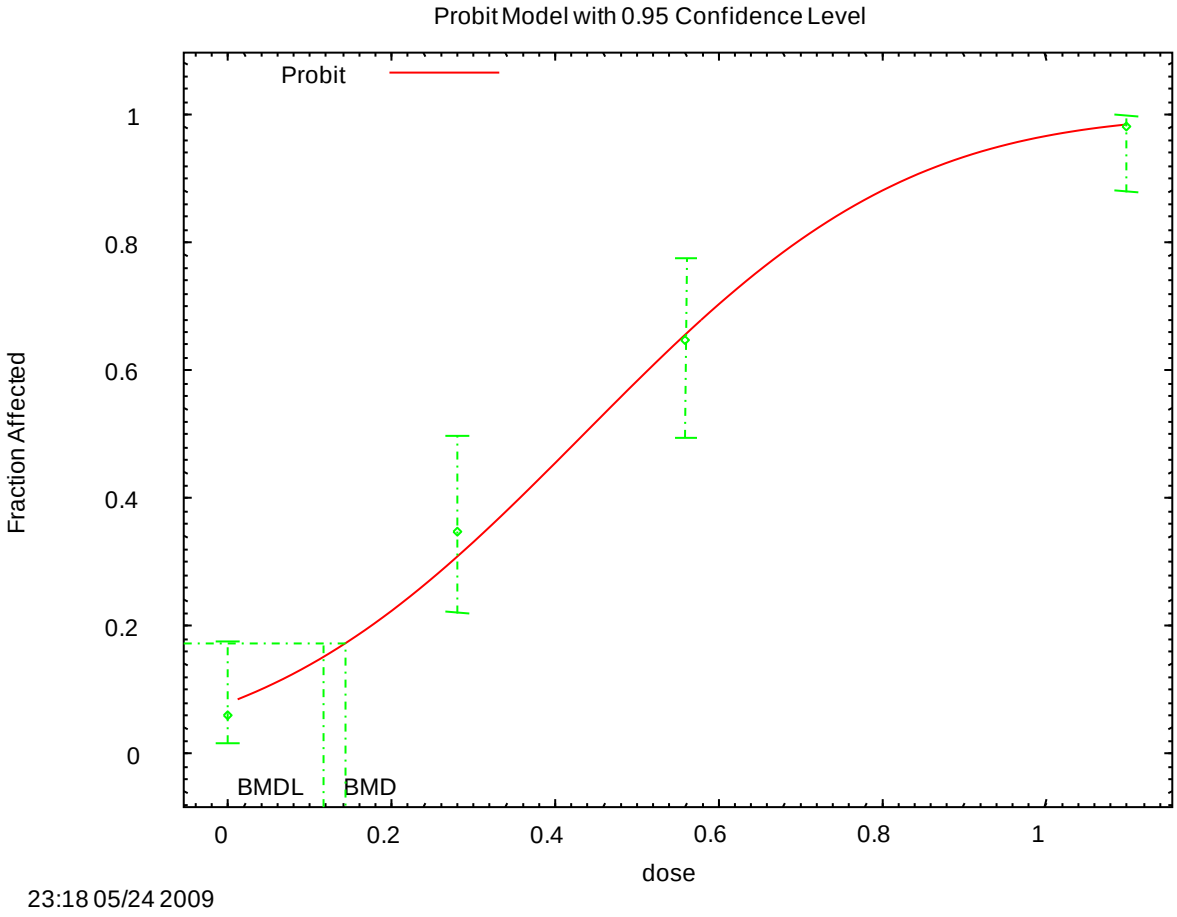
Figure A-2. Fit of Probit Model to Data on the Incidence of Alveolar Hyperplasia in Male Rats Exposed to Vanadium Pentoxide for 2 Years



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

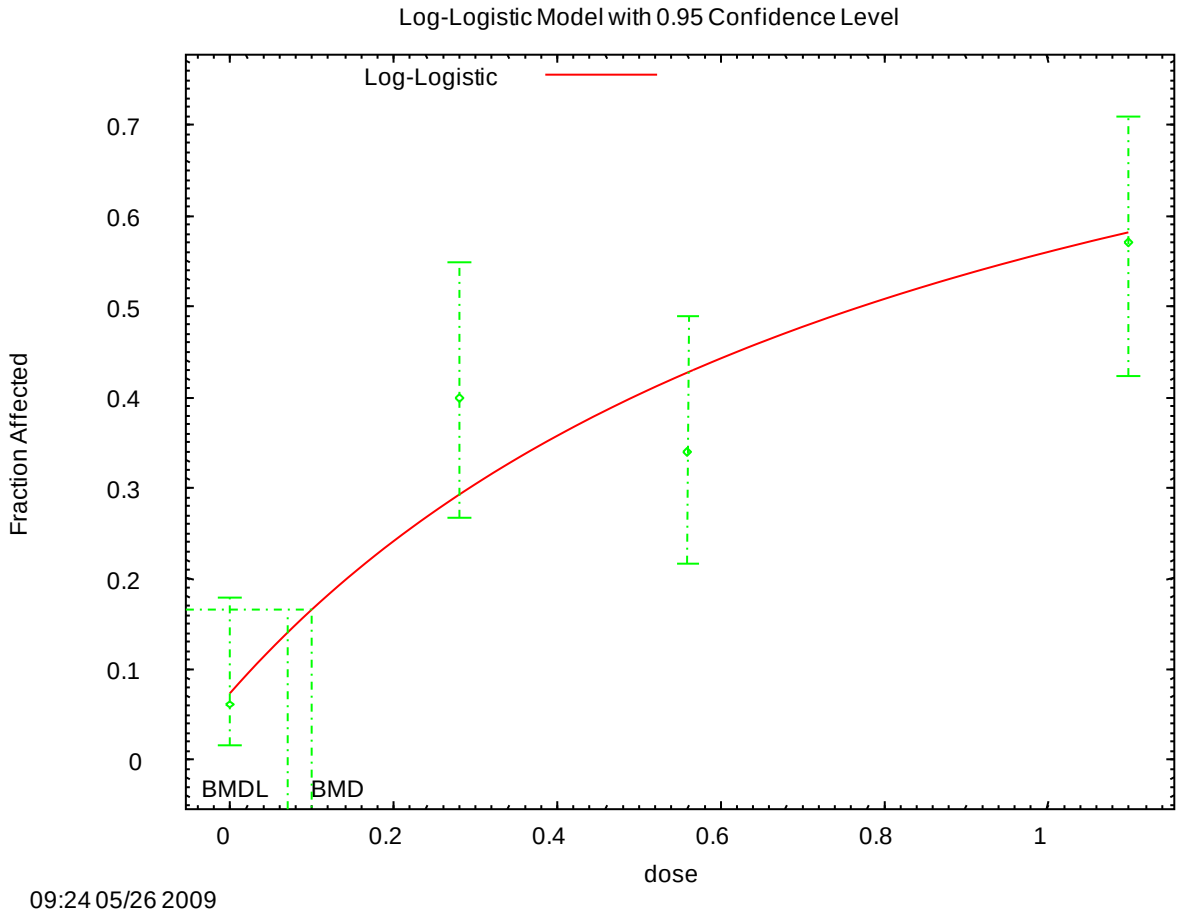
Figure A-3. Fit of Probit Model to Data on the Incidence of Bronchiolar Hyperplasia in Male Rats Exposed to Vanadium Pentoxide for 2 Years



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

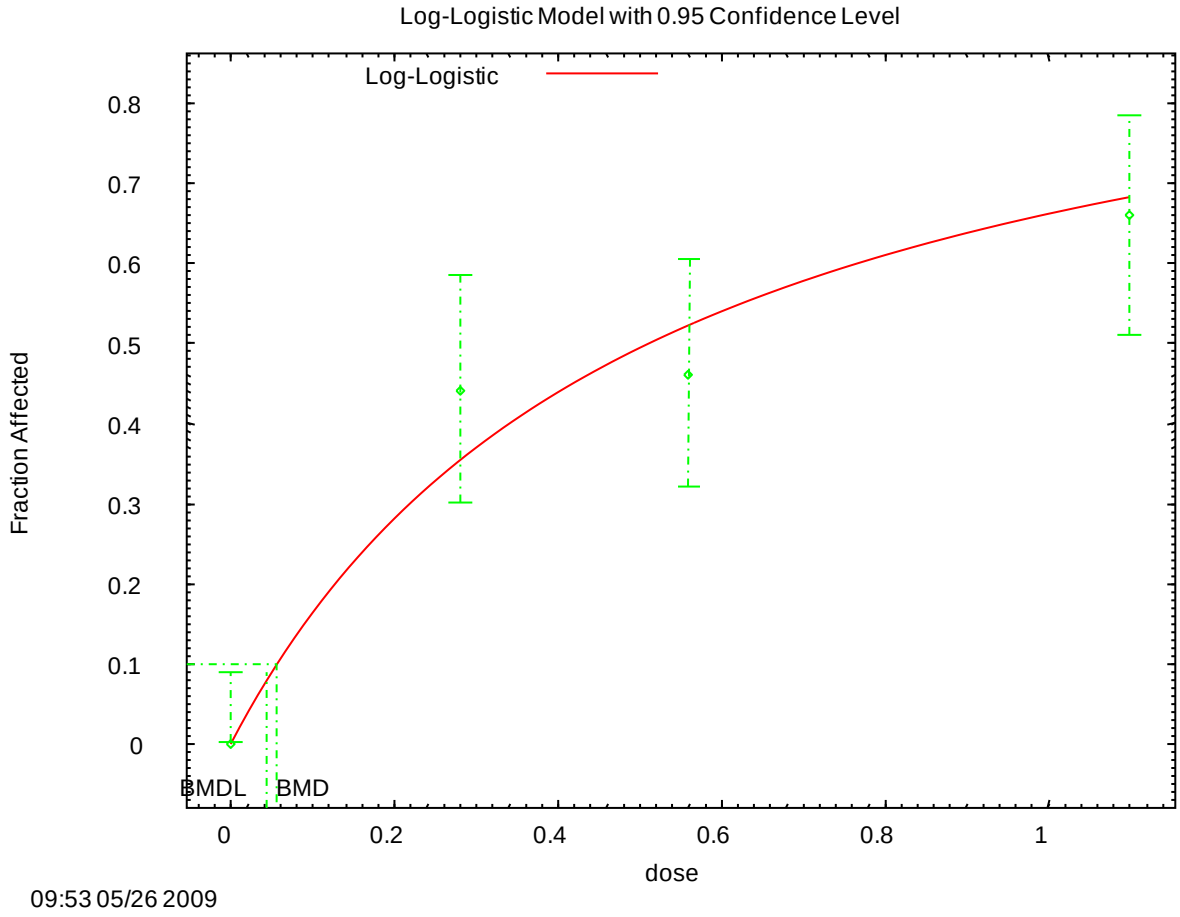
Figure A-4. Fit of Log-logistic Model to Data on the Incidence Chronic Inflammation in Larynx of Male Rats Exposed to Vanadium Pentoxide for 2 Years



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

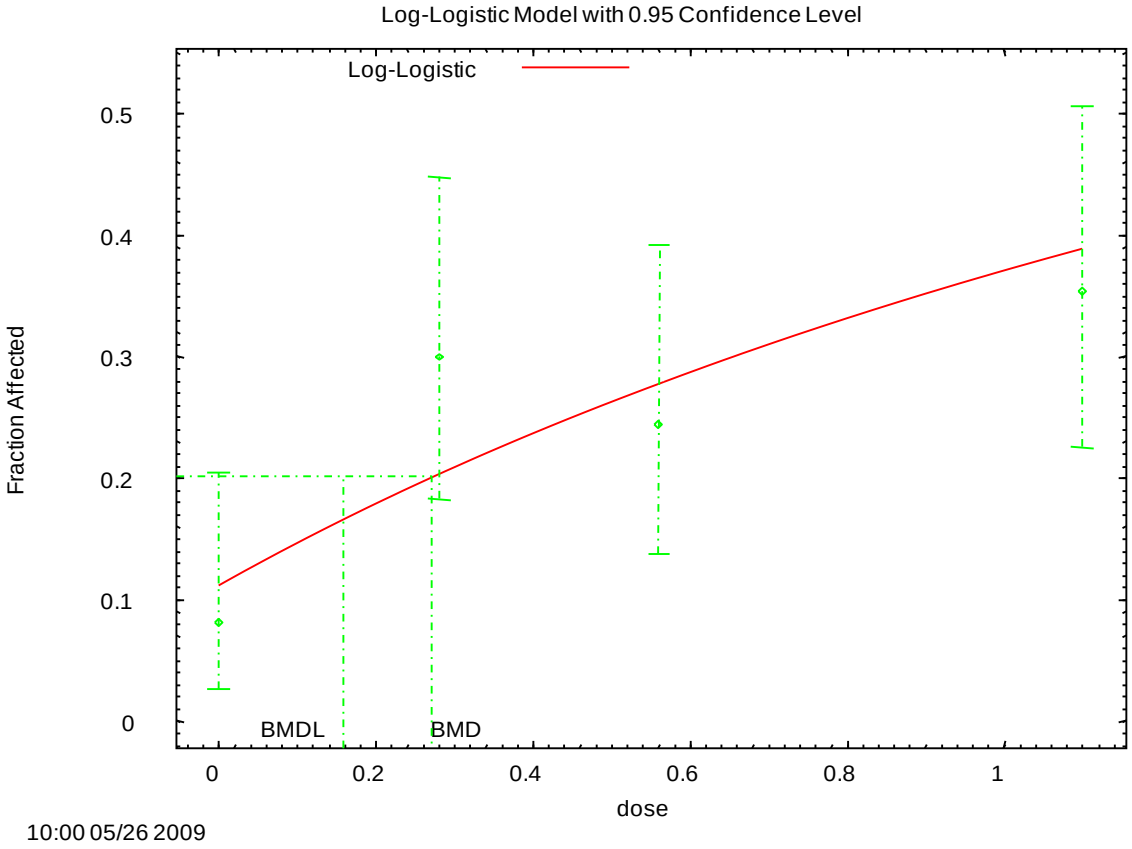
Figure A-5. Fit of Log-logistic Model to Data on the Incidence of Degeneration of Epiglottis Respiratory Epithelium in Male Rats Exposed to Vanadium Pentoxide for 2 Years



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

Figure A-6. Fit of Log-logistic Model to Data on the Incidence of Hyperplasia of Nasal Respiratory Epithelial Goblet Cells in Male Rats Exposed to Vanadium Pentoxide for 2 Years



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

In summary, the lowest $BMCL_{10}$ values for alveolar epithelial hyperplasia, bronchiolar epithelial hyperplasia, laryngeal chronic inflammation, degeneration of epiglottis epithelium, and hyperplasia of nasal goblet cells were 0.09, 0.10, 0.07, 0.04, 0.16 mg vanadium/m^3, respectively.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Human equivalent concentrations were calculated for each $BMCL_{10}$ using the following equation:

$$BMCL_{HEC} = BMCL_{ADJ} \times RDDR$$

where:
The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal to the predicted inhalation particulate exposure concentration for a human. The RDDR program (EPA 1994c) was used to calculate a multiplier for the different regions of the respiratory tract was determined using a default body weight of 0.380 kg (EPA 1994c) and a particle size MMAD of 1.2 µm with a geometric standard deviation of 1.9. The $BMDL_{HEC}$ values are presented in Table A-4

Table A-4. Summary of Human Equivalent Concentrations of BMCL Values for Rats Exposed to Vanadium Pentoxide for 2 Years

Effect	$BMCL_{10}$ (mg vanadium/m^3)	$BMCL_{ADJ}$[a] (mg vanadium/m^3)	RDDR	$BMCL_{HEC}$ (mg vanadium/m^3)
Alveolar epithelial hyperplasia	0.09	0.016	0.502[b]	0.008
Bronchiolar epithelial hyperplasia	0.10	0.018	0.971[c]	0.017
Laryngeal chronic inflammation	0.07	0.012	0.423[d]	0.005
Degeneration of epiglottis epithelium	0.04	0.0071	0.423[d]	0.003
Hyperplasia of nasal goblet cells	0.16	0.029	0.423[d]	0.012

[a]$BMCL_{ADJ}$= $BMCL_{10}$ x 6 hours/24 hours x 5 days/7 days
[b]Pulmonary region
[c]Thoracic region
[d]Extrathoracic region

BMCL = benchmark concentration, lower confidence limit RDDR = regional deposited dose ratio

Source: NTP 2002

Was a conversion used from intermittent to continuous exposure? The $BMCL_{10}$ was adjusted for intermittent exposure, as noted in Table A-4.

Other additional studies or pertinent information that lend support to this MRL: An increased combined incidence of alveolar/bronchiolar adenoma or carcinoma was observed in male rats (NTP 2002). Although the incidence was not significantly higher than concurrent controls, it was higher than historical controls and NTP considered it to be a vanadium-related effect.

In mice exposed to ≥0.56 mg vanadium/m^3 for 6 hours/day, 5 days/week for 2 years, significant increases in the incidence of alveolar and bronchiolar hyperplasia, chronic lung inflammation, squamous metaplasia of the respiratory epithelium of the epiglottis, goblet cell hyperplasia in the nasal respiratory epithelium and nasal olfactory epithelial atrophy, and hyaline degeneration were observed (NTP 2002). In addition to these effects, a significant increase in alveolar/bronchiolar carcinoma incidence was also observed in mice exposed to ≥0.56 mg vanadium/m^3.

Agency Contacts (Chemical Managers): Jessilynn Taylor, Sam Keith, Larry Cseh

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vanadium compounds
CAS Numbers: 7440-62-6
Date: August 2009
Profile Status: Pre-Public Comment, Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 12
Species: Human

Minimal Risk Level: 0.01 [X] mg vanadium/kg/day [ ] mg vanadium/m^3

Reference: Fawcett JP, Farquhar SJ, Thou T, et al. 1997. Oral vanadyl sulphate does not affect blood cells, viscosity or biochemistry in humans. Pharmacol Toxicol 80:202-206.

Experimental design: Groups of men and women enrolled in a weight training program for at least 1 year were administered capsules containing 0 (11 men and 4 women) or 0.5 mg/kg/day vanadyl sulfate trihydrate (0.12 mg vanadium/kg/day) (12 men and 4 women) for 12 weeks. Fasting blood samples were collected at 0 and 12 weeks and analyzed for hematological (erthyroctye count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, platelet count, and total and differential leukocyte count) and serum chemistry (cholesterol, high density lipoprotein, triglycerides, albumin, total protein, total and direct bilirubin, alkaline phosphatase, ALT) parameters. Body weight and blood pressure were measured at weeks 4, 8, and 12.

Effect noted in study and corresponding doses: No significant alterations in blood pressure, body weight, or hematological or clinical chemistry parameters were found.

Dose and end point used for MRL derivation: NOAEL of 0.12 mg vanadium/kg/day for hematological alterations and blood pressure.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Studies in laboratory animals have identified several sensitive effects including alterations in erythrocyte and reticulocyte levels, increased blood pressure, neurobehavioral alterations, and developmental toxicity. Significant increases in blood pressure have been observed in rats exposed to 0.12 mg vanadium/kg/day for 210 days (Boscolo et al. 1994); increases in blood pressure have been observed at higher doses in several other

studies by these investigators (Carmagnani et al. 1991, 1992). In general, other studies have not found increases in blood pressure in rats exposed to doses as high as 31 mg vanadium/kg/day (Bursztyn and Mekler 1993; Sušić and Kentera 1986, 1988). Decreases in erythrocyte levels have been observed in rats exposed to 1.18 mg vanadium/kg/day as ammonium metavanadate in drinking water for 4 weeks (Zaporowska et al. 1993); at higher concentrations, decreases in hemoglobin and increases in reticulocyte levels have been observed (Ścibior 2005; Ścibior et al. 2006; Zaporowska and Wasilewski 1990, 1991, 1992a, 1992b; Zaporowska et al. 1993). Decreases in pup body weight and length have been observed in the offspring of rats administered 2.1 mg vanadium/kg/day as sodium metavanadate for 14 days prior to mating and throughout gestation and lactation (Domingo et al. 1986). At higher doses (6, 10, or 12 mg vanadium/kg/day), decreases in pup survival, and increases in the occurrence of gross, visceral, or skeletal malformations and anomalies were observed (Elfant and Keen 1987; Morgan and El-Tawil 2003; Poggioli et al. 2001).

Agency Contacts (Chemical Managers): Jessilynn Taylor, Sam Keith, Larry Cseh

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

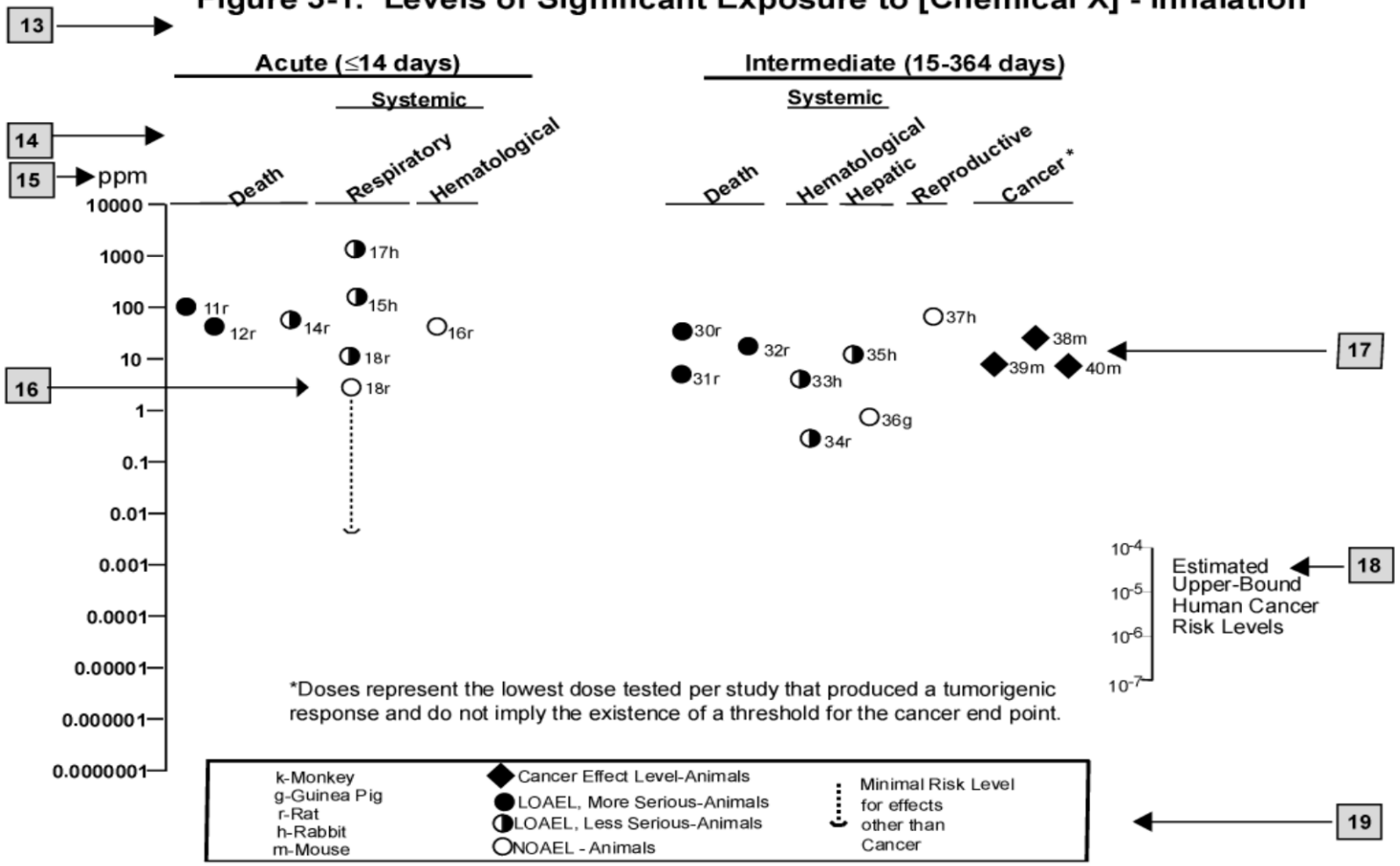
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 →							
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX

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